INPLASY

Pregnancy Safety of Biologics in IBD: A Systematic Review and Network Meta-Analysis

INPLASY202540012
doi: 10.37766/inplasy2025.4.0012
Received: 4 April 2025
Published: 4 April 2025

Huang, CW; Yen, HH; Chen YY.

Corresponding author:
Hsu-Heng Yen

blaneyen@gmail.com

Author Affiliation:
Division of Gastroenterology, Changhua Christian Hospital, Changhua, Taiwan.

ADMINISTRATIVE INFORMATION

Support - Changhua Christian Hospital.

Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202540012

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 4 April 2025 and was last updated on 4 April 2025.

INTRODUCTION

Review question / Objective This network meta-analysis was conducted based on the following PICO framework:P (Population): Pregnant women with IBD who received biologic therapy either during pregnancy or within three months prior to conception; I (Intervention): Biologic agents; C (Comparison): Conventional therapy or placebo; O (Outcome): Pregnancy safety.

Rationale With the development of advanced therapies in the treatment of inflammatory bowel disease (IBD), these agents have become an essential component of IBD management. However, data regarding the safety of newer biologic agents during pregnancy, as well as their effects on infants, remain limited. Although some observational studies and registries provide preliminary insights, current clinical guidelines still lack robust comparative data to inform treatment decisions for pregnant patients. Therefore, we conducted a network meta-analysis (NMA) to synthesize existing evidence and compare the safety profiles of biologic therapies versus conventional therapy and placebo in pregnant patients with IBD. By addressing this important evidence gap, our findings aim to support clinical decision-making and help physicians balance maternal disease control with fetal and infant safety in real-world practice.

Condition being studied This study uses a network meta-analysis (NMA) to integrate existing evidence and evaluate the safety of different biologic agents in pregnant patients with inflammatory bowel disease (IBD), as well as their potential effects on infant outcomes.

METHODS

Search strategy We performed a comprehensive literature search using the following databases: PubMed, EMBASE, Cochrane Reviews, Web of Science, and Google Scholar. Keywords included combinations of “pregnancy,” “inflammatory bowel disease,” and “biologics,” as well as the names of

specific agents such as "infliximab," "adalimumab," "certolizumab," "golimumab," "vedolizumab," "ustekinumab," "tofacitinib," "upadacitinib," and "filgotinib." Biosimilars of these agents were also included in the search strategy. Both MeSH terms and free-text keywords were used to maximize sensitivity. The search was restricted to human studies published in English.

Participant or population Pregnant women with IBD who received biologic therapy either during pregnancy or within three months prior to conception.

Intervention Biologic agents.

Comparator Conventional therapy or placebo.

Study designs to be included We included comparative studies with two or more arms that assessed the safety of biologic therapies during pregnancy in patients with IBD. Eligible study designs included randomized controlled trials (RCTs), cohort studies (both prospective and retrospective), and case-control studies. Only studies that directly or indirectly compared biologics with conventional therapy or placebo were considered for inclusion.

Eligibility criteria Studies were included if they met the following conditions (1) Involved pregnant patients diagnosed with inflammatory bowel disease (IBD);(2) Included a comparison of biologic therapies with conventional therapy, placebo, or other biologics; (3)Reported pregnancy safety outcomes (e.g., spontaneous abortion, preterm birth, low birth weight, congenital anomalies, or neonatal outcomes); (4)Provided access to full-text articles (conference abstracts alone were excluded).
Studies were excluded if they: (1) Focused on paternal exposure to biologic agents rather than maternal exposure; (2)Did not include a comparative analysis involving biologics; (3)Were case series or single-arm studies without a control group; (4) Included mixed treatment strategies in a single group without clear stratification.

Information sources We will systematically search the following electronic databases for eligible studies: PubMed, EMBASE, Cochrane Reviews, Web of Science, and Google Scholar. The search will include peer-reviewed journal articles and relevant grey literature, such as theses, dissertations, and reports identified through Google Scholar. In addition, we will screen clinical trial registries, including ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP), for ongoing or unpublished studies. Reference lists of included studies and relevant review articles will also be manually screened to identify additional eligible publications. If necessary, we will contact study authors to obtain missing or unpublished data. Only studies published in English will be considered.

Main outcome(s) The primary outcome of this study is to compare the effects of different biologic therapies versus placebo and conventional therapy on delivery outcomes in pregnant patients with IBD. The outcomes of interest include preterm birth, low birth weight (LBW), cesarean section (C-section), and spontaneous abortion.

Additional outcome(s) Secondary outcomes include congenital anomalies, neonatal infections, admission to the neonatal intensive care unit (NICU), and other infant-related complications reported in the included studies.

Data management Data extraction was performed independently by two reviewers (CWH and HHY), capturing information on patient demographics, study design, treatment regimens, and both primary and secondary outcomes. The procedures for data extraction, processing, and synthesis were carried out in accordance with the recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions and relevant medical literature.

Quality assessment / Risk of bias analysis The quality of included studies and the risk of bias were assessed independently by two reviewers (CWH and HHY) using appropriate tools based on study design. The quality of nonrandomized trials was assessed using the Newcastle-Ottawa Scale (NOS), which includes three main criteria: selection and comparability of the groups and the ascertainment of the outcome. Any discrepancies in assessment were resolved through discussion or consultation with a third reviewer (YYC). The risk of bias assessments were incorporated into the interpretation of results and sensitivity analyses.

Strategy of data synthesis A random-effects model was employed for the network meta-analysis to account for variations across different treatment regimens. All analyses were conducted within a frequentist framework using MetaInsight (version 4.0.2, Complex Reviews Support Unit, National Institute for Health Research, London, UK), an online tool that implements the Netmeta package in R for network meta-analysis.
Network diagrams and forest plots were used to visually represent all pairwise comparisons across

included studies. Summary forest plots were then produced to display odds ratios (ORs) or risk differences (RDs) for each outcome, comparing each biologic therapy to the control group. Effect estimates were reported as point estimates with corresponding 95% confidence intervals (CIs), and treatments were ranked accordingly. Tables were generated to present the numerical results from both direct and indirect comparisons. Inconsistency analyses were conducted to assess the coherence of the network. Statistical significance was defined as a two-sided p-value of less than 0.05.

Subgroup analysis Subgroup analyses were conducted to examine specific infant-related outcomes, including the risk of neonatal intensive care unit (NICU) admission and neonatal infections, across different biologic therapies. These analyses aimed to assess whether certain treatments were associated with higher or lower risks of adverse infant outcomes. Where applicable, consistency analyses were performed to evaluate the agreement between direct and indirect comparisons within the network and to determine the reliability of subgroup findings.

Sensitivity analysis Sensitivity analyses were conducted to assess the robustness of the primary findings. These included the exclusion of studies with high risk of bias, small sample sizes, or incomplete outcome data. In addition, analyses were repeated by restricting to studies with similar study designs (e.g., cohort studies only) or limiting to biologic agents with more substantial data. The impact of these exclusions on the overall treatment effect estimates and network consistency was evaluated to determine the stability of the results.

Language restriction This review included only studies published in English. The exclusion of non-English articles was based on feasibility and consistency in data extraction and interpretation.

Country(ies) involved Taiwan.

Keywords Inflammatory bowel disease; Biologic therapy; Pregnancy; Safety; Network meta-analysis.

Contributions of each author

Author 1 - Chih-Wen Huang - Author 1 contributed to literature search and analysis, data extraction and synthesis, development of the selection criteria and risk of bias assessment strategy, provided statistical expertise, and drafted the manuscript.

Email: hcwsy81512@gmail.com

Author 2 - Hsu-Heng Yen - Author 2 participated in the literature search and analysis, data synthesis, development of the selection criteria and risk of bias assessment strategy, and contributed to drafting the manuscript.

Email: blaneyen@gmail.com

Author 3 - Yang-Yuan Chen - Author 3 contributed to data synthesis and drafting of the manuscript.

Email: 27716@cch.org.tw