UPDATE ON PRESCRIBING IN PREGNANCY & BREASTFEEDING

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Overview

- What are some of the issues and challenges?
- Specific Drugs
- General principles of prescribing
- Case scenarios
Considerations

- Pre-pregnancy advice
  - 50% pregnancies are unplanned
- Starting medication in pregnancy
  - Previously used
  - First time
- If already on medication
  - Should you continue?
  - Should you stop it?
  - Should you change it?
- What about multiple medications?
- What about safety in breastfeeding?
## Risk of relapse during pregnancy – Stopping meds

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relapse rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD – stop meds in 1&lt;sup&gt;st&lt;/sup&gt; trimester</td>
<td>68%</td>
</tr>
<tr>
<td>BPAD – stop mood stabiliser</td>
<td>81-85.5%</td>
</tr>
<tr>
<td>BPAD – continue with mood stabiliser</td>
<td>29-37%</td>
</tr>
<tr>
<td>Schizophrenia – stop meds</td>
<td>50%</td>
</tr>
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</table>

### First Trimester
- **Period of organogenesis**, which is most critical for foetal growth and development

### Second Trimester
- **Continuous growth and development**, (focus is **length** of foetus)

### Third trimester
- **Period of most rapid growth and development**, (focus is **weight** of foetus)
### Risks associated with timing of medication

<table>
<thead>
<tr>
<th>Early pregnancy</th>
<th>risk of teratogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late pregnancy</td>
<td>neonatal toxicity</td>
</tr>
<tr>
<td></td>
<td>poor neonatal adaptation</td>
</tr>
<tr>
<td></td>
<td>long term impact on the infant’s neurodevelopment</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>short term toxicity</td>
</tr>
<tr>
<td></td>
<td>longer term neurodevelopment</td>
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</table>

**Teratogen**: Any agent that can disturb the development of an embryo or foetus
Explaining Risk

- Absolute vs Relative
- Language

Background risks

Irrespective of any drug or chemical exposure.

- Miscarriage: 10-20%
- Congenital abnormality: 2-3%
- Congenital heart defects (CHD): 0.6%
- Stillbirths: 0.5%
- Neural tube defects: 0.1%
- Ebstein’s anomaly: 0.002%
Why is research limited?

- Ethics
- Confounders
- Variable prescribing patterns
  - When started/stopped, dose etc

General advice

- Individualised assessment of benefit versus risk
- Do not abruptly discontinue medication in pregnancy without considering risk of illness and relapse
- If no clear evidence base that one drug is safer than another, the safest option is not to switch
- Seek expert advice if necessary (Pharmacy or your local Psychiatrist)
- If medication IS required,
  - choose treatments with the lowest known risk
  - aim for monotherapy
  - lowest effective dose for the shortest period necessary
  - preferable to avoid/minimise prescribing in the first trimester, if possible, due to organogenesis
  - For medications initiated in pregnancy, think ahead and consider its safety in breastfeeding
General advice

- effects of the pregnancy on drug metabolism
  - eg. need for dose adjustments in later pregnancy

**Neonate/Infant**

- If known risk, appropriate fetal screening
- monitor neonate for adverse effects
- **premature or ill babies** more at risk of harm
- monitor the infant for specific drug side effects, feeding patterns, growth and development
- caution women against sleeping in bed with the infant, particularly if taking sedative drugs.

What would you do?

- Jane has been on Sertraline for last 2 years
- Commenced after losing her job
  - Became depressed and anxious
- Continues to get brief episodes of low mood (often lasts 7-10 days)
- Has 2 children. No previous mental health issues specific to pregnancy/childbearing
- She has just found out she is pregnant and has come to see you.

- **What advice would you give re. medication?**
What would you do?

- Sarah has Bipolar disorder
- 2 previous psychiatric admissions, including detention under MHA
- Compliant with an antipsychotic. Well for 1 year. Known to CPN and OPC
- 1st pregnancy, unplanned. 1st trimester

What advice would you give re. medication?

Specific medications requiring caution

- Antenatal - Avoid Paroxetine due to risk of congenital cardiac malformations

- Antenatal - Avoid Valproate in pregnancy and women of childbearing potential due to risk of foetal abnormality and adverse neurodevelopmental outcomes

- Antenatal - Antipsychotics during pregnancy
  - Olanzapine, Clozapine - Monitor for blood glucose abnormalities
  - Close monitoring of foetal growth.
Antidepressants in pregnancy

- Evidence of harm is conflicting
- SSRI
  - **Paroxetine**: cardiac malformation
    - Background rate 0.6%  Increased rate 1%
  - **Persistent pulmonary hypertension of the newborn (PPHN)**
    - early and late SSRI exposure
    - Background rate 0.19%
    - Relative Risk x2-3  Absolute risk 0.2 to 0.3%
  - **Neonatal adaptation syndrome**
    - Clinically evident in 10% of babies

Neonatal adaptation syndrome

*aka poor neonatal adaptation, neonatal withdrawal or neonatal abstinence syndrome*

- A cluster of symptoms in the neonate due to psychotropic use in pregnancy
  - Irritability
  - sleep disturbance
  - persistent crying
  - tachypnoea
  - hypoglycaemia
  - poor thermal regulation
  - seizures
- Liaise with maternity services to ensure appropriate monitoring and management
- Symptoms are often self-limiting
PPHN

- Relatively rare outcome with an estimated baseline prevalence of 1.9 per 1000 live births
- **Normally** - Blood vessels in the lungs of the infant relax following delivery
  - PPHN - the resistance in the pulmonary vasculature following birth continues, leading to poor oxygenation. Evident soon after birth.
- **Symptoms** - range in severity from mild respiratory distress to the most severe form, with hypoxia necessitating intensive medical care
- PPHN defined as "a final common pathway of a variety of risk factors and insults that can cause pulmonary underdevelopment, maldevelopment, or poor postnatal adaptation."
- **Risk factors** - certain congenital malformations, premature birth, meconium aspiration, maternal obesity, and caesarean section mode of delivery

AD - Associations

- **Spontaneous abortion** - no increased risk associated with AD
- **Reduced birthweight** - no significant association compared to depressed mothers without AD exposure
- **Stillbirths & neonatal deaths** - no association with antenatal SSRIs after adjusting for confounders.
- **Autism spectrum disorders** - no significant association in large cohort study despite two nested case-control studies reporting an association with AD exposure in pregnancy
Mirtazapine

- Data limited. Consider use if alternatives are not clinically appropriate
- No significant increased risk of congenital malformation, but evidence too limited to exclude any increased risk
- Conflicting advice about spontaneous abortion and pre-term delivery
- Risk of neonatal hypoglycaemia may be increased

Venlafaxine

- No increased overall risk of congenital malformation.
  - Large case-control study: association with specific congenital malformations including hypospadias, gastroschisis, cleft palate, limb, and heart defects.
  - Currently the data are too limited to confirm or exclude an increased risk of malformations after in utero exposure to venlafaxine.
- Spontaneous abortion and preterm delivery: Some association reported but data not conclusive
- Theoretical risks of NAS and PPHN
- Neurodevelopment: Not known

Where maternal treatment with venlafaxine is clinically indicated it should be offered, provided the women is carefully counselled regarding the available human pregnancy safety data or the prescriber considers risk of not treating the maternal condition too great to withhold treatment on the basis of the undetermined fetal risk.
Prenatal antidepressant exposure and child behavioural outcomes at 7 years of age: a study within the Danish National Birth Cohort

![Graph showing the proportion of children with abnormal scores in different behavioural categories: Hyperactivity/Inattention, Conduct problems, Peer problems, Emotional symptoms, Total difficulties. The categories are compared across groups of Antidepressants, Untreated depression, and Unexposed.]

*Behavioural problems defined as scores above the 90th percentile on the parent-report version of the Strengths and Difficulties Questionnaire (SDQ)*

**Tapering AD before delivery?**

- Advantages vs Disadvantages
Antipsychotics

Congenital malformation
- no increased rate of any major malformation for any drug.

Neurological effects on neonate
- self-limiting extra-pyramidal symptoms
- association between low birth weight and typical antipsychotics in pregnancy
- large for gestational age in women taking atypical antipsychotics, especially olanzapine and clozapine.

Advice
- Women taking antipsychotics during pregnancy should be monitored for alterations in fetal growth.
- Monitor for blood glucose abnormalities where olanzapine or clozapine are prescribed.

NICE 2014: Antipsychotics

- Take into account risk factors for gestational diabetes and excessive weight gain.
- If a pregnant woman is stable on an antipsychotic and likely to relapse without medication, advise her to continue the antipsychotic.
- Monitor for gestational diabetes in pregnant women taking antipsychotic medication and offer an oral glucose tolerance test.
- Do not offer depot antipsychotics to a woman who is planning a pregnancy, pregnant or considering breastfeeding, unless she is responding well to a depot and has a previous history of non-adherence with oral medication.
## Antiepileptics

### Congenital malformation
- Use in early pregnancy increases the risk of congenital malformations
- Greatest risk with valproate.
- Overall major malformation rate was 2.9% for carbamazepine, 8.7% for sodium valproate and 2.7% for lamotrigine.

### Neurological effects on neonate
- Sodium valproate exposure: Poorer outcome on development eg. IQ, verbal ability and attention.
- No effects on development were found for carbamazepine or lamotrigine.
- Polytherapy was associated with highest risks.

### Advice
- Avoid valproate in pregnancy and women of childbearing potential

## NICE 2014: Anticonvulsants

### Valproate
- Do not offer valproate for acute or long-term treatment of a mental health problem in women who are planning a pregnancy, pregnant or considering breastfeeding.
- If a woman is already taking valproate and becomes pregnant, stop the drug because of the risk of fetal malformations and adverse neurodevelopmental outcomes.

### Carbamazepine
- Do not offer carbamazepine to treat a mental health problem in women who are planning a pregnancy, pregnant or considering breastfeeding.
- If a woman is already taking it, discuss with the woman the possibility of stopping the drug (because of the risk of adverse drug interactions and fetal malformations)

### Lamotrigine
- In pregnancy, check lamotrigine levels frequently during pregnancy and into the postnatal period because they vary substantially at these times.
Lithium - Risk

**Historical evidence**
- Retrospective data from the lithium baby registry: 225 exposed babies
  - 25 malformations (11%).
  - 18 (8%) cardiovascular defects, six of which were Ebstein's anomaly.
- Prospective data: 296 exposed babies
  - 8 malformations (3%), same rate as controls. 2 had Ebstein's anomaly
  - cw ZERO Ebstein's in 1354 controls (3% malformations)

**Recent evidence:** Systematic review and meta-analysis of lithium toxicity (62 studies)
- Evidence that exposure to lithium is teratogenic is weak
- Risk has been overestimated
- CIs were wide and the upper confidence limit was consistent with a clinically significant increase in risk of congenital malformations.

Lithium - Guidance

- Explain the uncertainty around risk to women and to consider the balance between harm to the baby and risk of worsening maternal mood instability.

- When lithium is used in pregnancy, lithium levels need to be checked more frequently because of the changes in blood volume, and particularly closely in women who develop pre-eclampsia.

- Some uncertainty surrounds when to stop lithium around the time of labour. However, once labour has begun, lithium should not be taken until after delivery when plasma levels and electrolyte balance can be checked and lithium reinitiated.
Benzodiazepines

*Data conflicting; Multiple confounders*

- **Teratogenicity**
  - Older studies suggested possible increased risks of congenital malformation including orofacial clefts and cardiac malformations.
  - More recent, better designed studies have failed to identify such associations.

- **Prolonged use near term, especially in high doses**
  - Associated with neonatal withdrawal syndrome and/or “floppy infant syndrome”
  - Use of diazepam around term should therefore be avoided unless use can be clinically justified.

- **Neurodevelopment**
  - Effects unknown

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Benzodiazepines

- **Spontaneous abortion**
  - Increased risk following exposure to benzodiazepines as a group has been reported but data too limited and confounded to be certain that a clinically relevant increased risk exists.

- **Avoid abrupt withdrawal of Diazepam**
Beta Blockers

Associated with

- Intrauterine growth retardation (IUGR) and low birth weight in 1st + 2nd trimester use
- Neonatal bradycardia, hypotension and hypoglycaemia if used near term
- Respiratory distress and apnoea: has been reported following in utero exposure

- Not associated with an increased risk of structural foetal malformations.
  - Recent studies suggest possible increased risk of congenital heart defects associated with antihypertensive therapy in general including beta blockers.
  - Unclear whether these result from the underlying maternal condition or the use of medication.

Breastfeeding
Encourage women with a mental health problem to breastfeed, unless they are taking carbamazepine, clozapine or lithium (valproate is not recommended to treat a mental health problem in women of childbearing potential). However, support each woman in the choice of feeding method that best suits her and her family.

**Breastfeeding: Antidepressants**

<table>
<thead>
<tr>
<th>LOW relative infant doses(&lt;10%)</th>
<th>HIGHER relative infant doses(&gt;10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sertraline, paroxetine, duloxetine, mirtazapine, fluvoxamine, reboxetine, bupropion, and nortriptyline.</td>
<td>citalopram, escitalopram, fluoxetine, and venlafaxine</td>
</tr>
</tbody>
</table>

**Advice: SIGN 127**
- Avoid doxepin
- If starting SSRI try to avoid fluoxetine, citalopram and escitalopram
SIGN 127 - Breastfeeding

- **Lithium**
  - Due to risk of infant toxicity, mothers should be encouraged to avoid breast feeding.
  - If decide to breastfeed, close monitoring of the infant (serum lithium levels, thyroid and renal monitoring)

- **Clozapine**
  - should not breast feed.

SIGN 127 - Antiepileptics

- **Sodium valproate**
  - excreted in low levels. Infant serum levels 1-2% of maternal serum level.
  - no short term adverse clinical effects have been noted

- **Carbamazepine**
  - excreted in significant quantities. Infant serum levels 6-65% of maternal serum levels.

- **Lamotrigine**
  - Infant plasma concentrations four hours after breast feeding were 18.3% of the maternal dose.

**Advice: SIGN 127**
Antiepileptic mood stabiliser prescription is not, of itself, a contraindication to breastfeeding, but decisions should be made individually with the woman, after full discussion of the risks and benefits.
SIGN 127 – Benzodiazepines

- excreted in breast milk with a low milk/plasma ratio.
- sedation, poor feeding, weight loss and apnoea

If a benzodiazepine is required during breast feeding short-acting agents should be prescribed in divided doses.

 Mothers should be advised not to stop medication suddenly and to contact their doctor if the infant is observed to have sleepiness, low energy or poor suckling.

What are the medication choices available during pregnancy and when breast feeding my baby?

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>Can I take if I'm pregnant?</th>
<th>Can I take if I'm breast feeding?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs) and bupropion (nortriptyline)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
| Lithium | Yes | Not recommended
| Benzodiazepine (diazepam) | Yes | Yes |
| Antiepileptic medication (for example clonazepam) | Yes | Yes |
| Antipsychotic medication (for example risperidone) | Yes | Yes |
| Alternative medicines (for example St john's Wort) | No | No |

If you decide that breastfeeding is not possible, you should talk to your doctor about other options.
Don’t forget....

- Contraception
- Non-pharmacological interventions
- ECT
- Driving advice

Questions