

Perinatal Psychiatry



**Evidence-based recommendations for psychotropic
medications
in pregnancy and breastfeeding**

Developing people

for health and

healthcare

Perinatal Psychiatry

Aims and Objectives

To develop an understanding of Evidence-based recommendations for psychotropic medication in pregnancy and lactation

Perinatal Psychiatry

Evidence-based recommendations for psychotropic medications in pregnancy and lactation

With thanks to Dr Angelika Wieck and Dr Aaron McMeekin

Transfer of psychotropic medication to the fetus

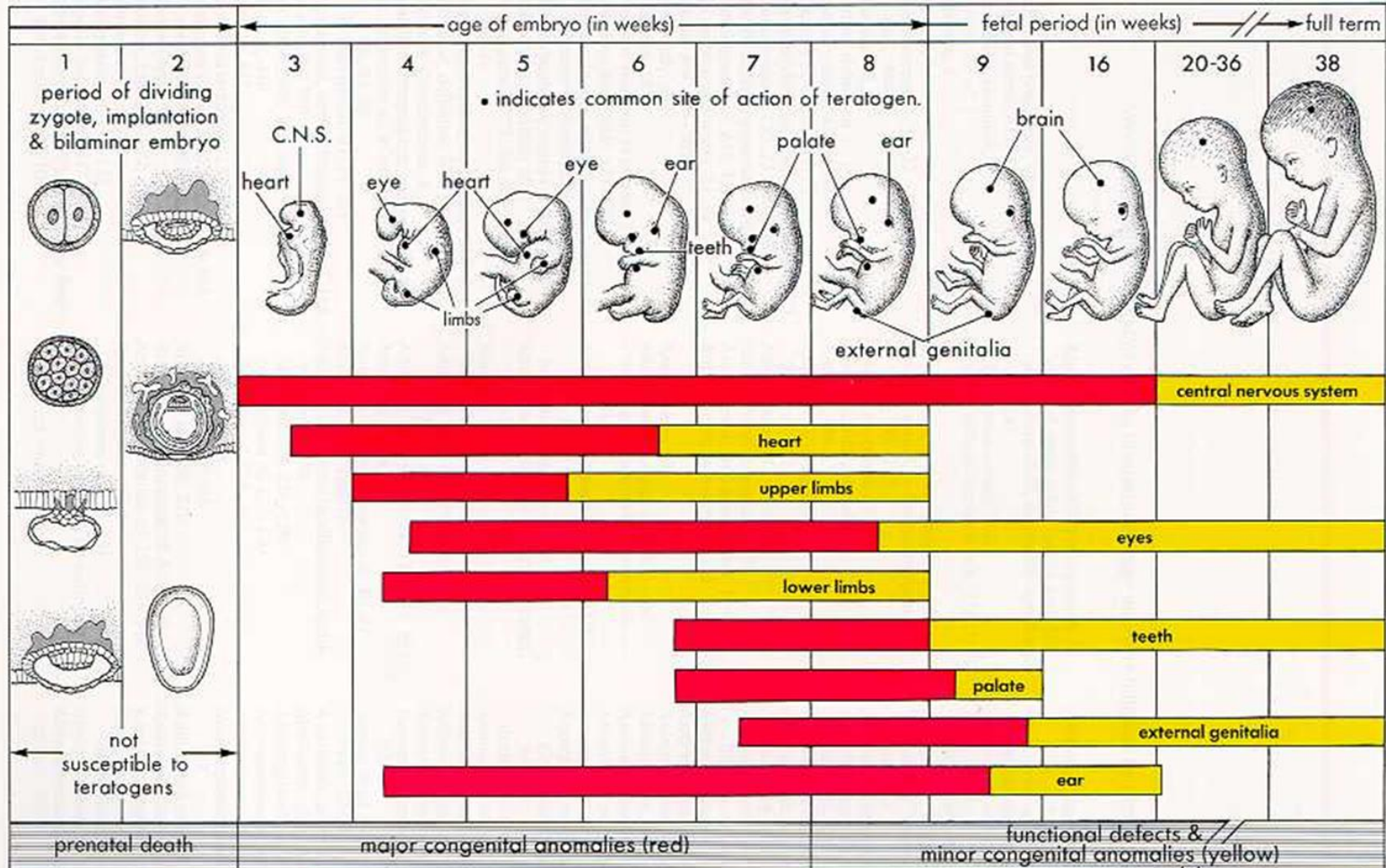
- All psychotropic drugs pass through placenta and are present in the amniotic fluid
- The degree varies between drugs but little as yet known
- Surveys estimate psychotropic medications taken in 21 – 33 percent of established pregnancies¹

• ¹ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation.

Timing of exposure & potential adverse outcomes

Early pregnancy	Major structural defects
Later pregnancy	Minor structural defects Functional defects (e.g. Valproate linked to developmental delay / Autism Spectrum Disorder) Preterm delivery Abnormal fetal growth
At delivery	Neonatal toxicity Neonatal withdrawal
Postnatal	Cognitive and Behavioural effects

CRITICAL PERIODS IN HUMAN DEVELOPMENT*



* Red indicates highly sensitive periods when teratogens may induce major anomalies.

Investigating whether a drug is harmful to the developing child

- Randomised, double-blind controlled trials not ethical
- Next best levels of evidence:
pregnancy registers, population studies, cohort studies, case series and control studies
- There are a lack of well designed prospective comparative studies for psychotropic use in pregnancy¹

• ¹Einarson A1, Boskovic R. (2009). *Use and safety of antipsychotic drugs during pregnancy*. J Psychiatr Pract. 15(3):183-92.

Sample Sizes Needed to test for congenital anomalies

- Depends on outcome in question and what risk increases are assumed
- Major congenital malformation rate is 3 % in general population:
1,000 exposed cases needed to test for doubling of risk¹
- Specific malformation with a 0.1 % occurrence in general population (e.g. cleft palate):
even when including 4 controls for each exposure, almost 11,000 exposed cases are needed to test for a doubling of the effect².
- Sample sizes in studies of first trimester exposure to **individual** psychotropic agents:

Antidepressants/
antiepileptics:
> 1,000

Lithium,
Anti-
psychotics:
< 600

- Sample sizes for studies of later pregnancy exposure are also often inadequate
- ¹European Medicines Agency (2008)
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003307.pdf
- ²Dellicour S, ter Kuile FO, Stergachis A (2008). PLoS Med 5(9): e187. doi:10.1371/journal.pmed.0050187

Quality of evidence

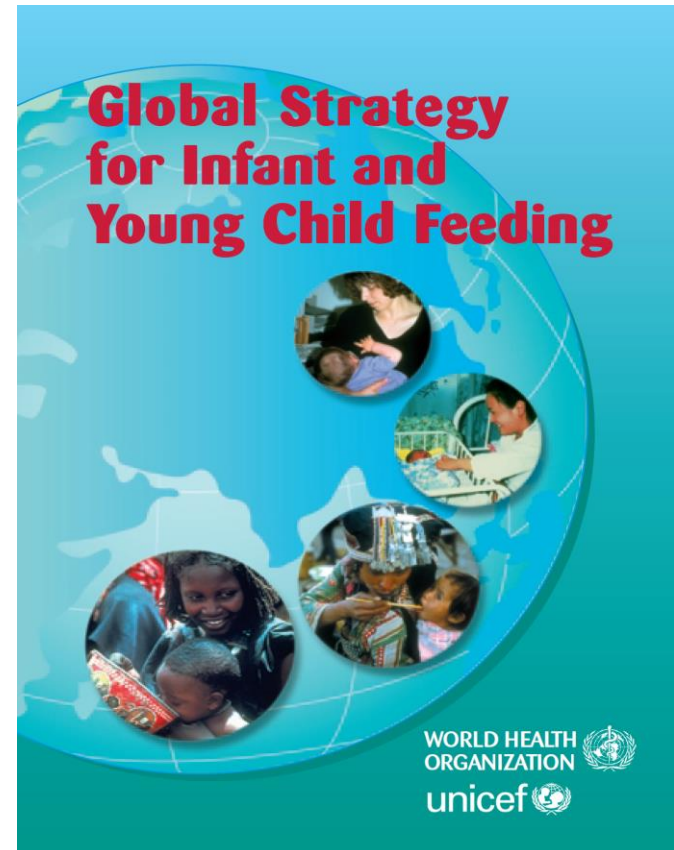
- Many other factors confound pregnancy and infant outcomes
- Little as yet known about untreated maternal mental illness, but preliminary insights point to an adverse effect (stress, life style, physical health, sleep, illness itself)
- Conversely women with SMI (serious mental illness) are more likely to smoke, drink alcohol or use illicit substances in pregnancy¹
- Studies control for different confounding factors – hampers comparison between studies
- Epidemiological studies have the advantage of large numbers but lack accuracy of infant diagnoses and diagnostic bias
- Research difficult to do !

• ¹McAllister-Williams et al (2017). British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. *Journal of Psychopharmacology*, 31(5), pp.519-552.

WHO Lactation Strategy

WHO, 2003¹:

- ‘Infants should be exclusively breastfed for the first six months of life. Thereafter, to meet their evolving nutritional requirements, infants should receive nutritionally adequate and safe complementary foods while breastfeeding continues for up to two years of age or beyond.’
- **RCM (2018)** have advised new mothers who formula feed to receive as much support as breastfeeding mothers



Lactation

- All psychotropic drugs are transferred into breast milk
- Exposure during breastfeeding is usually much less than during pregnancy
- Few data for most psychotropics.
- Measure of exposure : **relative infant dose (RID)**:
infant dose/kg bw : maternal dose/ kg bw
- RID < 10% regarded as 'relatively safe' – Hale (2014) ¹
- Most psychotropics are well below 10 %, but some exceptions
(Lithium levels range from 10 – 60% of maternal serum concentrations)

¹Hale T Medications & Mother's Milk. Hale Publishing. <http://www.medsmilk.com/>

Principles of treatment

- There are no risk free options !
- Optimize non-pharmacological treatments
- Addressing substance misuse, unhealthy lifestyle and physical illness as important as minimising medication effects for infant outcome
- Treatment decisions are highly individual – there is no right answer for everyone!

- **When choosing medication with the patient take into account:**

Past response to treatment

Side effect profile

Individual preferences

Principles of treatment

- Include partner / significant other in discussion
- Always record discussion in patient data file !

Women with childbearing potential

Discuss with patient once a year –

- How safe are the prescribed drugs in pregnancy ?
- What are your plans for childbearing ?
- Are you using contraception ?
- Do you require family planning advice ?

Consider the patient's ability to parent

Women with childbearing potential

- 2007: Less than a quarter of psychiatrists prescribing antiepileptic drugs or lithium ask women of childbearing potential whether they are pregnant or use adequate contraception^{1,2}
- 2015: Audits from Manchester and London shows only a small improvement³.

¹ Wieck *et al* Arch Womens Ment Health 2007; 10: 83-5

² James *et al* J Psychopharmacol 2007; 21: 815-9

³ Harper *et al*, Annual Scientific Meeting (Poster), Perinatal Faculty, London, November 2015

Principles of prescribing (Preconception and in Pregnancy)

- Avoid drugs with higher teratogenic risk
- Avoid drugs with the least safety data
- Avoid abrupt discontinuation on confirmation of pregnancy (unless it is **valproate**)
- Avoid polypharmacy, if possible
- Use lowest but still effective dose
- Women who are obese or have poor diet should take folic acid (folate) at a high dose (5 mg)

Folic acid, **at best**, provides only **partial** protection re Valproate effects¹

• ¹Wieck, A. and Jones, S. (2018). Dangers of valproate in pregnancy. *BMJ*, p.k1609.

Principles of prescribing (Preconception and in Pregnancy)

Teratogenic Risk

- Estimated risk of major congenital malformations (greatest to least teratogenic)
 - Valproate
 - Carbamazepine
 - Lithium
 - Lamotrigine
 - Antipsychotics
 - Antidepressants

Pregnant women with a previous mental illness

- Start perinatal care planning as early in pregnancy as possible
- Refer to perinatal psychiatry specialist if available
- ***Safety data change all the time*** – perinatal specialist is up to date and can integrate new data with specific clinical situation

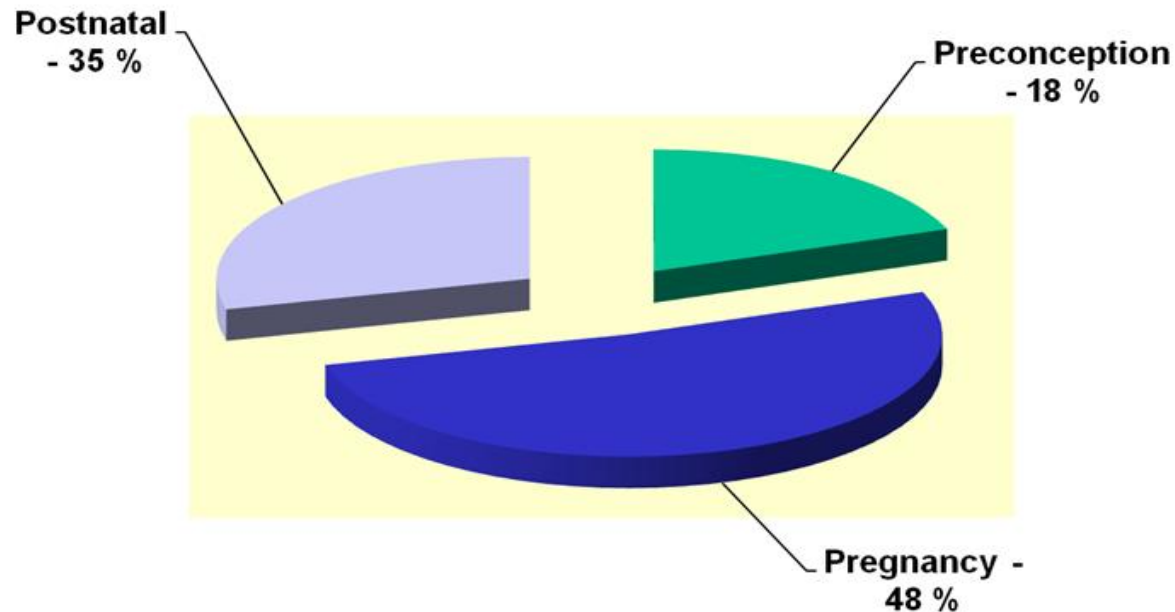
Pregnant women with a previous mental illness

- Identify risk factors for postnatal recurrence
- Discuss stress reduction, sleep optimisation
- Maximise postnatal support
- Formulate detailed perinatal plan and distribute among all involved professionals
- Pregnant women should be seen by psychiatrist within two weeks of referral (NICE, antenatal postnatal mental health guidelines, 2014)

Pregnant women with a previous mental illness

- Inform obstetric team of psychotropic medication
- Inform community midwife and health visitor of maternal medication
– neonatal withdrawal may commence after discharge

Childbearing status at first presentation in Manchester Perinatal Psychiatry Clinic



Evidence for reproductive safety of psychotropic drugs

- Evidence changes evolve continually
- Therefore prescribing practice must evolve in tandem to avoid evidence that can become quickly outdated
- In UK 3 main bodies produce sets of guidelines
 - National Institute for Health and Care Excellence (NICE)
 - Scottish Intercollegiate Guidelines Network (SIGN)
 - British Association for Psychopharmacology (BAP)
- However Google Scholar may provide the latest papers

Neurodevelopment

Peng et al, 2013¹

- Well-designed prospective study of 76 infants exposed to FGAs or SGAs in pregnancy, matched to 76 control children
- Scores indicate delay in several cognitive domains (Bayley Scale of infant and toddler development) in early postnatal months
- Scores normalized by 12 months postnatal

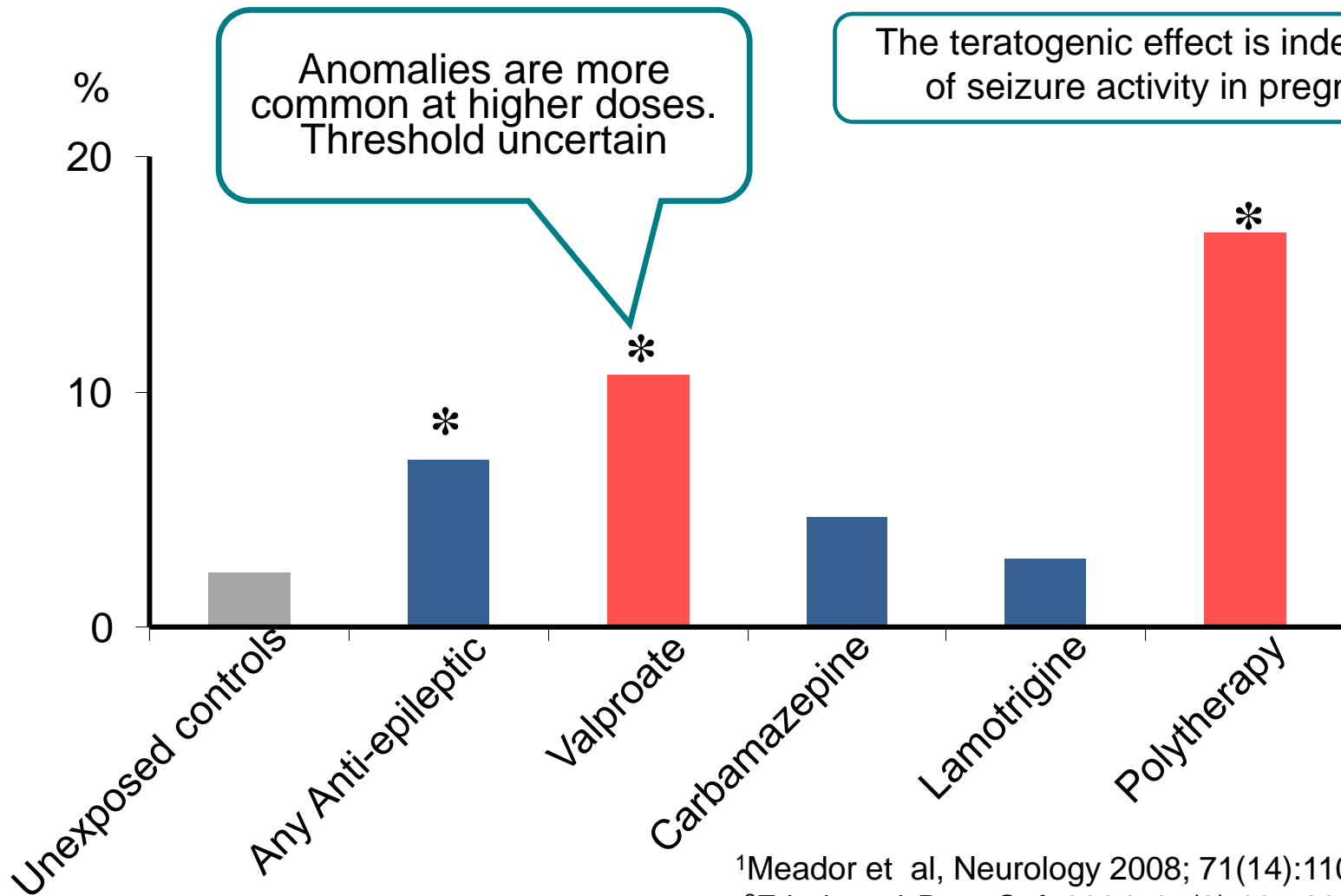
No difference at 12 months is consistent with findings in earlier studies^{2,3,4}

¹Peng et al. *Psychopharmacology (Berl)*. 2013 Apr 5. [Epub ahead of print]; ²Gentile S, *Schizophr Bull* 2010; 36: 518-44; ³Kris 1965, *Curr Ther Res Clin Exp*; 7: 785-9; ⁴Slone *et al* 1977, *Am J Obstet Gynecol*; 128: 486-8

Summary

- Current evidence does not suggest that antipsychotics are major teratogens.
- Small increase in major congenital anomalies (mostly cardiovascular, esp. septal defects) may be due to confounding factors. Larger samples and control for confounders is needed
- Association with a small increase in babies small for gestational age and pre-term birth may also be associated with confounding factors
- Possible association with 2X fold increase of gestational diabetes, possibly related to early pregnancy BMI. Further research needed.
- NICE (2014)¹ recommends screening for gestational diabetes in all women taking antipsychotics in pregnancy
- Possible association with 2X fold increase in stillbirth
Requires further research

Antiepileptic drugs and congenital anomalies¹



¹Meador et al, Neurology 2008; 71(14):1109-17

²Fried et al, Drug Saf 2004; 27(3):197-202

(* = significant difference to non-epileptic controls)

	Significant associations with	Risk of spina bifida
Valproate¹	<p>Spina bifida Hypospadias Cleft palate Atrial septal defects Polydactyly Craniosynostosis</p>	<p>OR: 12.7 (CI : 7.7 to 20.7)</p>
Carbamazepine²	<p>Spina bifida Cardiovascular anomalies ?</p>	<p>OR: 2.6 (CI : 1.2 to 5.3)</p>
Lamotrigine³⁻⁷	<p>1 study found increase in oral clefts from 7 : 10,000 to 7 : 1,000, subsequent studies did not confirm. Low teratogenicity compared with valproate but few comparisons with untreated infants yet</p>	

Valproate: other neurodevelopmental disorders

Several earlier studies suggest association¹

Christensen et al (2013)² - Population study from Denmark

- 14 year follow up
- Childhood autism : 2.50 % (adjusted hazard ratio: 5.2; 2.7-10.0)
- Autism spectrum disorder: 4.42 % (adjusted hazard ratio: 2.9; 1.7-4.9)

Cohen et al (2013)³

- At increased risk of ADHD diagnosis at age 6

Dose-relationships not yet sufficiently clarified^{4,5}

Dietary folate supplementation— is it preventative ?

- 400 microgram daily recommended at general population level for 3 months before and after conception to prevent congenital anomalies, particularly neural tube defects
- **High doses** (5mg daily) recommended for **high risk families**
- NICE (2004, 2007) recommends 5mg folic acid in periconceptual period for women taking antiepileptic drugs.
- Data from pregnancy registers and reviews:^{1,2,3,4}

**Folate's preventative effect of anomalies in women taking AEDs is at best uncertain. No protection seen in some studies.
Preventative effect of neurodevelopmental impairments unknown.**

Lithium

- **‘Lithium baby register’ (N=225) ¹**
 - 18 (8%) babies had cardiovascular defects compared to 1 % in general population
 - 6 (2.7 %) had Ebstein anomaly compared to 1 : 20,000 in general population
 - Poor design
- **Recent reviews ^{2,3} :**
 - Still small body of subsequent data
 - Original observations were most likely a significant overestimation
 - But actual risk remains uncertain
 - Evidence lithium causes the anomaly is uncertain⁴

¹ Weinstein ,1980, Handbook of lithium therapy, pp. 421-9. MTP Press, Lancaster.

² Yacobi and Ornoy. Isr J Psychiatry Relat Sci 2008; 45: 95–106,

³McKnight et al, Lancet. 2012 Feb 25;379(9817):721-8

⁴ Jones, I., Chandra, P., Dazzan, P. and Howard, L. (2014). Bipolar disorder, affective psychosis, and schizophrenia in pregnancy and the post-partum period. *The Lancet*, 384(9956), pp.1789-1799.

- **Fetal or neonatal effects – case reports of ¹**
 - Cardiac arrhythmias, hypoglycaemia, diabetes insipidus, polyhydramnios, thyroid dysfunction, goitre, floppiness, lethargy, hepatic anomalies and respiratory difficulties
 - Cases reported of maternal and neonatal toxicity

- **Neurobehavioural outcome² :**
 - 5 year prospective study of 60 children showed no adverse effects when compared with their unexposed siblings

1 American College of Obstetricians and Gynecologists 2007, Practice Bulletin Number 87

2 Schou, Acta Psychiatr Scan 1976; 54: 193-7

Summary for mood – stabilizers and recommendations

Valproate:

- The concerns about the use of valproate in pregnancy have increased.
- The administration of folate can only partially prevent harm to children
- Valproate should not be used during the whole of pregnancy

European Medicines Agency (2018)¹ recommends that:

- Valproate should not be used in pregnancy unless the women has a form of epilepsy that is unresponsive to other epileptic drugs
- Valproate should not be prescribed to women of childbearing potential unless they follow a comprehensive pregnancy prevention programme (assessment of potential to become pregnant, pregnancy tests before and during treatment and counselling on risks and contraception)
- Patients may be required to have specialist reviews and complete a risk acknowledgement form every year
- Valproate packing may carry a visual warning of the pregnancy risks and women will receive a warning card with each prescription

¹Wieck, A. and Jones, S. (2018). Dangers of valproate in pregnancy. *BMJ*, p.k1609.

Summary for mood stabilizers and recommendations

NICE¹:

- **Valproate** must not be used in women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), unless other options are unsuitable and the pregnancy prevention programme is in place
- **Valproate and Carbamazepine** should not be offered in pregnancy¹.
- **Lamotrigine**: no recommendations regarding its use. If used, monitor serum levels frequently in pregnancy (tend to fall) and into the postpartum period (increase again)

Lithium:

- Only continue lithium in first trimester if switch to a safer drug results in high risk of relapse
- Otherwise replace lithium with an antipsychotic agent until after delivery or until the 2nd trimester
- Measure serum levels frequently, particularly in month before expected delivery date (for details see NICE guidance¹)

Antidepressants – neonatal issues

Persistent pulmonary hypertension of the newborn

- SSRI exposure: odds ratio 2.50 (1.32 to 4.73) – meta-analysis by Grigoriadis et al, 2013¹
- Effect seen after late pregnancy exposure only
- Rare condition: number needed to harm : 286-351 for 1 additional case

¹ Grigoriadis et al (2013), BMJ, doi: 10.1136/bmj.f6932

Antidepressants – First trimester exposure

- Little known about tricyclics, clomipramine has been associated with a small increase in cardiovascular malformations
- SSRIs – much more data, mostly from epidemiological studies
- SSSRIs associated with small increase of cardiovascular anomalies (relative risk for cardiovascular malformations 1.36, septal heart defects 1.40)¹
- Data concerning small risks of other malformations is less consistent
- Differences between SSRIs – inconsistent evidence except for paroxetine being probable the SSRI with the highest risks (may be associated with small absolute increase in congenital heart defects but results across other studies inconsistent with some finding no association)

¹Grigoriadis et al (2013) J Clin Psychiatry 74: e293-308

Antidepressants – pregnancy outcomes

Premature delivery

- Inconsistent findings about association between antidepressants and pre-term delivery
- Preterm delivery may be associated with timing of exposure (>3rd trimester)
- Depression is also associated with preterm delivery

Antidepressants – poor neonatal adaptation

- All antidepressants – (meta-analysis by Grigoriadis et al, 2013)
- Poor neonatal adaptation symptoms (OR 5.07)
- Neonatal respiratory distress (OR 2.20)
- Neonatal tremors (OR 7.89)
- Affects 1:3 babies, but mild and transient, rarely needs more than monitoring

SSRIs – autism spectrum disorder

Meta-analysis by Man et al (2014)

- Small increase (Odds ratio 1.81, CI 1.47-2.24)
- Role of confounding factors unknown, 1 study found higher rate in untreated siblings²

Observational studies suggest risk of ASD secondary to SSRIs and SNRIs is small to negligible

Confounding factor may be that women with SMI have higher risk of children with ASD (Unipolar major depression may confer genetic risk for ASD)

- No effects seen with tricyclic antidepressants, SSRIs and venlafaxine in early childhood^{1,2}
- 1 study: weak association of SSRI exposure with delayed motor development at age 3 but not clinically significant³

¹ Nulman et al (2012) Am J Psychiatry, 169: 1165-74

² Santucci et al (2014) J Clin Psychiatry 75(10):1088-95

³ Handal et al (2015) BJOG, doi: 10.1111/1471-0528.13582

- **Antipsychotics:**
 - Avoid clozapine (agranulocytosis)
- **Mood stabilizers:**
 - Don't use lithium
 - Don't use valproate or carbamazepine
- **Antidepressants**
 - NICE (2014) no longer recommends sertraline and paroxetine
 - Differences between drugs appear to be small
- Advise mother to monitor baby for side effects (sedation, muscle tone, other side-effects) – discuss with community midwife/health visitor/ GP if in doubt

GA Module: Perinatal

MCQ

- 1. During pregnancy the following physiological changes occur**
- A. Plasma volume markedly increases and eGFR increases
 - B. Plasma volume markedly decreases and eGFR increases
 - C. Plasma volume markedly increases and eGFR decreases
 - D. Plasma volume markedly decreases and eGFR decreases
 - E. There is no change in either plasma volume or eGFR

GA Module: Perinatal

MCQ

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GA Module: Perinatal

MCQ

2. Which of the following is NOT associated with exposure to SSRIs in the Perinatal period?

- A. Perinatal Death
- B. Persistent Pulmonary Hypertension of the Newborn
- C. Postpartum haemorrhage
- D. Poor neonatal adaptation syndrome
- E. Preterm birth

GA Module: Perinatal

MCQ

2. Which of the following is NOT associated with exposure to SSRIs in the Perinatal period?

- A. Perinatal Death**
- B. Persistent Pulmonary Hypertension of the Newborn
- C. Postpartum haemorrhage
- D. Poor neonatal adaptation syndrome
- E. Preterm birth

GA Module: Perinatal

MCQ

- 3. Which of the following statements is TRUE regarding NICE guidelines?**
- A. Benzodiazepines can be offered in pregnancy for medium term treatment of anxiety
 - B. Consideration of medication dose changes do not have to be made during pregnancy
 - C. If this is a first pregnancy a women's previous response to medication should not influence the choice of antidepressant (being pregnant dictates the choice)
 - D. Lithium can be continued if the women is at high risk of relapse and an antipsychotic is unlikely to be effective
 - E. Measure prolactin levels in women planning pregnancy who are taking a prolactin raising antipsychotic as raised prolactin increases the chances of conception

GA Module: Perinatal

MCQ

3. Which of the following statements is TRUE regarding NICE guidelines?
- A. Benzodiazepines can be offered in pregnancy for medium term treatment of anxiety
 - B. Consideration of medication dose changes do not have to be made during pregnancy
 - C. If this is a first pregnancy a women's previous response to medication should not influence the choice of antidepressant (being pregnant dictates the choice)
 - D. Lithium can be continued if the women is at high risk of relapse and an antipsychotic is unlikely to be effective**
 - E. Measure prolactin levels in women planning pregnancy who are taking a prolactin raising antipsychotic as raised prolactin increases the chances of conception

GA Module: Perinatal

MCQ

4. Which of the following statements is TRUE?

- A. Valproate is associated with reduced fertility in women and men
- B. Taking Folic acid 5mg with Valproate will reduce teratogenicity
- C. Valproate monotherapy is not associated with an increased risk of Attention Deficit Hyperactivity Disorder
- D. Valproate monotherapy only affects the child in the 1st and 3rd trimester
- E. Valproate passes in higher concentrations than Lamotrigine in breastmilk

GA Module: Perinatal

MCQ

4. Which of the following statements is TRUE?

- A. Valproate is associated with reduced fertility in women and men
- B. Taking Folic acid 5mg with Valproate will reduce teratogenicity
- C. Valproate monotherapy is not associated with an increased risk of Attention Deficit Hyperactivity Disorder
- D. Valproate monotherapy only affects the child in the 1st and 3rd trimester
- E. Valproate passes in higher concentrations than Lamotrigine in breastmilk

GA Module: Perinatal

MCQ

5. Which of the following is TRUE regarding breastfeeding?

- A. Patients with postpartum mental health disorders who require pharmacotherapy should generally be discouraged from breastfeeding
- B. All psychotropic medications are transferred to breast milk in varying amounts
- C. Psychotropics should be chosen with regard to longer half life and less protein binding
- D. Mothers should change their pregnancy medication for breastfeeding
- E. Methadone and Nicotine Replacement Therapy are incompatible with breastfeeding

GA Module: Perinatal

MCQ

- 5. Which of the following is TRUE regarding breastfeeding?**
- A. Patients with postpartum mental health disorders who require pharmacotherapy should generally be discouraged from breastfeeding
 - B. All psychotropic medications are transferred to breast milk in varying amounts**
 - C. Psychotropics should be chosen with regard to longer half life and less protein binding
 - D. Mothers should change their pregnancy medication for breastfeeding
 - E. Methadone and Nicotine Replacement therapy are incompatible with breastfeeding

Thank you