HHS Public Access

Author manuscript

Am J Gastroenterol. Author manuscript; available in PMC 2021 November 29.

Published in final edited form as:

Am J Gastroenterol. 2021 February 01; 116(2): 243–253. doi:10.14309/ajg.0000000000000910.

Biologics During Pregnancy in Women With Inflammatory Bowel Disease and Risk of Infantile Infections: A Systematic Review and Meta-Analysis

John Gubatan, MD[1], **Ole Haagen Nielsen, MD, DMSc**[2], **Steven Levitte, MD, PhD**[1,3], **Carsten Bogh Juhl, PT, MPH, PhD**[4,5], **Cynthia Maxwell, MD**[6], **Sarah E. Streett, MD**[1], **Aida Habtezion, MD, MSc**[1]

[1]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, California, USA

[2]Department of Gastroenterology,Medical Section, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark

[3]Department of Pediatrics, Stanford University School of Medicine, Stanford, California, USA

[4]Department of Sports Science and Biomechanics, University of Southern Denmark, Odense, Denmark

[5]Department of Physiotherapy and Occupational Therapy, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark

[6]Department of Obstetrics & Gynaecology, Mount Sinai Hospital, Toronto, Ontario, Canada.

Abstract

INTRODUCTION: Biologics, such as tumor necrosis factor inhibitors, anti-integrins and anticytokines, are therapies for inflammatory bowel disease (IBD) that may increase the risk of infection. Most biologics undergo placental transfer during pregnancy and persist at detectable concentrations in exposed infants. Whether this is associated with an increased risk of infantile infections is controversial. We performed a systematic review and meta-analysis evaluating the risk of infantile infections after *in utero* exposure to biologics used to treat IBD.

METHODS: We searched PubMed, Embase, Scopus, Web of Science, and CENTRAL from inception to June 2020 to evaluate the association of biologic therapy during pregnancy in women with IBD and risk of infantile infections. Odds ratios of outcomes were pooled and analyzed using a random effects model.

RESULTS: Nine studies met the inclusion criteria comprising 8,013 women with IBD (5,212 Crohn's disease, 2,801 ulcerative colitis) who gave birth to 8,490 infants. Biologic use during pregnancy was not associated with an increased risk of all infantile infections (odds ratio [OR] 0.91, 95% confidence interval [CI] 0.73–1.14, I^2 = 30%). In a subgroup analysis for the type of

Correspondence: John Gubatan, MD. jgubatan@stanford.edu.

CONFLICTS OF INTEREST

Potential competing interests: None to report.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B752;http://links.lww.com/AJG/B753

infection, biologic use was associated with increased infantile upper respiratory infections (OR 1.57, 95% CI 1.02–2.40, I^2 = 4%). Biologic use during pregnancy was not associated with infantile antibiotic use (OR 0.91, 95% CI 0.73–1.14, I^2 = 30%) or infection-related hospitalizations (OR 1.33, 95% CI 0.95–1.86, I^2 = 26%).

DISCUSSION: Biologics use during pregnancy in women with IBD is not associated with the overall risk of infantile infections or serious infections requiring antibiotics or hospitalizations but is associated with an increased risk of upper respiratory infections.

INTRODUCTION

Inflammatory bowel disease (IBD) is increasing worldwide and is associated with significant healthcare utilization and suboptimal quality of life (1). The incidence of IBD is highest among women of reproductive age, with 25% of women becoming pregnant after diagnosis (2). Among women with IBD, active disease is associated with an increased risk of pregnancy complications and adverse outcomes (3). Although 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 (4).

Immunosuppressive medications are a mainstay of treatment for IBD, and biologic therapies such as monoclonal antibodies that abrogate tumor necrosis factor (TNF) activity increasingly form the backbone of management (5). The introduction of a variety of novel biologic therapies such as those targeting the integrin α4β7 (vedolizumab) (6) and p40 subunit of IL-12/IL-23 (ustekinumab) (7) have expanded the armamentarium of IBD therapies and led to a dramatic increase in the proportion of patients with controlled disease (8). Although biologics are effective treatments for IBD, their immunosuppressive effects increase the risk of infection (9–11).The risk of infection in infants exposed to biologics during pregnancy is of particular concern for patients and clinicians.

A broad array of biologics used to treat IBD have been detected in infants, with some persisting for up to 1 year through transplacental transfer *in utero* (12). Data regarding the risk of infantile infections after *in utero* exposure to biologic therapy are conflicting. A widely cited case report (13) demonstrated a fatal case of disseminated mycobacterial infection after BCG vaccination in an infant born to a mother with Crohn's disease treated with infliximab. Another study (12) showed that infants born to mothers treated with concomitant TNF inhibitor and thiopurine therapy during pregnancy had a 3-fold increased risk of infantile infection compared with anti-TNF monotherapy. By contrast, a large cohort study of patients with IBD (14) found that biologics during pregnancy were associated with an increased risk of maternal, but not infantile, infections. In light of these conflicting data, some clinicians turned to certolizumab, a monovalent Fab' fragment incapable of crossing the placental barrier (15). Although certolizumab may be a more appealing therapy during pregnancy in IBD, a previous network meta-analysis showed that infliximab and adalimumab are more effective than certolizumab in induction and maintenance therapy in IBD (16). 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 after fetal exposure to biologics.

METHODS

Study protocol

Our systematic review and meta-analysis was conducted according to the MOOSE (17) guidelines (see Supplementary Table 2, Supplementary Digital Content 2, http://links.lww.com/AJG/B753, MOOSE checklist), reported according to the PRISMA guideline (18), and was preregistered at the PROS-PERO Database (http://www.crd.york.ac.uk/PROSPERO) Reg. No. CRD42019135721. We performed a search of major electronic databases from inception to June 2020 including (i) MEDLINE (PubMed), (ii) EMBASE, (iii) Scopus, (iv) Web of Science, and (v) CENTRAL (Cochrane Central Register of Controlled Trials). 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]).

Definitions of clinical outcomes

Biologic exposure: any use of biologic therapy (infliximab, adalimumab, golimumab, certolizumab, natalizumab, vedolizumab, and ustekinumab) from the time of conception to the end of pregnancy. Patients with IBD who stopped using biologics during the third trimester of pregnancy were included. Primary outcome: infantile infections defined as any infection occurring within the first year of life. Secondary outcomes: (i) infantile antibiotic use and (ii) infection-related hospitalizations.

Inclusion and exclusion criteria

Two authors (J.G. and O.H.N.) independently reviewed the abstracts and manuscripts for eligibility. Conflicts were resolved with consultation of another author (C.B.J.). Our inclusion criteria included (i) interventional or observational studies, (ii) pregnant women with IBD with or without biologic exposure, and (iii) reported infantile infections. Our exclusion criteria were (i) case reports, (ii) studies only including patients without exposure to biologic therapy, (iii) no data on infantile infections, and (iv) no control group (pregnancy not exposed to biologics).

Data extraction

The following data were extracted: (i) author names, publication year, and country (or countries) of patient population; (ii) study design; (iii) type of biologic exposures and proportion of mothers with IBD continuing biologics during the third trimester of

pregnancy; (iv) maternal IBD type and proportion of patients with active (moderate or severe) disease (defined by individual studies) during pregnancy; (v) proportion of mothers with IBD on steroids during pregnancy; (vi) cohort mean maternal age at the time of pregnancy; (vii) the total number of live births/infants; (viii) the total number of infantile infections; (ix) infections requiring antibiotic use; (x) infection-related hospitalizations; and (xi) the number of acute otitis media (AOM), upper respiratory infection (URI), urinary tract infection (UTI), and gastrointestinal (GI) infection cases.

Assessment of study bias

Two authors (J.G. and O.H.N.) independently assessed the risk of bias in included studies using a modified Newcastle-Ottawa scale for case-control studies or cohort studies (19). Significant conflicts between Newcastle-Ottawa scores were resolved with the consultation of another author (C.B.J.). The following criteria were evaluated: selection, representativeness of cases, definition of controls, comparability (of cases and controls), ascertainment of exposure, and assessment of outcomes. Each domain of the Newcastle-Ottawa scale was judged for the risk of bias as low, uncertain, or high.

Statistical analyses

Outcomes were extracted from individual manuscripts or calculated using raw data and pooled using a random effects model. Review Manager v5.3 was used to calculate the pooled odds (and 95% confidence interval [CI] and *P* values) of our clinical outcomes. Heterogeneity was assessed using I^2 statistics defined by the Cochrane Handbook for Systematic Reviews (20). We performed a subgroup analysis for the type of infantile infections (AOM, URI, UTI, and GI). Because certolizumab does not cross the placenta and should not affect the risk of infections, we performed a sensitivity analysis comparing the risk of infantile infections in studies including certolizumab vs studies not including this drug. Additional sensitivity analyses included restricting the meta-analysis to studies with only anti-TNF agents, performing the meta-analysis according to the study design (retrospective vs prospective) and risk of bias (low vs high/uncertain). We also performed meta-regression analyses (metareg function, Stata/IC 15.1 for Windows; StataCorp, College Station, TX) to determine whether the proportion of mothers with IBD continuing biologics during the third trimester, on steroids, or with active disease during pregnancy associated with the effect size (Log odds ratio [OR]) of our clinical outcomes. A funnel plot and Egger test were used to assess for publication bias.

RESULTS

Search results

Our systematic review PRISMA flowchart is summarized in Figure 1. After removing duplicates, our search strategy yielded 1,262 citations. A total of 903 studies involving IBD and pregnancy but not biologic therapy were excluded by title and abstract. A total of 359 studies with IBD, pregnancy, and biologic therapy underwent full-text assessment for eligibility. Of these, 350 studies were excluded because they did not report infantile infections, were case reports, or lacked a control group. A total of 9 studies were included for qualitative assessment and meta-analysis.

Characteristics of included studies

The baseline characteristics of included studies are summarized in Table 1. The 9 included studies (14,21–28) comprised 8,013 women with IBD (5,212 Crohn's disease, 2,801 ulcerative colitis) who gave birth to 8,490 infants. The mean maternal age at the time pregnancy of was 31 years. 1,965 pregnancies were exposed to biologics, whereas 6,525 pregnancies were not exposed. All included studies were observational. All studies reported infantile infection outcomes with anti-TNF exposure except for 1 study (22), which also reported exposure to vedolizumab and another study which included patients with a mix of biologics including anti-TNF agents and ustekinumab (28). The risk of bias of included studies is summarized in Supplementary Table 1 (see Supplementary Digital Content 2, http://links.lww.com/AJG/B753): 6 studies had low risk of bias (14,21,23–25,27), 1 study was deemed to have uncertain risk of bias (22), and 2 studies had high risk of bias (26,27).

Risk of all infantile infections

Of the 1,965 pregnancies exposed to biologics, the incidence of all infections was 0.27 cases per infant-year, whereas of the 6,525 pregnancies not exposed to biologics, the incidence was 0.40 cases per infant-year. There were no reported infection-related deaths. We were unable to assess for age of infants at the time of infection because of limited data. Use of biologics in women with IBD during pregnancy was not associated with increased risk of all infantile infections (OR 0.91, 95% CI 0.73–1.14, I^2 = 30%) as summarized in Figure 2.

Subgroup analysis: risk of specific types of major infantile infections

Table 2 summarizes the major types of infantile infections (AOM, URI, UTI, and GI) documented in the included studies. Table 3 summarizes the incidence of major infections from our study compared with meta-analyses of infants in the general population (29–32). In infants exposed to biologics during pregnancy, the pooled incidence (cases per infant-year) of AOM, URI, UTI, and GI were 0.04, 0.02, 0.01, and 0.01, respectively, which were not higher than that of the general population (0.05, 0.18, 0.07, and 0.01, respectively). In infants not exposed to biologics during pregnancy, the pooled incidence (cases per infant-year) of AOM, URI, UTI, and GI were 0.02, 0.01, 0.01, and 0.01, respectively, which were not higher than that of the general population (0.05, 0.18, 0.07, and 0.01, respectively). In a subgroup analysis, biologic use during pregnancy was associated with an increased risk of URIs (OR 1.57, 95% CI 1.02–2.40, I^2 = 4%), but not AOM (OR 0.97, 95% CI 0.42–2.23, I^2 = 67%), UTIs (OR 1.50, 95% CI 0.82–2.75, I^2 = 0%), or GI infections (OR 1.33, 95% CI 0.78–2.27, I^2 = 0%) as summarized in Figure 3.

Risk of antibiotic use and infection-related hospitalizations

Eight studies (14,21–25,27,28) reported the rates of infantile antibiotic use, whereas all 9 studies (14,21–28) reported the rates of infection-related hospitalizations. In infants exposed to biologics during pregnancy, the incidence (cases per infant-year) of infections requiring antibiotics and infection-related hospitalizations were 0.13 and 0.13, respectively. In infants not exposed to biologics during pregnancy, the incidence (cases per infant-year) of infections requiring antibiotics and infection-related hospitalizations were 0.15 and 0.15, respectively. Biologic use in pregnant women with IBD was not associated with increased risk of infantile

antibiotic use (OR 0.91, 95% CI 0.73–1.14, I^2 = 30%) or increased risk of infection-related hospitalizations (OR 1.33, 95% CI 0.95–1.86, I^2 = 26%) as summarized in Figure 4.

Publication bias and sensitivity analyses

A funnel plot (see Supplementary Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B752) of included studies showed no evidence of publication bias. An Egger test did not suggest publication bias (P = 0.57). In a sensitivity analysis restricted to only anti-TNF studies (see Supplementary Figure 2, Supplementary Digital Content 1, http://links.lww.com/AJG/B752), biologics during pregnancy in women with IBD was not associated with the risk of infantile infections (OR 1.00, 95% CI 0.77–1.29, I^2 = 25%). There was no association between biologics in pregnancy and infantile infections in meta-analyses (see Supplementary Figure 3, Supplementary Digital Content 1, http://links.lww.com/AJG/B752) including studies without certolizumab (OR 1.12, 95% CI 0.52–2.39, I^2 = 59%) or with certolizumab (OR 0.91, 95% CI 0.80–1.04, I^2 = 0%). The meta-analysis (see Supplementary Figure 4, Supplementary Digital Content 1, http://links.lww.com/AJG/B752) stratified by study design (retrospective vs prospective) revealed significant differences (P = 0.04) in the risk of infantile infections. In prospective studies (2 studies), biologic exposure during pregnancy in women with IBD was associated with the decreased risk of infantile infections (OR 0.69, 95% CI 0.51–0.93, I^2 = 0%). By contrast, in retrospective studies (7 studies), there was no association (OR 1.04, 95% CI 0.80–1.35, I^2 = 19%) between biologic exposure and infantile infections. The meta-analysis stratified by the risk of bias (low vs uncertain/high bias) (see Supplementary Figure 5, Supplementary Digital Content 1, http://links.lww.com/AJG/B752) revealed no significant differences in the risk of infantile infections. Meta-regression analyses revealed that the proportion of mothers with IBD continuing biologics during the third trimester (Figure 5) on steroids during pregnancy (see Supplementary Figure 6, Supplementary Digital Content 1, http://links.lww.com/AJG/B752) or with active disease during pregnancy (see Supplementary Figure 7, Supplementary Digital Content 1, http://links.lww.com/AJG/B752) were not associated with the risk of all infantile infections, 4 major infantile infections (AOM, URI, UTI, and GI), antibiotic use, or infected-related hospitalizations.

DISCUSSION

To our knowledge, this is the first meta-analysis quantifying the risk of infantile infections after *in utero* biologic exposure as part of IBD therapy in pregnancy. In this systematic review and meta-analysis comprising over 8,000 infants, we demonstrate that biologic use is not associated with an increased risk of all infantile infections. Although we observed an increased risk of URIs in the subgroup analysis, biologic use during pregnancy was not associated with an increased risk of serious infections requiring antibiotics or hospitalizations. There was no reported infection-related infant mortality. We also show that the risk of infantile infection is comparable between certolizumab vs other TNF inhibitors and that continuing biologics during the third trimester does not seem to confer an increased infection risk.

The incidence of major infections in infants born to mothers with IBD with or without biologic exposure in our meta-analysis did not seem to be increased compared with infants in the general population. In a meta-analysis of 114 studies (29), the pooled global incidence of AOM was 0.05 cases per infant-year, which was comparable with our results. In another meta-analysis (30), the global incidence of viral respiratory infections was 0.18, which was much higher than our incidence of URIs in infants with or without biologic exposure during pregnancy. The incidence of UTI and GI infections in infants in our study were not higher than that reported in previous meta-analyses (31,32) of infants in the general population.

Our finding that the use of biologics during pregnancy in women with IBD is not associated with an increased risk of infantile infections could have several explanations. First, although biologics undergo transplacental transfer and persist at detectable drug concentrations in infantile circulation, it is possible that any immunocompromising effects are transient and changes in immune function normalize once the drug is cleared. Indeed, this is supported by a previous prospective study (33) which showed that infants exposed to TNF inhibitors *in utero* had detectable concentrations of anti-TNF at birth and a more immature B and helper-T phenotype and decreased regulatory T cell frequency. These immune changes normalized after anti-TNF levels became undetectable at 6 months of age. None of the infants experienced any infections. This idea is further supported by recent data demonstrating that biologic use by pregnant women with IBD does not affect infant response to routine (nonlive) vaccines at 2–6 months of age, which are routinely given in the first year of life (34). Second, it is possible that biologic exposure does cause some immunocompromise in the infant but that passive immunity from maternal transfer of cytokines and protective antibodies through the placenta and breastmilk (35–37) abrogates this effect. Transfer of biologics through breastmilk have been reported tobe very low (28). Third, an alternative explanation is that blockade of pathways by biologics may not be critical for common infections in infants or infections that are affected by biologic blockade (e.g., tuberculosis) were not endemic in the included patient populations and not captured by our analysis.

We observed that biologic therapy during pregnancy was associated with an increased risk of infantile URIs. The only other study adequately powered to detect this subtle risk did not quantify URIs in infants born to mothers treated with biologics (29). We hypothesize that this association may have been missed by other studies because the effect is subtle, and all of the infections were self-limited and not associated with an increased risk of hospitalization. The self-limited alterations in the immune cell repertoire of infants exposed *in utero* tobiologics (33) may cause a mildly immunocompromised state reflected in an increase in URI frequency, without compromising vaccine efficacy or predisposing to serious infections requiring hospitalization.

Our study has several strengths. First, we conducted a meta-analysis of multiple large populations, increasing the statistical power to detect a subtle association between biologic use during pregnancy and infantile infections and to resolve conflicting data and uncertainty from previous studies. Second, we included diverse cohorts of pregnant women with IBD from different countries to overcome geographic and institutional bias broadening the generalizability of our findings. Third, the clinical outcomes we examined were comprehensive including the risk of all infantile infections and more clinically meaningful

end points such as infantile antibiotic use and infection-related hospitalizations while being granular enough to detect subtle immune derangements that may result from biologic exposure. Fourth, heterogeneity and risk of bias of included studies was mostly low. Finally, we performed sensitivity analyses including meta-regression analyses to assess potential confounders for the association between biologics and infantile infection, such as maternal use of biologics during the third trimester, steroid use, and disease activity with our results remaining robustly consistent with our central conclusion. Our study has, however, some limitations. First, we performed meta-analyses of observational studies and thus cannot establish causality. Nevertheless, some factors in our study may support causality such as temporality (biologic exposure in pregnancy preceding outcome of infantile infection) and biologic plausibility (we provided possible mechanisms to explain why biologic therapy during pregnancy may not affect the risk of infection). Performing interventional studies to assess the impact of biologic therapy during pregnancy on the risk of infantile infections poses serious ethical dilemmas. Second, some of our pooled Ors were unadjusted, thus we were unable to adjust for unmeasured confounders such as maternal comorbidities, infant age, and concurrent thiopurine use. Third, our results predominantly reflect the impact of TNF inhibitors because our meta-analyses included only 1 study with vedolizumab and 1 mixed study with ustekinumab.

In conclusion, we provide reassuring evidence that biologic therapy in pregnant women with IBD is not associated with increased risk of infantile infections or serious infections requiring antibiotics or hospitalizations, although biologics may be associated with a subtle URI risk. We show that the risk of infantile infections in certolizumab is comparable with other anti-TNF agents, suggesting that avoiding more efficacious anti-TNF therapy in pregnant women with IBD may not be warranted. Finally, we demonstrate that continuing biologics during the third trimester does not confer additional infection risk. Our study addresses critical questions raised by patients and clinicians and reinforces that the benefits of continuing biologic therapy throughout pregnancy to maintain disease remission outweighs the risks of infantile infections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support: J.G. is in part supported by a Chan Zuckerberg Biohub Physician Scientist Scholar Award and an NIH NIDDK LRP Award.

Guarantor of the article: John Gubatan, MD.

Specific author contributions: J.G. and O.H.N. planned and designed the study and analyzed the data. J.G. and O.H.N. performed the systematic review and extracted the data from manuscripts. J.G. and O.H.N. performed the quality assessment of studies. J.G. performed the statistical analyses in collaboration with C.B.J. S.L. assisted with background literature review and manuscript drafting and provided clinical insight regarding pediatric infections. O.H.N., C.M., S.E.S., C.B.J., and A.H. provided critical review of the manuscript. J.G. drafted the manuscript. All authors interpreted the results and contributed to the critical review of the manuscript. J.G. had full access to the study data and takes responsibility for the integrity of the data and accuracy of the analysis.

Financial support: J.G. is in part supported by a Chan Zuckerberg Biohub Physician Scientist Scholar Award and an NIH NIDDK LRP Award.

REFERENCES

1. Kaplan GG. The global burden of IBD: From 2015 to 2025. Nat Rev Gastroenterol Hepatol 2015;12(12):720–7. [PubMed: 26323879]
2. Beaulieu DB, Kane S. Inflammatory bowel disease in pregnancy. Gastroenterol Clin 2011;40(2):399–413.
3. McConnell RA, Mahadevan U. Pregnancy and the patient with inflammatory bowel disease: Fertility, treatment, delivery, and complications. Gastroenterol Clin 2016;45(2):285–301.
4. Boyd HA, Basit S, Harpsøe MC, et al. Inflammatory bowel disease and risk of adverse pregnancy outcomes. PLoS One 2015;10(6):e0129567.
5. Nielsen OH, Ainsworth MA. Tumor necrosis factor inhibitors for inflammatory bowel disease. N Engl J Med 2013;369(8):754–62. [PubMed: 23964937]
6. Shelton E, Allegretti JR, Stevens B, et al. Efficacy of vedolizumab as induction therapy in refractory IBD patients: A multicenter cohort. Inflamm Bowel Dis 2015;21(12):2879–85. [PubMed: 26288002]
7. Dickson I. IBD: Ustekinumab therapy for Crohn's disease. Nat Rev Gastroenterol Hepatol 2016;14(1):4.
8. Yu H, MacIsaac D, Wong JJ, et al. Market share and costs of biologic therapies for inflammatory bowel disease in the USA. Aliment Pharmacol Ther 2018;47(3):364–70. [PubMed: 29164650]
9. Borman ZA, Côté-Daigneault J, Colombel JF. The risk for opportunistic infections in inflammatory bowel disease with biologics: An update. Expert Rev Gastroenterol Hepatol 2018;12(11):1101–8. [PubMed: 30277409]
10. Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor-α therapy in inflammatory bowel disease: Meta-analysis of randomized controlled trials. Am J Gastroenterol 2013;108(8):1268–76. [PubMed: 23649185]
11. Bonovas S, Fiorino G, Allocca M, et al. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: A systematic review and network meta-analysis. Clin Gastroenterol Hepatol 2016;14(10):1385–97. [PubMed: 27189910]
12. Julsgaard M, Christensen LA, Gibson PR, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. Gastroenterology 2016;151(1):110–9. [PubMed: 27063728]
13. Cheent K, Nolan J, Shariq S, et al. Case report: Fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. J Crohns Colitis 2010;4(5):603–5. [PubMed: 21122568]
14. Luu M, Benzenine E, Doret M, et al. Continuous anti-TNFα use throughout pregnancy: Possible complications for the mother but not for the fetus. A retrospective cohort on the French National Health Insurance Database (EVASION). Am J Gastroenterol 2018;113(11):1669–77. [PubMed: 29961771]
15. Mariette X, Förger F, Abraham B, et al. Lack of placental transfer of certolizumab pegol during pregnancy: Results from CRIB, a prospective, postmarketing, pharmacokinetic study. Ann Rheum Dis 2018;77(2):228–33. [PubMed: 29030361]
16. Hazlewood GS, Rezaie A, Borman M, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: A network meta-analysis. Gastroenterology 2015;148(2):344–54. [PubMed: 25448924]
17. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. JAMA 2000;283(15): 2008–12. [PubMed: 10789670]
18. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Ann Intern Med 2009;151(4):264–9. [PubMed: 19622511]
19. Bent S, Padula A, Avins A. Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. Brief communication: Better ways to question patients about adverse medical events: A randomized, controlled trial. Ann Intern Med 2006;144(4):257–61. [PubMed: 16490911]

20. Higgins JPT, Thomas J, Chandler J, et al. (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (Updated July 2019). Cochrane, London, 2019. (www.training.cochrane.org/handbook). Accessed October 11, 2019.
21. de Lima A, Zelinkova Z, van der Ent C, et al. Tailored anti-TNF therapyduring pregnancy in patients with IBD: Maternal and fetal safety. Gut 2016;65(8):1261–8. [PubMed: 25966992]
22. Moens A, van der Woude CJ, Julsgaard M, et al. Pregnancy outcomes ininflammatory bowel disease patients treated with vedolizumab, anti-TNF or conventional therapy: Results of the European CONCEIVE study. Aliment Pharmacol Ther 2020;51(1):129–38. [PubMed: 31692017]
23. Duricova D, Dvorakova E, Hradsky O, et al. Safety of anti-TNF-alpha therapy during pregnancy on long-term outcome of exposed children: A controlled, multicenter observation. Inflamm Bowel Dis 2018;25(4):789–96.
24. Casanova MJ, Chaparro M, Domenech E, et al. Safety of thiopurines andanti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease. Am J Gastroenterol 2013;108(3):433. [PubMed: 23318480]
25. Seirafi M, De Vroey B, Amiot A, et al. Factors associated with pregnancy outcome in anti-TNF treated women with inflammatory bowel disease. Aliment Pharmacol Ther 2014;40(4):363–73. [PubMed: 24980270]
26. Soares E, Gravito-Soares M, Mendes S, et al. Biologic therapy and pregnancy in inflammatory bowel disease: The long-term safety of in utero exposure in a tertiary center [Conference Abstract]. United Eur Gastroenterol J 2016;4(5S):P1418.
27. Chaparro M, Verreth A, Lobaton T, et al. Long-term safety of in utero exposure to anti-TNFα drugs for the treatment of inflammatory bowel disease: Results from the multicenter European TEDDY Study. Am J Gastroenterol 2018;113(3):396–403. [PubMed: 29460920]
28. Matro R, Martin CF, Wolf D, et al. Exposure concentrations of infants breastfed by women receiving biologic therapies for inflammatory bowel diseases and effects of breastfeeding on infections and development. Gastroenterology 2018;155(3):696–704. [PubMed: 29857090]
29. Monasta L, Ronfani L, Marchetti F, et al. Burden of disease caused by otitis media: Systematic review and global estimates. PLoS One 2012;7(4):e36226.
30. Shi T, McLean K, Campbell H, et al. Aetiological role of common respiratory viruses in acute lower respiratory infections in children under five years: A systematic review and meta–analysis. J Glob Health 2015;5(1):010408.
31. Shaikh N, Morone NE, Bost JE, et al. Prevalence of urinary tract infection in childhood: A meta-analysis. Pediatr Infect Dis J 2008;27(4):302–8. [PubMed: 18316994]
32. Ahmed SM, Hall AJ, Robinson AE, et al. Global prevalenceof norovirus in cases of gastroenteritis: A systematic review and meta-analysis. Lancet Infect Dis 2014;14(8):725–30. [PubMed: 24981041]
33. Esteve-Solé A, Deyà-Martínez A, Teixidó I, et al. Immunological changes in blood of newborns exposed to anti-TNF-α during pregnancy. Front Immunol 2017;8:1123. [PubMed: 28983301]
34. Beaulieu DB, Ananthakrishnan AN, Martin C, et al. Use of biologic therapy by pregnant women with inflammatory bowel disease does not affect infant response to vaccines. Clin Gastroenterol Hepatol 2018;16(1): 99–105. [PubMed: 28870657]
35. Zaretsky MV, Alexander JM, Byrd W, et al. Transfer of inflammatory cytokines across the placenta. Obstet Gynecol 2004;103(3):546–50. [PubMed: 14990420]
36. Eglinton BA, Roberton DM, Cummins AG. Phenotype of T cells, their soluble receptor levels, and cytokine profile of human breast milk. Immunol Cel Biol 1994;72(4):306–13.
37. Shahid NS, Steinhoff MC, Roy E, et al. Placental and breast transfer of antibodies after maternal immunization with polysaccharide meningococcal vaccine: A randomized, controlled evaluation. Vaccine 2002;20(17–18):2404–9. [PubMed: 12009297]

Study Highlights

WHAT IS KNOWN

- ✓ Biologic use in patients with inflammatory bowel disease is associated with an increased risk of infections.
- ✓ Biologics can cross the placenta during pregnancy and persist at detectable concentrations in infants.
- ✓ Maternal transfer of biologics during pregnancy may affect infant immune development.
- ✓ The risk of infections in infants exposed to biologics *in utero* is controversial.

WHAT IS NEW HERE

- ✓ Biologics during pregnancy is not associated with an increased risk of all infantile infections.
- ✓ The risk of upper respiratory infections may be higher in infants exposed to biologics during pregnancy.
- ✓ Biologics during pregnancy is not associated with the risk of infantile antibiotic use or infection-related hospitalizations.
- ✓ Therisk of infantile infections was not different between exposure to certolizumab vs other antitumor necrosis factor agents.

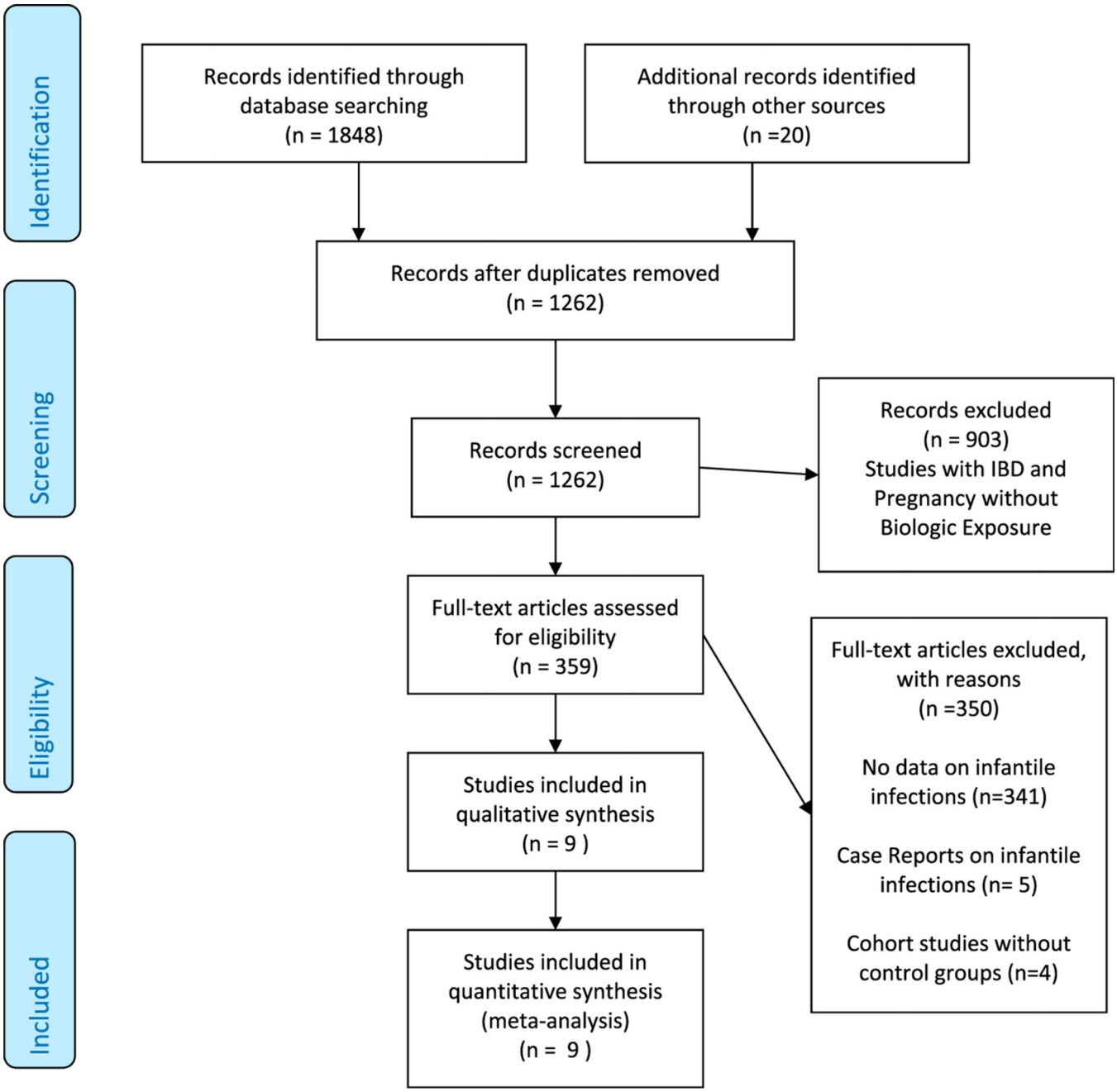

Figure 1.
PRISMA flowchart—study selection process in the risk of infantile infections with biologic therapy during pregnancy. IBD, inflammatory bowel disease.

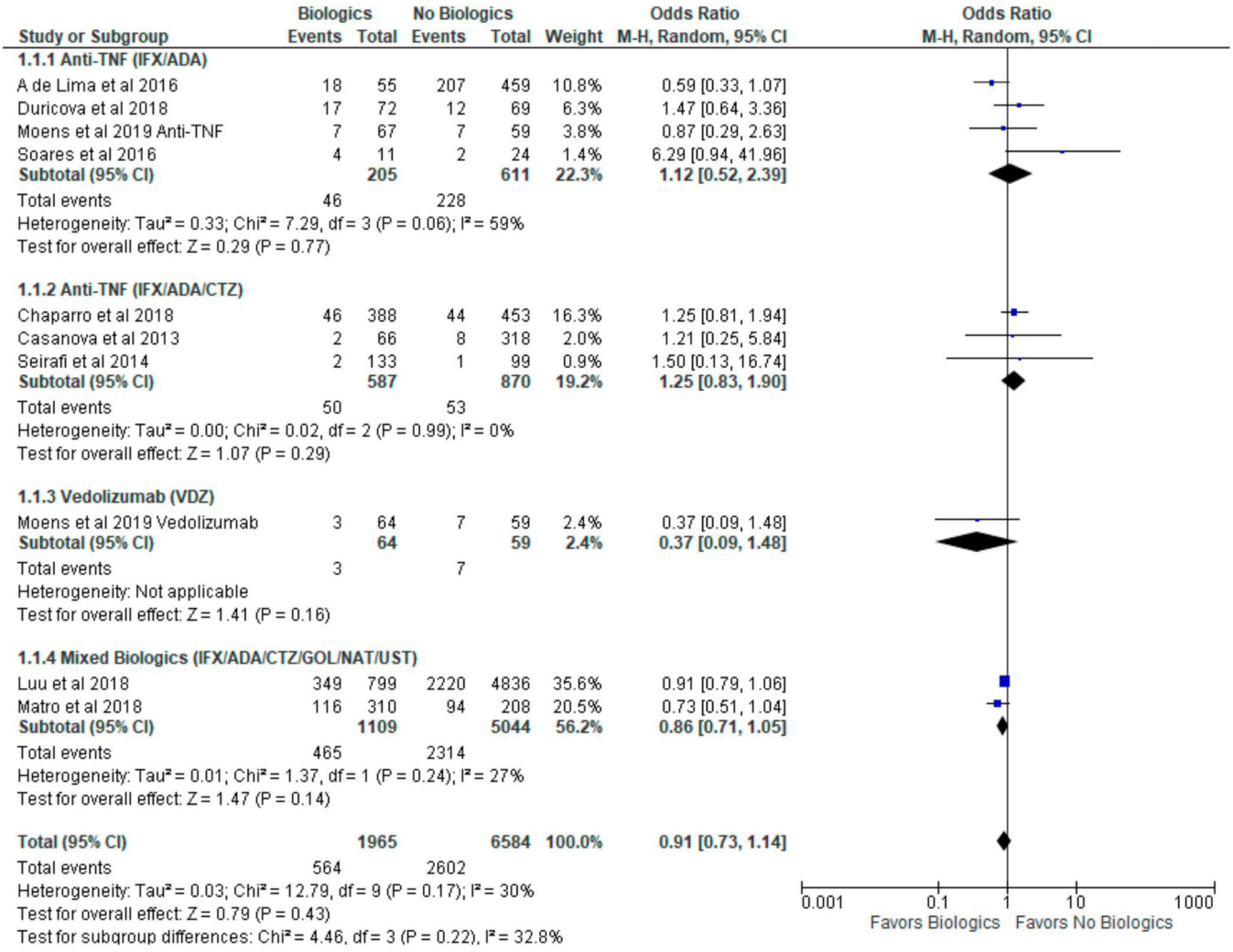

Figure 2.

The risk of subsequent infantile infections after *in utero* exposure to biologic therapy in women with inflammatory bowel disease. CI, confidence interval.

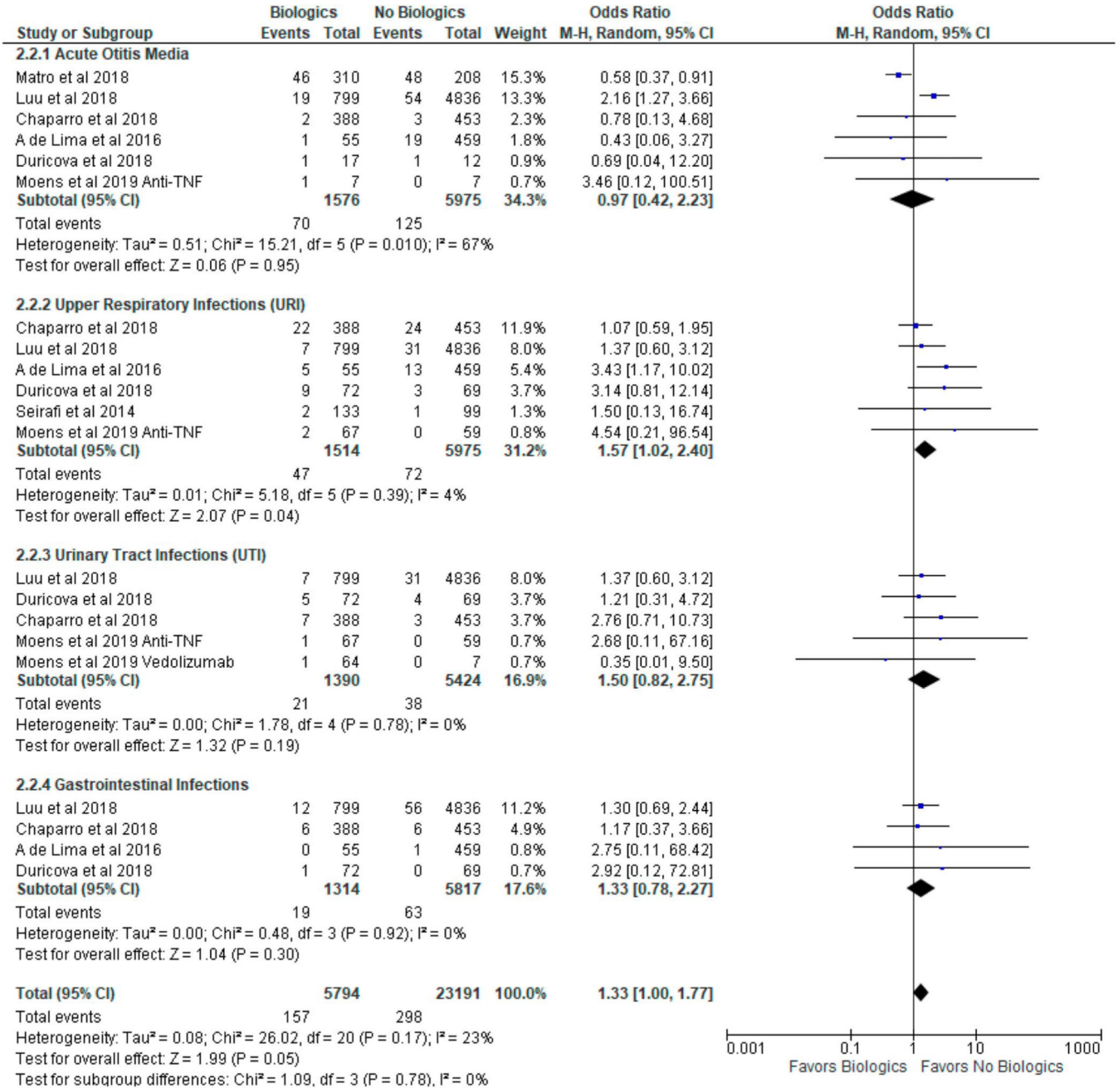

Figure 3.

Subgroup analysis of specific types of infantile infections after *in utero* exposure to biologic therapy in women with inflammatory bowel disease. CI, confidence interval.

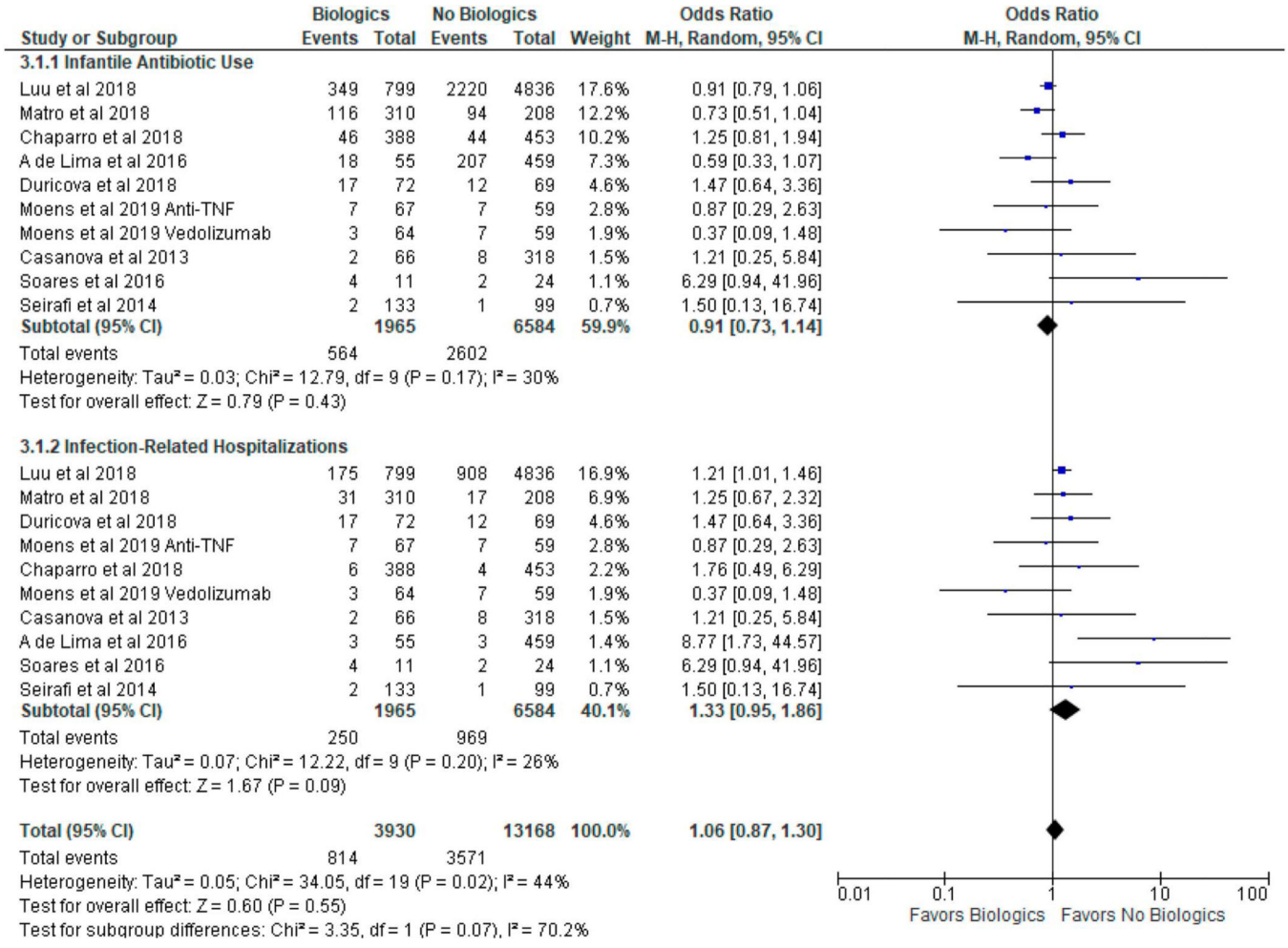

Figure 4.

The risk of infantile antibiotic use and infection-related hospitalizations after *in utero* exposure to biologic therapy in women with inflammatory bowel disease. CI, confidence interval.

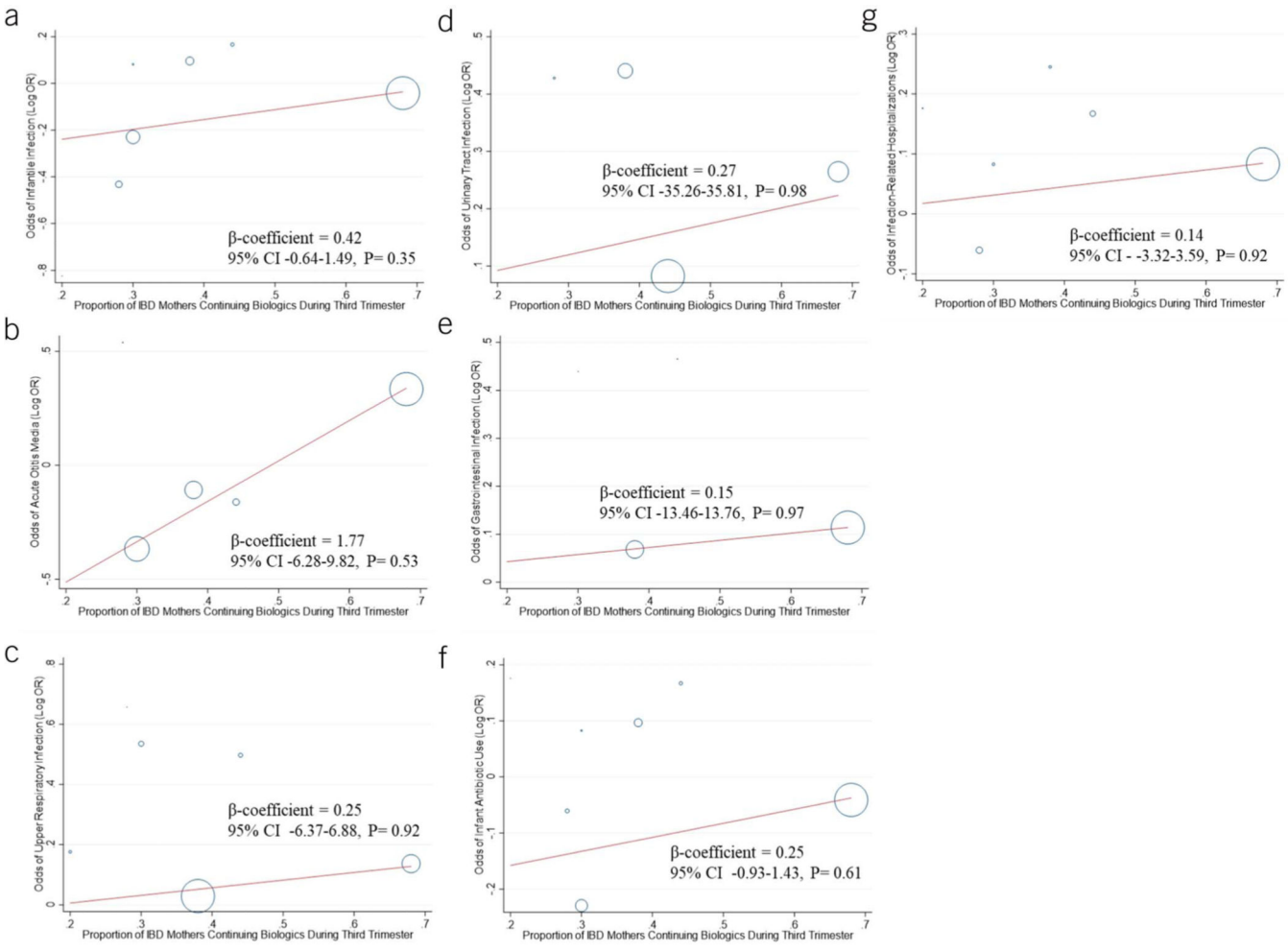

Figure 5.

Meta-regression analyses of the proportion of inflammatory bowel disease mothers continuing biologics during the third trimester and odds of (**a**) all infantile infections, (**b**) acute otitis media, (**c**) upper respiratory infections, (**d**) urinary tract infections, (**e**) gastrointestinal infections, (**f**) infantile antibiotic use, and (**g**) infection-related hospitalizations. CI, confidence interval; OR, odds ratio.

Table 1.

Baseline characteristics of included studies evaluating the risk of infantile infections from pregnancies in IBD women on biologic therapy

Study	Year	Country	Study design	Biologic therapy	Maternal IBDtype	Maternal age at the time of pregnancy (mean)	Continued biologics during third trimester (proportion)	Total no. of live births	Total infantile infections (≤12 mo old)	Antibiotic use	Infection-related hospitalizations
de Lima etal. (21)	2016	The Netherlands	Prospective	IFX, ADA	42 CD, 13 UC	29.9	0.30	55	18	4	3
			Cohort	Control (no anti-TNF)	No data	31.5		459	207	83	3
Moens et al. (22)	2019	Multicountry	Retrospective	VDZ	40 CD, 33 UC	30	0.28	64	3	1	3
			Case control	IFX, ADA	136 CD, 28 UC	30		67	7	3	7
				Control (no biologic)	86 CD, 69 UC	31		59	7	0	7
Duricova etal. (23)	2018	Czech Republic	Retrospective	IFX, ADA	52 CD, 20 UC	35.1	0.44	72	17	15	17
			Case control	Control (no anti-TNF)	No data	No data		69	12	12	12
Casanova etal. (24)	2013	Spain	Retrospective	IFX, ADA, CTZ	54 CD, 12 UC	32	0.30	66	2	2	2
			Case control	Control (no anti-TNF)	116 CD, 202 UC	No data		318	8	8	8
Seirafi et al. (25)	2014	France	Retrospective	IFX, ADA, CTZ	107 CD, 24 UC	29.3	0.20	133	2	2	2
			Case control	Control (no anti-TNF)	71 CD, 24 UC	28.9		99	1		1
Luu etal. (14)	2018	Multicountry	Retrospective	IFX, ADA, CTZ, GOL	655 CD, 144 UC	29.4	0.68	799	349	161	175
			Cohort	Control (no anti-TNF)	3,143 CD, 1,693 UC	31		4,836	2,220	839	908
Soares et al. (26)	2016	Portugal	Retrospective	IFX, ADA	40 CD, 59 UC	32	No data	11	4	No data	4
			Cohort	Control (no anti-TNF)	No data	No data		24	2	No data	2
Chaparro etal. (27)	2018	Multicountry	Retrospective	IFX, ADA, CTZ	291 CD, 97	31	0.38	388	46	15	6
			Cohort	Control (no anti-TNF)	190 CD, 263	32.5		453	44	9	4

Am J Gastroenterol. Author manuscript; available in PMC 2021 November 29.

Study	Year	Country	Study design	Biologic therapy	Maternal IBDtype	Maternal age at the time of pregnancy (mean)	Continued biologics during third trimester (proportion)	Total no. of live births	Total infantile infections (≤12 mo old)	Antibiotic use	Infection-related hospitalizations
Matro etal. (28)	2018	USA	Prospective	IFX, ADA, CTZ, GOL, NAT, UST	189 CD, 121 UC	31.2	No data	310	90	46	31
			Cohort	Control (no biologic)	No data	No data		208	94	48	17

ADA, adalimumab; CD, Crohn's disease; CTZ, certolizumab; GOL, golimumab; IBD, inflammatory bowel disease; IFX, infliximab; NAT, natalizumab; TNF, tumor necrosis factor; UC, ulcerative colitis; UST, ustekinumab; VDZ, vedolizumab.

Table 2.

Biologic therapy during pregnancy in women with inflammatory bowel disease and risk of major types of infantile infections

Study	Year	Biologic therapy	Acute otitis media	Upper respiratory infection infections	Urinary tract infections	Gastrointestinal infections
de Lima etal. (21)	2016	IFX, ADA	1	5	0	0
		Control (no anti-TNF)	19	13	0	1
Moens etal. (22)	2019	VDZ	0	0	1	0
		IFX, ADA	1	2	1	0
		Control (no biologic)	0	0	0	0
Duricova etal. (23)	2018	IFX, ADA	1	9	5	1
		Control (no anti-TNF)	1	3	4	0
Casanova etal. (24)	2013	IFX, ADA, CTZ	No data	No data	No data	No data
		Control (no anti-TNF)	No data	No data	No data	No data
Seirafi etal. (25)	2014	IFX, ADA, CTZ	0	2	0	0
		Control (no anti-TNF)	0	1	0	0
Luu et al. (14)	2018	IFX, ADA, CTZ, GOL	19	7	7	12
		Control (no anti-TNF)	54	31	31	56
Soares etal. (26)	2016	IFX, ADA	No data	No data	No data	No data
		Control (no anti-TNF)	No data	No data	No data	No data
Chaparro etal. (27)	2018	IFX, ADA, CTZ	2	22	7	6
		Control (no anti-TNF)	3	24	3	6
Matro etal. (28)	2018	IFX, ADA, CTZ, GOL, NAT, UST	46	No data	No data	No data
		Control (no anti-TNF)	48	No data	No data	No data

ADA, adalimumab; CTZ, certolizumab; GOL, golimumab; IFX, infliximab; NAT, natalizumab; TNF, tumor necrosis factor; UST, ustekinumab; VDZ, vedolizumab.

Table 3.

Incidence of infections in infants in the general population versus infants born to mothers with inflammatory bowel disease (IBD) with or without biologics during pregnancy

	Pooled incidence of infection (cases per infant-year)			
	Infants in general population		Infants born to IBD mothers	
Infantile infections	**Pooled incidence**	**Study details**	**Biologic pregnancy exposure**	**No biologic pregnancy exposure**
Acute otitis media	0.05	Monasta etal. (29), meta-analysis	0.04	0.02
	35.7 million cases, 788 million Infant-year	Global acute otitis media	70 cases, 1,965 infant-year	125 cases, 6,525 infant-year
Upper respiratory infections	0.18	Shi etal. (30), meta-analysis	0.02	0.01
	14, 898 cases, 83,220 infant-year	Global viral respiratory infections	47 cases, 1,965 infant-year	72 cases, 6,525 infant-year
Urinary tract infections	0.07	Shaikh etal. (31), meta-analysis	0.01	0.01
	1,159 cases, 17,421 infant-year	Urinary tract infections	21 cases, 1,965 infant-year	38 cases, 6,525 infant-year
Gastrointestinal infections	0.01	Ahmed etal. (32), meta-analysis	0.01	0.01
	431 cases, 69,040 infant-year	Global gastroenteritis	19 cases, 1,965 infant-year	63 cases, 6,525 infant-year