# Prenatal exposure to selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors and risk for persistent pulmonary hypertension of the newborn: a systematic review, meta-analysis, and network meta-analysis

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**BACKGROUND:** There is a marked increase in the use of selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors in the last decade. Many newborns are likely to be exposed during pregnancy and labor.

**OBJECTIVE:** We aimed to evaluate the association between exposure to selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors during pregnancy and the risk for persistent pulmonary hypertension of the newborn. We sought to compare the risk for persistent pulmonary hypertension of the newborn between specific selective serotonin reuptake inhibitor agents.

**STUDY DESIGN:** MEDLINE, Embase, and Cochrane were searched up to July 2017. No language restrictions were applied. Search key words included: "SSRI," "SNRI," "pregnancy," "risk," "new-born," and "pulmonary hypertension." Retrospective cohort studies and case-control studies reporting the risk for persistent pulmonary hypertension of the newborn in the offspring of women exposed to selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors during pregnancy, were extracted. Two independent researchers identified relevant data. Random effects meta-analysis was used to pool results. Odds ratios were calculated with subsequent 95% confidence intervals. Network meta-analysis was conducted, incorporating direct and indirect comparisons among different selective serotonin reuptake inhibitors. The primary outcome was risk for persistent pulmonary hypertension of the newborn after exposure to selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors during pregnancy.

**RESULTS:** A total of 11 studies were identified. A total of 156,978 women and their offspring were exposed to selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors during pregnancy. Persistent pulmonary hypertension of the newborn was detected among 452 exposed offspring, representing an incidence rate of 2.9 cases per 1000 live births and a number needed to harm of 1000. The risk for persistent pulmonary hypertension of the newborn was significantly increased in the analysis of exposure to selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor in any trimester (odds ratio, 1.82; 95% confidence interval, 1.31–2.54; $I^2 = 72\%$), as well as in analysis restricted to exposure week >20 (odds ratio, 2.08; 95% confidence interval, 1.44–3.01; $I^2 = 76\%$). In network meta-analysis, sertraline was ranked most likely to have the lowest risk for persistent pulmonary hypertension of the newborn among the different selective serotonin reuptake inhibitors ($P = .83$).

**CONCLUSION:** Exposure to selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors during pregnancy is associated with an increased risk for persistent pulmonary hypertension of the newborn. According to our findings, sertraline ranked as most likely to have the lowest risk for persistent pulmonary hypertension of the newborn compared to other selective serotonin reuptake inhibitors, suggesting it may have the best safety profile for use in pregnancy in this regard. Further studies are needed to fully establish these results.

**Key words:** antidepressants, cardiac anomalies, congenital anomalies, maternal depression, newborn, perinatal depression, persistent pulmonary hypertension of the newborn, pregnancy, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors

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## AJOG at a Glance

### Why was this study conducted?

To explore whether exposure to antidepressants during pregnancy increases the risk for persistent pulmonary hypertension of the newborn (PPHN).

### Key findings

In this meta-analysis and network meta-analysis, exposure to antidepressants during pregnancy was associated with a 2-fold increased risk for PPHN. Sertraline was ranked with lowest probability risk.

### What does this add to what is known?

Exposure to antidepressants during pregnancy is associated with a 2-fold increased risk for PPHN. Sertraline is a safe option for antidepressant treatment in pregnant women.

## Introduction

As many as 1 in 5 pregnant women experience some sort of depressive disorder during pregnancy.[1] Coupled with the marked increase in the use of selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, paroxetine, sertraline, citalopram, escitalopram, fluvoxamine) and serotonin norepinephrine reuptake inhibitors (SNRIs) (venlafaxine) in recent decades,[2,3] many newborns are likely exposed to SSRI or SNRIs in utero. Indeed, the rate of SSRI and SNRI use in pregnant women increased 2-fold (from 6.5−13%) in a cohort of Tennessee Medicaid pregnant women between the years 1999 through 2003.[4] Untreated maternal depression during pregnancy has been associated with perinatal adverse outcomes, including premature delivery and decreased breast-feeding initiation.[5]

SSRIs and SNRIs in late pregnancy are known to cross the placenta, and it is estimated that fetal exposure for fluoxetine, citalopram, escitalopram, and sertraline are 65%, 70%, 50%, and 30%, respectively.[6−8] Concerns have been raised regarding the prenatal safety of SSRIs and SNRIs, and their effect on delivery outcomes and neonatal health. Prenatal exposure to some SSRIs has been associated in some studies with an increased risk for preterm birth, low birthweight, spontaneous abortions, postpartum hemorrhage,[9] cardiac defects,[10] poor neonatal adaptation syndrome,[11] and persistent pulmonary hypertension of the newborn (PPHN).[12−15] Conflicting data have been reported regarding the association between exposure to SSRIs and SNRIs and birth defects, including cardiac defects.[16−18]

PPHN is a rare condition, resulting in failure of normal relaxation of fetal vascular bed during the transition period after birth, resulting in an increased resistance in the pulmonary blood vessels. It occurs in 2−6 cases per 1000 live births.[19,20] The condition has variable forms of presentation, and an increased risk of mortality.[21,22] Known factors that increase the risk for PPHN include cardiac malformations, pulmonary disease, cesarean delivery, and meconium aspiration syndrome.[23,24] A number of studies reported that SSRIs and SNRIs are associated with an increased risk for PPHN.[12,15,25] One possible mechanism for this is that SSRIs and SNRIs increase serotonin levels in the fetal circulatory bed leading to vasoconstriction and increased pulmonary vascular resistance.[23]

The Food and Drug Administration updated the data on SSRI safety in pregnancy in 2011 and concluded that due to conflicting results, a conclusion cannot be made regarding the association between exposure to SSRIs during pregnancy and PPHN.[26] The Medicines and Healthcare Products Regulatory Agency in the United Kingdom concluded that SSRIs are associated with an increased risk for PPHN >20th week of pregnancy; no clear conclusion could be made regarding SNRIs.[27] Because of the conflicting data, clinicians are advised not to change their current clinical practice in the treatment of pregnant women with depressive disorders.[26] Moreover, current practice guidelines encourage women who took effective antidepressant regimens prior to pregnancy, to continue with the same treatment regimen.[28] If therapy is to be initiated during pregnancy, illness severity, the woman's preferences, reproductive safety, and lactation safety must be taken into consideration.[29]

Due to the conflicting results and paucity of data regarding the association between prenatal exposure to SSRIs and SNRIs, and PPHN, we sought to conduct a systematic review and network meta-analysis to assess the risk for PPHN among different SSRIs and SNRIs used during pregnancy. We performed our meta-analysis in order to more accurately quantify the risk for PPHN by enlarging the number of studies and participants from the previous meta-analysis.[30] Moreover, we performed an indirect comparison between the different SSRI medications to rank the probability risk for PPHN, which has not been reported in the literature. Such an analysis can inform clinical practice and management of depression and perinatal care in pregnant women and newborns exposed to SSRIs and SNRIs during pregnancy and after delivery.

## Materials and Methods

### Data sources

This systematic review followed the Meta-analysis for Observational Studies in Epidemiology (MOOSE) checklist and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2009 guidelines (Appendixes A and B).[31] MEDLINE, Embase, and Cochrane databases were searched up to July 2017 to identify all published cohort and case-control studies assessing the association between exposure to SSRIs or SNRIs during pregnancy and PPHN. The search was updated on May 2018, with no relevant new cohorts or case-control studies. The following key words, in different combinations and Medical Subject Heading terms were used to identify relevant studies: "antidepressant," "pregnancy," "prenatal,"

"selective serotonin reuptake inhibitors," "SSRI," "selective norepinephrine reuptake inhibitors," "SNRI," "offspring," "risk" "new-born," "outcomes," "adverse effects," "pulmonary hypertension," and "persistent." In addition, we searched and evaluated published systematic reviews, online resources, and conference abstracts, to ensure identification of all studies. No language or date restrictions were applied. The review protocol was registered at PROSPERO registry: CRD42017080650. Authors of included studies were contacted for further data extraction. No approval from an institutional review board was required.

### Selection criteria

The following screening criteria were applied to assess eligibility: manuscripts and abstracts of cohort or case-control studies reporting the risk for PPHN in neonates of women exposed to SSRIs or SNRIs during pregnancy, using risk ratio (RR), incidence rate ratio, or odds ratio (OR). Outcomes reported by the same cohort in different publications were included only once in each analysis (most recent publication). We excluded cross-sectional studies, case reports and case series, guidelines, expert opinion, editorials, letters to the editor, and comments.

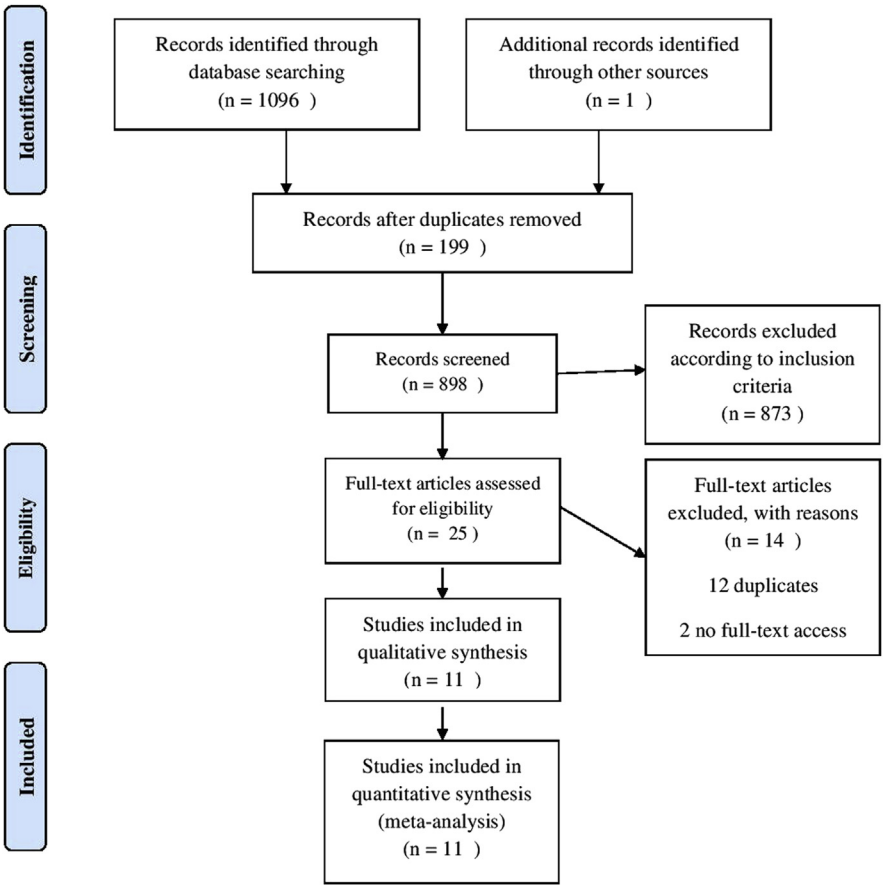
### Data extraction

Data were identified by 2 investigators (R.M. and E.G.). Titles and abstracts were independently screened by the 2 investigators. Disagreements were resolved by consensus or referral to a third investigator. Full text was retrieved by the 2 investigators. When no full text was available for relevant studies, the authors were contacted for data request. The primary outcome of this analysis was PPHN. Network meta-analysis was conducted to compare the risk of PPHN with the different SSRIs.

### Quality assessment

Risk of bias and quality were assessed using the Newcastle-Ottawa scale (NOS) for assessing quality of nonrandomized studies.[32,33] The scale is based on 8 criteria and provides a star rating score ranging from 0 (high risk for bias) to 9 (low risk for bias). Summary assessments of risk of bias were derived for each study. Assessments were carried out independently by 2 investigators (R.M. and E.G.).

**FIGURE 1**
**Search diagram**




Flow diagram of studies through review process.

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### Publication bias

Publication bias was assessed by visual inspection of the funnel plot and Egger test.[34] The nonparametric trim-and-fill technique was used to identify and correct funnel plot asymmetry if found. We used RevMan 5.3[35] and R Version 3.4.3[36] and the "metafor" package Version 1.9−9,[36] respectively.[37]

### Data synthesis and statistical analysis

Random effects meta-analysis (Mantel-Haenszel) was used to pool the results for PPHN risk using RevMan 5.3.[35] Random effects models were used under the assumption that the effect size varies across the studies because of real differences in the exposure effect and sampling variability.[38,39] Pooled ORs and 95% confidence intervals (CIs) for PPHN were calculated from the number of cases in the exposed and the number of cases in the nonexposed groups. Also, a pooled adjusted OR for PPHN was calculated from adjusted effect sizes from the included studies. Due to the rarity of the outcome, we assumed that RRs and ORs are expected to be very similar. We used the R Version 3.4.3 "compute.es 0.2−4" package to convert RRs to ORs.[40] Heterogeneity was assessed using the $I^2$ statistic. $I^2$ values of 25%, 50%, and 75% represented low, medium, and high heterogeneity, respectively.[41] Statistical significance was defined using a 2-sided $\alpha$ of $<.05$, and

**TABLE 1**
**Characteristics of studies included in analysis**

| Study, year | No. of cases of PPHN | Exposure assessment | Exposure timing and type |
|---|---|---|---|
| Chambers et al,[15] 2006 | Exposed: 14/20<br>Not exposed: 363/1193 | Telephone interview after delivery | Second and third trimesters: fluoxetine, paroxetine, sertraline |
| Källén and Olausson,[45] 2008 | Exposed: 5/2414<br>Not exposed: 493/828,910 | Interview at maternity care centers | All trimesters: fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine, escitalopram |
| Andrade et al,[46] 2009 | Exposed: 2/933<br>Not exposed: 3/1104 | Prescription dispensing | Second and third trimesters: SSRIs |
| Hammad et al,[47] 2009 | Exposed: 1/6569<br>Not exposed: 33/173,865 | NA | NA: SSRI and other antidepressants |
| Wichman et al,[48] 2009 | Exposed: 0/808<br>Not exposed: 16/24,406 | DBL and prescription dispensing | Second and third trimesters: fluoxetine, paroxetine, sertraline, citalopram, escitalopram, venlafaxine |
| Wilson et al,[44] 2011 | Exposed: 0/6<br>Not exposed: 20/134 | DBL and prescription dispensing | Second and third trimesters: SSRI |
| Colvin et al,[25] 2012 | Exposed: 8/3297<br>Not exposed:86/86,110 | DBL and prescription dispensing | All trimesters: fluoxetine, paroxetine, sertraline, citalopram, escitalopram, fluvoxamine |
| Kieler et al,[49] 2012 | Exposed: 33/30,115<br>Not exposed: 1899/1588140 | DBL and prescription dispensing | Second and third trimesters: fluoxetine, paroxetine, sertraline, citalopram, escitalopram |
| Huybrechts et al,[13] 2015 | Exposed: 322/102,179<br>Not exposed: 7630/3,360,380 | DBL and prescription dispensing | Second and third trimesters: fluoxetine, paroxetine, sertraline, citalopram, escitalopram, fluvoxamine |
| Nörby et al,[50] 2016 | Exposed: 60/9100<br>Not exposed: 2051/718,533 | DBL, prescription dispensing and interview | Second and third trimesters: NA |
| Bérard et al,[12] 2017 | Exposed: 7/1537<br>Not exposed: 258/141,097 | DBL, prescription dispensing | Second and third trimesters: fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine, venlafaxine |

*DBL*, database linkage; *NA*, not available; *PPHN*, persistent pulmonary hypertension of newborn; *SSRI*, selective serotonin reuptake inhibitor.

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interpretations of clinical significance emphasized CIs.

### Network meta-analysis

Network meta-analysis is a generalization of pairwise meta-analysis that compares all pairs of treatments within a number of treatments for the same condition. To assess differences in the risk for PPHN between SSRIs only, pairwise network meta-analysis was performed. We used random effects network meta-analysis. Agents compared included fluoxetine, sertraline, paroxetine, citalopram, and escitalopram, and the network incorporated data on results relative to no treatment and head-to-head comparisons. ORs and 95% CIs were modeled with the pairwise method. The risk of PPHN was ranked using *P* scores derived from network point estimates and SE. The *P* score is a frequentist equivalent to the Bayesian network surface under the cumulative ranking curve. The *P* score of a treatment can be interpreted as the mean extent of certainty that the treatment is better than another treatment, and can be used to rank a treatment within a range of treatments, measured on a scale from 0 (worst) to 1 (best).[42] Analysis was performed using R Version 3.4.3 and the "netmeta" package Version 0.9−8.[43]

### Sensitivity analysis

Sensitivity analysis was performed restricting analysis to studies with late pregnancy SSRIs or SNRIs exposure only (week ≥20), as the proposed mechanism of PPHN following prenatal exposure to SSRI is that the vascular pulmonary bed vasoconstricts in the presence of SSRIs in the fetuses' circulatory pulmonary system. Therefore, late exposure may carry a different risk for PPHN compared to early exposure. Additional sensitivity analysis was performed restricting analysis to fully published cohort studies reaching a NOS score of ≥7 (ie, excluding abstracts and studies with higher risk of bias). Sensitivity analysis was conducted by pairwise meta-analysis method.

### Subgroup analysis

Finally, the risk for PPHN was examined restricting analysis to studies including late preterm (week ≥33) and term deliveries only compared to all deliveries. Subgroup analysis was conducted by pairwise meta-analysis method.

## Results

### Search process

Systematic search yielded 1097 citations. Preliminary screening excluded 199

**TABLE 2**
**Study types, sites, and years**

| Study, year | Study type | Study site | Years (duration) |
|---|---|---|---|
| Chambers et al,[15] 2006 | Case-control | Slone Epidemiology | 1998 through 2003 |
| Källén and Olausson,[45] 2008 | Case-control | Swedish Medical Birth Register | 1997 through 2005 |
| Andrade et al,[46] 2009 | Cohort | HMO Research Network Center | 1996 through 2000 |
| Hammad et al,[47] 2009 | Cohort | General Practice Research Database | 1996 through 2004 |
| Wichman et al,[48] 2009 | Cohort | Mayo Clinic site in Rochester, MN | 1993 through 2005 |
| Wilson et al,[44] 2011 | Case-control | Madigan Army Medical Center | 2003 through 2009 |
| Colvin et al,[25] 2012 | Cohort | Western Australia Data Linkage System | 2002 through 2005 |
| Kieler et al,[49] 2012 | Cohort | Scandinavian National Health Register | 1996 through 2007 |
| Huybrechts et al,[13] 2015 | Cohort | Medicaid Analytic eXtract | 2000 through 2010 |
| Nörby et al,[50] 2016 | Cohort | Swedish Medical Birth Register | 2006 through 2012 |
| Bérard et al,[12] 2017 | Cohort | Quebec Pregnancy Cohort | 1998 through 2009 |

*HMO*, health maintenance organization.

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duplicate citations. The 898 remaining titles were reviewed by abstract. A total of 873 citations were excluded according to inclusion criteria, leaving 25 records for full-text review. Full review excluded 14 additional citations (duplicates and no full-text access), leaving 11 records for analysis. The search flow process is illustrated in Figure 1.

### Study characteristics

Study characteristics are summarized in Tables 1 and 2. Three studies were case-control studies[15,44,45] and 8 studies were historical cohorts.[12,13,25,46–50] In total, 156,978 women and their offspring were exposed to SSRIs or SNRIs during pregnancy; PPHN was detected among 452 exposed offspring (rate of 2.9/1000 live births). Assessment of exposure during pregnancy was carried out by interviews in 2 studies[15,45] and by prescription dispensing and database linkage in 8 studies.[12,13,25,44,46,48,50,51] Eight studies[12,13,15,44,46,48–50] reported on SSRI or SNRI exposure during late pregnancy (second and third trimesters) and 2 studies reported on exposure during all pregnancy trimesters.[25,45] Eight studies reached a NOS score of 7[12,13,15,25,44,48–50] and 3 studies reached NOS scores of 8, 6, and 3, respectively.[45–47] Quality assessment scores and adjustments made for potential confounders in each study are detailed in Supplementary Tables 1 and 2.

### Meta-analysis

*Exposure in all trimesters.* Eight historical cohorts and 3 case-control studies evaluated the risk for PPHN. Using random effects model, SSRI or SNRI exposure during pregnancy (any trimester) was significantly associated with an increased risk for PPHN, with high heterogeneity (OR, 1.82; 95% CI, 1.31–2.54; $I^2$ = 72%) (Figure 2). Adjusted meta-analysis (of adjusted ORs for 8 studies) demonstrated a >2-fold risk (adjusted OR, 2.42; 95% CI, 1.68–3.48; $I^2$ = 69%).

### Network meta-analysis

In a network meta-analysis, the risk of PPHN was compared between specific SSRI agents. Comparison pairs are illustrated in the network graph (Supplementary Figure 1). Based on the overall results of this network, sertraline was found most likely to have the lowest risk of PPHN among the SSRI agents and the highest *P* score indicating the lowest probability for PPHN (*P* score = .83) (Table 3). In addition, among the network's specific pairwise comparisons, sertraline was found to have a statistically significant decreased risk for PPHN compared to fluoxetine (OR, 0.34; 95% CI, 0.11–0.96) (Figure 3). The heterogeneity in network meta-analysis was high, $I^2$ = 72%. The number of cases for each study that contributed to the analysis is summarized in Appendix C.

### Sensitivity analysis

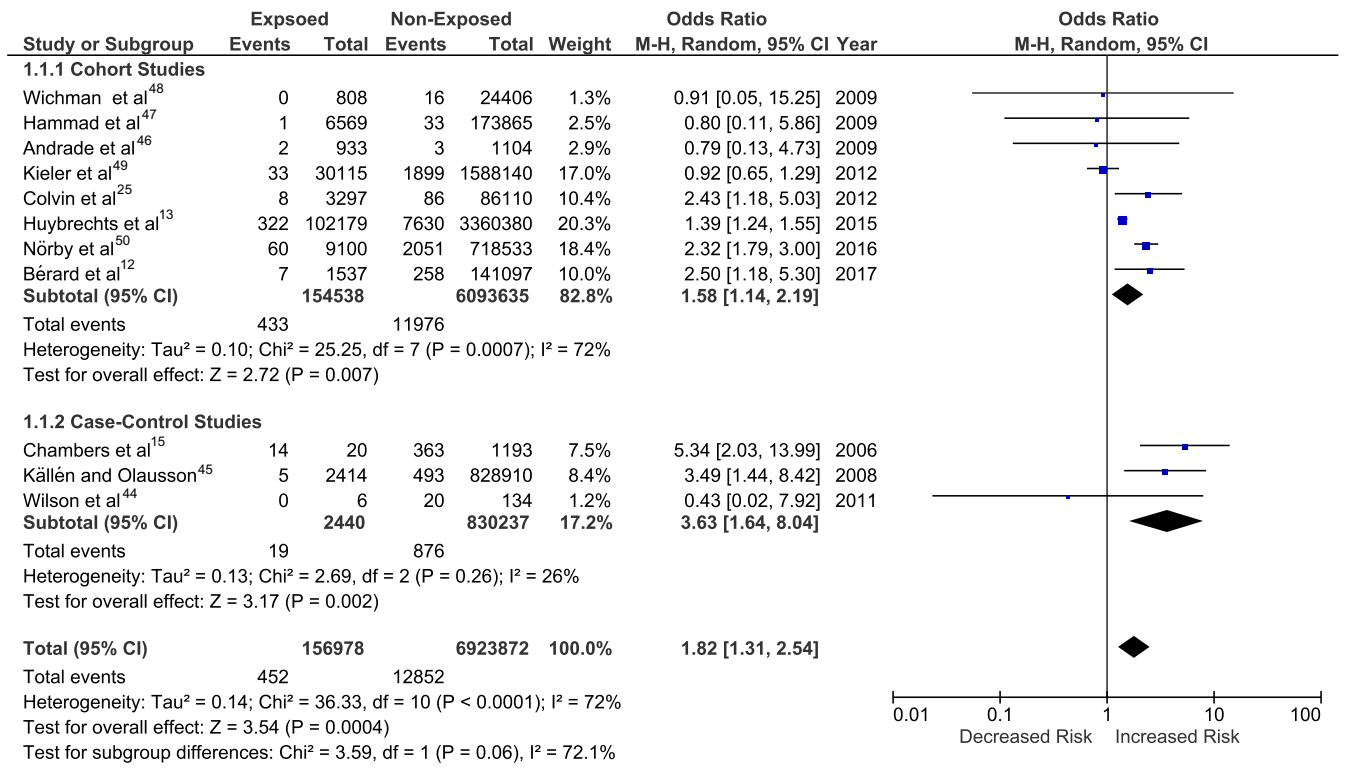
*Late exposure (week ≥20).* In analysis restricted to late pregnancy exposure to SSRI or SNRI, exposure was significantly associated with PPHN, with a similar point estimate of the relative risk (OR, 2.08; 95% CI, 1.44–3.01; $I^2$ = 76%) (Figure 4).

*Quality.* In analysis restricted to fully published cohorts reaching a NOS score of ≥7, the association with PPHN remained significant, with a similar point estimate (OR, 1.99; 95% CI, 1.43–2.78; $I^2$ = 75%) (Supplementary Figure 2).

### Subgroup analysis

*Late preterm and term deliveries vs all deliveries.* In analysis restricted to outcomes of term and late preterm deliveries only compared to all deliveries, we compared the association between exposure to SSRIs or SNRIs and PPHN in late preterm and term deliveries (OR, 1.60; 95% CI, 0.37–6.90; $I^2$ = 83%) versus all deliveries (OR, 1.84; 95% CI, 1.31–2.58) (Supplementary Figure 3). The test for subgroups differences was not statistically significant, *P* = .87.

**FIGURE 2**
**Meta-analysis of all studies**




Forest plot of odds ratio (OR) for persistent pulmonary hypertension of newborn in all weeks of exposure. Blue boxes represent point estimates for OR surrounded by 95% confidence interval (CI).

*M-H*, Mantel-Haenszel.

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### Publication bias

Publication bias was calculated for PPHN analysis including all 11 studies. Visual inspection of the funnel plot (Figure 5) shows slight asymmetry. When applying the trim-and-fill technique, no studies were missing in the plot. Egger test was not statistically significant ($P = .35$). Therefore, we conclude no publication bias was detected in our analysis.

**TABLE 3**
**Treatment ranks for selective serotonin reuptake inhibitors safety (*P* scores) and probability for persistent pulmonary hypertension of newborn**

| Medication | *P* score |
|---|---|
| Sertraline | .83 |
| Escitalopram | .69 |
| Paroxetine | .49 |
| Citalopram | .21 |
| Fluoxetine | .16 |

Higher score indicates lower probability.

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### Number needed to harm (NNH)

The incidence rate for PPHN according to our systematic review was 2.9/1000 live births in exposed mother-infant pairs and 1.8/1000 live births for nonexposed mother-infant pairs. This estimate is consistent with the literature (2–6/1000 live births).[19,20] The relative odds according to the incidence rate is 1.5, the unadjusted OR for PPHN, computed in meta-analysis is 1.82 and the adjusted OR is 2.42. The attributable risk based on the incidence rate is 0.1%. The NNH of SSRI and SNRIs exposure during pregnancy and PPHN is 1000, meaning that for 1000 women exposed to SSRIs and SNRIs during pregnancy 1 additional neonate will develop PPHN after birth.

## Comment

### Principal findings

In this systematic review and network meta-analysis, we found that exposure to SSRIs during pregnancy is associated with a doubled increased risk for PPHN. In network meta-analysis comparing the individual SSRI, sertraline was found most likely to carry the lowest risk for PPHN among the SSRIs. The lower risk for PPHN associated with sertraline, compared to other SSRIs, is biologically plausible, as sertraline has been shown to cross the placenta at a lower percentage than other SSRIs.[7]

The relative risk for PPHN in late pregnancy in our analysis was consistent with previously published cohort

studies[12,25,49,50] and the adjusted risk was similar to the previously published meta-analysis (RR, 2.5; 95% CI, 1.32–4.73).[30] Chambers et al[15] and Källén and Olausson[45] found a higher risk for PPHN than in our analysis. The higher risk in the later studies may be attributed to the case-control study design, which is often susceptible to bias.[52] According to the pooled risk estimate in our analysis, PPHN is relatively rare, such that 1000 women would need to be exposed to SSRI for each additional case of PPHN. This estimate suggests a lower absolute increased risk compared to previously published estimates, reporting a NNH of 351 for PPHN with SSRI.[30] We noted that the incidence of PPHN was slightly lower in the nonexposed groups, 1.8/1000 live births, indicating a lower rate than the total population rate in the literature (2–6/1000 live births).[19,20] This may be due to underreporting of PPHN cases in the offspring in mothers who were not exposed to SSRIs and SNRIs during pregnancy and due to the exclusion of infants with risk factors for developing PPHN.

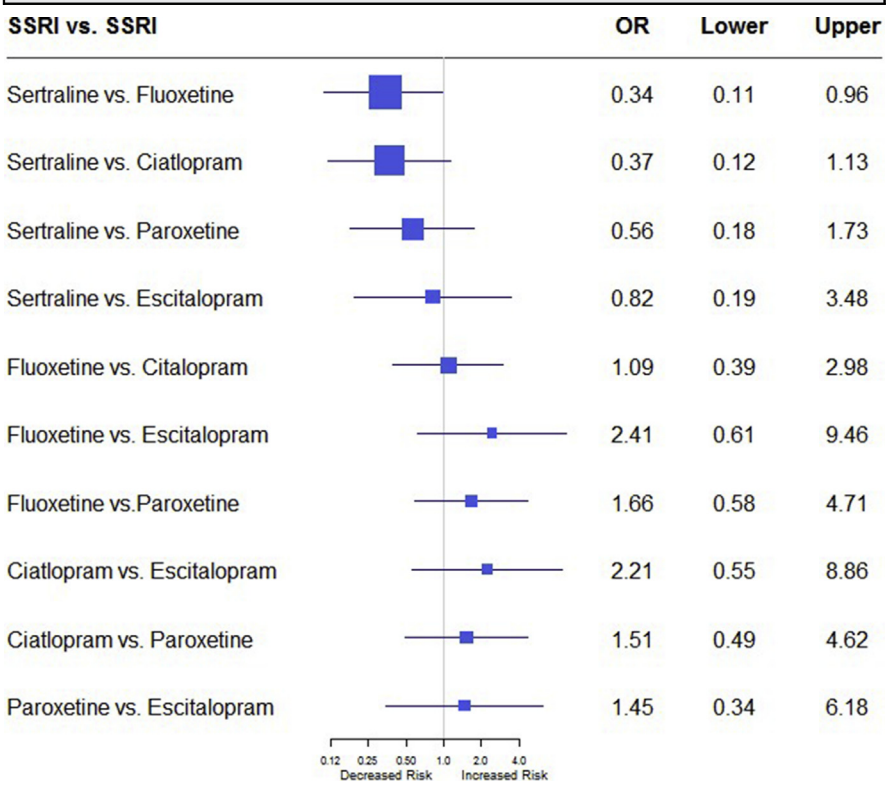
In our network meta-analysis, the risk for PPHN appears to be a class effect of SSRIs, when compared to no exposure. However, among the SSRIs, sertraline ranked most likely to have the lowest risk for PPHN. This result may be attributed to sertraline's pharmacokinetic properties, and specifically to sertraline's significantly lower placental penetration compared to other SSRIs likely leading to reduced fetal exposure.[6,7] In addition, sertraline has fewer clinically significant drug-drug interactions as compared to other SSRIs and SNRIs. It is a weak inhibitor of CYP2D6 as compared to fluoxetine and paroxetine and has almost no effect on other CYP450 enzymes.[53,54] Therefore, sertraline may also be preferred in pregnant women with concomitant drug therapy due to the lower potential for drug interaction and genetic polymorphism.

When assessing the risk for PPHN from adjusted effects sizes in the included studies, the OR was 2.42 (95% CI, 1.68–3.48). The crude and the adjusted risks for PPHN were similar, with the adjusted risk being slightly higher. This demonstrates that there are factors that may increase the risk for PPHN such as cardiac disease, meconium aspiration syndrome, and cesarean delivery.[23,55] Cardiac diseases and meconium aspiration syndrome themselves may increase the risk for PPHN;[23,55] of the included studies in the analysis, 3 studies[13,15,44] excluded neonates with cardiac or pulmonary diseases or meconium aspiration and 1 study[25] conducted a separate analysis for neonates with cardiac or pulmonary diseases. Studies that excluded children with background diseases showed a lower risk for PPHN than in our analysis, except that of Chambers et al,[15] which showed an adjusted OR of 6.1, which may be attributable to the small number of cases in the study and to the case-control design. Therefore, we may conclude that the observed risk is in our analysis is mainly attributable to drug exposure, despite the high heterogeneity, and we must keep in mind that fetal factors may distinctly increase the risk.

The included studies attempted to control for a range of factors likely associated with PPHN; maternal diabetes,[12,13,15,44,49] body mass index and obesity,[13,15,44,45,50] mode of delivery,[44,50] maternal asthma,[13] and gestational age.[46,50] Still, the differences in study methodology and the limited ability to control for all factors that may be associated with PPHN should be kept in mind when considering the pooled estimates of our meta-analysis.

In subgroup analysis, we examined data from studies that included deliveries from week ≥33, compared to all delivery weeks and the association between SSRI and PPHN was lower, for late preterm and term, however, the difference between subgroups was not significant, therefore we cannot conclude a greater risk for PPHN in late preterm and term deliveries.

**FIGURE 3**
**Pairwise network meta-analysis for different SSRIs**




Network meta-analysis forest plot of odds ratio (OR) for persistent pulmonary hypertension of newborn—comparison of selective serotonin reuptake inhibitors (SSRI). Blue boxes represent point estimates for OR surrounded by 95% confidence interval.

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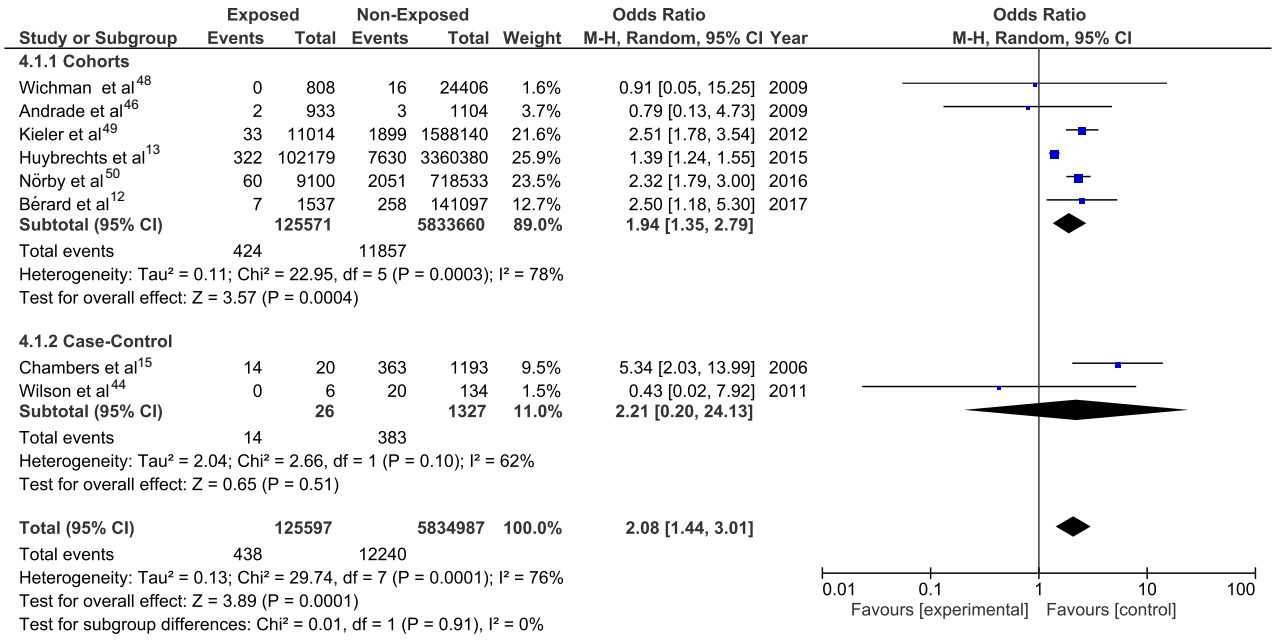
**FIGURE 4**
**Meta-analysis of studies reporting PPHN exposure after week 20**




Forest plot of odds ratio for persistent pulmonary hypertension of newborn—late (week >20) pregnancy exposure. Blue boxes represent point estimates for odds ratio surrounded by 95% confidence interval (CI).

*M-H*, Mantel-Haenszel.

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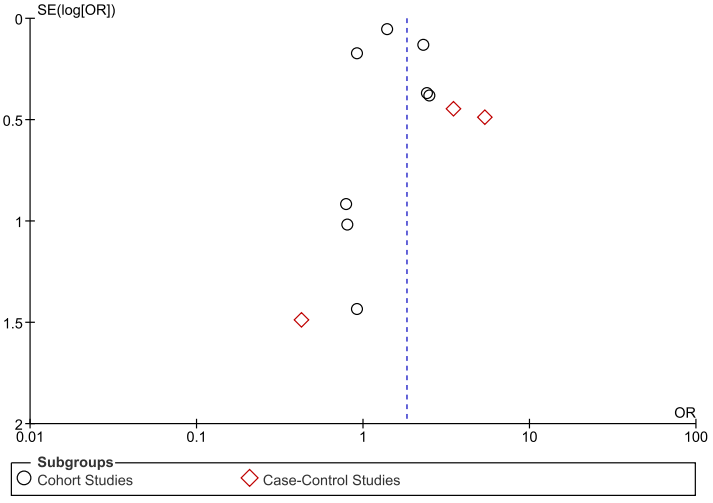
**Strengths and weaknesses**

Strengths of our analysis include a thorough and systematic review of all available published studies. We updated the data from the previous meta-analysis published in 2013, which included 5 studies,[30] by adding 6 studies to the analysis and updating the NNH. We used random effects meta-analysis to overcome the heterogeneity in our analysis. We conducted network-meta analysis to explore differences in the risk for PPHN among specific SSRIs and we found a lower risk with sertraline exposure. Lastly, we conducted sensitivity analysis to assess the risk for PPHN in late pregnancy.

Limitations of our study include, firstly, the methodology of the studies included in the analysis is susceptible to recall and exposure bias. Another limitation is that meta-analysis does not enable adjustment to covariates, however, we used adjusted effect sizes meta-analysis. Data on medication exposure were collected by interviews or follow-up on prescription dispensing and databases linking. Mothers of infants with a PPHN diagnosis are more likely to remember and to associate between exposure to medications during pregnancy and offspring morbidity. In addition, prescription dispensing does

**FIGURE 5**
**Publication bias assessment**




Funnel plot for publication bias assessment.

*OR*, odds ratio; *SE*, standard error.

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not necessarily indicate intrauterine exposure to SSRIs. Secondly, study-level meta-analysis does not allow for adjustment for all covariates that may affect the risk for PPHN. Lastly, it is important to keep in mind the exploratory nature of network meta-analysis, which includes indirect comparisons of results obtained in different studies. In addition, the number of exposed infants in each SSRIs group was small and therefore, our analysis may not be robust enough.

### Meaning and clinical implications

Our results indicate that clinicians treating women with depression and anxiety during pregnancy should be aware of the apparent increase in PPHN associated with these medications and encourage them to discuss the risks and benefits of the treatment with their patients. Though the absolute increase in risk is small, it justifies careful monitoring of infants exposed to SSRIs and SNRIs in late pregnancy. These infants must be under strict supervision after birth and appropriate follow-up for early detection of PPHN must be carried out. Our analysis suggests there may be reason to prefer sertraline for treatment of depression during pregnancy. Also, previous studies have suggested that among the SSRIs it is also less likely associated with congenital abnormalities.[16]

### Conclusions with future research implications

Exposure to SSRIs and SNRIs in late pregnancy is associated with an increased risk for PPHN. The association seems to be a class effect of all SSRIs and SNRIs when compared to no exposure. Sertraline ranked most likely to have the lowest risk for PPHN compared to other SSRIs, suggesting it may have the best safety profile for use in pregnancy in this regard. Further studies are needed to fully establish these results.

**Data sharing:** Statistical code and protocol are available upon request. ■

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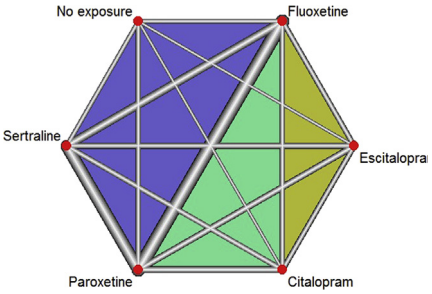
**SUPPLEMENTARY FIGURE 1**
**Network graph**




Network meta-analysis graph. Line thickness represents number of exposed mother-and-child pairs with diagnosis of persistent pulmonary hypertension of newborn, ie, thicker line represents larger number of exposed mothers and their infants and vice versa. Colors represent number of treatments (different selective serotonin reuptake inhibitors) compared in each study, in network meta-analysis. Area of each color is proportional to number of studies having same number of treatment comparisons. Purple: 6 treatments, 2 studies; green: 5 treatments, 1 study; yellow: 4 treatments, 1 study.

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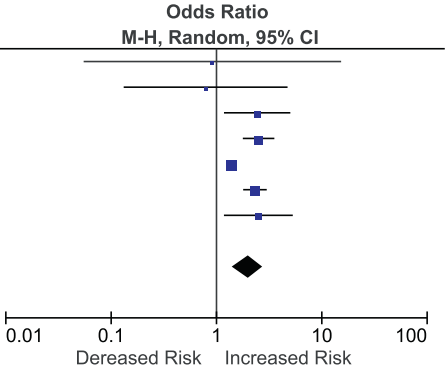
**SUPPLEMENTARY FIGURE 2**
**Meta-analysis of studies with high quality**

| | Exposed | | Non-Exposed | | | Odds Ratio | |
|---|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year |
| Wichman et al[48] | 0 | 808 | 16 | 24406 | 1.3% | 0.91 [0.05, 15.25] | 2009 |
| Andrade et al[46] | 2 | 933 | 3 | 1104 | 3.1% | 0.79 [0.13, 4.73] | 2009 |
| Colvin et al[25] | 8 | 3297 | 86 | 86110 | 12.0% | 2.43 [1.18, 5.03] | 2012 |
| Kieler et al[49] | 33 | 11014 | 1899 | 1588140 | 21.4% | 2.51 [1.78, 3.54] | 2012 |
| Huybrechts et al[13] | 322 | 102179 | 7630 | 3360380 | 26.8% | 1.39 [1.24, 1.55] | 2015 |
| Nörby et al[50] | 60 | 9100 | 2051 | 718533 | 23.8% | 2.32 [1.79, 3.00] | 2016 |
| Bérard et al[12] | 7 | 1537 | 258 | 141097 | 11.5% | 2.50 [1.18, 5.30] | 2017 |
| **Total (95% CI)** | | **128868** | | **5919770** | **100.0%** | **1.99 [1.43, 2.78]** | |
| Total events | 432 | | 11943 | | | | |

Heterogeneity: Tau² = 0.11; Chi² = 24.32, df = 6 (P = 0.0005); I² = 75%
Test for overall effect: Z = 4.04 (P < 0.0001)




Forest plot of odds ratio (OR) for persistent pulmonary hypertension of newborn high-quality cohort studies. Blue boxes represent point estimates for OR surrounded by 95% confidence interval (CI).

*M-H*, Mantel-Haenszel.

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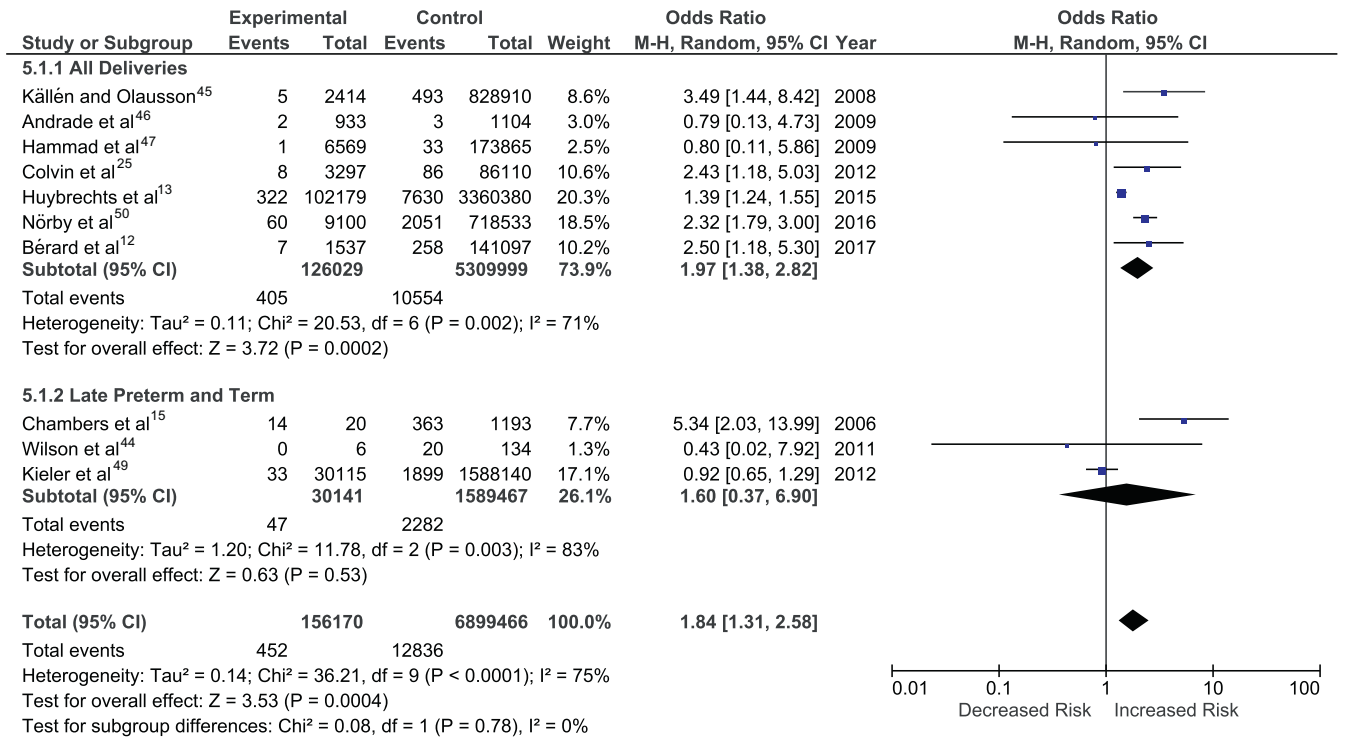
**SUPPLEMENTARY FIGURE 3**
**Meta-analysis of studies according to week of delivery**




Forest plot of odds ratio (OR) for persistent pulmonary hypertension of newborn late preterm and term deliveries vs all deliveries. Blue boxes represent point estimates for OR surrounded by 95% confidence interval (CI).

*M-H*, Mantel-Haenszel.

*Masarwa. SSRIs and SNRIs during pregnancy: risk for PPHN. Am J Obstet Gynecol 2019.*

**SUPPLEMENTARY TABLE 1**
**Newcastle-Ottawa quality assessment scale**

| Study, year | Selection | Comparability | Outcome | NOS score |
|---|---|---|---|---|
| Chambers et al,[15] 2006 | *** | * | *** | 7 |
| Källén and Olausson,[45] 2008 | **** | * | ** | 7 |
| Andrade et al,[46] 2009 | **** | * | *** | 8 |
| Hammad et al,[47] 2009 | ** | — | * | 3 |
| Wichman et al,[48] 2009 | **** | — | *** | 7 |
| Wilson et al,[44] 2011 | *** | * | *** | 7 |
| Colvin et al,[25] 2012 | **** | * | ** | 7 |
| Kieler et al,[49] 2012 | **** | * | ** | 7 |
| Huybrechts et al,[13] 2015 | **** | * | ** | 7 |
| Nörby et al,[50] 2016 | **** | * | ** | 7 |
| Bérard et al,[12] 2017 | **** | * | ** | 7 |

Score is represented by stars in each domain (selection, comparability and outcome). Total Score range from zero to nine.

*NOS*, Newcastle-Ottawa scale.

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**SUPPLEMENTARY TABLE 2**

## Covariates adjusted for outcome and gestational week included in studies

| Study ID | Covariates adjustment | Gestational wk included in studies |
|---|---|---|
| Chambers et al,[15] 2006 | Maternal diabetes, maternal race/ethnic group and prepregnancy body mass index, smoking, alcohol intake, and use of NSAIDs wk >20 | >34 |
| Källén and Olausson,[45] 2008 | Maternal age, smoking, parity, year of birth, and body mass index | All wk |
| Andrade et al,[46] 2009 | NA | All wk |
| Hammad et al,[47] 2009 | NA | All wk |
| Wichman et al,[48] 2009 | NA | All wk |
| Wilson et al,[44] 2011 | SSRI exposure >20 wk gestation, maternal diabetes, smoking, obesity, parity, advanced maternal age (age >35 y), chorioamnionitis, fetal gender, and mode of delivery | >34 |
| Colvin et al,[25] 2012 | Previous preterm birth, smoking, socioeconomic indexes for areas, parity, and maternal age | All wk |
| Kieler et al,[49] 2012 | Maternal age, dispensed nonsteroidal antiinflammatory drugs and anti-diabetes drugs, preeclampsia, chronic diseases during pregnancy, country of birth, birth year, level of delivery hospital, and birth order | >33 |
| Huybrechts et al,[13] 2015 | Year of delivery, age, race, multiple gestations, antidepressant indications, proxies for depression severity, hypertension, preexisting diabetes, gestational diabetes, epilepsy, renal disease, asthma, obesity, other psychotropic medication use | All wk |
| Nörby et al,[50] 2016 | Maternal age, year of birth, parity, maternal smoking, body mass index, mother born in Sweden, cohabiting with child's father, cesarean delivery, any use of mild sedatives and maternal use of other neurotropic drugs, gestational age, fetal weight for gestational age and sex | All wk |
| Bérard et al,[12] 2017 | Maternal age, maternal marital status, receipt of social assistance 1 y before or during pregnancy, area of residence, maternal chronic comorbidities during 12 mo prior to and during first trimester of pregnancy: depression, anxiety, hypertension, diabetes, and asthma, health care utilization during last 12 mo including: visits to psychiatrist or obstetrician, hospitalizations or emergency department visits, no. of medications used other than antidepressants, and no. of different prescribers | All wk |

*NA*, not available; *NSAID*, nonsteroidal anti-inflammatory drug; *SSRI*, selective serotonin reuptake inhibitor.

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