PRESCRIBING IN PREGNANCY AND BREASTFEEDING
Navigating shifting sands
Roch Cantwell
Pregnancy planning

• 50% unplanned
• Up to 80% unplanned in major mental illness
• Approx. 2/3rds of admissions to MBUs
• have past psychiatric history

“Let’s try getting up every night at 2:00 AM to feed the cat. If we enjoy doing that, then we can talk about having a baby.”
Women attending at booking clinics

- 4 in 100 women on psychiatric medications at conception
- Most on antidepressants
- Most stop in first trimester without seeking advice
  
  Imrie, Math & Cantwell, 2005

- Few women warned of effects of mood stabilising drugs
  
  Weick, 2007
At 21 days, the embryo begins to develop an indentation in the posterior portion of the neck, called the Notochord. By 22 days, the Notochord elongates to form the Spina bifida. At 28 days, the Spina bifida is fully formed.
SIGN 127
Prescribing issues – general guidance

• involve the woman, and her family where appropriate, in all decisions about treatment
• not treating mental illness in pregnancy or the postpartum period may be associated with adverse outcomes
• establish a clear indication for drug treatment
• choose treatments with the lowest known risk
• in choosing consider the implications for breast feeding and the benefits of avoiding the need to switch drugs
• use treatments in the lowest effective dose for the shortest period necessary
• be aware of potential drug interactions, particularly with non-psychotropics, and aim for monotherapy
• where there is no clear evidence base that one drug is safer than another, the safest option is not to switch. The only drug with a clear indication for switching on safety grounds is valproate
SIGN 127
Prescribing issues – general guidance

• be aware of the potential effects of pregnancy and childbirth on drug pharmacokinetics and pharmacodynamics
• be aware that although knowledge of teratogenic effects of psychotropic drugs is increasing, understanding of the long term neurodevelopmental effects of such medications in pregnancy and breast feeding is extremely limited
• be aware of the need for close monitoring for change in mental state where a woman decides to cease her usual medication
• where there is known risk, ensure that women are offered appropriate fetal screening and monitoring of the neonate for adverse effects
• premature or ill babies are more at risk of harmful drug effects
• monitor the infant for drug side effects, feeding patterns, growth and development
• caution women against sleeping in bed with the infant, particularly if taking sedative drugs.
Drug X
Published risks related to pregnancy

- Delayed conception
- Nausea
- Sleeplessness
- Irritability
- Decreased placental blood flow
- Miscarriage
- Stillbirth
- Low birth weight
- Faster heart rates in neonates
- Neonatal withdrawal
“The modern Western pregnant woman must not drink more than four cups of coffee a day, drink alcohol, smoke cigarettes, change cat litter trays, eat soft cheese, uncooked eggs or packaged salads or go into the lambing sheds. They should not work too hard or too long, nor at night or be ambivalent about their pregnancies. Now it seems they must not become anxious either.”

OATES, MR Editorial on: Adverse effects of maternal antenatal anxiety on children: causal effect or developmental continuum?
"C'mon, c'mon—it's either one or the other."

1985
Pharmacokinetics in pregnancy

- Absorption
  - Nausea and vomiting

- Distribution
  - Increased plasma volume (50%)
  - Reduced plasma binding

- Metabolism
  - Cytochrome P-450 induction
  - 50% increased GFR
Prescribing in pregnancy

- All psychotropics pass through the placental barrier
- Fetal serum concentrations 24% to 100% maternal levels
- No drug completely ‘safe’ and knowledge is always limited
Adverse effects of drugs in pregnancy

- Background rate of 2%-3% congenital malformations
- Approx. 2% of those due to drugs administered in pregnancy
- Need to take into account
  - Dose (e.g., valproate)
  - Timing
  - Synergism (additive effects of more than one drug)
  - Complicating factors (e.g., drugs, alcohol)
# Fetal development

![Diagram showing critical periods in human development](image)

**Critical Periods in Human Development**

<table>
<thead>
<tr>
<th>Age of Embryo (in weeks)</th>
<th>Fetal Period (in weeks)</th>
<th>Full Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>4</td>
<td>16</td>
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</table>

- **Period of dividing zygote, implantation & bilaminar embryo**
  - 1

- **C.N.S.**
  - 2

- Heart
  - 3

- Eye
  - 4

- Ear
  - 5

- Palate
  - 6

- Teeth
  - 7

- External Genitalia
  - 8

- Brain
  - 9

- Limb
  - 10

- Functional defects & minor congenital anomalies (yellow)

- Prenatal death major congenital anomalies (red)

*Red indicates highly sensitive periods when teratogens may induce major anomalies.*
Balancing risk and benefit of prescribing

**BENEFITS**
- Prevention of relapse or treatment of illness
- Avoidance of consequent adverse effects on mother, fetus, and neonate

**RISKS**
- Adverse effects on fetus
- Adverse effects on neonate
- Adverse effects on mother
Adverse effects

- Organ dysgenesis
- Intrauterine growth changes
- Neonatal complications
- Neurobehavioural toxicity
SSRIs
Congenital malformations

- Before 2005 - no teratogenicity demonstrated for antidepressants (TCAs and SSRIs)
  - But ..... many studies small cohorts with insufficient power to detect anything other than very large effects

- 2006 two large studies reported 1.5-2.0 x increased risk of cardiac defects with paroxetine exposure

- Cardiac defects 1/50 compared with 1/100
SSRIs
Congenital malformation

Cohort studies

- **US GSK study** (5,956,815 paroxetine)
  - CV malf rate OR=1.5 (0.8-2.9) **1.5% vs 2%**
  - Overall malf rate OR=1.8 (1.2-2.8) **4% vs 2%**

- **Swedish Registry Study** (6,481,943 paroxetine)
  - CV malf rate OR=1.8 (1.1-2.8) **2% vs 1%**

- **Quebec Registry Study** (1,403,542)
  - Risk only for doses above 25mg

- **Danish Registry Study** (1,051)
  - 3.4% controls, 4.8% SSRIs, 0.8% other ADs
  - aRR **1.34** (1.00-1.79)
  - sample size “too small” to allow analysis of individual SSRIs
SSRIs
Congenital malformation

Case control studies

- **National Birth Defects Prevention Study**
  - N = 9622 with major malformations and 4092 controls
  - anencephaly, craniosynostosis, omphalocele ORs 2.4 - 2.8 (1.1 - 5.7)
  - Not congenital heart defects

- **Slone Epidemiology Center Birth Defects Study**
  - N = 9849 with birth defect and 5860 controls
  - No significantly increased risks of malformations with SSRI use overall
  - sertraline and omphalocele (OR= 5.7, 1.6 - 20.7; 3 exposed subjects) and septal defects (OR=2.0, 1.2 - 4.0; 13 exposed subjects)
  - paroxetine and right ventricular outflow tract obstruction defects (OR= 3.3; 1.3 - 8.8; 6 exposed subjects)
SSRIs
Congenital malformation

- Swedish registry study 15,017 births
- > 10,000 on SSRIs / > 1600 on TCAs (>1200 on clomipraine)
- Association with pregnancy / neonatal complications / malformations / PPHN
- TCAs => SSRIs
- Effect of depression
- Small effects

Reis and Kallen. Psychological Medicine 2010
SSRIs
Congenital malformation

• Meta-analysis of 16 (out of 115) studies:

  • Fluoxetine (OR 1.14, 95% CI 1.01–1.30) and paroxetine (OR 1.29, 95% CI 1.11–1.49) associated with increased risk of major malformations

  • Paroxetine associated with increased risk of cardiac malformations (OR 1.44, 95% CI 1.12–1.86).

Myles et al, ANZJP, 2013
SSRIs
Congenital malformation

**Increased risk**

- 1,174 infants from eight teratology services
- No increased rates of cardiac defects in the paroxetine group (0.7%)
- In over 3000 deliveries – no indication of increased risk

Am J Psychiatry 2008; 165:749–752
SSRIs
Congenital malformation

• Finnish registry study of ADs in pregnancy

• Major congenital abnormalities OR 1.24 (1.1 – 1.39)

• Not significant when controlled for confounders OR 1.08 (0.96-1.22)

• Women taking ADs
  • Less likely to be married, twice as likely to smoke, 20 times more likely to take other psychiatric medication
  • Fetal alcohol syndrome OR 9.6 (4.6 – 20.0)

Malm et al, Obstetrics and Gynecology, 2011
Conclusions

- Lack of consistency re malformations and drugs

- Possible underlying class effect – all commonly used SSRIs implicated plus clomipramine

- ?Greater ‘signal’ for paroxetine

- Residual confounding
  - depression, obesity, drugs and alcohol, tobacco, use of folic acid, detection bias…

- Multiple testing

- Absolute risk for any pregnant women low
SSRIs
Fetal growth

- 7,696 women
  - 7.4% (7027) clinically significant depression
  - 1.3% (99) SSRIs

- U/S each trimester, birth weight, gestation

- Depression – reduced body and head growth

- SSRIs – reduced head growth (not body growth) and association with pre-term birth

El Marroun et al, 2012
SSRIs
Fetal growth
SSRIs
Neonatal complications - poor adaptation

Neonatal Signs After Late In Utero Exposure to Serotonin Reuptake Inhibitors
Literature Review and Implications for Clinical Applications

Eydie L. Moses-Kolko, MD
Debra Bogen, MD
James Perel, PhD
Amy Bregar
Kathleen Uhl, MD
Bob Levin, MD
Katherine L. Wisner, MD, MS

Context  A neonatal behavioral syndrome linked to in utero serotonin reuptake inhibitor (SRI) exposure during the last trimester of pregnancy has been identified. The US Food and Drug Administration (FDA) and drug manufacturers have recently agreed to a class labeling change for SSRIs, which include selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), to include information about potential adverse events in neonates exposed in utero. Integration of data about the neonatal behavioral syndrome into the management of pregnancy in women who take SSRIs is a current challenge for physicians.

Objectives  To review evidence regarding the SRI-related neonatal syndrome and to help clinicians guide their patients in a risk-benefit decision-making process.

JAMA 2005;293:2372-83
SSRIs

Neonatal complications - poor adaptation

Cohort studies

• 9 cohort studies identified - 5 which defined the neonatal behavioural syndrome (tremor, restlessness, increased muscle tone, crying)

• OR = 3.0 (2.0 - 4.4) for syndrome
  • 30% vs 10%

• OR = 2.6 (1.4 - 4.7) for Special Care Unit admission
SSRIs

Neonatal complications - poor adaptation

Maternal depression, antidepressant use in pregnancy and Apgar scores in infants

Hans Mørch Jensen, Randi Grøn, Øjvind Lidegaard, Lars Henning Pedersen, Per Kragh Andersen and Lars Vedel Kessing


“OR low Apgar score 1.72 (CI 1.34-2.20)”
SSRIs
Neonatal complications - PPHN

377 PPHN cases – OR 6 = 1%

N Eng J Med 2006;354:579-87

Selective Serotonin-Reuptake Inhibitors and Risk of Persistent Pulmonary Hypertension of the Newborn

SSRIs
Neonatal complications - PPHN

Lowered risk in subsequent studies?

• Wichman et al 2007
  • case note review of 25,214 deliveries – no association

• Kallen et al 2008
  • 831,324 infants – risk doubled – 0.15%

• Andrade et al 2009
  • 1104 SSRI and 1104 controls - case note review - no association

• Reis and Kallen 2010
  • RR 2.56 for late exposure – 0.2%

• Kieler et al, 2012
  • Scandinavian registries -1.6 million infants – 30,000 SSRI exposures
  • 0.3% (OR 2.1)
SSRIs (and others)

Neonatal complications - postpartum haemorrhage

- Palmsten et al, BMJ 2013
- Population based cohort study
- 106,000 women
- Current; recent; past; no exposure
Neonatal complications

Postpartum haemorrhage

But…

• Salkeld et al, 2008

• Population based case control study

• No evidence of increased risk
Not treating isn’t a great option either…

Relapse of Major Depression During Pregnancy in Women Who Maintain or Discontinue Antidepressant Treatment

Lee S. Cohen, MD
Lori L. Altschuler, MD
Bernard L. Harlow, PhD
Ruta Nonacs, MD, PhD
D. Jeffrey Newport, MD
Adele C. Viguera, MD
Rita Suri, MD
Vivien K. Burt, MD, PhD
Victoria Hendrick, MD
Alison M. Remnick, BA
Ada Loughhead, BA
Allison F. Vitonis, BA
Zachary N. Stowe, MD

Context: Pregnancy has historically been described as a time of emotional well-being, providing “protection” against psychiatric disorder. However, systematic delineation of risk of relapse in women who maintain or discontinue pharmacological treatment during pregnancy is necessary.

Objective: To describe risk of relapse in pregnant women who discontinued antidepressant medication proximate to conception compared with those who maintained treatment with these medications.

Design, Setting, and Patients: A prospective naturalistic investigation using longitudinal psychiatric assessments on a monthly basis across pregnancy; a survival analysis was conducted to determine time to relapse of depression during pregnancy. A total of 201 pregnant women were enrolled between March 1999 and April 2003 from 3 centers with specific expertise in the treatment of psychiatric illness during pregnancy. The cohort of women was recruited from (1) within the hospital clinics, (2) self-referral via advertisements and community outreach detailing the study, and (3) direct referrals from the community. Participants were considered eligible if they (1) had a history of major depression prior to pregnancy, (2) were less than 16 weeks’ gestation, (3) were euthymic for at least 3 months prior to their last menstrual period, and (4) were currently or recently (<12 weeks prior to last menstrual period) receiving antidepressant treatment. Of the 201 participants, 13 miscarried, 5 electively terminated their pregnancy, 12 were lost to follow-up prior to completion of pregnancy.

JAMA. 2006;295:499-507
Evidence of harm

- 201 euthymic women with history of MDD
  - 68% recurrence in those who discontinued AD
  - 26% recurrence in those who remained on AD

- Significantly higher in those with >4 previous episodes and >5 years of illness

- Highly selected sample
Effects of stopping treatment

Relapse of depression

No evidence of harm!

- 778 pregnant women with a history of major depression

- No effect of stopping antidepressant treatment

- Hazard Ratio 0.88 (0.51 – 1.50)
  - MDE in 6 months before pregnancy:  HR 1.84 (1.23 – 2.75)
  - 4 or more episodes:  HR 1.97(1.09 – 3.57)
  - Black (HR 3.69) or hispanic (HR 2.33)

Yonkers, 2011
Not treating isn’t a great option either…

- **Antenatal stress/anxiety related to:**
  - Emotional/cognitive problems
  - ADHD
  - Language delay

- **Independent of postnatal depression/anxiety**

- **Attributable load 15%**

- **Related to HPA axis responsiveness and cortisol production**

Talge, 2007
Long term implications

ASD

- 298 Autism Spectrum - 1507 controls
- 6.6% vs 3.3% at least 1 prescription or an antidepressant in the year prior to delivery
- OR 2.2 (1.2 – 4.3) attrib risk 2.1%
- Highest risk in first trimester (OR 3.8, 1.8 - 7.8)
- Numbers small - 20 ASD children with AD prescription
- Adequacy of controlling for confounders?
Long term implications

ASD

RESEARCH

Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study

Dheeraj Rai clinical lecturer,1,2 Brian K Lee assistant professor,1 Christina Dalman associate professor,1 Jean Golding professor emeritus1,2 Glyn Lewis professor4, Cecilia Magnusson professor2

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Abstract

Objective To study the association between parental depression and maternal antidepressant use during pregnancy with autism spectrum disorders in offspring.

Design Population based nested case-control study.

Results

Conclusions In utero exposure to both selective serotonin reuptake inhibitors (SSRIs; antidepressants) was associated with an increased risk of autism spectrum disorders, particularly without maternal obesity. Whether this exposure is causal or reflects the risk of autism with severe depression during pregnancy requires further research. However, assuming causality, antidepressant use during

“Antidepressants account for 0.6% of cases of autistic spectrum disorder”
Long term implications

ASD

<table>
<thead>
<tr>
<th>Prenatal exposure</th>
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<tbody>
<tr>
<td>376 maternal depression, no SSRI</td>
</tr>
<tr>
<td>69 maternal depression + SSRI</td>
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<tr>
<td>5531 unexposed</td>
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</tbody>
</table>

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<thead>
<tr>
<th>Mat. depression, no SSRI:</th>
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</thead>
<tbody>
<tr>
<td>Perv. dev. dis. (OR=1.44)</td>
</tr>
<tr>
<td>Autistic traits (p=0.01)</td>
</tr>
<tr>
<td>Affective probs (OR=1.44)</td>
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</table>

<table>
<thead>
<tr>
<th>Mat. Depression + SSRI:</th>
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<tbody>
<tr>
<td>Perv. dev. dis. (OR=1.91)</td>
</tr>
<tr>
<td>Autistic traits (p&lt;0.001)</td>
</tr>
</tbody>
</table>
• Croen et al, 2012 - modest increased risk with first trimester SSRI exposure

• El Marroun et al, 2013 - association with SSRI exposure and, independently and more weakly, depressive symptoms

• Hviid et al, 2013 - non-significant increased risk

• Rai et al, 2013 - increased risk with SSRIs and TCAs; usually without intellectual disability; explains <1% of cases

• Sorensen et al, 2013 - no increased risk after controlling for maternal illness and comparison with siblings

• Unpublised data - replicates modest increased risk
SSRIs
What should we advise?

- Currently:
  - Possible doubling of risk of VSD (1.5-2/100)
  - Possible doubling/trebling risk of PPHN (2-3/1000)
  - Possible slight increased risk of postpartum haemorrhage
  - Neonatal poor adaptation (1 in 10)

- Long-term neurodevelopmental effects?

- Overall effects are slight

- How to convey without alarming?
Mood stabilisers

• Effects of bipolar disorder v. effects of drug?
  • increased preterm births and obstetric interventions irrespective of prescribing
  • neonatal hypoglycaemia and small head circumference more common in untreated group

Boden, 2012
Mood stabilisers

- Variable susceptibility to adverse effects
  - Having previous child with malformation significantly increases risk
  - 9.8% - 16.8% - 50% (women with epilepsy) Campbell, 2013
  - 7% - 57% (valproate) Vaida, 2013
  - ? response to folate
Lithium

- Organ dysgenesis
  - cardiac malformation (Ebstein’s anomaly)
  - 0.05%-0.1% (×20-40 general population)
  - McKnight, 2012 - OR 2.0 (0.2-20.6) NS
  - ? overall rate of congenital abnormalities
Ebstein’s anomaly

- Downward displacement of tricuspid valve, with tricuspid incompetence
- Right heart enlargement
- Atrial septal defect (50%)
- Dysrrhythmias (especially atrial fibrillation)
Lithium

- IUG
  - ?increased weight
- Neonatal effects
  - pre-term delivery
  - ‘floppy baby’ syndrome
  - hypothyroidism, nephrogenic DI, polyhydramnios
- Neurobehavioural toxicity
  - no evidence
Newport, 2005
TABLE 2. Clinical Characteristics of Infants With Low Versus High Lithium Exposure at Delivery*  

<table>
<thead>
<tr>
<th></th>
<th>Infants With High Lithium Exposure (N=112)</th>
<th>Infants With Low Lithium Exposure (N=112)</th>
<th>Mean</th>
<th>95% CI</th>
<th>Mean</th>
<th>95% CI</th>
<th>Difference</th>
<th>95% CI</th>
<th>Analysis b</th>
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<tr>
<td><strong>Plasma lithium concentration at delivery</strong></td>
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<tr>
<td>Infant (meq/liter)</td>
<td>12</td>
<td>12</td>
<td>1.68</td>
<td>1.02–2.34</td>
<td>0.40</td>
<td>0.33–0.67</td>
<td>1.28</td>
<td>0.65–1.90</td>
<td>4.24</td>
<td>22</td>
<td>&lt;0.002</td>
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<tr>
<td>Mother (meq/liter)</td>
<td>8</td>
<td>10</td>
<td>1.64</td>
<td>0.38–2.70</td>
<td>0.42</td>
<td>0.30–0.63</td>
<td>1.22</td>
<td>0.37–2.07</td>
<td>2.71</td>
<td>16</td>
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<td>Infant/mother ratio</td>
<td>7</td>
<td>10</td>
<td>1.07</td>
<td>0.94–1.19</td>
<td>1.00</td>
<td>0.90–1.09</td>
<td>0.07</td>
<td>–0.07 to 0.21</td>
<td>1.09</td>
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<td>Maternal lithium dose (mg/day)</td>
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<td>8</td>
<td>654–1566</td>
<td>11</td>
<td>733–1145</td>
<td>169</td>
<td>–243 to 581</td>
<td>0.87</td>
<td>17</td>
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<td><strong>Pregnancy complications</strong></td>
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<td>Gestational diabetes</td>
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<td>0.04–6.55</td>
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<td>Polyhydramnios</td>
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<td>4.29</td>
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<td>Preeclampsia</td>
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<td>0.49</td>
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<td>Any complication</td>
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<td><strong>Obstetrical outcomes</strong></td>
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<td>Apgar score</td>
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<td>1 minute</td>
<td>9</td>
<td>9</td>
<td>4.3</td>
<td>2.2–6.6</td>
<td>7.0</td>
<td>5.9–8.1</td>
<td>–2.7</td>
<td>–5.0 to –0.4</td>
<td>–2.24</td>
<td>16</td>
<td>&lt;0.03</td>
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<td>5 minutes</td>
<td>7</td>
<td>8</td>
<td>7.6</td>
<td>5.9–9.3</td>
<td>8.50</td>
<td>8.1–9.0</td>
<td>–0.9</td>
<td>–2.4 to 0.5</td>
<td>–1.31</td>
<td>13</td>
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<tr>
<td>Estimated gestational age (weeks)</td>
<td>12</td>
<td>12</td>
<td>37.3</td>
<td>35.5–39.2</td>
<td>38.9</td>
<td>38.2–39.5</td>
<td>–1.5</td>
<td>–3.4 to 0.3</td>
<td>–1.75</td>
<td>22</td>
<td>0.11</td>
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<tr>
<td>Infant weight (kg)</td>
<td>10</td>
<td>10</td>
<td>3.05</td>
<td>2.5–3.62</td>
<td>3.48</td>
<td>3.15–3.81</td>
<td>–0.40</td>
<td>–0.99 to 0.19</td>
<td>–1.43</td>
<td>18</td>
<td>0.18</td>
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<tr>
<td>Hospital stay (days)</td>
<td>7</td>
<td>10</td>
<td>10.1</td>
<td>5.0–15.3</td>
<td>4.3</td>
<td>1.2–7.3</td>
<td>5.9</td>
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* Infants were assigned to study groups on the basis of a median split. Infants whose lithium concentration at delivery was greater than the median (0.64 meq/liter) were assigned to the high lithium exposure group. The remaining infants were assigned to the low lithium exposure group.

b For continuous data, the difference between means and 95% confidence interval are reported. For nominal data, the calculated risk ratio and 95% confidence interval (CI) are reported. A one-sample t test was used to test group differences in continuous variables. Fisher’s exact test was used to test group differences in nominal variables.

c The risk ratio is not available if either of the group percentages equals 0% or 100%.

d Complications for particular body systems included bradycardia, cardiomegaly, and systolic murmur (cardiovascular); lethargy and “depression” (CNS); hepatomegaly and jaundice (hepatic); hypotonia, “flaccidity,” diminished deep tendon reflexes, and poor suck or Moro reflexes (neuromuscular); polypia and diabetes insipidus (renal); apnea, cyanosis, labored breathing, and need for intubation (respiratory), and goiter (thyroid).
Valproate

- **Organ dysgenesis**
  - 1%-5% NTDs (x10 spina bifida) (esp. if >1000mg/d)
  - risk greatest 17-30 days post conception
  - craniofacial and cardiac anomalies (x4 gen. pop)
- **IUG**
  - probable
- **Neonatal toxicity**
  - hepatotoxicity, dysrrhythmias, hypoglycaemia, blood clotting problems, withdrawal
- **Neurobehavioural toxicity**
  - hyperexcitability and neurological dysfunction at 6 yrs
    - significantly lower mean verbal IQ
    - 40% neurodevelopmental & behavioural problems
Fetal valproate syndrome

- Craniofacial abnormalities
- NTDs
- Limb defects
- Low birth weight
- Retarded psychomotor development
Distribution of VIQ according to monotherapy drug exposure in utero compared to the expected score in the general population.

Adab N et al. J Neurol Neurosurg Psychiatry 2004;75:1575-1583

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Valproate

Figure 1: Prescribing volume of lithium and semisodium valproate in the community in England.
Folic acid?

- Reduces incidence of NTDs in general population
- High dose (4mg/d) reduces repeat NTD

But…

- No benefit in women with epilepsy taking AEDS in 2 recent studies (Wyszynski, 2005; Morrow, 2009)
“Not for use in pregnancy unless there is no effective alternative”

“Women of childbearing potential should not start treatment without specialist neurological or psychiatric advice”

“Adequate counselling should be made available to all women with epilepsy of childbearing potential to weigh the risk of teratogenic and neurodevelopmental effects against the benefits of treatment”
Retinoic acid?

- Pre-treatment verbal and written information of risks
- Pre-treatment pregnancy test
- Effective contraception
- Monthly pregnancy tests
Other associations

• Benzodiazepines and oral cleft
• 2nd generation antipsychotics and gestational diabetes mellitus
• Carbamazepine and NTDs
• Lamotrigine and oral cleft / changes in metabolism
Breastfeeding
General principles

• No conclusive findings regarding effects on mental state
• No good evidence for timing/discard ing
• Few drugs are incompatible with breastfeeding
• Think about breastfeeding with prescribing in pregnancy!
• Most recommendations assume a term and healthy baby
Breastfeeding

Antidepressants

- First choice if initiating - sertraline, paroxetine, imipramine, nortriptyline
- Particular caution with fluoxetine, citalopram, escitalopram, venlafaxine, clomipramine, dothiepin
- Don’t use doxepin
Breastfeeding
Antipsychotics

- Caution with sulpiride, amisulpride, haloperidol, risperidone
- Avoid clozapine
- NB sedation
Breastfeeding

Mood stabilisers

- Avoid lithium
- Great caution/avoid lamotrigine
High risk management
Pre-conception

• Early discussion of risks and management strategies
  – risks associated with personal or family history
  – include general risk reduction measures (smoking, drinking, weight, drug misuse, etc.)

• Options
  – stop medications before and throughout pregnancy
  – stop medications and reintroduce only if symptomatic in pregnancy
  – stop medications and reintroduce after first trimester
  – continue throughout
  – switch to lower risk drug

• Refer to specialist service if available
High risk management

Pre-conception

• **Illness factors**
  • diagnosis
  • course
  • frequency and triggers for relapse
  • duration of remissions on and off medication
  • severity of illness when unwell
  • time to relapse after previous discontinuation
  • time to recovery on reintroduction

• **General principles**
  • trial of withdrawal (not in schizophrenia)
  • gradual discontinuation
  • high dose folate (4mg/d) if on anticonvulsant *(but ?effectiveness)*
High risk management
During pregnancy

• Biological management
  – Consider switching from high to lower risk drugs (depending on timing)
  – Change from depot to oral and from low to high potency antipsychotic preparations if possible
  – Early detailed USS and echo cardiography if medication associated with significant teratogenic risk
  – Increased frequency of lithium checks (monthly)
  – Changes in fluid compartments and drug clearance may mean increased dose is required as pregnancy progresses (e.g., lamotrigine)

• Psychosocial management
  – Lower threshold for support
  – Preparation for parenthood
  – Child support & protection - ? social work involvement
High risk management

Late pregnancy

• Consider reduction (possible discontinuation) of medications in 4-6 weeks pre-delivery to minimise neonatal withdrawal

• Weekly lithium checks in last 4-6 weeks - stop at onset of labour; ?earlier reduction

• Vitamin K supplements in last month if on valproate (and i.m. to neonate)

• Pre-birth case discussion

• Late pregnancy / early postnatal care plan

• Decisions on breastfeeding
High risk management
Early postnatal period

- Restart full prophylactic regime immediately on delivery for high risk women (woman takes it with her to hospital)

- Very close monitoring

- Review on postnatal wards

- Postbirth case discussion where appropriate
Shared decision making
Shared decision making

- Discuss absolute and relative risks
- Acknowledge uncertainty
- Explain background risk
- Describe risk using natural frequencies rather than percentages/common denominators (1 in 10 and 25 in 100, not 10%, 25%, 1 in 4)
  - “risk of heart abnormalities with SSRIs is double the background rate”
  - “risk of heart abnormalities with SSRIs is 100% more than the background rate”
  - “risk of heart abnormalities with SSRIs is 2 in 100”
- Individualise risk and use aids
## Sample care plan*

*Pregnancy and early postnatal care pathway (to be completed between 28 and 32 weeks of gestation)*

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<tbody>
<tr>
<td>Sign/print name (patient):</td>
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Lithium in pregnancy

Narrow therapeutic to toxic ratio
Assessed by serum level

Therapeutic: 0.5 - 0.8 mmol/l
Toxic: >1.5 mmol/l

Symptoms of toxicity
• Early - restlessness, apathy, nausea, coarse tremor
• Later - vomiting, diarrhoea, ataxia, dysarthria, confusion
• Leading to - convulsions, renal failure, coma, death

Toxicity precipitated by
• Dehydration
• Impaired renal function
• Sodium restricted diet
• Drug interaction
• Overdose

Drug interactions
• Diuretics (esp. thiazides)
• NSAIDs
• ACE inhibitors
• Calcium channel blockers

Pregnancy-related risks
• Hyperemesis
• Pre-eclampsia
• Fluid loss at delivery
‘Contraception should be used on every conceivable occasion’

Spike Milligan