Neonates exposed to Prescribed Medications including Anti-depressants and other Drugs in Pregnancy - Neonatal Full Clinical Guideline - Joint Derby & Burton & Derby Maternity

Reference no.: NIC NE 09/Dec 20/v001.1

1. Introduction

Babies born to mothers on prescribed medications during pregnancy are at risk of problems both in the early neonatal period, and later in life. These guidelines outline the principles for the management of infants born to these mothers and provide information regarding monitoring and treatment of affected babies. Please refer to Neonatal abstinence syndrome guidelines for babies born to mothers using illicit drugs/alcohol (Reference no: Derby: PAED/03:16/S7 and Burton: WC/NP/21N).

In this guideline we discuss the following:

1. **Anti-depressants:**
    a. SSRI's (Selective Serotonin Reuptake Inhibitors) e.g. Citalopram, Fluoxetine, Sertraline, Paroxetine
    b. SNRI's (Serotonin and Noradrenaline Re-uptake Inhibitors) eg. Venlafaxine
    c. TCA's (Tricyclic Antidepressants) e.g. Amitriptyline, Lofepramine, Nortriptyline
2. **Antipsychotics**
    a. First Generation ('Typicals') - e.g. Haloperidol, Chlorpromazine, Promethazine, Flupenthixol
    b. Second Generation ('Atypicals') - e.g. Clozapine, Quetiapine, Olanzapine, Risperidone
3. **Anti-Epileptic Medications/ Mood stabilisers**
    a. Sodium Valproate, Lamotrigine, Carbamazepine, Topiramate
    b. Lithium, Semisodium Valproate (e.g. Depakote), Valproic Acid

2. Purpose and Outcomes

The purpose of this policy is to rationalise and formalise the care available to these infants and to reduce the number of complications in this cohort.

3. Background

Mental health disorders including depression are a common occurrence with an estimated lifetime prevalence of 16.2%[1]. The most common treatment for depression is currently Selective Serotonin Reuptake Inhibitors (SSRI's) which have been linked to Neonatal Abstinence Syndrome within the infant[2] with up to 30% of exposed infants showing symptoms. The other common medications used include Serotonin and Noradrenaline Re-uptake Inhibitors (SNRI's), Tricyclic's (TCA's) and Antipsychotic medications (both 'Typical and Atypicals')

Neonatal withdrawal syndrome occurs due to a sudden discontinuation of the drug being supplied to the infant after the cord has been clamped.

3.1 There is debatable evidence to suggest a link between the use of SSRI's during pregnancy and congenital malformations in the infant although the overall risk is very low[1]

3.2 The evidence of congenital cardiac malformations and infants exposed during the first trimester to paroxetine and fluoxetine suggest there may be evidence of right ventricular out tract flow malformations, omphalocele, and anencephaly[6]. It is important for regular antenatal care for these Mothers with an assessment of the Newborn Physical Examination once the infant has delivered[5.]

4. Types of Medications

Anti-depressants:

Anti-depressants have a wide range of use but are usually a prescribed medication (rather than a drug of abuse). They are used to treat depression, anxiety, panic attacks, obsessive-compulsive disorder and sometimes as pain relief.

4.1 **SSRI's** (Selective Serotonin Reuptake Inhibitors) e.g. Citalopram, Fluoxetine, Sertraline, Paroxetine

These are commonly used for mood related illness such as depression. There are substantial differences in term of their half-life between fluoxetine and others SSRIs. The half-life of fluoxetine and its active metabolite norfluoxetine is respectively 2 to 4 days and 7 to 15 days, more extended than other SSRIs (approximately 1 day).

Side effects:

- The common side effects are central nervous system, motor, respiratory and gastrointestinal symptoms. The symptoms in babies usually develop within 8-48 hours postpartum and fade within 72 hours.[4]

- SSRI and Neonatal Withdrawal Symptoms:
  There are a number of symptoms linked to in-utero exposure of SSRI's commonly include; jitteriness, poor feeding, irritability and excessive crying, abnormalities of muscle tone, poor sleeping and tachypnoea1. Less commonly these include; lethargy, hypoglycaemia, convulsions and a weak cry1. These symptoms are usually present within a few hours of birth, are mild and self-limiting and resolve within a few weeks, although symptoms may be severe in up to 10% of newborns.[1,2.]

- SSRI use and Persistent Pulmonary Hypertension of the Newborn (PPHN):
  Normally, the pulmonary vascular resistance falls after birth. In PPHN, this doesn't occur and can lead to right-to-left shunting of the blood and subsequent hypoxaemia. There is an increased risk of PPHN in infants that have been exposed to SSRI's during late pregnancy although the absolute risk remains low[3].

4.2 **SNRI's** (Serotonin and Noradrenaline Re-uptake Inhibitors) e.g. Venlafaxine

Similar to SSRI's and commonly used for mood related disorders. The common side effects are central nervous system, motor, respiratory and gastrointestinal symptoms.
The symptoms in babies usually develop within 8-48 hours postpartum and fade within 72 hours.[4]

4.3 **TCA's** (Tricyclic Antidepressants) e.g. Amitriptyline, Lofepramine, Nortriptyline

Used for mood related disorders such as depression but can also be used for migraine, panic-disorders, recurrent headaches, neuropathic pain and in certain cases as a sleep aid. The common side effects are central nervous system, respiratory, endocrine and metabolic disturbances. The symptoms in babies can develop within 8-48 hours postpartum and fade within 72 hours.[4]

Antipsychotics

There are a number of classes of medications that are used to treat psychoactive disorders, such as schizophrenia, psychoses, mania and hypomania.

4.4 **First Generation** ('Typicals')
e.g. Haloperidol, Chlorpromazine, Promethazine, Flupenthixol

Symptoms in babies - Assess and monitor for Extra-pyramidal symptoms (such as abnormal movements, hypertonia, tremor, dystonia, agitation and sedation. This can be done by monitoring alertness, waking for feeds, poor sucking response[4]

4.5 **Second Generation** ('Atypicals')
e.g. Clozapine, Quetiapine, Olanzapine, Risperidone

Similar to the first generation in terms of indications for treatment and possible symptoms in the neonate. Symptoms in babies - Assess and monitor for Extra-pyramidal symptoms (such as abnormal movements, hypertonia, tremor, dystonia, agitation and sedation. This can be done by monitoring alertness, waking for feeds, poor sucking response[4]

7. Recommendations

7.1 Where possible, the infant should remain with mother unless there are other comorbidities or an immediate risk of death or long-term impairment to the infant[4].

7.2 Admission to the neonatal unit or transitional care unit should be based only on clinical need[4]

7.3 The infant should be started on observations and monitored for symptoms of NAS; including a full assessment of alertness, feeding, muscle tone and irritability/jitteriness by a trained member of staff[1,4].

7.4 If the infant presents with symptoms of respiratory distress, lethargy/irritability or poor feeding, hypothermia and poor body temperature regulation, they should be assessed for other conditions such as sepsis or hypoglycaemia as it should not be assumed these symptoms are purely due to exposure to medications in utero[4].

7.5 Where possible, assessment should also include pulse oximetry to include the rare but possible complication of Primary pulmonary Hypertension. Any infant showing signs of respiratory distress should have pulse oximetry as standard[3,4].

7.6 Babies who are born to mothers on prescribed medications as above that have stable observations after 24 hours of monitoring, normal pulse oximetry, who have established feeding well, have no other concerns and who's newborn physical exam was normal, can be discharged home after 24 hours with the NAS parental information leaflet and follow up with the community midwife the following day. This will obviously need to be assessed on a case by case basis for each individual infant and their family/social situation[4].

8. Anti-Epileptic Medications/Mood stabilisers

8.1 Background

Epilepsy is one of the most common neurological conditions in pregnancy with a prevalence of 0.5-1%[7]. Infants born to mothers taking anti-epileptic drugs (AEDs) are 3.5 times more likely to have a small-for-gestational-age fetus (SGA) than mothers with epilepsy who are not taking AEDs[8].

The risk of congenital malformations in the fetus is increased in women with epilepsy taking AEDs. This risk is greatest in those taking valproate or AED polytherapy[9]. Valproate includes sodium valproate, semisodium valproate and valproic acid. Risk is lower in lamotrigine or carbamazepine monotherapy[10]. This should be taken into consideration when performing the Newborn and Infant Physical Examination (NIPE).

Rates of transfer of AEDs to the neonate across the placenta and in breast milk vary. Babies born to mothers taking AEDs can have withdrawal symptoms such as lethargy, difficulty feeding, excessive sedation and inconsolable crying. Women taking AEDs during pregnancy should have an individual assessment for the level of post-natal monitoring required for their infant[7]. Where there are concerns about toxicity in the infant serum levels of the AEDs should be checked[11].

8.2. Neonatal Withdrawal Symptoms

There are a number of symptoms linked to in-utero exposure of antiepileptics and commonly include; jitteriness, poor feeding, irritability and excessive crying, abnormalities of muscle tone, poor sleeping and tachypnoea1. Less commonly

these include; lethargy, hypoglycaemia, convulsions and a weak cry1. These symptoms are usually present within a few hours of birth, are mild and self-limiting and resolve within a few weeks, although symptoms may be severe in up to 10% of newborns.1,2.

In the case of AEDs there is no standard duration of observation for infants – this should be decided based on the AED regime taken during pregnancy.

8.3 Benzodiazepines e.g. Diazepam, Lorazepam, Clobazam, Temazepam can cause hypothermia, hyperbilirubinaemia and CNS depression in the neonate. Symptoms of withdrawal can present hours to weeks after delivery and is more likely to be seen after the infant has been discharged home. Local guidance is to treat with diazepam 3-6mg/day 8 hourly. Once the infant has been stabilized the dose should be reduced slowly over several weeks. Please refer to the Neonatal Abstinence Syndrome -Paediatric Full Clinical Guideline for more information[12].

8.4 AEDs and increased risk of haematological disorders in the newborn - It is thought that taking enzyme-inducing AEDs (carbamazepine, phenytoin, phenobarbital, primidone, oxycarbazepine, topiramate and eslicarbazepine) during pregnancy can increase the risk of haemorrhagic disease of the newborn. The evidence for this is mixed but current NICE guidance is that IM vitamin K should be given to all infants born to mothers taking enzyme inducing AED[7,13]. This should be discussed with the mother prior to delivery.

8.4 AEDs and Breastfeeding - NICE guidance is that breastfeeding is generally safe for women taking AEDs. Individual advice is available in the BNFc and this should be consulted in each individual case. Mothers should be counselled on the risks and benefits of breastfeeding against the potential risks of the AED affecting the child[13].

8.5 Recommendations

- All children born to mothers taking enzyme inducing AEDs should be given IM vitamin K at delivery

- NIPE should be performed with consideration that there is a greater risk of congenital malformations in infants whose mothers have taken AEDs during pregnancy

- AEDs can cause withdrawal symptoms in the neonate – this will depend on the drug regime taken and each mother should have an individual plan for duration of observation on the post-natal ward.

- Breastfeeding is generally safe for mothers taking AEDs but the BNFc should be consulted for individual drugs and mothers should be counselled about the risks and benefits to the infant

9. SUMMARY TABLE				
Drug Class	**Examples**	**Withdrawals ?**	**Duration of observation**	**Safe to breastfeed**
Drugs of abuse	**Cocaine**	Associated with preterm delivery and IUGR. No evidence for neonatal withdrawal but may be irritable and difficult to settle. Can persist for 6-9 months, does not respond to therapeutic treatment	**48 hours** (after last consumption). If consumed 24 hours before delivery observe for 24 hours. If not taken any for 48hrs at delivery – No observation needed.	No Advise mother against illicit drug use
	Heroin	Commonly seen. Typically starts within 24 hours of birth. CNS, metabolic, vasomotor, respiratory depression and GI symptoms. If severe infant may require treatment with morphine sulphate.	**24 hours**	
	Cannabis	No evidence for neonatal withdrawal. Associated with low birth weight.	**None**	Yes. Advice not to take Cannabis
	Amphetamines/ Stimulants: Ecstacy, Mamba, crack cocaine		**48 hours** (after last consumption). If consumed 24 hours before delivery observe for 24 hours. *If not taken any for 48hrs at delivery – No observation needed.*	No
Opiates	**Codeine**	CNS, metabolic, vasomotor, respiratory depression and GI symptoms may develop. If severe infant may require treatment with morphine sulphate.	**24 hours** (half life 6 hours)	No
	Oxycodone		**24 hours** (half life 3.5 – 5.5 hrs)	No

	Methadone		**Min 5 days** (half life 24-55hours)	Yes – at lowest dose possible
	Oromorph		**24 hours**	Yes
SSRIS	**Citalopram, Fluoxetine, Sertraline**	CNS, motor, respiratory and GI symptoms, develop within 8-48 hours, last up to 72 hours. Monitor for signs of Persistent Pulmonary Hypertension (PPHN).	**Min 24 hours**	Yes – unless other contraindications. If on Fluoxetine >60mg – not to breast feed Baby should be observed for sedation and adequate weight gain.
SNRIs	**Venlefaxine** **Doxepin** **Mirtazapine**	CNS, motor, respiratory and GI symptoms, develop within 8-48 hours, last up to 72 hours	**Min 24 hours**	Yes (unless doxepin – this is not safe in breast-feeding). Baby should be observed for sedation and adequate weight gain.
TCAs	**Amitriptyline, Noritriptyline**	CNS, respiratory, endocrine, metabolic disturbances, develop within 8-48 hours, last up to 72 hours	**Min 24 hours**	Yes (unless doxepin – this is not safe in breastfeeding)
Lithium	**Lithium carbonate** **Lithium citrate**	Confirm no congenital cardiac defects (Ebstein anamoly) Lethargy, flaccid muscle tone, hypotonia, Hypothyroidism, Hypoglycaemia	**Min 48 hours**	No - Contraindicated

Antipsychotics - 1st Generation	**Haloperidol, Chlorpromazine, Promethazine**	Extra-pyramidal symptoms – abnormal movements, tremor, dystonia, agitation, sedation	**Min 24 hours**	Yes (All antipsychotics pass into breastmilk, but mostly in small amounts). Observe infant for sedation and extrapyramidal symptoms.
Antipsychotics - 2nd Generation	**Clozapine, Quetiapine, Olanzapine, Risperidone**	Extra-pyramidal symptoms – abnormal movements, tremor, dystonia, agitation, sedation.	**Min 24 hours**	All antipsychotics pass into breastmilk, but mostly in small amounts. Except Clozapine which causes Agranulocytosis/seizures, where it is not advisable to breast feed.
Benzodiazepines	**Long acting:** **Diazepam, Clobazam, Clonazepam** **Shorter acting:** **Lorazepam, Temazepam**	CNS depression, hypothermia, lethargy, feeding difficulties, respiratory depression. Can develop hours to weeks after delivery. If severe infant may require treatment with diazepam.	**Dependent on drug regime - each mother should have anIndividual plan. (minimum 24 hours)**	Avoid if possible. Particularly long acting drugs. Shorter acting drugs are preferable if required whilst breastfeeding.
Antiepileptics	**Sodium valproate** **Phenytoin** **Lamotrigine** **Levetiracetam** **Carbamazepine** **Topiramate**	Increased risk of congenital malformations and hemorrhagic disease of newborn – risk varies depending on AED. Withdrawal symptoms include CNS depression, difficulty feeding, excessive sedation and inconsolable crying	**Dependent on drug regime - each mother should have an Individual plan. (minimum 24 hours)**	Most AEDs are safe to breast feed. Please check the individual plan.

Combination of drugs	**Opioids** **Antipsychotics** **Gabapentin** **Pregabalin**	60% risk of withdrawal	**5 days**	Avoid if possible.
Anxiolytics	**Propanolol**	Assess for congenital malformations including cleft lip, palate, cardiac and neural tube.	**Monitor for bradycardia, hypotension, hypoglycaemia – Once blood sugars are stable stop monitoring**	Yes
Hypnotics **'Z' drugs**	**Zopiclone** **Zolpidem** **Zaleplon**	Not associated with an increased risk of congenital malformations	**None**	Yes (avoid in Zopiclone – as no data available)

At discharge:

1. Ensure baby has NIPE examination within first 24 hours.
2. If concerns address social issues.
3. NAS parent information leaflet given at discharge.

References (including any links to NICE Guidance etc.)

1.Sie, S., Wennink, J., van Driel, J., te Winkel, A., Boer, K., Casteelen, G. and van Weissenbruch, M. (2012). Maternal use of SSRIs, SNRIs and NaSSAs: practical recommendations during pregnancy and lactation. Archives of Disease in Childhood - Fetal and Neonatal Edition, 97(6), pp.F472-F476.

2.Jefferies, A. (2011). Selective serotonin reuptake inhibitors in pregnancy and infant outcomes. Paediatrics & Child Health, 16(9), pp.562-562.

3. Grigoriadis, S., VonderPorten, E., Mamisashvili, L., Tomlinson, G., Dennis, C., Koren, G., Steiner, M., Mousmanis, P., Cheung, A. and Ross, L. (2014). Prenatal exposure to antidepressants and persistent pulmonary hypertension of the newborn: systematic review and meta-analysis. BMJ, 348(jan14 7), pp.f6932-f6932.

4. Pan-London Perinatal Mental Health: Guidance for Newborn Assessment. (2017). [pdf] London: London Neonatal Operational Delivery Network. Available at: http://www.londonneonatalnetwork.org.uk/wp-content/uploads/2016/10/FinalNeodoc-v3.pdf [Accessed 4 Jul. 2018].

5.Wurst, K., Poole, C., Ephross, S. and Olshan, A. (2009). First trimester paroxetine use and the prevalence of congenital, specifically cardiac, defects: A meta-analysis of epidemiological studies. Birth Defects Research Part A: Clinical and Molecular Teratology, 88(3), pp.159-170.

6. Reefhuis, J., Devine, O., Friedman, J., Louik, C. and Honein, M. (2015). Specific SSRIs and birth defects: bayesian analysis to interpret new data in the context of previous reports. BMJ, p.h3190.

7. RCOG Green-top guideline No 68

8 – Viale L, Allotey J, Cheong-See F, Arroyo-Manzano D, Mccory D, Bagary M et al.; EBM CONNECT Collaboration. Epilepsy in pregnancy and reproductive outcomes: a systematic-review and meta-analysis. Lancet 2015;386:1845-5

9 – Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy Outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res 2008;81:1-13

10 – Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al.; EURAP study group. Dose-dependent risk of malformations with entiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol 2011;10:609-17

11 – Davanzo R, Dal Bo S, Bua J, Copertino M, Zanelli E, Matarazzo L. Antiepileptic drugs and breastfeeding. Italian Journal of Paediatrics 2013:39-50

12 – Neonatal Abstinence Syndrome – Paediatric Full Clinical Guideline, Royal Derby Hospital, 2016

13 – NICE guidance – Epilepsies: diagnosis and management

Documentation Controls

Development of Guideline:	Dr Bala Subramaniam
Consultation with:	Derby and Burton Neonatal consultants and Derby and Burton Maternity. Version 1.1. Minor change to include all forms of valproate-containing medicine in section 1.3. Updated by James Hooley, Medication Safety Officer in consultation the Valproate Short Life Working Group (led by Richard Faleiro / Lara Raworth).
Approved By:	*Paediatric Business Unit Guidelines Group, Women and Children's Division – 7th December 2020* 22/03/2024: **Version 1.1** amendments Signed off via Sodium Valproate Short Life Working Group. Future versions will revert to Paediatric BU oversight.
Review Date:	Dec 2023 – Extended to March 2024
Key Contact:	Dr Bala Subramaniam

Appendices

Neonatal Abstinence Syndrome Leaflet - See link in main record