Pregnancy Outcomes Reported During the 13-Year TREAT Registry: A Descriptive Report

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OBJECTIVES: **We described pregnancy outcomes in Crohn's disease (CD) patients enrolled in the TREAT Registry who received infliximab before, or during pregnancy and those not treated with infliximab or any biologic agent.**

METHODS: **In the TREAT Registry (1999–2012), pregnancy outcomes were analyzed from maternal and paternal patients exposed to infliximab ≤365 days (gestational exposure), >365 days (pre-gestational exposure) of pregnancy outcome or without infliximab exposure (non-biologic exposed). "Healthy infants" were defined as those with no congenital abnormalities, neonatal complications (e.g., jaundice, prematurity, heart murmur, cortical vision/fine motor delay, cardiac failure, hemophilia, or torticollis), prolonged hospitalization, or those who received no special treatment. Disease activity and concomitant medications were also evaluated.**

RESULTS: **Overall, 92.3% (324/351) of pregnancies had known outcomes. The majority of both maternal pregnancies (92.6, 91.2, and 87.8%) and partner outcomes (92.7, 93.8, and 91.7%) resulted in live births of healthy infants across gestational, pre-gestational, and non-biologic exposure groups, respectively. Among these, rates of neonatal complications were low for both maternal (6.2, 7.0, and 8.5%), and partner outcomes (4.9, 0, and 0%) in gestational, pre-gestational, and non-biologic exposure groups, respectively. Among maternal pregnancies, numerically higher rates of spontaneous abortions were observed for the gestational exposure group than for the pre-gestational or non-biologic exposed groups.**

CONCLUSIONS: **The clinical condition of infants born to women with gestational infliximab exposure was similar to those without exposure. Although a lower live birth rate was reported among infliximab-exposed women, these patients had more severe CD and were more likely to have been exposed to immunosuppressives.**

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) that may negatively affect reproductive health.

Women with IBD whose disease is active during pregnancy have higher rates of adverse pregnancy outcomes, including miscarriage, preterm delivery, low birth weight, congenital abnormalities (CA), and caesarean section, than the general population [1–3]. Multiple studies have demonstrated that disease activity is the most important determinant of these negative outcomes [2, 4]. In a large retrospective study that assessed the relationship of pregnancy outcomes, IBD activity, and treatment in 298 pregnancies in 143 patients, major adverse pregnancy outcomes occurred far more frequently in patients with severe disease (35.7%) than inactive disease (4.9%) [3]. Accordingly, the use of effective and safe medical therapy to control inflammation is a critical part of

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management during pregnancy [5]. However, use of medication during pregnancy runs the potential risk of CAs and other fetal morbidities.

Although mesalamine formulations are generally regarded as safe in pregnancy [6], concern exists regarding the use of steroids and immunosuppressives [7, 8]. While the available data also suggest that tumor necrosis factor (TNF)-antagonists are safe in pregnancy [9–12], this experience is based upon a limited number of cases. The Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT™) Registry was discontinued in May 2012 and data collection continued until the final database closure in September 2012. We previously reported on the risks of mortality and serious infection, and malignancy at earlier time points in this registry [13, 14].

Here, we report the outcomes of this prospective observational analysis focusing on pregnancy outcomes among TNF-antagonist exposed patients and provide a descriptive summary of birth outcomes from pregnant women and pregnant partners of treated men which encompasses the 13-year duration of the TREAT Registry. This study is the longest duration prospective observational analysis performed evaluating pregnancy outcomes with biologic therapy in patients with IBD.

METHODS

Details of the TREAT Registry have been previously published [13–15]. Briefly, TREAT was a prospective, observational, multicenter, long-term registry that evaluated clinical safety outcomes in patients with CD in North America. More than half of the participants were treated with infliximab and the remainder with other agents. Approximately 350 gastroenterologists enrolled 6273 patients from 347 community (86%) and academic (14%) centers. Patients enrolled in the registry were treated at the discretion of their physicians. The design of the TREAT Registry was approved by the institutional review board at each participating site and all patients provided written informed consent.

Registry participants

TREAT was initiated in 1999 to examine the long-term safety outcomes of CD patients treated with infliximab in comparison to patients treated with non-biologic CD treatments in North America. Although not designed as a pregnancy registry, reported pregnancies led to interest in this post-hoc analysis of available pregnancy outcomes and experiences during the registry. To evaluate pregnancy outcomes in CD, we prospectively collected data on pregnant patients enrolled in the TREAT Registry.

Patients enrolled in TREAT had to have a diagnosis of CD and could not have been enrolled in any clinical trial concurrently. The pregnancy analyses reported herein are based on data collected for 6273 enrolled patients.

Registry evaluations

Patient data were collected at registry enrollment and then semi-annually (January, July). Enrolled patients were followed for at least 5 years. Patient demographic information, physicians' assessments of overall patient health and disease severity according to the American College of Gastroenterology (ACG) Guidelines (remission [no active disease], mild-to-moderate, moderate-to-severe, and fulminant) [16], medication use, adverse events, and the date and outcome of each infliximab infusion were documented. However, due to the design of the registry, neither disease activity for each trimester during pregnancy nor date of last menstrual period was recorded.

Throughout the registry period, the following measures were recorded: maternal and paternal age at pregnancy outcome; disease severity before, during, and after pregnancy; concomitant CD medication use; and the number of infliximab infusions before, during, and after pregnancy. Data were only recorded every 6 months for the pregnancies. All pregnancy outcomes including live births, spontaneous abortions, and elective abortions were reported. The pregnancy outcome data were date of delivery, spontaneous abortion, or elective termination. For all live births (full term or premature), the overall clinical condition of the infant was reported as healthy infant, congenital abnormality, neonatal complications (e.g., jaundice, prematurity, heart murmur, cortical vision/fine motor delay, cardiac failure, hemophilia, or torticollis), neonatal death, or stillbirth.

The term healthy infant was used to describe infants without neonatal complications, CAs, prolonged hospitalization, or who had not received any special treatment. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 11.1.

Data analysis

Pregnancy outcomes between July 1999 and September 2012 are reported herein. Pregnancy outcomes were classified as maternal exposure among treated women with CD and as partner outcomes (i.e., infants born to women whose partners were on infliximab at the time of conception). Patients who received at least one infliximab infusion were included in the infliximab-treated group. The infliximab-treated group was further subdivided into mutually exclusive groups of patients exposed to infliximab $\leq$365 days prior the pregnancy outcome date (gestational exposure group) and those exposed to infliximab >365 days before pregnancy outcome date (pre-gestational exposure group). Patients who received non-biologic CD treatments only, such as azathioprine, methotrexate, 6-mercaptopurine, prednisone, and antibiotics or narcotic analgesics, but not infliximab, were included in the non-biologic exposure group.

For both maternal pregnancies and partner outcomes, the influence of infliximab exposure on pregnancy and infant outcomes from women in the gestational exposure group were analyzed relative to the risk of those in the pre-gestational and non-biologic exposed groups with the use of the χ^2 test or Fisher's exact test as appropriate. No a priori sample size estimates were performed and no adjustment was made for multiple comparisons; accordingly, the nominal p-values reported should be interpreted with caution.

RESULTS

Patient disposition, characteristics, and treatment

Overall, 350 gastroenterologists enrolled a total of 6273 patients in the TREAT Registry from 1999–2004, and were followed through

2012. Among patients enrolled in the registry, 3440 received infliximab.

Overall, 351 pregnancies, 324 with known outcomes, were reported through the completion of the TREAT Registry (Fig. 1). Of these 324 pregnancies, 252 were maternal exposures; 99 with gestational exposure, 63 with pre-gestational exposure, and 90 with non-biologic exposure. Partner outcomes accounted for 72 pregnancies; 42 with gestational exposure, 17 with pre-gestational exposure, and 13 with non-biologic exposure.

Patients exposed to biologics other than infliximab (including adalimumab, alefacept, anti-gamma interferon, certolizumab, efalizumab, etanercept, natalizumab, sargramostim, and investigational biological agents) were excluded from all groups. No pregnancies were reported in these groups.

Maternal disease severity and concomitant medication use

Patients with non-biologic exposure had less severe disease at baseline (Table 1), and before, during, and after pregnancy (Fig. 2a–d). Pregnant women with gestational and pre-gestational exposure had greater disease activity during pregnancy than pregnant women with non-biologic exposure (Fig. 2b). In patients with gestational exposure, the overall number of infliximab infusions before and after pregnancy was greater than those received by patients with pre-gestational exposure (Table 2a). The median age of the mothers at baseline was 28.0, 25.5, and 28.0 years for patients in the gestational, pre-gestational, and non-biologic exposure groups, respectively (Table 1).

Maternal use of prednisone before (Fig. 3a) and during pregnancy (Fig. 3b) was more common for both the gestational exposure (21.3% and 26.3%, respectively) and the pre-gestational exposure groups (18.8% and 25.0%, respectively) than for patients with the non-biologic exposure (10.3%, $p = 0.144$ and 12.5%, $p = 0.048$, respectively). Immunosuppressive use during pregnancy was similar for pregnant women among exposure groups (33.3, 31.3, and 35.2%, for the gestational exposure, pre-gestational exposure, and non-biologic exposure groups, respectively; Fig. 3). In a substantial proportion of patients in the non-biologic exposure group, medication use continued throughout pregnancy with 59.1% receiving 5-ASAs, 35.2% receiving immunosuppressives, 12.5% receiving prednisone, 4.5% receiving antibiotics, and 4.5% receiving narcotic analgesics (Fig. 3b). During the TREAT registry, it was reported that 60 women stopped therapy before the third trimester. For these patients, across all exposure groups, 9 women reported a worsening of disease, 44 reported unchanged disease severities, and 7 women reported a decrease in disease severity after pregnancy (data on file).

Paternal disease severity and concomitant medication use

Patients with non-biologic exposure had less severe disease at baseline when compared with the pre-gestational and gestational exposure groups (Table 1). Patients with pre-gestational or non-biologic exposure were observed to have numerically lower disease activity before conception than patients with gestational exposure (Fig. 2d).

Paternal use of 5-ASAs and immunosuppressives was numerically higher before conception in the pre-gestational exposure group than in either the gestational exposure or non-biologic exposure groups (Fig. 3c). Use of prednisone and antibiotics before conception was higher in the gestational exposure group. Overall, the median number of infliximab infusions received by fathers before conception (3.0 in the gestational group, 1.0 in the pre-gestational group; Table 2b) were the same as those received by women before pregnancy (3.0 in the gestational group, 1.0 in the pre-gestational group; Table 2a). The median age of the fathers at baseline was 31.0, 27.0, and 31.0 years in the gestational, pre-gestational, and non-biologic exposure groups, respectively (Table 1).

Maternal birth outcomes

Birth outcomes were known for 93.4% (99/106) of pregnancies with gestational exposure, 95.5% (63/66) of pregnancies with pre-gestational exposure, and 84.9% (90/106) of pregnancies with non-biologic exposure (Table 3). Among pregnancies with gestational exposure, 81.8% (81/99) resulted in live births versus 91.1% (82/90) of pregnancies with non-biologic exposure. No significant difference was seen in the proportion of live

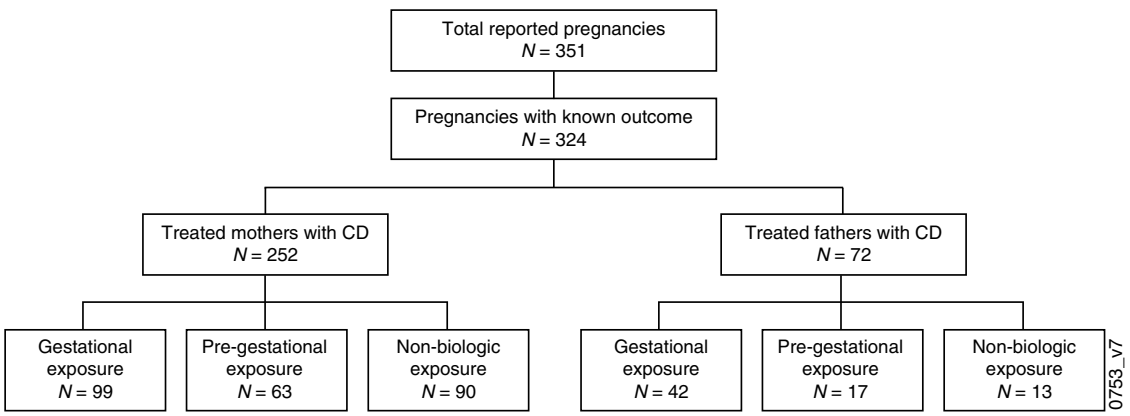

Fig. 1 TREAT maternal pregnancies and partner outcomes by exposure group. CD, Crohn's disease. Gestational exposure was defined as infliximab exposure ≤365 days before the pregnancy outcome date. Pregnancy outcome date is defined as the date of the delivery, spontaneous abortion, or elective termination. Pre-gestational exposure was defined as infliximab exposure >365 days before the pregnancy outcome date, including the year before registration

Table 1 Baseline characteristics of male and female patients with IBD[a]

Characteristics	Maternal treatment exposure			Paternal treatment exposure		
	Gestational[b] *N*=106	Pre-gestational[c] *N*=66	Non-biologic *N*=106	Gestational[b] *N*=42	Pre-gestational[c] *N*=18	Non-biologic *N*=13
Number of pregnancies	106	66	106	42	18	13
Baseline age (yrs)						
Mean (SD)	27.5 (5.5)	25.9 (4.7)	28.7 (5.4)	30.8 (5.7)	27.6 (2.9)	30.3 (5.9)
Median	28.0	25.5	28.0	31.0	27.0	31.0
(Min, max)	(18.0, 43.0)	(19.0, 39.0)	(18.0, 45.0)	(21.0, 46.0)	(22.0, 33.0)	(19.0, 39.0)
(25%, 75%)	(24.0, 31.0)	(22.0, 28.0)	(25.0, 32.0)	(27.0, 34.0)	(26.0, 30.0)	(27.0, 34.0)
Years with Crohn's disease						
Mean (SD)	6.1 (5.7)	5.9 (5.4)	6.6 (5.6)	7.5 (7.2)	7.5 (5.6)	8.3 (5.7)
Median	3.6	5.1	5.8	4.1	5.6	9.5
(Min, max)	(0.1, 27.7)	(0.0, 22.8)	(0.0, 22.3)	(0.0, 25.5)	(0.0, 19.1)	(0.1, 21.2)
(25%, 75%)	(2.0, 9.3)	(1.2, 8.1)	(1.7, 9.7)	(2.5, 11.5)	(3.3, 10.3)	(3.9, 10.6)
Disease severity, *N* (%)	105	66	102	41	18	13
Remission	15 (14.3)	10 (15.2)	44 (43.1)	8 (19.5)	3 (16.7)	8 (61.5)
Mild-moderate	60 (57.1)	37 (56.1)	55 (53.9)	25 (61.0)	12 (66.7)	4 (30.8)
Moderate-severe	30 (28.6)	18 (27.3)	3 (2.9)	8 (19.5)	3 (16.7)	1 (7.7)
Severe-fulminant	0	1 (1.5)	0	0	0	0
Medication use, N (%)[d,e]						
5-ASA	53 (50.0)	31 (47.0)	68 (64.2)	17 (40.5)	10 (55.6)	4 (30.8)
Immunosuppressive drugs	51 (48.1)	38 (57.6)	36 (34.0)	24 (57.1)	12 (66.7)	6 (46.2)
AZA	29 (27.4)	18 (27.3)	12 (11.3)	10 (23.8)	3 (16.7)	1 (7.7)
6-MP	16 (15.1)	18 (27.3)	23 (21.7)	14 (33.3)	8 (44.4)	5 (38.5)
Methotrexate	7 (6.6)	2 (3.0)	1 (0.9)	0	1 (5.6)	0
Cyclosporine	0	1 (1.5)	0	0	0	0
Prednisone	28 (26.4)	22 (33.3)	11 (10.4)	6 (14.3)	4 (22.2)	2 (15.4)
Infliximab	76 (71.7)	40 (60.6)	0	32 (76.2)	9 (50.0)	1 (7.7)
Antibiotics	16 (15.1)	13 (19.7)	14 (13.2)	7 (16.7)	3 (16.7)	0
Narcotic analgesics	9 (8.5)	7 (10.6)	2 (1.9)	2 (4.8)	0	0
Smoker, *N* (%)	23 (21.7)	15 (22.7)	17 (16.0)	6 (14.3)	4 (22.2)	3 (23.1)
Race/ethnicity, *N* (%)	106	66	106	42	18	13
White	96 (90.6)	60 (90.9)	99 (93.4)	39 (92.9)	17 (94.4)	13 (100.0)
Black	6 (5.7)	2 (3.0)	6 (5.7)	2 (4.8)	0	0
Hispanic	4 (3.8)	3 (4.5)	0	1 (2.4)	0	0
Other	0	1 (1.5)	1 (0.9)	0	1 (5.6)	0
Involved intestinal area, *N* (%)	106	66	104	40	18	13
Ileum Only	18 (17.0)	24 (36.4)	31 (29.8)	10 (25.0)	9 (50.0)	4 (30.8)
Colon Only	32 (30.2)	18 (27.3)	35 (33.7)	14 (35.0)	1 (5.6)	5 (38.5)
Ileum and colon	56 (52.8)	24 (36.4)	38 (36.5)	16 (40.0)	8 (44.4)	4 (30.8)
Prior surgery, *N* (%)	20 (18.9)	7 (10.6)	10 (9.4)	5 (11.9)	5 (27.8)	1 (7.7)

5-ASA 5-aminosalicylic acid, *6-MP* 6-mercaptopurine, *AZA* azathiopurine, *IBD* inflammatory bowel disease, *min* minimum, *max* maximum, *SD* standard deviation, *yrs* years

[a]All baseline data were collected at registry entry

[b]Gestational exposure was defined as infliximab exposure ≤365 days before the pregnancy outcome date. Pregnancy outcome date is defined as the date of the delivery, spontaneous abortion, or elective termination.

[c]Pre-gestational exposure was defined as infliximab exposure >365 days before the pregnancy outcome date, including the year before registration.

[d]Medication use was reported every 6 months.

[e]Medication use is reported at enrollment

births between gestational exposure and pre-gestational exposure groups (p=0.893). Spontaneous abortions were reported in 16.2% (16/106) of pregnant women with gestational exposure compared to 8.9% (8/106) of pregnant women with non-biologic exposure and 6.3% (4/66) in pregnant women with pre-gestational exposure (p=0.134 and p=0.762, respectively). Two elective abortions were reported for both gestational and pre-gestational exposure groups (p=0.168). No elective abortions were reported among women in the non-biologic exposure group. No significant differences were observed among exposure groups for the proportion of live births, or spontaneous or elective abortions (all $p>0.05$).

Live births resulted in healthy infants among 92.6% (75/81) of pregnancies with gestational exposure, 91.2% (52/57) of pregnancies with pre-gestational exposure, and 87.8% (72/82) of pregnancies non-biologic exposure ($p=0.522$ and $p=0.304$, respectively) (Table 3). Five CAs were noted (Table 3): one infant each with ectrodactyly (gestational exposure; positive family history, father with condition, no special treatment needed), small ventricular septal defect (pre-gestational exposure; no special treatment needed), Down syndrome (non-biologic exposure), diagnosis of a heart murmur detected after discharge (non-biologic exposure), and cortical vision delay and delayed development of fine motor skills (non-biologic exposure; infant received occupational therapy for fine motor skills). No significant differences ($p>0.05$) were observed among exposure groups for the proportion of healthy infants or CAs.

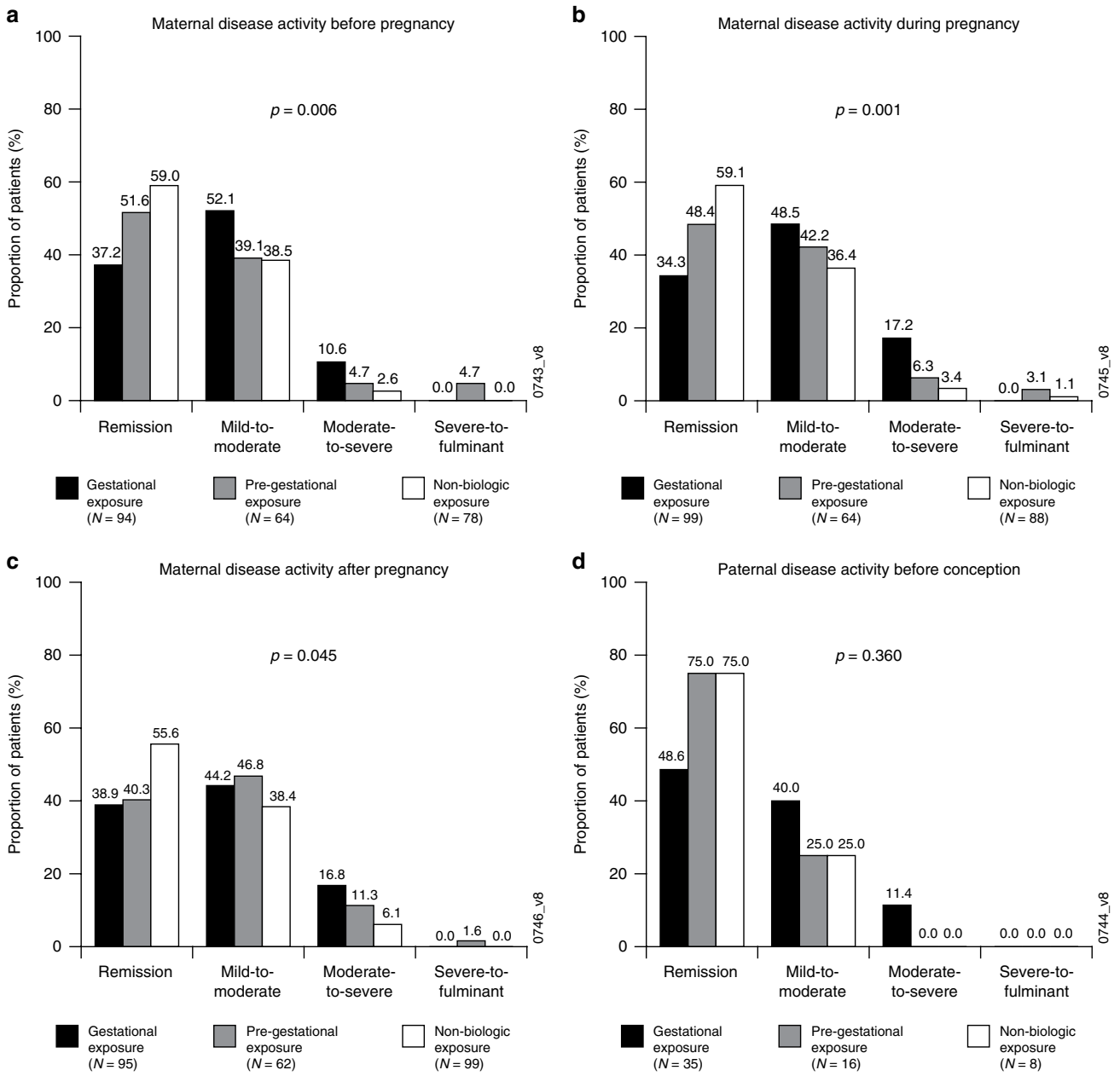

Fig. 2 Maternal and paternal disease activity

Table 2A Infliximab therapy; maternal exposure

	Maternal exposure		
	Gestational[a]	Pre-gestational[b]	Non-biologic
No. pregnancies	106	66	106
No. of infliximab infusions			
Before pregnancy[c]			
N	78	4	0
Mean (SD)	2.7 (0.9)	1.3 (0.5)	--
Median	3.0	1.0	--
(Min, max)	(1.0, 5.0)	(1.0, 2.0)	--
(25%, 75%)	(2.0, 3.0)	(1.0, 1.5)	--
Distribution, n *(%)*			
1	8 (10.3)	3 (75.0)	0
2	20 (25.6)	1 (25.0)	0
3	39 (50.0)	0	0
4	9 (11.5)	0	0
5	2 (2.6)	0	0
During pregnancy			
N	64	0	0
Mean (SD)	2.3 (1.1)	--	--
Median	2.0	--	--
(Min, max)	(1.0, 6.0)	--	--
(25%, 75%)	(1.0, 3.0)	--	--
Distribution, n *(%)*			
1	19 (29.7)	--	--
2	17 (26.6)	--	--
3	20 (31.3)	--	--
4	6 (9.4)	--	--
5	1 (1.6)	--	--
6	1 (1.6)	--	--
Post-partum[c]			
N	49	4	7
Mean (SD)	2.6 (1.1)	2.5 (0.6)	2.0 (0.8)
Median	3.0	2.5	2.0
(Min, max)	(1.0, 5.0)	(2.0, 3.0)	(1.0, 3.0)
(25%, 75%)	(2.0, 3.0)	(2.0, 3.0)	(1.0, 3.0)
Distribution, n *(%)*			
1	11 (22.4)	0	2 (28.6)
2	9 (18.4)	2 (50.0)	3 (42.9)
3	18 (36.7)	2 (50.0)	2 (28.6)
4	10 (20.4)	0	0
5	1 (2.0)	0	0

min minimum, *max* maximum, *no* number, *SD* standard deviation
[a]Gestational exposure was defined as infliximab exposure ≤365 days before the pregnancy outcome date. Pregnancy outcome date is defined as the date of the delivery, spontaneous abortion, or elective termination.
[b]Pre-gestational exposure was defined as infliximab exposure >365 days before the pregnancy outcome date, including the year before registration.
[c]If a pregnancy occurred in January or July, the third 6-month reporting interval prior to the outcome interval would be considered the "before pregnancy" interval.

Five (4.7%, 5/81) infants with gestational exposure had a prolonged hospital stay after delivery compared with 12 (11.3%, 12/82) infants with non-biologic and five (7.6%, 5/57) infants with pre-gestational exposure ($p > 0.05$ for all comparisons; Table 3).

Eleven preterm births were reported in the maternal pregnancy group (Table 4). Of these 11 births, 4 were reported with gestational exposure, 2 with pre-gestational exposure, and the other 5 with non-biologic exposure. The mean (SD) age of the mothers at the time of pre-term birth was 33.0 (3.7) years and the range was from 28.0–39.0. Common concomitant CD medications included mesalamine, azathioprine, and antibiotics.

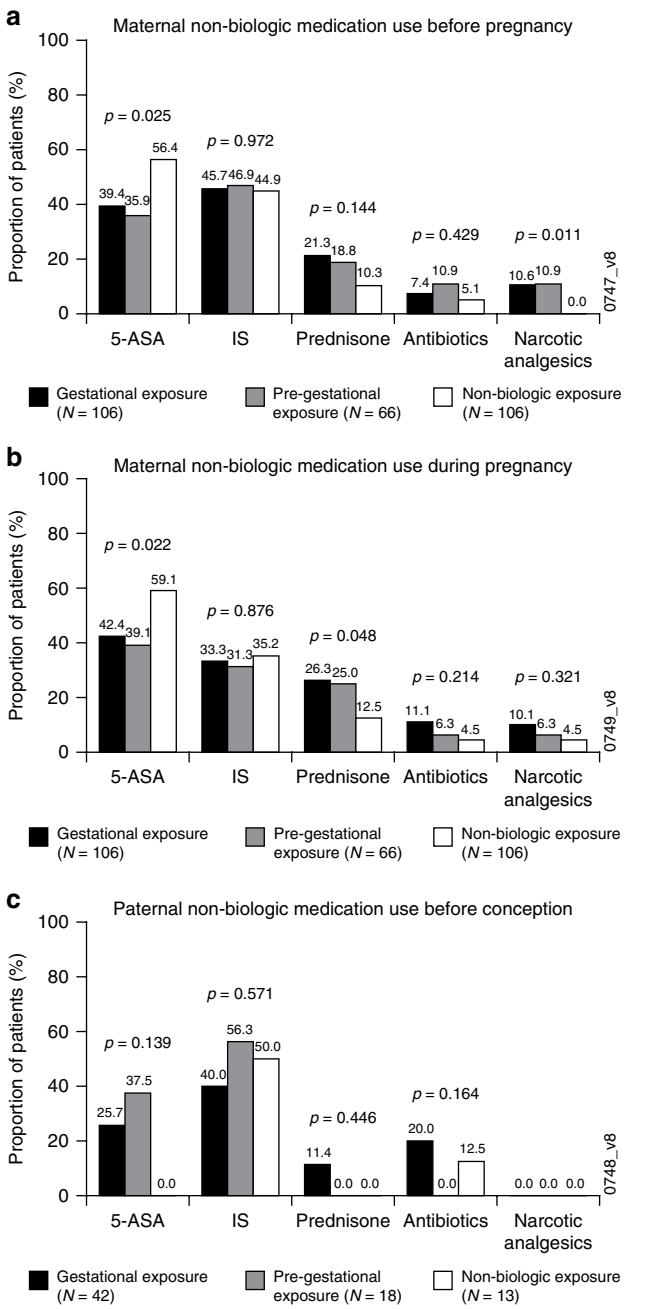

Fig. 3 *CD* Crohn's disease, *5-ASA* 5-aminosalicyclic acid, IS immunosuppresive Maternal and paternal non-biologic CD medication use during and around pregnancy

Table 2B Infliximab therapy; paternal exposure before conception

	Gestational[a] *N*=42	Pre-gestational[b] *N*=18	Non-biologic *N*=13
No. of pregnancies	42	18	13
No. of infliximab infusions			
N	25	1	0
Mean (SD)	2.6 (0.9)	1.0 (0.0)	--
Median	3.0	1.0	--
(Min, Max)	(1.0, 4.0)	(1.0, 1.0)	--
(25%, 75%)	(2.0, 3.0)	(1.0, 1.0)	--
Distribution, n (%)	25	1	--
1	3 (12.0)	1 (100.0)	--
2	8 (32.0)	0	--
3	11 (44.0)	0	--
4	3 (12.0)	0	--
5	0	0	--

min minimum, *max* maximum, *no* number, *SD* standard deviation.
[a]Gestational exposure was defined as infliximab exposure ≤365 days before the pregnancy outcome date. Pregnancy outcome date is defined as the date of the delivery, spontaneous abortion, or elective termination.
[b]Pre-gestational exposure was defined as infliximab exposure >365 days before the pregnancy outcome date, including the year before registration.

Partner birth outcomes

Pregnancy outcomes were known for all partner pregnancies except for one pre-gestational exposure pregnancy (Table 3). Live births were recorded in 97.6% (41/42) pregnancies with gestational exposure, in 94.1% (16/17) pregnancies with pre-gestational exposure, and 92.3% (12/13) pregnancies with non-biologic exposure. Spontaneous abortions accounted for the other known outcomes, one each with gestational exposure, pre-gestational exposure, and non-biologic exposure. No significant differences ($p > 0.05$) were observed among exposure groups for the proportion of live births, or spontaneous or elective abortions.

Live births resulted in healthy infants among 92.7% (38/41) of the gestational exposure pregnancies compared with 93.8% (15/16) of pre-gestational exposure pregnancies and 91.7% (11/12) of non-biologic exposure pregnancies (Table 3). Three CA were observed: one infant in the gestational exposure group, hemophilia (unknown family history for hemophilia; treatment with clotting factor infusion); one infant in the pre-gestational exposure group with a congenital malformation of a laryngeal cyst and one vocal cord; and one infant in the non-biologic exposure group with a case of torticollis (no additional treatment needed). No significant differences ($p > 0.05$) were observed among exposure groups for the proportion of healthy infants or CAs.

Three (7.1%) infants with gestational exposure required extended hospitalizations compared with two (15.4%) infants with non-biologic exposure ($p > 0.05$ for all comparisons; Table 3).

One preterm birth was reported in the paternal gestational exposure group (Table 4). The father's age at the time of per-term birth was 31 years and at baseline received azathioprine, mesalamine, antibiotics, and 8 infusions of infliximab. The infant was born healthy at 35 weeks and 6 days and hospitalization was not prolonged.

DISCUSSION

Overall, 92.3% of pregnancies reported in the TREAT Registry had known outcomes. The majority of both maternal pregnancies and partner outcomes resulted in live births of healthy infants across exposure groups (gestational, pre-gestational, and non-biologic). Among these, rates of neonatal complications were low for both maternal and partner outcomes across exposure groups. Among maternal pregnancies, higher rates of spontaneous abortions were observed for the gestational exposure than for pre-gestational or non-biologic exposed groups, but not for partner outcomes.

For both maternal pregnancies and partner outcomes, disease course remained mostly consistent throughout pregnancy overall. Pregnancy outcomes were favorable with no sign of harmful effects of biologics on the outcome of pregnancy for those mothers requiring continued treatment throughout pregnancy.

In a recent retrospective study of 1220 births in women with CD, it was observed that treatment with thiopurines, independent of disease activity, was associated with increased risk of adverse pregnancy outcomes, such as stillbirth, growth restrictions, and preterm birth [17], while other studies have shown no difference in rates of preterm birth between patients receiving thiopurines and those receiving TNF antagonists [18, 19] A large, US-based, pregnancy registry, of IBD patients, Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO), found that the use of TNF antagonists was not associated with increased congenital anomalies, pre-term births, or other adverse events, although TNF antagonists in combination with a thiopurine increased risks for pre-term birth [20]. More recently, a report from the PIANO registry showed that there was a trend towards preterm birth with the use of corticosteroids in pregnant patients with IBD [21].

In the TREAT Registry, the percentage of pregnant women with gestational-exposure pregnant women with moderate-to-severe disease activity [16] during pregnancy was increased compared with the period before pregnancy and remained elevated postpartum. This observation may reflect more severely active disease among pregnant women with gestational exposure compared to those with non-biologic exposure. Also, a lower rate of remission was observed among patients with gestational exposure during pregnancy compared with before or after pregnancy, further suggesting a more severe disease state in these women. Since women with increased disease severity are more likely to require continued treatment throughout pregnancy and combination therapy with thiopurines and concomitant corticosteroids, it is difficult to separate pregnancy outcomes that may be due to disease activity or medication use.

Taken together, the results presented here, in addition to the work of others, suggest that disease activity may play an important role on pregnancy outcome in CD patients. Interestingly, in this analysis, infants born to pregnant women with gestational expo-

Table 3 Birth Outcomes

	Maternal treatment exposure					Paternal treatment exposure				
	Gestational[a]	Pre-gestational[b]	*p*-value[c] for Pre-gestational vs. gestational	Non-biologic	*p*-value[c] for gestational vs. non-biologic	Gestational[a]	Pre-gestational[b]	*p*-value[c] for pre-gestational vs. gestational	Non-biologic	*p*-value[c] for gestational vs. non-biologic
Number of pregnancies, *N*	106	66	--	106	--	42	18	--	13	--
Known outcome, *n* (%)	99 (93.4)	63 (95.5)	0.032	90 (84.9)	0.047	42 (100.0)	17 (94.4)	>0.999F	13 (100.0)	--
Live birth, *n* (%)	81 (81.8)	57 (90.5)	0.893	82 (91.1)	0.064	41 (97.6)	16 (94.1)	>0.999F	12 (92.3)	0.420F
Spontaneous abortion, *n* (%)	16 (16.2)	4 (6.3)	0.762F	8 (8.9)	0.134	1 (2.4)	1 (5.9)	>0.999F	1 (7.7)	0.420F
Elective Abortion, *n* (%)	2 (2.0)	2 (3.2)	0.168F	0	0.498F	--	--	--	--	--
Overall clinical condition, *N*	81	57	--	82	--	41	16	--	12	--
Healthy infants, *n* (%)	75 (92.6)	52 (91.2)	0.522	72 (87.8)	0.304	38 (92.7)	15 (93.8)	>0.999F	11 (91.7)	>0.999F
Congenital abnormality, *n* (%)	1 (1.2)	1 (1.8)	0.644	3 (3.7)	0.620F	1 (2.4)	1 (6.3)	>0.999F	1 (8.3)	0.405F
Neonatal problem,[d] *n* (%)	5 (6.2)	4 (7.0)	--	7 (8.5)	--	2 (4.9)	0	--	0	--
Prolonged hospitalization, *n* (%)	5 (4.7)	5 (7.6)	0.253	12 (11.3)	0.060	3 (7.1)	0	0.188F	2 (15.4)	0.325F

F Fisher's exact test
[a]Gestational exposure was defined as infliximab exposure ≤365 days before the pregnancy outcome date. Pregnancy outcome date is defined as the date of the delivery, spontaneous abortion, or elective termination.
[b]Pre-gestational exposure was defined as infliximab exposure >365 days before the pregnancy outcome date, including the year before registration.
[c]Based on the χ^2 test unless specified otherwise.
[d]Defined as any adverse event at birth other than congenital abnormalities.

sure had numerically lower neonatal complications compared to infants born to women with pre-gestational or non-biologic exposure. This finding may highlight the importance of maintaining better control of disease symptoms during pregnancy.

Due to the unavailability of the doses and duration of immunosuppressive and corticosteroid use and the small number of adverse birth outcomes in the TREAT Registry, the relationship between the use of immunosuppressives or corticosteroids during pregnancy and adverse pregnancy outcomes could not be analyzed. In this TREAT cohort, we observed approximately one-third of women receiving immunosuppressives during pregnancy compared to approximately 45% receiving immunosuppressives before pregnancy. Further, an increased number of pateints with gestational and pre-gestational exposure patients were treated with prednisone during pregnancy compared to patients with non-biologic exposure. This finding supports the observation that more severe disease at baseline may require treatment with corticosteroids to control disease activity and even disease flares during pregnancy.

A lower rate of live births was reported among women with gestational infliximab-exposure in the TREAT Registry as compared to women with non-biologic exposure. This result may be subject to a reporting bias as more complete data are available for the gestational exposure group compared to women with non-biologic exposure. Despite the observed numerically lower rate of live births reported, the rates of spontaneous or elective abortions reported in TREAT do not show a significant difference between patients treated with infliximab during gestation and those who did not receive infliximab, and are consistent with data from the PIANO registry [22] and the US general population [23].

Table 4 Pre-term births

Parental age at birth	Gestational age at delivery	Medications	Baseline smoking status	Complications	Last known infliximab dose
Maternal pregnancy					
Gestational exposure					
37 years	34 weeks	Infliximab, mesalamine	Yes	Cesarean section with intrauterine growth restriction and pre-eclampsia. Infant experienced neonatal jaundice and methicillin-resistant Staphyloc occus aureus infection requiring prolonged hospitalization.	~12 days prior to delivery date
39 years	30.5 weeks	Infliximab	No	Pre-term birth of twins. Infants had neonatal complications due to twin-to-twin transfusion syndrome. Hospitalization was prolonged due to ventilation and a blood transfusion for one infant.	~7 months prior to delivery date
35 years	Unknown	Infliximab	Unknown	Healthy infant, no prolonged hospitalization or special treatment.	~1 month prior to delivery date
29 years	~34.5 weeks	Infliximab, antihistamine, acetaminophen, prednisone	Unknown	Prolonged hospitalization due to under-developed lungs.	~8 months prior to delivery date
Pre-gestational exposure					
28 years	Unknown	No infliximab, mesalamine, prednisone, antibiotics	Unknown	No special treatment or prolonged hospitalization.	6 years prior to delivery date
34 years	34 weeks	No infliximab, azathioprine, mesalamine, prednisone	No	Infant was hospitalized in the neonatal intensive care unit.	Dates unknown
Non-biologic exposure					
Unknown	Unknown	Non-infliximab exposure	Unknown	Infant had respiratory apnea which resolved upon discharge.	N/A
29 years	Unknown	Non-infliximab exposure	Yes	Infant had prolonged hospitalization due to temperature regulation.	N/A
35 years	Unknown	Non-infliximab exposure	Yes	Infant had prolonged hospitalization due to birth weight.	N/A
32 years	32 weeks	Non-infliximab exposure	Yes	Infant had neonatal complications in the context of poor fetal growth, decreased fetal movement, oligohydroamnos, 8 percentile and nuchal cord. The infant was doing well at 4 months with no abnormalities and progressing nicely.	N/A
35 years	35 weeks	Non-infliximab, exposure azathioprine	No	Pre-term birth of triplets by cesarean section: Infant 1 had slight respiratory distress, immature thermoregulation, and apnea of premature breathing. Infant 2 was discharged status post hemolytic crisis of undetermined etiology, reticulosis, and hyperbilirubin. Infant 3 had jaundice. The infants were reported as doing well and have recovered from the conditions noted.	N/A
Partner outcomes					
Gestational exposure					
31 years, partner pregnancy	35 weeks, 6 days	Infliximab-treated father	Unknown	Infant was healthy and hospitalization was not prolonged.	11 months prior to delivery date

N/A not applicable

The overall clinical condition of infants in TREAT was similar among all exposure groups for maternal pregnancies and partner outcomes. The rate of CAs reported in TREAT was similar to that of the general US population (28.9 per 1000 live births) [24], and similar rates of neonatal complications were observed among the maternal pregnancies and partner outcomes. Interestingly, a lower rate of prolonged hospitalizations was observed in maternal pregnancies and partner outcomes with gestational infliximab exposure compared with non-biologic exposure. This may be due to closer monitoring of biologic-exposed pregnancies in general; however, no definite conclusions can be drawn from these results.

Limited conclusions can be drawn from the paternal disease activity data in TREAT due to low numbers of treatment-exposed

pregnancies and missing date on the last menstrual period of the partner/surrogate.

One major limitation of this analysis was that the TREAT Registry was not designed to be a pregnancy registry or to evaluate gestational or birth outcomes. Therefore, the date of the mother's last menstrual period and exact dates of spontaneous/elective abortions were not recorded and broad categories were used to classify infliximab exposure relative to pregnancy outcomes. Additionally, infliximab drug concentrations in the mothers and in the newborn infants, and gestational smoking and concomitant medications (other than IBD medications during pregnancy) were not available. Many other medications, some of which are over the counter such as aspirin, non steroidal anti-inflammatory drugs, and other agents that are prescription medications, have been recognized as being teratogenic, although these data were not available from TREAT so no additional conclusions may be drawn from this population. Of note, 7 women are indicated as having received methotrexate within a year, although based on the limits of data collection in TREAT, the exact dates were not known. It is possible that these women discontinued methotrexate before or during pregnancy.

It has been suggested that TNF-antagonist therapy, including infliximab, may not pose a high risk during pregnancy, at least for short-term (ie, before the third trimester) use [25, 26]. Additionally, the Toronto Consensus statement suggested that TNF-antagonist therapy is associated with a low risk of adverse pregnancy outcomes, and that the short-term benefits of maintaining remission (especially in patients on TNF antagonist therapy) are likely to outweigh the potential risks to the fetus [27]. Although the TREAT Registry was not designed to be a pregnancy registry and lacks the ability to track infants after birth, careful examination of neonatal complications (ie, miscarriages and /infancy disorders) reported during the 13-year, real-world setting of the TREAT Registry do not suggest a relationship between infliximab exposure and adverse pregnancy outcomes.

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CONFLICT OF INTEREST

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Active Crohn's disease and ulcerative colitis may negatively affect reproductive health.
- ✓ Additional data are needed on TNF-antagonist use during pregnancy and effect on birth outcomes.

WHAT IS NEW HERE

- ✓ Pregnancy outcomes were recorded during the 13-year duration of the TREAT Registry.
- ✓ Represents the longest duration prospective analysis evaluating pregnancy outcomes in IBD patients receiving biologic therapy.
- ✓ TREAT Registry data does not suggest a relationship between infliximab exposure and adverse pregnancy outcomes.

REFERENCES

1. Kammerlander H, Nielsen J, Kjeldsen J, et al. The effect of disease activity on birth outcomes in a nationwide cohort of women with moderate to severe inflammatory bowel disease. Inflamm Bowel Dis. 2017;23:1011–8.
2. 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.
3. Mountifield RE, Prosser R, Bampton P, et al. Pregnancy and IBD treatment: this challenging interplay from a patients' perspective. J Crohns Colitis. 2010;4:176–82.
4. Bortoli A, Pedersen N, Duricova D, et al. Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom study, 2003-2006. Aliment Pharmacol Ther. 2011;34:724–34.
5. Sheibani S, Mahadevan U. Editorial: Are thiopurines and anti-TNFalpha agents safe to use in pregnant patients with inflammatory bowel disease? Am J Gastroenterol. 2013;108:441–3.
6. Mottet C, Vader JP, Felley C, et al. Appropriate management of special situations in Crohn's disease (upper gastro-intestinal; extra-intestinal manifestations; drug safety during pregnancy and breastfeeding): results of a multidisciplinary international expert panel-EPACT II. J Crohns Colitis. 2009;3:257–63.
7. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genet. 1999;86:242–4.
8. Gur C, Diav-Citrin O, Shechtman S, et al. Pregnancy outcome after first trimester exposure to corticosteroids: a prospective controlled study. Reprod Toxicol. 2004;18:93–101.
9. Katz JA, Antoni C, Keenan GF, et al. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. Am J Gastroenterol. 2004;99:2385–92.
10. Deepak P, Stobaugh DJ. Maternal and foetal adverse events with tumour necrosis factor-alpha inhibitors in inflammatory bowel disease. Aliment Pharmacol Ther. 2014;40:1035–43.
11. Khan N, Asim H, Lichtenstein GR. Safety of anti-TNF therapy in inflammatory bowel disease during pregnancy. Expert Opin Drug Saf. 2014;13:1699–708.
12. Chaparro M, Gisbert JP. Successful use of infliximab for perianal Crohn's disease in pregnancy. Inflamm Bowel Dis. 2011;17:868–9.
13. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT Registry. Clin Gastroenterol Hepatol. 2006;4:621–30.
14. Lichtenstein GR, Feagan BG, Cohen RD, et al. Drug therapies and the risk of malignancy in Crohn's disease: results from the TREAT Registry. Am J Gastroenterol. 2014;109:212–23.
15. 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.
16. Hanauer SB, Sandborn W. Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol. 2001;96:635–43.
17. Broms G, Granath F, Linder M, et al. Birth outcomes in women with inflammatory bowel disease: effects of disease activity and drug exposure. Inflamm Bowel Dis. 2014;20:1091–8.
18. 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.
19. Gisbert JP. Safety of immunomodulators and biologics for the treatment of inflammatory bowel disease during pregnancy and breast-feeding. Inflamm Bowel Dis. 2010;16:881–95.
20. Mahadevan U, McConnell RA, Chambers CD. Drug safety and risk of adverse outcomes for pregnant patients with inflammatory bowel disease. Gastroenterology. 2017;152:451–62 e2.
21. Lin K, Martin CF, Dassopoulos T, et al. 2 Pregnancy outcomes amongst mothers with inflammatory bowel disease exposed to systemic corticosteroids: results of the PIANO registry. Gastroenterology. 2014;146:S-1.
22. 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:S-149.
23. Ventura SJ, Abma JC, Mosher WD, et al. Estimated pregnancy rates by outcome for the United States, 1990-2004. Natl Vital Stat Rep. 2008;56:1–25. 28
24. Parker SE, Mai CT, Canfield MA, et al. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. Birth Defects Res A Clin Mol Teratol. 2010;88:1008–16.
25. Androulakis I, Zavos C, Christopoulos P, et al. Safety of anti-tumor necrosis factor therapy during pregnancy in patients with inflammatory bowel disease. World J Gastroenterol. 2015;21:13205–11.
26. O'Donnell S, O'Morain C. Review article: use of antitumour necrosis factor therapy in inflammatory bowel disease during pregnancy and conception. Aliment Pharmacol Ther. 2008;27:885–94.
27. Nguyen GC, Seow CH, Maxwell C, et al. The Toronto Consensus Statements for the management of inflammatory bowel disease in pregnancy. Gastroenterology. 2016;150:734–757.e1.