The University of Manchester

An introduction into perinatal psychiatry –

including psychopharmacology

Dr Cassia O'Prey
Consultant Psychiatrist
Specialist Perinatal Mental Health Team
Cheshire & Merseyside

TOPICS

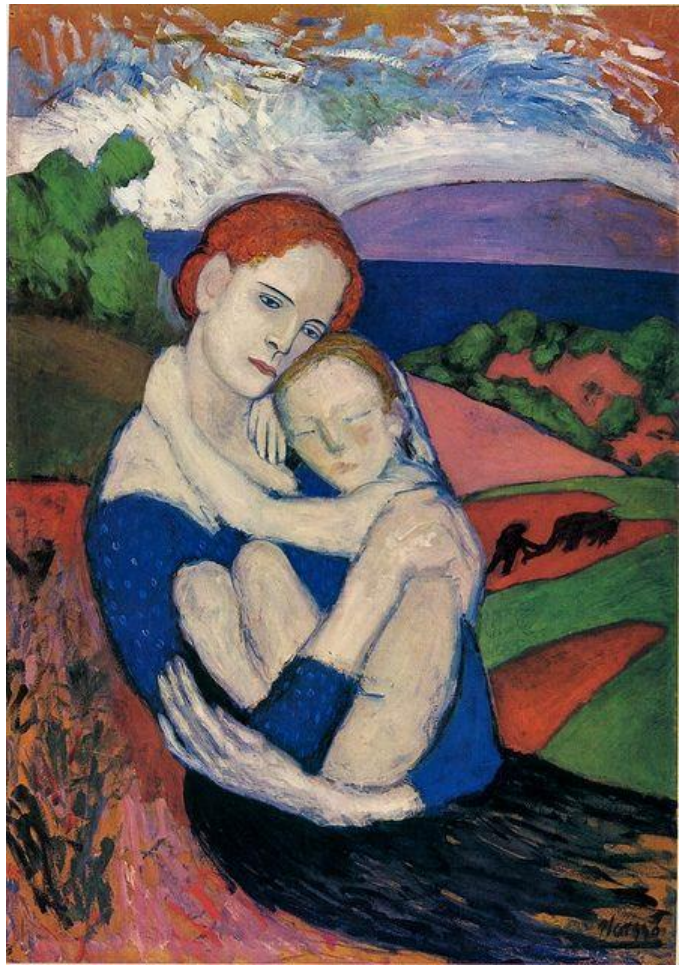
- Epidemiology
- Severe disorders
- Common disorders
- Impact on society and offspring
- Management
- Perinatal psychopharmacology
- Psychiatric medications in the perinatal period

EPIDEMIOLOGY

Rates of mental disorders per 1000 deliveries [1]

Postpartum psychosis	**2**
Chronic serious mental illness	?
Severe depression	30
Mild to moderate depression and anxiety states	100 - 150
Post-traumatic stress disorder	30
Adjustment disorders and distress	150 – 300

[1]JCP Guidance for commissioners of perinatal mental health services. RCPsych 2012

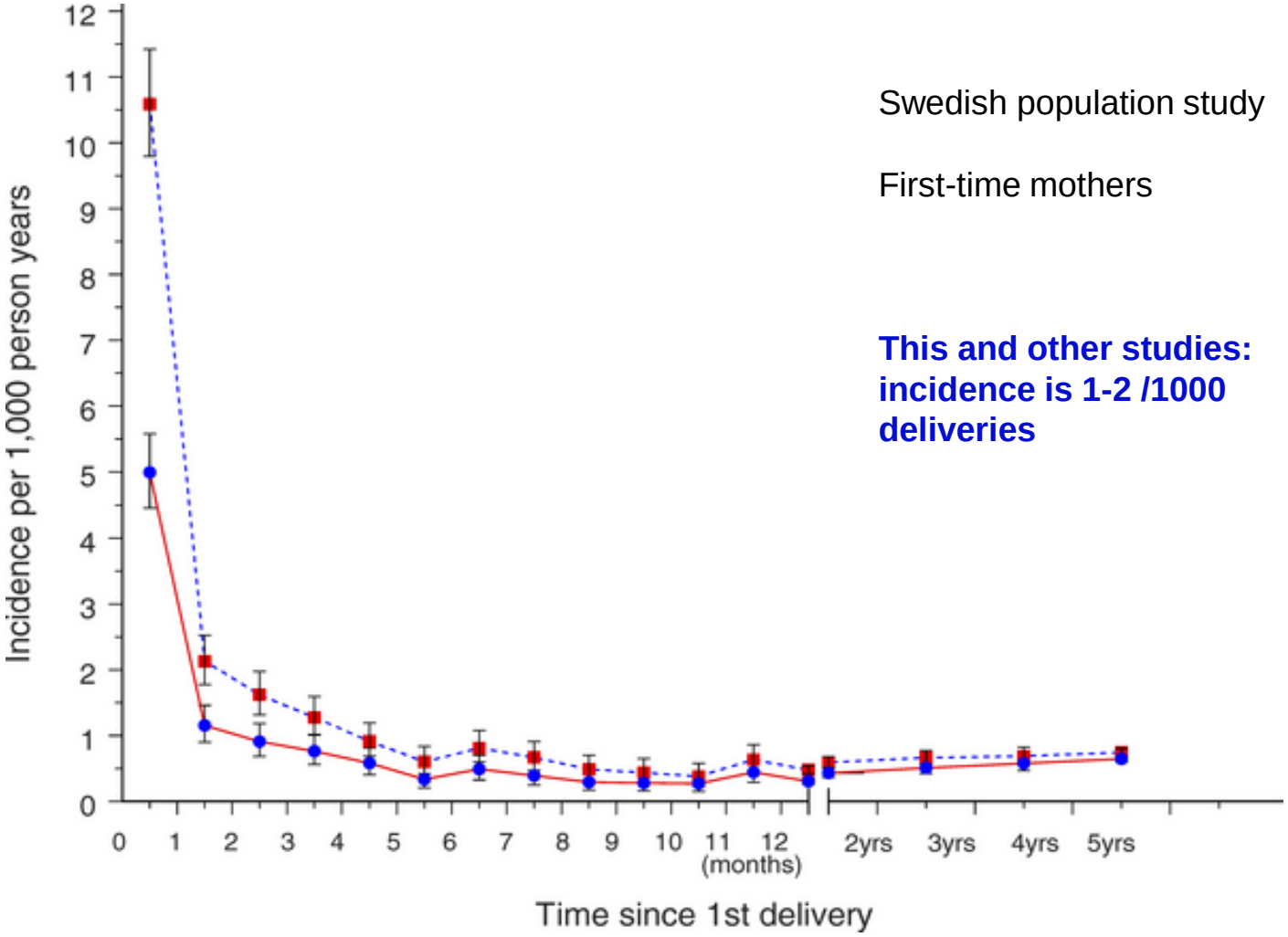


What makes perinatal mental illness different?

- Childbirth triggers affective psychosis
- Impact on Society
- Impact on child development
- Impact on family
- Catastrophic effects of maternal suicide
- Risk of harm and death of child

SEVERE DISORDERS

First-time mothers: incidence of psychosis
(admissions)



Swedish population study

First-time mothers

This and other studies: incidence is 1-2 /1000 deliveries

Valdimarsdóttir et al (2009) PLoS Med 6(2): e1000013. doi:10.1371/journal.pmed.1000013
http://journals.plos.org/plosmedicine/article?id=info:doi/10.1371/journal.pmed.1000013

Perinatal bipolar disorder

- Pregnancy does not protect from recurrences
- High risk of relapse in the early postnatal period

‘PUERPERAL PSYCHOSIS’

- Traditional term
- Includes cases with established bipolar disorder, mania, psychotic depression, schizo-affective psychosis, cycloid psychosis
- New onsets are common
- Psychiatric emergency !!!
- Often high risk situation for woman and baby
- Onset can be extremely acute
- Rapid deterioration
- Mental state can fluctuate

COMMON DISORDERS

Depression

- Pre-occupation with themes of motherhood
- Bonding impairment *'He isn't mine'*
  'it could be anybody's child'
  'I wish someone would adopt her'

  Guilt and self blame *'what kind of person am I not to love my own child ?'*

Risk factors for perinatal depression[1]

Mental health

- a past history of depression, anxiety, PTSD, substance misuse, and neurotic personality traits

Psychosocial adversities

- Domestic violence, major/negative life events, history of abuse, low socio-economic status, poor social support, low social support, migration

Most research in perinatal depression

Risk factors probably not specific for perinatal depression

1. Howard et al (2014), The Lancet, vol 384, 1775-1788

Anxiety disorders

- Often a co-morbidity with other disorders, eg mania, hypomania, depression etc
- Can be the first sign of a psychotic illness
- Anxious thinking and ruminations : serious harm coming to herself or the child, failing as a mother, being perceived as a poor mother

OCD (Russel and Mazamanian, 2013)

- Prevalence in perinatal period about 2 % (2 x increase)
- 1/3 OCD sufferers first become ill in pregnancy or after childbirth

Characterized by…

- Obsessions: Recurrent, intrusive, unwanted and distressing thoughts, images or impulses
- Compulsions: Repetitive mental or behavioural acts intended to decrease the distress associated with the obsessions
- Associated with significant life impairment

ppOCD characterized by

- Rapid onset
- Aggressive obsessions
- E.g., thoughts, images or impulses of harming one's infant, or of harm coming to one's infant

Eating Disorders

(Easter et al, 2012, Micali, 2010)

- 2 % of pregnant women
- Often symptoms improve in pregnancy but become

  more severe again after delivery
- Low birthweight
- Co-morbid depression and anxiety are common

Personality Disorders

- 4.5 % of pregnant women (Bjoeresson et al, 2007)
- Emotionally unstable personality disorder is most common
- Can worsen in perinatal period
- Can be associated with attachment difficulties

Obstetric PTSD (Andersen et al, 2012)

- 1-2 % in postnatal period
- Risk factors - obstetric emergencies and subjective distress in labour
- May lead to avoidance of future pregnancies
- Requests for Caesarean sections common

Tokophobia

- Fear of childbirth
- Previous traumatic delivery
- Can occur in first pregnancy
- Risk factors – other mental illness, history of sexual abuse, poor social support
- High level of subjective distress
- Requests for Caesarean Section

IMPACT ON SOCIETY

Perinatal mental disorders and child development

- Most evidence for perinatal depression
- Association of postnatal depression impairment in development (including delayed cognitive and language development, higher rates of behavioural problems, insecure or disorganized attachment, lower school-leaving grades and higher rates of depression in adolescence)[1-5]
- Antenatal depression associated with prematurity, low birthweight and aspects of long-term development[6.]

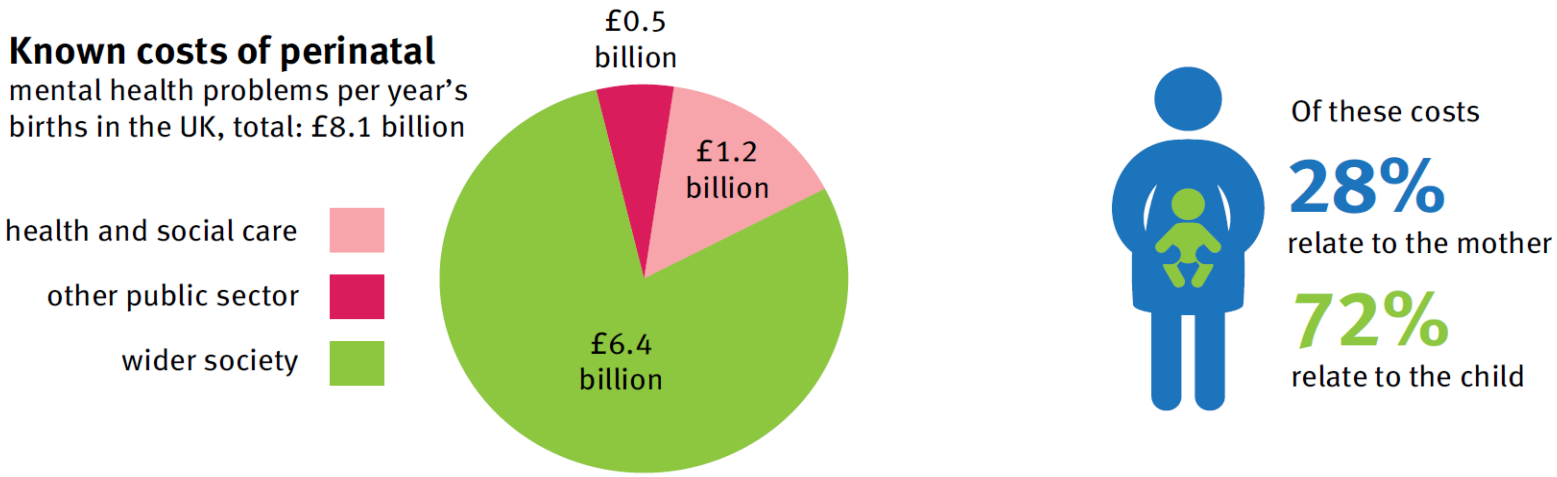
1. Stein A et al. Lancet. 2014;384(9956):1800-1819. 2. Sanger C et al. Arch Womens Ment Health. 2015;18(2):147-162. 3. Murray L et al. J Child Psychol Psychiatry. 2010;51(10): 1150-1159. 4. Murray L et al. J Am Acad Child Adolesc Psychiatry. 2011;50(5):460-470. 5. Netsi et al (2018). JAMA Psychiatry. 2018;75(3):247-253. doi:10.1001/jamapsychiatry.2017.4363. 6. McAllister-Williams et al (2017); Journal of Psychopharmacology, 1–34

Perinatal mental disorders and fathers

- Maternal perinatal depression is risk factor for father's depression[1]
- Also: history of severe depression, or symptoms of depression or anxiety prenatally.[1]

1. Grasser and Lerner-Geva. Persepctives in Public Health. Royal Society for Public Health, 2018
ISSN 1757-9139 DOI: 10.1177/1757913918790597. 2. Ramchandani P, Stein A, Evans J, O'Connor TG, ALSPAC Study Team. Lancet. 2005;365(9478):2201–2205pmid:15978928. 3. Fletcher RJ, Feeman E, Garfield C, Vimpani G. Med J Aust. 2011;195(11–12):685–689

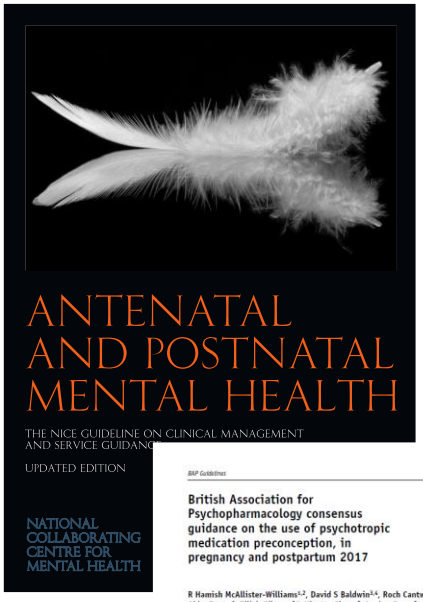
Costs of Perinatal Mental Illness[1]: 8.1 Billion/year



Bauer et al (2014) The costs of perinatal mental health problems, Centre for Mental Health, London, www.centreformentalhealth.org.uk

MANAGEMENT

GUIDELINES



BAP Guidelines

British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017

Psychopharm

SAGE

R Hamish McAllister-Williams[1,2], David S Baldwin[3,4], Roch Cantwell[5], Abby Easter[6], Eilish Gilvarry[7,7], Vivette Glover[8], Lucian Green[9], Alain Gregoire[3,10], Louise M Howard[11,12], Ian Jones[13], Hind Khalifeh[11,12], Anne Lingford-Hughes[14], Elizabeth McDonald[15,16,17], Nadia Micali[18], Carmine M Pariante[12,19], Lesley Peters[20], Ann Roberts[20,21,22], Natalie C Smith[23], David Taylor[12,24], Angelika Wieck[25,26], Laura M Yates[27,28] and Allan H Young[12,13]; endorsed by the British Association for Psychopharmacology

Abstract

Decisions about the use of psychotropic medication in pregnancy are an ongoing challenge for clinicians and women with mental health problems, owing to the uncertainties around risks of the illness itself to mother and fetus/infant, effectiveness of medications in pregnancy and risks to the fetus/infant from in utero exposure or via breast milk. These consensus guidelines aim to provide pragmatic advice regarding these issues. They are divided into sections on risks of untreated illness in pregnancy; general principles of using drugs in the perinatal period; benefits and harms associated with individual drugs; and recommendations for the management of specific disorders.

Keywords

Antidepressants, antipsychotics, anxiolytics, birth defects, breastfeeding, child development, conception, fertility, hypnotics, mood stabilisers, neonatal problems, postpartum, pregnancy, pregnancy outcome, psychiatric illness, psychotropics, teratogenicity

[1]Institute of Neuroscience, Newcastle University, Newcastle, UK
[2]Northumberland Tyne and Wear NHS Foundation Trust, Newcastle upon Tyne, UK
[3]Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK
[4]University Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa
[5]NHS Greater Glasgow and Clyde, Glasgow, UK
[6]Centre for Implementation Science, Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[7]Institute of Health and Society, Newcastle University, Newcastle, UK
[8]Institute of Reproductive and Developmental Biology, Imperial College London, London, UK
[9]Ealing, Hounslow, Hammersmith & Fulham Perinatal Mental Health Service, West London Mental Health Trust, London, UK
[10]Hampshire Perinatal Mental Health Service, Winchester, UK
[11]Section of Women's Mental Health, Institute of Psychiatry Psychology and Neuroscience, King's College London, London, UK
[12]South London and Maudsley NHS Foundation Trust, London, UK
[13]National Centre for Mental Health, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK
[14]Centre for Psychiatry, Imperial College London, London, UK
[15]Royal College of Psychiatrists, London, UK
[16]East London Foundation Trust, London, UK
[17]Tavistock and Portman NHS Foundation Trust, London, UK
[18]Behavioural and Brain Sciences Unit, GOSH Institute of Child Health, University College London, London, UK
[19]Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[20]St Martin's Healthcare Services CIC, Leeds, UK
[21]Hertfordshire Partnership University NHS Foundation Trust, Hatfield, Hertfordshire, UK
[22]Postgraduate School of Medicine, University of Hertfordshire, Hatfield, Hertfordshire, UK
[23]Tees, Esk and Wear Valleys NHS Foundation Trust, Darlington, County Durham, UK
[24]Institute of Pharmaceutical Science, King's College London, London, UK
[25]Greater Manchester Mental Health NHS Foundation Trust, Manchester, UK
[26]University of Manchester, Manchester, UK
[27]UK Teratology Information Service, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[28]Institute of Genetic Medicine, Newcastle University, Newcastle, UK

Corresponding author:
R H McAllister-Williams, Academic Psychiatry, Wolfson Research Centre, Campus For Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK.
Email: r.h.mcallister-williams@ncl.ac.uk

- NICE guidelines on Antenatal and Postnatal Mental Health (2014)

- Guidelines of the British Association for Psychopharmacology (2017)

Suspected postpartum psychosis (NICE, 2014)

If woman has sudden onset of symptoms suggesting postpartum psychosis,

- she should be referred immediately for assessment by the secondary mental health service

- preferably a specialist perinatal mental health service and preferably by a senior psychiatrist

- The assessment should be immediate -within 4 hours of referral

Psychological therapy

- Perinatal patients – Assessment within 2 weeks
- Course of treatment should start within 6 weeks (National outcomes, pathway 3).

- Parenting interventions where problems. Evidence of benefit still limited for parents with severe mental health problems.

PRESCRIBING IN PREGNANCY - GENERAL PRINCIPALS

Risks of untreated depression, anxiety

- Low birth weight
  - Associated with depression severity

- Preterm delivery
  - Associated with depression severity

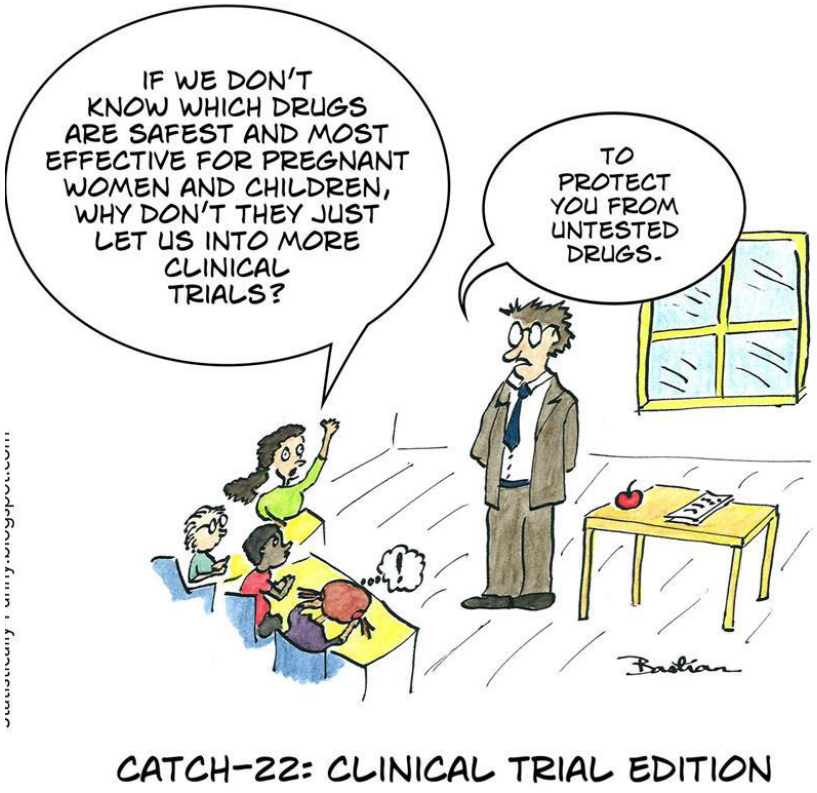
- Adverse childhood outcomes e.g.
  - Emotional and conduct problems, ADHD

- Poor engagement/bonding with child
  - Poor infant learning and cognitive development

- Long term behavioural and other mental problems in offspring

Difficulties with the evidence

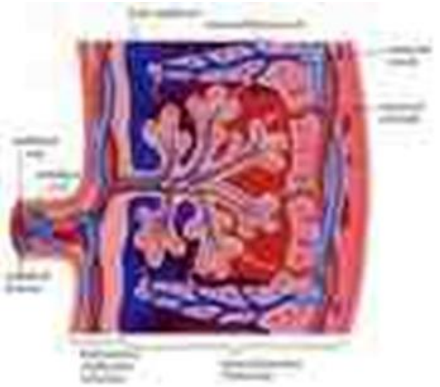
- Limited data although some more robust studies especially with antidepressants
- Studies often show conflicting results - therefore difficult to generalise to clinical practice.
- Difficult to control for confounders (obesity, alcohol, tobacco, folic acid, smoking and the mental illness itself)
- Detection bias - are children known to be exposed more likely to be examined more thoroughly?
- Severity of malformation often not described.
- Likely high incidence of non compliance will skew data
- Background population risk of congenital abnormalities 1-2 in 100
- You need high exposure rates to see results, most are 1 in 1000 therefore need very large studies to find associations (2000 pts)



Prescribing in the perinatal period

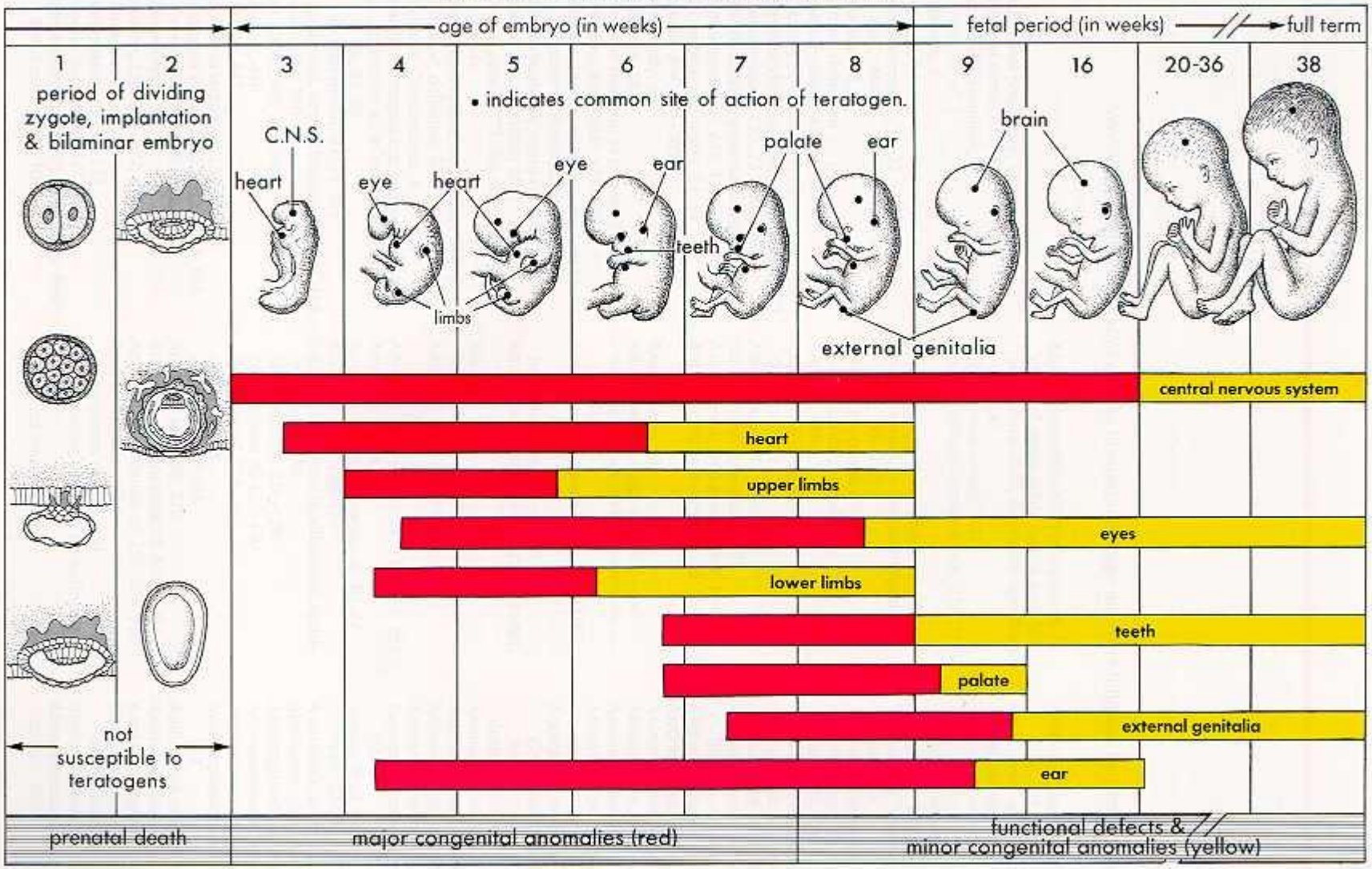
- Individual choice
- Complex risk-benefit analysis for mother and baby
- Avoid abrupt discontinuation when pregnancy is discovered
- Start low, go slow, but make sure it's a therapeutic dose
- Avoid polypharmacy if possible
- Use what works
- Clear documentation

Transfer of psychotropic medication to the fetus



- All psychotropic drugs pass through placenta
- How much, varies with the drug

CRITICAL PERIODS IN HUMAN DEVELOPMENT*



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

Timing of exposure & potential adverse outcomes

Early pregnancy	Major structural defects
Later pregnancy	Minor structural defects Functional defects Premature delivery Abnormal fetal growth
Before delivery	Neonatal toxicity Neonatal withdrawal
Developmental effects	Intelligence, behaviour, motor and social development

ANTIDEPRESSANTS

General

- NICE no longer gives guidance about specific antidepressants in pregnancy – 'TCA/SSRI/SNRI'
- SSRIs are usually prescribed for depression in pregnancy (avoid paroxetine)
- If someone is already on Mirtazapine/Venlafaxine need to consider the risks of cross-titrating and exposing the feotus to 2 antidepressants.
- Association with congenital heart defects and other defects may be less than previously thought, even for paroxetine.
- No consistent association with spontaneous abortion, still birth, neonatal death and low birth weight
- Associated with lower gestational age at birth
- Neonatal Adaption Syndrome – agitated, restless, jittery, poor feeding, insomnia, respiratory distress, seizures (higher incidence with paroxetine/venlafaxine)
- Increased risk of Persistent Pulmonary Hypertension of New Born (from 1-2/1000 in general population to 2-3/1000) but still very unlikely!!

Impact of confounding factors

- Finnish registry study of SSRIs[1]
- Major congenital abnormalities OR 1.24 (1.1 – 1.39)
- Not significant when controlled for confounders OR 1.08 (0.96-1.22)
- Women with 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)

1. Malm et al (2011) Obstet Gynecol. Jul;118(1):111-20. doi: 10.1097/AOG.0b013e318220edcc

Impact of genetic factors[1]

RESEARCH

OPEN ACCESS

Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design

Kari Furu,[1] Helle Kieler,[2] Bengt Haglund,[2] Anders Engeland,[1 3] Randi Selmer,[1] Olof Stephansson,[2 4] Unnur Anna Valdimarsdottir,[5 6] Helga Zoega,[5] Miia Artama,[7 8] Mika Gissler,[9 10] Heli Malm,[11 12] Mette Nørgaard[13]

For numbered affiliations see end of article.

Correspondence to: K Furu kari.furu@fhi.no

Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmj.h1798)

Cite this as: *BMJ* 2015;350:h1798 doi: 10.1136/bmj.h1798

Accepted: 10 March 2015

ABSTRACT

OBJECTIVE

To assess whether use of specific selective serotonin reuptake inhibitors (SSRIs) or venlafaxine in early pregnancy is associated with an increased risk of birth defects, with emphasis on cardiovascular birth defects even when accounting for lifestyle or other familial confounding.

DESIGN

Multicountry population based cohort study, including sibling controlled design.

to 1.06 (0.91 to 1.24). The odds ratios for any cardiac birth defect with use of any SSRI or venlafaxine were 1.15 (95% confidence interval 1.05 to 1.26) in the covariate adjusted analysis and 0.92 (0.72 to 1.17) in the sibling controlled analysis. For atrial and ventricular septal defects the covariate adjusted odds ratio was 1.17 (1.05 to 1.31). Exposure to any SSRI or venlafaxine increased the prevalence of right ventricular outflow tract obstruction defects, with a covariate adjusted odds ratio of 1.48 (1.15 to 1.89). In the sibling controlled analysis the adjusted odds ratio

- 2.3 million births
- 36,772 SSRI exposures
- Cardiac defect adjusted OR =1.15
- Sibling controls - OR lower and not significant (0.92)

- "Although the prevalence of septal defects and right ventricular outflow tract defects was higher in the exposed infants, the lack of an association in the sibling controlled analyses points against a teratogenic effect of these drugs"

Furu et al (2015) BMJ; Apr 17;350:h1798. doi: 10.1136/bmj.h17985

Do SSRIs cause congenital anomalies ?

Meta-analysis by Gao et al (2018)

- 1st trimester exposure
- N=29 cohort studies
- > 9 million births
- All SSRIs together: Major Congentital Abnormalities: RR 1.11 (CI 1.03-1.19)

  Heart anomalies: RR 1.24 (CI 1.11-1.37)

  But:

  no effects in analyses of medicated vs unmedicated women with psychiatric disorder psychiatric disorder !

  SO.. Is this the impact of the illness rather then meds?
- Individual SSRIs: Same finding

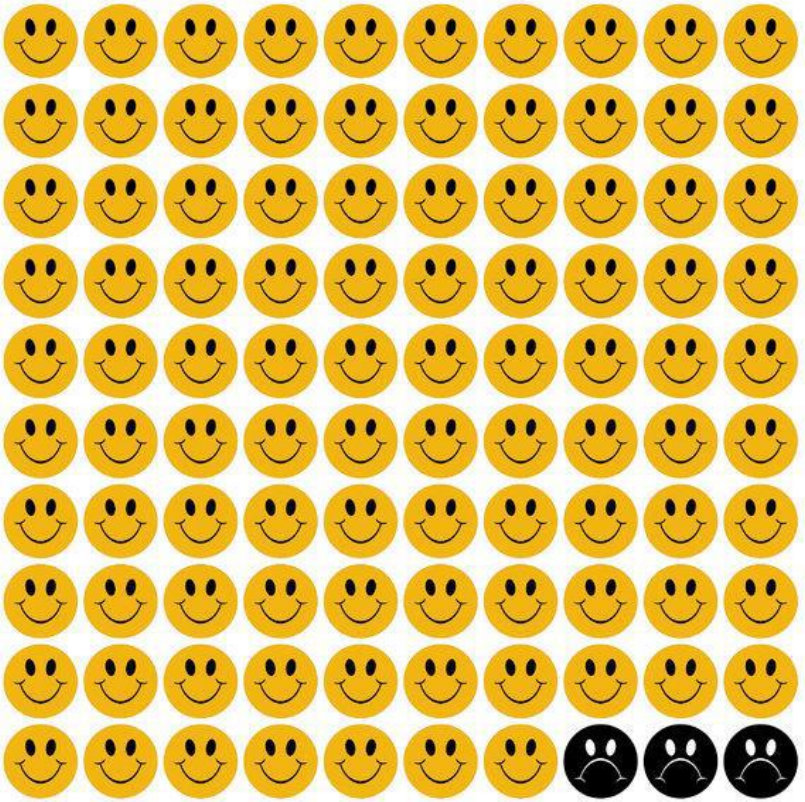
1. Gao SY et al (2018) BMC Med. 2018 Nov 12;16(1):205. doi: 10.1186/s12916-018-1193-5.

Do SSRIs cause congenital anomalies ?

- When effects are reported they are really small.
- The better confounding factors are controlled for the smaller the medication effect.

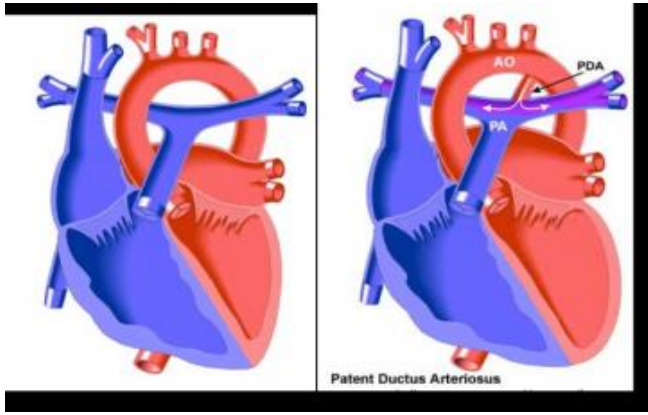
It depends how you say it

- –“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”



Persistent pulmonary hypertension of the newborn: SSRIs and SNRIs

- Rare condition (2-6 / 1,000)
- Increased resistance in pulmonary blood vessels
- Can be fatal
- Original study (Chambers et al, 2016 ref) reported 6 x increase !



Recent meta-analysis[1]

- 11 studies
- 156,978 women - 452 cases
- SSRI use at any time of pregnancy :
  OR 1.82 (CI 1.31-2.54)
- No higher risk when exposure late in pregnancy

But -

- Incomplete adjustment of confounders
- Still small number of cases !

[1] Masarwa et al (2019) AJOG Jan;220(1):57.e1-57.e13. doi: 10.1016/j.ajog.2018.08.030

Exposure in late pregnancy

Poor neonatal adaptation

- All antidepressants can cause it [1]
- About 3-fold increased risk of adaptation symptoms
- Neonatal respiratory distress, tremors, problems in temperature regulation and
- In most cases mild and transient

Hypoglycaemia - common (19%)[2]

[1] Grigoriadis et al (2013) J Clin Psychiatry, 74(4): e309-e320
[2]Forsberg et al (2014) PLoS One, 9(11): 2111327

Is SSRI use in pregnancy associated with long-term effects ?[1,2]

- Association reported with autism spectrum disorder
- Range of odds/ hazard/ relative risk ratios in meta-analyses : about 1.0 –2.5; Sujan et al 2019.
- What is the explanation for this ?

1. Sujan AC, Öberg AS, Quinn PD, D'Onofrio BM. Annual Research Review: Maternal antidepressant use during pregnancy and offspring neurodevelopmental problems - a critical review and recommendations for future research. J Child Psychol Psychiatry. 2019 Apr;60(4):356-376. doi: 10.1111/jcpp.13004. Epub 2018 Dec 5. Review.
2. Morales DR, Slattery J, Evans S, Kurz X. Antidepressant use during pregnancy and risk of autism spectrum disorder and attention deficit hyperactivity disorder: systematic review of observational studies and methodological considerations. BMC Med. 2018 Jan 15;16(1):6. doi: 10.1186/s12916-017-0993-3. Review.

- **Could it be maternal mental illness ?**

  When taken into account it reduces or abolishes the risk[1,2]

- **Or genetic factors ?**

  - Comparison with unexposed siblings supports this on the whole[1,2,3]

- **Assessment**

  - Association could be explained by confounders but still some uncertainty explained by confounders

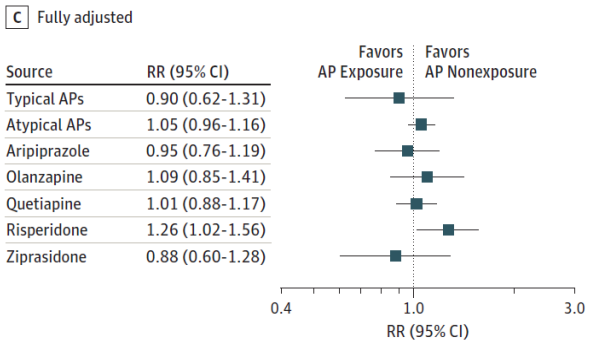
1. Sujan AC, Öberg AS, Quinn PD, D'Onofrio BM. Annual Research Review: Maternal antidepressant use during pregnancy and offspring neurodevelopmental problems - a critical review and recommendations for future research. J Child Psychol Psychiatry. 2019 Apr;60(4):356-376. doi: 10.1111/jcpp.13004. Epub 2018 Dec 5. Review.
2. Morales DR, Slattery J, Evans S, Kurz X. Antidepressant use during pregnancy and risk of autism spectrum disorder and attention deficit hyperactivity disorder: systematic review of observational studies and methodological considerations. BMC Med. 2018 Jan 15;16(1):6. doi: 10.1186/s12916-017-0993-3. Review
3. Andrade (2017) J Clin Psychiatry. 2017 Sep/Oct;78(8):e1047-e1051. doi: 10.4088/JCP.17f11903

ANTIPSYCHOTICS
USED FOR PSYCHOSIS OR MOOD STABILISERS

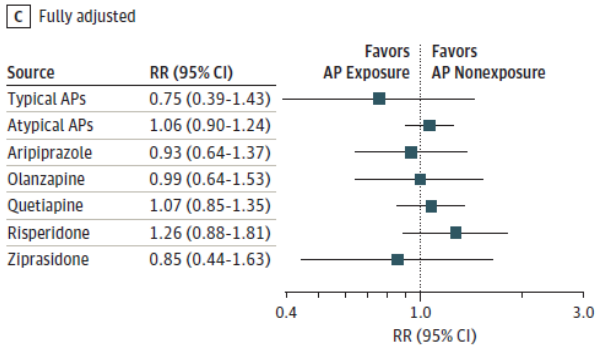
Antipsychotics: study with largest number of exposures and confounding factors controlled for[1]

- 1.3 million women enrolled in Medicaid, US
- N= 9,991 first trimester exposures

Any Major Cong. Mal.



Cardiovascular MCM



No increased risks, except for risperidone:

- Overall malformations: RR 1.26; 95%, CI 1.02-1.56
- Cardiac MCMs at doses > 2mg : RR 2.08, 95% CI 1.32-3.28

[1]Huybrechts et al (2016) Jama Psychiatry, 73(9):938-946. doi:10.1001/jamapsychiatry.2016.1520

Is there an increase of gestational diabetes ?

1. Two population-wide studies from Sweden[1,2]

- Incidence of GDM almost two-fold increased (odds ratios: 1.78, 1.77; 1.94)
- Effect accounted for by early pregnancy BMI
  dropped below significance level[2]

2. Cohort study from US

- Atypical antipsychotics
- Control group: women who discontinued antipsychotics at beginning of pregnancy
- Only quetiapine and olanzapine associated with GDM
  (adjusted relative risks: quetiapine 1.28, CI=1.01-1.62, olanzapine 1.61, CI=1.13-2.29)

1. Reis and Källen, J Clin Psychopharmacol.2008; 28(3):279-88; 2. Boden et al. Archives of General Psychiatry 2012, 69: 715-721. 3. Park et al, Am J Psychiatry. 2018 Jun 1;175(6):564-574.

Neurodevelopment[1]

- 2934 children and 9 cohort studies
- Several studies reported a delay in neurodevelopment after intrauterine exposure to antipsychotics
- Delays were mostly transient
- Most controls were children of mothers with no psychiatric illness

[1]Poels et al (2018) European Child & Adolescent Psychiatry (2018) 27:1209–1230 https://doi.org/10.1007/s00787-018-1177-1

Summary of evidence for antipsychotics

- Current evidence does not suggest that antipsychotics are major teratogens.
- Suggested increase of general and cardiac MCMs associated with risperidone is small
- Association with gestational diabetes may (at least partially) be mediated by early pregnancy BMI
- Any neurodevelopmental effects appear to be transient. Lack of control for confounding.
- Insufficient data for lurasidone, paliperidone

- Antipsychotics can be used as alternative to mood stabilizers where there are more reproductive safety concerns

- Monitor for gestational diabetes (NICE, 2014) – oGTT in all women who are on antipsychotic medication and have been negative so far for GDM screening

ANTIEPILEPTICS

Reproductive safety of anti-epileptic drugs

Valproate – compared to children of mothers with untreated epilepsy and healthy controls -

- Rate of major congenital malformations is increased 3-fold
- Likelihood of poor neurodevelopmental outcomes is increased :
  - Cognitive developmental delay 7-fold
  - Autism spectrum disorder 3-fold
  - Autism 3-fold
  - Delay of psychomotor and language development
- Unborn children are vulnerable throughout pregnancy
- Although harm is dose dependent there is no established safe dose
- Folic acid is not or only partially preventative

Reproductive safety of anti-epileptic drugs

Carbamazepine[1]

- General increase of major congenital malformations up to 2-fold.
- Smaller risk of spina bifida than valproate

Lamotrigine[1,2]

- Current literature does not suggest that teratogenic effect is likely
- 1 meta-analysis suggests association with autism spectrum disorder, but data very limited

[1] *McAllister-Williams, 2017. J Psychopharm 31(5) 519-552*
[2] *BMJ Open* 2017;7:e017248. doi:10.1136/bmjopen-2017-017248

Implications for prescribing – Valproate MHRA 2018

Women with childbearing potential

- Valproate should not be used in girls and women of childbearing potential unless other treatments are ineffective or not tolerated.

- Valproate may be initiated in girls and women of childbearing potential only if the conditions of **the valproate pregnancy prevention programme** are fulfilled.

Pregnant women

- Women presenting with an unplanned pregnancy should have their treatment switched

- Women ***with epilepsy*** who have to continue treatment in pregnancy (i.e. if switching to an alternative treatment is not possible) should be referred for appropriate monitoring.

Carbamazepine[1,2]:

- Do not offer carbamazepine in preconception or pregnant women because of it's teratogenic potential and uncertain efficacy in bipolar disorder

- If a woman is already taking carbamazepine, discuss with the woman the possibility of stopping the agent

Lamotrigine:

- Although current evidence suggests that lamotrigine is not a major teratogen, the new finding of an association with autism spectrum disorder is a concern

- Avoid if possible, in women who are pregnant or of childbearing potential

Pregabalin : little data

[1]National Institute of Health and Care Excellence (2014) Clinical Practice Guideline 192
[2]Goodwin et al (2016). J Psychopharm 1 – 59, DOI: 10.1177/0269881116636545

LITHIUM

Lithium

- May cause cardiovascular anomalies in first trimester
- Risk is much lower than originally thought (initial report 8 %)
- Best study to date reports an adjusted risk ratio of 1.65 (1.02 to 2.68)[1]

1. N Engl J Med 376; 23

Lithium

- Uncertain whether there is a risk of congenital malformation in general
- If confirmed it is likely to be very small

Lithium

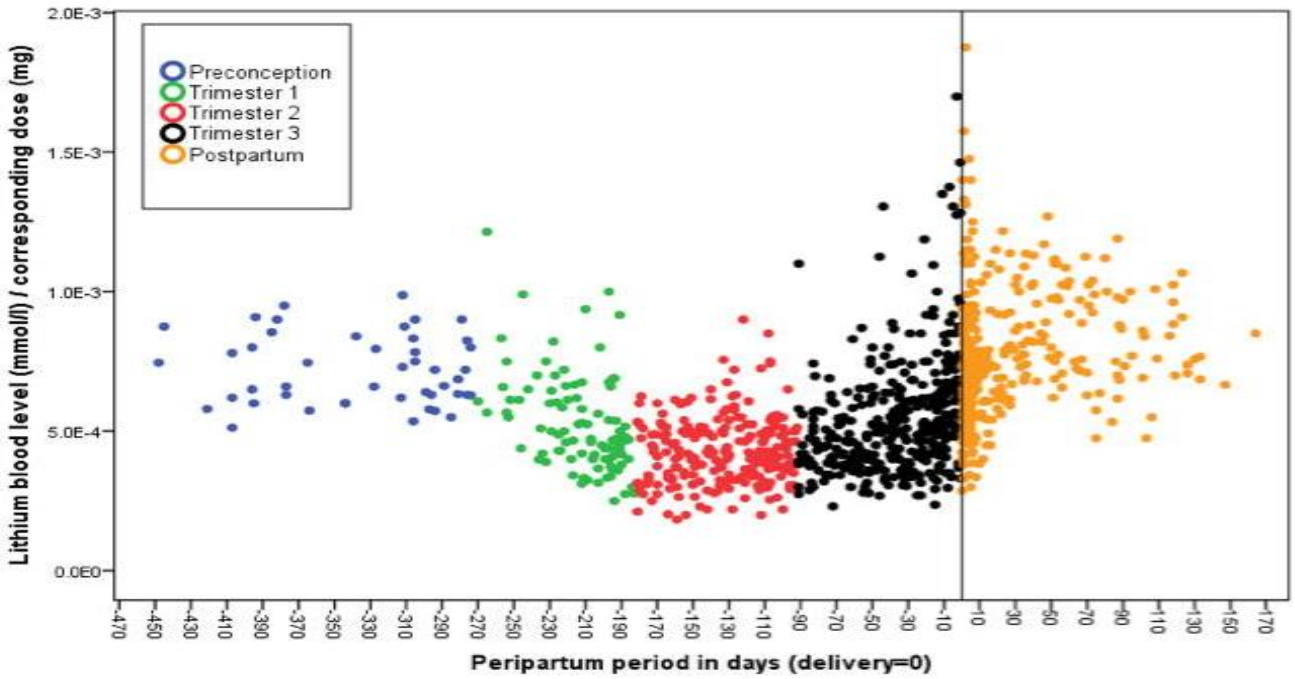
- Occasional cases reported of:
  - Hydramnios
  - Neonatal problems
  - Maternal and neonatal toxicity (usually related to high maternal dose)

- Requires obstetrician lead delivery in hospital
- Can’t breastfeed

LITHIUM

Renal function in pregnancy
increases until mid-pregnancy and decreases again in third trimester
Lithium levels change accordingly (analysis of 1,101 lithium levels by Wesseloo et al, 2017)

Figure 1. Course of Lithium blood level/dose ratios during the peripartum period



Wesseloo et al (2017), BJP 211: 31-36; **DOI:** 10.1192/bjp.bp.116.192799

Measuring lithium levels in pregnancy

- Measure frequently, particularly in the month before expected delivery date[1]

- NICE (2014)[1] recommends: 1 x / month up to week 36 of pregnancy

  1 x / week in month before expected delivery date

[1]National Institute of Health and Care Excellence (2014) Clinical Practice Guideline 192

ANXIOLYTICS

Benzodiazepines

- Probably not teratogenic
- Neonatal withdrawal, floppy babies
- Only to be used short term for severe anxiety or agitation in pregnancy

Sleep promoting medications

'Z-drugs' : zopiclone, zolpidem, zaleplon

- Not teratogenic
- Zolpidem: possibly some increased risk for PTB, SGA, LBW, but small effect (ORs 1.5-1.7)
- Only use short-term in pregnancy for severe insomnia

Sleep promoting medications

Promazine /promethazine

- Hardly any/ good data on use in pregnancy
- Not recommended

BREASTFEEDING

Lactation

- All psychotropic drugs are transferred into breast milk
- Exposure during breastfeeding is usually much less than during pregnancy
- Few data for most psychotropic drugs
- Measure of exposure : **relative infant dose (RID):**
- RID < 10% regarded as 'relatively safe' – Hale (2011) [1]
- Most psychotropics are well below 10 %, but some exceptions

[1]1Hale T (2011) Medications & Mother's Milk. Hale Publishing.
Available at: http://www.medsmilk.com/ (accessed 31st December 2012)

Lactation

Drugs that should not be used during breastfeeding

- Clozapine (agranulocytosis in baby)
- Lithium (risk of intoxication)
- Valproate and carbamazepine
- Benzodiazepines: avoid. If essential use short acting drugs, and only for short term or intermittent use. Don't breastfeed at night
- Z-drugs: only short-term use. Avoid breastfeeding at night

Advice to mothers

When breastfeeding mothers take psychotropics they should be advised to monitor their babies for side-effects, particularly excessive sedation.

Take Home messages

- Women can take antipsychotics and antidepressants during pregnancy
- Don’t stop medications just because they are pregnant
- Women can breastfeed on medication
- It is a complex decision for the woman and can cause guilt/anxiety
- BUMPs/LACTMED excellent for patient information leaflets
- If woman is on medication but not pregnant yet can have PRE-CONCEPTION COUSELLING appointment with SPNMHT

Useful Resources

- Bumps – Medicines in Pregnancy – www.medicinesinpregnancy.org
- Drugs & Lactation Database (Lactmed) – www.toxnet.nlm.nih.gov
- Lactmed App – can be downloaded free on smart phones
- Perinatal Mental health Toolkit www.rcgp.org.uk/clinical-and-research/.../toolkits/perinatal-mental-health-toolkit.aspx
- British Association for Psychopharmacology consensus guidance https://www.bap.org.uk/pdfs/BAP_Guidelines-Perinatal.pdf

QUESTIONS?