**Supplementary Table 1:** Assessment of Bias of Studies by Modified Newcastle-Ottawa Scale

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Selection** | **Comparability** | **Outcome** |  |
| **Study** | **D1** | **D2** | **D3** | **D4** | **D5** | **D6** | **D7** | **D8** | **Overall** |
| A de Lima et al 2016 | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** |
| Moens et al 2019 | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** |
| Duricova et al 2018  | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** |
| Casanova et al 2013 | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** |
| Seirafi et al 2014 | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** |
| Luu et al 2018 | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** |
| Soares et al 2016 | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing, clock  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing, clock  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing, clock  Description automatically generated** |
| Chaparro et al 2018 | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** |
| Matro et al 2018 | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing, clock  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing  Description automatically generated** | **A picture containing drawing, clock  Description automatically generated** |

|  |  |  |
| --- | --- | --- |
|  | **Bias Judgement**  | **Domains** |
| **A picture containing drawing  Description automatically generated** | **Low** | D1: Representativeness of exposed cohort  |
| D2: Selection of non-exposed cohort  |
|  | D3: Ascertainment exposure  |
| **A picture containing drawing  Description automatically generated** | **Uncertain** | D4: Demonstration that outcome of interest was not present at start of study |
| D5: Comparability of cohorts on the basis of the design or analysis |
|  | D6: Assessment of outcome |
| **A picture containing drawing, clock  Description automatically generated** | **High**  | D7: Was follow-up long enough for outcome to occur  |
| D8: Adequacy of follow-up of cohorts  |

**Supplementary Table 2:** Meta-analysis of Observational Studies in Epidemiology (MOOSE) Checklist

|  |  |
| --- | --- |
| **Criteria** | **Brief description of how the criteria were handled in the meta-analysis** |
| **Reporting of background should include** |
|  | Problem definition | "While many studies have investigated the frequency of adverse pregnancy outcomes attributable to a variety of IBD therapies, the magnitude of these effects as they relate to infantile infections subsequent to exposed pregnancies remains a topic of debate..." |
|
|
|  | Hypothesis statement | To address these conflicts and to better guide clinicians and patients, we performed a systematic review and meta-analysis to quantify the subsequent risk of infantile infections following fetal exposure to biologic medications used by pregnant patients with IBD.  |
|
|  | Description of study outcomes | Primary Outcome: Infantile infections defined as any infection occurring within the first year of life. Secondary Outcomes: 1) Infantile antibiotic use, and 2) Infection-related hospitalizations.  |
|  | Type of exposure or intervention used |   |
| Biologic use (infliximab, adalimumab, golimumab, certolizumab, natalizumab, vedolizumab, ustekinumab)  |
|  | Type of study designs used | Systematic Review and Meta-Analysis included observational study design (cross-sectional, retrospective, prospective) |
|  | Study population | Women with Inflammatory Bowel Disease (Ulcerative Colitis, Crohn’s Disease), infants exposed to biologic during pregnancy  |
| **Reporting of search strategy should include**  |
|  | Qualifications of searchers | The credentials of the three investigators (who contributed to the search strategy) JG, ON, CJ are indicated in the authors list |
|  | Search strategy, including time period included in the synthesis and keywords |   |
| The following research strategy was performed in MEDLINE and adapted to the other databases: (“Inflammatory Bowel Diseases” [MeSH] OR Inflammatory Bowel Disease\*[TIAB] OR Crohn\*[TIAB] OR Ulcerative Colitis\*[TIAB] OR IBD[TIAB] OR Proctocolitis\*[TIAB] OR Proctosigmoiditis\*[TIAB] OR Rectocolitis\*[TIAB] OR Rectosigmoiditis\*[TIAB] OR Proctitis\*[TIAB]) OR "Pregnancy"[MeSH] OR Pregnanc\*[TIAB] OR new-born\*[TIAB] OR Lactation\*[TIAB] OR "Infant"[MeSH] OR Infant\*[TIAB]) AND ("Biological Products"[MeSH] OR Biological Products\*[TIAB] OR biologics\*[TIAB] OR infliximab\*[TIAB] OR adalimumab\*[TIAB] OR golimumab\*[TIAB] OR certolizumab\*[TIAB] OR vedolizumab\*[TIAB] OR natalizumab\*[TIAB] OR ustekinumab\*[TIAB]).  |
|   |
|   |
|   |
|  | Databases and registries searched | (1) Medline (Pubmed), Inception- June 2020 |
| (2) EMBASE, Inception- June 2020 |
| (3) Scopus, Inception- June 2020 |
| (4) Web of Science, Inception- June 2020 |
| (5) The Cochrane Central Register of Controlled Trials CENTRAL Inception- June 2020 |
|  | Search software used, name and version, including special features | We detailed the MeSH Headings and text words in Methods Section, Study Protocol.  |
|  | Use of hand searching | Bibliographies of the retrieved papers (only the included studies) were hand searched for additional references, |
|  | List of citations located and those excluded, including justifications | Details of the literature search process are outlined in the PRISMA flow chart (Figures 1 ) |
|  | Method of addressing articles published in languages other than English | Search limited to English language manuscripts |
|  | Method of handling abstracts and unpublished studies | We included data from abstracts or unpublished studies, but excluded them if they were subsequently published as full manuscripts |
|  | Description of any contact with authors | We did not contact authors of studies for additional data/information and clarification.  |
| **Reporting of methods should include**  |
|  | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | Detailed inclusion and exclusion criteria are described in the paper |
|  | Rationale for the selection and coding of data | A data extraction sheet was developed and summarized in Table 1, Table 2 |
|  | Assessment of confounding | We conducted subgroup and sensitivity analyses summarized in methods and results |
|  | Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results | We used the Newcastle Ottawa Scale (NOS) to assess the quality/bias of each study as described in the manuscript |
|  | Assessment of heterogeneity | We used the I2 value to assess heterogeneity |
|  | Description of statistical methods in sufficient detail to be replicated | Using Review Manager v5.3, a random-effects model was utilized to calculate the pooleed odds ratios (and 95% CI and p-values) of our infantile infection outcomes. Review Manager was used to generate forest plots and funnel plots to test for publication bias. Heterogeneity was assessed using the I2 statistic defined by the Cochrane Handbook for Systematic Reviews. The I2 statistic was calculated using Review Manager v5.3. An I2 value of 50% or more was considered to represent significant heterogeneity. |
|  | Provision of appropriate tables and graphics | We included PRISMA flow chart to show the method of studies identification, Table 1 and 2 showing characteristics of included studies |
| **Reporting of results should include**  |
|  | Graph summarizing individual study estimates and overall estimate | Figure 2, Figure 3, Figure 4, Supplementary Figure 2,3,4 |
|  | Table giving descriptive information for each study included | Table 1 and 2 |
|  | Results of sensitivity testing | Fiugure 3, Figure 5, Supplementary Figures 2,3,4,5,6,7 |
|
|  | Indication of statistical uncertainty of findings | 95% CI intervals were presented for all analyses together with I2 values |
| **Reporting of discussion should include** |
|  | Quantitative assessment of bias | Results of subgroup analyses are discussed with main potential confounding factors discussed. Results of Funnel plot and risk of publication bias is highlighted |
|  | Justification for exclusion | Reasons for exclusion were reported mainly in Figures 1 of systematic reviews  |
|  | Assessment of quality of included studies | Results of Newcastle-Ottawa scores summarized in manuscript |
| **Reporting of conclusions should include** |
|  | Consideration of alternative explanations for observed results |  Biologic use during pregnancy may increase risk of infantile infections that are not endemic in the patient populations studies |
|  | Generalization of the conclusions | The patients included in the systematic review and meta-analysis come from different countries and institutions and represent diverse IBD patient populations. Our results have good generalizability  |
|  | Guidelines for future research | Future research should focus on association of vedolizumab and ustekinumab during pregnancy and risk of infantile infections |
|  | Disclosure of funding source | No funding was required for conducting this review |