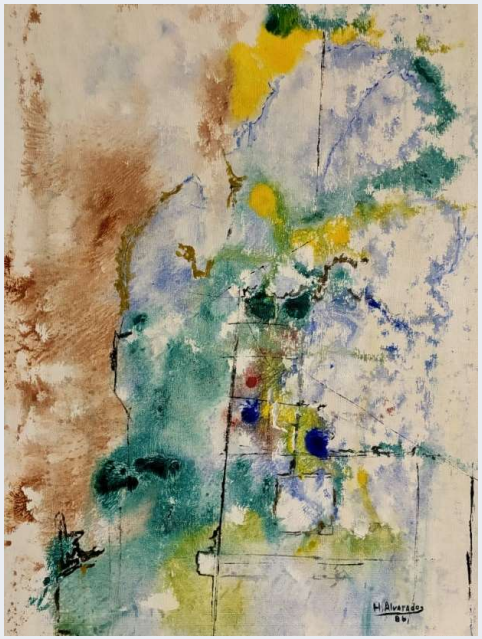
# Psychiatric Disorders During Pregnancy and Psychopharmacological Treatment



Dr. Verinder Sharma, MBBS, FRCP(C)

Professor of Psychiatry and Obstetrics & Gynaecology

Western University, London, Ontario, Canada

# Disclosures

Dr. Verinder Sharma has received grant support from the Academic Medical Organization of Southwestern Ontario, and Pooler Charitable Foundation.

# Outline

- Section 1: Epidemiology, illness course, outcomes
- Section 2: Screening, assessment, and diagnosis
- Section 3: Treatment benefits and risks
- Section 4: Changing the paradigm

# Section 1

## Epidemiology, illness course, outcomes

# Prevalence of Psychiatric Disorders in Pregnancy

- Cross-sectional survey of over 10,000 women in early pregnancy

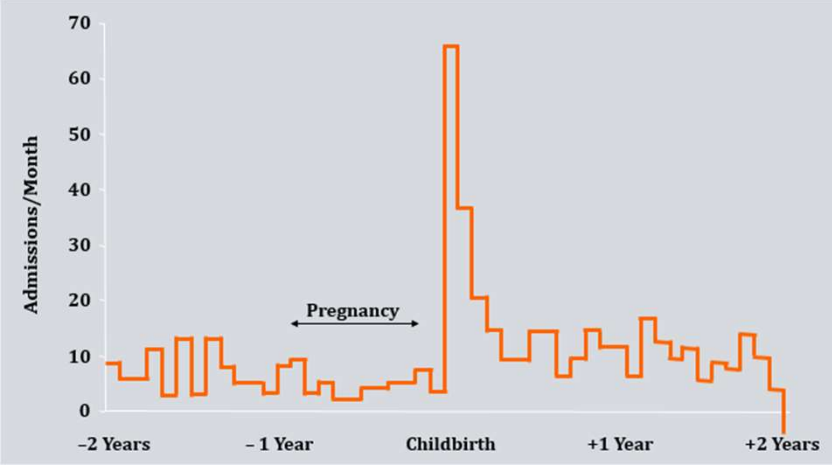
| **Population prevalence: 27% (95% CI 22-32)** | |
|---|---|
| Depressive Disorder | 11% (95% CI 8-14) (>half mild depressive disorder) |
| Anxiety Disorders | 15% (95% CI 11–19) |
| OCD | 2% (95% CI 1–4) |
| PTSD | 0.8% (95% CI 0–1 |
| Eating Disorder | 2% (95% CI 0.4–3) |
| Bipolar I Disorder | 0.3% (95% CI 0.1–1) |
| Bipolar II Disorder | 0.7% (95% CI 0–1) |

Howard LM. Br J Psychiatry. 2018;212(1):50-56

# DSM-5 Core Anxiety and Related Disorders During Pregnancy and Postpartum

| | |
|---|---|
| Core anxiety Disorders | Panic disorder, agoraphobia, generalized anxiety disorder, social phobia and specific phobia |
| Related Disorders | Bipolar I or II disorders with anxious distress, major depressive disorder with anxious distress, acute stress disorder, and illness anxiety disorder |
| | Tocophobia |

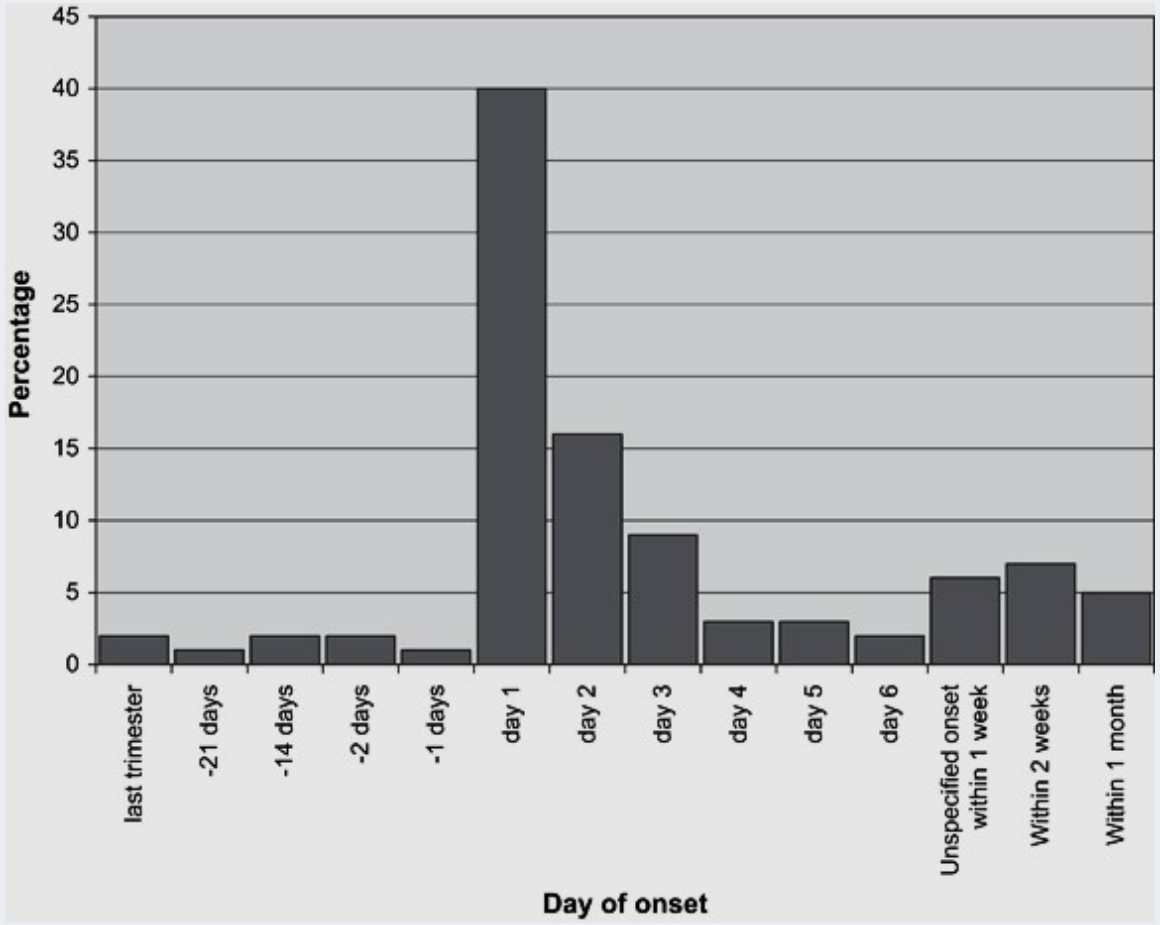
# Effect of Pregnancy on the Course of Psychiatric Disorders




- BD-median = 24%, range = 4-73%
- MDD-dynamic effect (*chronic*, delayed, *recovered*, and resilient)
  - depression symptoms appear to significantly alleviate over time, suggesting a form of recovery
- Panic disorder- protective effect
- OCD symptoms seem to intensify

Kendell et al. Br J Psychiatry 1987; 150: 662-673
Salim M et al. Arch Womens Ment Health. 2018
Bandelow et al. Eur Psychiatry.2006;7: 495-500
Dekel et al. J Psychiatr Res. 2019 Jun;113:72-78

# Pregnancy Onset of Puerperal Psychosis (N=127)




**The most recalled symptoms were:**

- feeling excited, elated, or high (52%),
- not needing to sleep or not able to sleep (48%),
- feeling active or energetic (37%)
- talking more or feeling very chatty (31%)

Heron et al. BJOG 2008;115: 348–53.

# Maternal Outcomes

Perinatal mental disorders are associated with:

- Maternal deaths ( pregnancy and 1-year after delivery) from suicide (2.30 per 100,000 live births in 2006-2012), 60% had a previous psychiatric history
  - 1.18 per 100,000 after giving birth
  - 2.77 after an induced abortion and
  - 2.90 after a miscarriage
- Substance misuse complications
- Misattribution of physical symptoms ( diagnostic overshadowing) of life-threatening complications to mental illness
- More life-threatening complications than those without mental illness

Lega et al. AWMH 2020; 2: 199–206
ACOG Clinical Practice Guideline NUMBER 4 JUNE 2023

# Obstetric and Neonatal Outcomes

Women with both common and severe mental illness have an increased risk of:

- Preterm birth
- Fetal growth restriction
- Pre-eclampsia
- Antepartum and postpartum hemorrhage
- Placental abruption
- Stillbirth

Risks elevated regardless of pharmacotherapy, are generally greater in low-middle income countries than in high-income countries, and those with obstetric risk factors (domestic violence, poor/delayed antenatal care, obesity, HT, DM, and smoking)

Howard and Khalifeh World Psychiatry 2020; 3: 313–327

# Infant and Child Outcomes

- Association of antenatal depression with childhood cognitive and behavioral problems, ADHD, and autism
- Antenatal anxiety is associated with a small increase in emotional problems in early and middle childhood, the associations are attenuated or disappear after adjustment for confounders
- Heightened risk is related to the separate and joint effects of inherited genetic vulnerabilities for psychopathology and environmental influences
- Limited evidence for direct causation……evidence largely comes from preclinical research and observational studies

Howard and Khalifeh, World Psychiatry, 2020
Aktar et al. Front. Psychiatry, 2019.

Section 2

# Screening, assessment and diagnosis

# ACOG Guidelines

- Everyone receiving well-woman, prepregnancy, prenatal, and postpartum care be screened for depression and anxiety-PHQ-9, GAD-7, EPDS

- Systems in place to ensure timely access to assessment, diagnosis, monitoring, and follow-up

- Everyone receiving prenatal and postpartum care be screened for BD-MDQ or CIDI-based BD screening scale
  - Screening for BD before initiating pharmacotherapy for anxiety or depression
  - Consult a mental health professional if BD, safety concerns (intent, planning, inability to state reasons for not proceeding with a suicide attempt)

Number 4, June 2023
(Replaces Committee Opinion 757, *Nov. 2018*)

# The Canadian Task Force on Preventive Health Care

- Recommends against screening using questionnaires due to very low–certainty evidence
- Uncertain evidence as to whether screening confers benefits above usual clinical care
- Usual care during pregnancy and the postpartum period should include inquiry and attention to mental health and well-being

Lang et al., CMAJ 2022; 194(28): E981-E989.

# Commonly Used Perinatal Mental Health Validated Screening Instruments

| PMH Condition | Screening Instrument | No. of Items/Self-Administered (Y/N) | Sensitivity and Specificity | Score for Positive Screen |
|---|---|---|---|---|
| Depression | EPDS | 10/Y | Sensitivity: 55-98%<br>Specificity: 68-97% | ≥10 |
| | PHQ-9 | 9/Y | Sensitivity: 53-77%<br>Specificity: 85-94% | ≥10 |
| Anxiety | GAD-7 | 7/Y | Sensitivity: 73%<br>Specificity: 67% | ≥5 |
| | EPDS—anxiety subscale (items 3, 4, 5) | 3/Y | Not enough data to estimate correlates with GAD-7 | ≥5 |
| | STAI | 20/Y | Sensitivity: 81%<br>Specificity: 78% | ≥40 |
| Bipolar Disorder | MDQ | 3 (Q1 with 13 items)/Y | Sensitivity: 44-90%<br>Specificity: 61-92% | ≥7 of the 13 items in Q1 |
| | CIDI | 2-3 (branching logic)/N | Sensitivity: 69-100%<br>Specificity: 98-99% | Yes to Q3 (Q3 is asked if Q1 or Q2 are affirmed) |

Byatt, N. et al. Curr. Psychiatry Rep. 2020; 22:62

# Risk Factors

## Modifiable Risk Factors

- Sleep loss/insomnia during and after delivery
- Poor sleep quality in 3rd trimester
- Chronic/physical illnesses
- Preeclampsia
- Substance use
- Unplanned pregnancy
- Bereavement
- Adolescent mothers
- Mothers of preterm babies
- Lack of social support at home
- Recent stressful life events
- Abusive or other relationship problems
- History of sexual or physical violence

## Non-Modifiable Risk Factors

- Personal history of mood or anxiety disorders (puerperal or non-puerperal)
- Family history of mood or anxiety disorders (puerperal or non-puerperal)
- Adverse childhood events/maltreatment
- PMDD or depressive symptoms while taking oral contraceptives
- Premenstrual syndrome

# Assessment

*Pre-pregnancy*

Age at onset, frequency and sequence of episodes, threshold vs. subthreshold episodes, type of symptoms (e.g. atypical), both physical and psychiatric comorbidity, psychiatric hospitalization, reproductive history, safety assessment, family history of psychiatric illness, response ( lack of response thereof or worsening) to and tolerability of medications

*Pregnancy*

Timing of symptom onset (during or before pregnancy), the impact of pregnancy on illness course, physical and psychiatric comorbidity, psychiatric hospitalization, safety assessment, response (or lack thereof or worsening), and tolerability of medications

*Postpartum*

Symptom onset (pregnancy or postpartum), type of symptoms, first onset vs. recurrence, polarity, timing of onset, duration, and course, maternal and infant safety, pharmacologic and psychotherapeutic treatment.

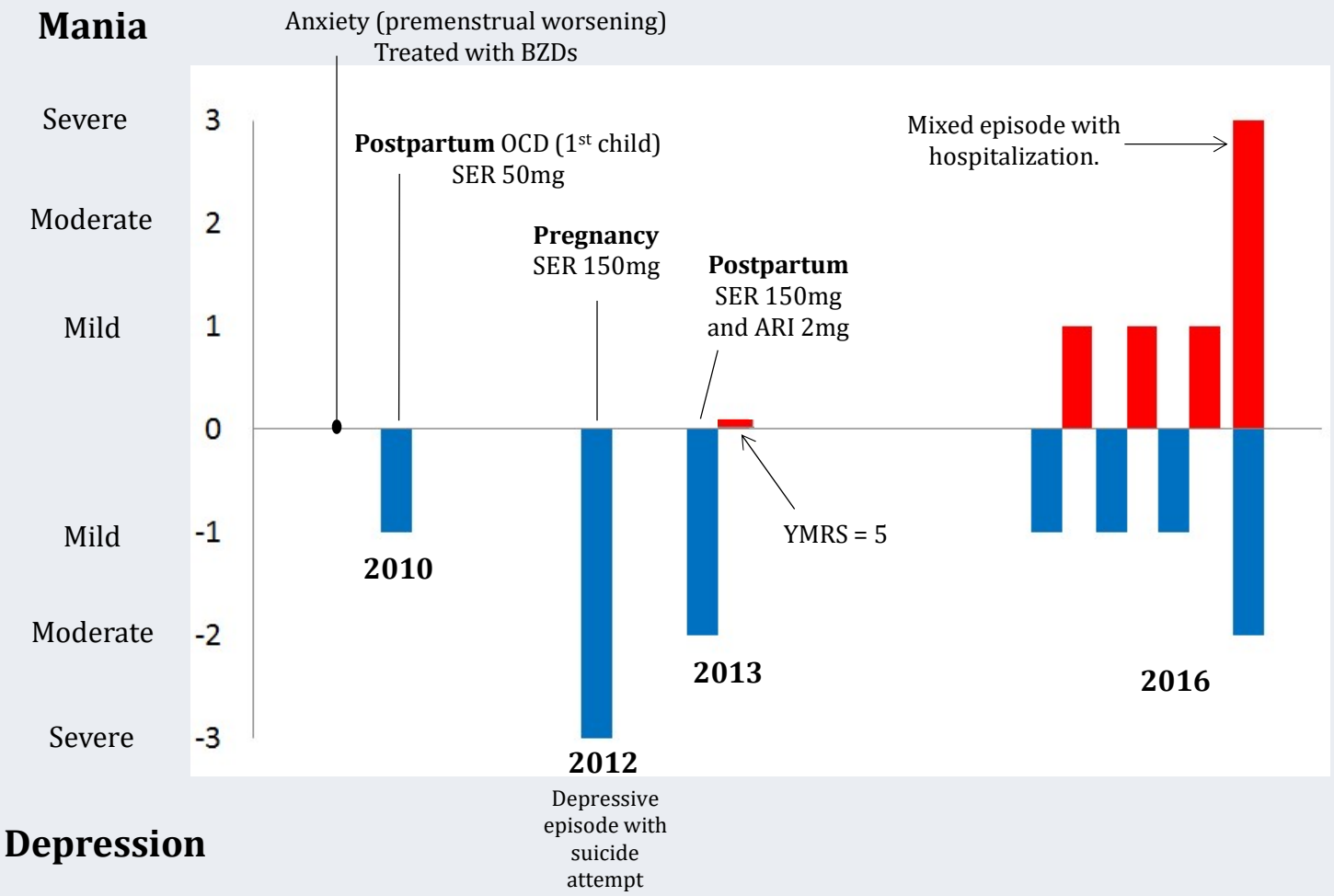
.

# Features of depression that may increase suspicion of a Bipolar Illness

| Feature | Suggestive of Bipolarity |
|---|---|
| **Symptomatology and Mental State Signs** | • Hypersomnia and/or increased daytime napping<br>• Hyperphagia and/or increased weight<br>• Other 'atypical' depressive symptoms such as leaden paralysis (extreme fatigue in arms and legs)<br>• Psychomotor retardation<br>• Psychotic features and/or pathological guilt<br>• Lability of mood; irritability; psychomotor agitation; racing thoughts |
| **Course of Illness** | • Early onset of first depression<br>• (<25 years)<br>• Multiple prior episodes<br>• (≥ 5 episodes) |
| **Family History** | • Positive family history of bipolar disorder |

Adapted from (Mitchell et al. 2008 (Ref 38), Schaffer et al. 2010 (Ref 39))

# Diagnostic Challenges




Current Medications

- LI 750mg daily
- QUE 500mg daily
- RIS 0.5mg daily

Sharma V, Al-Farayedhi, Bipolar Disord. 2023

# Suicidality During the Perinatal Period

- UK National Confidential Inquiry-a 15-year retrospective study of all people who had been in contact with psychiatric services before suicide
    - 2% of women in the perinatal period aged 16-50 years
    - 4% among women aged 20-35 years
- Perinatal suicide occurs mainly through violent methods compared to suicide in non-pregnant women
- Risk factors for suicide attempt
    - During pregnancy: ETOH use, smoking during pregnancy, and miscarriage
    - Postpartum: major depressive episode and recurrent depression

Khalifeh et al. The Lancet 2016; 3 (3): 233-42.
Orsolini et al. Front Psychiatry 2016; 7: 138. 1-6.
Gressier et al. J Psychiatr Res 2017; 84:284-291.

# Section 3

## Treatment-Benefits and Risks

# Psychotropic Drug Use before, during, and after Pregnancy: A Population-Based Study in a Canadian Cohort

- Rates of psychotropic use (ADs, anxiolytic/sedative-hypnotics, AED, AP, lithium, and stimulants) among women with a hospital-recorded pregnancy outcome were assessed in the 3-12 months before pregnancy, 0-3 months before pregnancy, during pregnancy, or 3 months after pregnancy
- From 2001 to 2013 the weighted percentage of pregnant women who received at least 1 psychotropic medication prescription
    - 1.5-fold from 11.1% to 16.2% ($p < 0.0001$) in the 3 to 12 months before pregnancy,
    - 1.6-fold from 6.4% to 10.5% ($p < 0.0001$) in the 3 months before pregnancy,
    - 1.8-fold from 3.3% to 6.0% ($p < 0.0001$) during pregnancy
- 38.5% stopped the agent before pregnancy and only 10.3% continued use throughout pregnancy

Leong et al. The Canadian Journal of Psychiatry. 2017;62(8):543-550

# Risk of Relapse of Depression During Pregnancy After Discontinuation of Antidepressants

## A Systematic Review and Meta-Analysis

- 6 studies met quality criteria and 4 studies for the meta-analysis
- Rates of D/C 3 months before or during pregnancy  22%-78%
- Pooled data did not show a higher risk of relapse who d/c'd ADs than for those who continued ADs (RR=1.74;95% CI,0.97 to 3.10; p=.06)
- Risk of relapse was sig. higher for the group with severe or recurrent depression (RR=2.30;95% CI,1.58 to 3.35) but not for the group with mild or moderate depression ( RR=1.59;95%CI, 0.83 to 3.04)
- Women with severe/recurrent depression should be informed about the increased risk of relapse following AD discontinuation, and those who discontinue AD  should be monitored for relapse.

Bayrampour et al. J Clin Psychiatry 81:4, 2020

# Interventions for Depression-NICE guidance

## Facilitated self-help/psychological intervention

- Mild-Moderate
- Moderate to severe depression- wants to stop AD

## TCA, SSRI, SNRI

- Moderate or severe in pregnancy
- H/O severe disorder
- Wants to stop and has moderate depression
  - Consider previous response, stage of pregnancy, risk of relapse, risk associated with medication

National Institute for Health and Care Excellence. *Antenatal and postnatal mental health: clinical management and service guidance*. London: National Institute for Health and Care Excellence, 2014

# Interventions for Anxiety-NICE guidance

- TCA, SSRI, or SNRI for an anxiety disorder becomes pregnant,
- discuss the following options:
- stopping the medication gradually and switching to a high-intensity psychological intervention (for example, CBT)
- continuing with medication if she understands the risks associated with the medication and the mental health problems in pregnancy and the postnatal period and:
- has expressed a preference for medication or — declines psychological interventions or — her symptoms have not responded to psychological intervention

National Institute for Health and Care Excellence. *Antenatal and postnatal mental health: clinical management and service guidance.* London: National Institute for Health and Care Excellence, 2014

# Preventing Postpartum Depression
# A Personalized Approach

- Prospective study of predictive associations between variables assessed in the third trimester and the development of PPD in 300 women
    - Women with third-trimester depression (n = 45) versus euthymia (n = 255) had a significantly higher risk for having depression after delivery (24% vs 11%, P = .013)
    - For pregnant euthymic women, third-trimester total HDRS scores significantly predicted PPD (P < .0001); specifically, scores on 3 HDRS items alone-work activities, early insomnia, and suicidality
    - AD use in the third trimester in euthymic women did not confer protection against the onset of PPD

Suri R, J Clin Psychiatry. 2017 Sep/Oct;78(8):1110-1116.

# Bipolar Disorder-NICE Guidelines

**Mania**

- Taking prophylactic medication-check the dose and adherence
- Suggest changing to an antipsychotic if taking another type of medication
- Increase the dose if the prophylactic medication is an antipsychotic
- Consider lithium if there is no response and the woman has severe mania
- consider ECT if there has been no response to lithium

**Depression**

- CBT, IPT, or behavioral couples therapy

# Effectiveness of Interventions to Prevent Perinatal Depression
# An Umbrella Review of SRs and MAs

| **INTERVENTION** | **EFFECT SIZE** |
|---|---|
| Exercise/physical activity-based | 0.43 |
| Psychological | 0.28 |
| Any type of intervention | 0.36 |

- Insufficient evidence to conclude that pharmacological interventions are effective

Motrico et al. General Hospital Psychiatry, 2023.

# Safety of Psychotropic Drugs

- Untreated psychiatric illness also carries substantial risks for the mother, fetus, infant, and family
- SSRIs or SNRIs are not associated with higher rates of birth defects or long-term changes in mental development after adjustment for confounding psych. illness factors
- Lithium exposure is associated with an increased risk for fetal cardiac malformations, but the risk is lower than previously thought (absolute risk of Ebstein's anomaly 6/1,000)

Betcher, HK and Wisner, KLJ Womens Health (Larchmt) 2020; 29(3):310-318

# Safety of psychotropic drugs

- Antipsychotics
  - other than risperidone and potentially paliperidone, have not been associated with an increased risk of birth defects;
  - olanzapine and quetiapine have been linked with ↑ risk of GD

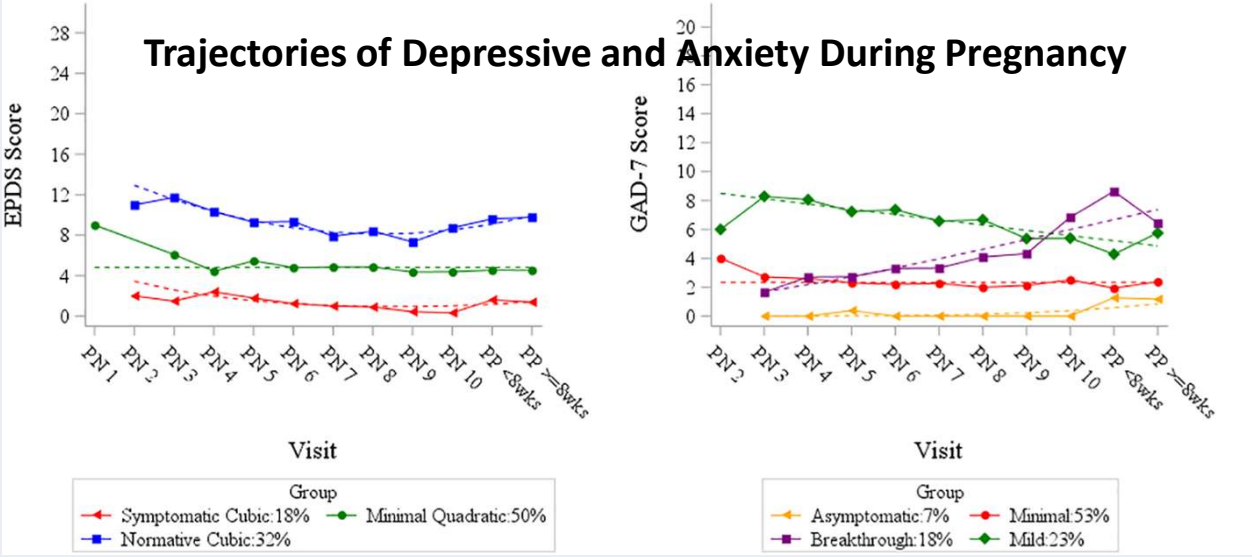
- Due to the physiological changes in pregnancy and enhanced hepatic metabolism, drug doses may need to be adjusted during pregnancy to maintain effectiveness

# Section 4

## Changing the paradigm

# Trajectories of Depressive and Anxiety During Pregnancy

- A prospective longitudinal observational study of pregnant women interviewed at baseline (≤18th gestational week), every four weeks through delivery and at 6 and 14 weeks postpartum
- 18% minimal (<5 on EPDS), 50% mild (5 on EPDS), and **32% subthreshold ( 8-11 on EPDS) despite maintenance treatment with SSRIs**

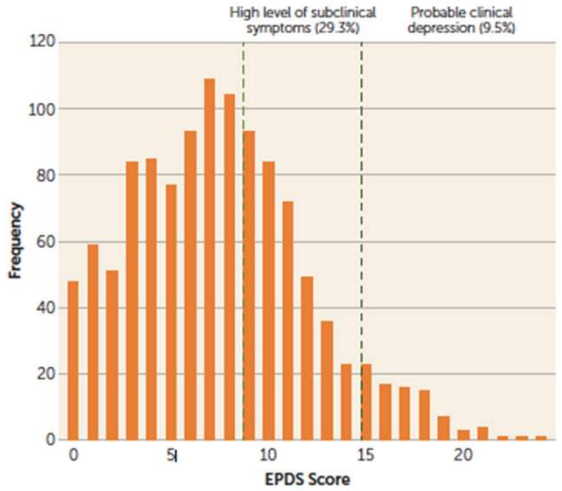



Mesches et al., Psychiatr Res Clin Pract. 2022; 4(2): 32-41.

# Subclinical Symptoms During Pregnancy



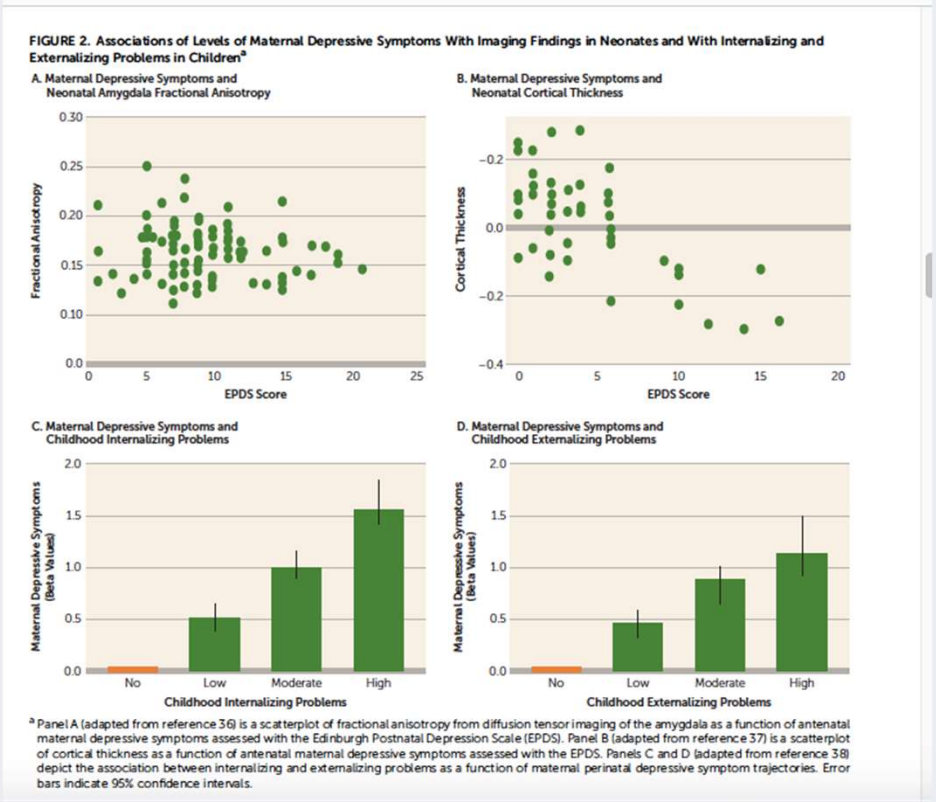
**FIGURE 1. Distribution of Maternal Scores on the Edinburgh Postnatal Depression Scale (EPDS) in the Growing Up in Singapore Towards Healthy Outcomes Cohort (N=1,143) at 26 Weeks of Gestation[a]**




[a] Probable clinical depression and high subclinical levels of depressive symptoms are based on established cutoffs (scores of 15 or more and of 9 to 13, respectively. The mean score was 7.5 (SD=4.5). The estimated portion of "probable cases" in this study is comparable to those of studies in North American and Western Europe.

Meaney MJ, Am J Psychiatry; 175:1084-1093.

# EPDS Symptoms During Pregnancy and Imaging Findings in Neonates




Meaney MJ, Am J Psychiatry; 175:1084-1093.

# Categorical and Dimensional Approach

## DSM-5 Level 1 Cross-Cutting Symptom Measure

- More in-depth information on potentially significant symptoms

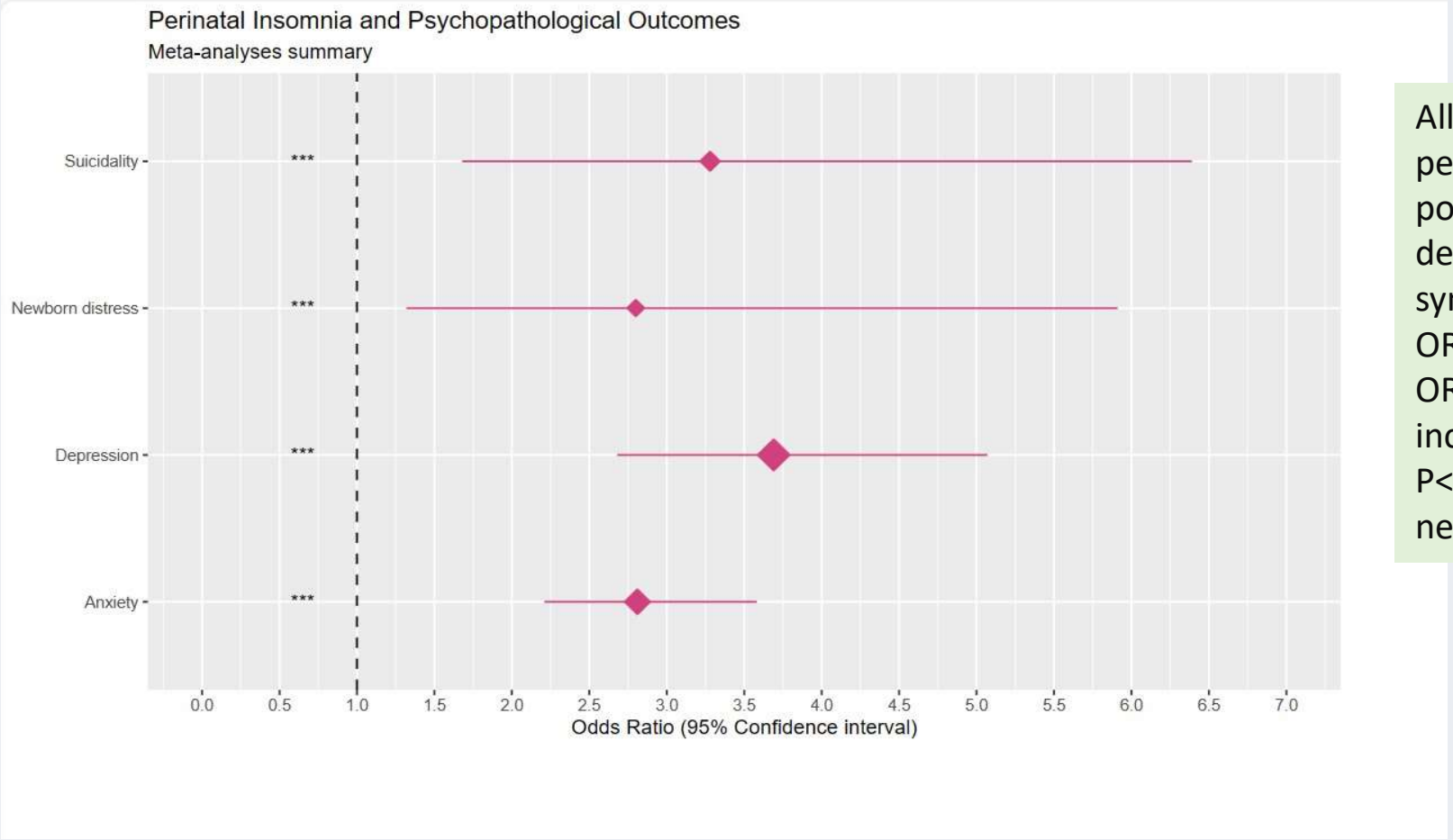
- 23 questions that assess 13 psychiatric domains: depression, anger, mania, anxiety, somatic symptoms, SI, psychosis, memory, repetitive thoughts and behavior, dissociation, personality functioning, and substance use

- Each domain has 1 or 2 questions—during the past 2 weeks, how much or how often have you been bothered by the following problems?
    - Feeling irritated, grouchy, angry than usual?
    - 0-4 (none, slight, mild, moderate, and severe)
    - For most domains, a rating of 2 or greater requires additional inquiry and follow-up

American Psychiatric Association. (2022). *Diagnostic and statistical manual of mental disorders* (5th ed., text rev.). https://doi.org/10.1176/appi.books.9780890425787

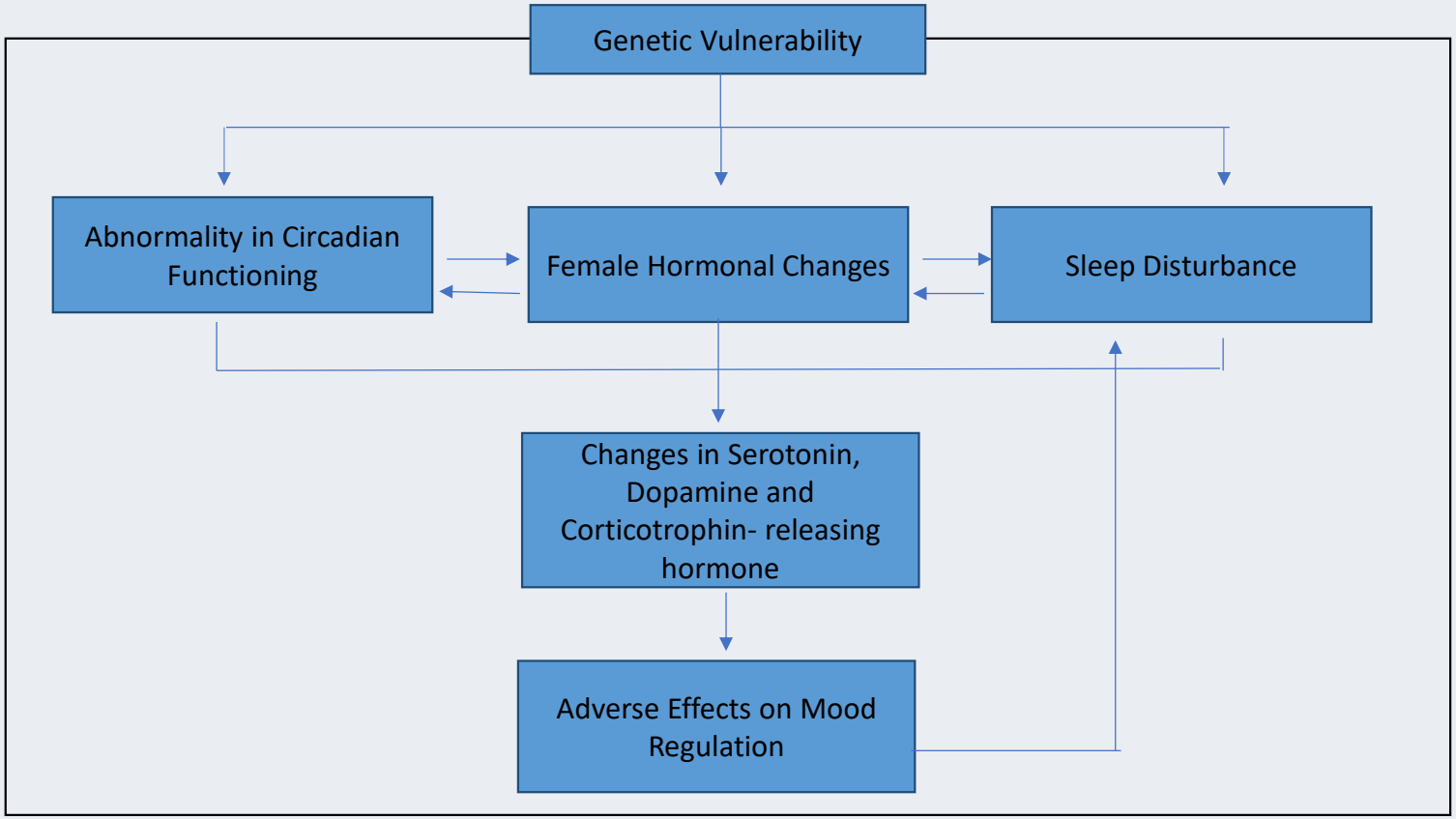
# Insomnia during the perinatal period and its association with maternal and infant psychopathology: a systematic review and meta-analysis

Palagini L, Cipriani E, Bramante A, Gemignani A, Sharma V, Riemann D, Current Psychiatry Reports 2023




All models show that women with perinatal symptoms of insomnia possess increased odds of developing clinically relevant symptoms of depression OR = 3.69, P= 0.001 and anxiety OR = 2.81; P< 0.001, as well as increased suicidality OR = 3.28; P< 0.001, and distress in the newborn OR = 2.80 ( p = 0.007).

# Relationship Between Sleep, Female Sex Hormones, Circadian Functioning, and Mood Regulation




Harvey et al., Am J Psychaitry, 2008.

# Insomnia treatment in the third trimester of pregnancy reduces postpartum depression symptoms: an RCT

- 54 pregnant ( 26-30 weeks) women with insomnia were randomly assigned to trazodone, diphenhydramine, or placebo treatment.
- Sleep quality was measured by actigraphy at baseline, and after 2 and 6 weeks of treatment.
- Depression was assessed 2 and 6 weeks after delivery.
- Trazodone and diphenhydramine improved sleep profile compared to placebo after 6 weeks of treatment.
- Depressive symptoms were reduced 2 and 6 weeks after delivery in trazodone and diphenhydramine groups compared to placebo.
- No differences in depressive symptoms were observed between the trazodone and diphenhydramine groups

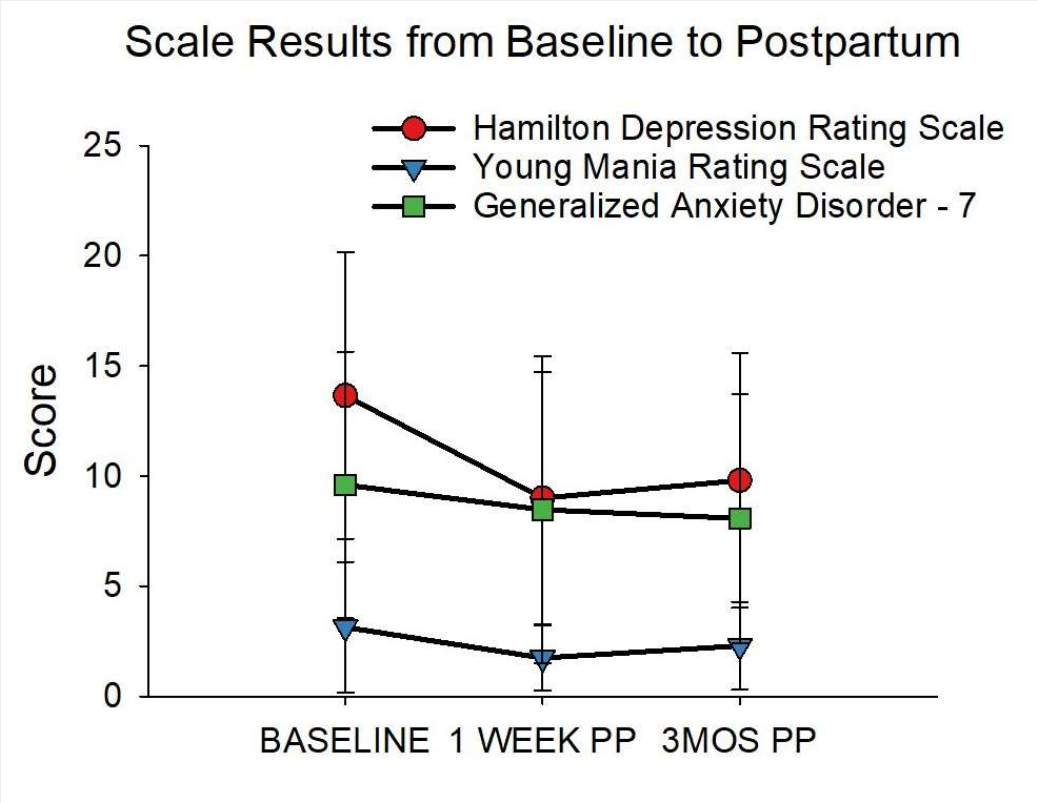
Khazaie H, et al. Psychiatry Res. 2013 Dec 30;210(3):901-5. doi: 10.1016/j.psychres.2013.08.017. Epub 2013 Aug 30. PMID: 23993464.

# A Pilot Study on the Prevention of Bipolar Disorder after Delivery

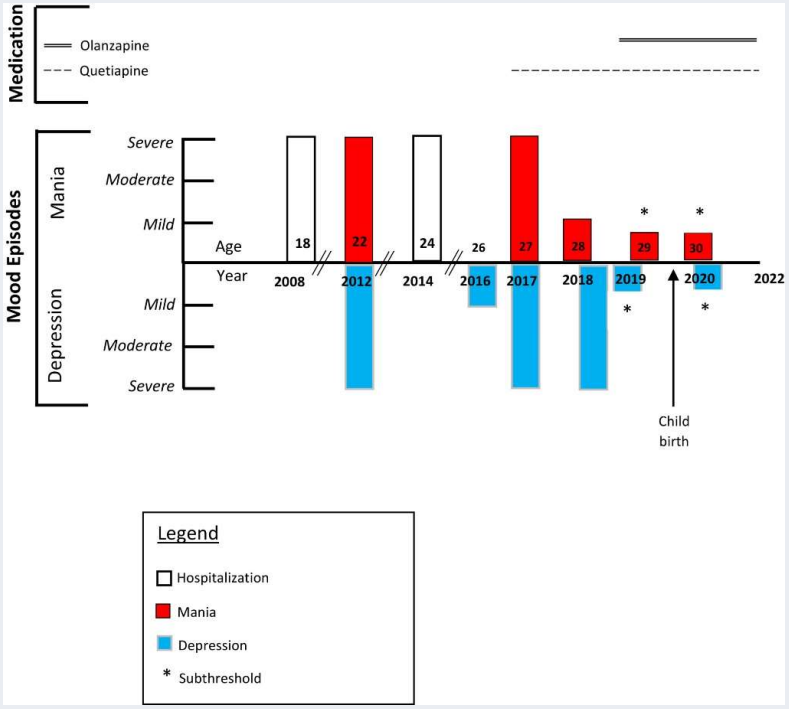
- Pregnant women, aged 18-45 years, with a gestation of 15-37 weeks and a known family history of BD or subsyndromal hypomania were invited to participate.
- Prevention strategies include:
  1. Psychoeducation about the effect of pregnancy and postpartum on the course of bipolar disorder
  2. Role of sleep loss/insomina as a trigger of perinatal mood episodes
  3. Avoidance of antidepressants
  4. Early identification and treatment of prodromal/early symptoms of hypo/mania with atypical antipsychotic drugs

| | Initial Visit | Pregnancy Visits (every 4wks) | Postpartum Visits (1wk, 2wks, 2mo, 3mo) |
|---|---|---|---|
| **Scales** | • SCID-5 (DSM-5)<br>• Psychoeducation<br>• HDRS<br>• YMRS<br>• GAD-7 | • HDRS<br>• YMRS<br>• GAD-7 | • HDRS<br>• YMRS<br>• GAD-7 |

A Pilot Study on the Prevention of Bipolar Disorder after Delivery



# Prevention of Postpartum Recurrence in a Primigravida with Bipolar I Disorder




Sharma, V. and Subramanian, P., Bipolar Disord. First published: April 25 2023, DOI: (10.1111/bdi.13329)

# Conclusion

- Both threshold and subthreshold psychiatric disorders are common during pregnancy
- Pregnancy appears to have a pathoplastic effect on the illness course
- Consider using a categorical and dimensional approach to assess and treat
- Early identification/management of emerging psychopathology is necessary to prevent recurrences
- A transdiagnostic approach to treatment has the potential to improve maternal and child/infant outcomes