RegioneEmilia-Romagna

Il trattamento del disagio psichico perinatale

Northwestern Medicine®

Pharmacological Treatment of Bipolar Disorder in the Perinatal Period and Puerperal Psychosis

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Maternal Mental Health

American College of Obstetrics and Gynecology: "Perinatal Mood and Anxiety Disorders are associated with increased risks of maternal and infant mortality and morbidity and are recognized as a significant patient safety issue." *Obstetrics & Gynecology 2017;129:422–430*

- **Obstetric– Neonatal Complications**
  - Miscarriage
  - Hypertensive Disorders/ Preeclampsia
  - Preterm birth
  - Cesarean delivery
  - Low birth weight
  - NICU admission
- **Early Social – Emotional Impact**
  - Poor infant self-regulation
  - Insecure attachment
- **Long Term Impairments**
  - Developmental and cognitive delays
  - Behavioral problems, psychopathology

Developmental Origins of Health and Disease

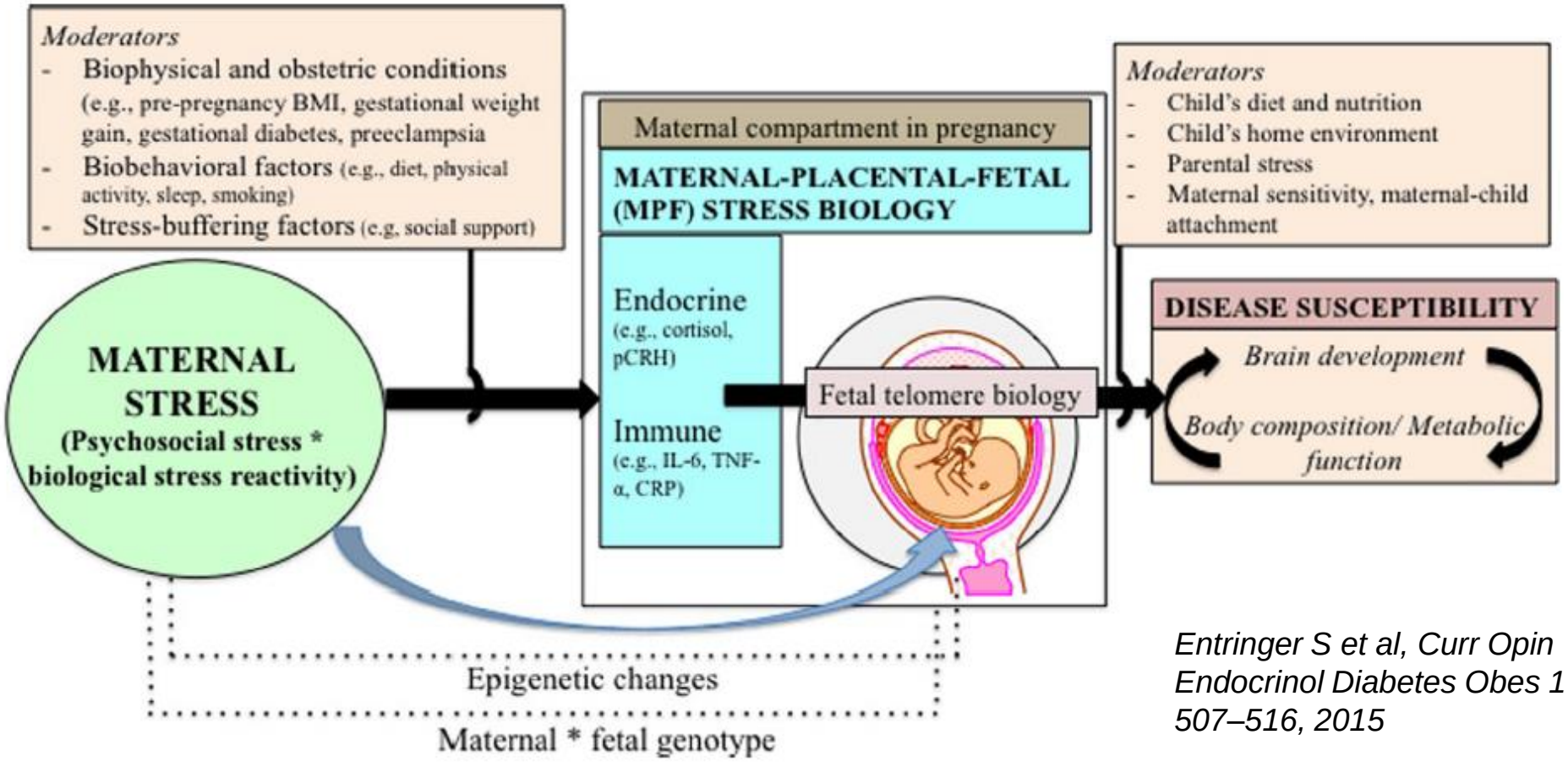


Fig. 1. Conceptual framework to study the effects of maternal stress during pregnancy on disease susceptibility.

Entringer S et al, Curr Opin Endocrinol Diabetes Obes 17: 507–516, 2015

Hutchison SM, et al. Perinatal selective serotonin reuptake inhibitor (SSRI) and other antidepressant exposure effects on anxiety and depressive behaviors in offspring: A review of findings in humans and rodent models. Reproductive Toxicol 99:80-95, 2021. PMID: 33253794

Primary Axis 1 SCID Diagnoses

Wisner et al, JAMA Psychiatry 70(5): 490-8, 2013. PMID: 23487258

Primary Diagnoses, N = 826		
	N	%
Depressive Disorders	**566**	**68.5**
Major Depression- Recurrent	368	65.0
Major Depression - Single Episode	146	25.8
Depressive Disorder NOS	38	6.7
Adjustment Disorder With Depressed Mood	11	1.9
Mood Disorder NOS	2	0.4
Dysthymic Disorder	1	0.2
Bipolar Disorders	**187**	**22.6**
Bipolar 2 Disorder	58	31.0
BPD1-Recent Episode Depressed	54	28.9
Bipolar Disorder NOS	35	18.7
BPD1-Recent Episode Mixed	32	17.1
BPD1-Single Manic Episode	7	3.7
Schizoaffective Disorder	1	0.5
Anxiety Disorders	**46**	**5.6**
Generalized Anxiety Disorder	24	52.2
Obsessive-Compulsive Disorder	8	17.4
Anxiety Disorder NOS	8	17.4
Adjustment Disorder With Anxiety	3	6.5
Panic Disorder Without Agoraphobia	1	2.2
Post-traumatic Stress Disorder	1	2.2
Specific Phobia	1	2.2
Substance Use Disorders	**4**	**0.5**
Substance-Induced Mood Disorder	1	25.0
Alcohol Abuse/Dependence	1	25.0
Opioid Abuse/Dependence	1	25.0
Polysubstance Dependence	1	25.0
Other Disorders	**6**	**0.7**
No Diagnosis	**17**	**2.1**

With anxiety disorder comorbidity

N=248 mothers with BD	
GAD and Anxiety Disorder NOS	42%
Panic Disorder	28%
PTSD	23%
Substance Use	13%
Obsessive-Compulsive Disorder	23%

Bipolar Disorder

- Prevalence=1-1.5% to 5%
- Mania/ mixed / hypomania with depressive episodes.
- Onset in mid to late teens
- Postpartum onset particularly common
- “Plugged in” symptoms: grandiosity, less need for sleep but not tired, pressured speech, flight of ideas, distractibility, increased involvement in goal-directed activities, psychomotor agitation, excessive involvement in pleasurable activities with likelihood of painful consequences
- Antidepressant alone risks agitation/rapid cycling
- **Screen for bipolar disorder MDQ** (Mood Disorders Questionnaire) www.dbsalliance.org/pdfs/MDQ.pdf

Screening for bipolar disorder

Mood Disorders Questionnaire (MDQ)

www.dbsalliance.org/pdfs/MDQ.pdf

7 items

	YES	NO
1. Has there ever been a period of time when you were not your usual self and...		
...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	○	○
...you were so irritable that you shouted at people or started fights or arguments?	○	○
...you felt much more self-confident than usual?	○	○
...you got much less sleep than usual and found you didn't really miss it?	○	○
...you were much more talkative or spoke much faster than usual?	○	○
...thoughts raced through your head or you couldn't slow your mind down?	○	○
...you were so easily distracted by things around you that you had trouble concentrating or staying on track?	○	○
...you had much more energy than usual?	○	○
...you were much more active or did many more things than usual?	○	○
...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	○	○
...you were much more interested in sex than usual?	○	○
...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	○	○
...spending money got you or your family into trouble?	○	○
2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time?	○	○
3. How much of a problem did any of these cause you – like being unable to work; having family, money or legal troubles; getting into arguments or fights? *Please circle one response only.* XXX No Problem Minor Problem Moderate Problem Serious Problem		
4. Have any of your blood relatives (i.e. children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?	○	○
5. Has a health professional ever told you that you have manic-depressive illness or bipolar disorder?	○	○

Postpartum Screen: EPDS plus MDQ

- Goal: Distinguish unipolar vs. bipolar disorder at the level of screening
- Screen mothers with the MDQ plus EPDS
- Screen positive EPDS ≥10 plus MDQ positive compared to clinical SCID diagnosis for DSM IV
- MDQ identified 50% of women with impairment included (traditional scoring)
- 70% when the MDQ was scored without the impairment criterion

Clark CT et al. Does screening with the MDQ and EPDS improve identification of bipolar disorder in an obstetrical sample? Depression & Anxiety 32(7):518-26, 2015.

Pharmacotherapy:
Weigh the Benefits as well as the Harms

9

Guidelines for Treatment of Pregnant Women with BD

- Preconception evaluation for pregnancy planning is optimal
- Clinical factors that influence treatment planning are
  - illness history and course
  - treatment responses
  - comorbid psychiatric and medical disorders
  - patient's responsibilities (children, employment)
  - reproductive risks of medications
  - Views about acceptability of medication during pregnancy and breastfeeding

Yonkers, Wisner, Stowe et al. Am J Psychiatry 2004; 161:608-620; Management of Bipolar Disorder During Pregnancy and the Postpartum Period

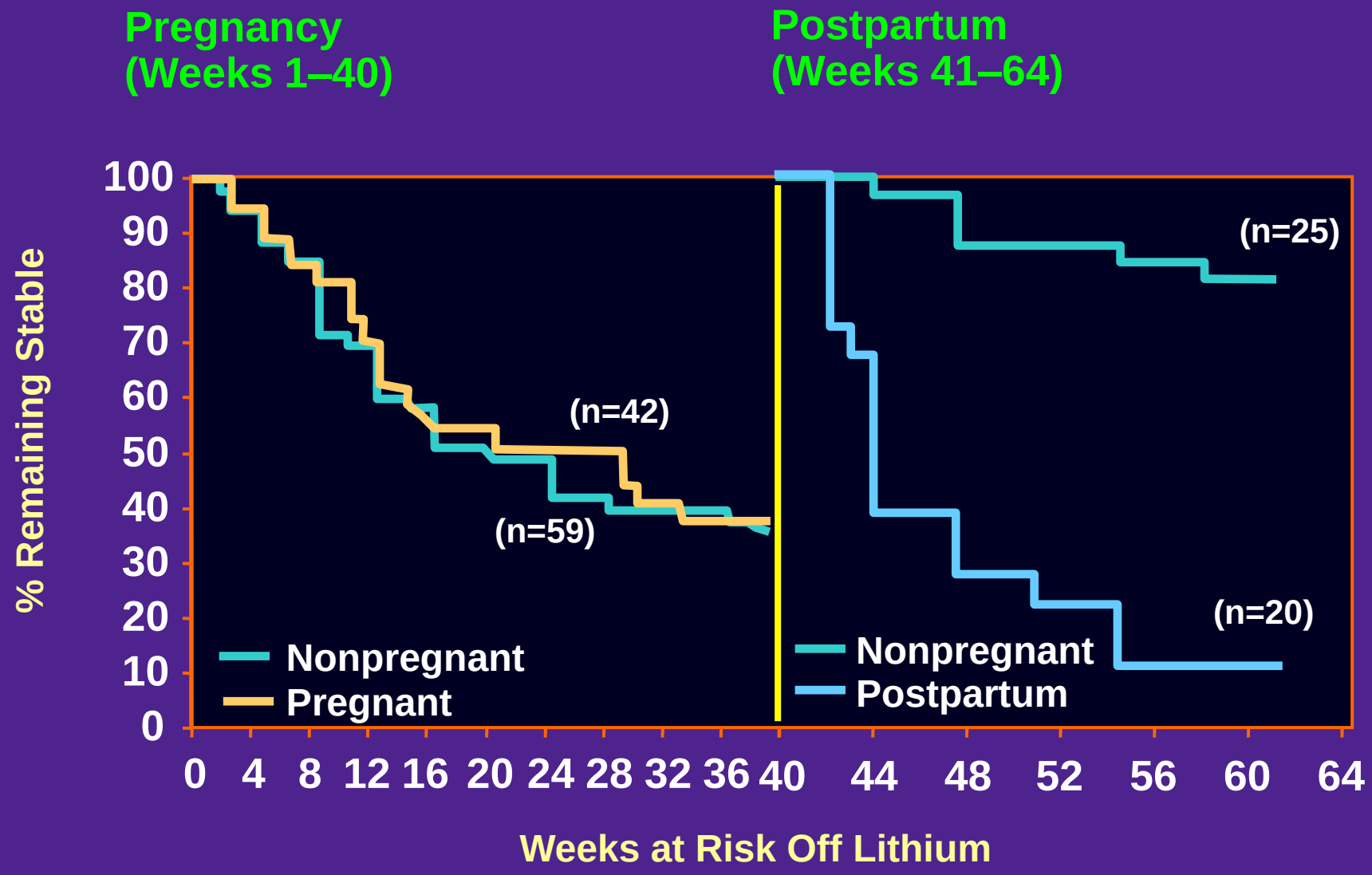
APA Practice Guideline for the Treatment of Bipolar Disorder: First Line Drugs

Acute Mixed/Manic Episode	ValpXroate+ Antipsychotic or Lithium + Antipsychotic
Acute Depressive Episode	Lithium or Lamotrigine *Antidepressant monotherapy is not recommended
Acute Rapid Cycling (4 or more episodes in previous 12 months, with partial/full remission for 2 months or a switch to an episode of opposite polarity)	Lithium or ValpXroate, with Lamotrigine as alternative
Maintenance Treatment	Lithium or ValpXroate *Lamotrigine, Carbamazepine, or Oxcarbazepine as alternatives

Little consensus across international evidence-based guidelines for drug management of bipolar disorder during the perinatal period?. Graham RK et al. Journal of Affective Disorders. 228:216-221, 2018 03 01.

Lithium

Risk of Relapse Following Lithium Discontinuation



Viguera AC. *Am J Psychiatry.* 2000;157:179-184.

Lithium and Cardiac Defects

- *Patorno E et al. N Engl J Med 2017; 376:2245-2254*
- Cohort n=1,325,563 Medicaid database
- **Outcome=cardiac defects** Li vs. LTG exposed vs. unexposed
- Unexposed=1.15%; LTG=1.39%; Li=2.41%, aRR=1.65 (95% CI=1.02- 2.68)
- Small increased risk of cardiac defects
- Folic acid supplementation? *Huhta JC et al, When should we prescribe high-dose **folic acid** to prevent congenital heart defects? Curr Opinion Cardiol 30:125-31, 2015.*

Lithium: Pregnancy Outcomes

Hastie R et al, Maternal lithium use and the risk of adverse pregnancy and neonatal outcomes: a Swedish population-based cohort study. BMC Med. 2021 Dec 2;19(1):291. PMID: 34856987

	No lithium *n*= 853,583	Lithium use *n*=434		
	n (%)	*n* (%)	Relative risk (95% confidence interval)	
			Crude	Adjusted
Primary outcomes				
Preeclampsia	24,008 (2.8)	15 (3.5)	1.29 (0.75, 2.02)	1.01 (0.59, 1.73)
Spontaneous preterm birth Missing *n*=723	25,268 (3.0)	36 (8.7)	2.80 (2.02, 3.88)	2.64 (1.82, 3.82)
Small for gestational age Missing *n*=1446	19,794 (2.3)	13 (3.0)	1.29 (0.70, 2.38)	1.05 (0.54, 2.06)
Large for gestational age Missing *n*=1446	29,619 (3.5)	39 (9.0)	2.59 (1.91, 3.51)	2.64 (1.91, 3.66)
Secondary outcomes				
Macrosomia Missing *n*=1116	158,461 (18.6)	93 (21.4)	1.01 (0.25, 4.03)	1.05 (0.25, 4.32)
Hypoglycaemia	20,877 (2.5)	24 (5.5)	2.26 (1.54, 3.33)	1.46 (0.89, 2.40)
Five-minute Apgar < 6 Missing *n*=5011	11,221 (1.3)	11 (2.5)	1.92 (1.02, 3.61)	0.92 (0.38, 2.22)
Malformations (all)	29,240 (3.4)	19 (4.4)	1.28 (0.83, 1.98)	1.41 (0.90, 2.23)
Cardiac malformations	6513 (0.8)	9 (2.1)	2.72 (1.43, 5.17)	3.17 (1.64, 6.13)
Perinatal death	3567 (0.5)	2 (0.5)	1.58 (0.39, 6.27)	1.08 (0.15, 7.67)

Lithium and Offspring Development

- Development as assessed by neuropsychiatric testing is normal in exposed offspring
- *Poels EMP et al, The effect of prenatal lithium exposure on the neuropsychological development of the child. Bipolar Disord 2021 Sep 29. doi: 10.1111/bdi.13133. PMID: 34585812*
- Maternal BD, offspring aged 6-14 years, 56 Li exp, 43 unexposed
- No association between Li exposure and IQ; no relationship to blood level
- Neuropsychological outcomes in both groups were comparable to the general population

Serum Lithium Concentrations before/during/after pregnancy

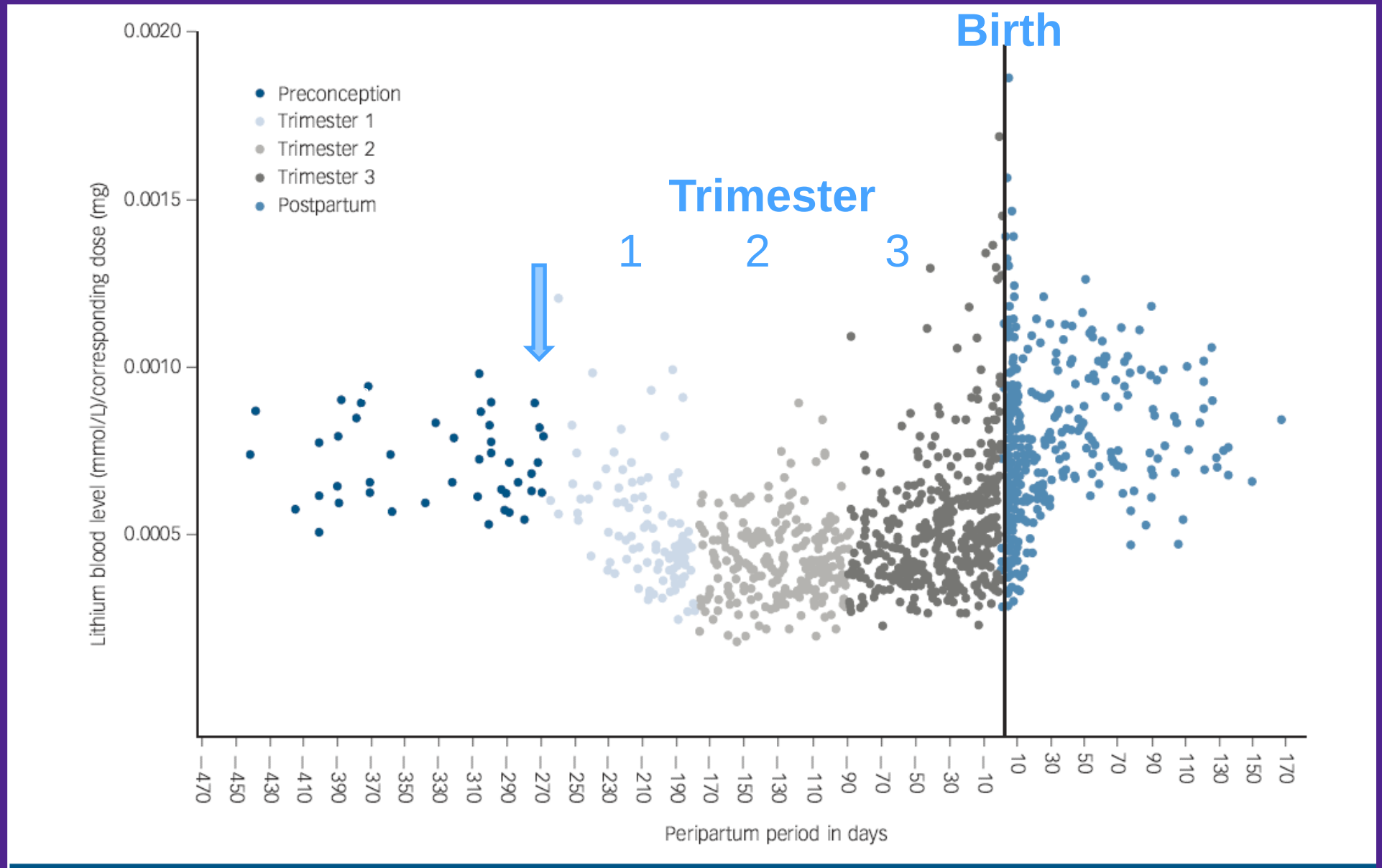


Fig. 1 Course of lithium blood level/dose ratio during the peripartum period. Wesseloo R et al, Br J Psych 211:31-36, 2017

Lithium

- Concentrations drop rapidly with pregnancy onset and stabilize in the second trimester
- BID to TID dosing during pregnancy to avoid high peak concentrations with higher doses
- Education about nausea/vomiting/fluid loss
- Suspend dosing when labor begins, ensure adequate hydration
- Restart lithium at pre-pregnancy dose

Breastfeeding:
Balancing Risks and Benefits

- Not simply a question of how much drug will be in breastmilk?
- Risks of formula feeding need to be included in decision
- Which is more risky to infant - breast milk with small amount of drug or infant formula?
- Most medications are acceptable during breastfeeding

Imaz ML et al: Neonatal Feeing Trajectories in Mothers with Bipolar Disorder Taking Lithium. Frontiers Pharmacology. 12:752022, 2021.

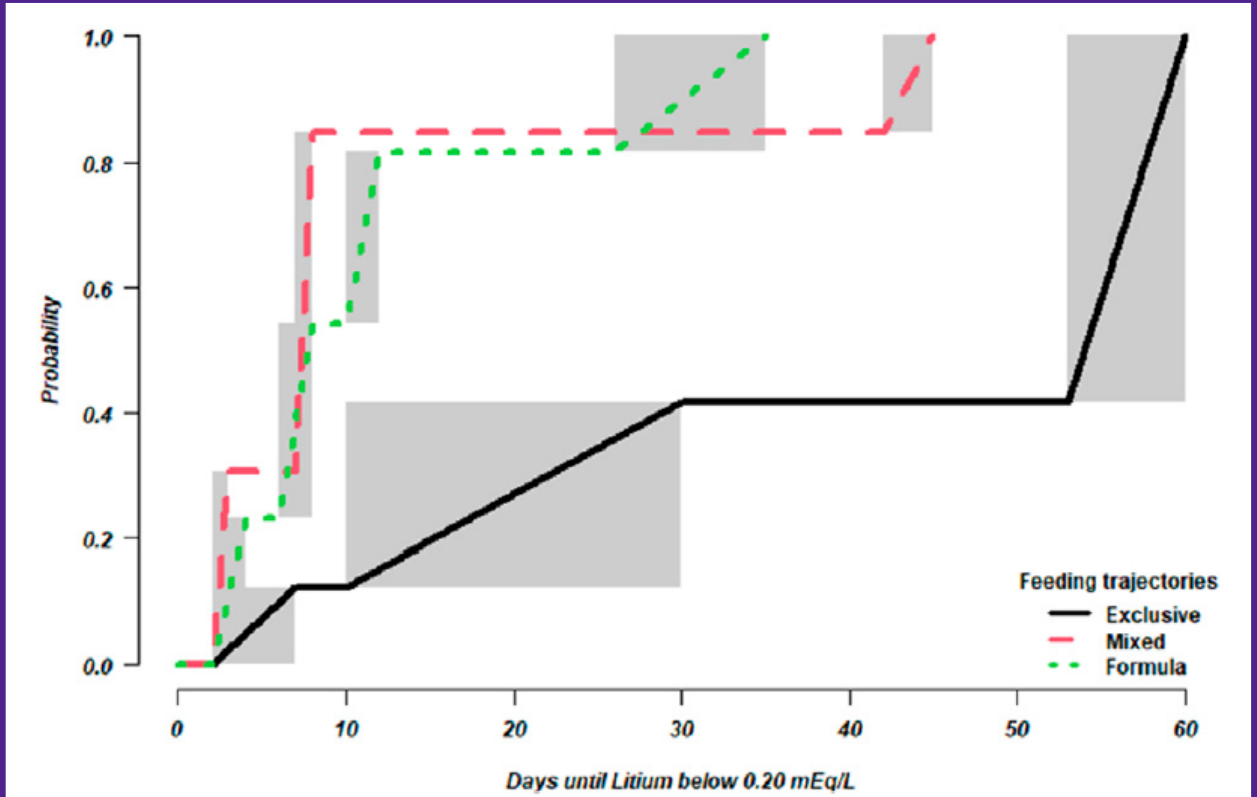


FIGURE 2 | Estimated cummulative probability that lithium serum concentrations falls below LoQ. Shaded areas indicate that the estimation of the probability is not defined in the corresponding intervals, but only known to increase monotonically.

Neonates had some complications (hypotonia, respiratory distress following operative delivery, and hypertonia), resolved before discharge

Umbilical cord lithium concentration= maternal concentration

Atypical Antipsychotics

Antipsychotic Exposure- Malformations

- *Huybrechts, KF JAMA Psychiatry 2016 Sep 1;73(9):938-46.*
- Antipsychotics exp (AP) -risk for overall and cardiac birth defects
- Sample= 1 341 715 pregnant women
- No Expos. Birth Defects=32.7/1000 births
- Atypical Antipsychotic Exposure -Birth Defects=44.5/1000 births
- With adjustment for confounders
  - aRR=1.05 (95% CI, 0.96-1.16) for atypical AP NOT significant
- RRs for cardiac malformations were also not significant
- Individual AP – Risperidone
  - small increased risk in overall malformations (RR= 1.26; 95% CI, 1.02-1.56) and cardiac malformations (RR= 1.26; 95% CI, 0.88-1.81) independent of confounders.

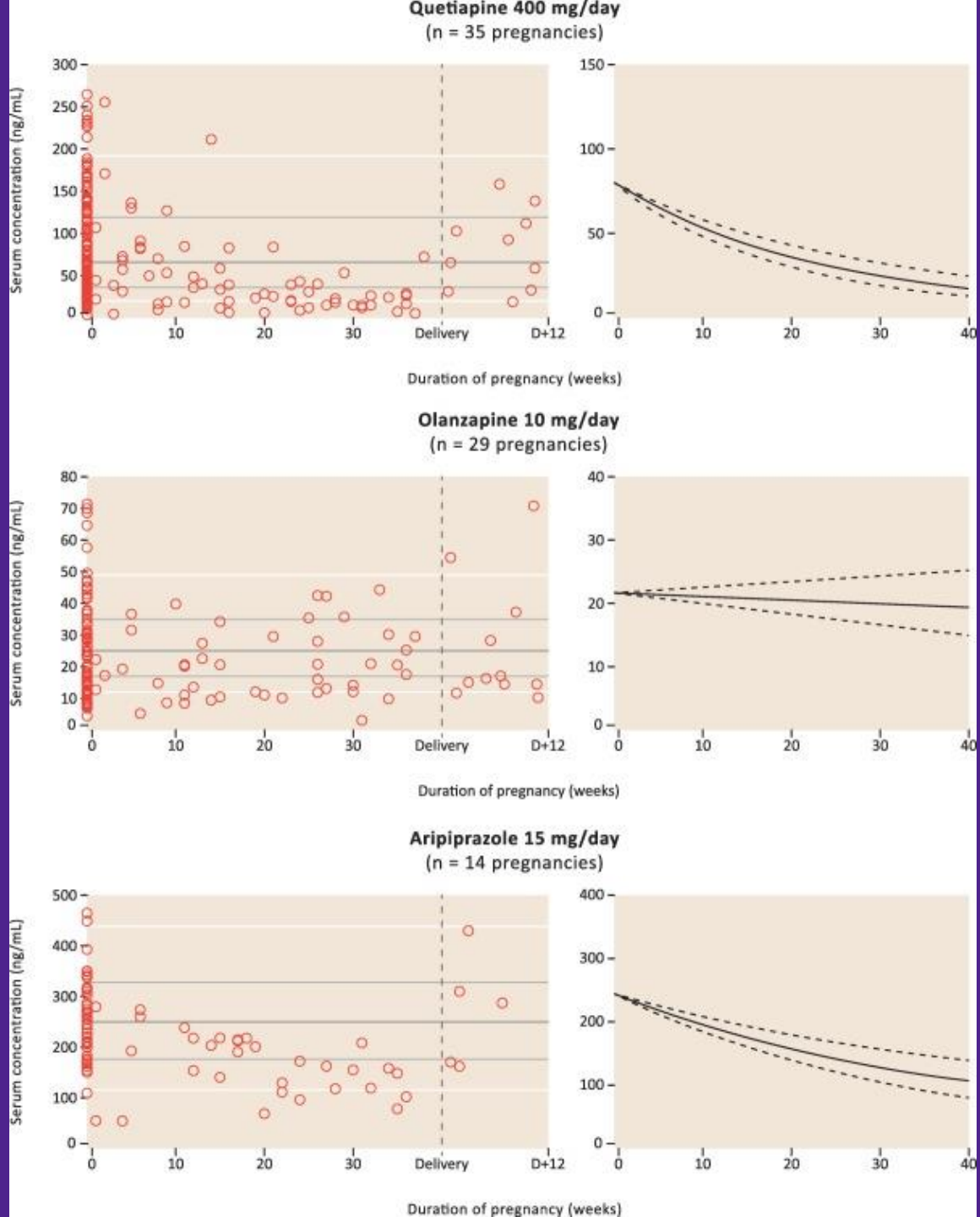
Offspring Development

- Straub L et al: JAMA Intern Med. 1;182(5):522-533, 2022. PMID: 35343998
- 3.3 M pregnancies
- 8 outcomes: ASD; ADHD; learning disability; developmental speech/language disorder; developmental coordination disorder; intellectual disability; behavioral disorder, conduct and/or emotions; any NDD
- >2 M unexposed, >10,000 with AP drug dispensings
- Pooled unadjusted 1.91 [1.79-2.03]
- Adjusted 1.08 [1.01-1.17]), NOT SIGNIFICANT with the exception of aripiprazole (1.36 [1.14-1.63]).
- Increased risk of NDD in children explained by maternal characteristics--not associated with *in utero* AP exposure.
- Closely monitoring the neurodevelopment of the offspring of women with mental illness to support early intervention.

The drug dose may need to be increased in pregnancy to sustain remission of symptoms

Westin AA et al
2018 Mar; 103(3): 477–484. PMID: 28643331

Quetiapine – CYP 3A4
Olanzapine – CYP 1A2
Aripiprazole – CYP 2D6



Atypical Antipsychotics: Metabolism in Pregnancy

Atypical Antipsychotic	Major Metabolic Pathways	Expected Change in Pregnancy
Aripiprazole	CYP3A4, CYP2D6*	Decreased concentration
Asenapine	UGT1A4, CYP1A2	Decreased concentration
Brexipiprazole	CYP3A4, CYP2D6	Decreased concentration
Clozapine	CYP1A2, CYP2D6, CYP3A4	Increased or Decreased concentration
Illoperidone	CYP2D6, CYP3A4	Decreased Concentration
Lurasidone	CYP3A4	Decreased Concentration
Olanzapine**	UGT1A4, CYP2D6	Concentration remains stable
Quetiapine	CYP3A4	Decreased Concentration
Risperidone	CYP2D6*	Decreased Concentration
Ziprasidone	CYP3A4	Decreased Concentration

Antipsychotics - Breastfeeding

- **Low levels in breastmilk and infants**
  - Olanzapine -1.6-4.0% of the maternal dose; at 2 and 6 weeks of age, infant concentration was below limit of quantifiability (<2 ng/mL).
  - Risperidone - Calculated relative infant doses=2.3%, 2.8%, 4.7% of maternal weight-adjusted doses; nondetectable serum drug/metabolite levels
  - Quetiapine - 0.09-0.43% of maternal dose; Infant plasma concentration of 1.4 mcg/L was 6% of the maternal plasma concentration.
  - Aripiprazole - 0.7% maternal dose

    -potential interference with lactation due to partial D_2 agonism

Antiseizure Medications

Anticonvulsant Drugs: Planning Pregnancy

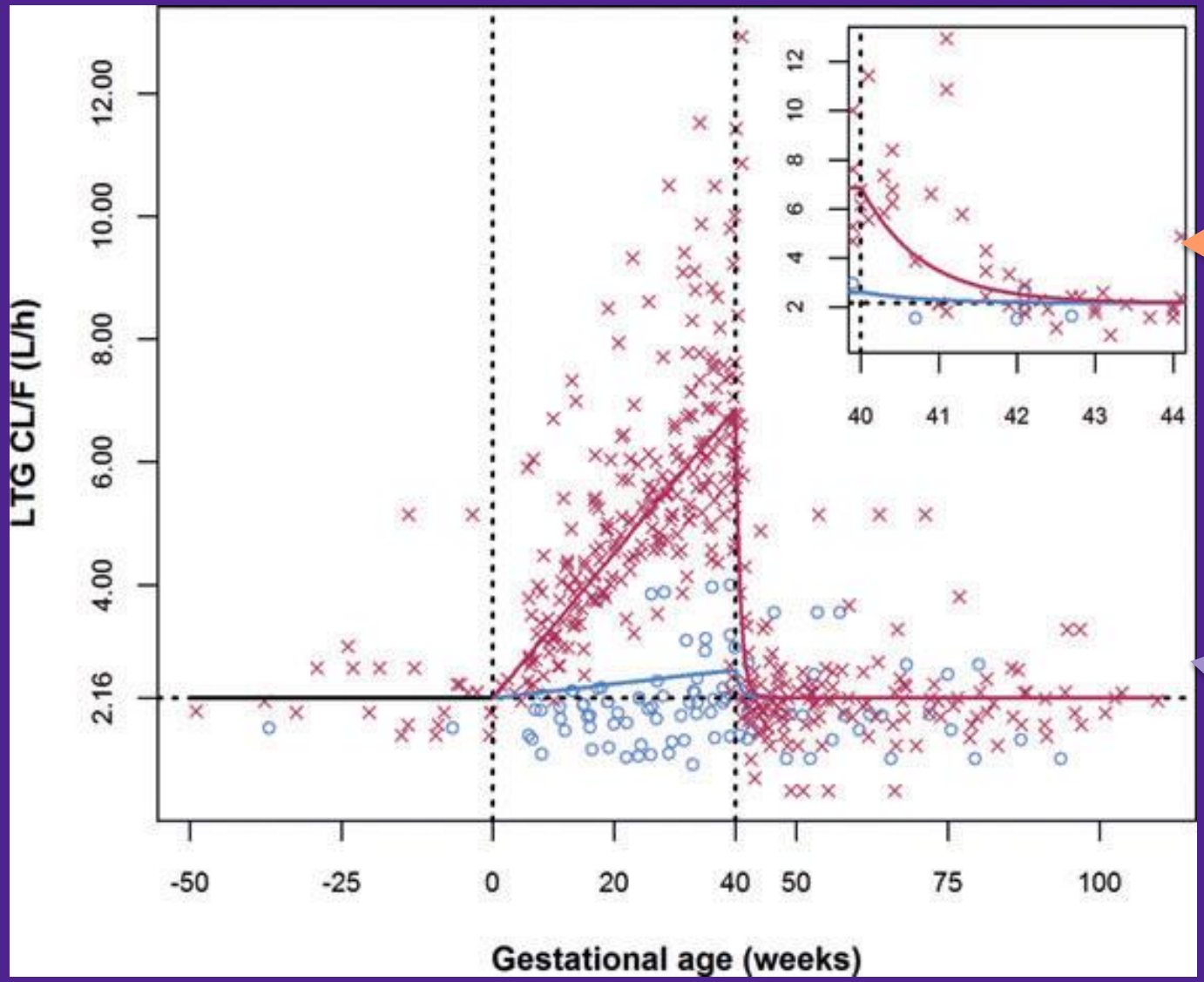
- Establish therapeutic drug level, consistent time of day, ideally at trough
- Check drug levels at least every 4 weeks throughout pregnancy for most drugs
  - Adjust dosing to maintain target blood level
- Consider dosing drugs more frequently than in non-pregnant state (for example, every 8 hours rather than every 12 hours)

	LTG
Australian Pregnancy Registry	4.6% (307)
Danish Registry	3.7% (1019)
EURAP	2.9% (1280)
Finland National Birth Registry	
GSK Lamotrigine Registry	2.2% (1558)
North American AED Pregnancy Registry	2.0% (1562)
Norweigan Medical Birth Registry	3.4% (833)
Swedish Medical Birth Registry	2.9% (1100)
UK/Ireland pregnancy registry	2.3% (2098)

Lamotrigine

- > 6,000 pregnancies
- MCM rate 2-4%
- Lamotrigine cleared by glucuronidation
- Levels drop throughout pregnancy
- Lamotrigine dose may increase by 200-300% to maintain concentration
- Dose must be decreased immediately after delivery to avoid side-effects (usually by 2/3 of amount at delivery)

Variability in Lamotrigine Clearance



In both groups clearance returns to baseline within 2 weeks postpartum

77% demonstrate marked increase in LTG clearance during pregnancy

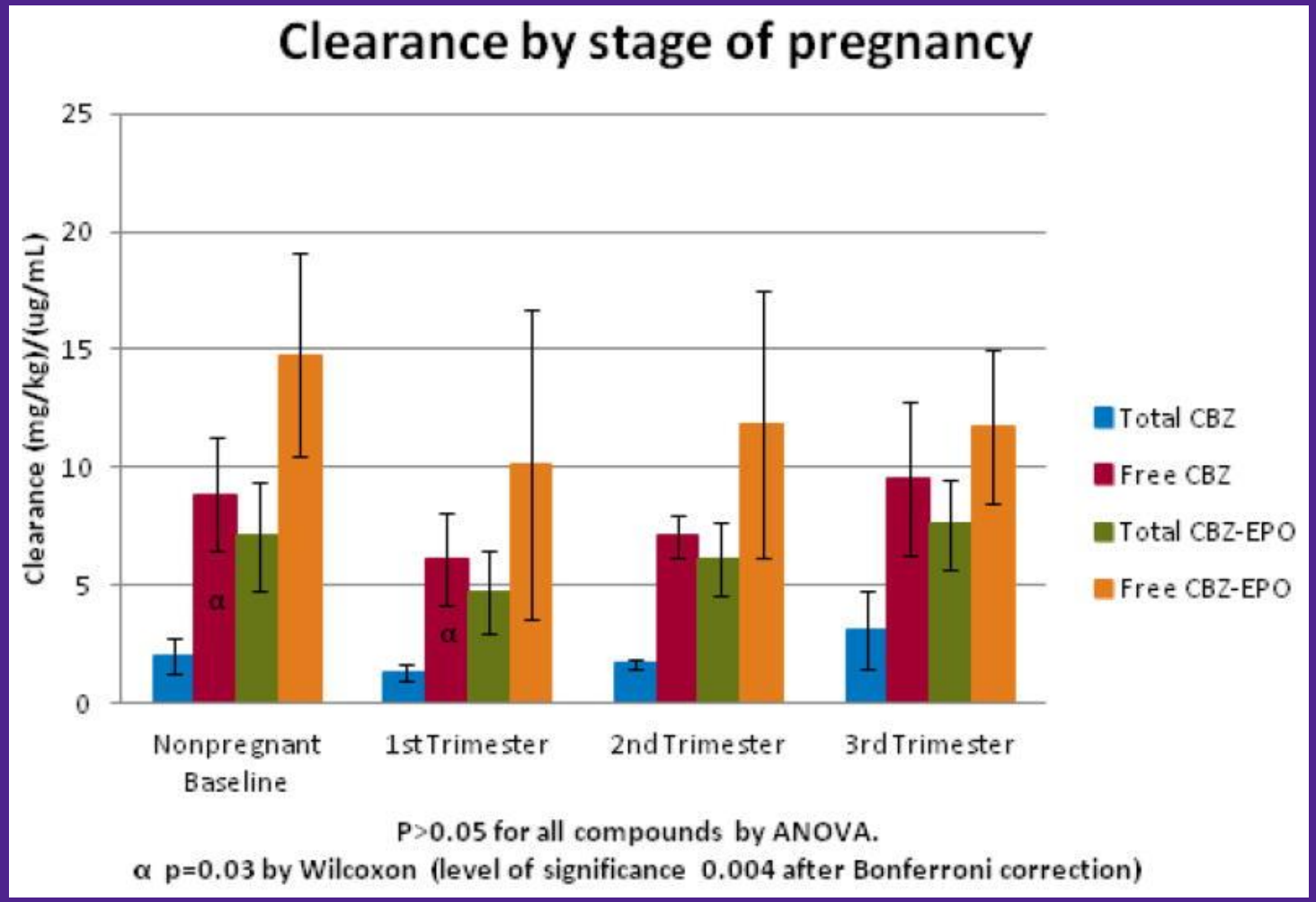
Polepally et al 2014
PMID: 24883336

	CBZ
Australian Pregnancy Registry	5.5% (346)
Danish Registry	
EURAP	5.6% (1402)
Finland National Birth Registry	2.7% (805)
GSK Lamotrigine Registry	
North American AED Pregnancy Registry	3.0% (1033)
Norweigan Medical Birth Registry	2.9% (685)
Swedish Medical Birth Registry	2.7% (1430)
UK/Ireland pregnancy registry	2.6% (1657)

Carbamazepine

- > 5,000 pregnancies
- 2-4% MCM in most registries
- 5-6% in EURAP and Australian registries
- CBZ concentrations stable across pregnancy
- Enhanced metabolism of other drugs

Clearance of carbamazepine and carbamazepine metabolites relatively stable during pregnancy



Clearance of compounds through pregnancy (95% confidence intervals shown with error bars).

Emily L. Johnson, et al PMID: 24632353 Epilepsy & Behavior, Volume 33, 2014, 49–53
Carbamazepine clearance and seizure stability during pregnancy

	VPA
Australian Pregnancy Registry	13.8% (253)
Danish Registry	
EURAP	9.7% (1010)
Finland National Birth Registry	10.7% (263)
GSK Lamotrigine Registry	
North American AED Pregnancy Registry	9.3% (323)
Norweigan Medical Birth Registry	6.3% (333)
Swedish Medical Birth Registry	4.7% (619)
UK/Ireland pregnancy registry	6.7% (1290)

Valproic Acid X

- Now > 3,000 pregnancies
- MCM rates are consistently higher than other drugs
- Association with Autism and Neurodevelopmental Disorders

JAMA. 2013;309(16):1696-1703. doi:10.1001/jama.2013.2270 PMID: 23613074

	No.		Adjusted Hazard Ratio (95% CI)
	Unexposed	Exposed	
Valproate			
Total	655 107	388	
Childhood autism	2058	7	4.9 (2.3-10.3)
Autism spectrum disorder	5423	12	3.0 (1.7-5.4)

Folic Acid Supplementation

Current Guideline Recommendations for FAS	
AES/AAN	Consider **at least 400 mcg/day** FA prior to conception and continued throughout pregnancy in women with epilepsy taking AEDs.
ILAE	Recommends **at least 400 mcg/day** FA in women of childbearing potential taking AEDs prior to pregnancy and continued through pregnancy.
CDC	Recommend **400 mcg/day** for all women of reproductive age starting one month before becoming pregnant through the first 12 weeks of pregnancy in addition to obtaining folate from a varied diet.
ACOG	Recommend in all women of reproductive age (15-45 years) starting 1 month prior to conception through the first 12 weeks of pregnancy. • **Average risk: 400 mcg/day** (most prenatal vitamins should be adequate) • **High risk of NTDs***: **4 mg/day** three months prior to conception and for the first three months of pregnancy

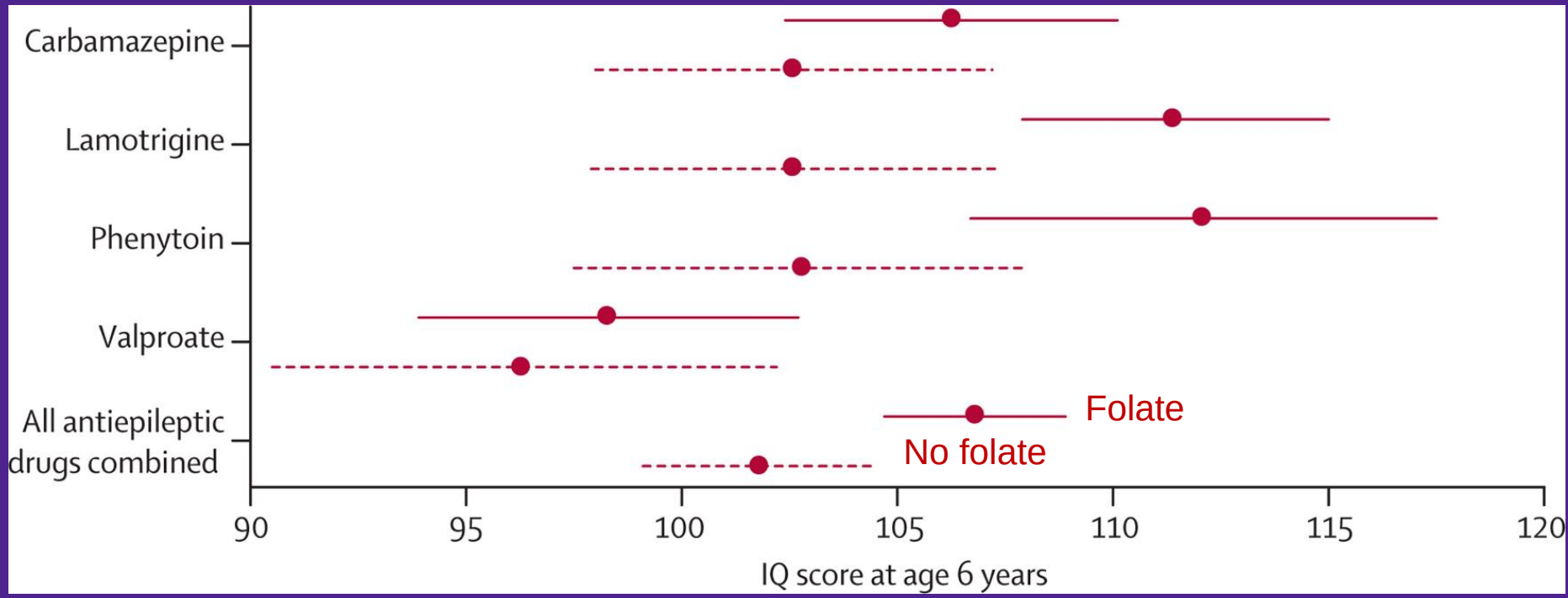
*includes women with a prior NTD-affected pregnancy, women affected with an NTD themselves, those with a partner affected with an NTD, or those with a partner with a previous affected child (2017 practice bulletin) or women with seizure disorders (2019 committee opinion)

Harden CL, et al. *Neurology*. 2009.
ACOG. *Obstet Gynecol*. 2019.
Centers for Disease Control. 2021.
Tomson. *Epileptic Discord*. 2019.

Folic Acid Supplementation

Summary of Findings	Conclusion
• Observed increasing use of FAS prior to conception through early pregnancy with additional supplementation through diet in some countries • **Hospital-based registries:** FA at 5 mg/day was associated with a slightly increased rate of spontaneous abortion without significant changes in rates of MCMs • **Population-based registries:** Did not demonstrate an effect on MCM rates with maternal exposure to AEDs in the 1st trimester. Similar rates of malformations at low vs high doses of FA • Increasing rates of MCMs were associated with increasing dosages of VPA and CBZ	Inconclusive data on high dose FAS in reducing MCM outcomes in women taking VPA or other AEDs before and/or during pregnancy
• Positive association of higher IQs at age 6 in children of women receiving periconceptional FA >400 mcg/day	FA 400 mcg – 1 mg/day may be beneficial for WWE of childbearing potential

Neurodevelopmental Effects of Antiseizure Medications



Child IQ at 6 years, by exposure to maternal AED use and Periconceptional Folate; (retrospective exposure data collection)

Kimford J Meador , Gus A Baker, Nancy Browning et al. The Lancet Neurology Volume 12, Issue 3 2013 244 – 252 PMID 23352199
Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study

ECT during pregnancy

- *Electroconvulsive Therapy in Pregnancy: Safety, Best Practices, and Barriers to Care. Rose S et al. Obstetrical & Gynecological Survey 75(3):199-203, 2020*
- Appropriate for use in pregnancy for suicidality, psychosis, catatonia
  - Elevate pregnant woman's right hip to avoid large vessel compression
  - external fetal cardiac monitoring
  - Avoid intubation due to maternal vascularity and airway edema
  - Avoid hyperventilation – it is associated with decreased placental blood flow

Non-Pharmacologic Treatments

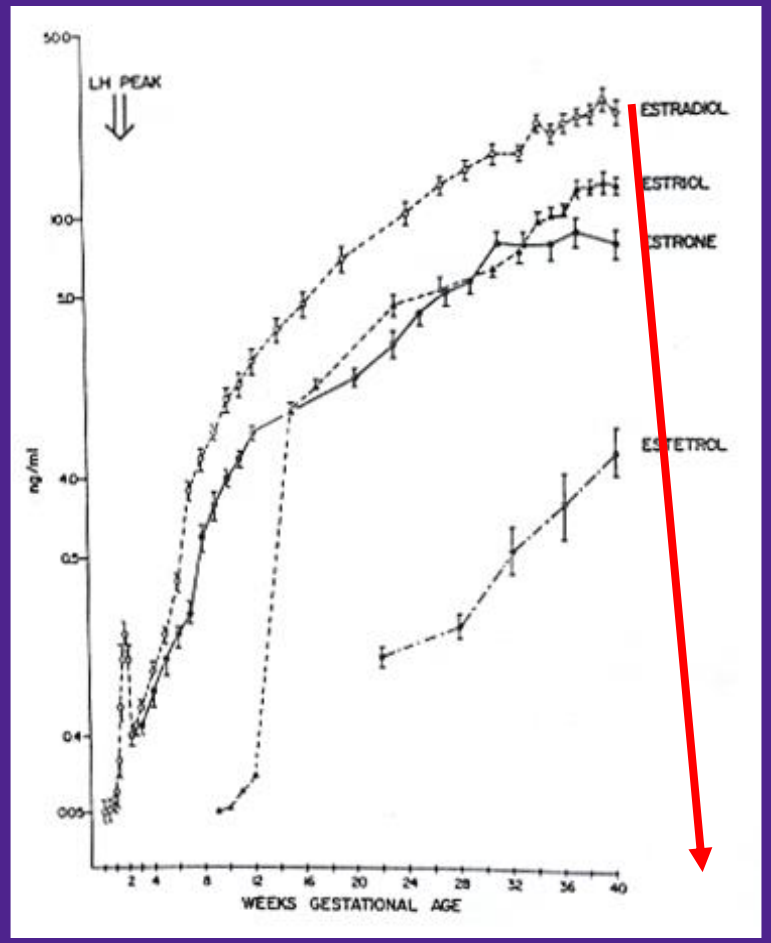
- Many effective types of short-term focused psychotherapy
- Monotherapy or combined with other treatment
  - Interpersonal Social Rhythm Therapy targets interpersonal distress, medication compliance and biological rhythms https://www.ipsrt.org/
  - Cognitive Behavior Therapy – correct distorted and dysfunctional automatic thoughts
  - Dialectical Behavior Therapy--combines CBT techniques with skill building - distress tolerance, acceptance, and mindfulness
  - Behavioral Activation
- Yoga with mindfulness component
- Exercise
- Bright Light Therapy *Sit et al, Am J Psychiatry 2018;175:131-139.*
- Transcranial magnetic stimulation *McGirr A et al. JAMA Netw Open. 2021;4(3):e210963. doi:10.1001/jamanetworkopen.2021.0963*
- Electroconvulsive therapy

Postpartum Psychosis

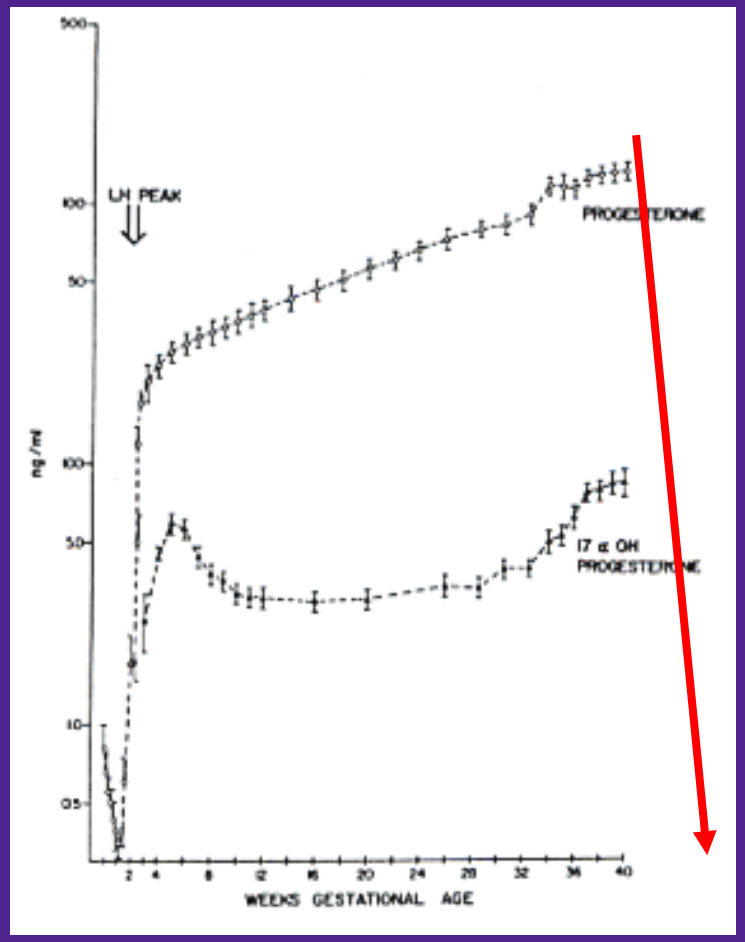
Postpartum Mood Disorders:

Estrogen drops to follicular levels within 24 h of delivery

ESTROGENS



PROGESTINS

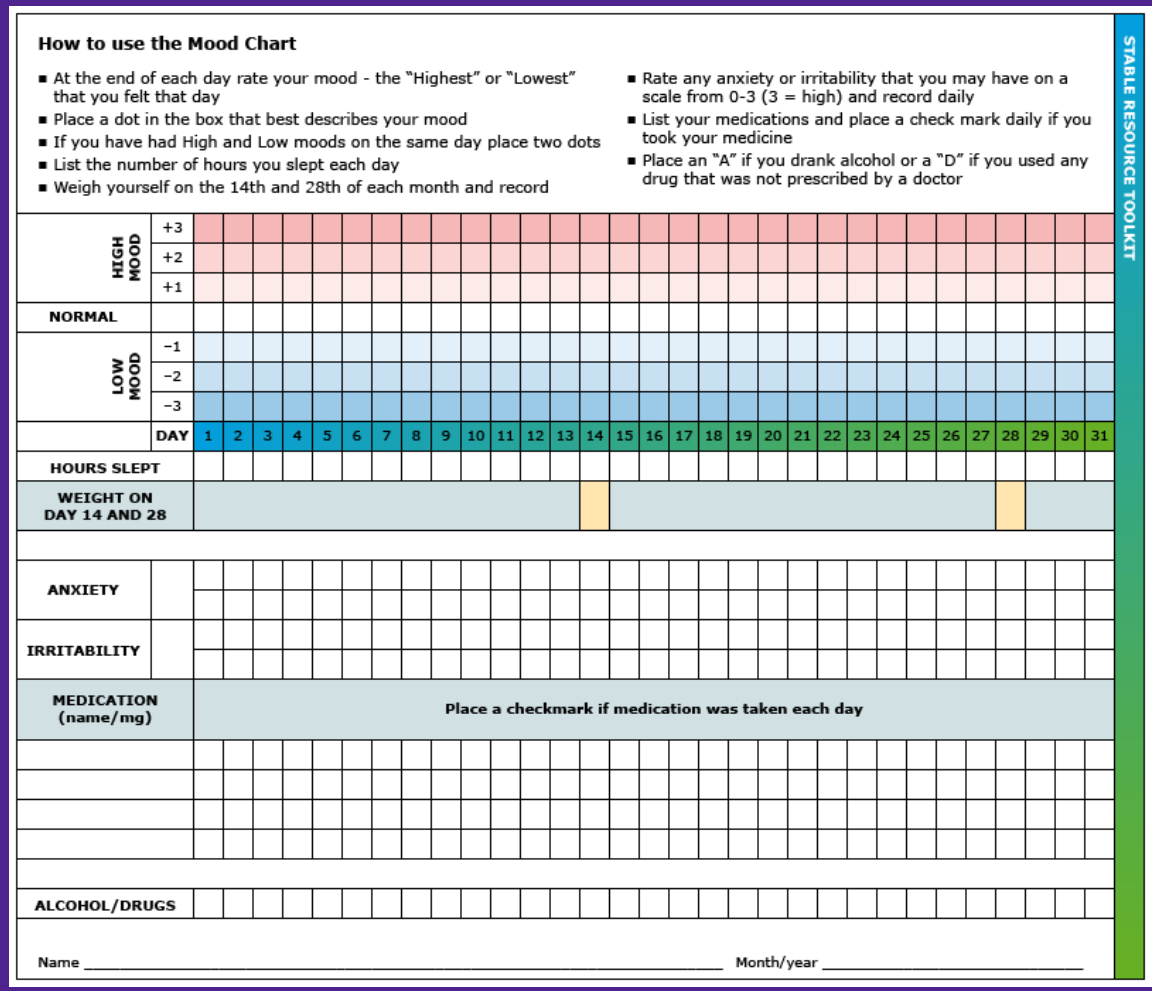


Postpartum Psychosis

- 1-2 /1000 births
- Rapid onset post-birth; bizarre delusions/ hallucinations, cognitive disorganization
- Bipolar disorder! Mania/mixed or depression with psychosis
- ECT, mood stabilizers (Lithium, atypical antipsychotic medications, antiseizure medications)
- Differentiate from obsessional thoughts *Hudak & Wisner. Clinical case conference: Postpartum obsessions and compulsions. Am J Psych 169(4):360-3, 2012.*
- Very high risk for recurrence after later births; preventive treatment is warranted

Clinical Points

1. The most common symptom in pregnant people with BD is depression or mixes state not mania.
2. The first-choice drug for pregnant person is the one that is effective (exception: valproic acid)
3. Use mood tracking monthly to engage and educate patient.
4. Plasma drug concentration monitoring (Li, LTG, CBZ).
5. Reduce dose after birth when mother is stable.
6. Engage another person close to the mother to assist in monitoring symptoms, particularly after birth



https://www.uptodate.com/contents/image?imageKey=PSYCH%2F96534

Mental Health is **Fundamental** to Health

David Satcher, M.D.

We must prioritize the mental health of the mothers of our next generation!