



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 days¹⁻³
- 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)⁴

• **Infant Risks**

- **Congenital malformations**^{1,5-7}
 - 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**^{8,9}
 - 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**^{10,11}
 - 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**¹²⁻¹⁶
 - 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

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Antidepressant Risks in Breastfeeding ¹⁷⁻¹⁹

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 ^{3,20}

- 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.^{21,22} May consider supra-therapeutic doses in the context.



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SSRIs (Selective Serotonin Reuptake Inhibitors)²³

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

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SNRIs (Serotonin Norepinephrine Reuptake Inhibitors)^{23,24}						
<ul style="list-style-type: none"> Second line to SSRI's in pregnancy and postpartum May be beneficial for patients with comorbid neuropathic pain Some studies show small increased risk of spontaneous abortion Rebound symptoms with missed doses Often require slow taper due to discontinuation symptoms (dizziness, nausea, headache, paresthesia, fatigue, vomiting, irritability, insomnia, diarrhea, anxiety, hyperhidrosis) 						
	Medication	Advantages	Disadvantages	Absolute Infant dose in breast milk (mg/d)	Lactation Rating*	Potential adverse effects of breastfeeding
SNRIs (Serotonin Norepinephrine Reuptake Inhibitors)	Desvenlafaxine (50mg)	<ul style="list-style-type: none"> Also treats neuropathic pain Absolute infant dose in breastfeeding half that of venlafaxine 	<ul style="list-style-type: none"> Least studied of the SNRI's 		L3	
	Duloxetine (60mg-120mg) Start 40mg, increase 20-30mg/day increments per week	<ul style="list-style-type: none"> Also treats neuropathic pain and fibromyalgia Can be given in two divided doses to aid tolerability 	<ul style="list-style-type: none"> Less studied than Venlafaxine in pregnancy Small increased risk of miscarriage 	<0.03	L3	
	Venlafaxine XL (37.5- 225 mg) increase in 37.5mg increments	<ul style="list-style-type: none"> Also treats neuropathic pain at higher doses More studied than other SNRI's in pregnancy 	<ul style="list-style-type: none"> Small increased risk of miscarriage Higher rates of discontinuation symptoms than duloxetine 	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 https://docassistillinois.org</p>

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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	Bupropion²⁵ Bupropion Registry XL (150-450 mg) Increase in 150mg increments	<ul style="list-style-type: none"> Fewer sexual side effects than SSRI's or SNRI's Less risk of weight gain Aids smoking cessation Does not appear to be associated with increased risk of congenital malformations in limited studies 	<ul style="list-style-type: none"> Not recommended in those with eating disorders or seizure disorders Decreases seizure threshold May sometimes worsen anxiety 	0.20	L3	<ul style="list-style-type: none"> Sleep disturbance of infants reported Isolated case reports of infant seizure
	Mirtazapine²⁶ (15-45mg) Increase in 15 mg increments	<ul style="list-style-type: none"> Aids with sleep and promotes appetite 	<ul style="list-style-type: none"> Sedating Less studied than SSRIs 	0.04	L3	
	Nortriptyline (100-150 mg daily) Start 25mg daily increase in 25mg increments	<ul style="list-style-type: none"> Can also be used for migraine prophylaxis 	<ul style="list-style-type: none"> Maternal side effects additive to pregnancy effects (sedation, constipation, tachycardia) Orthostatic hypotension, risking decreased placental perfusion Fetal and neonatal side effects: tachycardia, urinary retention 	0.07	L2	<ul style="list-style-type: none"> Dry mouth, constipation, urinary retention
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						



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