RESEARCH

Comparative safety of infliximab and adalimumab on pregnancy outcomes of women with inflammatory bowel diseases: a systematic review & meta-analysis

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Abstract

Background: Inflammatory bowel disease (IBD) is a condition that affects most of the digestive tract. There is no report of fertility reduction in medically managed IBD women compared with the general population. On the other hand, active IBD can lead to significantly decreased fertility. Over the previous 2 decades, anti-tumor necrosis factor (anti-TNF) has been an effective treatment for managing patients with IBD, increasing the use of infliximab and adalimumab in clinical practice. However, it is unclear which biologics are better for pregnant women with IBD.

Aim: We conducted a systematic review and meta-analysis for the risk of adverse pregnancy outcomes following treatment with infliximab and adalimumab in women with IBD.

Methods: Bibliographic databases were retrieved from their inception to July 2022. The results were adverse pregnancy outcomes, including congenital malformations and spontaneous abortion.

Results: A total of 8 studies included 527 pregnant women with IBD. Of these, 343 received infliximab, and 184 received adalimumab therapy. Compared to adalimumab, adverse pregnancy outcomes were not increased in infliximab therapy including congenital malformations and spontaneous abortion.

Conclusion: Infliximab and adalimumab therapy did not show the difference of risk in adverse pregnancy outcomes in women with IBD.

Systematic review registration: http://www.crd.york.ac.uk/PROSPERO, identifier: CRD 42,021,277,869.

Keywords: Inflammatory bowel disease, Adverse pregnancy outcomes, Infliximab, Adalimumab

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disease that affects most of the digestive tract [1]. According to the phenotypic manifestations, IBD can be divided into ulcerative colitis (UC) and Crohn's disease (CD). IBD affects people of all ages, including young patients in the reproductive stage. Active disease is associated with an increased risk of adverse pregnancy outcomes (APOs) such as preterm delivery, low birth weight, spontaneous abortion and congenital malformations[2]. However, the cause of IBD is still unknown, but there is increasing evidence of familial susceptibility to transmittable intestinal antigens [3]. The peak age of IBD diagnosis occurs during the childbearing years. Therefore, treatment of IBD during pregnancy is very common [4]. However, the probable adverse effects of drugs on an unborn infant, complications after different delivery

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modes, lactation, predisposal to genetic diseases, and other beliefs may lead to intentional failure to have children [5].

Tumor necrosis factor (TNF)-α is a major proinflammatory and pathological cytokine having pleiotropic effects on various cell types [6]. Its plays a key role in the pathogenesis of systemic inflammatory diseases such as rheumatoid arthritis and IBD. Anti-TNF-α therapy was the first type of biotherapy approved to treat IBD, which revolutionized IBD treatment [7, 8]. At present, infliximab and adalimumab are the most widely used in clinical practice for IBD treatment. When compared with placebo, infliximab and adalimumab demonstrate similar clinical outcomes [7, 9–12], including the requirements for corticosteroids, rates of remission, disease-related surgery, and hospitalizations. Of note, data on pregnant women are limited, and the differences between the study populations preclude determining comparative APOs. Nevertheless, there is growing recognition of the need for studies on the comparative APOs for pregnant women to inform clinical practice accurately. Our previous study has shown that anti-TNF can be advocated for IBD women with pregnancy. With this current meta-analysis, our study aims to quantify the risk of APOs in IBD women exposed to infliximab and adalimumab. The outcome of this study will provide valuable evidence for guiding the best clinical decision-making.

Method

The systematic evaluation was conducted using predefined protocols and reported according to the preferred reporting items of the system evaluation and the presentation of the system evaluation meta-analysis (PRISMA) incorporating health care interventions (PROSPERO registration number: CRD 42,021,277,869).

Search strategy

Medline, PubMed, Web of Science, Embase, and Cochrane Library were searched to identify relevant studies assessing the pregnancy outcomes in women with IBD who received infliximab or adalimumab at pregnancy. Only studies published in English were included. At the same time, we searched the reference list of the retrieved articles to carry out other relevant research as completely as possible. The database search was performed on 11th September 2021, and then updated on 12th July 2022.

Study selection

Two reviewers independently reviewed the title and summary of each article to eliminate duplicates, annotations, case reports, and small case series ($n < 10$). We screened the titles and abstracts of published articles

and excluded studies unrelated to this study. Full-text articles were obtained if at least one reviewer considered them qualified. Our analysis included RCTs, observational studies, and case-control studies. Infliximab and adalimumab received marketing authorization from the US Food and Drug Administration, or the European Medicines Agency were also considered in our research. In literature selection, any differences were resolved through discussion and consultation.

Inclusion criteria: (1) Patients: Pregnancy in IBD patients older than 18 years who were taking infliximab or adalimumab; (2) Intervention: infliximab therapy at any stage of pregnancy; (3) Comparator: adalimumab therapy at any point during pregnancy; (4) Outcomes: the primary outcome was adverse pregnancy outcomes in patients with IBD pregnancy, including preterm birth, low birth weight, spontaneous abortion, and congenital malformations.

Exclusion criteria: (1) trials evaluating any medical treatment protocol other than infliximab and adalimumab; (2) studies on the use of infliximab or adalimumab in pregnant women for an underlying disease other than IBD; (3) inadequate or absent control groups, information on birth outcomes was not available in full, provision of data obtained from other research, or trials assessing differences between combination therapy and monotherapy only.

Data extraction and quality assessment

Two reviewers reviewed the full-text candidate articles to confirm the characteristics of the target population, disease treatment, medications used, the number of sample populations, and adverse results. The article's authors were contacted if the data were not available fully. Any dispute was settled through mutual discussion or negotiation with the third reviewer.

The Newcastle Ottawa scale (NOS) was selected for assessing the literature qualities of selected case-control and cohort studies [13]. NOS is an assessment tool for the quality of observational research. It classified quality levels into three categories: group comparability, study group selection, exposure (case-control study), or result (cohort study). The research with 5 or more points in the 9-point system was rated as high-quality, while other studies were considered low-quality. Any differences between reviewers were discussed and resolved by negotiation.
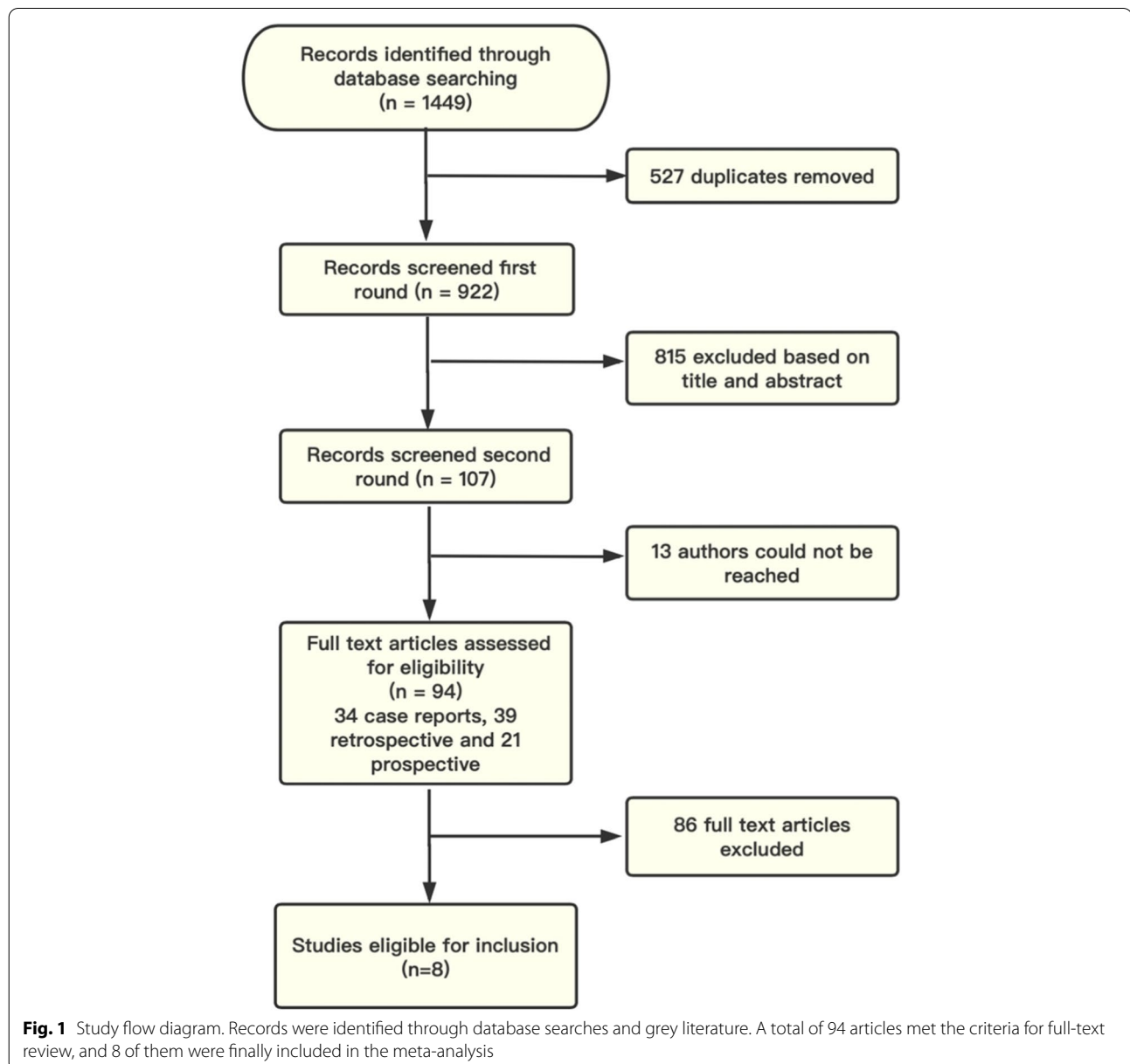
Statistical analysis

We used the Mantel Haenszel method to calculate the odds ratio (OR) and 95% confidence interval (CI). The selection of a random or fixed model was based on heterogeneity analysis [14]. I^2 statistics were used to

evaluate heterogeneity, and a fixed-effect model was used for $I^2 < 50\%$, while a random-effect model was used for $I^2 \geq 50\%$ [15]. $I^2 > 50\%$ indicated significant heterogeneity in the study. For the evaluation of publication bias, we checked the asymmetry of the funnel chart, which was more conducive to determining whether small studies were effective [16]. All statistical analyses were performed using RevMan (version 5.3.0, Copenhagen, Denmark).

Results
Study selection
The initial electronic and manual searches produced a total of 1449 studies. Among them, 94 studies met our research criteria, including 34 reports or small case series (n<10), 39 retrospective studies, and 21 prospective studies. Finally, 8 studies (4 prospective studies, 2 retrospective studies, and 2 both) with final compliance for selection criteria were included in the meta-analysis (Fig. 1).

Fig. 1 Study flow diagram. Records were identified through database searches and grey literature. A total of 94 articles met the criteria for full-text review, and 8 of them were finally included in the meta-analysis

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Study characteristics

A total of 527 cases were included in the 8 eligible studies. In addition, 343 pregnant women with IBD were treated with infliximab therapy and 184 with adalimumab therapy. These studies characteristics and pregnancy outcomes are summarized in Tables 1 and 2, respectively.

Adverse pregnancy outcomes

Eight studies reported the APOs associated with spontaneous abortion and congenital malformations after exposure to biological agents in pregnant women with IBD. The OR for the pooled crude rates of APOs was 0.74 (95% CI: 0.33, 1.66; $P = 0.46$), comparing infliximab ($n = 343$) with adalimumab ($n = 184$), without obvious heterogeneity ($P = 0.95$, $I^2 = 0\%$).

Spontaneous abortion

Five studies reported the outcome of spontaneous abortion in IBD pregnant women exposed to biological agents. The pooled OR for the crude rate of spontaneous abortion was 0.61 (95% CI: 0.19, 1.97; $P = 0.41$). There

was no heterogeneity between studies when comparing infliximab ($n = 193$) and adalimumab ($n = 97$) ($P = 0.93$, $I^2 = 0\%$).

Congenital malformations

Six studies reported congenital malformation outcomes in IBD pregnant women exposed to anti TNF-α. The pooled OR for the crude rate of congenital malformations was 0.81 (95% CI: 0.29, 2.25; $P = 0.69$) comparing patients treated with infliximab ($n = 325$) and adalimumab ($n = 171$). There was no significant heterogeneity observed between studies ($P = 0.46$, $I^2 = 0\%$) (Fig. 2).

Sensitivity analysis

The sensitivity analysis with "leave-one-out " shows that our results were robust. In addition, we excluded each included study separately and found that the original research results did not change substantially.

Among the 8 studies included, there was one with a large number of patients, so we removed this study [23] and evaluated again. Our results are as follow:

Table 1 Characteristics of the studies included on the use of Infliximab and Adalimumab during pregnancy

| Study	Design	Pregnancies (n)	No. of pregnancies in infliximab-exposed group	No. of pregnancies in adalimumab-exposed group	Study quality
Kiely CJ [17]	P	21	10 Infliximab	11 Adalimumab	★★★★★
Schnitzler F [18]	P	42	35 Infliximab	7 Adalimumab	★★★★★★
Seirafi M [19]	P + R	128	86 Infliximab	42 Adalimumab	★★★★★★
Casanova MJ [20]	R	29	20 Infliximab	9 Adalimumab	★★★★★★
Julsgaard M [21]	P	80	44 Infliximab	36 Adalimumab	★★★★★
Arsenescu R [22]	R	10	8 Infliximab	2 Adalimumab	★★★★
Slama W [23]	P	186	122 Infliximab	64 Adalimumab	★★★★
Zelinkova Z [24]	P + R	31	18 Infliximab	13 Adalimumab	★★★★★

R Retrospective, *P* Prospective

Table 2 Pregnancy outcomes (proportion of adverse outcome to number of exposed pregnancies) of included studies

Outcomes Group	preterm delivery		low birth weight		spontaneous abortion		congenital malformations	
	A	B	A	B	A	B	A	B
Kiely CJ [17]	2/21		2/21		0/10	1/11[a]	0/21	
Schnitzler F [18]	8/42		6/42		6/35	1/7	0/35	1/7
Seirafi M [19]							1/86	0/42
Casanova MJ [20]							0/20	1/9
Julsgaard M [21]	3/80		6/80				2/44	1/36
Arsenescu R [22]					1/8	0/2	0/10	
Slama W [23]					1/122	1/64	3/122	1/64
Zelinkova Z [24]					1/18	2/13	1/18	0/13

A: exposed to Infliximab B: exposed to Adalimumab

[a] This patient underwent an emergency colectomy following failed treatment with adalimumab. The stillbirth occurred at week 21 gestation, 11 days following the colectomy
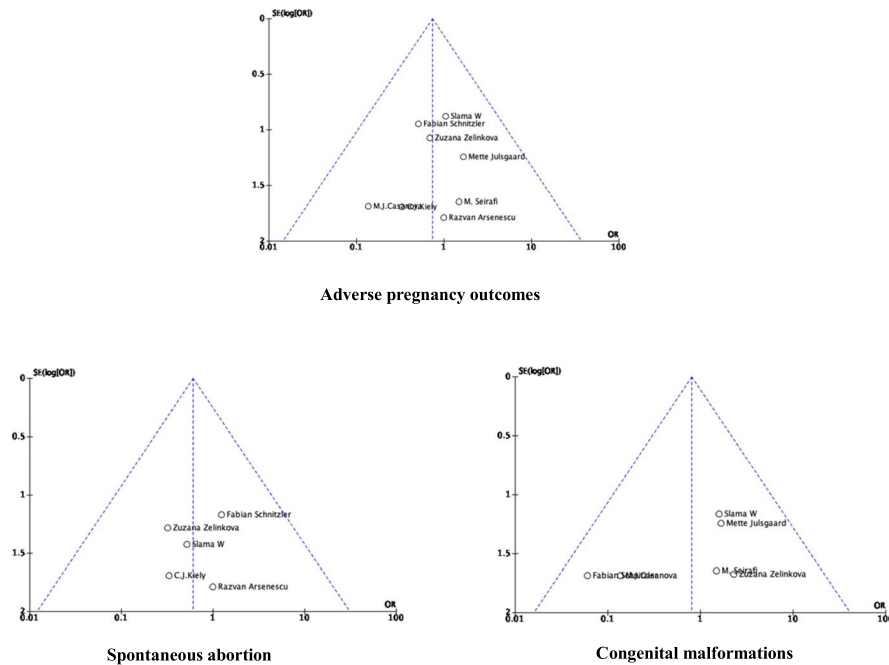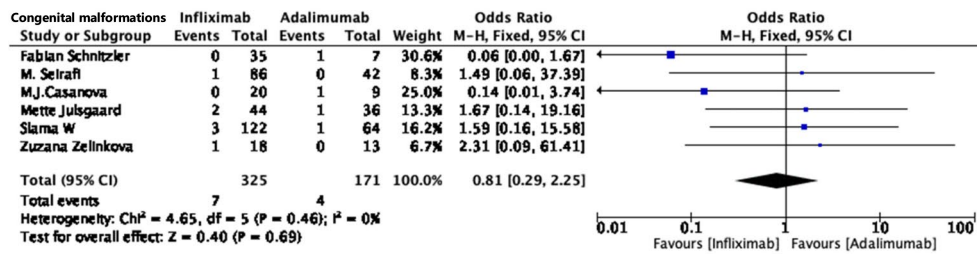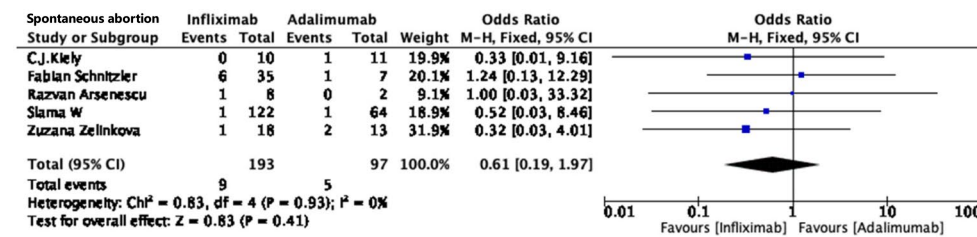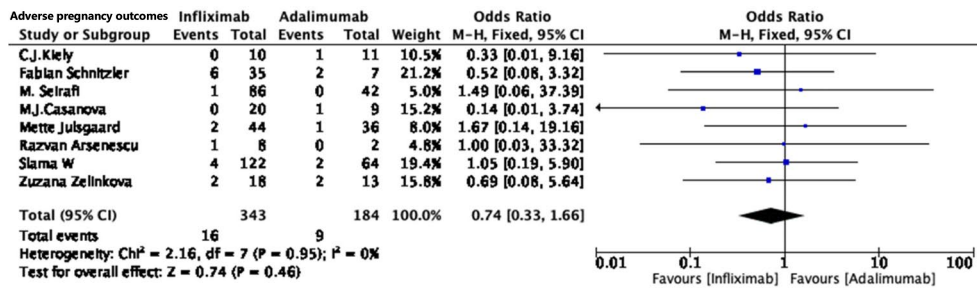
Fig. 2 Risk of APOs in pregnant women treated with infliximab and adalimumab for IBD.

Seven studies reported the APOs associated with spontaneous abortion and congenital malformations after exposure to biological agents in pregnant women with IBD. The OR for the pooled crude rates of APOs was 0.66 (95% CI: 0.26, 1.68; $P = 0.38$), comparing infliximab ($n = 221$) with adalimumab ($n = 120$), without obvious heterogeneity ($P = 0.92$, $I^2 = 0\%$).

Spontaneous abortion
Four studies reported the outcome of spontaneous abortion in IBD pregnant women exposed to biological agents. The pooled OR for the crude rate of spontaneous abortion was 0.63 (95% CI: 0.17, 2.29; $P = 0.48$). There was no heterogeneity between studies when comparing infliximab ($n = 71$) and adalimumab ($n = 33$) ($P = 0.85$, $I^2 = 0\%$).

Congenital malformations
Five studies reported congenital malformation outcomes in IBD pregnant women exposed to anti TNF-α. The pooled OR for the crude rate of congenital malformations was 0.66 (95% CI: 0.20, 2.12; $P = 0.48$) comparing patients treated with infliximab ($n = 203$) and adalimumab ($n = 107$). There was no significant heterogeneity observed between studies ($P = 0.38$, $I^2 = 5\%$) (Fig. 3).

Discussion
The high incidence rate of IBD accounts for more than 0.3% of cases in North America and many European countries. Many patients are diagnosed with IBD as young adults, which affects the peak of fertility and family planning [25]. Many patients take 5-amino salicylate (5-ASA), corticosteroids, biologics, and immunosuppressants [26, 27]. Female patients with active IBD have an ascendant risk of developing adverse maternal and infant outcomes. Therefore, the best practice for both mothers and infants is to optimize disease control during pregnancy [28, 29]. However, before or during pregnancy, women often reduce or stop prescribing drugs without discussing them with their physicians [30]. Most patients with IBD require long-term medication to control and maintain the disease [31, 32]. All anti-TNF drugs effectively maintain clinical remission and mucosal healing in the case of infliximab and adalimumab therapy [33]. The Toronto [28] and ECCO [4, 32] consensus statements showed that sustained remission is important for pregnancy success. At the same time, anti-TNF therapy does not lead to adverse maternal and infant outcomes. For 5-ASA, thiopurines, or anti-TNF-α, women with well-controlled medical maintenance therapy should continue treatment throughout pregnancy. Nevertheless, patient misconceptions and unsubstantiated fears of treatment teratogenicity contribute to medication non-adherence
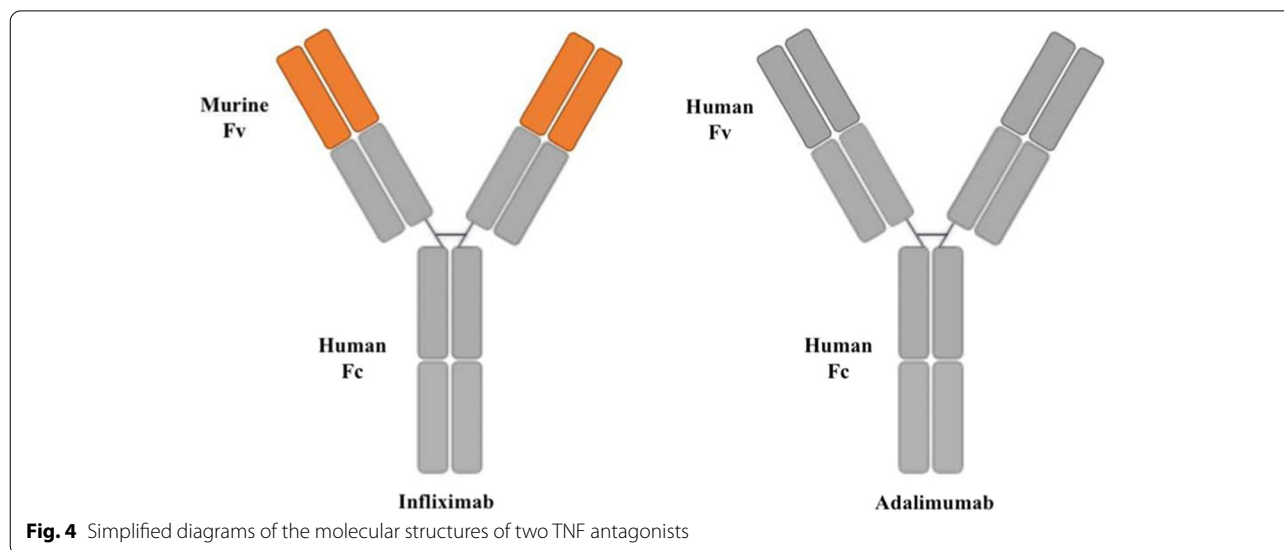
during pregnancy and breastfeeding [34–38]. Anti-TNF therapies are reported to be effective in many high-quality placebo-controlled trials, but data comparing the APOs of the two drugs in clinical practice are limited. Women with IBD already in the active phase before pregnancy have a higher risk of premature birth. This is also associated with poorer fetal outcomes, including the ascendant risk of small gestational age preterm delivery and low birth weight [39]. Therefore, it is necessary to study the comparative APOs of therapies for pregnant women with IBD. The basis for selecting anti-TNF monoclonal antibodies is not clearly stated in the consensus. Moreover, there is no evidence on the comparative APOs of infliximab and adalimumab in pregnant women with IBD.

Although many regulatory bodies strongly encourage various studies to incorporate pregnant women and women of childbearing age in RCTs, pregnant and lactating women are often excluded from the trial due to unknown potential harm to the fetus. Therefore, treatment options during pregnancy often lack strong evidence-based recommendations. Safety information comes from voluntary reports of adverse events or uncontrolled observational studies during post-marketing monitoring. The current meta-analysis explored the risk of adverse pregnancy outcomes (we collected the data on preterm delivery, low birth weight, spontaneous abortion, and congenital malformations) following the infliximab and adalimumab therapy in women with IBD. 343 pregnant women with IBD who received infliximab were compared with 184 pregnant women who received adalimumab. In our study, the ORs for adverse pregnancy outcomes in IBD patients taking infliximab therapy during pregnancy compared with those taking adalimumab were 0.74 (95% CI: 0.33, 1.66). The OR of pooled crude rates of congenital malformations and spontaneous abortion were 0.81 (95% CI: 0.29, 2.25) and 0.61 (95% CI: 0.19, 1.97), respectively. However, no significant difference was observed between infliximab and adalimumab in the risk of APOs.

A retrospective analysis of "real" data from 3205 patients showed that infliximab was superior to adalimumab and certolizumab in treating CD [40]. In contrast, a series of recent studies in Austria showed that infliximab and adalimumab were equally effective in treating CD [41]. These results were neither uniform nor different. During pregnancy, the pharmacodynamics and pharmacokinetics of many drugs changes. Infliximab and adalimumab are complete IgG1 anti-TNF monoclonal antibodies with strong anti-inflammatory effects. They are actively transferred through the placenta in exponential form through the Fc receptor from the second trimester of pregnancy. In one small study by Seow et al

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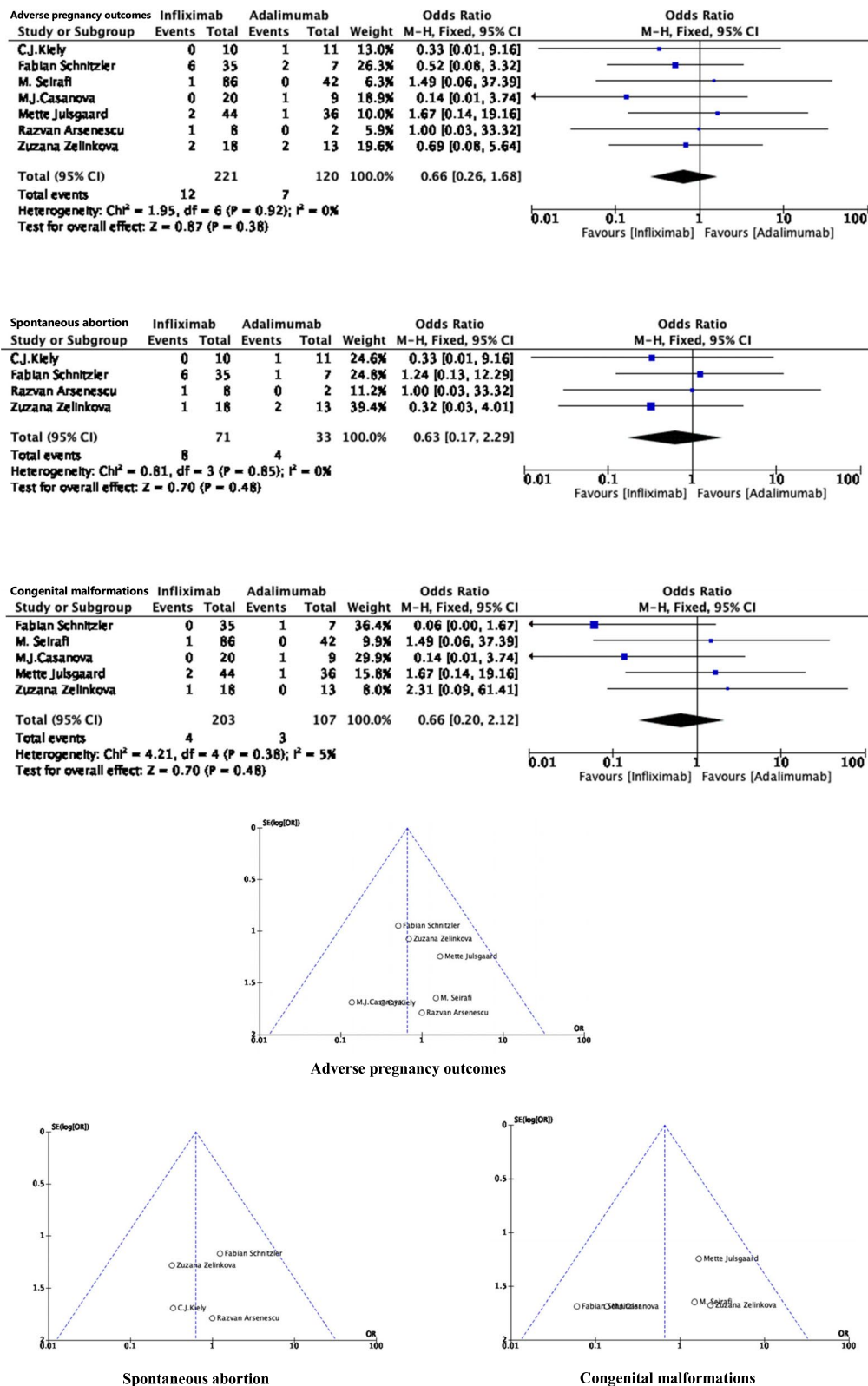
Fig. 3 Risk of APOs in pregnant women treated with infliximab and adalimumab for IBD (sensitivity analysis)

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Fig. 4 Simplified diagrams of the molecular structures of two TNF antagonists

[42], 15 pregnant women treated with infliximab and 10 pregnant women treated with adalimumab increased infliximab levels while adalimumab levels remained stable. IgG1 is transported across the placenta more readily than other IgG subclasses, with passage increasing exponentially toward the later stages of pregnancy [43]. Several cohort studies, systematic reviews, and meta-analyses have reported no adverse effects of infliximab, adalimumab, or certolizumab during pregnancy. There was no increased risk of congenital malformations, preterm birth, spontaneous abortion, or low birth weight [20, 44–50]. These observations were consistent with our study, which shows that pregnant women with IBD on infliximab and adalimumab therapy did not show the difference in the risk of APOs. Like other anti-TNFs, infliximab and adalimumab are classified as pregnancy category B (no documented human toxicity) by the US Food and Drug Administration. Infliximab is a murine/human chimeric anti-TNF- α Monoclonal antibody containing murine variable and human IgG1 constant regions. Infliximab contains 25% murine sequences, which may be related to the occurrence of adverse reactions. Adalimumab is a completely humanized anti-TNF- α Monoclonal antibody with no difference from normal human IgG1 [6, 51] (Fig. 4). Infliximab and adalimumab can efficiently cross the placenta in the second and third trimesters due to their specific FcRn receptor-mediated mechanisms [43, 52].

Our study had some limitations. First, the conclusions of the expert group were based on the opinions of experts and the interpretation of existing evidence. However, the evidence for certain scenarios included in the study was limited. We attempted to obtain the data on preterm delivery and low birth weight. However, some articles did not clearly distinguish between the infliximab and adalimumab groups. Thus we analyzed the risk of congenital malformations and spontaneous abortion. Secondly, our results did not rule out other factors, such as patient compliance, local drug access, or lack through the local medical level. Inevitably, clinicians need to consider the best treatment for a particular patient, considering the numerous associated factors. Although good control of disease activity during pregnancy is beneficial for a better outcome, there is no strong evidence to prove the safety of drug exposure to developing fetuses.

In conclusion, clinicians should be very cautious. There are still many aspects that need optimization in this field. Thus, larger prospective trials involving pregnant patients are required to establish a drug safety database. Additionally, larger RCTs research outcomes will help promote the clinical decision-making of the treatment of women with IBD of childbearing age to optimize the pregnancy outcomes.

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Declarations

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