# Neonatal outcomes after neuraminidase inhibitor use during pregnancy: a meta-analysis of cohort studies

Jiangshan Lian[1], Munire Adilijiang[1], Caihua Chang[1], Hai-yin Jiang[1], and Yongping Zhang[1]

[1]Affiliation not available

May 23, 2021

**Abstract**

AIM: Influenza infection poses a severe threat to pregnant mothers, and antiviral treatment is recommended. However, the safety of neuraminidase-inhibitor antiviral medications during pregnancy has not been well described. METHODS: A systematic review and meta-analysis were performed to evaluate the adverse neonatal outcomes associated with exposure to neuraminidase inhibitors during pregnancy. The PubMed, Embase, and Cochrane Library databases were searched to identify potential studies for inclusion. RESULTS: Nine cohort studies that estimated adverse neonatal outcomes associated with exposure to neuraminidase-inhibitor medication during pregnancy were included. Exposure to a neuraminidase inhibitor during pregnancy was not associated with an increased risk of congenital malformation (odds ratio [OR] 0.9, 95% confidence interval [CI] 0.72–1.12, P = 0.341), low Apgar score (OR 0.96, 95% CI 0.77–1.2, P = 0.733), or preterm birth (OR 0.99, 95% CI 0.89–1.09, P = 0.771) compared with no exposure. However, exposure to a neuraminidase inhibitor was associated with a reduced risk of low birth weight (OR 0.79, 95% CI 0.68–0.92, P = 0.002) and giving birth to a small-for-gestational-age infant (OR 0.78, 95% CI 0.69–0.88, P < 0.001). Further analyses limited to oseltamivir exposure were consistent with the overall results. CONCLUSION: Exposure to neuraminidase-inhibitor medication during pregnancy does not appear to be associated with adverse neonatal outcomes. We recommend further studies to investigate this association, which will help clinicians determine whether to prescribe a neuraminidase inhibitor during pregnancy.

**Neonatal outcomes after neuraminidase inhibitor use during pregnancy: a meta-analysis of cohort studies**

**Running title: Neuraminidase inhibitors and neonatal outcomes**

Jiangshan Lian[1,2], Munire Adilijiang[2], Caihua Chang[2], Hai-yin Jiang[1], Yongping Zhang[2*]

[1]State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Department of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine.

[2]Department of Infectious Diseases, People's Hospital of Xinjiang Uygur Autonomous Region

**Contact information**

*Corresponding author: Yongping Zhang, Department of Infectious Disease, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi 830001, Xinjiang Uygur Autonomous Region, China. E-mail: zhangyongpingxj@126.com

**Conflicts of Interest**

The authors declare no competing interest.

**Funding**

None.

**Authors' contributions**

JSL and YPZ conceived the study and revised the manuscript critically for important intellectual content. MA made substantial contributions to its design, acquisition, analysis and interpretation of data. CC and HYJ participated in the design, acquisition, analysis and interpretation of data. All authors read and approved the final manuscript.

**AIM:** Influenza infection poses a severe threat to pregnant mothers, and antiviral treatment is recommended. However, the safety of neuraminidase-inhibitor antiviral medications during pregnancy has not been well described.

**METHODS:** A systematic review and meta-analysis were performed to evaluate the adverse neonatal outcomes associated with exposure to neuraminidase inhibitors during pregnancy. The PubMed, Embase, and Cochrane Library databases were searched to identify potential studies for inclusion.

**RESULTS:** Nine cohort studies that estimated adverse neonatal outcomes associated with exposure to neuraminidase-inhibitor medication during pregnancy were included. Exposure to a neuraminidase inhibitor during pregnancy was not associated with an increased risk of congenital malformation (odds ratio [OR] 0.9, 95% confidence interval [CI] 0.72–1.12, P = 0.341), low Apgar score (OR 0.96, 95% CI 0.77–1.2, P = 0.733), or preterm birth (OR 0.99, 95% CI 0.89–1.09, P = 0.771) compared with no exposure. However, exposure to a neuraminidase inhibitor was associated with a reduced risk of low birth weight (OR 0.79, 95% CI 0.68–0.92, P = 0.002) and giving birth to a small-for-gestational-age infant (OR 0.78, 95% CI 0.69–0.88, P < 0.001). Further analyses limited to oseltamivir exposure were consistent with the overall results.

**CONCLUSION:** Exposure to neuraminidase-inhibitor medication during pregnancy does not appear to be associated with adverse neonatal outcomes. We recommend further studies to investigate this association, which will help clinicians determine whether to prescribe a neuraminidase inhibitor during pregnancy.

**Keywords:** flu, antiviral, prenatal, maternal.

## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

Neuraminidase inhibitors are now increasingly used to treat influenza in pregnant women. It remains controversial whether neuraminidase inhibitor exposure during pregnancy affects the risk of adverse neonatal outcomes.

## WHAT THIS STUDY ADDS

Current evidence does not indicate that neuraminidase inhibitor exposure during pregnancy is not associated with increased risks of overall congenital malformations in offspring.

Furthermore analysis did not indicate increased risks of other adverse neonatal outcomes in offspring exposed to neuraminidase inhibitors.

This study supports the current guidelines stating that oseltamivir is recommended for influenza treatment during pregnancy.

## Introduction

Influenza is an acute infectious disease caused by the influenza A, B, and C viruses that threatens pregnant mothers[1]. During seasonal influenza and pandemic influenza outbreaks, pregnant women have increased susceptibility to severe infection and worse clinical outcomes from influenza[2]. Maternal influenza exposure during pregnancy is associated with adverse maternal and neonatal outcomes[3], suggesting that influenza should be prevented and treated in pregnant women.

The neuraminidase-inhibitor antiviral medications oseltamivir and zanamivir have been recommended for preventing and treating influenza among exposed and/or infected pregnant women since the 2009 HIN1

pandemic[4]. Since then, there has been a notable increase in the number of pregnant women treated with neuraminidase inhibitors[5]. However, little is known about the reproductive safety of these drugs. A study using an *ex vivo* human placental model showed that transplacental transfer of the oseltamivir metabolite is incomplete and its accumulation is minimal[6]. Several cases of adverse outcomes have been reported in mothers exposed to oseltamivir[7, 8]. Some studies without control women suggest that maternal exposure to laninamivir does not increase the rate of adverse pregnancies or fetal outcomes[9, 10]. Previous systematic reviews with small sample sizes have summarized this association and reported that exposure to a neuraminidase inhibitor during pregnancy does not appear to increase the overall risk of congenital malformations[11, 12]. Additional studies have been published since that systematic review, enabling a more detailed analysis of the association between neuraminidase-inhibitor use during pregnancy and congenital malformation risk. Those studies also investigated the effects of neuraminidase inhibitors on other pregnancy outcomes, but the results were inconsistent. Therefore, we conducted a meta-analysis to collect evidence-based, relevant research regarding maternal neuraminidase-inhibitor exposure during pregnancy and neonatal outcomes to provide a scientific basis for recommendations to avoid adverse outcomes.

## Methods

### Literature search

To ensure that the work was of high quality, this study was performed following the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines[13] (Table S1). English-language publications were comprehensively searched in the Cochrane Library, PubMed, and EMBASE databases from the dates of inception until May 2021. The search terms used were "pregnancy OR mothers OR pregnant OR gestational OR prenatal OR perinatal OR gestation" and "neuraminidase inhibitors OR oseltamivir OR zanamivir." The reference lists of the retrieved articles were manually examined to identify studies not found in the database search.

### Inclusion criteria

Studies were initially identified based on their title and abstract and later included after a full-text evaluation. Observational studies were included if they met all of the following criteria: used a cohort study design, explored whether maternal neuraminidase inhibitor use during pregnancy increased the risk of adverse maternal or neonatal outcomes, and had sufficient available data to allow the calculation of risk estimates if adjusted data were not provided. Reviews, letters to the editor, or conference abstracts; basic studies or those using animal experiments; case reports or series; studies without a control group; and studies that included other congenital malformations where it was not possible to separate the data regarding oral clefts were excluded.

**Data extraction and quality assessment** Data were independently extracted by two investigators, and any discrepancies were resolved by the third author. The extracted information included author names, publication date, study design, study location, study period, drug exposure assessment results, outcome measures, statistical analyses used, and study quality. The most-adjusted effect size estimate was used when more than one estimate was provided. The risk of bias was estimated using the Newcastle Ottawa Scale to assess the nonrandomized study quality[14], as recommended by the Cochrane Collaboration. The risk of bias concerning selection, comparability, and assessment of the exposure/outcome was estimated according to nine items using a star allocation scheme. The scale features eight criteria and yields scores ranging from 0 (high risk of bias) to 9 (low risk of bias). Studies with scores $> 7$ were considered high quality. Summary bias risk assessments were derived for each study.

### Outcome assessment

The pregnancy outcomes were analyzed based on the following categories: overall congenital malformations and heart malformations; and other neonatal outcomes including low birth weight, low Apgar score, small for gestational age (SGA), or preterm birth.

### Data synthesis

Meta-analyses were performed using STATA version 13 software (Stata Corp, College Station, TX, USA). Heterogeneity among studies was assessed using the $\chi^2$ test and $I^2$statistic; an $I^2 > 50\%$ or $P < 0.05$ for the Q-statistic indicated significant heterogeneity[15]. The DerSimonian and Laird random-effects model was used when studies were heterogeneous; otherwise, the Mantel-Haenszel fixed-effects model was used[16]. When possible, adjusted effect estimates (odds ratio [OR], relative risk, and hazard risk) of outcome measures from exposure to a neuraminidase inhibitor were extracted, along with standard errors. Associations between maternal neuraminidase-inhibitor exposure during pregnancy and adverse neonatal outcomes were estimated using ORs and corresponding 95% confidence intervals (CIs), generated by comparing cases and controls. Publication bias was evaluated using Begg's test[16, 17]. A P-value $< 0.05$ was considered to indicate significance.

## Results

### Search results

A total of 865 records without duplicates were identified using our search strategy with the aforementioned keywords (309 from Pubmed, 643 from Embase, and 8 from the Cochrane Library database). After the titles and abstracts were screened, 822 citations were selected for full-text assessment. Finally, nine cohort studies[18-26] were included in the analysis. Figure 1 summarizes the number of articles remaining after the exclusion of non-relevant articles at each stage of the eligibility assessment.

### Characteristics of the included studies

The main characteristics of the included studies are presented in Table 1. The publication years ranged from 2010 to 2021, with the first members of the offspring cohort delivered in 1997. The sample sizes of the included studies ranged from 476 to 698,056, and 10,010 pregnant mothers were exposed to neuraminidase inhibitors during pregnancy; only one study examined an Eastern population. Overall, two were hospital-based cohort studies. Based on the methodological quality assessment scores, most studies were deemed to be of high quality; only one was categorized as low quality. The score breakdown is shown in Table S2.

### Meta-analysis

### Overall congenital malformations

A meta-analysis of seven studies assessing the risk of congenital malformations concerning neuraminidase-inhibitor exposure during pregnancy indicated that the combined OR of congenital malformation risk was 0.9 (95% CI 0.72–1.12, P = 0.341) (Figure 2). No heterogeneity was observed among the studies ($I^2 = 0\%$, P = 0.852). As shown in Figure S1, we did not observe any evidence of publication bias (Begg's test, P = 1; Egger's test, P = 0.63). The sensitivity analyses revealed no substantial change in the pooled risk estimates upon the exclusion of any single study from the same database. Six studies reported the risk of congenital malformations in relation to oseltamivir exposure during pregnancy; the combined OR was 0.89 (95% CI 0.69–1.14, P = 0.361; $I^2 = 0\%$) (Figure S2).

We also analyzed the association between neuraminidase-inhibitor exposure and heart malformations, which was reported by two studies. The rates of heart malformations (OR 1.11, 95% CI 0.61–2.03, P = 0.735; $I^2 = 0\%$) (Figure S3) were similar in the two groups.

### Other neonatal outcomes

Table 1 presents the results for other neonatal outcomes. Six studies evaluated the rate of low birth weight, and we found a reduced risk of low birth weight involving neuraminidase-inhibitor exposure (OR 0.79, 95% CI 0.68–0.92, P = 0.002; $I^2 = 0\%$) (Figure 3A). Also, oseltamivir exposure during pregnancy was associated with a reduced risk of low birth weight (OR 0.84, 95% CI 0.71–0.99, P = 0.039; $I^2 = 0\%$) (Figure S4A).

We identified five studies reporting low Apgar scores that were eligible for inclusion. No significant association was detected between neuraminidase-inhibitor use and a low Apgar score in comparison with mothers who were not exposed to a neuraminidase inhibitor (OR 0.96, 95% CI 0.77–1.2, P = 0.733; $I^2 = 0\%$) (Figure

3B). When our analysis was limited to oseltamivir exposure, we observed no significant association between oseltamivir exposure and a low Apgar score (OR 0.96, 95% CI 0.74–1.25, P = 0.785; $I^2$ = 0%) (Figure S4B).

Four studies reported the risk of an SGA outcome in relation to neuraminidase-inhibitor exposure during pregnancy; the combined OR of an SGA outcome was 0.78 (95% CI 0.69–0.88, P < 0.001; $I^2$ = 0%) (Figure 3C). Oseltamivir exposure during pregnancy was associated with a lower risk of an SGA outcome (OR 0.77, 95% CI 0.68–0.88, P < 0.001; $I^2$ = 0%) (Figure S4C).

We also analyzed the association between neuraminidase-inhibitor exposure and the preterm birth rate (OR 0.99, 95% CI 0.89–1.09, P = 0.771; $I^2$ = 0%) (Figure 3D). When our analysis was limited to oseltamivir exposure, we observed no significant association between oseltamivir exposure and preterm birth (OR 1.03, 95% CI 0.93–1.15, P = 0.542; $I^2$ = 0%) (Figure S4D).

**Discussion**

Our meta-analysis of nine cohort studies suggests that exposure to a neuraminidase inhibitor during pregnancy is not associated with a significantly increased risk of adverse neonatal outcomes. By contrast, we observed a small decrease in the risk of low birth weight or an SGA outcome after exposure to a neuraminidase inhibitor. Further analyses limited to oseltamivir exposure were consistent with the overall results.

Pregnant women have an elevated risk of complications and poorer outcomes than the general population when infected with influenza. A previous meta-analysis[27] demonstrated that maternal influenza exposure is associated with an increased risk of overall congenital malformation, suggesting that preventing influenza in pregnant women may reduce the risk of congenital anomalies. During the 2009 H1N1 pandemic, treating pregnant women with a neuraminidase inhibitor for suspected or confirmed influenza or prophylaxis was recommended by the World Health Organization and the US Centers for Disease Control and Prevention[4]. Therefore, the association between neuraminidase-inhibitor use during pregnancy and developmental disorders in offspring has been a controversial topic for decades. In theory, neuraminidase inhibitors, such as oseltamivir, pass the placental barrier and directly affect embryonic development[8]. However, preclinical animal studies reported no adverse effects of oseltamivir at normal dosages on reproduction parameters in rats or rabbits[12]. Oseltamivir has no direct effects on embryonic or fetal development even at higher dosages in rabbits[12]. Our meta-analysis found no significant increased risk of congenital malformations in children who were exposed to a neuraminidase inhibitor *in utero* .

An unanticipated finding was that neuraminidase-inhibitor use during pregnancy was associated with a reduced risk of low birth weight or an SGA outcome. This may have occurred for three reasons. First, the protective effect of neuraminidase inhibitors on fetal growth suggests a "healthy user effect." Pregnant mothers who have been exposed to a neuraminidase inhibitor may be more likely to receive more extensive assessment and prenatal care from their attending physician, which may then reduce the risk of growth restrictions in the neonate. This bias might have affected the true association. Second, this association may be a chance finding. In our analysis of low birth weight, the study by Graner et al.[23] accounted for 75% of the analytical weight, and when this study was excluded from the analysis, no protective effect of neuraminidase inhibitors was detected. Thus, our results pertaining to neuraminidase-inhibitor use and the risk of low birth weight may be limited by sample size, and further investigation is needed to clarify the issue. Third, an epidemiological study[3] demonstrated that fever associated with influenza is linked with adverse neonatal outcomes; thus, the protective effect observed in our findings might have been driven by several of the included studies, which enrolled pregnant mothers infected with influenza without antiviral treatment as their comparisons.

This systematic review with a meta-analysis is the first to provide an overall estimate of the effect of neuraminidase inhibitors on neonatal outcomes. The strength of our meta-analysis lies in the exclusive use of cohort studies, which are less prone to bias in terms of assessing drug exposure during pregnancy. In addition, the level of heterogeneity for the analyses was low, making the pooled results more convincing.

Nonetheless, this study had some major limitations. The most important limitation of our meta-analysis

was the residual number of unknown confounders. Further well-designed studies considering more covariates are required to examine the association between neuraminidase-inhibitor use during pregnancy and adverse neonatal outcomes. Second, we only conducted subgroup analysis to evaluate the effect of oseltamivir due to limited studies that evaluated zanamivir. Third, our study focused on neonatal outcomes, and further research is required to clarify the effects on maternal outcomes. Fourth, various definitions for assessing neonatal outcomes were used among the studies. Finally, the number of eligible studies and the sample size of exposed pregnant mothers were small, which might have influenced the accuracy of our results.

In conclusion, our results suggest that *in utero* exposure to a neuraminidase inhibitor does not appear to increase the risk of adverse neonatal outcomes. This study supports the current guidelines stating that oseltamivir is recommended for influenza treatment during pregnancy.

**Reference**

1. Abdullahi H, Elnahas A, Konje JC. Seasonal influenza during pregnancy. Eur J Obstet Gynecol Reprod Biol 2021; 258: 235-39.

2. Mertz D, Geraci J, Winkup J, Gessner BD, Ortiz JR, Loeb M. Pregnancy as a risk factor for severe outcomes from influenza virus infection: A systematic review and meta-analysis of observational studies. Vaccine 2017; 35: 521-28.

3. Wang R, Yan W, Du M, Tao L, Liu J. The effect of influenza virus infection on pregnancy outcomes: A systematic review and meta-analysis of cohort studies. Int J Infect Dis 2021; 105: 567-78.

4. CfDCa P. Updated Interim Recommendations for Obstetric Health Care Providers Related to Use of Antiviral Medications in the Treatment and Prevention of Influenza for the 2009–2010 Season. Accessed October 10, 2010.

5. Havers F, Flannery B, Clippard JR, Gaglani M, Zimmerman RK, Jackson LA, Petrie JG, McLean HQ, Nowalk MP, Jackson ML, Monto AS, Belongia EA, Eng HF, Lamerato L, Campbell AP, Fry AM. Use of influenza antiviral medications among outpatients at high risk for influenza-associated complications during the 2013-2014 influenza season. Clin Infect Dis 2015; 60: 1677-80.

6. Berveiller P, Mir O, Vinot C, Bonati C, Duchene P, Giraud C, Gil S, Treluyer JM. Transplacental transfer of oseltamivir and its metabolite using the human perfused placental cotyledon model. Am J Obstet Gynecol 2012; 206: 92.e1-6.

7. Ward P, Small I, Smith J, Suter P, Dutkowski R. Oseltamivir (Tamiflu) and its potential for use in the event of an influenza pandemic. J Antimicrob Chemother 2005; 55 Suppl 1: i5-i21.

8. Meijer WJ, Bruinse HW, van den Broek MP, Kromdijk W, Wensing AM. Oseltamivir and its active metabolite cross the placenta at significant levels. Clin Infect Dis 2012; 54: 1676-7.

9. Minakami H, Kubo T, Nakai A, Saito S, Unno N. Pregnancy outcomes of women exposed to laninamivir during pregnancy. Pharmacoepidemiol Drug Saf 2014; 23: 1084-7.

10. Saito S, Minakami H, Nakai A, Unno N, Kubo T, Yoshimura Y. Outcomes of infants exposed to oseltamivir or zanamivir in utero during pandemic (H1N1) 2009. Am J Obstet Gynecol 2013; 209: 130.e1-9.

11. Tanaka T, Nakajima K, Murashima A, Garcia-Bournissen F, Koren G, Ito S. Safety of neuraminidase inhibitors against novel influenza A (H1N1) in pregnant and breastfeeding women. CMAJ 2009; 181: 55-8.

12. Donner B, Niranjan V, Hoffmann G. Safety of oseltamivir in pregnancy: a review of preclinical and clinical data. Drug Saf 2010; 33: 631-42.

13. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12.

14. Higgins JP. Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane collaboration. Available at: www.cochrane-handbook.org [6 December 2014]. 2014.

15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-58.

16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60.

17. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34.

18. Greer LG, Sheffield JS, Rogers VL, Roberts SW, McIntire DD, Wendel GD, Jr. Maternal and neonatal outcomes after antepartum treatment of influenza with antiviral medications. Obstet Gynecol 2010; 115: 711-16.

19. Svensson T, Granath F, Stephansson O, Kieler H. Birth outcomes among women exposed to neuraminidase inhibitors during pregnancy. Pharmacoepidemiol Drug Saf 2011; 20: 1030-4.

20. Xie HY, Yasseen Iii AS, Xie RH, Fell DB, Sprague AE, Liu N, Smith GN, Walker MC, Wen SW. Infant outcomes among pregnant women who used oseltamivir for treatment of influenza during the H1N1 epidemic. American Journal of Obstetrics and Gynecology 2013; 208: 293.e1-93.e7.

21. Beau AB, Hurault-Delarue C, Vial T, Montastruc JL, Damase-Michel C, Lacroix I. Safety of oseltamivir during pregnancy: A comparative study using the EFEMERIS database. BJOG: An International Journal of Obstetrics and Gynaecology 2014; 121: 895-900.

22. Dunstan HJ, Mill AC, Stephens S, Yates LM, Thomas SHL. Pregnancy outcome following maternal use of zanamivir or oseltamivir during the 2009 influenza A/H1N1 pandemic: A national prospective surveillance study. BJOG: An International Journal of Obstetrics and Gynaecology 2014; 121: 901-06.

23. Graner S, Svensson T, Beau AB, Damase-Michel C, Engeland A, Furu K, Hviid A, Håberg SE, Mølgaard-Nielsen D, Pasternak B, Kieler H. Neuraminidase inhibitors during pregnancy and risk of adverse neonatal outcomes and congenital malformations: Population based European register study. BMJ 2017; 356.

24. Ehrenstein V, Kristensen NR, Monz BU, Clinch B, Kenwright A, Sørensen HT. Oseltamivir in pregnancy and birth outcomes 11 Medical and Health Sciences 1117 Public Health and Health Services. BMC Infectious Diseases 2018; 18.

25. Chambers CD, Johnson D, Xu R, Luo Y, Jones KL. Oseltamivir use in pregnancy: Risk of birth defects, preterm delivery, and small for gestational age infants. Birth Defects Research 2019; 111: 1487-93.

26. Abraham K, Abraham A, Regi A, Lionel J, Thomas E, Vijayaselvi R, Jeyaseelan L, Abraham AM, Santhanam S, Kuruvilla KA, Steinhoff MC. Maternal and Perinatal Outcomes of Influenza in Pregnancy after Treatment with Oseltamivir. J Glob Infect Dis 2021; 13: 20-26.

27. Luteijn JM, Brown MJ, Dolk H. Influenza and congenital anomalies: a systematic review and meta-analysis. Hum Reprod 2014; 29: 809-23.

**Table 1** Characteristics of the included studies

| Author, year | Location, setting |
|---|---|
| Svensson et al, 2011 | Sweden, population-based |
| Xie et al, 2013 | Canada, population-based |
| Greer et al, 2010 | USA, hospital-based |
| Graner et al, 2017 | Denmark, Norway, Sweden and France, populati |
| Ehrenstein et al, 2018 | Denmark, population-based |
| Chambers et al, 2019 | United States and Canada, population-based |
| Dunstan et al, 2014 | UK, population-based |

| | |
|---|---|
| Beau et al, 2014 | France, population-based |
| Abraham et al, 2021 | India, hospital-based |
| ICD, international Classification of diseases; SGA, small gestational age. | ICD, international Classification of diseases; SGA |

**Table 2** Meta-analysis for studies included in the analysis

| Subgroup analysis | Number of studies | N |
|---|---|---|
| Congennital malformations | | |
| Neuraminidase inhibitor | 7 | 8 |
| Oseltamivir | 6 | 6 |
| Heart malformations | 2 | 2 |
| Low birth weight | | |
| Neuraminidase inhibitor | 6 | 8 |
| Oseltamivir | 5 | 6 |
| Low Apgar score | | |
| Neuraminidase inhibitor | 5 | 6 |
| Oseltamivir | 4 | 5 |
| SGA | | |
| Neuraminidase inhibitor | 4 | 6 |
| Oseltamivir | 4 | 6 |
| Preterm birth | | |
| Neuraminidase inhibitor | | |
| Oseltamivir | 7 | 9 |

**Table 2** Meta-analysis for studies included in the analysis **T**

**Figure 1** Flow chart of the studies considered and finally selected for review.

**Figure 2** Neuraminidase inhibitor exposure during pregnancy and the risk of congenital malformations in the offspring.

**Figure 3** Neuraminidase inhibitor exposure during pregnancy and the risk of adverse neonatal outcomes in the offspring (A) low birth weight (B) low Apgar score (C) SGA (D) preterm birth.