Assessing Serious Infections in Children Exposed In Utero to Ustekinumab

To the Editor:

Chronic inflammatory conditions, including inflammatory bowel disease (IBD), psoriasis (PsO), and psoriatic arthritis (PsA), have a high burden among women of reproductive age. There has been significant interest in finding safe ways of controlling disease activity during pregnancy without adversely affecting the pregnancy or offspring. Ustekinumab, an interleukin (IL)-12/23 inhibitor, is indicated in adult patients with IBD, PsO, and PsA. Monoclonal antibodies harboring an Fc portion such as ustekinumab (UST) are actively transported across the placenta during pregnancy, often reaching higher fetal than maternal levels. As fetuses could be exposed to therapeutic or supratherapeutic levels of these drugs, there are concerns that these agents could cause immunosuppression after birth; however, evidence is lacking. In a retrospective cohort study, we compared the risk of serious infections in offspring exposed to UST, tumor necrosis factor inhibitors (TNFi), and nonbiologic immunosuppressives, vs offspring unexposed during pregnancy, among women with PsO, PsA, and/or IBD.

We conducted a retrospective cohort study using the US MarketScan database, an employment insurance database. We included live births (January 2011 to December 2018) among women with PsO, PsA, and/or IBD. Presence of chronic inflammatory disease was defined as having ≥ 2 same outpatient or ≥ 1 inpatient relevant diagnostic codes before delivery. Drug exposure was defined as ≥ 1 filled prescription or infusion procedure code during pregnancy. In offspring, we evaluated serious infections within the first year of life as any single inpatient infection.4,5 We performed univariate and multivariate analyses using logistic regression with generalized estimating equations (GEEs) to calculate crude and adjusted odds ratios (aORs), respectively; multivariate analyses were adjusted for maternal age, comorbidities, corticosteroid use, concomitant drug use, and preterm birth. This study was approved by the McGill Faculty of Medicine Institutional Review Board (number A11-M107-14A).

We identified 16,130 offspring born to 14,712 mothers with chronic inflammatory disease (PsA/PsO = 7623, IBD = 8319, PsA/PsO + IBD = 188). The study cohort included 52 offspring exposed to UST during pregnancy, 1585 exposed to TNFi, 51 exposed to other biologic drugs, 1857 exposed to traditional disease-modifying antirheumatic drugs (DMARDs), and 12,585 unexposed to any systemic DMARDs (Table 1). Of the 1585 women exposed to TNFi during pregnancy, 650 were exposed to infliximab, 610 to adalimumab, 167 to etanercept, 142 to certolizumab pegol, and 16 to golimumab. Patient characteristics are presented in Table 1.

During the first year of life, serious infections occurred in 3.8% (95% CI 1.0-13.0) of offspring exposed to UST, 2.6% (95% CI 2.0-3.6) exposed to TNFi, 3.9% (95% CI 1.1-13.2) exposed to other non-TNFi biologics, 2.4% (95% CI 1.8-3.2) exposed to traditional DMARDs, and 2.6% (95% CI 2.3-2.8) unexposed to any relevant drug in utero. The most frequent types of serious infections were viral or bacterial lower respiratory tract infections, viral or systemic infections other than lower respiratory tract infections, and urinary tract infections; infection types were similar between offspring regardless of maternal disease status. Of note, we detected no cases of tuberculosis nor other types of mycobacteria infection.

Results of univariate and multivariate logistic regression using GEEs are presented in Table 2. In the multivariate analysis of children exposed to UST, our point estimates were consistent with increased risk, but the CIs were wide and included the null value (adjusted odds ratio [aOR] 1.58, 95% CI 0.37-6.84). Effect estimates were similar among offspring exposed to other non-TNFi biologics (aOR 1.26, 95% CI 0.33-4.74). For those exposed to TNFi (aOR 0.85, 95% CI 0.59-1.22) or traditional DMARDs (aOR 0.76, 95% CI 0.55-1.06), there was no clear excess risk.

Overall, we did not detect a clear excess risk of infection among offspring exposed in utero to UST or TNFi as compared to unexposed patients. There was a potential signal for more events with UST, but CIs were wide. This study used a large administrative database to investigate UST use during pregnancy and represents one of the largest population-based cohorts of offspring exposed in utero to UST, to our knowledge. As well, due to the availability of maternal medical diagnoses and pharmaceutical claims in administrative databases like MarketScan,
we were able to perform multivariate models controlling for important covariates and potential confounders. In addition, findings from administrative databases are relatively free from the reporting bias seen in the currently available studies investigating UST exposure in utero. This said, our study has some limitations. First, there may have been residual confounding from disease activity. We adjusted for disease activity using corticosteroid use and/or concomitant drug use as a proxy for disease activity, but these variables are not perfect, with no established gold standard measure for disease activity in administrative database research. Also, due to the small number of exposed subjects, we could not ascertain timing of UST exposure and its effect on the risk of infection in exposed offspring. In addition, there was potential for imperfect ascertainment of cases and/or outcomes using administrative data, although we used previously validated definitions.

In conclusion, our findings provide some evidence to help guide pregnancy counseling in women using UST, although ongoing caution (weighting benefits vs potential risks) as well as more research on short- and long-term effects are warranted.

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REFERENCES


Table 2. Univariate and multivariate estimates of the odds ratios (ORs) for the risk of serious infections comparing different exposure categories among offspring born to mothers with inflammatory diseases (n = 16,130).

<table>
<thead>
<tr>
<th>Exposure Groups</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>aOR (95% CI)*</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>1.53 (0.37-6.35)</td>
<td>1.58 (0.37-6.84)</td>
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<tr>
<td>TNF inhibitor</td>
<td>1.04 (0.75-1.43)</td>
<td>0.85 (0.59-1.22)</td>
</tr>
<tr>
<td>Other biologics</td>
<td>1.55 (0.38-6.23)</td>
<td>1.26 (0.33-4.74)</td>
</tr>
<tr>
<td>Traditional DMARDs</td>
<td>0.94 (0.69-1.29)</td>
<td>0.76 (0.55-1.06)</td>
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*aORs were adjusted for maternal age, maternal diabetes status, preterm status, exposure to corticosteroids, concomitant drug exposure, and disease state. aOR: adjusted odds ratio; DMARD: disease-modifying antirheumatic drug; OR: odds ratio; TNF: tumor necrosis factor inhibitor.