Neuraminidase Inhibitors During Pregnancy and Adverse Birth Outcomes: A Meta-Analysis

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Abstract: Neuraminidase inhibitors (NAIs) are commonly used to treat influenza and are also considered the potential treatment for COVID-19. The association of using NAIs during pregnancy with the risk of adverse birth defects has been investigated repeatedly by epidemiological studies; however, results are largely inconsistent. We herein performed this meta-analysis to investigate the true association of NAIs with adverse birth defects, including preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA). A systematic search was performed through PubMed, Scopus, and Embase to identify all pertinent studies; The ORs with their corresponding 95% CIs were extracted or calculated. Heterogeneity was assessed using the Cochrane Q test and the I² statistic. A random-effect model was used for this meta-analysis due to existing heterogeneity. Overall, eight studies were included in our analysis, meta-analysis using a random-effect model showed that NAIs during pregnancy reduced the risk of LBW (OR=0.78, 95% CI=0.66–0.91) and SGA (OR=0.76, 95% CI=0.67–0.86) but is not associated with PTB (OR=1.01, 95% CI=0.87–1.16). Results of the present study suggested that NAIs during pregnancy are safe and may reduce the risk of LBW and SGA. However, further studies from different ethnic populations are warranted to confirm our results.

Keywords: neuraminidase inhibitors; pregnancy; birth defects; birth outcomes; meta-analysis.
<37 weeks of pregnancy), small for gestational age (SGA, babies have birth weight <10th percentile for their gestational age) and low birth weight (LBW, babies born weighing <2,500 grams)), however, results are almost inconsistent, while some studies found an association between use of NAIs during pregnancy and birth defects, others not [11,12]. Therefore, we performed this meta-analysis to summarize the published results and investigate the true association of NAIs use during pregnancy and the risk of LBW, SGA, and PTB.

2. Materials and Methods

2.1. Data source and search strategy.

A comprehensive search was carried out in PubMed, Scopus and Embase to find all pertinent papers up to to December 2020. The following key words were employed: small for gestational age [Title/Abstract] OR SGA [Title/Abstract] OR low birth weight [Title/Abstract] OR preterm [Title/Abstract] OR preterm delivery [Title/Abstract] OR premature [Title/Abstract] OR LBW [Title/Abstract] OR pregnancy outcomes [Title/Abstract] OR birth outcome [Title/Abstract] AND oseltamivir [Title/Abstract] OR Tamiflu [Title/Abstract] OR antivirals [Title/Abstract] OR neuraminidase inhibitors [Title/Abstract] OR Laninamivir [Title/Abstract] OR Rapivab [Title/Abstract] OR Peramivir [Title/Abstract] OR Relenza [Title/Abstract] OR Zanamivir [Title/Abstract]. Moreover, references of all included papers were checked for other relevant papers.

2.2. Study selection.

The following inclusion criteria were used in this study: Case-control, cohort, or cross-sectional studies; Assessed the association of maternal NAIs exposure and risk of PTB, SGA, and LBW; Studies that enrolled women who were ≥16 years old had a singleton gestation and a live birth; ORs with 95% confidence intervals (CI) were indicated or have sufficient information to calculate it; Published in English

2.3. Data extraction and quality assessment.

Two researchers (AHS and MA) independently used a predefined customized form to extract the following information from each included article: the first author, publication date, country, study design, birth outcome, number of cases, the sample size in the exposed group, the age range of participants, and odds ratios with 95% confidence interval. The methodological quality of articles was evaluated using Newcastle–Ottawa Quality Assessment Scale (NOS) [13,14], and studies that achieved ≥7 score out of 9 were considered to be of high quality [15].

2.4. Statistical analysis.

ORs with their 95% CIs were employed as the effect size of each study and were combined to determine total risk. If several ORs based on different times of pregnancy, type of used NAIs, or other parameters were reported in a study, we pooled these ORs using fixed effects and used the combined OR in our primary analysis [16,17]. To evaluate the heterogeneity within the included articles Cochran Q test and the $I^2$ statistic were employed. We primarily used a fixed-effect model to determine the association with a forest plot, but if there was a significant heterogeneity (p < 0.1 or $I^2 > 50$%), we used a random-effects model
Furthermore, a subgroup analysis based on the type of birth defects, including PTB, SGA, and LBW was done. Sensitivity analysis was performed to estimate the effect of every single article on the final results [17,20]. Egger’s linear regression test was employed to investigate the publication bias [15,21]. All statistical analysis was conducted using STATA software, RRID: SCR_012763 (version 15.0; Stata Corporation, College Station, TX, USA). Results were considered statistically significant where p-values were less than 0.05 [22,23].

3. Results and Discussion

3.1. Search results and Characteristics of the included studies.

A total of 382 studies were identified from PubMed, Scopus, and Embase, one more study was added from the references of included studies; of these studies, 96 were duplicates, 275 studies were excluded after the title and abstract screening, and 12 studies found to be eligible for full-text reading. Finally, 8 studies were identified as eligible and included in our analysis. The study flow is shown in Figure 1. The main features of the eligible studies are given in Table 1. The NOS scores for included studies ranged from 6 to 8.

3.2. Association between maternal NAIs exposure and adverse birth outcomes.

To investigate the association of maternal NAIs use during pregnancy and the risk of adverse birth outcomes, Overall OR for each study was employed to estimate the total OR using a random-effect model since there was heterogeneity within included studies ($I^2 = 39.6, \ P = 0.044$). Analyses of 8 included studies showed that maternal NAIs exposure reduced the risk of adverse birth outcomes (OR=0.88, 95% CI=0.78–0.98) as shown in Figure 2. Subgroup analysis based on the type of birth outcome revealed that NAIs exposure reduced the risk of LBW (OR=0.78, 95% CI=0.66–0.91) and SGA (OR=0.76, 95% CI=0.67–0.86), but is not associated with PTB (OR=1.01, 95% CI=0.87–1.16)
### Table 1. Characteristics of studies included in the meta-analysis of maternal NAIs exposure and risk of LBW, SGA, and PTB.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Outcome</th>
<th>No. of cases*</th>
<th>Sample size* (n)</th>
<th>Age, Median/Range(yrs.)</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greer</td>
<td>2010</td>
<td>USA</td>
<td>Retrospective cohort</td>
<td>PTB</td>
<td>13</td>
<td>135</td>
<td>24.8±5.8</td>
<td>1.67(0.94-2.97)</td>
</tr>
<tr>
<td>Svensson</td>
<td>2011</td>
<td>Sweden</td>
<td>Cohort</td>
<td>LBW</td>
<td>3</td>
<td>86</td>
<td>19-30</td>
<td>1.08(0.42-2.81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.96(0.40-2.30)</td>
<td></td>
</tr>
<tr>
<td>Xie</td>
<td>2013</td>
<td>Canada</td>
<td>Retrospective cohort</td>
<td>SGA</td>
<td>85</td>
<td>1232</td>
<td>20-40</td>
<td>0.77(0.60-0.98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.26(0.99-1.61)</td>
<td></td>
</tr>
<tr>
<td>Beau</td>
<td>2014</td>
<td>France</td>
<td>Cohort</td>
<td>LBW</td>
<td>16</td>
<td>337</td>
<td>30.2±5.4</td>
<td>0.38(0.07-1.39)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.64(0.31-1.27)</td>
<td></td>
</tr>
<tr>
<td>Dunstan</td>
<td>2014</td>
<td>UK</td>
<td>Prospective cohort</td>
<td>LBW</td>
<td>6</td>
<td>207</td>
<td>16-46</td>
<td>1.73(0.41-7.23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.08(0.57-2.03)</td>
<td></td>
</tr>
<tr>
<td>Graner (A)</td>
<td>2017</td>
<td>Denmark, Norway,</td>
<td>Cohort</td>
<td>LBW</td>
<td>157</td>
<td>5502</td>
<td>19-30</td>
<td>0.77(0.65-0.91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sweden</td>
<td></td>
<td>SGA</td>
<td>111</td>
<td></td>
<td>0.72(0.59-0.88)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.97(0.86-1.11)</td>
<td></td>
</tr>
<tr>
<td>Graner (B)</td>
<td>2017</td>
<td>France</td>
<td>Cohort</td>
<td>LBW</td>
<td>12</td>
<td>322</td>
<td>19-30</td>
<td>0.76(0.42-1.41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SGA</td>
<td>4</td>
<td></td>
<td>0.60(0.22-1.62)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.97(0.56-1.68)</td>
<td></td>
</tr>
<tr>
<td>Ehrenstein</td>
<td>2018</td>
<td>Denmark</td>
<td>Cohort</td>
<td>SGA</td>
<td>153</td>
<td>1855</td>
<td>-30</td>
<td>0.81(0.64-1.03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.85(0.65-1.11)</td>
<td></td>
</tr>
<tr>
<td>Chambers</td>
<td>2019</td>
<td>USA-Canada</td>
<td>Prospective cohort</td>
<td>PTB</td>
<td>5</td>
<td>97</td>
<td>-34</td>
<td>0.65(0.26-1.63)</td>
</tr>
</tbody>
</table>

*Sample size and number of cases are from exposed groups. Graner A and B are from a single study with two different populations (France and Scandinavian countries).

![Figure 2](https://biointerfaceresearch.com/)  
**Figure 2.** Forest plot of the association between maternal NAIs exposure and birth outcomes; subgroup for PTB/ LBW/ SGA, and overall result.

### 3.3. Sensitivity analysis and publication bias.

Sensitivity analysis demonstrated that pooled OR and 95% CI were not changed by removing any individual study (Figure 3). Moreover, no evidence of publication bias was observed after performing Egger’s test (Figure 4; P value for Egger’s test, 0.945).
To the best of our knowledge, this is the first study that provided comprehensive insights into the association of NAI use during pregnancy with adverse birth outcome, including LBW, SGA, and PTB, through meta-analysis. The overall results of this meta-analysis indicated that maternal NAI use during pregnancy reduced the risk of adverse birth outcome (OR = 0.88; 95% CI: 0.78, 0.98). However, subgroup analysis showed that while NAI use reduced the risk of LBW (OR = 0.78; 95% CI: 0.66, 0.91) and SGA (OR = 0.76; 95% CI: 0.67, 0.86), it was not associated with PTB (OR = 1.01; 95% CI: 0.87, 1.16).

In line with our results, Greer and colleagues in a cohort study with 135 American subjects showed that exposure to oseltamivir was not associated with PTB [24]. Three years later, Xie and colleagues, in a study with 1237 Canadian pregnant women, showed that oseltamivir use during pregnancy reduced the risk of SGA but was not associated with PTB [11]. In contrast to our results, in 2011, Svensson and colleagues, in a study with 81 pregnant
women from Sweden, found no association between NAIs use during pregnancy and adverse birth outcomes [25]. In 2014, Beau and colleagues, in a cohort study with 337 pregnant women exposed to oseltamivir, showed no significant association between oseltamivir use and the risk of adverse pregnancy outcomes [26]. Moreover, this year, results of another cohort study with 207 pregnant women from the UK showed that NAIs were not associated with adverse birth defects [27]. More recently, Graner and colleagues in a multinational observational cohort study from Denmark, Norway, Sweden (collectively indicated as the Scandinavian countries), and France, reported that exposure to NAIs during pregnancy did not affect the birth outcomes in the French population, however in Scandinavian population caused a decrease in the incidence of LBW and SGA, which is in line with our results [28]. Furthermore, in another study with 1855 pregnant women that used oseltamivir, no association was observed between oseltamivir use during pregnancy and birth outcomes [29]. The last research on this association is a cohort study that included 112 pregnant women from the United States and Canada that were exposed to oseltamivir; their results also showed no association between the use of oseltamivir during pregnancy and the risk of PTB [12].

The NAIs, including zanamivir and oseltamivir, halt the spread of the influenza virus by blocking the release of progeny influenza virus from infected cells and infecting new cells. Previous studies have indicated the association of influenza infection during pregnancy and the increased risk of adverse birth outcomes [30-33]; therefore, using NAIs during pregnancy reduced the risk of adverse birth outcomes through its protective effects against influenza infection, however, herein results of this meta-analysis showed that NAIs reduced the risk of adverse birth outcomes including LBW and SGA even in healthy women that were not affected by the influenza virus; therefore it also can a potentially safe treatment for Covid-19 during the pregnancy.

The present meta-analysis had two main limitations: first, most of the included studies used oseltamivir as the NAI in their studies; therefore, subgroup analysis based on the type of NAIs was not possible. Second, significant heterogeneity was observed within the included studies, which undermined our results' reliability.

4. Conclusions

In conclusion, our results suggested that the use of NAIs during pregnancy is safe and may decrease the risk of LBW and SGA. However, further studies are needed to confirm our results and reveal the mechanism underlying the protective effects of NAIs against adverse birth outcomes.

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Conflicts of Interest

The authors declare no conflict of interest.
References


