Are negative findings all down to confounding factors?

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Introduction

• Reader (Statistics and Epidemiology)
• Research team epidemiologists/statisticians/PhD students
• Primary care databases THIN and CPRD - 60+ studies

• Research topics
  – Prescribed medicine in pregnancy
  – Mental health
  – Methodological questions
    • Missing data
    • Regression Discontinuity Design (RDD)
    • Confounding (by indication)

• [link](http://www.ucl.ac.uk/pcph/research-groups-themes/thin-pub/)
• Or just google THIN UCL
Acknowledgments and funding

• Serious team work
  – Irwin Nazareth
  – Stephen Evans
  – Shuk Li Man
  – Rachel McCrea
  – and many others…..

• Funding: MRC, National School of Primary Care Research, NIHR, HTA

• No funding from companies producing psychotropic medication
Today

- Antidepressants and pregnancy – do they cause autism?
- What are the consequences?
Antidepressants and pregnancy – do they cause autism?

• It is a good question!
What do we know....

- Number of women in child bearing age on antidepressants is increasing

  However, few women continue antidepressants in pregnancy (come back to this later)

- Number of children diagnosed with autism is increasing
Autism

• Spectrum
• Cause is *still* unclear
• Exposure in childhood
  – For many years focus was on MMR
  – No link to MMR
Link between antidepressants in pregnancy and autism??
Is this another red herring?
Before we start to make causal links between antidepressants and autism….

- Genetics
- Indication for treatment
  - Depression/Anxiety
- Other characteristics of the women
The genetic link

• Hypothesis:

• Same genes may predispose depression/anxiety and autism
Children of depressive/anxious mothers

- **Hypothesis:**
- **Pregnancy exposure**
  - Depression/anxiety has a negative impact on the unborn child
- **Early childhood exposure**
  - Depression/anxious in mothers may ‘trigger’ autism
Other factors/characteristics

• Hypothesis

• Other factors/characteristics may cause autism
So let’s take a look at antidepressant prescribing in pregnancy

- The Health Improvement Network (THIN)
- Primary care database
- 5% of UK population
- Drugs prescribed in primary care
- Diagnosis and symptoms (Read codes)
- Cohort of pregnant women and their children
  - Household Id
  - Child birth and delivery date
Antidepressants in pregnancy

- Identified women who were on antidepressants
- Time to last prescription
  - Pregnant women
  - Non-pregnant women
Time to last antidepressant prescription

- Many women stop antidepressants once they are aware of the pregnancy

  - Before pregnancy
    HR 1.70 (95% CI: 1.62 to 1.70)
  
  - First six weeks
    HR 5.19 (95% CI: 4.85 to 5.56)
  
  - Rest of pregnancy
    HR 1.57 (95% CI: 1.45 to 1.71)

This suggests

• Pregnant women more likely to discontinue antidepressants and they do so early in pregnancy

• There are serious concerns about safety of antidepressant prescribing in pregnancy

• Women who continue antidepressants in pregnancy may be different from those who stop
Factors associated with discontinuation of antidepressants in pregnancy – who stop?

- Those with limited prior experience
  - HR 1.73 (95% CI: 1.63 to 1.84) for 0-1 Rx vs. 2+ Rx

- Younger women more likely to stop
  - HR 1.31 (95% CI: 1.19 to 1.43) for 15-24 year vs. 35+
  - HR 1.15 (95% CI: 1.06 to 1.24) for 25-35 vs. 35+
Later we examined this in more detail...

- Cohorts of women
- Women who received Rx of SSRIs in 1\textsuperscript{st} trimester
- Women who received Rx before pregnancy
- Women NOT on SSRI before or in pregnancy
Characteristics of women on antidepressant treatment in pregnancy in more detail

Three cohorts:

Not on antidepressants (N = 200,213)

On SSRI in before pregnancy (N = 5,154)

On SSRI in 1st trimester (N = 2,776)
## Characteristics of pregnant women

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Not on SSRI (%)</th>
<th>On SSRI before (%)</th>
<th>On SSRI in pregnancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetics</td>
<td>5,188 (2.6)</td>
<td>178 (3.5)</td>
<td>127 (4.6)</td>
</tr>
<tr>
<td>Alcohol problems</td>
<td>735 (0.4)</td>
<td>80 (1.6)</td>
<td>114 (4.1)</td>
</tr>
<tr>
<td>Illicit drug</td>
<td>867 (0.4)</td>
<td>83 (1.6)</td>
<td>118 (4.3)</td>
</tr>
<tr>
<td>Smoking</td>
<td>39,358 (19.7)</td>
<td>1,625 (31.5)</td>
<td>984 (35.5)</td>
</tr>
<tr>
<td>Obese</td>
<td>9,782 (4.9)</td>
<td>426 (8.3)</td>
<td>296 (10.7)</td>
</tr>
</tbody>
</table>
Women who continued antidepressant treatment in pregnancy

• Also more likely to be prescribed other psychotropic medication
  – Anxiolytics
  – Hypnotics
  – Antipsychotics
  – AED

• Although it is a small proportion of women on multiple drugs in pregnancy
Link between antidepressants in pregnancy and autism??
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Link between antidepressants in pregnancy and autism??
Before we can make link....

Antidepressants in pregnancy → Autism
Before we can make link we have to exclude the indication for treatment

- Depression
- Antidepressants in pregnancy
- Autism
Before we can make link we have to exclude the genetic component

Genetics

- Depression
- Antidepressants in pregnancy
- Autism
Before we can make link we have to exclude other factors

Other factors

Genetics

Depression

Antidepressants in pregnancy

Autism
Is it all down to confounding factors?

• I don’t know

• Need to be much more cautious about making a link

• Confounding is a serious issue in observational data
The risk of communicating risk….

• Just a few words about communication of risk
Think about the message we communicate to pregnant women

• What does a relative risk of 1.5 mean?
• 50% increased risk

• In absolute terms:
• 10 out of 10 000 children (9990 without) versus
• 15 out of 10 000 children (9985 without)
Need to think about how women perceive the risk?
Need to think about the consequences of stopping antidepressants in pregnancy

• Some women may be fine without antidepressants

• Others may not….
How do we weigh up risks and benefits?

- Autism
- Depression
- Antidepressants
- Guilt
- Anxiety
- Self medication
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