



This chart is produced by the University of Illinois at Chicago (UIC) by Illinois DocAssist as a summary of research on antidepressants in human pregnancy and breastfeeding

### Antidepressants Risks in Pregnancy

**Safety Data:** No randomized control trials. Safety data derived largely from cohort studies, registry data, and prescription monitoring registries. Older studies suggested more adverse outcomes as they did not control for confounders such as presence and severity of maternal depression which is associated with adverse outcomes. Newer and better designed studies demonstrate less risks than previously believed.

**Safety Ratings:** Transition from Pregnancy Category (A, B, C, D, X) to PLLR (Pregnancy, Lactation, and Reproductive Labeling) as categories are confusing and did not accurately or consistently communicate differences in fetal risk. PLLR provides a risk summary based on available data in animal and human studies as well as clinical considerations for prescribers.

- **Obstetric Risks**

- Both maternal depression and perinatal antidepressant use are associated with increased risk of Preterm Labor by 3 gestational days<sup>1-3</sup>
- SSRI's are associated with increased risk of postpartum hemorrhage (reported incidence of postpartum hemorrhage ranges between 4-18% for SSRI exposure versus 3-11% for non-exposure in women with depression)<sup>4</sup>

- **Infant Risks**

- **Congenital malformations**<sup>1,5-7</sup>
  - New and well-designed studies show no associated increased risk for congenital malformations (including cleft lip or cardiac defects)
- **Persistent Pulmonary Hypertension of the Newborn**<sup>8,9</sup>
  - Slightly increased risk with late gestational antidepressant exposure however absolute risk is still very small
  - Magnitude of risk of PPHN is smaller than previously believed
  - No association between antidepressant exposure and severe PPHN (requiring respiratory intervention)
- **Neonatal Adaptation**<sup>10,11</sup>
  - Risk of transient adaptation symptoms after delivery. Non-specific criteria so rates vary widely between studies
  - Symptoms if present are usually mild and include jitteriness, restlessness, irritability, increased muscle tone, sleep disturbance, feeding problems, and rapid breathing and spontaneously resolve
  - Discontinuing SSRIs shortly (2wks) before delivery does not appear to improve neonatal outcomes (Warburton et al 2010). Stopping Medication to decrease risks of adaptation syndrome is not recommended.
- **Neurodevelopmental**<sup>12-16</sup>
  - New studies do not demonstrate an association between SSRI exposure and Autism Spectrum Disorder, Intellectual Disability or ADHD
  - Previous negative studies did not control for maternal/paternal depression which increases risk of ASD in offspring
  - Some studies suggested increased risk of motor delay in antidepressant exposed infants; however infants caught up before 24 months of age

## Information for Providers on Antidepressants during Pregnancy and Breastfeeding – January 2018

This chart is produced by the University of Illinois at Chicago (UIC) by Illinois DocAssist as a summary of research on antidepressants in human pregnancy and breastfeeding

### Antidepressant Risks in Breastfeeding <sup>17-19</sup>

**Safety data:** Includes limited studies examining relative infant dose, medication concentration in breastmilk, and infant plasma concentration as well as reports of adverse events

#### **Safety rating:**

- **Risks:** poor feeding, lethargy, irritability, not waking to feed, jitteriness, poor weight gain.
- Infants are exposed to much higher doses in-utero, therefore women should not be counseled to discontinue medications or not breastfeed due to low comparative exposure from breast milk; most SSRIs have undetectable serum concentrations in breastfed infants
- Dr. Hale's Lactation Risk Categories L1-L5
  - L1 SAFEST** – Drug has been taken by many breastfeeding women without evidence of adverse effects in nursing infants OR controlled studies have failed to show evidence of risk.
  - L2 SAFER** – Drug has been studied in a limited number of breastfeeding women without evidence of adverse effects in nursing infants.
  - L3 MODERATELY SAFE** – Studies in breastfeeding have shown evidence for mild non-threatening adverse effects OR there are no studies in breastfeeding for a drug with possible adverse effects.
  - L4 POSSIBLY HAZARDOUS** – Studies have shown evidence for risk to a nursing infant, but in some circumstances the drug may be used during breastfeeding.
  - L5 CONTRAINDICATED** – Studies have shown significant risk to nursing infants. The drug should NOT be used during breastfeeding.

#### **Clinical Considerations** <sup>3,20</sup>

- No medication is risk free
- The risks of psychotropic use in pregnancy and lactation must be weighed with the risks of untreated or undertreated psychiatric illness to the mother and child
- In psychotropic naive women sertraline is the drug of choice in pregnancy and breastfeeding, followed by all other SSRIs other than paroxetine
- If a patient is pregnant and euthymic on a non-first line medication, the risk of changing medications (relapse of symptoms, multiple drug exposures in pregnancy) may outweigh the benefits for the mother-infant dyad.
- Untreated or undertreated depression is associated with preterm labor, preeclampsia, increased rates of substance use, suicide, impaired bonding and attachment with infant, postpartum depression, and risk of mental disorders in infant.
- Treatment target is remission of symptoms
- Drug metabolism in pregnancy may change due to alterations in enzymatic activity such as CYP 2D6 and 3A4 and increased creatinine clearance.<sup>21,22</sup> May consider supra-therapeutic doses in the context.



## Information for Providers on Antidepressants during Pregnancy and Breastfeeding – January 2018

This chart is produced by the University of Illinois at Chicago (UIC) by Illinois DocAssist as a summary of research on antidepressants in human pregnancy and breastfeeding

### SSRIs (Selective Serotonin Reuptake Inhibitors)<sup>23</sup>

- First line for perinatal and postpartum depression due to preferred safety data, tolerability, and efficacy
- SSRI's are amongst the most well studied medications in pregnancy
- Sertraline drug of choice in psychotropic naive women who are pregnant or breastfeeding
- Paroxetine 2nd line to other SSRI's given less favorable safety data and short half life

	Medication	Advantages	Disadvantages	Absolute Infant dose in breast milk (mg/d)	Lactation Rating *	Potential adverse effects of breastfeeding
SSRIs (Selective Serotonin Reuptake Inhibitors)	<b>Citalopram</b> (10-40mg) Increase in 10mg increments	<ul style="list-style-type: none"> <li>• Few interactions with other medications</li> </ul>		0.14	L2	
	<b>Escitalopram</b> (5-20 mg) Increase in 5-10 mg increments	<ul style="list-style-type: none"> <li>• Few interactions with other medications</li> <li>• Less GI side effects than other SSRI's</li> </ul>		0.04	L2	
	<b>Fluoxetine</b> (20-80 mg) Increase in 10-20mg increments	<ul style="list-style-type: none"> <li>• First line for depressive symptoms in adolescents</li> </ul>	<ul style="list-style-type: none"> <li>• Higher incidence of neonatal adaptation syndrome than other SSRI's</li> <li>• Can be more activating than other SSRI's</li> </ul>	0.14	L2	<ul style="list-style-type: none"> <li>• Longer half-life less favorable than other SSRI's in breastfeeding</li> </ul>
	<b>Paroxetine</b> (20-50mg) Increase by 10mg increments		<ul style="list-style-type: none"> <li>• 2nd line to other SSRI's</li> <li>• Short half-life, increased risk of withdrawal with missed doses</li> </ul>	0.03	L2	
	<b>Sertraline</b> (50-200 mg) Increase in 25-50 mg increments	<ul style="list-style-type: none"> <li>• First choice for depression during pregnancy and breastfeeding in psychotropic naive women</li> </ul>	<ul style="list-style-type: none"> <li>• More GI side effects than other SSRI's</li> </ul>	0.04	L2	

L1 SAFEST – Drug has been taken by many breastfeeding women without evidence of adverse effects in nursing infants OR controlled studies have failed to show evidence of risk. \*

L2 SAFER – Drug has been studied in a limited number of breastfeeding women without evidence of adverse effects in nursing infants.


L3 MODERATELY SAFE – Studies in breastfeeding have shown evidence for mild non-threatening adverse effects OR there are no studies in breastfeeding for a drug with possible adverse effects.

L4 POSSIBLY HAZARDOUS – Studies have shown evidence for risk to a nursing infant, but in some circumstances the drug may be used during breastfeeding.

L5 CONTRAINDICATED – Studies have shown significant risk to nursing infants. The drug should NOT be used during breastfeeding

## Information for Providers on Antidepressants during Pregnancy and Breastfeeding – January 2018

This chart is produced by the University of Illinois at Chicago (UIC) by Illinois DocAssist as a summary of research on antidepressants in human pregnancy and breastfeeding

<b>SNRIs (Serotonin Norepinephrine Reuptake Inhibitors)<sup>23,24</sup></b>						
<ul style="list-style-type: none"> <li>Second line to SSRI's in pregnancy and postpartum</li> <li>May be beneficial for patients with comorbid neuropathic pain</li> <li>Some studies show small increased risk of spontaneous abortion</li> <li>Rebound symptoms with missed doses</li> <li>Often require slow taper due to discontinuation symptoms (dizziness, nausea, headache, paresthesia, fatigue, vomiting, irritability, insomnia, diarrhea, anxiety, hyperhidrosis)</li> </ul>						
	Medication	Advantages	Disadvantages	Absolute Infant dose in breast milk (mg/d)	Lactation Rating*	Potential adverse effects of breastfeeding
SNRIs (Serotonin Norepinephrine Reuptake Inhibitors)	<b>Desvenlafaxine</b> (50mg)	<ul style="list-style-type: none"> <li>Also treats neuropathic pain</li> <li>Absolute infant dose in breastfeeding half that of venlafaxine</li> </ul>	<ul style="list-style-type: none"> <li>Least studied of the SNRI's</li> </ul>		L3	
	<b>Duloxetine</b> (60mg-120mg) Start 40mg, increase 20-30mg/day increments per week	<ul style="list-style-type: none"> <li>Also treats neuropathic pain and fibromyalgia</li> <li>Can be given in two divided doses to aid tolerability</li> </ul>	<ul style="list-style-type: none"> <li>Less studied than Venlafaxine in pregnancy</li> <li>Small increased risk of miscarriage</li> </ul>	<0.03	L3	
	<b>Venlafaxine</b> XL (37.5- 225 mg) increase in 37.5mg increments	<ul style="list-style-type: none"> <li>Also treats neuropathic pain at higher doses</li> <li>More studied than other SNRI's in pregnancy</li> </ul>	<ul style="list-style-type: none"> <li>Small increased risk of miscarriage</li> <li>Higher rates of discontinuation symptoms than duloxetine</li> </ul>	0.5	L2	
<p>L1 SAFEST – Drug has been taken by many breastfeeding women without evidence of adverse effects in nursing infants OR controlled studies have failed to show evidence of risk. *</p> <p>L2 SAFER – Drug has been studied in a limited number of breastfeeding women without evidence of adverse effects in nursing infants.</p> <p>L3 MODERATELY SAFE – Studies in breastfeeding have shown evidence for mild non-threatening adverse effects OR there are no studies in breastfeeding for a drug with possible adverse effects.</p> <p>L4 POSSIBLY HAZARDOUS – Studies have shown evidence for risk to a nursing infant, but in some circumstances the drug may be used during breastfeeding.</p> <p>L5 CONTRAINDICATED – Studies have shown significant risk to nursing infants. The drug should NOT be used during breastfeeding.</p>						
						 <p style="font-size: x-small;">Illinois DocAssist 866-986-2778 <a href="https://docassistillinois.org">https://docassistillinois.org</a></p>

## Information for Providers on Antidepressants during Pregnancy and Breastfeeding – January 2018

This chart is produced by the University of Illinois at Chicago (UIC) by Illinois DocAssist as a summary of research on antidepressants in human pregnancy and breastfeeding

Non-SSRIs (Selective Serotonin Reuptake Inhibitors)/SNRIs (Serotonin Norepinephrine Reuptake Inhibitors)						
	Medication	Advantages	Disadvantages	Absolute Infant dose in breast milk (mg/d)	Lactation Rating*	Potential adverse effects of breastfeeding
Non-SSRIs/SNRIs	<b>Bupropion<sup>25</sup></b> Bupropion Registry XL (150-450 mg) Increase in 150mg increments	<ul style="list-style-type: none"> <li>Fewer sexual side effects than SSRI's or SNRI's</li> <li>Less risk of weight gain</li> <li>Aids smoking cessation</li> <li>Does not appear to be associated with increased risk of congenital malformations in limited studies</li> </ul>	<ul style="list-style-type: none"> <li>Not recommended in those with eating disorders or seizure disorders</li> <li>Decreases seizure threshold</li> <li>May sometimes worsen anxiety</li> </ul>	0.20	L3	<ul style="list-style-type: none"> <li>Sleep disturbance of infants reported</li> <li>Isolated case reports of infant seizure</li> </ul>
	<b>Mirtazapine<sup>26</sup></b> (15-45mg) Increase in 15 mg increments	<ul style="list-style-type: none"> <li>Aids with sleep and promotes appetite</li> </ul>	<ul style="list-style-type: none"> <li>Sedating</li> <li>Less studied than SSRIs</li> </ul>	0.04	L3	
	<b>Nortriptyline</b> (100-150 mg daily) Start 25mg daily increase in 25mg increments	<ul style="list-style-type: none"> <li>Can also be used for migraine prophylaxis</li> </ul>	<ul style="list-style-type: none"> <li>Maternal side effects additive to pregnancy effects (sedation, constipation, tachycardia)</li> <li>Orthostatic hypotension, risking decreased placental perfusion</li> <li>Fetal and neonatal side effects: tachycardia, urinary retention</li> </ul>	0.07	L2	<ul style="list-style-type: none"> <li>Dry mouth, constipation, urinary retention</li> </ul>
<p>L1 SAFEST – Drug has been taken by many breastfeeding women without evidence of adverse effects in nursing infants OR controlled studies have failed to show evidence of risk. *</p> <p>L2 SAFER – Drug has been studied in a limited number of breastfeeding women without evidence of adverse effects in nursing infants.</p> <p>L3 MODERATELY SAFE – Studies in breastfeeding have shown evidence for mild non-threatening adverse effects OR there are no studies in breastfeeding for a drug with possible adverse effects.</p> <p>L4 POSSIBLY HAZARDOUS – Studies have shown evidence for risk to a nursing infant, but in some circumstances the drug may be used during breastfeeding.</p> <p>L5 CONTRAINDICATED – Studies have shown significant risk to nursing infants. The drug should NOT be used during breastfeeding</p>						

## Information for Providers on Antidepressants during Pregnancy and Breastfeeding – January 2018

This chart is produced by the University of Illinois at Chicago (UIC) by Illinois DocAssist as a summary of research on antidepressants in human pregnancy and breastfeeding

1. Huybrechts KF, Sanghani RS, Avorn J, Urato AC. Preterm Birth and Antidepressant Medication Use during Pregnancy: A Systematic Review and Meta-Analysis. Hawkins SM, ed. *PLoS ONE*. 2014;9(3):e92778. doi:10.1371/journal.pone.0092778.
2. Ross LE, Grigoriadis S, Mamisashvili L, et al. Selected Pregnancy and Delivery Outcomes After Exposure to Antidepressant Medication: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2013;70(4):436. doi:10.1001/jamapsychiatry.2013.684.
3. Wisner KL, Zarin DA, Holmboe ES, et al. Risk-benefit decision making for treatment of depression during pregnancy. *Am J Psychiatry*. 2000;157(12):1933–1940.
4. Lindqvist PG, Nasiell J, Gustafsson LL, Nordstrom L. Selective serotonin reuptake inhibitor use during pregnancy increases the risk of postpartum hemorrhage and anemia: a hospital-based cohort study. *J Thromb Haemost*. 2014;12(12):1986-1992. doi:10.1111/jth.12757.
5. Bellantuono C, Migliarese G, Gentile S. Serotonin reuptake inhibitors in pregnancy and the risk of major malformations: a systematic review. *Hum Psychopharmacol Clin Exp*. 2007;22(3):121-128. doi:10.1002/hup.836.
6. Furu K, Kieler H, Haglund B, et al. Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design. *bmj*. 2015;350:h1798.
7. Reefhuis J, Devine O, Friedman JM, Louik C, Honein MA. Specific SSRIs and birth defects: bayesian analysis to interpret new data in the context of previous reports. *Bmj*. 2015;351:h3190.
8. Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med*. 2006;354(6):579–587.
9. Malm H, Sourander A, Gissler M, et al. Pregnancy Complications Following Prenatal Exposure to SSRIs or Maternal Psychiatric Disorders: Results From Population-Based National Register Data. *Am J Psychiatry*. 2015;172(12):1224-1232. doi:10.1176/appi.ajp.2015.14121575.
10. Yang A, Ciolino J, Pinheiro E, Rasmussen-Torvik L, Sit D, Wisner K. Neonatal Discontinuation Syndrome in Serotonergic Antidepressant-Exposed Neonates. *J Clin Psychiatry*. 2017;78(5):605–611.
11. Warburton W, Hertzman C, Oberlander TF. A register study of the impact of stopping third trimester selective serotonin reuptake inhibitor exposure on neonatal health: Gestational SSRI exposure and neonatal health. *Acta Psychiatr Scand*. 2009;121(6):471-479. doi:10.1111/j.1600-0447.2009.01490.x.
12. Viktorin A, Uher R, Kolevzon A, Reichenberg A, Levine SZ, Sandin S. Association of Antidepressant Medication Use During Pregnancy With Intellectual Disability in Offspring. *JAMA Psychiatry*. 2017;74(10):1031. doi:10.1001/jamapsychiatry.2017.1727.
13. Brown HK, Ray JG, Wilton AS, Lunskey Y, Gomes T, Vigod SN. Association Between Serotonergic Antidepressant Use During Pregnancy and Autism Spectrum Disorder in Children. *JAMA*. 2017;317(15):1544. doi:10.1001/jama.2017.3415.

## Information for Providers on Antidepressants during Pregnancy and Breastfeeding – January 2018

This chart is produced by the University of Illinois at Chicago (UIC) by Illinois DocAssist as a summary of research on antidepressants in human pregnancy and breastfeeding

14. Sujan AC, Rickert ME, Öberg AS, et al. Associations of Maternal Antidepressant Use During the First Trimester of Pregnancy With Preterm Birth, Small for Gestational Age, Autism Spectrum Disorder, and Attention-Deficit/Hyperactivity Disorder in Offspring. *JAMA*. 2017;317(15):1553. doi:10.1001/jama.2017.3413.
15. Sorensen MJ, Christensen J, Parner ET, et al. Antidepressant exposure in pregnancy and risk of autism spectrum disorders. *Clin Epidemiol*. November 2013;449. doi:10.2147/CLEP.S53009.
16. Nulman I, Koren G, Rovet J, et al. Neurodevelopment of Children Following Prenatal Exposure to Venlafaxine, Selective Serotonin Reuptake Inhibitors, or Untreated Maternal Depression. *Am J Psychiatry*. 2012;169(11):1165-1174. doi:10.1176/appi.ajp.2012.11111721.
17. Lanza Di Scalea T, Wisner KL. Antidepressant Medication Use During Breastfeeding: *Clin Obstet Gynecol*. 2009;52(3):483-497. doi:10.1097/GRF.0b013e3181b52bd6.
18. Oystein Berle J, Spigset O. Antidepressant use during breastfeeding. *Curr Womens Health Rev*. 2011;7(1):28–34.
19. Chad L, Pupco A, Bozzo P, Koren G. Update on antidepressant use during breastfeeding. *Can Fam Physician*. 2013;59(6):633–634.
20. The Management of Depression During Pregnancy: A Report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists: *Obstet Gynecol*. 2009;114(3):703-713. doi:10.1097/AOG.0b013e3181ba0632.
21. Hodge LS, Tracy TS. Alterations in drug disposition during pregnancy:: implications for drug therapy. *Expert Opin Drug Metab Toxicol*. 2007;3(4):557-571. doi:10.1517/17425255.3.4.557.
22. Haas DM, D’Alton M. Pharmacogenetics and other reasons why drugs can fail in pregnancy: higher dose or different drug? *Obstet Gynecol*. 2012;120(5):1176.
23. Nakhai-Pour HR, Broy P, Berard A. Use of antidepressants during pregnancy and the risk of spontaneous abortion. *Can Med Assoc J*. 2010;182(10):1031-1037. doi:10.1503/cmaj.091208.
24. Andrade C. The safety of duloxetine during pregnancy and lactation. *J Clin Psychiatry*. 2014;75(12):1423–1427.
25. Neuman G, Colantonio D, Delaney S, Szykaruk M, Ito S. Bupropion and escitalopram during lactation. *Ann Pharmacother*. 2014;48(7):928–931.
26. Smit M, Dolman KM, Honig A. Mirtazapine in pregnancy and lactation – A systematic review. *Eur Neuropsychopharmacol*. 2016;26(1):126-135. doi:10.1016/j.euroneuro.2015.06.014.