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Variation in the management of SSRI-exposed babies across England

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Manuscripts

Variation in the management of SSRI-exposed babies across England

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ABSTRACT**Background**

Depression in pregnancy is commonly treated using selective serotonin reuptake inhibitors (SSRIs). A possible withdrawal syndrome following in utero exposure has been reported but there is currently no UK guidance on the management of these neonates.

Methods

All 160 neonatal units in England were asked for information regarding their management of SSRI-exposed babies.

Results

Responses were obtained from 112/160 (70%) units. Only four units had a specific protocol for managing SSRI-exposed neonates. 21 units (19%) conduct routine observations on exposed neonates, whilst 37 units (33%) would consider treating babies with signs of withdrawal or toxicity.

Conclusions

Very few neonatal units in England have specific guidelines for the management of babies exposed to SSRIs in utero, with practice varying greatly between units. Further research is needed on the outcomes of SSRI-exposed babies to support development of standardised evidence-based guidelines to ensure all mothers and babies receive similar high quality care.

KEY MESSAGES**What is known about the subject:**

- Antenatal depression affects up to 1 in 8 pregnancies, and selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed for affected women
- Some babies exposed to SSRIs in utero can display a form of withdrawal syndrome during the newborn period
- There is currently no UK national guideline as to the management of SSRI-exposed babies

What this study adds:

- Very few neonatal units in England have a protocol for managed SSRI-exposed babies
- There is wide variation across England in the periods of observation required for SSRI-exposed babies
- Treatment of SSRI-exposed babies displaying withdrawal symptoms varies widely between different neonatal units in England

INTRODUCTION

Depression in pregnancy is a significant clinical problem, with estimates of prevalence up to 13.5% in the third trimester.[1] The British National Formulary (BNF) makes no specific recommendations as to which antidepressants should be prescribed for pregnant women. However, in clinical practice selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed with an estimated 1.8-2.8% of pregnancies being exposed.[2] This translates to more than 12,000 babies born each year within England and Wales.

The BNF advises that 'SSRIs should not be used during pregnancy unless the potential benefit outweighs the risk' and highlights the potential risks that have been found to be associated with SSRIs, including 'neonatal withdrawal symptoms'. The concept of a neonatal withdrawal syndrome from SSRIs was backed by a 2005 database analysis which presented 93 confirmed cases of a neonatal withdrawal syndrome, including 13 instances of seizures.[3] A later cohort study found that 30% of neonates were affected following in utero exposure.[4]

At present there is a paucity of research examining exactly what symptoms and signs are seen in neonates suffering from an SSRI withdrawal syndrome, with a number of presentations being suggested. There has also been some debate about whether observed symptoms represent a true withdrawal syndrome, or are due instead to toxicity.[5]

Prior to 2014 there was no national guideline in the UK as to the management of neonates born to mothers taking SSRIs during pregnancy. The 2014 NICE guideline on Antenatal and Postnatal Mental Health advises that SSRI-exposed babies receive a full neonatal assessment but gives no further detail as to signs and symptoms to look out for, or on what observations may be required and for how long.[6]

A 2012 study in the Netherlands demonstrated variation in practice across the country in postnatal care for neonates born following in utero SSRI exposure.[7] This study sought to assess current practice in England with regards management of babies exposed to SSRIs in utero.

METHODS

All 160 neonatal units in England (not including neonatal surgical units) were contacted to request details as to their management of babies exposed to SSRIs during pregnancy. Units were initially contacted by email (to the unit's Clinical Lead) and sent a short questionnaire (Table 1), with those who failed to respond contacted by telephone. Units who did have a written guideline on the management of neonates exposed to SSRIs in utero were asked to forward a copy of this.

Table 1: Questions sent to all neonatal units in England

1	Do you have a written guideline/protocol for the assessment and/or treatment of neonates exposed to SSRIs in utero?
2	Are any routine observations/scoring carried out on neonates known to have been exposed to SSRIs in utero?
3	If neonates exposed to SSRIs in utero show symptoms of withdrawal/toxicity, do they receive any medication, and if so, what is your usual first line treatment?

From the responses received it was noted whether the protocols included what were considered to be key information including:

- information on the signs and symptoms of withdrawal from SSRIs
- recommended duration of hospital stay
- regime of observations
- type of withdrawal scoring system to use, if any
- indications for treatment and recommended treatment

RESULTS

Responses were received from 112 (70%) of the 160 neonatal units contacted. Twenty-one units (19%) reported that they carry out routine observations on SSRI-exposed babies, with periods of observation up to 48 hours. 37 units (33%) reported that they would consider treating symptomatic babies, with a variety of treatments mentioned: oramorph (23 units), chlorpromazine (4 units), phenobarbitone (3 units), chloral hydrate (1 unit). Of the 112 units that responded, only four had a protocol specific to the management of neonates exposed to SSRIs, all of which provided a copy of their protocol. All four protocols listed possible signs and symptoms of SSRI withdrawal, although there was some variation between protocols. All four mentioned irritability or agitation, and three out of four mentioned feeding difficulties. Two protocols mentioned increased muscle tone, and one listed the possibility of seizures. Suggested frequency and length of routine observations varied between the four protocols. Two of the protocols used the Finnegan scoring system to guide need for treatment.

DISCUSSION

A survey of neonatal units in England has demonstrated wide variation in the management of neonates exposed to SSRI antidepressants in utero. Only four units had written protocols on the subject and much of this guidance relies on principles used and designed for exposure to other drugs, including the Finnegan and Rivers withdrawal scoring systems.[8,9] These scores are designed for monitoring opiate withdrawal and are non-validated tools for SSRI-exposed neonates.

This study has demonstrated variation in the length of routine observations (if any) carried out on SSRI-exposed babies. It is therefore possible that either some units are not adequately assessing exposed babies and may miss important signs and symptoms, or that in some units babies are being kept unnecessarily in hospital for prolonged periods of observation. Maternal health and wellbeing may not be best supported by prolonged periods of hospital admission and there is a potential

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3 stigma associated with not being able to have an early discharge. There is also ever increasing
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5 pressure on postnatal bed availability in neonatal units across the country. For all these reasons, it is
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7 essential that any routine periods of observation are evidence-based, cost-effective, and baby-
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9 friendly.

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12 There was much variation in what treatment, if any, neonatal units reported they would give to a
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14 baby withdrawing from SSRIs, likely reflecting the lack of clear evidence supporting any particular
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16 pharmacological treatments. There is also some uncertainty as to whether SSRI exposure in utero
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18 produces a withdrawal syndrome or toxicity, both of which could present with a similar clinical
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20 picture, but would require very different management.

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23 A strength of this study is the high response rate, with 70% of neonatal units providing information
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41 neonatal community we need to seek to better understand the clinical problem posed by SSRI-
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43 exposed babies, how we identify babies most at risk, and whether any additional observations or
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47 and enable the development of evidence-based guidelines to support neonatal units and individual
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49 clinicians in managing SSRI-exposed babies.

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We are grateful to all the neonatal units who responded to the questionnaire and provided details about their management of SSRI-exposed babies.

COMPETING INTERESTS

The authors declare they have no conflicts of interest to disclose.

FUNDING

There are no funding sources to disclose.

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- Antenatal depression affects up to 1 in 8 pregnancies, and selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed for affected women
- Some babies exposed to SSRIs in utero can display a form of withdrawal syndrome during the newborn period
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What this study adds:

- Very few neonatal units in England have a protocol for managed SSRI-exposed babies
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INTRODUCTION

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The BNF advises that 'SSRIs should not be used during pregnancy unless the potential benefit outweighs the risk' and highlights the potential risks that have been found to be associated with SSRIs, including 'neonatal withdrawal symptoms'. The concept of a neonatal withdrawal syndrome from SSRIs was backed by a 2005 database analysis which presented 93 confirmed cases of a neonatal withdrawal syndrome, including 13 instances of seizures.[3] Cohort studies have found that between 22% and 30% of neonates were affected following in utero exposure, with 3-13% demonstrating a severe withdrawal syndrome.[4,5]

At present there is a paucity of research examining exactly what symptoms and signs are seen in neonates suffering from an SSRI withdrawal syndrome, with a number of presentations being suggested. There has also been some debate about whether observed symptoms represent a true withdrawal syndrome, or are due instead to toxicity.[6]

Prior to 2014 there was no national guideline in the UK as to the management of neonates born to mothers taking SSRIs during pregnancy, although guidelines do exist in other countries.[7] The 2014 NICE guideline on Antenatal and Postnatal Mental Health advises that SSRI-exposed babies receive a full neonatal assessment but gives no further detail as to signs and symptoms to look out for, or on what observations may be required and for how long.[8]

A 2012 study in the Netherlands demonstrated variation in practice across the country in postnatal care for neonates born following in utero SSRI exposure.[9] This study sought to assess current practice in England with regards management of babies exposed to SSRIs in utero.

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From the responses received it was noted whether the protocols included what were considered to be key information including:

- information on the signs and symptoms of withdrawal from SSRIs
- recommended duration of hospital stay
- regime of observations

- type of withdrawal scoring system to use, if any
- indications for treatment and recommended treatment

RESULTS

Unit protocols

Responses were received from 112 (70%) of the 160 neonatal units contacted. Of these, only four units had a protocol specific to the management of neonates exposed to SSRIs, all of which provided a copy of their protocol. (Table 2) All four protocols listed possible signs and symptoms of SSRI withdrawal, although there was some variation between protocols. All four mentioned irritability or agitation, and three out of four mentioned feeding difficulties. Suggested frequency and length of routine observations varied between the four protocols. Two of the protocols used the Finnegan scoring system to guide need for treatment.[10]

Table 2: Comparison of protocols for the management of SSRI-exposed neonates

	Protocol 1	Protocol 2	Protocol 3	Protocol 4
Signs and symptoms of withdrawal	<ul style="list-style-type: none"> • Irritability • Tremor • Increased tone • Feeding difficulties 	<ul style="list-style-type: none"> • Agitation • Irritability • Somnolence 	<ul style="list-style-type: none"> • Poor feeding • Jitteriness / tremors • Agitation • Respiratory distress • Lethargy • Seizures 	<ul style="list-style-type: none"> • Tremors • Jitteriness • Irritability • Muscle tone abnormalities • Excess crying • Sleep disturbance • Tachypnoea • Feeding problems
Duration of hospital stay	24 hours	Not mentioned	48 hours	48 hours
Regime of observations	4 hourly	Not mentioned	8 hourly (increased if high scores)	8 hourly (increased if high scores)
Scoring system used	Not mentioned	Not mentioned	Adapted Rivers scoring chart, with Finnegan scoring thresholds.[10,11]	'Inpatient scoring system' recommended but no reference to a specific system made. Finnegan scoring thresholds used.[10]
Treatment of symptomatic infants	Not mentioned	Not mentioned	Chlorpromazine or phenobarbitone	Phenobarbitone

Observations, scoring and treatment

Twenty-one units (19%) reported that they carry out routine observations on SSRI-exposed babies, with periods of observation up to 48 hours. 37 units (33%) reported that they would consider treating symptomatic babies, with 27 of these suggesting specific medication(s) (Figure 1).

DISCUSSION

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3 A survey of neonatal units in England has demonstrated wide variation in the management of
4 neonates exposed to SSRI antidepressants in utero. Only four units had written protocols on the
5 subject and much of this guidance relies on principles used and designed for exposure to other
6 drugs, including the Finnegan and Rivers withdrawal scoring systems.[10,11] These scores are
7 designed for monitoring opiate withdrawal and are non-validated tools for SSRI-exposed neonates.
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9 An adapted version of the Finnegan scoring system has been developed in the Netherlands for
10 screening babies exposed to SSRIs, but we are not aware of any English units currently using this.[12]
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19 This study has demonstrated variation in the length of routine observations (if any) carried out on
20 SSRI-exposed babies. It is therefore possible that either some units are not adequately assessing
21 exposed babies and may miss important signs and symptoms, or that in some units babies are being
22 kept unnecessarily in hospital for prolonged periods of observation. Estimates of the prevalence of
23 neonatal symptoms in the literature vary, possibly reflecting differences in length of exposure and
24 individual SSRIs used between studies.[4,5] The Canadian Paediatric Society advocate for a 48 hours
25 period of hospital observation for all babies with third trimester exposure to SSRIs,[7] with a review
26 article from the Netherlands taking a similar stance whilst also acknowledging that in the majority of
27 cases any neonatal symptoms are mild and self-limiting.[13] Maternal health and wellbeing may not
28 be best supported by prolonged periods of hospital admission and there is a potential stigma
29 associated with not being able to have an early discharge. There is also ever increasing pressure on
30 postnatal bed availability in neonatal units across the country. For all these reasons, it is essential
31 that any routine periods of observation are evidence-based, cost-effective, and baby-friendly.
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48 There was much variation in what treatment, if any, neonatal units reported they would give to a
49 baby withdrawing from SSRIs, likely reflecting the lack of clear evidence supporting any particular
50 pharmacological treatments. There has been uncertainty as to whether SSRI exposure in utero
51 produces a withdrawal syndrome or toxicity,[6] with treatment generally aimed at treating
52 symptoms rather than gradual weaning of the causative medication as with opiate withdrawal.
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3 There is also some evidence to suggest breastfeeding reduces the risk of developing symptoms.[14]

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5 More recent studies have suggested potential neurodevelopmental consequences beyond the first
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7 few days of life with research demonstrating lower motor scores and increased stress signs
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9 throughout the first month of life in babies of mothers treated with SSRIs compared to those with
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11 untreated depression.[15] Additionally there is evidence of subtle electroencephalogram changes in
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13 neonates exposed to SSRIs in utero compared to healthy controls.[16] In both of these studies
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15 potential confounding of maternal depression could not be fully excluded, but this does challenge
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17 some units' focus on the first 24 or 48 hours of life rather than longer term neurodevelopment.
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21 A strength of this study is the high response rate, with 70% of neonatal units providing information
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ACKNOWLEDGEMENTS

We are grateful to all the neonatal units who responded to the questionnaire and provided details about their management of SSRI-exposed babies.

CONTRIBUTORSHIP STATEMENT

ET and PJP designed the study, with advice from SEB. ET collected and analysed the data. ET produced the first draft of this paper, with PJP and SEB contributing to the final version.

COMPETING INTERESTS

The authors declare they have no conflicts of interest to disclose.

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FIGURE LEGEND

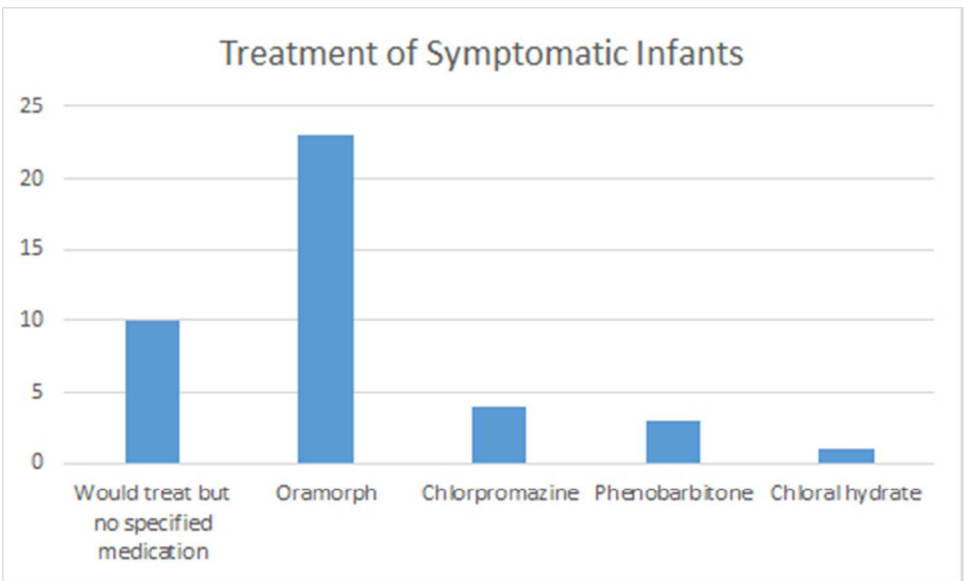
Figure 1: Treatments used for symptomatic infants

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