Anti-TNF Therapy in Pregnant Women With Inflammatory Bowel Disease: Effects of Therapeutic Strategies on Disease Behavior and Birth Outcomes

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Background: Active inflammatory bowel disease (IBD) adversely affects pregnancy outcomes. Little is known about the risk of relapse after stopping anti–tumor necrosis factor (anti-TNF) treatment during pregnancy. We assessed the risk of relapse before delivery in women who discontinued anti-TNF treatment before gestational week (GW) 30, predictors of reduced infant birth weight, a marker associated with long-term adverse outcomes, and rates and satisfaction with counseling.

Methods: Pregnant women with IBD receiving anti-TNF treatment were prospectively invited to participate in an electronic questionnaire carried out in 22 hospitals in Denmark, Australia, and New Zealand from 2011 to 2015. Risk estimates were calculated, and birth weight was investigated using *t* tests and linear regression.

Results: Of 175 women invited, 153 (87%) responded. In women in remission, the relapse rate did not differ significantly between those who discontinued anti-TNF before GW 30 (1/46, 2%) compared with those who continued treatment (8/74, 11%; relative risk, 0.20; 95% confidence interval [CI], 0.02 to 1.56; $P = 0.08$). Relapse ($P = 0.001$) and continuation of anti-TNF therapy after GW 30 ($P = 0.007$) were independently associated with reduced mean birth weight by 367 g (95% CI, 145 to 589 g; relapse) and 274 g (95% CI, 77 to 471 g; anti-TNF exposure after GW 30). Of 134 (88%) women who received counseling, 116 (87%) were satisfied with the information provided.

Conclusions: To minimize fetal exposure in women in remission, discontinuation of anti-TNF before GW 30 seems safe. Relapse and continuation of anti-TNF therapy after GW 30 were each independently associated with lower birth weight, although without an increased risk for birth weight <2500 g. Most women received and were satisfied with counseling.

Key Words: anti–tumor necrosis factor alpha, counseling, inflammatory bowel disease, pregnancy, pregnancy outcome

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INTRODUCTION

Anti–tumor necrosis factor α (anti-TNF) drugs are used early in the course of aggressive inflammatory bowel disease (IBD). The peak age of disease onset in women is during the fertile period.[1–3] Therefore, women with IBD on anti-TNF treatment may consider pregnancy.

To ensure remission throughout pregnancy, the guidelines from the American Gastroenterological Association recommend anti-TNF treatment throughout pregnancy or third-trimester dosing.[3] For women in remission, the guidelines from the European Crohn's and Colitis Organisation recommend stopping infliximab and adalimumab treatment in the middle of the second trimester to minimize fetal exposure.[2] Data regarding risk of relapse in patients who stop anti-TNF during pregnancy are sparse and conflicting.[4–6] It remains controversial if and when anti-TNF treatment should be stopped during pregnancy.

The risks of adverse pregnancy outcomes after anti-TNF exposure in utero are similar to those in nonexposed pregnancies.[1–3] Although TNF-α signaling may be involved in neonatal growth, no study has investigated its influence on birth weight controling for disease activity and other predictors of birth weight.[7, 8]

Pregnant women with IBD often have significant concerns regarding the impact of IBD therapy on pregnancy outcomes.[9–11] Counseling improves adherence to medical therapy and reduces risk of relapse during pregnancy.[12–14] The impact of the provision of counseling on patient satisfaction and residual knowledge needs among women with IBD who were exposed to anti-TNF during pregnancy has not been described.

The present multinational cohort study of pregnant women with IBD who received anti-TNF therapy during pregnancy had 2 general aims. First, it aimed to investigate strategies of anti-TNF therapy, specifically discontinuation of anti-TNF before gestational week (GW) 30 during pregnancy, and their association with disease relapse in the third trimester of pregnancy and neonatal birth outcomes. Second, it aimed to address the use of and satisfaction with counseling and its influence over disease outcomes and attitudes toward anti-TNF therapy in pregnancy.

METHODS

Study Design and Study Population

This was an international prospective multicenter cohort-based patient survey. Pregnant women with IBD who received treatment with infliximab or adalimumab during pregnancy were recruited from 22 referral hospitals in Denmark, Australia, and New Zealand from December 2011 to December 2015. Multiple pregnancies (ie, twins, triplets, or more) were excluded because these are associated with an increased risk of adverse outcomes for reasons unrelated to IBD. If a woman gave birth to a singleton more than once during the study period, all pregnancies were included as independent events.

Development of the Pregnancy Questionnaire

A structured online questionnaire was specifically developed by M.J., L.A.C., and S.J.B. using the software package Survey Monkey. The English questionnaire was tested for

comprehension in 7 women with IBD from the study population. Answers and comments were evaluated by an expert consensus panel consisting of 4 Australian and 3 Danish gastroenterologists, and this led to only minor changes in the final design. The English version was directly translated from English to Danish by M.J. The Danish translation and the original English version were reviewed by an expert consensus panel consisting of 3 Danish gastroenterologists, resulting in minor changes in the Danish questionnaire, which was subsequently tested for comprehension in 5 women with IBD from the study population. Answers and comments to the questionnaire were evaluated by the Danish expert consensus panel, which only led to minor changes in the final design of the questionnaire.

Self-Reported Data From Pregnant Women With IBD

All eligible women were asked to complete the online questionnaire no later than 2 weeks after their estimated due date. Electronic reminders including the link to the questionnaire were sent twice with 14 days' interval. The questionnaire covered detailed questions regarding demographic, disease, medical treatment, complications during pregnancy, birth, neonatal details, and counseling. There was no structured process with counseling. It was provided on an individual basis by the treating gastroenterologist. The participant was instructed to state if she was in remission or had experienced a relapse in IBD resulting in increased medical treatment during pregnancy. Two previous population-based pregnancy and postpartum studies that used the same definition of relapse as in the present study found that patient-reported relapse in pregnancy was consistent with disease activity scores calculated by the physicians.[15, 16]

Maternal obesity before pregnancy, a known factor for adverse pregnancy outcome, was defined as a body mass index (BMI) ≥30 kg/m^2.[5, 17] Small for gestational age (SGA) was defined as a child with a birth weight of >2 SD below the mean for children of similar gestational age, according to the reference curve of estimated fetal growth.[5] "Low birth weight" was defined as a child with a birth weight <2500 g, and "preterm" as birth at <37 weeks of gestation.[5] Apgar scores <7 at 5 minutes were considered low.[5] Congenital malformations were defined as structural or functional anomalies that were present at the time of birth, according to World Health Organization (WHO) criteria.[5]

Statistical Analysis

Frequency tables of major study variables were constructed for the total population and separately for adalimumab- and infliximab-treated women, for the Danish and Australian/New Zealand cohorts, and duration of anti-TNF treatment in pregnancy (≤GW 30 vs >GW 30), respectively. Pearson's chi-square and Fisher exact tests were used for the comparison of these groups. Two-sample *t* tests of major study variables were constructed by type of anti-TNF drug. Relative risks (RRs) with associated 95% confidence intervals (CIs) were used to describe relapse in the third trimester by the time of anti-TNF discontinuation, cesarean section by previous perianal surgery and disease activity, respectively; preterm birth by small for gestational age, relapse by satisfaction with counseling, and counseling by relapse. Initially, bivariate analysis was conducted to investigate associations between the predictor variables—comprising relapse, continuation of anti-TNF after GW 30, thiopurine treatment, type of anti-TNF drug (adalimumab vs infliximab), type of IBD, previous pregnancy, previous abdominal surgery, smoking, maternal age ≥30 years, and maternal BMI ≥30—and the influence on infant birth weight using the Student *t* test. A multiple linear regression was performed to investigate the combined impact of all predictor variables on infant birth weight. In addition, a 2-way analysis of variance (ANOVA) was conducted to test for interaction between disease activity and continuation of anti-TNF after GW 30. A P value <0.05 was regarded as statistically significant. All analyses were performed using Stata, version 13.0 (Stata Corporation LP, College Station, TX, USA).

Ethical Considerations

Written informed consent was obtained from all participating women. The study was approved by the Danish Data Protection Agency (reference 116-02-174-13), by the St Vincent's Hospital Ethics Committee in Australia (reference LRR 021/12), and by the Southern Ethics Committee in New Zealand (reference 12/NTB/14).

RESULTS

Study Population

A total of 169 women with IBD who received infliximab or adalimumab during 175 documented pregnancies were prospectively invited to participate in the present study. Of the 153 (87%) women who completed the electronic questionnaire, 75/86 (87%) were from Denmark, 63/72 (88%) from Australia, and 15/17 (88%) from New Zealand. Demographics, clinical details, and lifestyle factors are presented in Table 1.

Medical Therapy

Most women (n = 138, 90%) received anti-TNF for at least 6 months preceding conception and during pregnancy, whereas 15 women (10%) commenced anti-TNF treatment during the first or early second trimester of their pregnancies.

The timing of the last anti-TNF dose given during pregnancy significantly varied between infliximab and adalimumab; infliximab at a median GW (interquartile range [IQR]) of 30 (19–36) and adalimumab at 34 (17–40;

TABLE 1. Characteristics of 153 Women With Inflammatory Bowel Disease Who Received Anti-TNF Therapy in Pregnancy

	No.	(%)
Inflammatory bowel disease	153	(100)
Crohn's disease	126	(82)
Active perianal disease in pregnancy	20	(13)
Ulcerative colitis	27	(18)
Anti-TNF alpha induction therapy in pregnancy	15	(10)
Medications during pregnancy		
Adalimumab	62	(41)
Infliximab	91	(59)
Thiopurine	56	(37)
5-aminosalicylic acid	28	(8)
Prednisolone & budesonide	33	(22)
Allopurinol (co-administered with thiopurine)	3	(2)
Combination therapy		
Adalimumab and thiopurine	22	(36)
Infliximab and thiopurine	34	(37)
Discontinued anti-TNF before **third** trimester (<GW 30)	54	(35)
Continued anti-TNF in **third** trimester (≥GW 30)	99	(65)
Previous abdominal IBD surgery	41	(27)
Previous perianal IBD surgery	28	(18)
Remission throughout pregnancy	111	(73)
Disease relapse in pregnancy	41	(27)
Disease relapse <**GW** 30[a]	32	(18)
Disease relapse ≥**GW** 30[a]	17	(11)
Active disease at delivery	17	(11)
Primiparous	79	(52)
Planned pregnancy	113	(74)
Smoking during pregnancy	13	(9)
	Median	(IQR)
Maternal age at the date of birth**, y**	31	(28–34)
Years since diagnosis	9	(4–13)
Years since abdominal/perianal IBD surgery	5	(2–7)
Body mass index prepregnancy, kg/m^2	23.4	(20.5–26.5)
GW at delivery	39	(38–40)
Delivery, number of weeks since last IFX treatment	9	(7–14)
Delivery, number of weeks since last ADA treatment	4	(2–9)

There were no significant differences between adalimumab (ADA)- and infliximab (IFX)-treated women or between women from Denmark and Australia/New Zealand, except that ADA was administrated closer to delivery than IFX ($P = 0.0001$), and the Danish cohort had a higher rate of smokers ($P = 0.04$) and women on thiopurine ($P = 0.04$).
[a]Eight women experienced relapse before and after gestational week 30.

$P = 0.0001$). Treatment was stopped before GW 30 in 54 (35%) women. Combination therapy with anti-TNF and thiopurine therapy during pregnancy was provided to 56 (37%) women. Of the 54 women who discontinued anti-TNF before GW 30, monotherapy with thiopurine or 5-ASA in the remaining part of the pregnancy was provided to 21 (39%) and 6 (11%) women, respectively. Of the 73 (48%) women who had been pregnant before, 29 (40%) reported that the previous pregnancy experience had influenced their choice regarding medical treatment during the current pregnancy.

Disease Relapse During Pregnancy

Maternal disease relapse rates are shown in Table 1. In case of relapse before gestational week 30, most women

(24/32, 75%) received treatment with anti-TNF in the third trimester. One woman who experienced a relapse in the first trimester and discontinued anti-TNF treatment before gestational week 30 had a new flare in the third trimester, which was treated with prednisolone. In a subgroup analysis that only included women in remission during first and second trimesters (n = 120), we observed no significant difference in relapse rates among women who stopped anti-TNF treatment before gestational week 30 (1/46, 2%) compared with women who continued treatment after gestational week 30 (8/74, 11%), with an RR of 0.20 (95% CI, 0.02 to 1.56; $P = 0.08$).

TABLE 2. Pregnancy Complications and Outcomes Among 153 Women With IBD Who Received Anti-TNF Treatment During Pregnancy

	Total		Stopped Anti-TNF <GW 30		Continued Anti-TNF ≥GW 30		*P* <GW30 vs ≥GW 30
	No.	(%)	No.	(%)	No.	(%)	
Total	153	(100)	54	(35)	99	(65)	0.0005
Complications							
Morning sickness	91	(60)	25	(46)	66	(67)	0.01
Gestational hypertension	10	(7)	2	(4)	8	(8)	0.37
Gestational diabetes	6	(4)	3	(6)	3	(3)	0.27
Obesity (BMI ≥30 **kg/m**^{2})	23	(15)	7	(13)	16	(16)	0.60
Pre-eclampsia	4	(3)	2	(4)	2	(2)	0.52
Pregnancy outcome							
Cesarean section	83	(54)	21	(39)	49	(50)	0.21
C**esarean section** due to IBD	60	(72)	18	(33)	42	(42)	0.001
Very preterm (GW <32)	0	-	0	-	0	-	-
Moderately preterm (GW 32–36)	9	(6)	2	(4)	7	(7)	0.40
Small for gestational age	4	(3)	0	-	4	(4)	0.13
Low birth weight (<2500 g)	10	(7)	1	(2)	9	(9)	0.10
Congenital malformation[a]	5	(3)	2	(4)	3	(3)	1.00
Stillbirth	0	-	0	-	0	-	
Apgar score <7:							
1 min after birth	9	(6)	2	(4)	7	(7)	0.49
5 min after birth	2	(1)	0	-	2	(2)	0.54
Sex: **g**irl	72	(47)	26	(48)	46	(47)	0.63
Infant birth weight <3400 g	81	(53)	23	(43)	58	(59)	0.06
Infant admitted intermediate/intensive care							
Yes	22	(14)	4	(7)	18	(18)	0.09
No	131	(86)	50	(93)	81	(82)	0.08
Reason for **intensive care**							
Respiratory distress syndrome	4	(3)	1	(2)	3	(3)	
Apnea	3	(2)	1	(2)	2	(2)	
Preterm delivery	5	(3)	0	-	5	(5)	
Low birth weight	2	(1)	0	-	2	(2)	
Newborn jaundice	1	(1)	0	-	1	(1)	
Low glucose level	2	(1)	1	(2)	1	(1)	
Swallowed meconium	1	(1)	1	(2)	0	-	
Reason not stated	4	(3)	0	-	4	(4.0)	
	Median	(IQR)	Median	(IQR)	Median	(IQR)	*P*
Weight, g	3374	(3000–3700)	3505	(3220–3950)	3282	(2910–3620)	0.0005
Length, cm	51	(49–52)	52	(50–53)	50	(49–52)	0.006

There were no significant differences between adalimumab (ADA)- and infliximab (IFX)-treated women or between women from Denmark and Australia/New Zealand, except that the Danish children were longer in size (cm) ($P = 0.04$).

[a]Two infants were exposed to ADA and 3 to IFX.

Pregnancy Outcomes

Mode of delivery

In total, 83 (54%) women had a cesarean section (Table 2), which was performed twice as frequently in women who had previous perianal surgery (25/28, 89%) compared with no previous perianal surgery (58/125, 46%; RR, 1.92; 95% CI, 1.53 to 2.42; $P < 0.0001$). Of the 60 (72%) women who stated that the caesarean section was performed due to their IBD, 43 (72%) provided detailed reasons. It was recommended by a gastroenterologist in 31 (52%) cases due to a history of perianal disease, current active disease, or an increased likelihood of pouch surgery in the future; cesarean section was the personal choice for 8 (13%) women who were afraid of potential damage to their perineum during labor and was recommended by the obstetrician due to IBD in 4 (7%).

Adverse pregnancy outcome

The rates of preterm delivery, small for gestational age, low birth weight (<2500 g), APGAR <7, and congenital malformations were low. None of the infants born preterm were small for gestational age. The percentage of infants with a birth weight below 3400 g was higher among infants exposed to anti-TNF after GW 30 (58/99, 59%) compared with infants in whom anti-TNF was discontinued before GW 30 (23/54, 43%), although not statistically significantly so (RR, 1.38; 95% CI, 0.97 to 1.95; $P = 0.058$) (Table 2).

Predictors influencing infant birth weight

Potential predictors influencing infant birth weight are displayed in Table 3. All potential predictors influencing birth weight were subsequently entered into a multivariate linear regression model. The results of this multivariate regression analysis showed that relapse ($P = 0.001$) and continuation of maternal anti-TNF therapy beyond GW 30 ($P = 0.007$) were retained as independently associated with reduced infant birth weight (Table 3). To identify a potential interaction between relapse and continuation of anti-TNF after GW 30 on the risk for reduced infant birth weight, a 2-way ANOVA was performed, and no significant interaction was found (F(1,148), 0.21; $P = 0.65$).

In a subgroup analysis that only included women in self-reported remission throughout pregnancy (n = 111), the reduced birth weight associated with anti-TNF treatment beyond GW 30 was still statistically significant ($P = 0.003$), equivalent to a 300-g (95% CI, 104 to 496 g) lower birth weight in infants of mothers who continued anti-TNF after GW 30 (n = 66; 3367 g; 95% CI, 3240 to 3494 g) than infants of mothers who discontinued anti-TNF before GW 30 (n = 45; 3667 g; 3515–3818 g).

Patient Preparedness for Anti-TNF Therapy During Pregnancy

Counseling regarding treatment with biological therapy during pregnancy was received by 134 (88%) of the women in the study. The gastroenterologist was the counselor in 88% of these, and the vast majority were satisfied with the information obtained (Table 4). The risk of relapse was not significantly related to being satisfied or not (RR, 1.29; 95% CI, 0.55 to 3.04; $P = 0.56$) or whether counseling was received or not (RR, 1.77; 95% CI, 0.48 to 6.52; $P = 0.35$). Postpartum, 26 (17%) of the women requested more information regarding anti-TNF treatment during pregnancy: 23 requested information regarding long-term effects on the infant from in utero exposure to anti-TNF, 2 on immunization advice for infants born immune-suppressed, and 1 on whether she could breastfeed while receiving anti-TNF.

When asked about their view on treatment during a potential future pregnancy, the majority of women would accept biological therapy during a future pregnancy (n = 134, 88%). Among the 18 (12%) women who stated "no" or "don't know," 13 (72%) provided a reason: 10 stated that they would have to balance the risks of both the biological treatment and a flare to their unborn child, and 3 had decided not to have more children for personal reasons unrelated to biological therapy.

DISCUSSION

This international multicenter study of women with IBD who received anti-TNF treatment during pregnancy provides important insights regarding the mothers' preparedness for and attitudes toward therapy and the behavior of their disease in relation to therapeutic strategies taken and birth outcomes. In mothers who were in remission during the first 2 trimesters, discontinuation of anti-TNF before GW 30 did not increase the risk of relapse before delivery. Further, both continuation of anti-TNF treatment after GW 30 and relapse were independently associated with a reduction in infant birth weight. No other adverse infant outcomes were reported. There was high patient satisfaction with the counseling provided, and 9 out of 10 would readily accept biological therapy in a future pregnancy.

In terms of disease outcomes, strategies for the use of anti-TNF drugs were addressed. Whether to stop maternal anti-TNF treatment late in pregnancy depends on 2 key competing aspects. First is the risk of relapse from withdrawing therapy. We found that anti-TNF can be discontinued before GW 30 without an increased risk of relapse before delivery when the pregnant woman has been in remission during the first and second trimester. This finding supports 2 smaller prospective studies (n = 83 and n = 80) demonstrating no increased risk of relapse before delivery when anti-TNF was discontinued before GW 25 and 30, respectively.[4, 5] On the other hand, a retrospective French registry-based study among 327 pregnant IBD women found a nearly 2-fold increased risk of relapse before delivery if anti-TNF was discontinued before GW 24.[6] However, this study relied on a surrogate marker of disease activity (initiation of steroid prescriptions in steroid-free women), which is likely to underestimate disease activity in those who continued

TABLE 3. Predictors That Affected Infant Birth Weight Among 153 Live-born Infants of Women With Inflammatory Bowel Disease

		No. (%)	Unadjusted Mean Birth Weight (95% CI), g	*P*	[a]Adjusted Mean Birth Weight (95% CI), g	*P*
Disease activity in pregnancy	No	111 (73)	3488 (3389 to 3588)			
	Yes	41 (27)	3062 (2881 to 3244)			
			426 (230 to 622)	<0.0001	367 (145 to 589)	0.001
Continuation of maternal anti-TNF treatment after GW 30	No	54 (35)	3592 (3431 to 3752)			
	Yes	99 (65)	3261 (3154 to 3367)			
	Difference		331 (146 to 516)	0.0005	274 (77 to 471)	0.007
Combination therapy with thiopurine	No	91 (60)	3292 (3168 to 3417)			
	Yes	56 (37)	3493 (3354 to 3633)			
	Difference		–201 (–392 to –10)	0.04	–136 (–329 to 57)	0.17
Counseling regarding treatment with anti-TNF during pregnancy	No	13 (9)	3332 (2979 to 3685)			
	Yes	134 (88)	3382 (3284 to 3480)			
	Difference		–50 (–380 to 281)	0.77	–115 (–456 to 225)	0.50
Primiparous	No	73 (48)	3403 (3276 to 3531)			
	Yes	79 (52)	3354 (3219 to 3489)			
	Difference		49 (–136 to 234)	0.60	93 (–91 to 277)	0.32
Abdominal IBD surgery before pregnancy	No	112 (73)	3365 (3255 to 3476)			
	Yes	41 (27)	3410 (3244 to 3576)			
	Difference		–45 (–252 to 163)	0.67	25 (–195 to 246)	0.82
Smoking during pregnancy	No	138 (90)	3376 (3282 to 3469)			
	Yes	13 (9)	3306 (2855 to 3758)			
	Difference		69 (–260 to 399)	0.68	84 (–244 to 412)	0.61
Type of anti-TNF drug	Adalimumab	62 (41)	3362 (3214 to 3509)			
	Infliximab	91 (59)	3388 (3269 to 3507)			
	Difference		–26 (–213 to 161)	0.78	–20 (–215 to 175)	0.84
Type of IBD	Ulcerative colitis	27 (18)	3176 (2941 to 3411)			
	Crohn's disease	126 (82)	3421 (3321 to 3520)			
	Difference		–245 (–482 to –7)	0.04	–160 (–424 to 105)	0.23
Maternal BMI at conception	<30	130 (85)	3366 (3270 to 3461)			
	≥30	23 (15)	3443 (3140 to 3746)			
	Difference		–77 (–334 to 180)	0.55	–135 (–383 to 114)	0.29
Maternal age at the date of birth, y	<30	66 (43)	3383 (3235 to 3532)			
	≥30	87 (57)	3373 (3255 to 3491)			
	Difference		11 (–175 to 196)	0.91	53 (–139 to 246)	0.58

[a]Adjusted for the following variables apart from the variable that is the outcome in each analysis: disease activity in pregnancy (yes/no), continuation of anti-TNF after gestational week 30 (yes/no), counseling (yes/no), primiparous (yes/no), abdominal IBD surgery before pregnancy (yes/no), smoking (yes/no), type of anti-TNF drug (adalimumab/infliximab), type of IBD (CD/UC), maternal BMI at conception (<30/≥30 kg/m^2), and maternal age (<30/≥30).

anti-TNF because increased dose or shorter intervals between anti-TNF doses are often used to control relapse without a requirement for steroids.

The second key aspect is the risk to the neonate. Minimizing neonatal exposure to anti-TNF will mitigate any potential effect of inhibition of TNF on the development of the infant's immune system and on the risk of live vaccination. The former is under surveillance in previous studies with, as yet, no adverse signals.[5, 18, 19] The latter still needs in-depth investigation, but international guidelines recommend no live vaccines for the first 6–12 months after exposure to anti-TNF in utero.[1–3, 20] A previous study reported an association between anti-TNF therapy and reduced neonatal growth. Thus, anti-TNF-exposed singletons (n = 399) had a median birth weight (IQR) of 3130 (2798–3460) g, whereas nonexposed singletons (n = 1299) had a higher median birth weight of 3374 (3080–3680) g.[21] It could not be determined whether this was related to anti-TNF itself or the associated disease activity. It is accepted

TABLE 4. Counseling of 153 Women With IBD Receiving Anti-TNF-Alpha Treatment During Pregnancy

	Counseling		No Counseling		Missing Counseling Status	
	No. (%)		No. (%)		No. (%)	
Received anti-TNF counseling	134	(88)	13	(9)	6	(9)
The counselor's profession						
Gastroenterologist	118	(88)				
Gynaecologist/obstetrician	7	(5)				
Nurse	6	(5)				
The Internet	3	(2)				
Another person	0	-				
Satisfied with the information provided						
Yes	116	(87)				
No	12	(9)				
Don't know	6	(4)				
Retrospectively is there anything the patient would have liked to have been informed about regarding IBD and treatment with biological therapy in pregnancy?						
[a]Yes	22	(16)	3	(23)	1	(17)
[a]No	95	(71)	7	(54)	0	-
[a]Don't know	15	(11)	3	(23)	1	(17)
[a]Missing	2	(2)	0	-	4	(66)
Acceptance of biological therapy in a future pregnancy						
[a]Yes	122	(91)	10	(77)	2	(33)
[a]No	2	(2)	3	(23)	1	(17)
[a]Don't know	10	(7)	0	-	2	(33)
[a]Missing	0	-	0	-	1	(17)

There were no significant differences between adalimumab (ADA)- and infliximab (IFX)-treated women or between women from Denmark and Australia/New Zealand.
[a]There were no significant differences between women who received counseling and women who did not receive counseling.

that relapse during pregnancy predicts a reduced infant birth weight.[1, 2, 22] Indeed, the present study found that relapse was associated with a reduced mean infant birth weight of 367 g (95% CI, 145 to 589 g). A novel and important finding in the present study was that continuation of anti-TNF therapy beyond GW 30 during pregnancy was associated with a statistically significantly reduced mean infant birth weight of 274 g (95% CI, 77 to 471 g), independently of disease activity.

There have been indications in the published literature that TNF-α may be an important cytokine for fetal growth,[7, 8] but potential mechanisms behind this have not been clarified. Our finding may represent a causal relationship between fetal growth and anti-TNF use after GW 30. However, research in this area is needed to draw any firm conclusions. An important question then is whether the magnitude of reduction in neonatal weight (mean, 274 g; 95% CI, 77 to 471 g) is of clinical significance. The median birth weight in the present study was 3374 g. Hence, most infants had a birth weight within the normal range. More than half of the infants were born with a birth weight <3400 g. It has been suggested that infants with a birth weight <3400 g, although within the normal range, may have an increased risk of cardiovascular diseases and type 2 diabetes in later life.[23–25] Of note was that all other birth outcomes, such as prematurity, small for gestational age, and need for admission to intensive care unit, were not increased with continued use of anti-TNF beyond GW 30, in line with previous studies.[4–6, 18, 26] Further, the percentage of congenital malformations was lower than globally reported irrespective of anti-TNF treatment duration in pregnancy.[27]

Thus, the weight of evidence from this and other studies tends to favor stopping anti-TNF treatment before GW 30 if the mother is in remission during the first and second trimesters of pregnancy; risk of relapse is not increased, fetal growth will not be affected, and problems with TNF-α inhibition in the infant will be minimized. However, the evidence is suggestive rather than conclusive, and disease behavior in individuals varies and cannot be captured in a study such as the present study. The decision of whether to continue anti-TNF therapy throughout pregnancy remains, therefore, a joint clinician and patient choice mainly determined by the risk of relapse in an individual woman.

The majority of mothers in this cohort were well prepared for biological use during pregnancy, as shown by the rate of counseling, mainly delivered by gastroenterologists, and their satisfaction with the information provided. The high percentage of counseling is in accordance with 2 Danish population-based studies with counseling rates of 76% and 80% among pregnant IBD patients who received other kinds of medical treatment than biological therapy during pregnancy,[12, 13] whereas in an American population, only 19% had received reproductive health counseling.[28] Too few patients reported dissatisfaction with counseling to enable the association of counseling with outcomes to be meaningfully examined. Of importance is that the vast majority of the women were ready to accept biological therapy in a future pregnancy.

The percentage of births by cesarean section was high (54%) in the present study, but this should be compared with 52% of 31 deliveries in the United States[29] and 44% of 388 deliveries in the European multicenter study TEDDY.[18] These results most likely reflect the severity of IBD in pregnant women who receive anti-TNF, as, in the European experience, the rate of cesarean sections was lower in IBD pregnancies without anti-TNF exposure (32% of 453 deliveries; $P = 0.001$).[18]

The present study has important strengths. It is one of the few prospective studies—and the largest to date—to assess risk of relapse before delivery after discontinuation of anti-TNF before GW 30. We had a high response rate of 87%, which strengthens the validity of the results. Bias due to differential recruitment was limited by the distribution to 22 hospitals in 3 countries. We observed no differences between response rates or outcomes in the 3 countries. This indicates that our results are independent of nation and, therefore, may be generalizable to other countries.

We acknowledge several limitations of the study. First, we restricted data collection to patient-reported outcomes and did not document the physician's assessment. Two similar previous population-based studies using the same definition of relapse as in the present study found that patient-reported relapse in pregnancy was consistent with disease activity scores calculated by the physicians.[15, 16] Second, no biomarker of inflammation, such as fecal calprotectin, which is not affected by pregnancy, was measured to confirm active disease.[30] Third, the reason for discontinuation of anti-TNF in pregnancy (ie, patient choice or gastroenterologist recommendation) and disease activity before pregnancy were not investigated, and both could potentially influence the relapse rate. Lastly, all participating hospitals were referral centers for IBD. If the level of medical counseling is related to the degree of specialization, this would skew the rates of women who receive counseling and who report satisfaction with this counseling.

In conclusion, it remains a clinical challenge to decide if and when anti-TNF treatment should be discontinued during pregnancy, and it requires close patient–clinician collaboration. We have shown that anti-TNF discontinuation before the third trimester can be safely considered in women in remission during the first and second trimester. However, we suggest close monitoring of disease activity after cessation, for example, by regular fecal calprotectin measurement, and a well-communicated flare management plan, which can include restarting anti-TNF if required. Alternatively, if there has been active disease shortly before conception or during pregnancy, we suggest continuing anti-TNF treatment throughout pregnancy. Our results highlight the importance of individualized counseling and close monitoring of IBD patients during pregnancy. Further studies on long-term outcomes in children who were exposed to anti-TNF prenatally remain important.

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