

Continuous Anti-TNF α Use Throughout Pregnancy: Possible Complications For the Mother But Not for the Fetus. A Retrospective Cohort on the French National Health Insurance Database (EVASION)

Maxime Luu, MD^{1,2}, Eric Benzenine^{3,4}, Muriel Doret, MD, PhD⁵, Christophe Michiels, MD⁶, Alan Barkun, MD, CM, MSc⁷, Thibault Degand, MD⁶, Catherine Quantin, MD, PhD^{3,8} and Marc Bardou, MD, PhD^{1,2,9}

- OBJECTIVES:** Inflammatory bowel diseases (IBD) need long-term treatment, which can influence pregnancies in young women. Uncontrolled IBD is associated with poor pregnancy outcomes. Despite the labeling of Anti-tumor necrosis factor (TNF) antibodies (anti-TNF α) which indicates that their use is not recommended during pregnancy, anti-TNF α are increasingly being used during pregnancy and may expose women and their fetuses to treatment-related complications. Existing recommendations on the timing of treatment during pregnancy are inconsistent. We aimed to assess the safety of anti-TNF α treatment in pregnant women with IBD, and up to the first year of life for their children.
- METHODS:** An exposed/non exposed retrospective cohort was conducted on the French national health system database SNIIRAM (Système National d'Information Inter-Régimes de l'Assurance Maladie). All IBD women who became pregnant between 2011 and 2014 were included. Women with concomitant diseases potentially treated with anti-TNF α were excluded. Anti-TNF α exposure (infliximab, adalimumab, golimumab or certolizumab pegol) during pregnancy was retrieved from the exhaustive prescription database in SNIIRAM. The main judgment criterion was a composite outcome of disease-, treatment- and pregnancy-related complications during pregnancy for the mother, and infections during the first year of life for children.
- RESULTS:** We analyzed data from 11,275 pregnancies (8726 women with IBD), among which 1457 (12.9%) pregnancies were exposed to anti-TNF α , mainly infliximab or adalimumab, with 1313/7722 (17.0%) suffering from Crohn's disease and 144/3553 (4.1%) from ulcerative colitis. After adjusting for disease severity, steroid use, age, IBD type, and duration and concomitant 6-mercaptopurine use, anti-TNF α treatment was associated with a higher risk of overall maternal complications (adjusted Odds Ratio (aOR) = 1.49; 95% confidence interval (CI): 1.31–1.67) and infections (aOR = 1.31; 95% CI: 1.16–1.47). Maintaining anti-TNF α after 24 weeks did not increase the risk of maternal complication, but interrupting the anti-TNF α increased relapse risk. No increased risk for infection was found in children (aOR = 0.89; 95% CI: 0.76–1.05) born to mother exposed to anti-TNF α during pregnancy.
- CONCLUSIONS:** Anti-TNF α treatment during pregnancy increased the risk of maternal complications compared to unexposed; however, discontinuation before week 24 increased the risk of disease flare. There was no increased risk for children exposed to anti-TNF α up to 1 year of life.

SUPPLEMENTARY MATERIAL accompanies this paper at <https://doi.org/10.1038/s41395-018-0176-7>

Am J Gastroenterol (2018) 113:1669–1677. <https://doi.org/10.1038/s41395-018-0176-7>

¹Clinical Investigation Center, Clinical Epidemiology/Clinical Trials Unit, Dijon-Bourgogne University Hospital, Dijon, France. ²Inserm, CIC 1432, Dijon, France.

³Biostatistics and Bioinformatics (DIM), Dijon-Bourgogne University Hospital, Dijon, France. ⁴Bourgogne Franche-Comté University, Dijon, France. ⁵Hospices

Civils de Lyon, Hôpital Femme-Mère-Enfant, Department of Obstetrics and Gynaecology, Bron, France. ⁶Division of Gastroenterology, Dijon-Bourgogne

University Hospital, Dijon, France. ⁷The McGill University Health Centre, Montreal General Hospital, McGill University, Montreal, QC, Canada. ⁸Biostatistics,

Biomathematics, Pharmacoeconomics and Infectious Diseases (B2PHI), INSERM, UVSQ, Institut Pasteur, Université Paris-Saclay, Paris, France.

⁹Department of Gastroenterology and Hepatology and Public Health Department, Erasmus MC, University Medical Center, Rotterdam, The Netherlands.

Correspondence: M.L. (email: Maxime.luu@chu-dijon.fr)

Received 14 December 2017; accepted 11 May 2018; Published online 2 July 2018

INTRODUCTION

Inflammatory bowel diseases (IBD), mainly Crohn's disease (CD) and ulcerative colitis (UC), are common conditions affecting a significant proportion of women, including women of childbearing age. The peak incidence of IBD occurs in the second to fourth decade of life according to most CD and UC studies [1]. The prevalence of IBD is increasing worldwide, and ~25% of women with IBD are expected to become pregnant over the course of their disease [2]. Therefore, for most patients who require long-term treatment to maintain a quiescent state, IBD can interfere with the desire for pregnancy.

Disease activity at the time of conception increases the risk of fetal complications, such as preterm birth (HR 2.20, 95% CI 1.71–2.84) [3], low birth-weight, cesarean delivery (Prevalence OR, 1.93; 95% CI, 1.76–2.12) [4], and spontaneous abortion [3, 5–7], and is strongly associated with disease relapse for the mother (adjusted OR (aOR) = 7.66, 95% CI: 3.77–15.54) [7]. Although most studies do not support an association between IBD and the risk of congenital malformations, this issue is still a matter of debate [3, 4, 8, 9].

TNF α antagonists (anti-TNF α), infliximab, adalimumab, golimumab, and certolizumab pegol, are backbone therapies for patients whose disease is not controlled by first-line therapies, mainly 5ASA, steroids or immunosuppressants. The use of anti-TNF α during pregnancy, although off label, has become much more popular. However, as anti-TNF α use is associated with an increased risk of infection, several groups have published guidelines for their use during pregnancy in patients with IBD and more generally across all the approved indications, but as yet there is no general consensus [10–12]. In the recommendations of the French Society for Rheumatology, endorsed by the National Authority of Health, and with European Medicines Agency approval, anti-TNF α should not be proposed during pregnancy. For the European Crohn and Colitis Organisation (ECCO) [10], they should be stopped before the 24th week of amenorrhea (WA) [11], and for the American Gastroenterological Association (AGA), they should be maintained throughout pregnancy because of the impact of uncontrolled disease on pregnancy outcomes [12]. Food and Drug Administration approval for infliximab states that infliximab should be given to a pregnant woman only if clearly needed without recommendations for how long it can be used during pregnancy. A study published in 2016 suggested that, in women with IBD in sustained remission, anti-TNF α can be stopped safely for the mother in the second trimester [13]. The impact of fetal anti-TNF α exposure must also be taken in account, because infliximab and adalimumab, like maternal immunoglobulins, are actively transferred across the placental barrier [14]. This transfer starts as early as 13WA and is substantial after 20 WA. A study published in 2017 reported that after adjusting for albumin, BMI and CRP, infliximab trough levels increased by 4.2 μ g/mL per trimester during pregnancy, while adalimumab drug levels remained stable [15]. In consequence, high blood anti-TNF α levels persist in the infant several months after delivery [16]. Yet the PIANO (Pregnancy in IBD And Neonatal Outcomes) registry found no increased risk of infections during the first year of life in children born to mothers exposed to anti-TNF α during pregnancy, except for those born to mothers exposed to both anti-TNF α and thiopurine (RR 1.50; 1.08–2.09) [17]. As no randomized clinical

trials have included pregnant or breast-feeding women, existing guidelines are mostly based on expert opinion or very low quality data (supplementary file). Most of evidence supporting the safety of anti-TNF α in pregnant women [18, 19] and their children [20–22] comes from small-sized monocentric and/or retrospective studies. The aims of our study were thus, (i) to determine the risk-to-benefit ratio of anti-TNF α treatments for both mothers and their children during the first year of the infant's life and (ii) to evaluate the impact of anti-TNF α cessation or maintenance after 24WA for both mothers and their children.

METHODS

We carried out an exposed/non-exposed retrospective cohort study in pregnant women with IBD between January, 1st 2011 and December 31st 2015, using data from the French Health Insurance database (Système National Inter Régimes d'Assurance Maladie, SNIIRAM). This study was conducted in accordance with the Declaration of Helsinki.

Data Source

Data for all diagnoses and complications were extracted from the SNIIRAM database. SNIIRAM is the French national information system that contains individual, exhaustive and linkable but anonymous data on health expenditures for about 87% of the French population. It aggregates data from: (i) the hospital discharge abstract database (Programme de Médicalisation des Systèmes d'Informations, PMSI), which collects first and associated diagnoses (secondary events and current comorbidities), encoded using the International Classification of Diseases, 10th revision (ICD-10), and procedures performed during hospital stays using the common classification system for medical procedures (Classification commune des actes médicaux, CCAM); (ii) the database containing all prescriptions for expensive drugs fully reimbursed by the national health insurance, Common Dispensing Units (UCD for Unités de Dispensation Communes,) such as anti-TNF α , in order to ensure equal access to health care, (iii) the codes for long-term diseases (ALD for Affection de Longue Durée) that give access to full coverage of health expenditures by the national health insurance scheme iv) the reimbursement data for out-of-hospital drug purchases with the Presentation Identifier Code codes (CIP for Code Identifiant de Présentation), such as anti-infectious agents (antibiotics, antivirals, antifungals), steroids and thiopurines (azathioprine and 6-mercaptopurine). To avoid any misclassification of anti-TNF α exposure, UCD and PMSI databases were crosschecked to verify that anti-TNF α prescriptions were associated with hospital stays for IBD treatment. To ensure the quality of hospital data, various quality control procedures were carried out on samples a posteriori by the Medical Information Departments of each healthcare establishment and by territorial medical inspectors, in accordance with legislation. For 20 years, hospital data have been used for medical research purposes and the quality of the French hospital database has been confirmed in recent validation and epidemiological studies [23, 24]. This is the database that has been recently used to show, among adults with IBD, an association between the

use of thiopurine monotherapy or anti-TNF α monotherapy and a small but statistically significant increased risk of lymphoma [25].

Patients Included

We extracted data for all women with a diagnostic code for IBD and a singleton pregnancy that began between January 1st 2012 and December 31st 2014. IBD diagnoses were retrieved by linking ALD code n°24 (CD or UC) with the hospital stays containing the corresponding ICD-10 codes for CD and UC. Children born to a mother with IBD were included after 2013, when the linkage of mothers and their children became effective. Multiple pregnancies were excluded because they are independently associated with an increased risk of adverse outcomes [26]. We excluded women with other inflammatory diseases potentially treated by anti-TNF α (psoriasis, non-infectious uveitis, rheumatoid arthritis, ankylosing spondylitis).

Variables of Interest

The primary endpoint was a composite criterion, defined by the occurrence of maternal complications, irrespective of suspected origin (related to treatment, IBD or pregnancy). In-hospital complications were retrieved using the corresponding ICD-10 codes and the CCAM codes for in-hospital medical procedures. Reimbursement data related to out-of-hospital prescriptions for anti-infection agents were assumed to denote community-acquired infections. Secondary endpoints were the occurrence of (i) disease-related, (ii) treatment-related and (iii) pregnancy-related complications, specifically, and (iv) infectious episodes during the first year of life. Complications were retrieved using the corresponding ICD-10 codes, detailed in the supplementary file.

Assessment of Disease Severity And Disease Relapse

CD and UC disease severity was assessed with a quantitative risk score, ranging from 0 to 13, and stratifying the risk as mild (0–1), moderate (2–4), and severe (5–13) [27]. This score is used to predict the risk of severe hospitalized course among patients with CD. It was constructed and validated on the Nationwide Inpatient Sample (NIS). Components of the score with ICD-10 and CCAM codes are detailed in the supplementary file. Women not hospitalized the year prior to the pregnancy were categorized as mild risk. As there is no specific ICD-10 code to identify disease relapses, initiation of steroid prescriptions in steroid free women was assumed to reflect disease relapse.

Statistical Analyses

Univariate analysis was first used to compare the characteristics of women exposed and not exposed to anti-TNF α . Factors that were predictive of complications in univariate analysis with a p -value < 0.05, were added to the model. Qualitative variables were tested using χ^2 or Fischer's exact test, as appropriate. Quantitative variables were described as means with their standard deviations and compared using Student's test or a non-parametric Mann–Whitney test after distribution assessment with the Shapiro–Wilk test.

A multiple logistic regression model was then used to assess the independent factors for complications. To take into account

the possible correlation between the outcomes of consecutive pregnancies for the same woman, a generalized estimating equations approach to logistic regression was used, assuming an exchangeable correlation structure, with robust variance estimators. Secondary analyses were performed to assess the risk of infections in pregnant women and in children during their first year of life. Initially, all infections were considered, and then analysis was restricted to infections requiring hospitalization. Finally, in women exposed to anti-TNF α and who delivered at ≥ 24 WA, outcomes were compared between those who stopped anti-TNF α before 24WA and those who continued during the third trimester. All analyses were performed using SAS v9.4 software (SAS Institute, Cary, NC, USA). A p -value < 0.05 was considered significant for all tests. Results are given as odds ratios (OR) with 95% confidence intervals (95% CI). This study was conducted in accordance with the policy of our institution and did not require institutional review board agreement. Approval for data extraction from the SNIIRAM was prior approved by The Comité National Informatique et Libertés (CNIL) (MMS/ALU/AE161142).

Role of the Funding Source

The National Research Agency and Dijon-Bourgogne University Hospital provided funding for the study. The funding sources had no role in the design of the study, analysis or interpretation of the data, or preparation or final approval of the manuscript. The research presented in this article is original. The content of this article is solely under the authors' responsibility.

RESULTS

Pregnancy Outcomes

Baseline characteristics of the cohort are described in Table 1. A total of 8726 women with a diagnosis of IBD and their 11,275 pregnancies were included, among which 1457 (12.9%) were exposed to anti-TNF α , 1313/7722 (17%) of CD and 145/3552 (4.1%) of UC. Overall, 8596 resulted in live births. Infliximab or adalimumab accounted for 54.9% and 43.3% of anti-TNF α use, respectively, and 223 exposed women (15.3%) were concomitantly treated with thiopurines, mainly azathioprine (88.8%). About a third of exposed women had at least one prescription for steroids (29.7%), but only 3.2% were treated throughout pregnancy. Women exposed to anti-TNF α were younger (29.4 ± 5.0 years versus 31.0 ± 5.2 ; $p < 0.001$) and had a longer history of IBD (72.3 ± 56.1 months versus 66.5 ± 56.4 ; $p < 0.001$) than non-exposed women. The mean duration of anti-TNF α treatment during pregnancy was 23.4 ± 13.1 weeks, but nearly half of the patients (46.7% overall, 49.2% for infliximab, and 45.3% for adalimumab) were still on anti-TNF α in the third trimester (Fig. 1). Among these, 33.6% were still being treated at the time of delivery (33.2% for infliximab and 34.7% for adalimumab).

More women in the exposed (43.3%) than in the non-exposed (33.6%) group experienced at least one complication (crude OR = 1.53; 95% CI, 1.34–1.68). The same difference was observed when disease-related, treatment-related, or pregnancy-related complications were assessed separately (Table 1). The overall infection rate was 51.1% in the exposed group versus 42.6% in the

Table 1 Comparison of the characteristics of the pregnancies exposed to anti-TNF α and those not exposed to anti-TNF α ($n = 8726$)

	Pregnancies exposed to anti-TNF α	Pregnancies not exposed to anti-TNF α	P-value
<i>Population characteristics</i>			
Pregnancies, no (%)	1457 (12.9)	9818 (87.1)	
Order, no (%)			0.968
1st	1131 (77.6)	7595 (77.4)	
2nd	289 (19.8)	1939 (19.8)	
≥ 3 rd	37 (2.5)	284 (2.9)	
Age at start of pregnancy, mean (SD), years	29.4 (5.0)	31.0 (5.2)	<0.001
Term at delivery, mean (SD), WA	31.4 (12.3)	32.3 (11.9)	<0.001
≤ 12 WA	362 (24.9)	2171 (22.1)	
>12 SA– ≤ 24 WA	22 (1.5)	124 (1.3)	
>24 SA– ≤ 37 WA	205 (14.1)	1216 (12.4)	
>37 WA	868 (59.6)	6307 (64.2)	
Current smoker, no (%)	98 (6.7)	409 (4.2)	<0.001
Length of IBD before pregnancy, mean (SD), months	72.3 (56.1)	66.5 (56.4)	<0.001
<i>IBD characteristics</i>			
Type of IBD, no (%)			<0.001
Crohn's disease	1313 (90.1)	6409 (65.3)	
Ulcerative colitis	144 (9.9)	3409 (34.7)	
Disease severity, no (%)			<0.001
Mild	1145 (78.6)	9399 (95.7)	
Moderate	173 (11.9)	295 (3.0)	
Severe	139 (9.5)	124 (1.3)	
<i>Anti-TNFα treatment</i>			
Duration, mean (SD), weeks	23.4 (13.1)	–	
Treatment scheme, no (%)			
IFX only	800 (54.9)	–	
IFX then ADA	18 (1.2)	–	
IFX then CER	2 (<1)	–	
ADA only	631 (43.3)	–	
GOL only	1 (<1)	–	
CER only	5 (<1)	–	
Anti-TNF stoppage, no (%)			
<12 WA	266 (18.3)	–	
≥ 12 WA and <24 WA	493 (33.8)	–	
≥ 24 WA	688 (47.2)	–	
≥ 37 WA	460 (31.6)	–	
<i>Use of thiopurine</i>			

	Pregnancies exposed to anti-TNF α	Pregnancies not exposed to anti-TNF α	P-value
Duration, mean (SD), weeks	21.2 (13.3)	25.5 (13.0)	0.945
Patients, no (%)	223 (15.3)	1306 (13.3)	0.040
AZA	198 (88.8)	1256 (96.2)	
MCT	25 (11.2)	50 (3.8)	
<i>Use of steroids</i>			
At least 1 prescription	399 (27.4)	1880 (19.2)	<0.001
≥ 3 prescriptions, no (%)	95 (6.5)	336 (3.4)	<0.001
<12 WA	209 (14.3)	940 (9.6)	<0.001
≥ 12 WA and <24 WA	163 (11.2)	737 (7.5)	
≥ 24 WA	196 (13.5)	798 (8.1)	
Whole pregnancy	47 (3.2)	167 (1.7)	<0.001
relaying antiTNF ≥ 24 WA	79 (5.4)	–	
<i>Complications, no (%)</i>			
Disease-related			<0.001
Digestive	93 (6.4)	116 (1.2)	
Extra-digestive	32 (2.2)	60 (0.6)	
Treatment-related			
Hematology	9 (0.6)	7 (<0.1)	<0.001
Hepatic	12 (0.8)	28 (0.3)	
Infections	744 (51.1)	4180 (42.6)	<0.001
In-hospital infections	175 (12.0)	908 (9.3)	<0.001
General	128 (8.8)	623 (6.4)	
Digestive and hepatic	12 (0.8)	56 (0.6)	
Neurological	–	1 (<0.1)	
Cutaneous	19 (1.3)	54 (0.8)	
Respiratory	7 (0.5)	31 (0.3)	
ENT	2 (0.1)	2 (<0.1)	
Perinatal	–	1 (<0.1)	
Genitourinary	7 (0.5)	31 (0.3)	
Pregnancy	95 (6.5)	511 (5.2)	
Parasite	1 (<0.1)	11 (0.1)	
Community infections	710 (48.7)	3820 (38.9)	<0.001
Antibiotics	672 (46.1)	3708 (37.8)	
Antivirals	10 (0.7)	10 (0.1)	
Antifungals	28 (1.9)	102 (1.0)	
Pregnancy-related	502 (34.5)	2977 (30.3)	0.001
Pregnancy loss	383 (26.3)	2279 (23.2)	
Premature delivery	31.4 (12.3)	32.3 (11.9)	
≤ 12 WA	362 (24.9)	2171 (22.1)	
>12 SA– ≤ 24 WA	22 (1.5)	124 (1.3)	
>24 SA– ≤ 37 WA	205 (14.1)	1216 (12.4)	
Malformations	1 (<0.1)	21 (0.2)	NS

	Pregnancies exposed to anti-TNF α	Pregnancies not exposed to anti-TNF α	P-value
Composite criterion	631 (43.3)	3302 (33.6)	<0.001

Univariate comparisons were performed with a Student's test or a non-parametric Mann-Whitney test after assessment of distribution using the Shapiro-Wilk test. Qualitative variables were tested with χ^2 or Fischer's exact test, as appropriate. *WA* weeks of amenorrhea, *IFX* infliximab, *ADA* adalimumab, *CER* certolizumab pegol, *GOL* golimumab, *AZA* azathioprine, *MCT* mercaptopurine, *NS* non-significant. $P < 0.05$ for all comparisons. Percentages may not sum to 100% due to rounding.

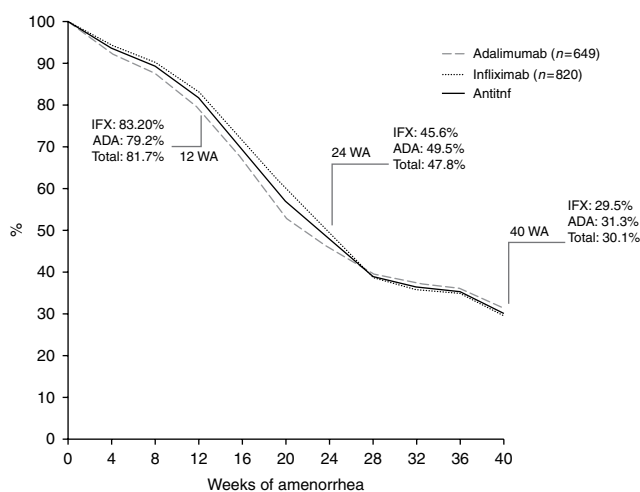


Fig. 1 Anti-TNF α exposure during pregnancy. IFX infliximab, ADA adalimumab, WA weeks of amenorrhea

non-exposed group (crude OR=1.41; 95% CI, 1.26–1.57). The difference remained significant when in-hospital or community-acquired infections were assessed separately (Table 2).

Results of the multivariate analysis are shown in Table 2. Exposure to anti-TNF α was an independent risk factor for pregnancy complications (aOR=1.49; 95% CI, 1.31–1.67), and was also associated with an increased overall risk of maternal infections (aOR=1.31; 95% CI, 1.16–1.47), as well as in-hospital only infections (aOR=1.25; 95% CI, 1.04–1.50). Treatment with thiopurines independently increased the risk of overall infection, although modestly (aOR=1.21; 95% CI, 1.09–1.35).

Infections in The Children During Their First Year of Life

As mother-to-child data linkage in the SNIIRAM database only became available in 2013, only 50% of the full cohort (5635 children) was available for analysis. Among these, 799 children (14.2%) were born to anti-TNF α -exposed mothers (Table 3). These babies were more often premature than those born to non-exposed mothers (10.4% versus 8.1% respectively, $p=0.03$). There were no differences between the two groups for overall infection rates (43.7% versus 45.9% in the exposed and non-exposed group, respectively, $p=0.242$), or for community-acquired or in-hospital infections. The rate of congenital malformations was also similar in the two groups (6.1% exposed versus 6.3% non-exposed, $p=0.886$). In multivariate analysis, only preterm birth (before 37WA) was strongly associated with the risk of in-hospital infection (aOR=2.90; 95% CI 2.25–3.75).

Outcomes for Women Exposed During the Third Trimester and Their Children

In the subgroup of pregnancies attaining at least 24WA, exposure to anti-TNF α was associated with an increased risk of complications (OR=1.6; 95% CI, 1.40–1.95), overall maternal

Table 2 Risk for overall maternal complications, infections, and in-hospital infections during pregnancy, and infectious risk (overall and in-hospital) for children during their first year of life

	Pregnant women (1457 women exposed versus 9818 non-exposed)			Children 0–1 year (797 exposed versus 4836 non-exposed)	
	Composite criterion ^a	All Infections ^a	In-hospital infections only ^a	All infections children ^b	In-hospital infections children ^b
Exposure to anti-TNF OR (95% CI)	1.49 [1.31–1.67]	1.31 [1.16–1.47]	1.25 [1.04–1.50]	0.89 [0.76–1.05]	0.85 [0.64–1.13]
Age at pregnancy OR (95% CI) (years)	1.01 [0.99–1.02]	1.01 [0.99–1.01]	0.99 [0.97–0.99]	0.99 [0.98–1.00]	0.98 [0.96–0.99]
Delivery < 37 WA term OR (95% CI)	–	–	–	1.13 [0.93–1.37]	2.90 [2.25–3.75]
IBD type (CD vs UC (ref)) OR (95% CI)	0.95 [0.87–1.04]	1.10 [1.01–1.20]	1.00 [0.87–1.16]	0.98 [0.87–1.10]	1.03 [0.84–1.27]
IBD disease duration (months) OR (95% CI)	1.00 [0.99–1.01]	0.99 [0.99–1.00]	1.00 [0.99–1.00]	0.99 [0.99–1.00]	0.99 [0.99–0.99]
Severe disease (yes/ no (ref)) OR (95% CI)	1.93 [1.50–2.49]	1.55 [1.20–2.00]	1.30 [0.85–1.99]	1.05 [0.72–1.52]	1.36 [0.76–2.43]
Exposure to thiopurines OR (95% CI)	0.90 [0.81–1.02]	1.21 [1.09–1.35]	1.02 [0.84–1.22]	0.90 [0.78–1.05]	0.82 [0.62–1.08]
Exposure to steroids ^c (yes/ no (ref)) OR (95% CI)	0.58 [0.45–0.73]	2.10 [1.71–2.57]	1.46 [1.10–1.94]	1.34 [1.05–1.71]	1.56 [1.09–2.24]

WA weeks of amenorrhea, IBD inflammatory bowel disease, CD Crohn disease, UC ulcerative colitis

^aAdjusted for exposure to anti-TNF, age at pregnancy, IBD type, IBD disease duration, disease severity, and exposure to thiopurines

^bAdjusted for exposure to anti-TNF, age at pregnancy, term of delivery, IBD type, IBD disease duration, disease severity, and exposure to thiopurines

^cPatients were considered exposed to steroids when ≥ 3 steroid prescriptions were detected during pregnancy

Bold text indicates a statistically significant difference with a p-value less than 0.05 between exposed to anti-TNF α and non-exposed to anti-TNF α groups

Table 3 Univariate comparison between children born to mothers exposed to anti-TNF during pregnancy and those not exposed, during their first year of life ($n=5635$)

Characteristic	Mothers exposed to anti-TNF α	Mothers not exposed to anti-TNF α	P value
Children, no (%)	799 (14.2)	4,836 (85.8)	
Maternal exposure to thiopurines during pregnancy, no (%)	137 (17.2)	744 (15.4)	0.20
Delivery <37WA, no (%)	83 (10.4)	392 (8.1)	0.03
Infections, no (%)			
Overall infections	349 (43.7)	2,220 (45.9)	0.32
Community infections	330 (41.2)	2,067 (42.8)	0.34
Antibiotics	325 (40.7)	2,037 (42.1)	
Antifungals	4 (0.5)	28 (0.6)	
Antivirals	1 (0.0)	2 (0.1)	
In-hospital infections	66 (8.3)	419 (8.7)	0.58
General	26 (3.3)	141 (2.9)	
Digestive and hepatic	18 (2.3)	86 (1.8)	
Neurological	–	11 (0.2)	
Mucosal and cutaneous	2 (0.3)	21 (0.4)	
Respiratory	37 (4.6)	194 (4.0)	
ENT	2 (0.3)	22 (0.5)	
Perinatal	24 (3.0)	167 (3.5)	
Genitourinary	8 (1.1)	55 (1.0)	
Parasite	–	2 (<0.1)	
Malformations, no (%)	49 (6.1)	303 (6.3)	0.89
Univariate comparisons were performed with a Student's test or a non-parametric Mann-Whitney test after assessment of their distribution using the Shapiro-Wilk test. Qualitative variables were tested using χ^2 or Fischer's exact test, as appropriate			
WA weeks of amenorrhea, ENT ear nose throat			
P<0.05 for all comparisons. Percentages may not sum to 100% due to rounding.			

infections (OR=1.42; 95% CI, 1.24–1.59) and in-hospital infections (OR=1.31; 95% CI, 1.09–1.59), compared with never-exposed pregnancies (Table 4). In exposed women who attained at least 24WA, maintaining the anti-TNF α during the third trimester was not associated with more complications (OR=0.93; 95% CI, 0.69–1.25) or infections during pregnancy (OR=0.95; 95% CI, 0.73–1.22), or with infections in the children (OR=1.14; 95% CI, 0.85–1.53). In steroid-naïve women, significantly more IBD relapses occurred in women who stopped anti-TNF α before 24WA (60/131, 45.8%) compared to those who continued anti-TNF α over 24WA (63/206, 30.6%, $p=0.005$). This difference remained in the multivariate analysis after adjustment for disease severity, age, IBD type and duration and concomitant 6-mercaptopurine use (aOR=1.98; 95% CI 1.25–3.15).

DISCUSSION

To our knowledge, this is the largest cohort of pregnancies in IBD women exposed to anti-TNF α with data linkage between mothers and their children. Our study suggests that exposure to anti-TNF α during pregnancy in women with IBD is associated with an increased risk of maternal complications, and particularly of infections. In contrast, no such risk was observed during the first year of life in children born to mothers exposed to anti-TNF α , even when treatment was pursued in the third trimester. The strength of this analysis is the vast quantity of data available in the French nationwide database, resulting in statistical power sufficient to reach conclusive findings as compared to previously published studies. This database has already been used to detect even small increased risks [25]. Few studies have assessed the risk of infection during pregnancy in women exposed to anti-TNF α . In a study by Julsgaard et al. [28], only women receiving adalimumab ($n=36$) or infliximab ($n=44$) were included. Although the study showed that the risk of infection was 2.7 times higher with the treatment combination of anti-TNF α and thiopurine compared with anti-TNF α alone, it did not allow for an assessment of the risk compared with patients not receiving anti-TNF α . In the paper by de Lima et al. [13], the control group included non-IBD non-anti-TNF α -treated women, and thus did not formally compare pregnancy outcomes in IBD mothers treated or not treated with anti-TNF α as we did in the present study.

Casanova et al. [19], did not find a significant increase in unfavorable global pregnancy outcomes, but it is more than likely that their results only failed to reach statistical significance because of the small sample size, as they included only 66 anti-TNF α -exposed and 318 non-exposed women. Interestingly, the increase in risk found in the Casanova study (OR=1.62, 95% CI, 0.92–2.87, $P=0.09$) was the same as that in our study (OR=1.45; 95% CI, 1.29–1.64). Because most cohort studies used a very small sample [29], even the meta-analyses lacked statistical power, as for example Mozaffari et al. [30], whose study included a total of only 1461 patients.

Our study does not support the recommendation to stop anti-TNF α at the beginning of the third trimester. This is one of the major inconsistencies in current guidelines, but we found no difference in the risk of complications between women treated during the third trimester and those who stopped anti-TNF α at, or before 24WA. In the prospective study by de Lima et al. [13], which included only 106 pregnant women exposed to anti-TNF α and 83 completed pregnancies, neither maternal nor birth outcomes varied according to the timing of anti-TNF α cessation during pregnancy [13]. This study suggested, although the difference was not statistically significant, that the relapse rate may be lower in women who stop anti-TNF α before 25 weeks, than in women who continue with the treatment (9.8% vs 15.6%, respectively, relative risk 0.79; 95% CI 0.42–1.51). This finding is unsurprising as only women in sustained remission at around 20 weeks gestation had permission to stop anti-TNF α at around week 25.

North American guidelines state that pregnant women with IBD on anti-TNF α maintenance therapy should continue treatment

Table 4 Subgroup analysis in women with a delivery term >24 weeks of amenorrhea: risk for overall maternal complications, infections, and in-hospital infections during pregnancy, and infectious risk (overall and in-hospital) for children during their first year of life

	Pregnant women (1073 women exposed versus 7523 non-exposed)			Children 0–1 year (716 exposed versus 4444 non-exposed)	
	Composite criterion ^a	All infections ^a	In-hospital infections only ^a	All infections children ^b	In-hospital infections children ^b
Exposure to anti-TNF α in 3rd trimester OR (95% CI)	1.66 [1.40–1.95]	1.42 [1.24–1.63]	1.31 [1.09–1.59]	0.89 [0.76–1.05]	0.85 [0.64–1.13]
Age at pregnancy OR (95% CI) (years)	0.99 [0.98–1.01]	1.01 [0.99–1.01]	0.99 [0.97–1.01]	0.99 [0.98–1.00]	0.98 [0.96–0.99]
Delivery <37 WA term OR (95% CI)	–	–	–	1.19 [0.98–1.45]	3.01 [2.33–3.88]
IBD type (CD vs UC (ref)) OR (95% CI)	1.01 [0.88–1.16]	1.05 [0.95–1.16]	0.98 [0.85–1.14]	0.98 [0.87–1.10]	1.03 [0.83–1.27]
IBD disease duration (months) OR (95% CI)	1.00 [0.99–1.00]	0.99 [0.99–1.00]	1.00 [0.99–1.00]	0.99 [0.99–1.00]	0.99 [0.99–1.00]
Severe disease (yes/ no (ref)) OR (95% CI)	2.95 [2.18–3.99]	1.63 [1.20–2.20]	1.35 [0.92–1.99]	1.04 [0.72–1.51]	1.35 [0.75–2.41]
Exposure to thiopurines OR (95% CI)	1.17 [0.99–1.38]	1.19 [1.05–1.35]	1.00 [0.86–1.54]	0.90 [0.78–1.05]	0.82 [0.62–1.08]
Disease relapse in 3rd trimester OR (95% CI)	1.40 [1.09–1.81]	1.82 [1.48–2.25]	1.15 [0.86–1.54]	1.32 [1.04–1.69]	1.54 [1.08–2.21]

WA weeks of amenorrhea, IBD inflammatory bowel disease, CD Crohn disease, UC ulcerative colitis
^aAdjusted for exposure to anti-TNF α at 3rd trimester, age at pregnancy, IBD type, IBD disease duration, disease severity, and exposure to thiopurines
^bAdjusted for exposure to anti-TNF α at 3rd trimester, age at pregnancy, term of delivery, IBD type, IBD disease duration, disease severity, and exposure to thiopurines
 Bold text indicates a statistically significant difference with a p-value less than 0.05 between exposed to anti-TNF α and non-exposed to anti-TNF α groups

(strong recommendation, very-low level of evidence), and that only selected pregnant women with a low risk of relapse of IBD and who have a compelling reason to discontinue anti-TNF α may do so at 22–24 weeks to minimize fetal exposure (conditional recommendation, very low level of evidence) [12].

We have shown that, for women on anti-TNF α at the beginning of the third trimester of pregnancy, pursuing treatment after 24 WA did not increase the risk of adverse events for the women or for their children. On the other hand, interrupting anti-TNF α during the third trimester was associated with a significant risk of IBD relapse during last trimester. These may give physicians a motive to prescribe anti-TNF α throughout pregnancy. One limitation of this finding is that relapse was only assessed by initiation of steroid treatment, the best surrogate marker in the absence of specific ICD-10 code for relapse. We may thus have underestimated the risk of relapse, in women who maintained anti-TNF α at the third trimester, if relapses were managed through treatment intensification, although it seems clinically quite unlikely.

In contrast to the uncertainty concerning the risk of anti-TNF α during pregnancy, it has been well established that active disease around conception increases the risk of disease relapse during pregnancy by more than 7-fold [7], and that IBD increases the risk of negative pregnancy outcomes by about twofold [31]. The benefits appear to outweigh the risks, despite the possible increased risk of maternal complications associated with the use of anti-TNF α during pregnancy, seeing as risk estimates for adverse pregnancy outcomes in women with active disease are much higher [31], and no signs of increased risks of adverse event was observed in the children. Moreover, a recent study conducted among 230 women

with IBD showed that women were willing to accept a 2% risk of birth defects, a 5% risk of loss of an unborn child, or a 15% risk of premature delivery to avoid a disease flare-up [32]. These results, which suggest that anti-TNF α are perceived as safe, combined with emerging data in favor of maintenance of anti-TNF α treatment throughout the pregnancy should lead to an increase in the proportion of women treated with anti-TNF α all through their pregnancies in the near future. It is therefore particularly important to obtain robust safety data from prospective studies on exposure during the last trimester.

It has been suggested [17], although not unanimously [13, 33, 34], that combination therapies during pregnancy may increase the risk of complications such as preterm birth (OR = 2.4; 95% CI 1.3–4.3) and any of a number of other pregnancy complication (OR = 1.7; 95% CI 1.0–2.2). In our study, exposure to thiopurines only increased the risk of infections during pregnancy. Moreover, we found that maintaining thiopurines over 24WA was safe in women exposed to anti-TNF α during the whole pregnancy (data not shown). These results have been cautiously interpreted, because they are based on a small group of women (175 women with a term >24 WA exposed to both anti-TNF α and thiopurines during pregnancy). Therefore, our study cannot help physicians to decide, as suggested by North American Guidelines [12], whether to switch certain patients to monotherapy (conditional recommendation, very low level of evidence). Prospective studies including only pregnant women treated with concomitant immune-modulators and biotherapies should be conducted to assess this safety question.

As linkage between mothers and children only became available in 2014, our infant population only matched 49.9% of the overall

pregnancies, but was exhaustive within the period. The absence of an increased risk of infection in children during the first year of life is very reassuring and builds on the findings of earlier, smaller studies [13, 17, 18]. However, there are individual reports of serious infections [35].

Our study has some limitations inherent to working on medico-administrative databases and the associated issues of confounding factors and bias. Disease severity is a key point in the accurate estimation of the risk in IBD, but seldom available due to lacking specific ICD-10 codes. As a surrogate we used a severity score which has been shown to predict, though only in CD, the risk of severe hospitalization [27]. This score does not truly predict disease activity, and consequently we may have overestimated the risk associated with anti-TNF α exposure. However, This score performed better for predicting the severity of hospitalization than the commonly used Charlson, or Elixhauser general comorbidity indexes [36, 37]. In the study by Casanova et al. [19], however, the frequency of a negative global pregnancy outcome was similar in pregnancies with inactive and active disease (28% vs. 27%, respectively), suggesting that disease status may not be a significant confounder. Sensitivity analyses performed without adjusting for the severity score [27], resulted in higher risks, with wider CIs, but no significant changes when compared with our primary results.

We defined steroid exposure as 3 or more deliveries during the pregnancy, which may have led to an underestimation of the exposure. The difference observed in steroid exposure between anti-TNF α -exposed and non-exposed women (6.5% vs 3.4%, $p < 0.001$) may therefore not reflect actual use and should be interpreted with caution. Exposure to steroids in our analyses was an independent risk factor for infections (aOR = 2.10; 95% CI, 1.71–2.57), but also protective for overall maternal complications (aOR = 0.58; 95% CI, 0.45–0.73). The benefit of steroids on pregnancy outcomes is well established. They are recognized for the prevention of recurrent miscarriages [38], or in the lung maturation process in case of premature delivery for infants [39], even if long-term neurological impairment has been suggested [40]. As miscarriage and premature delivery accounted for nearly 40% of pregnancy related complications in our study, this protective association is not surprising.

Use of anti-TNF α is known to increase the risk of infection, and physicians may therefore have been inclined to monitor women exposed to anti-TNF α more closely and report infectious events more accurately. This notoriety bias might have led to an overestimation of infection rates in the anti-TNF α exposed population. However, because the definition of community infections was based on out-of-hospital antibiotics prescriptions, it is likely that only confirmed or highly suspected infectious events have been captured in our analysis.

The question of an increased risk of infection solely due to anti-TNF α exposure, regardless of pregnancy status, may also be raised. In the TREAT registry, infliximab therapy was independently associated with an increased risk of serious infections (HR = 1.43, 95% CI 1.11–1.84) in over 6000 CD patients monitored for more than 5 years [41]. Contrary to our study, disease activity or use of concomitant treatments were not analyzed. On the contrary, in

the latest published Cochrane meta-analysis on the safety of biotherapies in autoimmune diseases, Singh et al. [42], did not detect an increased risk of serious infections in an analysis limited to IBD studies (pooled OR = 1.28; 95% CI 0.67–2.44). Their controversial results emphasize the need to assess the safety of anti-TNF α in the pregnant population specifically, and confirm the relevance of our study.

Another limitation of this study is the fact that well-known prognostic factors of IBD, such as smoking status, and pre-pregnancy Body Mass Index were either unavailable or absent from the SNIIRAM database. Further epidemiological studies adjusting for this type of missing data are needed to confirm our results.

CONCLUSION

Our study showed that exposure to anti-TNF α during pregnancy in women with IBD is associated with an increased overall risk for maternal complications, and more specifically infections. However, anti-TNF α appears to be safe for children born to exposed women, at least for the first year of life. Our results also strongly suggest that, when indicated during pregnancy, anti-TNF α treatment can be safely continued after 24 weeks gestation, because of an increased risk of relapse in case of anti-TNF α treatment cessation, without specific concern about the risk of overall complications or infection. Given the statistical power of our study, our results should be taken into account during discussions on treatment during pregnancy in women with IBD. Further prospective studies with a longer follow-up and that take into account outcomes in both the mother and child, and in specific populations like pregnant women given combined treatments, are needed to fully assess the safety of anti-TNF α during pregnancy. Such studies should lead to updated guidelines with a higher level of evidence.

CONFLICT OF INTEREST

Guarantor of the article: Maxime Luu.

Specific author contributions: ML: designed the study, performed analyses, drafted manuscript, and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. EB: data collection, performed analyses, critically revised manuscript. CM: critically revised manuscript. AB: critically revised manuscript. TD: critically revised manuscript. CQ: data collection, critically revised manuscript. MB: project initiator, designed the study, critically, and extensively revised manuscript.

Financial support: National Research Agency (ANR-15-CE36-0006-01) and Dijon- Bourgogne University Hospital (LUU-AOI-2016).

Potential competing interests: CM: lecture fees from MSD and Abbvie, invitations to congresses from MSD, Abbvie and Ferring. TD: lecture fees from AbbVie, invitations to congresses from Janssens, MB: expert and chairman of the committee for initial assessment on the risks and benefits of health products at the French Medicines Agency (Agence Nationale de la Sécurité des Médicaments et des Produits de Santé, ASNM).

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Disease control by anti-tumor necrosis factor- α (anti-TNF α) is currently a cornerstone in pregnancy outcome.
- ✓ Robust data on anti-TNF α maternal and fetal safety during pregnancy are lacking.
- ✓ The impact of pursuing anti-TNF α treatment over 24 weeks of amenorrhea (WA) is not well known.

WHAT IS NEW HERE

- ✓ Anti-TNF α treatment significantly increases the risk of overall maternal complications, especially infections, compared with non-exposed women.
- ✓ Interrupting anti-TNF α during pregnancy ≤ 24 WA increases the risk of disease relapse.
- ✓ Anti-TNF α appears safe for children up to 1 year of age, with no increased risk of infection.

REFERENCES

- Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012;142:46–54 e42. quiz e30
- Beaulieu DB, Kane S. Inflammatory bowel disease in pregnancy. *World J Gastroenterol*. 2011;17:2696–701.
- Boyd HA, Basit S, Harpoe MC, et al. Inflammatory bowel disease and risk of adverse pregnancy outcomes. *PLoS ONE*. 2015;10:e0129567.
- Stephansson O, Larsson H, Pedersen L, et al. Crohn's disease is a risk factor for preterm birth. *Clin Gastroenterol Hepatol*. 2010;8:509–15.
- Shand AW, Chen JS, Selby W, et al. Inflammatory bowel disease in pregnancy: a population-based study of prevalence and pregnancy outcomes. *BJOG*. 2016;123:1862–70.
- Abdul Sultan A, West J, Ban L, et al. Adverse pregnancy outcomes among women with inflammatory bowel disease: a population-based study from England. *Inflamm Bowel Dis*. 2016;22:1621–30.
- de Lima-Karagiannis A, Zelinkova-Detkova Z, van der Woude CJ. The Effects of Active IBD During Pregnancy in the Era of Novel IBD Therapies. *Am J Gastroenterol*. 2016; 111: 1305–12.
- Dominitz JA, Young JC, Boyko EJ. Outcomes of infants born to mothers with inflammatory bowel disease: a population-based cohort study. *Am J Gastroenterol*. 2002;97:641–8.
- Ban L, Tata LJ, Fiaschi L, et al. Limited risks of major congenital anomalies in children of mothers with IBD and effects of medications. *Gastroenterology*. 2014;146:76–84.
- Goeb V, Ardizzone M, Arnaud L, et al. Recommendations for using TNF α antagonists and French Clinical Practice Guidelines endorsed by the French National Authority for Health. *Joint Bone Spine*. 2013;80:574–81.
- van der Woude CJ, Ardizzone S, Bengtson MB, et al. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. *J Crohn's Colitis*. 2015;9:107–24.
- Nguyen GC, Seow CH, Maxwell C, et al. The Toronto consensus statements for the management of inflammatory bowel disease in pregnancy. *Gastroenterology*. 2016;150:734–57 e1.
- de Lima A, Zelinkova Z, van der Ent C, et al. Tailored anti-TNF therapy during pregnancy in patients with IBD: maternal and fetal safety. *Gut*. 2016;65:1261–8.
- Kane SV, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. *Am J Gastroenterol*. 2009;104:228–33.
- Seow CH, Leung Y, Vande Castele N, et al. The effects of pregnancy on the pharmacokinetics of infliximab and adalimumab in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;45:1329–38.
- Zelinkova Z, de Haar C, de Ridder L, et al. High intra-uterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. *Aliment Pharmacol Ther*. 2011;33:1053–8.
- Mahadevan U, Martin CF, Sandler RS, et al. PIANO: A 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. *Gastroenterology*. 2012;142:S149–S49.
- Nielsen OH, Loftus EV Jr., Jess T. Safety of TNF-alpha inhibitors during IBD pregnancy: a systematic review. *BMC Med*. 2013;11:174.
- Casanova MJ, Chaparro M, Domenech E, et al. Safety of thiopurines and anti-TNF-alpha drugs during pregnancy in patients with inflammatory bowel disease. *Am J Gastroenterol*. 2013;108:433–40.
- Guiddir T, Fremont ML, Triki TB, et al. Anti-TNF-alpha therapy may cause neonatal neutropenia. *Pediatrics*. 2014;134:e1189–93.
- Freud A, Beharier O, Walfisch A, et al. Maternal inflammatory bowel disease during pregnancy is not a risk factor for long-term morbidity of the offspring. *J Crohn's Colitis*. 2016;10:1267–72.
- Komaki F, Komaki Y, Micic D, et al. Outcome of pregnancy and neonatal complications with anti-tumor necrosis factor-alpha use in females with immune mediated diseases; a systematic review and meta-analysis. *J Autoimmun*. 2017;76:38–52.
- Quantin C, Benzenine E, Ferdynus C, et al. Advantages and limitations of using national administrative data on obstetric blood transfusions to estimate the frequency of obstetric hemorrhages. *J Public Health*. 2013;35:147–56.
- Hanf M, Quantin C, Farrington P, et al. Validation of the French national health insurance information system as a tool in vaccine safety assessment: application to febrile convulsions after pediatric measles/mumps/rubella immunization. *Vaccine*. 2013;31:5856–62.
- Lemaitre M, Kirchgessner J, Rudnichi A, et al. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. *J Am Med Assoc*. 2017;318:1679–86.
- Vohr BR, Tyson JE, Wright LL, et al. Maternal age, multiple birth, and extremely low birth weight infants. *J Pediatr*. 2009;154:498–503 e2.
- Ananthakrishnan AN, McGinley EL, Binion DG, et al. A novel risk score to stratify severity of Crohn's disease hospitalizations. *Am J Gastroenterol*. 2010;105:1799–807.
- Julsgaard M, Christensen LA, Gibson PR, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. *Gastroenterology*. 2016;151:110–9.
- Bortlik M, Machkova N, Duricova D, et al. Pregnancy and newborn outcome of mothers with inflammatory bowel diseases exposed to anti-TNF-alpha therapy during pregnancy: three-center study. *Scand J Gastroenterol*. 2013;48:951–8.
- Mozaffari S, Abdolghaffari AH, Nikfar S, et al. Pregnancy outcomes in women with inflammatory bowel disease following exposure to thiopurines and antitumor necrosis factor drugs: a systematic review with meta-analysis. *Hum Exp Toxicol*. 2015;34:445–59.
- Cornish J, Tan E, Teare J, et al. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut*. 2007;56:830–7.
- Fairchild A, Kushner T, Johnson F, et al. Women's preference for IBD medical therapy during pregnancy. *Gastroenterology*. 2017;152(5 Suppl 1):S84.
- Zelinkova Z, van der Ent C, Bruin KF, et al. Effects of discontinuing anti-tumor necrosis factor therapy during pregnancy on the course of inflammatory bowel disease and neonatal exposure. *Clin Gastroenterol Hepatol Assoc*. 2013;11:318–21.
- 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;40:363–73.
- Johnsson A, Avlund S, Grosen A, et al. Chicken pox infection in a three months old infant exposed in utero to Adalimumab. *J Crohn's Colitis*. 2013;7:e116–7.
- Charlson M, Szatrowski TP, Peterson J, et al. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47:1245–51.
- Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. *Med Care*. 1998;36:8–27.
- Kemp MW, Newnham JP, Challis JG, et al. The clinical use of corticosteroids in pregnancy. *Hum Reprod Update*. 2016;22:240–59.
- Travers CP, Clark RH, Spitzer AR, et al. Exposure to any antenatal corticosteroids and outcomes in preterm infants by gestational age: prospective cohort study. *BMJ*. 2017;356:j1039.
- Carson R, Monaghan-Nichols AP, DeFranco DB, et al. Effects of antenatal glucocorticoids on the developing brain. *Steroids*. 2016;114:25–32.
- Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT registry. *Am J Gastroenterol*. 2012;107:1409–22.
- Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev*. 2011;CD008794.