Why do We Let Mothers Suffer?

Comparing Exposure to Antidepressants vs Exposure to Illness in Perinatal Depression

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Faculty/Presenter Disclosure

- **Faculty/Presenter: Dr. Sanjeev Bhatla**

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Objectives

1. To understand the risks of untreated depression on pregnancy.
2. To understand the risks of SSRI medications on pregnancy.
3. To suggest that the indications for SSRI use in the treatment of perinatal depression be similar to non pregnant patients.

What does the Google God say ? ...

SSRI Effects

- Miscarriage?
- Hypertensive Disorders?
- Prematurity?
- LBW?
- SGA?
- Decreased APGARs?

SSRI Effects

- Teratogenicity? (Cardiac)
- Persistent Pulmonary Hypertension?
- Neonatal “Withdrawal”? “Poor Adaptation”? “Distress Syndrome”?
- Developmental Delay?
- ASD?

Teratogenicity (Cardiac)

- GlaxoSmithKline. New safety information regarding paroxetine: findings suggest increased risk over other antidepressants of congenital malformations following first trimester exposure to paroxetine. GSK advisory September 2005.

And so…

- Health Canada endorsed important safety information on Paxil (paroxetine) and possible increased risk of birth defects. Health Canada advisory October 2005. Ottawa, Ont.

Teratogenicity cont'd

- Advisory was based on retrospective, unpublished, non-peer-reviewed studies[1]
- A dizzying number of studies have conflicting conclusions
- 3 published peer-reviewed studies have refuted the association[2-4]
- Majority of VSDs close spontaneously.
- Background risk < 2/1000, therefore any increased risk would be minimal.
- Any risk would be limited to first trimester exposure.
- ...Studies have shown an association between untreated depression and cardiac malformations[5]

Teratogenicity cont'd

2013 meta-analysis: [6]

"Overall, antidepressants do not appear to be associated with an increased risk of congenital malformations, but statistical significance was found for cardiovascular malformations"...

Relative Risks were "marginal", "none reached clinically significant levels"

PPHN

- Chambers et al. NEJM, 2006:
  - Association with SSRI use after 20 weeks
  - Non-exposed 1/700 vs SSRI 7/1000 (OR= 6.1)
  - No fatalities
  - Small study
- Kieler et al. BMJ, 2011
  - Base rate 1.2/1000 increased to 3/1000
  - Small study

Conflicting results from different studies

- ...Studies have shown an association between untreated depression and PPHN[5]

PPHN cont'd

2014 meta-analysis: [7]

"The risk of persistent pulmonary hypertension of the newborn seems to be increased for infants exposed to SSRIs in late pregnancy"...

"An estimated 286 to 351 women would need to be treated with an SSRI in late pregnancy to result in an average of one additional case of persistent pulmonary hypertension of the newborn"

Poor Neonatal Adaptation Syndrome

- Jitteriness, poor muscle tone, weak cry, respiratory distress, feeding problems, hypoglycemia, seizures, need for respiratory support
- Usually mild, transient, resolves in days to 2 weeks (typically 1-2 days)
- Incidence? 15%? 30%?
- Need to consider exposed vs non-exposed
  - Respiratory distress 13.9% vs 7.8%
  - Feeding problems 9.4% vs 7.5%

    (Oberlander TF et. Gen Psych 2006)

PNAS cont'd

2013 meta-analysis: [8]

"An increased risk of PNAS exists in infants exposed to antidepressant medication during pregnancy"

- Odds ratio PNAS 5.07
- Odds ratio respiratory distress 2.2
- Odds ratio tremors 7.89

Developmental Delay

- No difference in IQ, language, behavioral development (several studies).
- Association with later gross motor developmental milestones, within normal range, catch up by 19 months (Pedersen, et al Pediatrics, 2010).
- **No demonstrable significant development delay**[5]

ASD

- Association of ASD made in a retrospective, population-based, case-controlled study (Croen LA, et al. Arch Gen Psych, 2011).
- 2013 cohort analysis of 668,468 children in Denmark: [9]

  "After controlling for important confounding factors, there was no significant association between prenatal exposure to antidepressant medication and autism spectrum disorders in the offspring."

What Else Came Up on Google?

What about the effects of depression on maternal and child health? ...

Risks of Depression

- Miscarriage?
- Hypertensive disorders?
- Prematurity?
- LBW?
- SGA?
- Decreased APGARs?

Risks of Depression

- Impaired maternal-infant bonding?
- Poor latching to breast?
- Attachment disorders?[10]
- Social, cognitive, and Emotional Development?
- Neglect and Abuse?
- Increased risk of child/adolescent depression?[11.12]

“Mr. Osborne, may I be excused? My brain is full.”

Gary Larson

?

Confounding array of…

CONFOUNDING FACTORS

(SES, Substance/alcohol use, co-morbidities, severity of depression, medication adherence, OTC medication, timing of exposure, ascertainment bias…)

But…..

What do we **Know**?

"Decades of rigorous science across multiple disciplines indicate perinatal depression and anxiety can negatively impact the maternal-child relationship, as well as, the developmental, social, and emotional state of the child".(Center on the Developing Child, Harvard University, 2009)

What else do we **KNOW**?...

Depression in Pregnancy

- Incidence similar to non pregnant[13,14]
  - 14.5%, 7.5% MDD
- Prevalence[13-15]
  - 8.5-11%, 3.1-4.9% MDD
- Five-fold increased risk of **recurrence** in pregnant women who discontinued medication as compared to those who maintained[16]
- Strongest risk factor for postpartum depression[17]

What else do we know?...

Depression

- Delayed treatment increases treatment resistance
- Delayed treatment increases recurrence rate

What else do we know?...

Depression

ANGUISH

PAIN

SUFFERING

But do Meds really Work??

- Who is the author?
- Which journal published it?
- Who sponsored it?
- How did they choose to define mild, moderate, severe?
- How was “improvement” defined?
- Good luck!...

PHQ-9 Depression Questionnaire

Over the last two weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
Trouble falling or staying asleep, or sleeping too much	0	1	2	3
Feeling tired or having little energy	0	1	2	3
Poor appetite or overeating	0	1	2	3
Feeling bad about yourself, or that you are a failure, or have let yourself or your family down	0	1	2	3
Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
Moving or speaking so slowly that other people could have noticed? Or the opposite, being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
Total ___ =	_____	+_____	+_____	+_____

PHQ-9 Score ≥10: Likely major depression.

Depression score ranges:
5 to 9: mild
10 to 14: moderate
15 to 19: moderately severe
≥20: severe

PHQ-9 Details

- Were PHQ Scores used in studies for classifying depression? (not what the PHQ was designed for)
- A score that might be classified as “mild depression” is unlikely to be true MDD
- A score that might be classified as “moderate depression” may or may not be true MDD
- So, what is the validity for an intervention that has been shown to be effective for “mild to moderate depression” defined by a PHQ score?

Severity is key

National Institute of Mental Health (JAMA 2010;303(1):47-53:

Meta-analysis of 6 trials (718 patients):

- HAM-D </= 18: NNT 16
- HAM-D 19-22: NNT 11
- HAM-D >/= 23: NNT 4
- **BENEFIT PROPORTIONAL TO SEVERITY**

What About Exercise?

BMJ 2013:347:f5585:

- Review from the Cochrane Library
- 35 trials, 1356 patients

➢ Trials considered high quality: “effect of exercise was small and not statistically significant”

But do meds work in Pregnancy?

- Are they as effective in pregnancy ? …YES[18]
- Is there **evidence** that the treatment of depression in pregnancy prevents the associated poor child development outcomes? (studies pending, but what if, for now, an intelligent leap of logic is the best we can do?…)

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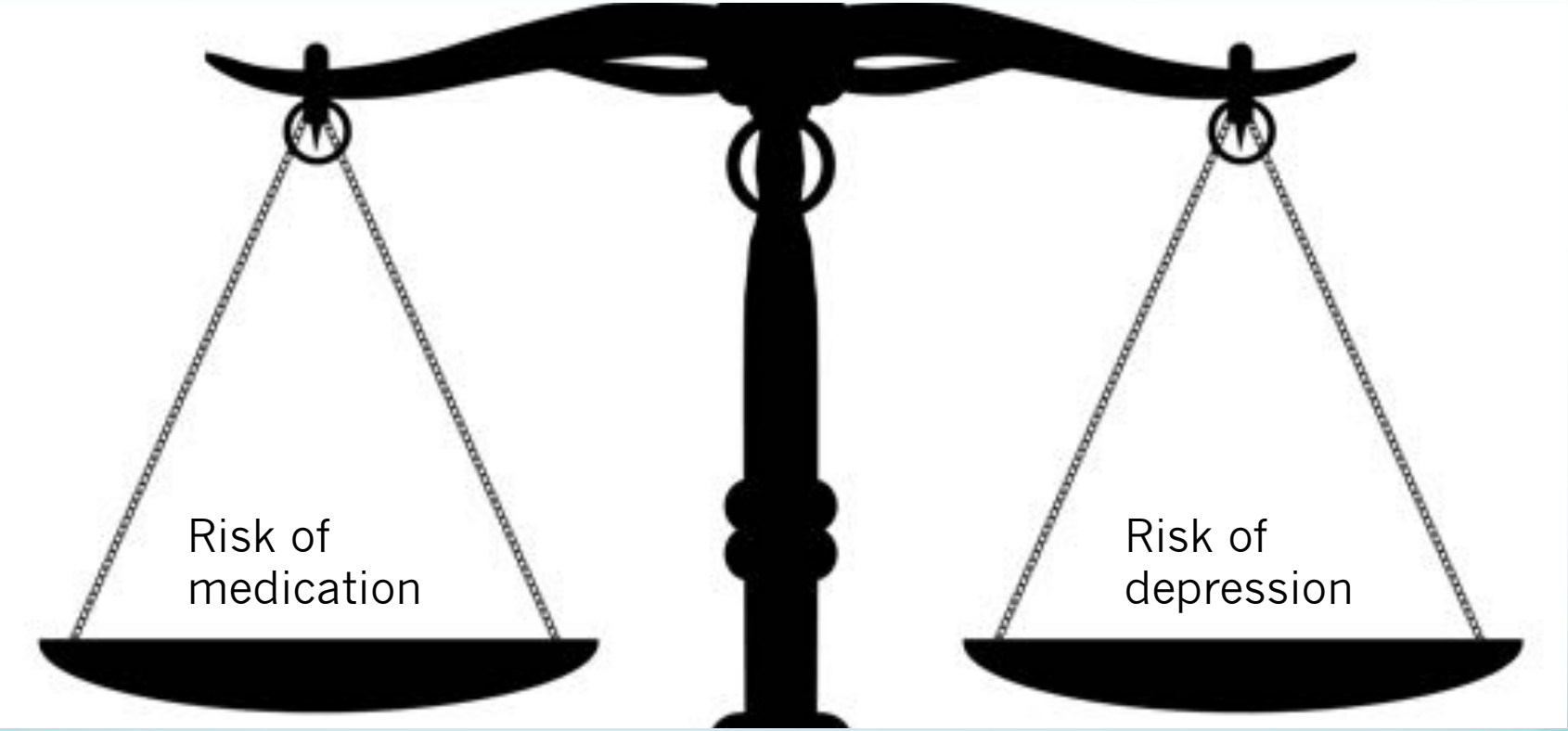
Avoiding Exposure is not an Option



Difficult Choice?

What would YOU choose if you were 3 months old???

Still Face Experiment:

https://www.youtube.com/watch?v=apzXGEbZht0

Motherisk's Choice

"A growing body of literature suggests that the risks of adverse effects of untreated depression is high. Because Selective Serotonin Reuptake Inhibitors have been shown to be safe in pregnancy, the risk-benefit ratio is clear"[19]

Motherisk

To date, antidepressants are the most studied drugs during pregnancy, with more than 30 000 outcomes examining increased risks of adverse effects on exposed infants. The results of the studies can appear to be conflicting owing to differing interpretation of statistical analysis and subsequent knowledge transfer and translation of the information. However, there does not appear to be a clinically significant increased risk of any of the adverse outcomes reported in peer-reviewed published studies that would preclude a woman from taking a needed antidepressant during pregnancy[20]

Objectives and Case Re-Visited

1. To understand the risks of SSRI medications on pregnancy.
2. To understand the risks of untreated depression on pregnancy.
3. To suggest that the indications for SSRI use in the treatment of perinatal depression should be similar to non pregnant patients.

and so...

Conclusion

There is no need to let mothers suffer

Discussion

- Medication perspective:
  - It is a **trial**
  - We could re-visit the decision after seeing what the effect of medication is
  - Decision is not “forever”
  - “But what if it really helps and I can’t come off the medication?..”
  - Offer to make a parallel with ANY other health condition (etiology and treatment)
  - ?Harmful neurobiological substrates of the Illness[21,22]

Discussion cont'd

- "Would physicians question the logic of providing thyroid replacement?"...physicians generally assume that the risk of the chemical imbalance outweighs the risk of correcting the imbalance. What's the difference for neurochemistry? ....**inadvertent stigmatization**

Discussion cont'd

- Given that sound decision-making can be challenged by depression, how can the ethical physician abstain from giving non-ambivalent treatment advice?
- Do we hide behind "First do no harm" to avoid the risk of giving our patients medication that may get blamed for an adverse outcome?
- Concept of "borrowed confidence"
- How many patients have ever looked back and said "I wish I had never tried that medication"?

Resources/References

- Motherisk: www.motherisk.org/women/drug
- Center on Developing Child, Harvard University: www.developingchild.harvard.edu
- Massachusetts General Hospital Center for Women's Mental Health: www.womensmentalhealth.org
- http://www.mothertobaby.org

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