**MOOSE Checklist for Meta-analyses of Observational Studies**

|  |  |  |
| --- | --- | --- |
| **Item No** | **Recommendation** | **Reported on Page No** |
| Reporting of background should include | | |
| 1 | Problem definition | 3 |
| 2 | Hypothesis statement | 3 |
| 3 | Description of study outcome(s) | 6 |
| 4 | Type of exposure or intervention used | 4 |
| 5 | Type of study designs used | 4 |
| 6 | Study population | 4 |
| Reporting of search strategy should include | | |
| 7 | Qualifications of searchers (eg, librarians and investigators) | 5 |
| 8 | Search strategy, including time period included in the synthesis and key words | 4 |
| 9 | Effort to include all available studies, including contact with authors | 4 |
| 10 | Databases and registries searched | 4 |
| 11 | Search software used, name and version, including special features used (eg, explosion) | N/A |
| 12 | Use of hand searching (eg, reference lists of obtained articles) | 4 |
| 13 | List of citations located and those excluded, including justification | OSM, Figure S2 |
| 14 | Method of addressing articles published in languages other than English | 5 |
| 15 | Method of handling abstracts and unpublished studies | 4 |
| 16 | Description of any contact with authors | 4 |
| Reporting of methods should include | | |
| 17 | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | 5, 6 |
| 18 | Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | 5 |
| 19 | Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability) | 5 |
| 20 | Assessment of confounding (eg, comparability of cases and controls in studies where appropriate) | 5 |
| 21 | Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results | 5 |
| 22 | Assessment of heterogeneity | 6 |
| 23 | Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | 6, 7 |
| 24 | Provision of appropriate tables and graphics | 27-31, and OSM |
| Reporting of results should include | | |
| 25 | Graphic summarizing individual study estimates and overall estimate | Figure S3, Tables S4 and S5 |
| 26 | Table giving descriptive information for each study included | Table S1 |
| 27 | Results of sensitivity testing (eg, subgroup analysis) | 10-12,  Figures S4 and S5 |
| 28 | Indication of statistical uncertainty of findings | 10-12, Table S6 |

|  |  |  |
| --- | --- | --- |
| **Item No** | **Recommendation** | **Reported on Page No** |
| Reporting of discussion should include | | |
| 29 | Quantitative assessment of bias (eg, publication bias) | 10-12,  Figures S4 and S5 |
| 30 | Justification for exclusion (eg, exclusion of non-English language citations) | 5 |
| 31 | Assessment of quality of included studies | 5-7, Table S2 |
| Reporting of conclusions should include | | |
| 32 | Consideration of alternative explanations for observed results | 3, 14 |
| 33 | Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) | 14-16 |
| 34 | Guidelines for future research | 14 |
| 35 | Disclosure of funding source | 16 |

N/A: Not Applicable

**Figure S1.** Search strategy used for PubMed

#1Offspring[tiab]

#2 Infant[tiab]

#3 Baby[tiab]

#4 Neonate[tiab]

#5 Newborn[tiab]

#6 Neonatal[tiab]

#7 Fetus[tiab]

#8 Fetal[tiab]

#9 Utero[tiab]

#10 intrauterine[tiab]

#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7#8 OR #9 OR #10

#12 Infant, Newborn[Mesh]

#13 #11 OR #12

#14SSRI[tiab]

#15 selective serotonin reuptake inhibitor[tiab]

#16 citalopram[tiab]

#17 escitalopram[tiab]

#18 fluoxetine[tiab]

#19 fluvoxamine[tiab]

#20 paroxetine[tiab]

#21 sertraline[tiab]

#22 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21

#23 Serotonin Uptake Inhibitors[Mesh]

#24 #22 OR #23

#25 #13 AND #24

Studies included in the quantitative synthesis (meta-analysis) on SSRIs/venlafaxine (n=6)

**Figure S2.** Flow-chart of study selection

**Identification**

**Screening**

**Eligibility**

**Inclusion**

List of excluded studies and reason:

* No adjustment for concomitant exposure to psychotropic medications other than SSRIs/venlafaxine (n=18)\*
* Not mothers’ late exposure to SSRIs/venlafaxine (n=28)\*\*
* Insufficient information on the exposure status of the control group (n=12)\*\*\*
* No outcomes of interest (n=3)\*\*\*\*

Records screened

(n=2,269)

Records excluded

(n=2,195)

Full-text articles assessed for eligibility (n=74)

Full-text articles excluded (n=61)

Records identified through

MEDLINE, Web of Science, EMBASE (n=2,448)

Additional records identified through other sources (e.g. reference lists of identified reports and reviews) (n=49)

Records after duplicates removal

(n=2,269)

Studies included in the quantitative synthesis (meta-analysis) on SSRIs (n=3)

Studies included in the qualitative analysis (n=13)

\*Cohen et al., 2000; Casper et al., 2003; Laine et al., 2003; Zeskind and Stephens, 2004; Pearson et al., 2007; Suri et al., 2007; Boucher et al., 2008; Maschi et al., 2008; Galbally et al., 2009; Lewis et al., 2010; Suri et al., 2011; Hayes et al., 2012; Jensen et al., 2013; Michielsen et al., 2014; Sutter-Dallay et al., 2015; Kieviet et al., 2015; Kieviet et al., 2017a; Kieviet et al., 2017b

\*\* Källén, 2004; Oberlander et al., 2004; Suri et al., 2004; Oberlander et al., 2006; Wen et al., 2006; Lennestal and Kallen, 2007; Oberlander et al., 2007; Lund et al., 2009; Rampono et al., 2009; Reis and Källén, 2010; Colvin et al., 2011; Roca et al., 2011; Colvin et al., 2012; Kallen and Reis, 2012; Brummelte et al., 2013; De Gaspari et al., 2013; Leibovitch et al., 2013; Engelstad et al., 2014; Bellissima et al., 2015; Malm et al., 2015; Kivisto et al., 2016; Robinson-Wolrath et al., 2016; Salisbury et al. 2016; Hogue et al., 2017; Sparla et al., 2017; Yang et al., 2017; Bandoli et al., 2020; Levy et al., 2020

\*\*\* Goldstein, 1995; Ho et al., 2000; Nordeng et al., 2001; Simon et al., 2002; Hendrick et al., 2003; Sivojelezova et al., 2005; Davis et al., 2007; Klinger et al., 2011; Sit et al., 2011; Forsberg et al., 2014; Eleftheriou et al., 2017; Bellissima et al., 2020

\*\*\*\* Nulman et al., 2002; Casper et al., 2011; Grzeskowiak et al., 2012

**Table S1.** Characteristics of studies included in the qualitative analysis

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **STUDIES ON SSRIs** | | | | | | | | |
| **No** | **Source** | **Design** | **Sample size** | **Definition of exposure** | **Confounders** | **Follow-up duration** | **Results** | **Assessment of main outcome** |
| 1 | Norby et al., 2016 | Retrospective population-based cohort | Late exposure, n=9100 Early exposure, n=8636 | 1) Late exposure: any SSRIs dispensed during the last 90 days of the pregnancy with or without early use. 2) Early exposure: any SSRI dispensed during pregnancy but not during the last 90 days of the pregnancy. | Adjusted for opioids, antiepileptics, psycholeptics, centrally acting sympathomimetics, and any use of mild sedatives during pregnancy | During neonatal wards | 1) Respiratory distress syndrome: aOR: 0.5 (0.3 - 0.9) 2) Transient tachypnea/other respiratory distress: aOR:1.6 (1.4 - 1.8) 3) Meconium aspiration syndrome: aOR:1.9 (1.0 - 3.6) 4) Hypoglycemia: aOR: 1.3 (1.1 - 1.6) 5) Hyperbilirubinemia: aOR:0.8 (0.6 - 0.9) 6) Intracranial hemorrhage: aOR: 1.0 (0.6 - 1.8) 7) Feeding difficulties: aOR: 1.4 (1.1 - 1.9) | Chart review of ICD-10 codes |
| 2 | Wisner et al., 2009 | Prospective cohort | Late exposure, n=48; Non-exposure, n=130; | Late exposure: continuous SSRIs exposure during the entirety pregnancy or for the majority of each of the three trimesters. | Excluded subjects with psychosis, bipolar disorder, active substance use disorder, alcohol abuse or dependence at intake, and subjects who were exposed to benzodiazepines and drugs in the FDA-defined category of D or X | Within first 2 weeks after birth | 1) Apgar-1 min ≤7: 8/48 vs 17/130, p=0.54 2) Apgar-5 min ≤7: 3/48 vs 1/130, p=0.06 | Peripartum Events Scale |
| 3 | Pawluski et al., 2009 | Prospective cohort | Late exposure, n=37 Non-exposure, n=15 | Late exposure: continuous SSRIs use until the time of delivery. | Excluded mothers who were exposed to other psychotropic or serotonergic medications during pregnancy | Within first 48h after birth | 1) Rapid breathing: 12/37 vs 3/15, p=0.51  2) Jitteriness: 10/37 vs 0/15, p=0.05  3) Respiratory distress: 6/37 vs 0/15, p=0.17 4) Increased tone: 5/37 vs 0/15, p=0.31 5) Apgar-1 min: 7.50±1.66 vs 8.72±0.57, p=0.00 6) Apgar-5 min: 8.83±0.64 vs 9.0±0.34, p=0.22 | Blinded chart review of clinical records |
| 4 | Davidson et al., 2009 | Prospective cohort | Late exposure, n=21 Non-exposure, n=20 | Late exposure: continuous SSRIs use during the entire pregnancy. | Excluded subjects with diabetes, chronic hypertension, and cardiovascular diseases. No between-group differences were noted in smoking and alcohol consumption | From birth until discharge | 1) The most frequent symptoms were: regurgitations, constant crying, jitteriness | Finnegan score |
| 5 | Malm et al., 2005 | Prospective cohort | Late exposure, n=597 Early exposure, n=1000 | Late exposure: at least 1 SSRI during the third trimester Early exposure: no SSRIs in the first trimester | Excluded subjects with chronic illnesses requiring continuous medication (such as hypertension, epilepsy, psychosis). Adjusted for smoking and other medications purchased in third trimester | Within first 7 days after birth | 1) Apgar-1 min＜7: aOR 1.6 (95%CI 1.0 - 2.4) | Chart review of clinical records |
| 6 | Costei et al., 2002 | Prospective cohort | Late exposure, n=55;  Early exposure, n=27 | Late exposure: continuous paroxetine use throughout the third trimester Early exposure: no antidepressant exposure or paroxetine discontinuation before the third trimester | Excluded mothers with use of opioids, benzodiazepines, barbiturates, or heavy use of ethanol during pregnancy. Matched for alcohol and smoking and other non-teratogenic drugs (e.g., acetaminophen, vitamins, and calcium supplements) | Within perinatal period after delivery | 1) Respiratory distress: 9/54 vs 1/27, p=0.15 2) Hypoglycemia: 2/55 vs 0/27, p=1.00  3) Suckling problems: 1/55 vs 0/27, p=1.00  4) Tachycardia: 1/55 vs 0/27, p=1.00  5) Bradycardia: 1/55 vs 0/27, p=1.00 6) Meconium aspiration: 0/55 vs 1/27, p=0.33  7) Jaundice: 1/55 vs 1/27, p=1.00 | Telephone standardized interview |
| 7 | Chambers et al., 1996 | Prospective cohort | Late exposure, n=73 Early exposure, n=101 | Late exposure: continuous fluoxetine use in the third trimester Early exposure: fluoxetine discontinuation before the third-trimester | Adjusted for use of preterm-labor medications, smoking status, average dose of fluoxetine, alcohol use, and other psychotherapeutic drugs near delivery | From shortly after delivery to discharge | 1) PNA: aOR=8.7 (2.9 - 26.6) | Telephone interview and chart review |
| **STUDIES ON SSRIs/VENLAFAXINE** | | | | | | | | |
| 1 | Warburton et al., 2010 | Retrospective register cohort | Late exposure, n=239; Early exposure, n=239; | Late exposure: continuous SSRIs/venlafaxine use in all 14 days before delivery﹡.  Early exposure: discontinued SSRIs/venlafaxine use in the 2 weeks before delivery. | Excluded mothers who were exposed to benzodiazepines and antipsychotics. Infants in each group were paired with the closest propensity score | During hospital  stay | 1) Convulsions: 0/239 vs 0/239; p=1.000 2) Feeding problems: 7/239 vs 12/239, p=0.359  3) Jaundice: 24/239 vs 29/239, p=0.568 | Chart review of ICD-9 codes |
| 2 | Oberlander et al., 2008a | Retrospective cohort | Late exposure, n=429 Early exposure, n=429 | Late exposure: any SSRIs/venlafaxine use in the third trimester for at least 185 days of gestation. Early exposure: SSRIs discontinuation before the third trimester | Propensity score matching was undertaken to match for prescription of antipsychotic drugs and tricyclic antidepressants between two groups | During hospital stay | Matched sample: Late (n=429) vs Early (n=429) 1) Respiratory distress:44/429 vs 40/429, p=0.65 2) Feeding problem: 11/429 vs 16/429, p=0.33 | Chart review of clinical records |
| 3 | Oberlander et al., 2008b | Prospective cohort | Late exposure, n=37 Non-exposure, n=47 | Late exposure: continuous SSRIs/venlafaxine use up to the time of delivery﹡. | Excluded mothers who were exposed to other psychotropic or serotonergic medications during pregnancy. The two groups were matched | From 2 h after birth to discharge | 1) Tachycardia: 13/37 vs 8/47, p=0.06 2) Bradycardia: 0/37 vs 2/47, p=0.50 3) Tachypnea breathing: 13/37 vs 8/47, p=0.06 4) Respiratory distress: 17/37 vs 5/47, p=0.00 5) Jitteriness: 13/37 vs 3/47, p=0.00 6) Increased motor tone: 5/37 vs 0/47, p=0.01 7) Hypoglycemia: 8/37 vs 4/47, p=0.09 8) Hyperglycemia: 2/37 vs 0/47, p=0.19 9) Apgar-1 min: 7.54±1.46 vs 8.13±1.36, p=0.06 10) Apgar-5 min: 8.70±0.85 vs 9.06±0.48, p=0.03 | Blinded chart review of clinical records |
| 4 | Jordan et al., 2008 | Retrospective cohort | Late exposure, n=46 Non-exposure, n=59 | Late exposure: SSRIs/venlafaxine use through delivery.  Non-exposure: discontinued SSRIs/venlafaxine exposure prior to the last month of pregnancy or without any SSRIs/venlafaxine exposure | Excluded patients who were treated with a non-SSRI or non-SNRI psychiatric medication alone and who were concurrent benzodiazepine use. Controlled: illicit substances, alcohol, or tobacco No between-group differences were noted in illicit substances, alcohol, or tobacco use | Prior to hospital discharge | 1) Irritability: 1/46 vs 2/59, p=1.00 2) Jitteriness: 4/46 vs 4/59, p=0.73 3) Hypotonia: 1/46 vs 1/59, p=1.00 4) Hypertonia: 3/46 vs 4/59, p=1.00 5) Hyperreflexia: 1/46 vs 1/59, p=1.00 6) Apnea: 0/46 vs 0/59, p=1.00 7) Tachypnea: 2/46 vs 3/59, p=1.00 8) Flaring/grunting/retractions: 3/46 vs 1/59, p=0.32 9) Vomiting: 1/46 vs 1/59, p=1.00 10) Poor feeding: 1/46 vs 3/59, p=0.63 11) Hypoglycemia: 0/46 vs 3/59, p=0.25 12) Any NBS component: 13/46 vs 10/59, p=0.16 13) Apgar-5 min: 9 (8,9) vs 9 (9,9) | Chart review of clinical records |
| 5 | Ferreira et al., 2007 | Retrospective cohort | Late exposure, n=76 Non-exposure, n=90 | Late exposure: SSRIs/venlafaxine exposure during the third trimester or at least the 2 last weeks before delivery | Excluded mothers using benzodiazepines, barbiturates, and any other antidepressant Candidates in the control group were selected randomly. Adjusted for smoking and illicit drug use | Within first 7 days after birth or until discharge | Neonatal behavioral signs: aOR: 3.1 (1.3 - 7.1) 1)Abnormal movements: 31/76 vs 10/90, p=0.00 2)Shaking: 15/76 vs 6/90, p=0.01 3)Agitation: 19/76 vs 4/90, p=0.00 4)Spasms: 7/76 vs 0/90, p=0.00 5)Hypertonia: 7/76 vs 0/90, p=0.00 6)Hypotonia: 18/76 vs 7/90, p=0.00 7)Irritability: 15/76 vs 1/90, p=0.00 8)Insomnia: 16/76 vs 9/90, p=0.05 9)Indrawing: 22/76 vs 7/90, p=0.00 10)Apnea/bradycardia: 13/76 vs 1/90, p=0.00 11)Tachypnea: 31/76 vs 14/90, p=0.00 12)Vomiting: 4/76 vs 11/90, p=0.12 13)Hypoglycemia: 4/76 vs 2/90, p=0.41 14)Tachycardia: 12/76 vs 3/90, p=0.01 15)Jaundice: 17/76 vs 5/90, p=0.00 | Chart review of medical records and nursing observation notes |
| 6 | Levinson-Castiel et al., 2006 | Prospective cohort | Late exposure, n=60 Non-exposure, n=60 | Late exposure: prolonged SSRIs/venlafaxine use at least through third-trimester or during the entire pregnancy | Excluded subjects who were exposed to illicit drugs, alcohol, or other concomitant medications that can cause withdrawal symptoms | Up to 4 days after birth | 1) High-pitched cry: 18/60 vs 0/60, p=0.00 2) Sleep disturbance: 21/60 vs 2/60, p=0.00 3) Exaggerated Moro reflex: 3/60 vs 0/60, p=0.24 4) Tremor: 37/60 vs 11/60, p=0.00 5) Hypertonicity or myoclonus: 14/60 vs 1/60, p=0.00 6) Convulsions: 2/60 vs 0/60, p=0.50 7) Sweating: 1/60 vs 0/60, p=1.00 8) Fever: 3/60 vs 0/60, p=0.24 9) Tachypnea: 12/60 vs 0/60, p=0.00, p=0.00 10) Neonatal abstinence syndrome: 18/60 vs 0/60, p=0.00 | Finnegan score |

SSRIs: selective serotonin reuptake inhibitors, SNRIs: serotonin noradrenaline reuptake inhibitors, aOR: adjusted odds ratio, CNS: central nervous system, ICD-10: international Classification of diseases 10th version, NBS: neonatal behavioral syndrome, NAS: neonatal abstinence syndrome, PNA: poor neonatal adaptation; Apgar: abbreviations for appearance, pulse, grimace, activity, and respiration

**Table S2.** Methodological quality of cohort studies included in the qualitative analysis

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Source** | **Representativeness of the exposed cohort** | **Selection of the unexposed cohort** | **Ascertainment of exposure** | **Outcome of interest not present at start of study** | **Control for important factor/additional factor a** | **Assessment of outcome** | **Follow-up long enough for outcomes to occur b** | **Adequacy of follow-up of cohorts c** | **Total scores** |
| Norby et al, 2016 | \* | \* | \* | \* | \*\* | \* | \* | \* | 9 |
| Warburton et al, 2010 | \* | \* | \* | \* | \*\* | \* | \* | \* | 9 |
| Wisner et al, 2009 | \* | \* | \* | \* | \*\* | \* | \* | \* | 9 |
| Pawluski et al, 2009 | \* | \* | \* | \* | \*\* | \* | — | \* | 8 |
| Davidson et al, 2009 | \* | \* | — | \* | \*\* | \* | \* | \* | 8 |
| Oberlander et al, 2008a | \* | \* | \* | \* | \*\* | \* | \* | \* | 9 |
| Oberlander et al, 2008b | \* | \* | \* | \* | \*\* | \* | \* | \* | 9 |
| Jordan et al, 2008 | — | — | \* | \* | \*\* | \* | \* | \* | 7 |
| Ferreira et al, 2007 | \* | \* | \* | \* | \*\* | \* | \* | \* | 9 |
| Levinson-Castiel et al, 2006 | \* | \* | \* | \* | \*\* | \* | — | \* | 8 |
| Malm et al, 2005 | \* | \* | \* | \* | \*\* | \* | — | \* | 8 |
| Costei et al, 2002 | — | — | \* | \* | \*\* | — | \* | \* | 6 |
| Chambers et al, 1996 | — | — | \* | \* | \*\* | — | \* | \* | 6 |

A study could be awarded a maximum of one star for each item except for the item Control for important factor or additional factor. The definition/explanation of each column of the Newcastle–Ottawa Scale is available from http://www.ohri.ca/programs/clinical\_epidemiology/oxford.asp  
a A maximum of two stars could be awarded for this item. Studies that controlled for age received one star, whereas studies that controlled for (or excluded) other important confounders such as smoking, alcohol and/or other medications received an additional star  
b A cohort study with a follow-up of 2 weeks or before discharge was assigned one star  
c A cohort study with a follow-up rate > 75% was assigned one star

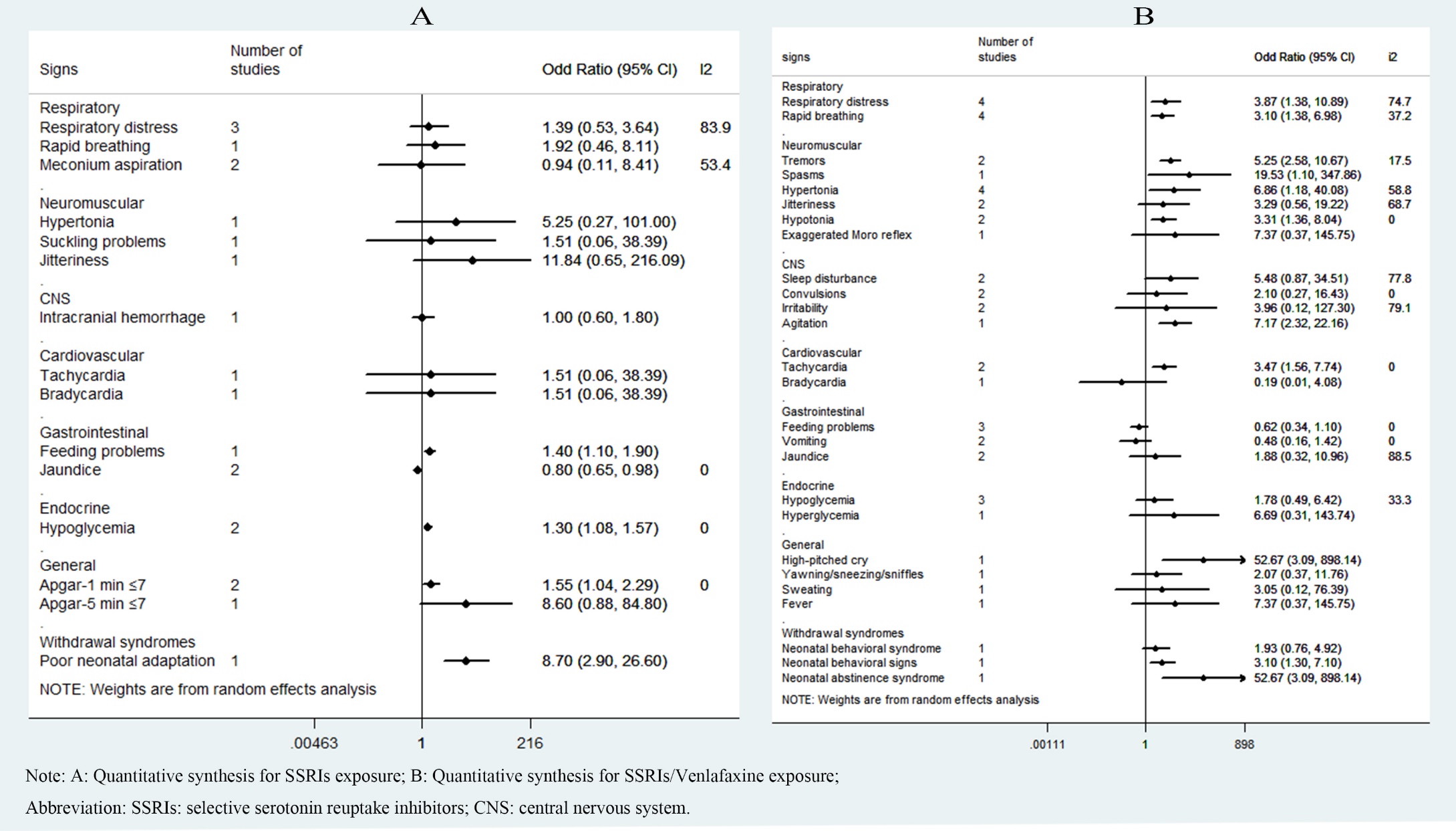
**Table S3.** SSRI withdrawal signs emerged from the present review were compared with new withdrawal symptoms in adults and other neonatal related syndromes

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Signs** | **Neonatal SSRI Withdrawal Signs** | | **New withdrawal symptoms1** | **Poor neonatal adaptation** | **Neonatal behavioral signs** | **Neonatal abstinence syndrome** | **Neonatal behavioral syndrome** |
| **SSRIs** | **SSRIs/venlafaxine** |
| Rapid breathing | - | √ | N/A | √ | N/A | √ | N/A |
| Respiratory distress | - | √ | N/A | √ | √ | Nasal stuffiness, sneezing, nasal flaring | √ |
| Meconium aspiration | - | N/A | N/A | N/A | √ | N/A |
| Hypertonia | - | √ | √ | N/A | √ | √ | √ |
| Hypotonia | N/A | √ | N/A | √ | √ | N/A | √ |
| Tremors | N/A | √ | √ | N/A | √ | √ | N/A |
| Spasms | N/A | √ | √ | N/A | √ | N/A | N/A |
| Jitteriness | - | - | Muscle rigidity, ataxia, restlessness, facial numbness1, neuralgias1 | √ | N/A | N/A | √ |
| Exaggerated Moro reflex | N/A | - | N/A | N/A | √ | √ |
| Suckling problems | - | N/A | N/A | N/A | √ | N/A |
| Sleep disturbance | N/A | - | √ | N/A | √ | √ | N/A |
| Agitation | N/A | √ | √ | N/A | √ | N/A | N/A |
| Convulsions | N/A | - | √ | N/A | N/A | √ | N/A |
| Irritability | N/A | - | √ | N/A | √ | N/A | √ |
| Intracranial hemorrhage | - | N/A | N/A | N/A | N/A | N/A | N/A |
| Tachycardia | - | √ | √ | N/A | √ | N/A | N/A |
| Bradycardia | - | - | N/A | N/A | N/A | N/A | N/A |
| Vomiting | N/A | - | √ | N/A | √ | √ | √ |
| Feeding problems | √ | - | Diarrhea,  abdominal pain1, nausea1, anorexia1,loose stools | √ | N/A | √ | √ |
| Jaundice | - | - | N/A | √ | Loose/watery stools | N/A |
| Hypoglycemia | √ | - | N/A | √ | √ | N/A | √ |
| Hyperglycemia | N/A | - | N/A | N/A | N/A | √ | N/A |
| High-pitched cry | N/A | √ | √ | Weak or absent cry | N/A | √ | N/A |
| Yawning/sneezing/sniffles | N/A | - | √ | N/A | N/A | √ | N/A |
| Sweating | N/A | - | √ | N/A | N/A | √ | N/A |
| Fever | N/A | - | Flushing | Hypothermia | N/A | Excoriation, mottling | Lethargy |

1Signs part of the New withdrawal symptoms should be assessed by subjective complains, thus cannot be available in infants: Visual: Visual changes, blurred vision; Sensory: Paresthesia, electric shock sensations, brain zaps, tinnitus, altered taste, pruritus; Mental: Anxiety, agitation, tension, panic, depression, intensification of suicidal ideation, impulsiveness, aggression, anger, mood swings, depenalization and depersonalization, confusion, amnesia, disorientation, decreased concentration, visual and auditory hallucinations; Sexual: Premature ejaculation, genital hypersensitivity; Others: Dizziness, light-headedness, vertigo, dyspnea, fatigue, weakness, tiredness, lethargy.

Abbreviation: N/A, Not available.

**Figure S3.** Odds ratios of the association between maternal SSRIs or SSRIs/venlafaxine exposure and signs obtained as neonatal outcomes



**Table S4. Heterogeneity analysis for studies on SSRIs exposure**

| **Signs** | **I2** | **Publication bias** | | | | | **Sensitivity analyses** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Funnel plot** | **Begg's Test** | | **Egger's test** | |
| **z** | **Pr > |z|** | **t** | **P>|t|** |
| Respiratory distress | 83.9 |  | 0.34 | 0.73 | 0.34 | 0.73 | \*1 Norby et al 2016 |
| Meconium aspiration | 53.4 |  | 0.00 | 1.00 | 0.00 | 1.00 |  |
| Jaundice | 0.0 |  | 0.00 | 1.00 | 0.00 | 1.00 |  |
| Hypoglycemia | 0.0 |  | 0.00 | 1.00 | 0.00 | 1.00 |  |
| Apgar-1 min ≤7 | 0.0 |  | 0.00 | 1.00 | 0.00 | 1.00 |  |

**Table S5. Heterogeneity analysis for studies on SSRIs/venlafaxine exposure**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | | | | | |
| **Signs** | **I2** | **Publication bias** | | | | | **Sensitivity analyses** |
| **Funnel plot** | **Begg's Test** | | **Egger's test** | |
| **z** | **Pr > |z|** | **t** | **P>|t|** |
| Respiratory distress | 74.7 |  | 0.00 | 1.00 | 0.00 | 1.00 |  |
| Rapid breathing | 37.2 |  | -0.34 | 1.00 | -0.34 | 1.00 |  |
| Tremors | 17.5 |  | 0.00 | 1.00 | 0.00 | 1.00 |  |
| Hypertonia | 58.8 |  | -0.34 | 1.00 | -0.34 | 1.00 | \*1 Levinson-Castiel et al; \*2 Oberlander et al b; \*4 Ferreira et al |
| Jitteriness | 68.7 |  | 0.00 | 1.00 | 0.00 | 1.00 |  |
| Hypotonia | 0.0 |  | 0.00 | 1.00 | 0.00 | 1.00 |  |
| Sleep disturbance | 77.8 |  | 0.00 | 1.00 | 0.00 | 1.00 |  |
| Convulsions | 0.0 |  | 0.00 | 1.00 | 0.00 | 1.00 |  |
| Irritability | 79.0 |  | 0.00 | 1.00 | 0.00 | 1.00 |  |
| Tachycardia | 0.0 |  | 0.00 | 1.00 | 0.00 | 1.00 |  |
| Feeding problems | 0.0 |  | 1.04 | 0.30 | 1.04 | 0.30 |  |
| Vomiting | 0.0 |  | 0.00 | 1.00 | 0.00 | 1.00 |  |
| Jaundice | 88.5 |  | 0.00 | 1.00 | 0.00 | 1.00 |  |
| Hypoglycemia | 33.3 |  | 1.04 | 0.30 | 1.04 | 0.30 |  |

**Table S6.** GRADE Quality of Evidence Assessment for withdrawal signs following late in utero exposure to SSRIs or SSRIs/venlafaxine

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure and outcomes** | **Number of studies** | **Study design** | **Certainty assessment** | | | | |  | **Effect estimates** | **Certainty** |
| **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **OR (95%CI)** |
| **SSRIs exposure** | | | | | | | | | | |
| Respiratory distress | 3 | Observational studies | Not serious | Very seriousa | Not serious | Very serious c | Seriously suspected publication bias i |  | 1.39 (0.53, 3.64) | ⨁◯◯◯ VERY LOW |
| Rapid breathing | 1 | Observational studies | Not serious | Not serious | Not serious | Very serious cd | None | 1.92 (0.46, 8.11) | ⨁◯◯◯ VERY LOW |
| Meconium aspiration | 2 | Observational studies | Not serious | Not serious | Not serious | Very serious c | None | 0.94 (0.11, 8.41) | ⨁◯◯◯ VERY LOW |
| Hypertonia | 1 | Observational studies | Not serious | Not serious | Not serious | Very serious cd | None | 5.25 (0.27, 101.00) | ⨁◯◯◯ VERY LOW |
| Suckling problems | 1 | Observational studies | Not serious | Not serious | Serious b | Very serious cd | None | 1.51 (0.06, 38.39) | ⨁◯◯◯ VERY LOW |
| Jitteriness | 1 | Observational studies | Not serious | Not serious | Not serious | Very serious cd | None | 11.84 (0.65, 216.09) | ⨁◯◯◯ VERY LOW |
| Intracranial hemorrhage | 1 | Observational studies | Not serious | Not serious | Not serious | Very serious c | None | 1.0 (0.6, 1.8) | ⨁◯◯◯ VERY LOW |
| Tachycardia | 1 | Observational studies | Not serious | Not serious | Serious b | Very serious cd | None | 1.51 (0.06, 38.39) | ⨁◯◯◯ VERY LOW |
| Bradycardia | 1 | Observational studies | Not serious | Not serious | Serious b | Very serious cd | None | 1.51 (0.06, 38.39) | ⨁◯◯◯ VERY LOW |
| Feeding problems | 1 | Observational studies | Not serious | Not serious | Not serious | Not serious | None | 1.40 (1.10, 1.90) | ⨁⨁◯◯ LOW |
| Jaundice | 2 | Observational studies | Not serious | Very serious a | Not serious | Not serious | None | 0.80 (0.65, 0.98) | ⨁◯◯◯ VERY LOW |
| Hypoglycemia | 2 | Observational studies | Not serious | Not serious | Not serious | Not serious | None | 1.30 (1.08, 1.57) | ⨁⨁◯◯ LOW |
| **SSRIs/venlafaxine exposure** | | | | | | | | | | |
| Respiratory distress | 4 | Observational studies | Not serious | Very serious a | Not serious e | Serious d | None a, g, h |  | 3.87 (1.38, 10.89) | ⨁◯◯◯ VERY LOW |
| Rapid breathing | 4 | Observational studies | Not serious | Not serious | Not serious e | Serious d | None g, h | 3.10 (1.38, 6.98) | ⨁◯◯◯ VERY LOW |
| Tremors | 2 | Observational studies | Not serious | Not serious | Not serious | Serious d | None g, h | 5.25 (2.58, 10.67) | ⨁◯◯◯ VERY LOW |
| Spasms | 1 | Observational studies | Not serious | Not serious | Not serious | Very serious f | None g, h | 19.53 (1.10, 347.86) | ⨁◯◯◯ VERY LOW |
| Hypertonia | 4 | Observational studies | Not serious | Not serious | Not serious e | Very serious f | None g, h | 6.86 (1.18, 40.08) | ⨁◯◯◯ VERY LOW |
| Jitteriness | 2 | Observational studies | Not serious | Serious a | Serious b | Very serious c, d | None | 3.29 (0.56, 19.22) | ⨁◯◯◯ VERY LOW |
| Hypotonia | 2 | Observational studies | Not serious | Not serious | Serious b | Serious d | None | 3.31 (1.36, 8.04) | ⨁◯◯◯ VERY LOW |
| Exaggerated Moro reflex | 1 | Observational studies | Not serious | Not serious | Not serious | Very serious c, d | None | 7.37 (0.37, 145.75) | ⨁◯◯◯ VERY LOW |
| Sleep disturbance | 2 | Observational studies | Not serious | Very serious a | Not serious | Very serious c, d | None | 5.48 (0.87, 34.51) | ⨁◯◯◯ VERY LOW |
| Convulsions | 2 | Observational studies | Not serious | Not serious | Not serious | Very serious c, d | None | 2.10 (0.27, 16.43) | ⨁◯◯◯ VERY LOW |
| Irritability | 2 | Observational studies | Not serious | Very serious a | Serious b | Very serious c, d | None | 3.96 (0.12, 127.30) | ⨁◯◯◯ VERY LOW |
| Agitation | 1 | Observational studies | Not serious | Not serious | Not serious | Serious d | None g, h | 7.17 (2.32, 22.16) | ⨁◯◯◯ VERY LOW |
| Tachycardia | 2 | Observational studies | Not serious | Not serious | Not serious | Serious | None g, h | 3.47 (1.56, 7.74) | ⨁◯◯◯ VERY LOW |
| Bradycardia | 1 | Observational studies | Not serious | Not serious | Not serious | Very serious c, d | None | 0.19 (0.01, 4.08) | ⨁◯◯◯ VERY LOW |
| Feeding problems | 3 | Observational studies | Not serious | Not serious | Not serious e | Serious c | None | 0.62 (0.34, 1.10) | ⨁◯◯◯ VERY LOW |
| Vomiting | 2 | Observational studies | Not serious | Not serious | Serious b | Very serious c, d | None | 0.48 (0.16, 1.42) | ⨁◯◯◯ VERY LOW |
| Jaundice | 2 | Observational studies | Not serious | Very serious a | Not serious | Very serious c | None | 1.88 (0.32, 10.96) | ⨁◯◯◯ VERY LOW |
| Hypoglycemia | 3 | Observational studies | Not serious | Not serious | Not serious e | Very serious c, d | None | 1.78 (0.49, 6.42) | ⨁◯◯◯ VERY LOW |
| Hyperglycemia | 1 | Observational studies | Not serious | Not serious | Not serious | Very serious c, d | None | 6.69 (0.31, 143.74) | ⨁◯◯◯ VERY LOW |
| High-pitched cry | 1 | Observational studies | Not serious | Not serious | Not serious | Very serious d, f | None g, h | 52.67 (3.09, 898.14) | ⨁◯◯◯VERY LOW |
| Yawning/sneezing/sniffles | 1 | Observational studies | Not serious | Not serious | Not serious | Very serious c, d | None | 2.07 (0.37, 11.76) | ⨁◯◯◯ VERY LOW |
| Sweating | 1 | Observational studies | Not serious | Not serious | Not serious | Very serious c, d | None | 3.05 (0.12, 76.39) | ⨁◯◯◯ VERY LOW |
| Fever | 1 | Observational studies | Not serious | Not serious | Not serious | Very serious c, d | None | 7.37 (0.37, 145.75) | ⨁◯◯◯ VERY LOW |
| a. Very serious: considerable heterogeneity with I2 ＞ 75%, or the confidence intervals did not overlap; Serious: substantial heterogeneity with I2 ＞ 50%. b Representativeness of samples inclusion and recall bias in evaluation based on telephone interview, which can explain partially the bias of selection and assessment, thus we only rated down indirectness one level, did not rate down risk of bias. c. The confidence interval included a considerable reduction or considerable increase. d. Small sample size with optimal information size not met. e. Studies that were conducted by telephone interview contributed little for small sample size and were not degraded f. The confidence interval closed to no effect (1% increase) to a substantial increase g. Large magnitude of OR > 2 h. Considerable or substantial imprecision i. Potential reporting bias raised by equivalent number of trials with obvious neonatal complicates | | | | | | | | | | |

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation

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