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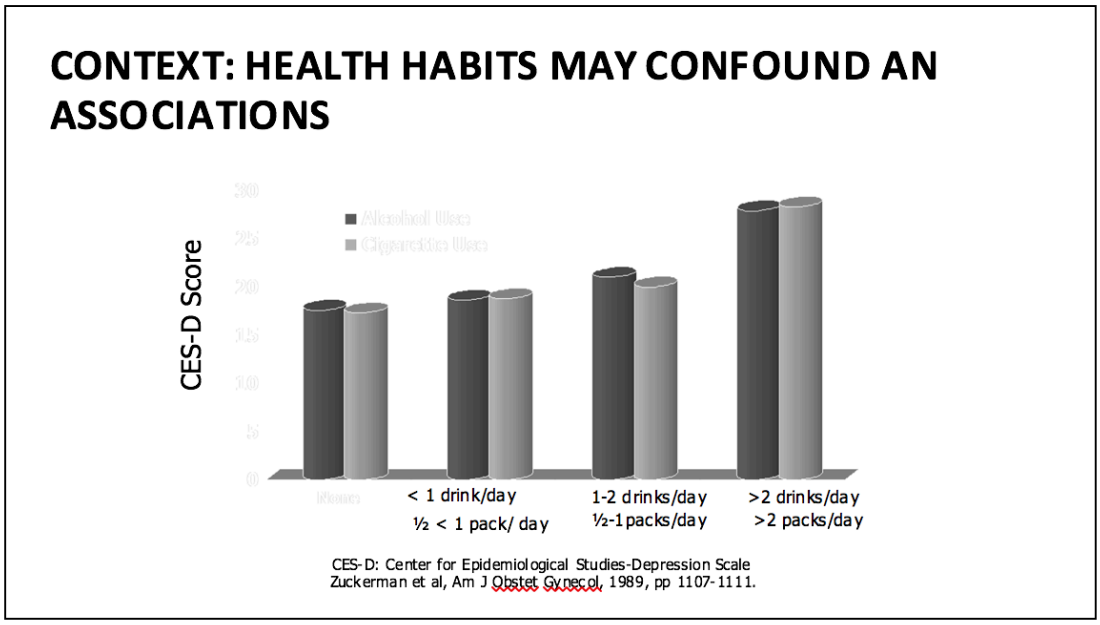
Anxiety and Depression and Pregnancy

- Depression during pregnancy (see also separate handout on depression)
  - Risk of developing a major depressive disorder is twice as high for women as for men, with rates up to 20%
  - Onset is often during childbearing years
  - 15% of pregnant women are depressed (vs. 7-9% in the general population)
  - Roughly 7% of all American women experience episodes of major depression during their first pregnancy
  - The proportion increases to 12-14% for second and third pregnancies
  - At any one time 7-11% are depressed in their first trimester, 9-13% in the second trimester, and 8-12 in the third trimester
  - Cohen et al 2004, 2004, 2006, depressed women who continued vs discontinued maintenance treatment of depression before or during their pregnancy (201 patients):
    - Relapse rates in women who continued treatment: 26%
    - Relapse rates in women who discontinued treatment: 68%
  - Pregnant women with depression have 10-15% of women become depressed in the postpartum period
  - In pregnant women with depression (separate from antidepressant use),
    - Higher levels of cortisol and adrenocorticotrophic hormone levels (stress hormones)
    - Earlier gestational age/preterm birth
    - More obstetrical complications
      - Preeclampsia
    - Reduced infant growth
    - Low birth weight (Grote, 2013)
    - Elevated fetal stress hormones
    - Reduced infant growth
    - Elevated fetal stress hormones
    - Altered fetal neurobehavioral function
      - Poorer quality of movement
      - Increased hypotonia
    - More likely to use nicotine, illicit drugs, and alcohol



    - Less likely to seek prenatal care
    - Post-partum depression (which can adversely affect the infant's temperament, mother-infant interaction, and infant cognitive ability)

- More medication use in those taking antidepressants than those not taking antidepressants

CONTEXT: USE OF OTHER MEDICATION IS MORE COMMON AMONG PREGNANT WOMEN PRESCRIBED ANTIDEPRESSANTS

Drug Group	Percent Increase	95% Confidence Interval
Drugs for Stomach Ulcer	320%	270%-368%
Opioids	295%	247%-352%
Drugs for Migraine	250%	190%-329%
Anticonvulsants	292%	221%-376%
Neuroleptics	690%	593%-803%
Sedatives	3020%	2570%-3200%
Anti-asthmatics	150%	134%-168%
Antihistamines	164%	148%-181%

Kallen & Olausson, *Birth Defects Research, Vol 79, pp. 301-308, 2007*

- Increased risks in children of pregnant women with depression
  - Delivery, and obstetrical complications
  - Excessive crying/more inconsolable
  - More difficult temperament—more distress, sadness, fear, shyness, frustration
  - Poor growth of infant, more infections
  - Developmental delay
- Increased risks in children and adolescents associated with post-partum 2epression
  - Poorer health-related quality of life
  - Behavioral and social difficulties
  - Violent behavior in youth
  - Antisocial behavior at ages 11 and 16
  - Higher rates of depression (via stress/stress hormone effects on hypothalamic-pituitary-adrenal axis?)
  - Lower cognitive abilities/reduced adolescent IQ
  - Worse performance on high school entrance exams
- NB: panic disorder is associated with increased risk of cleft palate and other congenital anomalies, lower birth weight, and shorter birth length
- Omega-3 fatty acids (up to 2.8 g/day) may boost mood in pregnant women.

- ***Post-partum blues:***
  - 50-80% of women experience this transient condition within 10-14 days of childbirth; elsewhere: 26-85%
  - This is not considered pathologic.
  - Symptoms include:
    - Tearfulness
    - Anxiety
    - Irritability
    - Emotional lability
    - Sleep disturbance
  - Usually begins 3-4 days after delivery
  - Peaks between days 5-7
  - 80% resolve by day 12
  - 20% of those with post-partum blues may proceed to development of formal post-partum depression
- ***Post-partum depression:***
  - 10-20% of pregnant women (and 20% of pregnant adolescents) will experience a post-partum depression; in some studies the rate is as high as 30%

- 13-19% prevalence within the first 3 months post-partum
- Depression often accompanied by obsessions
- Without a prior psychiatric history, the risk is 10%
- With a history of depression, the risk is 25%
- With a history of post-partum depression, the risk is 50%
- Usually by 6 weeks postpartum
- Sevenfold increase rate of psychiatric admission within the first postpartum month compared with prepregnancy rate
- Postpartum depression is serious and disabling
- Potentially damaging to the mother-child attachment.
- Risk of post-partum depression is very high (~60%) when a client has a history of a prior post-partum depression
- Restarting antidepressant treatment at the end of the third trimester or in the first 24-48 hours post-partum reduces relapse by 90%
- Need to rule out post-partum hypothyroidism, which occurs in 10% of women and peaks at 4-6 months post-delivery

- ***Post-partum psychosis***
  - Usually occurs within six weeks of childbirth
  - Usually presents with delusions
  - Women with bipolar disorder have 100-fold higher risk than women without a psychiatric illness
  - 40% of women with bipolar disorder experience post-partum mania or depression
    - 67% within one month of delivery
- ***Medications in Pregnancy***
  - Rate of relapse during pregnancy is 26% if medication is continued and 68% if medication is discontinued
  - Einarson, et al: 70% of women who discontinued medication had adverse psychiatric outcomes and 33% became suicidal
  - **In many (or most) of the studies below, the following variable were not controlled or were poorly controlled:**
    - **Whether or not the women were actually taking the medications as prescribed**
    - **Severity of depression (those taking meds may have more severe forms of depression than those without)**
    - **Presence or severity of other co-morbid psychiatric conditions**
    - **Presence or severity of co-morbid medical conditions**
    - **Presence other non-psychiatric medications**
    - **Presence of severity of alcohol or drug abuse**
    - **Degree of prenatal care**
    - **Nutritional status**
    - **Family history of pregnancy/congenital problems**

CONTEXT: ANTIDEPRESSANT USE IN PREGNANCY AND ASSOCIATIONS WITH SELECTED ADVERSE FETAL OUTCOMES

Outcome	Strength of Finding
Spontaneous miscarriage	Mixed results
Fetal demise	Not associated
Preterm Birth	Highly replicated but small effects
Small for Gestational Age/Low Birth Weight	Mixed but weak results
Major Congenital Anomalies	Mixed by weak results with exception of paroxetine
Persistent Pulmonary Hypertension	Mixed results
Neonatal adaptation	Moderately well replicated
Autism	Mixed results with preponderance not associated
Pre-eclampsia	Not replicated
Attention Deficit Hyperactivity Disorder	Not replicated (bupropion only)
Asthma	Not associated

- ***Summary of studies on birth defects***
  - SSRI's and SNRI's (Effexor XR, Cymbalta, (Remeron (which is not formally an SNRI)
    - Majority of studies show no increased risk
    - Denmark study (2012) confounded by indication
    - US study (2014): no increase in cardiovascular defects for SSRI's or other antidepressants
    - Nordic study (2015): sibling controlled analysis showed no increase in total malformations or cardiac malformations
    - No human data for Viibryd or Trintellix
  - Tricyclic antidepressants
    - Majority of studies show no increased risk
  - Wellbutrin
    - Majority of studies show no increased risk
  - MAOI's
    - Very limited human data; experimental animal data does not suggest increased risk
- ***Some specific medications***
  - Cymbalta
    - Einarson, 2012: does not appear to increase risk of congenital malformation above background rate of 1-3%
  - Tricyclic antidepressants and pregnancy
    - Worsen constipation
    - Worsen orthostatic hypotension
    - May worsen cardiovascular problems
    - Not associated with congenital malformations
  - Wellbutrin and pregnancy
    - Overall thought to be safe
    - Overall not associated with increased risk of birth defects (Einarson, 2009; Chun-Fai-Chan, 2005; Cole, 2007)
    - May be associated with an increase in left outflow tract heart defects
    - Increased risk of miscarriage in one study (Chun-Fai-Chan, 2005)
    - Animal data suggests safety
    - Lowered seizure threshold (at higher doses); problematic with preeclampsia
  - Remeron

        - No nausea
        - Useful in women with hyperemesis gravidarum (especially disintegrating tablet)
        - No increased risk of birth defects (Einarson, 2009; Lennestal, 2007; Djulus, 2008)
        - Increased rate of preterm birth in one study (Djulus, 2008)
    - SAMe and pregnancy
        - Thought to be safe
- ***Congenital anomalies***
    - ***Baseline rate in the general overall population of birth defects is 2-4%***

CLINICAL IMPLICATIONS: THE EFFECTS OF ANTIDEPRESSANTS ON RISK OF BIRTH DEFECTS

- Whether SRIs, including paroxetine, increase the risk of malformations, particularly heart defects, is possible but remains controversial
- If risks are real, the absolute risk is low and must be viewed in the context of whether medication is needed
- Other exposures such as alcohol may confound results, particularly in registry studies that typically have limited information about the mother

    - ***Important for context:***

CONTEXT: ABSOLUTE RISK FOR BIRTH DEFECTS WITH ESTABLISHED TERATOGENS

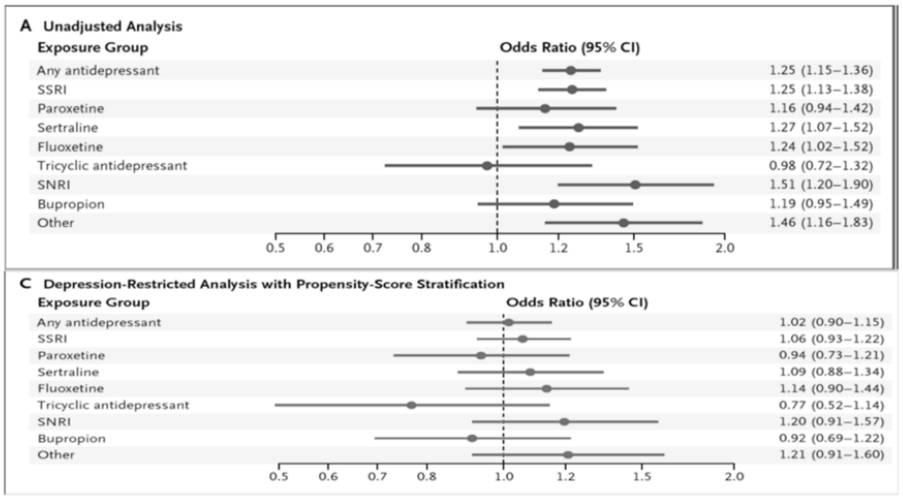
Exposure	Outcome	Estimated absolute risk
valproic acid	Any major defect (3/100 births in population)	11/100 exposed
isotretinoin	Heart, CNS, ear thymus defects	18/100 exposed
alcohol	Craniofacial, brain, growth defects: Fetal Alcohol Spectrum Disorders	25/100 heavily exposed
serotonin reuptake inhibitors	Any malformation	3/10000

Wyzynski DF et al Neurology 64: 961-5 2005
Lammer EJ et al N Engl J Med 313:637-41 1985

    - Zhao et al, 2017
        - 18,847 women (women on vs. not on antidepressants
        - Not clear if both groups suffered from depression and anxiety and if the severity of depression and anxiety were controlled for
        - Risks very small and defects very rare
        - Paxil associated with
            - Heart defects (VSD, ASD)
        - Celexa associated with

        - Musculoskeletal defects
        - Craniosynostosis
    - Effexor associated with
        - Respiratory defects
    - TCA's associated with
        - Eye problems
        - Ear problems
        - Face problems
        - Neck problems
        - Digestive problems
- Note that some studies demonstrating an association between prenatal SSRI use and congenital anomalies have also shown an increase (up to 10-fold) rate of fetal alcohol syndrome and thus prenatal alcohol use which are associated with increased risk of congenital anomalies
- When adjusted for depression, risk for all SSRI's overlaps with 1.0 (zero risk):

UPDATE: SRIS & RISK OF CONGENITAL CARDIAC MALFORMATIONS



Medicaid Analytic eXtract; n=949,504 and 217,342 in depression restricted; Huybrechts et al NEJM, 2014

- Cowley et al, 2014:
    - 949,504 women aged 12-155 yo and their liveborn infants
    - 64,389 women (6.8% of total) used an antidepressant, 2/3's of which used an SSRI
    - Cardiac malformations
        - 90/10,000 antidepressant-exposed infants
        - 72/10,000 unexposed infants
        - Fully adjusted analyses restricted the cohort to women with depression and controlled for confounding factors such as sociodemographics, multiple gestation, chronic maternal illness, use of other psychotropic medications or suspected teratogens, and smokings
            - No associations were found between antidepressant use and cardiac malformations
            - No dose-response relationship was found between antidepressant use and cardiac malformations
            - No association between Paxil and right ventricular outflow tract obstruction
            - No association between Zoloft and ventriculoseptal defects
            - Only associations found were between cardiac malformations and
                - Maternal diabetes
                - Antiepileptic exposure
                - Multiple gestation
- ***Consensus as of October, 2013:***

- SSRI's do not as a whole increase risk of birth defects (see below re: Paxil)
- Prospective controlled studies and meta-analyses find no increased risk (Einarson, 2011)
  - One meta-analysis found statistically significant but not clinically significant increase in cardiovascular malformations (Grigoriadis, 2013)
- Retrospective database studies:
  - Most find no increased risk of general anomalies
  - Others are contradictory
    - One shows increased risk of general anomalies (Wogelius, 2006)
    - One shows no increased risk of general anomalies, but increased risk of septal heart defects (Pedersen, 2009)
    - One shows no increased risk of cardiovascular defects, but increased risk of anencephaly, craniosyntosis, and omphalocele (Alwan, 2007)

- Huge database from Swedish registry shows slight increase, primarily with Paxil and TCAs:

CONTEXT: MALFORMATIONS & SWEDISH REGISTRY

(N=15,017 EXPOSED; N= 1,236,053 TOTAL)

Malform-ation	Any TCA (N=1662)	Any SSRI (N=10170)	Any SNRI (N=1351)	Fluoxetine (N=1522)	Citalopram (N=3950)	Paroxetine (N=1208)
Severe Malform-ation	**N=77 OR=1.36 (1.07-1.72)**	N=345 OR= 1.08 (0.97-1.21)	N=43 OR=1.00 (0.73-1.37)	**N=60 OR=1.29 (1.00-1.67)**	N=133 OR=1.06 (0.88-1.26)	N=49 OR=1.2 (0.9-1.61)
Any CV	**N=30 OR=1.63 (1.12-2.36)**	N=109 OR=0.99 (0.77-1.29)	N=20 OR=1.33 (0.84-2.09)	N=21 OR=1.31 (0.85-2.02)	N=37 OR=0.86 (0.62-1.20)	**N=24 OR=1.66 (1.09-2.53)**
VSD/ASD	**N=17 OR=1.84 (1.13-2.97)**	N=61 OR=1.0 (0.77-1.29)	N=11 OR=1.26 (0.63-2.26)			
Hypospad	N=9 OR=1.93 (.88-3.67)	N=38 OR=1.3 (0.94-1.8)	N=6 OR=1.47 (0.54-3.19)	N=5 OR=1.10 (0.36-2.57)	N=38 OR=1.30 (0.94-1.80)	**N=9 OR=2.45 (1.12-4.64)**
Cystic Kidney	N=0	**N=9 OR=2.39 (1.09-4.54)**	N=0			

Reis & Kallen, Psychological Medicine, 2010, Vol 40, pp 1723-1733

- Einarson, et al: SSRI's (and Wellbutrin and Serzone) were not associated with congenital anomalies (but see above)
- Other studies demonstrate no increase in congenital anomalies with SSRI's (but see below), Effexor, trazodone, and Serzone
- Lexapro demonstrated no increase in congenital anomalies in one study
- Louik et al, 2007:
  - Case control study with 9,849 infants with congenital malformations and 5,860 infants without congenital malformations
  - No association found between SSRIs overall exposure and
    - Craniosynostosis
    - Omphalocoele
    - Overall congenital heart anomalies
  - Specific agents
    - Zoloft was associated with
      - 5.7-fold increased risk of omphalocoele
      - 2-fold increased risk of septal defects
      - Anal atresia
      - Limb-reduction defects
    - Paxil was associated with
      - 3.3-fold increased risk of right ventricular outflow tract obstruction defects
      - Neural tube defects
      - Club foot

        - Undescended testes
    - Non-SSRI antidepressants were associated with anal atresia
- Alwan et al, 2007, case-control study looking at 9,622 with birth defects vs. 4,092 without birth defects
    - SSRI was found to be associated with a 2.4-fold to 2.8-fold increased risk of
        - Anencephaly
        - Craniosynostosis
        - Omphalocoele
    - None of the individual SSRI's were associated with overall risk of birth defects or combined totals of cardiac or non-cardiac defects
    - Paxil and Celexa were each associated with the combined group of anencephaly, craniosynostosis, and omphalocoele
- Rahimiet al, 2006,
    - Meta-analysis of 9 studies looking at Celexa, Prozac, Paxil, Zoloft vs. general population:
    - No association with increased risk of major malformations
    - No association with cardiovascular malformations
    - No association with minor malformations
    - However, increased risk of spontaneous abortions (but is this related to depression or treatment?)
- King et al, 2006; looking prospectively at 19,691 cases
    - In general population the risk of major congenital malformation is 3-4%
    - In exposed cases the risk is 2.6%
- Malm, 2005:
    - 1782 pregnancies in Finland
    - First trimester SSRI use
        - major malformations were not associated with first trimester SSRI use (in the 1398 women who were prescribed SSRI's in the first trimester)
        - 11.2% of infants of moms with first trimester SSRI use were treated in special or intensive care units
    - Third trimester use:
        - 15.7% of infants of moms with third trimester SSRI use were treated in special or intensive care units
    - 0.2% absolute risk increase in right ventricular outflow track defects; however, drug and alcohol use as well as the use of other medications could not be rules out as contributory
    - In the first year of life there is spontaneous resolution of 90% of ventricular septal defects
    - No increased risk of preterm birth, birth 32 weeks of gestation or less, small for gestational age, or low birth weight in women with second or third term SSRI use compared to women with only first trimester use.
- In studies through 2004:
    - Tricyclic antidepressants and Prozac do not appear to increase risk for congenital malformations.
    - There has not appeared to be an association between use of SSRI's in pregnancy and major congenital malformations or clear behavioral sequelae, including over 2000 women on Prozac in a national data-base.
- Newport, 2004:
    - 2219 reports of SSRI use in pregnancy
    - No association with congenital anomalies.
- Kalra, 2005:
    - review assessed more than 1700 pregnancies described in literature
    - Prozac was not associated with elevated risk of major congenital malformations, with other adverse pregnancy outcomes, or with long-term developmental delays.
- **8-12/05:**

        - **first trimester Paxil use may be associated with 1.5-2% risk of cardiac defect (vs. 1% in general population) and 1.8-fold increased risk in congenital malformations overall.**
        - **first trimester Paxil use may be associated with 4% incidence of birth defects (including ventricular septal defects) versus 2% in those taking other antidepressants.**
        - **Teratology Society meeting**:
            - **5,357 SSRI-exposed (22% Paxil) infants (exposure b/w 1 mo prior and 3 mo after conception)**
            - **3,366 non-exposed infants**
            - **SSRI use associated with:**
                - **3.3-fold increased risk of omphalocele** (**highest with Paxil--increased risk is 6.4-fold)**
                - **6.3-fold increase in risk of tetralogy of Fallot**
                - **no other major congenital malformations.**
        - The baseline rate of omphalocoele is 2.5/10,000 in one study, 30/10,000 in another (so that the increased risk from SSRI exposure is 7-90/10,000 overall (and 15-180/10,000 from Paxil exposure)
    - King et al, 2006; looking prospectively at 19,691 cases
        - In general population the risk of major congenital malformation is 3-4%
        - In exposed cases the risk is 2.6%
    - Einarson, et al: no association between Paxil and cardiac defects
    - Kallen and Olaussen, 2007:
        - 6,481 women delivered 6,555 infants exposed to SSRI's during 1st trimester
        - No increased risk for any cardiac defects in SSRI-exposed infants
            - 78/6555 in SSRI-exposed infants
            - 11367/873876 in non-exposed infants
            - Relative risk 0.7
    - Bar-Oz et al, 2007
        - Meta-analysis
        - 2061 unpublished cases cardiac deficit rate of infants exposed to Paxil: 1.5%
        - 1174 teratology register cases cardiac defect infants exposed to Paxil: 0.7%
    - INFORMATION ON VENTRICULAR SEPTAL DEFECT
        - ~1% of births in the general population
        - Most common congenital heart defects
        - Small defects are most common (80-90%)
        - 30-50% small defects close spontaneously prior to age 4
        - Small muscular defects are more likely to close than membranous (80% vs. 35%)
        - Risk factors include maternal alcohol use, valproic acid
    - Chun-Fai et al, 2005, 2007
        - Wellbutrin not associated with congenital defects
- ***Spontaneous miscarriage***
    - ***2.7-15% in women not taking medication***
    - 5.5-13% in women taking antidepressants (though the role of depression itself is not clear)
    - Many of the studies do not document whether a patient deemed to be on medication is actually taking it
    - ***Risk adjusted for prior history of induced abortions***
        - Adj'd risk of deprn w/o meds (corrected for hx of induced abortions): 1.1 (1-1.2)
        - Adj'd risk of deprn w/ meds (corrected for hx of induced abortions): 1.3 (1.1-1.5)

UPDATE: RISK OF MISCARRIAGE WITH SRI EXPOSURE IN PREGNANCY

	Total				
	Births + Miscarriage[a]	Births + Miscarriage + ½ Induced Abortions[b]	Miscarriage	Adjusted RR Uncorrected for Induced Abortions (95% CI)	Adjusted RR Corrected for Induced Abortions (95% CI)
Comparison groups					
No medication, no depression	19,335	23,839	1,685	1	1
No medication, depression	7,034	8,877	720	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)
Antidepressant use, depression	1,041	1,498	165	1.5 (1.2, 1.7)	1.3 (1.1, 1.5)
Hypothyroid medication use	697	822	71	1.0 (0.82, 1.3)	1.1 (0.85, 1.3)
Age					
15–20	3,571	5,056	341	1.2 (1.1, 1.3)	1.0 (0.90, 1.1)
21–35	21,873	26,454	1,813	1	1
>35	2,663	3,527	487	2.1 (1.9, 2.3)	2.0 (1.8, 2.2)

Corrected for induced abortion, use of teratogens, but not cigarettes or drugs;
Almeida et al, Epidemiology, 2016 Vol 27 (4)

- ***Consensus as of October, 2013***
  - They MAY be a connection
  - Statistically significant in several, but not all, prospective, controlled studies (Santone, 2009; Einarson, 2009)
  - In those studies
    - Miscarriage rate in antidepressant-exposed group is SIMILAR to general population rate
    - Miscarriage rate in control group is LOWER than general population rate
  - Meta-analysis of highest quality studies showed no statistically significant difference in miscarriage rate with or without antidepressant exposure (Ross, 2013)
- Ross et al, 2013
  - No significant association between antidepressant medication exposure and spontaneous abortion
- Einarson et al, 2009:
  - 937 women not on antidepressants, 937 women on antidepressants
  - 338 women had a history of miscarriage
  - 13% of women not on antidepressants had spontaneous miscarriage
  - 20% of women on antidepressants had spontaneous miscarriage
  - Relative risk 1.63
- Hemels et al, 2005:
  - 7.5-9% (average 8.7%) in women not exposed to antidepressants
  - 8.8-14% (average 12.4%) in women exposed to antidepressants

- ***Birth weight***

CONTEXT: ANTIDEPRESSANTS AND FETAL GROWTH

- Studies are mixed but both TCAs and new agents are weakly associated with LBW
- Registry studies are more likely to be positive but may have confounding
- Outcomes may differ for offspring exposed only in the 1st tri vs the 2nd and 3rd tri
- The lack of difference for small for gestational outcomes suggest that the smaller babies may be a result of earlier delivery

- Adjusting for parental and genetic factors, shows the risk is minimal

UPDATE: CONTROL OF PARENTAL & GENETIC FACTORS QUESTIONS ASSOCIATION BETWEEN SSRI USE IN PREGNANCY AND DECREASED FETAL GROWTH

		Population analysis (*N*=392 029)		Within-family analysis (*N*=1007)	
		Coefficient	95% CI	Coefficient	95% CI
Birth Length[a,b]					
	SSRI Exposure	−.14	−.16 to −.11	.01	−.1 to .11
	Depression without SSRI exposure	.06	.01 to .11		
Birth Head Circumference[a,b]					
	SSRI Exposure	−.08	−.10 to −.05	−.03	−.14 to .08
	Depression without SSRI exposure	.05	−.01 to .10		
Birth Weight[a,b]					
	SSRI Exposure	−.01	−.04 to .02	.05	−.05 to .14
	Depression without SSRI exposure	.03	−.026 to .01		

Swedish Birth Registry; controls for smoking & other medication use
Victorin et al.2016; International J of Epidemiology

- ***Consensus as of October, 2013***
  - May be a connection; clinical significance is not clear
  - Meta-analysis of 20 studies: mean reduction of 74 grams associated with in utero SSRI exposure (Ross, 2013)
  - Most studies unable to control for the effects of depression
  - Two studies directly compared effects of depression and antidepressants on growth
    - In one, no significant differences for infant weight, length or head circumference among groups with SSRI exposure, untreated major depression, or both (Wisner, 2013)
    - In the other, slower fetal growth with depression, growth same between those with SSRI exposure and controls (Marroun, 2012)
- Ross et al, 2013
  - No significant association between antidepressant medication exposure and low birth weight when compared to depressed women without antidepressant exposure
- Wisner et al, 2013
  - Neither prenatal depression NOR SSRI exposure was significantly associated with infant weight, length or head circumference

- Marroun et al, 2012
  - Maternal depressive symptoms associated with
    - Reduced fetal body growth
    - Reduced fetal head growth
  - Mothers using prenatal SSRI
    - Fewer maternal depressive symptoms
    - Not associated with reduced fetal head growth
    - Higher risk for preterm birth (2.14-fold increased risk)
- Ramos, et al
  - No association with SSRI's
  - No association with TCA's
  - Increased risk with Effexor (based on very few people; use not well documented; only seen at subtherapeutic doses and may actually indicate undertreated depression as the causal factor)
- Suri, et al
  - No association with SSRI's
  - No association with SNRI's
  - No association with nortriptyline (a TCA)
  - No association with Wellbutrin
- Einarson, et al
  - No association with antidepressants

- ***Prematurity***
  - After adjusting for parental and genetic factors:

UPDATE: AFTER CONSIDERING GENETIC & ENVIRONMENTAL FACTORS DEPRESSION & ANTIDEPRESSANTS SHORTEN GESTATION SLIGHTLY

Gestational Age at Delivery[a]					
	SSRI Exposure	−3.12	−3.53 to −2.70	−2.27	−3.79 to −.75
	Depression without SSRI exposure	−1.69	−2.51 to −.86		
Preterm Birth[a]					
	SSRI Exposure	1.45	1.31 to 1.61	1.36	.77 to 2.42
	Depression without SSRI exposure	1.31	1.07 to 1.60		

Swedish Birth Registry; controls for smoking & other medication use but not other hazardous substances
Victorin et al.2016; International J of Epidemiology

  - ***Consensus as of October, 2013***
    - Probably is connected (but depression itself increases the risk of premature labor; most studies could not disentangle this confound (and keep in mind, those women with more serious depressions are more likely to be using antidepressant treatment than those women with less severe depressions (or without depression))
    - Meta-analysis of 13 high-quality studies found pooled risk 1.55-fold higher (Ross, 2013)
    - One study comparing depression exposure to antidepressant exposure found approximately equal effects on premature labor; both increased risk compared to no exposure (Wisner, 2009)
    - Clinical significance

        - Gestational age is reduced by 3-4 days with antidepressant exposure (Ross, 2013; Einarson, 2011; Marroun, 2012); Yonkers, 2012)
        - When defined as dichotomous (meaning, ANY degree of preterm labor versus NONE):
            - >20% with continuous antidepressant exposure experience pre-term labor
            - 4-9% in control group experience it
    - Kulin et al, 1999:
        - SSRIs
        - 267 women
        - No difference
    - Einarson et al, 2001
        - Effexor XR vs. SSRI vs no treatment
        - 150 women per group
        - No difference
    - Hendrick et al, 2003
        - SSRIs, no control
        - 147 women
        - 6.5% pre-term
    - Suri et al, 2004
        - Prozac
        - 59 women
        - No difference
    - Malm et al, 2005
        - Finnish registry
        - SSRIs
        - 1782 women
        - Not significant
    - Chun-Fai-Chen, 2005
        - Wellbutrin
        - 136 women
        - No difference
    - Oberlander et al, 2006
        - Canadian Health Care Registry
        - No difference
    - Djuluk et al, 2006
        - Remeron
        - 104 women
        - 10% preterm with Remeron
        - 2% preterm with no Remeron
    - Suri, et al, 2007
        - 93 women: 1) depressed WITH antidepressant, 2) depressed WITHOUT antidepressant, 3) controls
        - Some association with antidepressant use (by less than one week; not clear if the risk is connected to depression vs. medication)
            - Lower average gestational age at birth (by about 1 week)
            - Higher percentage of preterm delivery (14.3% vs. 0% vs. 5.32%)
            - Higher percentage of special care nursery admissions (20% vs. 9% vs. 0%)
    - Ross et al, 2013
        - Positive association between antidepressant medication exposure and gestational age/preterm delivery
- ***Lower Apgar Scores***
    - Ross et al, 2013
        - Positive association between antidepressant medication exposure and lower Apgar scores at 1 and 5 minutes

- Jensen et al, 2013:
  - Infants exposed to antidepressants during pregnancy had a ~two-fold increased rate of a low Apgar score (odds ratio (OR) = 1.72, 95% CI 1.34-2.20).
  - The increased rate was only found among infants exposed to selective serotonin reuptake inhibitors (SSRIs) (OR = 1.96, 95% CI 1.52-2.54), not among those exposed to newer (OR = 0.83, 95% CI 0.40-1.74) or older antidepressants (OR = 0.53, 95% CI 0.19-1.45).
  - Maternal depression before or during pregnancy, without prescription of antidepressants, was not associated with a low Apgar score (OR = 0.44, 95% CI 0.11-1.74).
  - Women who had only used antidepressants prior to pregnancy had no increased rate of a low Apgar score in their subsequent pregnancy, regardless of depression status.
- ***Preeclampsia***
  - Late use in pregnancy of SSRIs and SNRIs associated with increased risj in this 2016 study

UPDATE: GH AND PRE-ECLAMPSIA ARE MORE STRONGLY ASSOCIATED WITH LATE USE IN PREGNANCY AND SNRIS THAN SSRIS

Outcome	Number	Number (%) with outcome	Adjusted Odds Ratio
Gestational Hypertension			
Non-use	3119	109 (3.5)	
Discontinuer	102	3 (2.9)	0.69 (0.21,2.38)
Continuer	250	17 (6.8)	**1.83 (1.05,3.21)***
Pre-eclampsia			
Non-use	3119	123 (3.9)	
Discontinuer	102	7 (6.9)	1.69 (0.73,3.91)
Continuer	250	11 (4.4)	1.3 (0.67, 2.51)
Either			
Non-use	3119	232 (7.4)	
Discontinuer	102	10 (9.8)	1.16 (0.57,2.36)
Continuer	250	28 (11.2)	**1.57 (1.01,2.44)**

*SNRI users alone; O'Campo et. Al. , Archives of Womens Mental Health, 2016)

  - SSRI's not associated (but see below for other types of antidepressants) in this 2013 study

CONTEXT: ANTIDEPRESSANTS & PREECLAMPSIA

	N	Rate	OR	95% CI
Depressed & No Antidepressant Use (Referent)	59,219	5.4%		
SSRIs	19,000	5.4%	1.00	(0.93-1.07)
SNRI	1216	8.8%	1.52	(1.26-1.83)
TCA	441	10.7%	1.62	(1.23-2.12)
Bupropion	2622	6%	1.06	(0.91-1.25)
Other monotherapy (traz & mirt)	647	5%	0.71	(0.50-1.00)

Rate for preeclampsia and non depressed and non treated was 4.7%. 130 days of exposure to SSRI was significantly associated as was high doses and mediumto long exposure to SNRIs.
Palmsten et al Epidemiology, 2013; 24:682-691

- ***SSRI's and other issues in pregnancy***
  - Fetal serum levels of antidepressants may approach 50% of the maternal levels

- In addition to above there may be an association between SSRI use in pregnancy and
  - lower prolactin cord-blood levels (associated with respiratory distress)
  - higher serotonin-related symptoms scores at 4 days (in Prozac but not Celexa in one study)
  - respiratory functions (in women taking SSRI's after 29 weeks (not before))
    - ?pulmonary vasoconstriction
    - Respiratory distress
    - Oberlander et al, 2006: gestational age, birth weight, feeding difficulties, convulsions, and jaundice all happened in the same proportions in depressed women whether or not they were being treated with antidepressants; HOWEVER, respiratory distress WAS associated with SSRI use
  - mild motoric difference
  - speech/language disorders in children of moms exposed to SSRI's—Brown et al, 2016
    - 845,345 women
      - 15,596 in SSRI-exposed/depression group
      - 9,537 in SSRI-unexposed/depression group
      - 31.207 in SSRI-unexposed/not depressed group
    - Risk
      - 0.0087 risk of speech/language disorders in SSRI-exposed group
      - 0.0061 risk in unexposed group
      - Risk is 1.37-fold higher
      - Degree of depression in the two depression groups not controlled for
      - Degree of adherence to SSRI-treatment not controlled for
  - post-natal bleeding/neonatal bleeding
    - Post-natal bleeding risk increased 1.7-2 fold
  - post-natal neonatal hypertension
  - 2005: self-resolving thalamic cysts in 6 SSRI-exposed infants
  - Chambers et al, 1996: Prozac during pregnancy
    - Not associated with major structural anomalies
    - Not associated with pregnancy loss
    - Was associated with
      - increased rates of prematurity
      - admission to special-care nurseries
      - poor neonatal adaptation
      - decreased weight
      - decreased size
      - minor structural anomalies (three or more)
  - Jimenez-Solem et al, 2013: no association between SSRI use in pregnancy and risk of stillbirth/neonatal mortality
  - HOWEVER, it is difficult to tease apart the risk on pregnancy outcome due to depression from the risk due to the treatment of depression.

- ***Neonatal adaptation syndrome/side effects***
  - Associated with use of SSRI's and SNRI's in the third trimester

UPDATE: NEONATAL EFFECTS OF IN UTERO ANTIDEPRESSANTS (N=741,040)

	OR Any point in pregnancy	95% CI		OR Late vs Early	95% CI
NICU admission --SSRIs	1.5	1.4-1.5	NNH=29	1.5	1.4-1.6
--SNRIs	2.7	2.6-3.5		2.2	1.6-3.0
--TCAs	2.6	1.7-3.4		1.7	1.1-3.7
PPHN	1.7	1.1-2.7	Death=3.4%	3.0	1.6-5.5
Resp Distress	1.3	1.0-1.7		1.8	1.5-2.2

Adjusted estimates(fetal and maternal factors including opioids, antiepileptics, centrally acting sympathomimetics, Smoking, birth defects) Norby et al, Pediatrics, 2016, Vol 138 (5)

UPDATE: BEYOND NEONATAL ADAPTATION

- 184 infants were assessed 2 and 4 weeks post delivery
- Groups included no exposure (n= 66); depression only exposure (n=56); SSRI only exposure (n=52); SSRI and benzodiazepine (n=10)
- Outcome was the Neonatal Intensive Care Unit Network Neurobehavioral Scale
- SSRI and SSRI/benzo had lower motor scores and higher stress signs, arousal, and excitability than other groups at day 14; depressed exposure group had lower arousal than other groups

Salisbury, O'Grady, Battle, Wisner, Anderson, Stroud, Miller-Loncar, Young, Lester, AJP, 2016; 173: 147-157

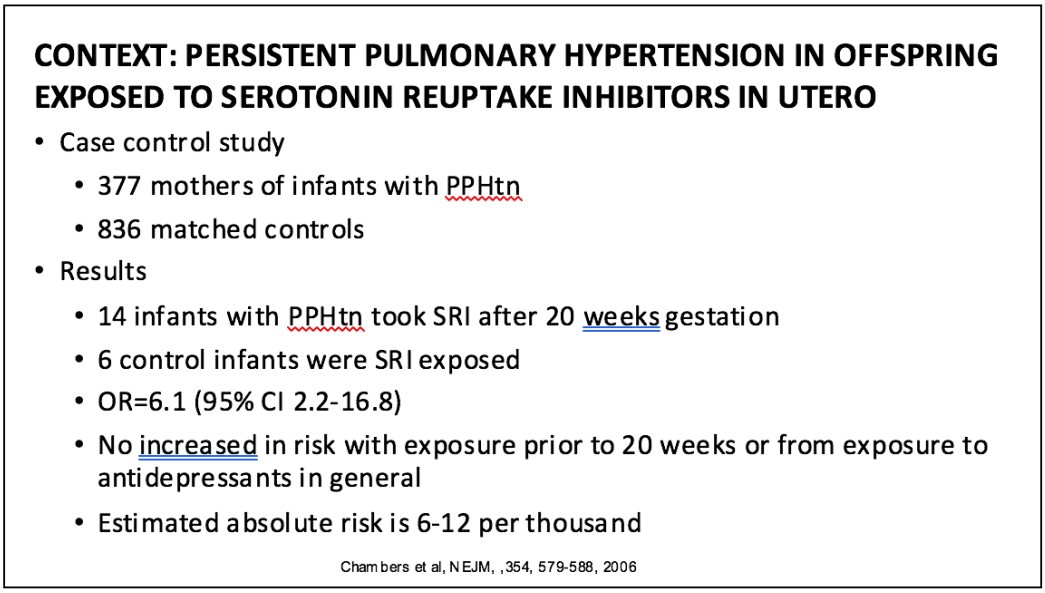
CONTEXT: POOR NEONATAL ADAPTATION SYNDROME

- All antidepressants are associated with perinatal complications including, jaundice, hypoglycemia, low APGAR scores and convulsions, neonatal ICU admission
- PNAS Meta-analysis
  - 2.2-fold increased risk of respiratory distress (CI=1.81-2.66)
  - 7.9 fold increase in tremors (CI=3.33-18.73)

Grigoriadis et al, J Clin Psychiatry, 2013, vol 74 (4); e309-e320.

- Consists of (Kallen, 2004; Zeskind, 2004; Oberlander, 2004; Boucher, 2008; Dubnov-Raz, 2008; Hayes, 2012)
    - Increased muscle tone
    - Tremulousness
    - Jitteriness/restlessness
    - Increased or decreased muscle tone
    - Myoclonus
    - Feeding problems
    - Sleeping problems
    - Respiratory problems (in 15-30%)
    - Autonomic instability
    - Irritability
    - Prolonged QT interval/cardiac arrhythymias
    - Risk of seizure—more rare
- Begins within minutes to hours after burth
- Usually transient, lasting 1-2 days, resolving on it own by 2 weeks; but it can last 2-6 weeks (Moses-Kolko, 2005; Alehan, 2008)
- Usually mild
- Usually requires only supportive care
- Occurs in 30% of neonates exposed to SSRIs in utero (Levinson-Castiel, 2006)
- Rare:
    - Seizures
    - Dehydration
    - Excessive weight loss
    - Fever
    - No deaths reported
- **11/05: Celexa (20-40 mg/day) associated with 228 adverse events since 1998, 120 of which involved developmental events, 38 of which occurred during peri- or post-natal period, 31 of which in early neonatal period (first week of life), 18 of which involved neonatal withdrawal:** jitteriness, rigidity, tremor
- Malm et al, 2005
    - SSRI's purchased (by pregnant women) in the 3rd trimester associated with
    - Increased rates of admission to special units or ICU's (15.7%; 11.2% if exposed in first trimester
    - Not associated with
        - Increased rate of preterm
        - Small for gestational age
        - Low birth weights
        - Perinatal death
        - Need for C-Section
        - Malformations
- Levinson-Castiel et al, 2006:
    - 30% of infants exposed to SSRI's (18 of 60 such infants in this study) had evidence of the syndrome
    - Paxil was associated with 6 of the 18 cases.
- In a study of 93 cases withdrawal due to SSRI exposure
    - 64 associated with Paxil
    - 14 with Prozac
    - 9 with Zoloft
    - 7 with Celexa
- Ferreira et al, 2007
    - Retrospective study of 76 mothers treated with SSRIs/Effexor during third trimester
    - 100% of premature infants had neonatal adaption symptoms
    - 69% of term infants had symptoms
    - Median length of stay in hospital ~4 times longer for preterm compared to term infants

- ***Neurobehavioral functioning in infancy***
  - Salisbury, et al, 2016
    - 184 women and their infants (ND: "SSRIs", in this study, includes SSRIs and SNRIs)
    - Depression but no meds
      - Low arousal throughout newborn period
    - SSRI and SSRI+benzo groups
      - Lower motor scores in first postnatal month
      - More CNS stress signs in first postnatal month
      - Lower self-regulation at day 14
      - Higher arousal at day 14
    - SSRI+benzo group
      - Least favorable neurobehavioral functioning scores
- ***Psychological issues in pre-school children after pre-natal exposure to SSRI's***
  - Lupattelli et al, 2018
    - 8359 mother-child dyads, of which 4128 children had complete outcome data at age 5
    - No evidence for a substantial prenatal SSRi effect on externalizing, social, and emotional problems
- ***Pulmonary hypertension in newborns (PPHN)***
  - Rare condition in the general population estimated at 1-1.9/1000 births
  - Risk factors
    - Obesity
    - Smoking
    - Reduced length of gestation
    - Caesarian section
    - Hypoxia and hypercarbia at birth (e.g., from meconium aspiration, complicated deliveries)
    - Increased medical muscle thickness of pulmonary arteries
    - Vasoactive mediator abnormalities (nitrous oxide, leukotrienes, platelet activating factor)
    - Depression is associated with the first three
  - ***Consensus as of October, 2013***
    - Most, but not all studies have found increased risk of PPHN after exposure to SSRIs in late pregnancy (Chambers, 2006; Kallen, 2008; Reis, 2010; Wilson, 2011; Kieier, 2011)
    - Animal studies find same risk (Fornaro, 2007; Delaney, 2013)
    - RARE (Occhiogrosso, 2012):
      - 1.9/1000 in general population
      - 2.0/1000 in combined reported cases after SSRI exposure
  - Chambers, 2006:
    - Use of SSRI after 20th week associated with PPHN (odds ratio 6.1); risk calculated at 1%
    - Use of SSRI before 20th week not associated with PPHN
    - Included only 14 patients on SSRI's and 6 control patients not on SSRI's
    - Relief on after-the-fact patient interviews and incomplete records
    - 99.5% of those assessed had no problems



- Wichman, 2007:
  - evaluated records of 25,214 newborns, including 745 who had been treated with SSRI's
  - no association with PPHN
  - of those newborns with PPHN, none of moms had taken SSRI's
- Kallen, 2008:
  - evaluated 831,324 infants, 506 of which diagnosed with PPHN
  - use of SSRI was associated with PPHN (risk ratio 2.01); risk calculated at 0.15% (1.5 per 1000)
- Wilson, et al:
  - Case control study of infants with PPHN from 2003-2009
  - C/S before onset of labor increased risk of PPHN (odds ratio 4.9)
  - No association with late-term use of SSRI's
- Andrade, 2009:
  - retrospective study
  - no association between SSRI use and PPHN
  - 5 cases of PPHN observed, 2 among SSRI-exposed, 3 among non-SSRI-exposed
  - Among 1104 exposed to SSRIs in 3rd trimester, prevalence of PPHN 2.14/1000
  - Among 1104 not exposed to SSRIs in 3rd trimester, prevalence of PPHN 2.72/1000
- Occhiogross, et al, 2012
  - Review of 6 studies examining the connection between prenatal use of SSRIs and persistent pulmonary hypertension of the newborn (PPHN)
  - 3 studies found no association
  - 3 found associations; of these 3 studies 2 looked at the same database, incorporating additional recent births
  - Examined altogether, the 6 studies found a rate of PPHN to be LOWER in those exposed prenatally to SSRI's than in the general population.

- Relatively safer SSRI's in Pregnancy
  - Prozac
    - Relatively well studied
    - Longer half-life means less neonatal withdrawal syndrome (but perhaps more serotonin side effects)
  - Zoloft
    - Relatively well studied
    - Fewer neonatal side effect reports in WHO database (Alehan, 2008)
    - Less exposure during breast feeding
- Should Paxil/Paxil CR be avoided in pregnancy?
  - Possibly, though, as always, depends on clinical picture
  - The only antidepressant with FDA advisory about use in pregnancy
  - No increased risk in prospective, controlled studies and a meta-analysis (O'Brien, 2008)

- Several retrospective studies and 2 meta-analyses show increased risk of cardiovascular malformations (Louik, 2007; Berard, 2007; Bar-Oz, 2007; Meriob, 2009; Maim, 2011; Bakker, 2010; Painully, 2013)
- Most recent meta-analysis shows statistically but not clinically significant difference in risk of cardiovascular malformations (Painully, 2013)
- One study shows these associations are dose-dependent, only significant for exposure > 25 mg/day (Berard, 2007)
- Some animal studies show Paxil as the only teratogen among antidepressants (Sloot, 2009)
- May cause more neonatal side effects (Sanz, 2005)

- Breast feeding
  - Overall
    - General recommendations
      - Don't change an effective medication; continue what was working in pregnancy
      - Do not "pump and dump"
      - Minimize sleep deprivation
      - Coordinate care with pediatrician
    - less than 1% of maternal dose of antidepressants is present in breast milk
    - levels in infants who are breastfed by mom's taking antidepressants often have undetectable levels.
    - a recent study looked at 22 breast feeding women on Celexa (9 women), Zoloft (5 women), Paxil (4 women), Prozac (1 woman), and Effexor (3 women) and found very low infant serum concentrations for all medications.
    - Another study (AJP, 6/04) confirmed low levels of Zoloft, Paxil and Nortriptyline in breast milk and nursing infants.
    - Percentage of maternal dose to breastfeeding baby/reported (possibly connected) side effects (through 2013)

Zoloft	0.4-2.3%	Benign sleep myoclonus, transient agitation
Nortriptyline	1.3%	None
Cymbalta	0.14-0.82%	None
Desipramine	1%	None
Remeron	0.6-3.5%	More rapid weight gain, sleeping thru night earlier
Paxil	0.1-4.3%	Agitation, difficulty feeding, irritability, sleepiness, constipation, SIADH
Wellbutrin	2-5.1%	Possible seizures
Celexa	2.5-9.4%	Uneasy sleep, drowsiness, irritability, weight loss, restlessness
Lexapro	3.9-7.9%	Enterocolitis
Pristiq	5.5-8.1%	None
Prozac	1.1-12%	Excessive crying, irritability, vomiting, watery stools, difficulty sleeping, tremor, somnolence, hypotonia decreased weight gain, hyperglycemia, hyperactivity, reduced rooting, reduced nursing, grunting, moaning
Effexor	3-11.8%	None

  - Zoloft
    - does not appear to be passed into the breast milk to a clinically significant extent
    - maximum daily infant dose in one study 0.026-0.044 mg/kg
    - nursing infants exposed to Zoloft in breast milk: no problems on growth charts, number of illnesses, milestones; no adverse effects (see above)
  - Prozac is passed into the breast milk but at low levels
  - Paxil may be passed into the breast milk at high levels and is more associated with discontinuation syndrome when tapered in pregnancy or after delivery (in the newborn) than other SSRI's

- ***Behavioral/Emotional/IQ issues in children of women with depression exposed to SSRI use in pregnancy***

CLINICAL IMPLICATIONS: OTHER MATERNAL AND OFFSPRING EFFECTS

The most commonly noted effects are neonatal adaptation, hypertensive diseases of pregnancy and persistent pulmonary hypertension

- Risk seems to be higher when antidepressants are used later in pregnancy
- Most studies had poor data on possible confounding effects of hazardous substances
- SNRIs may shower larger effects than SSRIs
- Absolute risks of PPHN are small

-
- Consensus as of October, 2013
  - Probably not connected to SSRI use
  - Prospective studies have found no IQ reductions and no increased risk of behavior problems in children up to age 7 exposed in utero to SSRIs, tricyclic antidepressants, or Effexor (Nulman, 1997; Nulman, 2002; Nulman, 2012)
- Delayed language maturation associated with maternal depressive symptoms, not with SSRI use (Welkum, 2012)
- Autism spectrum
  - Some evidence of possible risk when given in 2nd and 3rd trimester, but doesn't control for presence of autism spectrum disorder in parent

UPDATE: ANTIDEPRESSANT USE IN PREGNANCY AND OFFSPRING AUTISM SPECTRUM DISORDER

Table 2. Association Between Antenatal AD Exposure and the Risk of ASD

Variable	Infants, No. (N = 145 456)	Infants With Diagnosis of ASD, No. (n = 1054)	ASD Follow-up, No. of Person-Years	HR (95% CI)	
				Crude	Adjusted[a]
Exposure to ADs					
1 y Before first day of gestation	9207	82	322.69	1.35 (1.08-1.70)	1.05 (0.78-1.42)
First trimester	4200	40	145.64	1.51 (1.10-2.07)	0.84 (0.52-1.36)
Second and/or third trimester	2532	31	111.30	2.23 (1.56-3.19)	1.87 (1.15-3.04)
Infant characteristics at birth					
Male sex	74 498	836	3927.27	3.68 (3.17-4.27)	3.66 (3.15-4.25)
Calendar year	NA	NA	NA	1.08 (1.05-1.11)	1.07 (1.04-1.10)

Controlled for maternal psychiatric illness, Boukhris et. al, 2016, JAMA Pediatrics

  - Summary of two studies have found increased risk of autism spectrum disorders (ASDs) (Croen, 2011; Rai, 2013)
    - Methodologic flaws limit reliability of conclusions
    - In the most recent, antidepressants only associated with ASD WITHOUT intellectual

disability) and ONLY with maternal depression
        - If the finding is true, which is NOT clear, antidepressants account for 0.6% of observed cases of ASD, and not 99.4% of the rest.
    - One study
        - risk doubles with SSRI treatment for the mother in the year prior to delivery
        - risk triples with SSRI treatment in the first trimester
        - not clear if this is a correlation or causal link
        - even if there was a causal link, it would explain only 2-3% of cases of autism, suggesting the vast majority (97-98%) have other causes
    - Croen et al, 2011
        - SSRI use in first trimester modestly increases risk
        - Number of cases of autism in women "exposed" to SSRI's during pregnancy 15
        - "Exposure" defined as having at least one prescription for an antidepressant in the year before the birth of the child
        - Usage based on pharmacy records
        - No verification that the mother ever took the medication
        - Failed to control for
            - maternal stress
            - burden of illness
            - postpartum disorders

- Pediatrics, 2010
    - Antidepressant use in 2nd or 3rd trimester
    - Associated with some delays in motor functions at 6 months, though within normal limits
        - 15.9 day delay in sitting
        - 28.9 day delay in walking
    - Differences no longer apparent at 19 mo
        - Though less likely to be able to occupy themselves for at least 15 minutes (at 19 mo)
- Nullman et al, 1997
    - Prozac vs. tricyclic antidepressant vs. control
    - 219 individuals
    - IQ, Bayley, McCarthy similar up to age 7
- Mattson et al, 1999
    - Prozac vs. control
    - 96 individuals
    - WPPS-RI: no differences
- Nulman et al, 2002
    - Prozac vs. tricyclic antidepressant vs. control
    - 122 individuals
    - IQ, Bayley: no differences at 15-71 months
    - Number of depressive episodes since delivery associated with lower language development
- Casper et al, 2003
    - SSRIs vs. control
    - 44 individuals
    - Lower Bayley psychomotor developmental indexes and motor quality in follow-up (6-40 months)
- Misri et al, 2006:
    - SSRI vs. SSRI + Klonopin vs. controls
    - 36 individuals
    - 4 yo children exposed to psychotropic medications in utero do not exhibit internalizing (e.g., anxiety) symptoms
    - Maternal stress, anxiety and depression associated with higher scores
- Oberlander et al, 2007
    - SSRI vs. controls
    - 36 individuals

        - No difference in ratings of externalizing behaviors at 4 yo
        - Maternal stress, anxiety and depression associated with higher scores
    - There is no association between Prozac or TCA use in pregnancy (in 135 children) with abnormal mental development.
    - Reddy et al, 2006:
        - 302 parent-infant pairs
        - 11/302 mothers took SSRIs during pregnancy
        - 13/302 had a history of serious psychiatric illness
        - Women with psychiatric illness who took SSRIs during pregnancy had infants with less fear behavior than those with psychiatric illness who did not take SSRIs during pregnancy
    - Generally not thought to be associated with antidepressant use
- The risk(s) of fetal exposure to SSRIs must be balanced with the risk of relapse upon stopping medication during pregnancy or upon birth; post-partum depression and anxiety may negatively affect attachment
- ***Other issues***
    - Fetal serum levels of anticonvulsants are around 50-80% of the maternal dose
        - Lamictal, Topamax, and Neurontin have little evidence.
    - First generation antipsychotic medications appear to be safe in pregnancy
    - Second generation antipsychotic medications do not have evidence
    - More information on effects of medications on the fetus
        - California Teratogen Information Service: 800-532-3749 Organization of Teratology Information Services—www.otispregnancy.org
        - Illinois Teratogen Information Service—www.fetal-exposure.org

Neonatal Discontinuation Syndrome in Serotonergic Antidepressant-Exposed Neonates

Amy Yang, Jody D Ciolino, Emily Pinheiro, Laura J Rasmussen-Torvik, Dorothy K Y Sit, Katherine L Wisner

Journal of Clinical Psychiatry 2017, 78 (5): 605-611

OBJECTIVE: To determine whether infants exposed in utero to serotonin reuptake inhibitor (SRI) antidepressants or a DSM-IV-TR-defined mood disorder have significantly more neonatal discontinuation signs compared to an unexposed group of infants at 2-4 weeks after birth.

METHODS: This secondary analysis was derived from 2 observational studies with enrollment from July 2000 to December 2011 in Cleveland, Ohio, and Pittsburgh, Pennsylvania. Mothers (n = 214) belonged to one of 3 groups based on exposure status during pregnancy: (1) Comparison-women who did not take psychotropics during pregnancy and had no major mood disorder; (2) SRI-exposed-women with a mood disorder who were taking an SRI but no benzodiazepines; and (3) Mood Disorder-women with depression or bipolar disorder who did not take psychotropic medications. The infants were examined for signs according to the Finnegan Scale by evaluators blind to maternal exposure status.

RESULTS: The rates of sign presence (defined as a score ≥ 2 on the Finnegan Scale) in the SRI, Mood Disorder, and Comparison groups were similar at 34.1%, 35.1%, and 30.4%, respectively. Women in the SRI group had a significantly higher preterm birth rate (24.4%) compared to the other 2 groups (7.4% and 8.9% in the Mood Disorder and Comparison groups, respectively; P = .012). Preterm newborns had a significantly higher sign rate compared to full-term newborns (54% vs 31%, P = .020). We observed a significant relationship between Finnegan signs and preterm birth.

CONCLUSIONS: The presence of neonatal signs at 2-4 weeks was more closely associated with prematurity than with in utero SRI or mood disorder exposure.

Effect of Time-Dependent Selective Serotonin Reuptake Inhibitor Antidepressants During Pregnancy on Behavioral, Emotional, and Social Development in Preschool-Aged Children

Angela Lupattelli, Mollie Wood, Eivind Ystrom, Svetlana Skurtveit, Marte Handal, Hedvig Nordeng

Journal of the American Academy of Child and Adolescent Psychiatry 2018, 57 (3): 200-208

OBJECTIVE: To evaluate the effect of prenatal exposure to selective serotonin reuptake inhibitors (SSRIs) on children's behavioral, emotional, and social development by age 5 years, and over time since age 1.5 years.

METHOD: The prospective Norwegian Mother and Child Cohort Study was linked to the Medical Birth Registry of Norway. We included women who reported depressive/anxiety disorders before and/or during pregnancy. Children born to women who used SSRIs in early (weeks 0-16), mid- (weeks 17-28), or late (> week 29) pregnancy were compared to those who were unexposed. Children's internalizing and externalizing behaviors (Child Behavior Checklist) and temperament traits (Emotionality, Activity and Shyness Temperament Questionnaire) were measured at 1.5, 3, and 5 years. Mean scores were calculated and standardized. General linear marginal structural models were fitted to account for time-varying exposure and confounders, and censoring; 3-level growth-curve models were used.

RESULTS: A total of 8,359 mother-child dyads were included, and 4,128 children had complete outcome data at age 5 years. Children exposed to SSRIs in late pregnancy had an increased risk of anxious/depressed behaviors by age 5 years compared with unexposed children (adjusted β = 0.50, 95% CI = 0.04, 0.96). Such risk was not evident for earlier timings of exposure. There was no evidence for a substantial prenatal SSRI effect on externalizing, social, and emotional problems.

CONCLUSION: These findings suggest no substantial increased risk for externalizing, emotional, or social problems in preschool-aged children following prenatal SSRI exposure. Although the role of chance and potential unmeasured confounding cannot be ruled out, late-pregnancy SSRI exposure was associated with greater anxious/depressed behaviors in the offspring.

Management of Unipolar and Bipolar Depression During Pregnancy

MARCH 5, 2018 · POSTED IN CURRENT TREATMENTS, POTENTIAL TREATMENTS · COMMENT

At the Maryland Psychiatric Research Society's continuing medical education conference in November, Lauren Osbourne, Assistant Director of the Women's Mood Disorders Clinic at Johns Hopkins Hospital, gave a presentation on the management of mood and anxiety during pregnancy and lactation. She had a number of important ideas for physicians and patients to consider in their decision-making process.

According to Osbourne, 60%-70% of pregnant women with unipolar depression who discontinue their antidepressants relapse. Of those with bipolar disorder who discontinue their mood stabilizers, 85% relapse, while 37% of those who stay on their medications relapse.

Something to consider when deciding whether to continue medication while pregnant is that **depression in pregnancy carries its own risks for the fetus. These include preterm delivery, low birth weight, poor muscle tone, hypoactivity, increased cortisol, poor reflexes, and increased incidence of attention deficit hyperactivity disorder (ADHD) and other behavioral disorders.** The placenta makes an enzyme 11-BHSD2 that lowers the stress hormone cortisol in the baby. However, this enzyme is less active in depression, exposing the fetus to higher levels of cortisol.

Thus, the decision about whether to continue medications during pregnancy should consider the risks to the fetus of both the mother's depression and the mother's medications.

Most antidepressants are now considered safe during pregnancy. There have been reports of potential problems, but these data are often confounded by the fact that women with more severe depression are more likely to require antidepressants, along with other risk variables such as smoking or late delivery (after 42 weeks). When these are accounted for by using matched controls, the apparent risks of certain antidepressants are no longer significant. This includes no increased risk of persistent pulmonary hypertension, autism, or cardiac malformations.

There may be a possible increased risk of Neonatal Adaption Syndrome (NAS) in the first weeks of life in babies who were exposed to selective serotonin reuptake inhibitor (SSRI) antidepressants in the third trimester. This syndrome presumably results from antidepressant withdrawal, and can include respiratory distress, temperature changes, decreased feeding, jitteriness/irritability, floppiness or rigidity, hypoglycemia, and jaundice. There is not yet a robust literature on the syndrome, but Osbourne suggested that it disappears within 2 weeks of birth.

In her practice, Osbourne prefers to prescribe sertraline, which has the best safety data, along with fluoxetine. Sertraline is also OK for breastfeeding. There is less data on bupropion, but it also appears to be safe during pregnancy. Endocrine and enzyme changes in pregnancy typically cause a 40% to 50% decrease in concentrations of antidepressants, so doses of antidepressants typically must be increased in order to maintain their effectiveness.

Osbourne ranked mood stabilizers for bipolar disorder, from safest to most worrisome. Lamotrigine is safest. There is no evidence linking it to birth defects, but higher doses are required because of increased clearance during pregnancy. Lithium is next safest. There are cardiac risks for one in 1,200 patients, but these can be monitored. Carbamazepine is third safest. One percent of babies exposed to carbamazepine will develop spina bifida or craniofacial abnormalities. Valproate is least safe during pregnancy. Seven to ten percent of babies exposed to valproate will develop neural tube defects, other malformations, or developmental delay, with a mean decrease of 9 IQ points. The atypical antipsychotics all appear safe so far.