Drugs in Pregnancy: Feeling Queasy

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Faculty/Presenter Disclosure

- **Faculty/Presenter:** Adrienne Lindblad
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- Some SSRI slides courtesy of Tina Korownyk

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Learning Objectives

- By the end of this session, participants will be able to:
  - Deliberate on the efficacy and safety of 4 medications for nausea and vomiting in pregnancy (ondansetron, doxylamine/pyridoxine, pyridoxine, ginger).
  - Describe the evidence for fetal cardiac harm of SSRI use in pregnancy.
  - Discuss with a patient whether omega-3's in pregnancy can decrease atopy in offspring.

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Perspective

- ~4% babies born with major congenital birth defect
- 65% have unknown etiology
- "chemically induced" defects (including drug exposure) "probably account for <1% of all birth defects".
- ~20 drugs or groups of drugs are recognized as increasing risk when used clinically in humans.

https://www.fda.gov/downloads/Drugs/.../Guidances/ucm071645.pdf
accessed 15-MAR-2017

Breaking Bias

- Recall bias
- Predisposition bias
- Detection bias
  - Example: 30% increase ultrasounds on SSRIs
- Sample size inadequate
- Severity of malformations unknown
- Data on spontaneous abortions rare

Clin Ther. 2007;29:918-26.

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Nausea and Vomiting of Pregnancy

Diclectin

- Five systematic reviews on antihistamine safety, 22-37 observational studies, 17,00-50,000 women exposed to antihistamines.[1-5]
  - No risk of fetal malformations with doxylamine [example OR=0.94 (0.80-1.10)].[2]
  - 4 systematic reviews have industry connections.[1,3-5]
- Childhood cancer: 2 case-control studies, increased risk with longer use (ie. >10 weeks), but no risk when based on mother-reported use.

[1]Am J Perinatol. 1997 Mar;14(3):119-24.
[2]Am J Perinatol. 2014 Sep;31(8):701-10. Epub 2013 Dec 9.
[3]Drug Saf. 2016 Nov 22. [Epub ahead of print]
[4]Drugs. 2000 Apr;59(4):781-800.
[5]Teratology. 1994 Jul;50(1):27-37.

But does it work?

- Industry-sponsored (n=259), placebo-controlled, double-blind RCT:[1]
  - Statistically different mean change in 15-point nausea and vomiting scale at day 15: -0.90 (-1.55, -0.25). Clinical significance unknown
  - No significant change in individual nausea, vomiting or retching scores.[2]
  - 1 point improvement on 10-point global assessment (2.8 versus 1.8).
  - More compassionate use requests after study over (48.9% versus 32.8%)
  - Potential selective reporting of outcomes.

[1]Am J Obstet Gynecol. 2010;203:571:e1-7.
[2]Am J Obstet Gynecol. 2016 May;214:664-6.

But does it work?

- Industry sponsored (n=2359) from 1970's; 8 arms (pyridoxine, doxylamine, dicyclomine, placebo and combinations)
  - Overall effectiveness (78% versus 57%), nausea (75% versus 52%), but not vomiting (73% versus 66%) when physician evaluated.
    - Patients rated doxylamine/B6 better on nausea and vomiting.
  - Drowsiness: 5.6% versus 3%, number need to harm=38.
  - Limitations: no demographics, high attrition (only 66% completed study), questionable data integrity (included potentially falsified data), possible selective reporting, inadequate adverse event reporting.

PLoS One. 2017;12(1):e0167609.

B6 Alone

- 4 Systematic reviews.[1-4]
- Vit B6 "difficult to interpret". Sometimes it was active intervention, sometimes control. Sometimes taken in addition to intervention.[1]
- 2 RCTs compared to placebo: no difference when combined.
  - One: Change VAS nausea score better with B6: 2.9 vs 2 and less vomiting (1.2 vs 0.65, P=0.055).
  - Other: severe nausea better with B6: 4.3 vs 1.8 and less vomiting episodes (OR=0.30, 0.10-0.89).
- 1 RCT compared high dose (10 mg) to low (1.28mg); high dose better (change on 1 on PUQE score)
- 1 RCT from Iran found dimenhydrinate better
- 1 RCT from Malaysia found no difference from mint tictacs (placebo)
- 8-way: only improved nausea as per MD.

[1]Matthews CDSR, [2]Festin BMJ Clin Evid, [3]McParlin JAMA, [4]O'Donnell HTA

Ginger

- 7 Systematic Reviews of RCTs, no meta-analysis (example Cochrane: 12 efficacy outcomes, 8 positive). At best:
  - Improves nausea and vomiting by ~4 points on a 40-point scale compared to placebo
  - Stop vomiting for 1 in 3 women at 6 days.[1]
  - Similar efficacy to B6 (4 RCTs), ondansetron and doxylamine/ pyridoxine (1 RCT each).
- Largest cohort (n~1000): no fetal harm[2]
- Smaller cohort (441 women): trend to more stillbirths (2.7% vs 0.3%) and major malformations (3.3% vs 0.7%).[3]

[1]CDSR 2014;3:CD007575.
[2]Eur J Clin Pharmacol. 2013;69:269-77.
[3]J Obstet Gynaecol. 2015;35:125-30.

Ondansetron

- Cleft palate (5 studies): 1 study found increased risk, 1 found trend to risk, 1 found prevented and 2 found nothing.
- Renal defects (2 studies): both found increased risk based on small numbers of cases (renal agenesis/dysplasia or obstructive defects).
- Heart defects (3 studies): 2 studies found increased risk, likely septal defects. Largest harm study is unpublished.
- 3 studies found no risks at all.
  - Including one using same databases as big heart defect study.
- Bottom-Line: Ondansetron may pose a small risk, particularly of cardiac or renal defects, but the effects are inconsistent and the severity of these defects is unknown.

Future TFP. Obstet Gynecol. 2016 May;127(5):878-83.

But does it work?

- 3 systematic reviews on similar 3 studies, all vs metoclopramide:
  - 2 RCTs (n=70 and 160): no difference
  - 1 RCT (n=83): inconsistent
    - Nausea:
      - Days 1 and 7: no diff
      - Day 3: ondan better 5.4 vs 6.0 on VAS, p=0.024
    - Vomit: favours metoclopramide (by ~1 point)
- RCT compared to doxylamine/pyridoxine (n=36):
  - Ondansetron better for nausea, no difference vomiting.

Matthews CDSR. 2014;3:CD007575.
BMJ Clin Evid. 2014;03:1405.
O'Donnell. HTA 2016;20(74).

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So What to Use?

- "There is a lack of high quality evidence to support any particular intervention"
  - CDSR 2015;9:CD007575.
  - This is NOT saying none of them work.
- Questions about ondasetron safety remain.
  - If there is a risk, it is small.
  - Awaiting published research…
- Consider cost, availability, tolerability.

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Serious Shortage of Reliable Info & Cardiac Malformations

- 1 new cohort and 9 systematic reviews.[1-10]
- 5 suggest effect is important.
  - Including one sponsored by industry.[4]
- 5 suggest the effect is not important[1,5,6,8,10]
  - 4 have ties to industry[1,5,6,8]
  - Other only included 4 studies[10]

[1]J Clin Psychiatry 2013;74(4):e293-e308. [2]Aust N Z J Psychiatry 2013 47:1002 [3]Daru. 2012 Nov 1;20(1):75. [4]Birth Defects Res A Clin Mol Teratol. 2010 Mar;88(3):159-70 [5]J Obstet Gynaecol Can. 2008 Aug; 30(8):696-701 Clin Ther. 2007 May;29(5):918-26. [7]PLoS One 2016;11(12):00165122. [8]J Obstet Gynaecol Can. 2013;35(4): 362-9. Br J Clin Pharmacol. 2015;81(4):589-604. [10]J Am Heart Assoc. 2015;4:e001681.

Are women with depression at higher risk?

- Cohort 949,504 women, 6.8% antidepressants 1st trimester. Association with cardiac defects attenuated with increasing adjustment for confounding:
  - Unadjusted: RR 1.25 (1.13 to 1.38), NNT = 558
  - Restricted to depression: RR 1.12 (1.00 to 1.26)
  - Fully adjusted & depression: RR 1.06 (0.93 to 1.22)

N Engl J Med. 2014 Jun 19;370(25):2397-407.

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Does pregnancy have a protective effect on depressive relapse?

1) Cohort 201 high-risk women· Depression relapse with antidepressant discontinuation proximate to conception[1]:
   - 68% vs 26% NNT = 3 (p<0.0001)
2) Cohort 778 women with hx of depression in past 5 years: no difference if on SSRI or not.[2]

1) JAMA. 2006 Feb 1;295(5):499-507. 2) Epidemiology. 2011 Nov;22(6):848-54

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Fish Oil and Atopy in Offspring

- Cochrane Systematic Review: 8 RCTs, 3366 pregnant women.
  - Mostly, 400-4500mg Fish Oil OD, start gestation week 20-30.
  - 76 meta-analyses: 6 significant, with 4 based on ≥2 RCTs, at 1-3 yrs.
    - Any allergy: RRR 34%, NNT=23 & Eczema: RRR 39%, NNT=23
    - Plus skin prick tests for eggs and any allergen
- 6 individual RCTs: Inconsistent
  - 695 x6 yrs:[5] Persistent wheeze/asthma, RRR 31%, NNT 15.
    - Nothing else positive!
  - 706 children x3 years:[6,7] Non-significant reduction in many outcomes,
    - Example: Any allergic disease with sensitization: RR 0.78 (0.58-1.06)
  - Rest trickier: E.g. In 533, fish oil better than olive but same as nothing!
- **Bottom-Line**: Fish oil in pregnancy is likely ineffective at preventing allergic disease in offspring as decreases in either eczema, food allergies or asthma in one study are generally not found in others and any positive effects seem to wane over time. Enthusiastic mothers could try fish oil supplements from ~20th week of gestation to delivery to prevent allergic disease in, at best, one in ~20 children.

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N Engl J Med 2016;375:2530-9. J Allergy Clin Immunol 2003; 112: 1178-84.; Acta Paediatr 2009; 98: 1461-7. Allergy 2013; 68: 1370-6. J Allergy Clin Immunol. 2017;139(1):104-111

Summary

- There is limited evidence that any drug for nausea/ vomiting of pregnancy is better than another. Selection depends on cost, tolerability, availability.
- SSRIs: data inconsistent, much of the safety data potentially biased. If real, the risk of cardiac malformations low (NNH~200).
- Omega-3s: unlikely to have much benefit in preventing atopy, might work for ~1 in 20 women.

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