ORIGINAL RESEARCH—CLINICAL

Outcomes of Continuation vs Discontinuation of Adalimumab Therapy During Third Trimester of Pregnancy in Inflammatory Bowel Disease

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BACKGROUND AND AIMS: Adalimumab (ADA) transport across the placenta increases with gestational age advances. We evaluated child–mother health outcomes related to the timing of the last ADA dose before delivery. **METHODS:** Using IBM MarketScan data, we collected records for all children exposed to ADA during intrauterine life. We compared milestone achievements, congenital malformations, and respiratory infections rates in children from mothers of 2 groups: (1) a late ADA group, which continued therapy until 90 days or fewer before delivery; and (2) an early ADA group, which discontinued therapy more than 90 days before delivery. We also assessed the risk of flaring for mothers in the early group. **RESULTS:** There were no significant differences in growth ($P = .48$), developmental delays ($P = .25$), or congenital malformations ($P = .61$) in the 427 children of the late group vs 70 children of early ADA group. Continuing ADA late in pregnancy did not increase the respiratory infection rate ($P = .38$). No differences occurred between groups in cesarean and premature delivery, intrauterine growth retardation, and stillbirths. ADA discontinuation was the only predictor of flaring in the third trimester of pregnancy (odds ratio = 6.04, 95% confidence interval 2.66–13.7). In the late group, mothers' risk of flaring decreased (16/447 vs 13/73, $P < .001$). Mothers with active disease were more likely to deliver prematurely vs mothers with quiet disease (6/29 vs 31/491, $P = .003$). **CONCLUSION:** Continuation of ADA in pregnancy close to delivery is of low risk for children. Early discontinuation, however, increases the risk of flaring in mothers and the likelihood of premature deliveries.

Keywords: Adalimumab; Congenital Malformation; Pregnancy; Inflammatory Bowel Disease

Introduction

The use of biologics to manage inflammatory bowel disease (IBD) has greatly improved the clinical and endoscopic appearance of moderate to severe forms of IBD.[1] Maintaining disease remission is crucial for successful pregnancy outcomes. Provided the disease is under control, pregnancy outcomes in IBD are similar to those of healthy mothers. Active disease is associated with both premature and low birth weight babies.[2,3]

Many women with IBD who are or wish to become pregnant experience anxiety about the effect on the fetus of intrauterine exposure to biologics. The 2 largest IBD medical associations, the European Crohn's and Colitis Organization and the American Gastroenterological Association (AGA), provide conflicting recommendations. The former advocates discontinuation of biologics before the third trimester to avoid transplacental transfer of the drug,[4] whereas the AGA encourages the continuation of biologics throughout pregnancy to control disease activity.[5] The AGA's approach is supported by the findings of the largest prospective study on pregnant women with IBD, the Pregnancy Inflammatory bowel disease AND Neonatal Outcomes study, which showed no increase in harm from continuing biologics during pregnancy.[6]

We recently demonstrated that the use of infliximab (IFX), an anti-tumor necrosis factor (TNF) alpha used to treat moderate to severe IBD, does not result in increased adverse maternal-fetal outcomes. However, discontinuing IFX in the first or second trimester increases the risk of flaring even for mothers who are in remission.[7]

We assessed adalimumab (ADA) in the present study, another anti-TNF drug frequently used in pregnant women with IBD. As with IFX, blood concentrations of ADA in the umbilical cords of exposed infants are significantly higher than that in their mothers (by 153%) when therapy is continued throughout the pregnancy.[8,9] Studies showed that pausing ADA therapy 10 weeks or more before delivery lowers this level significantly.[8,9] This observation led the

gastroenterological community to adopt therapeutic strategies involving discontinuation of ADA in the third trimester of pregnancy to minimize fetal exposure.[10]

The pharmacokinetics of ADA are different from that of IFX. While IFX reaches peak plasma concentration in 4 weeks with bi-monthly and intravenous administration, ADA plasma concentration peaks 2–7 days after bi-weekly subcutaneous administration.[11,12] Maternal IFX levels increase significantly as the pregnancy progresses, whereas maternal ADA levels and transport across the placenta remain stable.[13,14] Furthermore, the systematic clearance of ADA is faster than for IFX (4 vs 7.3 months) in mothers and exposed newborns.[8] Subsequently, one would expect that discontinuing therapy in the third trimester of pregnancy could have different consequences across biologics with different pharmacokinetics. Recent studies on ADA use in pregnancy did not evaluate the effect of different therapeutic strategies on children's and mother's outcomes.[9,10,15–17]

Therefore, using a large administrative database, we investigated whether the timing of discontinuation of ADA in pregnancy led to different outcomes in children and their mothers.

Methods

We conducted a retrospective analysis of all pregnancies exposed to ADA and registered with the IBM MarketScan database from 2010 to 2017. IBM MarketScan includes more than 100 million individuals with private insurance from the United States. We used the International Classification of Disease 9th (ICD-9) revision codes and 10th (ICD-10) revision codes to identify all women with Crohn's disease (CD; 555.X and K50) and ulcerative colitis (UC; 556.X and K51) who delivered while on ADA maintenance therapy.[18] The use of ADA was identified by pharmacy claims and prescriptions sent for insurance payment. We considered a patient on "maintenance therapy" if she received at least one prescription for 2–12 pens of 40 mg of ADA, to be administered bi-weekly or weekly. Patients requiring corticosteroid therapy at any time before discontinuation of ADA were excluded from the study. Using National Drug Codes and RED BOOK (Truven Health Analytics), we also noted any additional immunosuppressive therapy such as thiopurines (6-mercaptopurine and azathioprine) before and after the discontinuation of ADA.

We reported the timing of the last ADA dose in pregnancy related to delivery date. If a pregnant woman continued ADA therapy 90 days or less before delivery, we considered the continuation of therapy "late." If a pregnant woman discontinued therapy more than 90 days before delivery, we considered that discontinuation of therapy "early."

In our IFX study, the timing of the last dose was accurately established using the Current Procedural Terminology (CPT) code of the last infusion. In the present study, however, we interpolated the timing of the last ADA dose by assuming that all the pens of the last prescription were injected ("late stop").

We performed a secondary sensitivity analysis based on a more conservative approach: we assumed the last ADA dose was the day the last prescription was filled ("early stop"). We compared these results with our primary analysis, in which we assumed that all the pens of the last prescription were injected ("late stop").

We defined a full-term pregnancy at 40 weeks and a premature delivery at 37 weeks or less from delivery (www.cdc.org). To identify premature delivery, we looked for ICD-9-CM code 644.21 and ICD-10-CM codes O60.12, O60.13, and O.60.14 in the mother's records and subcategories 765.2, PO7.2, and PO7.3 in the child's records. Alternatively, we used CPT codes 76801 and 76802 (identifying ultrasound at ≤14 weeks gestation) and 76805 and 76810 (identifying ultrasound >14 weeks gestation) to determine the length of pregnancy.

Outcome Measures

The primary analysis compared 9 health outcomes of pregnancies exposed vs nonexposed to ADA in the last 90 days before delivery. The outcomes, identified using ICD-9 and ICD-10 codes, included (1) growth (weight and height) abnormalities, (2) developmental delays (other than growth abnormalities), (3) acute respiratory infections, (4) major congenital malformations, (5) preterm delivery, (6) intrauterine growth retardation, (7) small for gestational age babies, (8) stillbirths, and (9) C-section among pregnancies exposed vs nonexposed to ADA in the last 90 days before delivery. The secondary analysis evaluated the risk of flaring in mothers of the 2 groups by comparing the number of steroid prescriptions, hospital or emergency room admissions, related to IBD.[19]

Severity of IBD Before Last ADA Injection

We define the severity of IBD using previously published severity scores for CD[20] and UC[21] that are based on the presence of certain complications, such as anemia, malnutrition, and requirement for partial or total parenteral nutrition. We adjusted these scores to reflect acuity of complications, hospital admission, and recent IBD-related surgeries. The scores ranged from 0 to 19 for UC and 0 to 22 for CD, where higher scores represented greater severity (Table A1). We used the Montreal classification to classify the disease extent and behavior.[22]

Statistical Analysis

We used Stata 14.2 (StataCorp LP, College Station, TX) to compare pregnancy outcomes in the late ADA and early ADA groups. Adjusted severity scores for CD[20] and UC[21] and Grouped Charlson index Score,[23] a measure of overall comorbidity weighted by severity of maternal risk for poor outcomes, were used to define the patient population. To determine the effect of timing of ADA injection on disease activity, we performed multivariable logistic regression of any IBD flare reported after the last dose. We included in the model the independent variables identified by bivariate analysis of the outcomes. As in our previous study,[7] via the t-effects module for Stata, we used inverse probability-weighted regression adjustment to adjust for potential bias in each group.[24] For all statistical analyses, we considered a P value less than .05 as statistically significant. This study was approved by the Johns Hopkins Medicine Institutional Review Board.

Results

Patient Population

Between January 2010 and December 2017, we identified 520 deliveries from mothers with IBD registered with

IBM Market Scan Database. We were able to link the mother and children records in 497 instances (95.5%; Figure). Of the 497 children exposed to ADA during their intrauterine life, 427 (86%) were born to mothers who discontinued late or continued ADA throughout pregnancy, and 70 (17%) were born to mothers who discontinued ADA early. Children's records were available up to 1 year (66%), 2 years (18%), 3 years (7%), 4 years (6%), and 5 years (3%) of age.

Mothers in the late ADA group were no different in age at delivery, parity, smoking status, and comorbidities (determined by the Charlson index) from mothers in the early ADA group. However, there were more primigravida mothers in the late ADA group. Most of the mothers had CD (CD:UC = 4:1) and predominantly ileocolonic disease (Table 1). Fifty-eight (12.9%) of those in the late group and none in the early group (P < .05) were treated with combination therapy (thiopurine and ADA).

Pregnancy Outcomes

There were no significant differences in children's growth (weight and stature) abnormalities, motor, cognitive, social, and behavioral developmental delays between the children of the late and early ADA group (Table 2). The rate of premature deliveries, intrauterine growth retardation, small for gestational age babies, and stillbirth babies was the same in the 2 groups. Major congenital malformations, as defined by the European Surveillance of Congenital Abnormalities (www.eurocat-network.eu), were reported as frequent in the late ADA and early ADA groups (7.5% vs 7.15%, P = .613; Table 2). No specific pattern was associated with the use of ADA (Table A2).

We found no increase in respiratory infection rate in the children of mothers who discontinued late or continued ADA throughout pregnancy, compared with those whose mothers who discontinued ADA early.

Mothers' Disease Activity

After ADA discontinuation, significantly fewer mothers in the late ADA group required a steroid prescription than those in the early ADA group (P < .001) to control their disease (Table 3). One mother from the early ADA group required emergency care for severe IBD flare. Four months later, she developed mild pre-eclampsia and delivered a baby with jaundice, frequent acute respiratory infections, and congenital anomalies of the skull and face bones. None of the patients required hospitalization for the management of IBD.

As in our IFX study, ADA discontinuation was the only significant predictor of disease flare in the last trimester of pregnancy (odds ratio = 6.04, 95% confidence interval = 2.66–13.7). There was an absolute difference in flare activity of 10.5%, favoring the late ADA discontinuation group (P < .05). The risk of flaring was independent of the frequency of ADA administration (14% vs 31%, on weekly vs bi-weekly dose, P = .112).

The risk of premature delivery was higher in mothers who flared during pregnancy than in those who did not flare (6/29 vs 31/491, P = .003). This difference was significant only in the early ADA group (5/6 vs 8/67, P < .001) and lost significance when we analyzed the risk of flaring in the late ADA group only (1/31 vs 15/416, P = .913).

Conclusions

There is growing evidence demonstrating the safety of anti-TNFs during pregnancy.[7,17,25–27] In the present study, we showed that continuing ADA beyond the second trimester of pregnancy is associated with low risk for the baby and decreased risk of flaring for the mother.

We found no difference in the rates of growth abnormalities, developmental delays, or congenital malformations between the late ADA and early ADA groups (Table 2). Blindness was unique to the early ADA group; however, we could not draw a conclusion based on one even. The incidence of major congenital malformations in our study was higher than reported in the general population: 7.5% in the late ADA group, 7.1 % in the early ADA group, and 2%–3% in the general polupation.[28–31] Incidence was similar to that reported by the Organization of Teratology Information Specialists Research Center registry.[16]

As in the Pregnancy Inflammatory bowel disease and Neonatal Outcomes study,[32] which compared anti-TNF exposed and nonexposed pregnancies, using ADA during the third trimester did not increase the risk of respiratory infections in children.

Both anti-TNFs, IFX and ADA, can be found in supratherapeutic concentrations in the cord blood of newborns.[8,9] Therefore, a strategy including discontinuation of the drugs in the third trimester seems justified if there is a proven benefit for the child and no risk for the mother. Interestingly, only 14% of our pregnant patients discontinued ADA in the third trimester compared with almost half of the pregnant patients participating in the largest European study (EVASION).[19] This reflects the growing confidence in the safe utilization of biologics in pregnancy among US
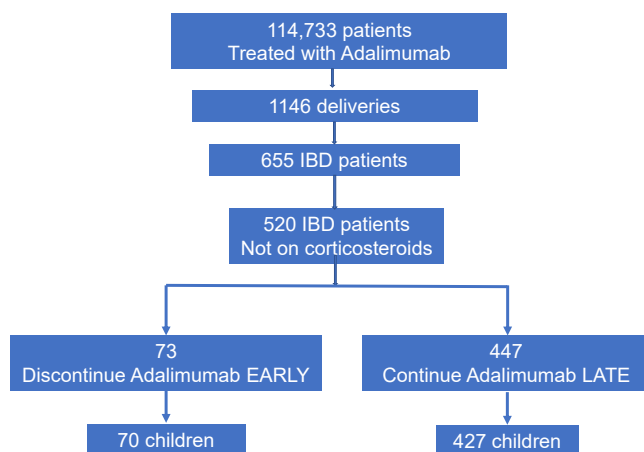

Figure. Algorithm used for selecting patient population.

Table 1. Characteristics of the Mothers Treated With Adalimumab

Characteristic	Late adalimumab (N = 447)	Early adalimumab (N = 73)	P value
Age at delivery (y), median [range]	30 [16–40]	30 [19–43]	N/A
Age at delivery (y), mean (SD)+	29.73 (4.5)	29.48 (5)	.335
Multiparous, n (%)	292 (65.3)	48 (66.7)	.943
Multigestational, n (%)	18 (4)	4 (5.5)	.568
Primigravida, n (%)	219 (49)	24 (33)	.011
Smoker, n (%)	3 (0.7)	1 (1.4)	.526
High-risk pregnancy, n (%)	201 (45)	36 (49)	.489
Comorbidities, n (%)			
Obesity	28 (6.3)	7 (9.6)	.293
Diabetes	4 (0.9)	1 (1.4)	.7
HTN	58 (13)	9 (12.3)	.878
CHF	0 (0)	0 (0)	.526
Lung disease	20 (4.5)	3 (4.1)	.888
Renal disease	0 (0.0)	1 (1.4)	.013
Liver disease	1 (22)	0 (0.0)	.686
Group Charlson index, n (%)			.067
0	401 (89.7)	59 (80.8)	
1	42 (9.4)	12 (16.4)	
2	4 (0.9)	2 (2.7)	
Crohn's disease, n (%)[a]	371 (83)	63 (86.3)	.906
Crohn's disease severity score, mean (SD)	2.6 (1.7)	2.5 (1.4)	.375
0–1	0 (0.0)	0 (0.0)	
2–4	417 (93.3)	66 (90.4)	
5+	30 (6.7)	7 (9.6)	
Ulcerative colitis, n (%)[a]	138 (30.9)	19 (26)	.403
Ulcerative colitis severity score, mean (SD)	0.32 (1.0)	0.32 (1.0)	.947
0–1	420 (94.0)	68 (93.2)	
2–3	12 (2.7)	2 (2.7)	
4+	15 (3.4)	3 (4.1)	
Cesarean section, n (%)	213 (47.7)	29 (39.7)	.208

CHF, congestive heart failure; HTN, hypertension; N/A, not available; SD, standard deviation.
[a]Includes patients labeled Crohn's disease but also ulcerative colitis , no significant difference between the 2 groups (20 vs 5, p=ns)

providers following the AGA proposed clinical care pathways.[5]

In the present study, we analyzed the largest North American data set on children of mothers with IBD exposed to ADA during pregnancy. We found no benefit of discontinuing ADA therapy early. Moreover, we noticed a direct correlation between early discontinuation of ADA and increased risk of flaring. This risk was independent of treatment intensity (every other week or every week). Mothers with active disease also had an increased likelihood of premature deliveries. This finding has been previously reported in literature.[2,3] Only a few mothers were treated with combination therapy (thiopurine and ADA); therefore, that subsample was too small for us to draw a conclusion on the possible effect of thiopurine after ADA discontinuation.

The main limitation of our study was the inability to assess the activity of the disease before conception and during pregnancy. As shown previously,[2,3,26] IBD disease activity is an important variable associated with pregnancy outcome. We tried to overcome this limitation using validated activity scores for CD[20] and UC.[21] To identify disease flares after the last ADA injection, we used the number of new steroid prescriptions and/or emergency care visits as surrogates. This approach, used also by a large retrospective French study (EVASION),[19] offers a fair assessment of disease severity during pregnancy. By contrast, endoscopy has limited role in pregnancy due to associated risks.

In our IFX study, the timing of the last dose was accurately established using the CPT code of the last infusion. However, to establish the timing of the final ADA dose for our primary analysis, we relied on the assumption that patients used all the pens of the last prescription ("late stop"); this assumption may not have held true. Therefore, we investigated potential scenarios that could have taken place and influence the results. (1) We performed a secondary sensitivity analysis based on a more conservative approach to overcome this limitation. We assigned the date of ADA discontinuation to the day patients filled their final

Table 2. Outcomes of Children in the Late and Early Adalimumab Discontinuation Group

	Late adalimumab (N = 427)	Early adalimumab (N = 70)	P value
Growth abnormalities, n (%)			
Abnormal weight[a]	60 (14.05)	4 (5.71)	.054
Small stature	3 (0.70)	0 (0)	.482
Developmental delays, n (%)			
Motor developmental delay	16 (3.75)	5 (7.14)	.191
Social, emotional, behavioral delays[b]	9 (2.11)	0 (0.0)	.220
Cognitive developmental delays/retardation	1 (0.23)	0 (0.0)	.685
Language impairment	21 (4.92)	4 (5.71)	.778
Hearing impairment	21 (4.92)	5 (7.14)	.438
Vison impairment	0 (0.0)	1 (0.20)	.013
Acute respiratory infections, n (%)	225 (52.69)	33 (47.14)	.389
Major congenital abnormalities, n (%)	32 (7.50)	5 (7.15)	.613
Preterm, n (%)	31 (6.9)	6 (8.2)	.692
Intrauterine growth retardation, n (%)	74 (16.6)	12 (12.3)	.361
Small for gestational age, n (%)	51 (11.94)	5 (7.14)	.686
Stillbirth, n (%)	5 (1.1)	0 (0.0)	.364

[a]Weight gain, weight loss.
[b]Hyperkinetic syndrome of childhood,[2] social, emotional, and behavioral delays, including autism, attention deficit hyperactivity disorder, hyperkinetic syndrome (behavior disorder in which the essential features are signs of developmentally inappropriate inattention, impulsivity, and hyperactivity).

prescription (so-called "early stop"). We compared the results of the secondary analysis with our primary analysis. In either circumstance, the results were similar, whether "late stop" or "early stop," confirming the initial conclusion. (2) We also considered a scenario in which the pharmacy refill was late, and there were "left over shots" in excess of those needed for the third trimester of pregnancy treatment. We analyzed the pharmacy refill data of the script filled after delivery and how soon it was filled to determine if women had unused "extra shots" at the end of pregnancy. We retrieved the postdelivery data on 430 patients (82.7% of our cohort). The early ADA group stopped earlier (by definition) and resumed later than the ADA group. Overall median time to refill was 25 days: 51 days for the early ADA group and 23 days for the late ADA group (P < .0001), making it unlikely that the early ADA group had unutilized ADA pens. (3) Finally, we recognize that in clinical practice, some pregnant women are advised to skip ADA only in the last 2 weeks before delivery. We performed a supplementary analysis changing the cutoff point for ADA discontinuation from 90 to 30 days before delivery to address this

situation. There were 158 patients who discontinued ADA in the last 30 days of pregnancy, about twice the number who discontinued in the first 2 trimesters. Patients who discontinued ADA 30 days early were at higher risk of flaring than those who discontinued ADA late (24/158 vs 5/362, P < .0001). There were no differences in child outcomes between the new 2 groups.

We considered reasons why some women with IBD would opt for early ADA discontinuation. There were no reports of allergic reactions or changes in biologic therapy associated with early ADA discontinuation. However, we did notice that primigravida patients were more likely to discontinue ADA early in pregnancy (Table 1), suggesting patient concerns related to the effect of fetal exposure during pregnancy.

Our results should reassure mothers and providers of the low risk of ADA therapy in the third trimester of pregnancy. We showed no child health benefit associated with early discontinuation of ADA in pregnancy, at least in the first year of life. In contrast, continuing ADA maintained disease remission and minimized the risk of flaring.

Table 3. Disease Activity After Last Adalimumab During Pregnancy

	Late adalimumab (N = 447)	Early adalimumab (N = 73)	P value
Emergency room admissions, n (%)	1 (0.2)	0 (0.0)	.688
Inpatient admissions, n (%)	0 (0.0)	0 (0.0)	N/A
New steroid prescriptions, n (%)	16 (3.6)	13 (17.8)	<.001
Any flares, n (%)	16 (3.6)	13 (17.8)	<.001

N/A, not available.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2022.04.009.

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Conflicts of Interest:
The authors disclose no conflicts.

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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

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