




ORIGINAL ARTICLE

Observational data from the adalimumab post-marketing PYRAMID registry of patients with Crohn's disease who became pregnant: A post hoc analysis

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Abstract

Background: PYRAMID was an international post-marketing registry that aimed to collect data on the long-term safety and effectiveness of adalimumab treatment per local standard of care in patients with moderately to severely active Crohn's disease (CD). Here, we present post hoc analyses of observational data from patients who became pregnant while participating in this registry and receiving adalimumab.

Methods: From the subpopulation of patients receiving adalimumab who became pregnant while taking part in PYRAMID, data on patient characteristics, pregnancy outcomes, and complications of pregnancy were analysed retrospectively.

Results: Across the PYRAMID registry, 293 pregnancies occurred in patients who had gestational adalimumab exposure (average disease duration at last menstrual period: 8.6 years), resulting in 300 pregnancy outcomes. A total of 197 pregnancies (67.2%) were exposed to adalimumab in all trimesters per physician's decision. Of the known reported outcomes (96.3%), 81.7% (236/289) were live births, 10.4% (30/289) were spontaneous abortions, 4.8% (14/289) elective terminations, 2.8% (8/289) ectopic pregnancies, and 0.3% (1/289) was a stillbirth. Congenital malformations (pulmonary valve stenosis and tricuspid valve incompetence) were reported in one infant. In addition to the pregnancy outcomes described above, 23 complications of pregnancy were reported in 20 patients.

Conclusions: This analysis showed that adalimumab treatment in patients with CD, who became pregnant whilst participating in the PYRAMID registry, contributed no additional adverse effects during the pregnancy course or on pregnancy outcomes.

KEYWORDS

adalimumab, anti-tumour necrosis factor, Crohn's disease, pregnancy, PYRAMID registry

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD), with characteristic symptoms including abdominal pain, diarrhoea, and fatigue.¹ Almost half of female patients diagnosed with CD are under 40 years of age and still in their peak reproductive years.² Compared with healthy controls, patients with IBD have been shown to be at significantly higher risk of adverse pregnancy outcomes.^{3,4} These included a higher risk of preterm births (odds ratio [OR] = 1.4, 95% confidence interval [CI], 1.1–1.8), low birth weight (OR = 1.4 [95% CI, 1.1–1.8]), and postpartum haemorrhage (OR = 1.3 [95% CI, 1.0–1.6]) versus healthy controls.³ Further studies have demonstrated that disease activity is an important risk factor for adverse pregnancy outcomes^{4–7}; therefore, maintaining clinical remission or low disease activity is important during pregnancy.

Anti-tumour necrosis factor (anti-TNF) therapies, including adalimumab, certolizumab pegol (in certain countries), and infliximab, are available for the treatment of CD.⁸ Adalimumab is a fully human monoclonal antibody that has been licenced to treat adults and children with CD in the United States and Europe, and is currently also approved for the treatment of ulcerative colitis (adults and children), rheumatoid arthritis (RA), juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, hidradenitis suppurativa, and noninfectious uveitis.⁹ Monoclonal antibodies, such as adalimumab, are increasingly transported across the placenta as the pregnancy progresses, with active transport during the third trimester.¹⁰ While the European Crohn's and Colitis Organisation (ECCO) 2015 guidelines recommend that anti-TNF therapies may be discontinued around gestational week 24–26 if appropriate to minimise risk due to transplacental transfer,⁶ more recent guidelines recommend that most patients with active CD should continue treatment throughout pregnancy.^{11,12} This is supported by data from a prospective observational study in the United States, which showed that exposure to biologic therapies during pregnancy was not associated with adverse pregnancy outcomes.¹³ In addition, a multicentre retrospective study in the Netherlands of 1000 children born to mothers with IBD showed no association between maternal anti-TNF and/or thiopurine use during pregnancy and adverse long-term health outcomes of their offspring, up to 5 years of age.¹⁴ ECCO guidelines also recommend that live vaccines in infants whose mothers have had exposure to anti-TNF agents during pregnancy should be avoided in the first 6 months after birth.^{6,9}

PYRAMID was a 6-year, prospective, multicentre, post-marketing, observational registry (NCT00524537) designed to assess the long-term safety and effectiveness of adalimumab in routine clinical practice in adult patients with CD, with the primary objective of ruling out a doubling of lymphoma risk in patients receiving adalimumab. Patients included in this registry received adalimumab administered by their treating physician according to the local product label. Data from PYRAMID revealed that adalimumab therapy was well tolerated, and improved physician- and patient-reported disease outcomes, with maintained remission rates of up to 6 years in clinical practice.^{15,16}

Key summary

Summarise the established knowledge on this subject

- Compared with healthy controls, patients with inflammatory bowel disease have been shown to be at significantly higher risk of adverse pregnancy outcomes.
- Maintaining clinical remission or low disease activity is important during pregnancy to minimise adverse pregnancy outcomes in patients with Crohn's disease (CD).
- Data from observational studies suggest that exposure to biologic therapies during pregnancy is not associated with adverse pregnancy outcomes or adverse health of their offspring.
- There are few real-world studies on pregnancy outcomes among those receiving adalimumab during pregnancy.

What are the significant and/or new findings of this study?

- In this large single cohort of 293 pregnancies, adalimumab treatment contributed no additional adverse effects during the pregnancy course or on pregnancy outcomes in patients with CD who became pregnant while participating in the PYRAMID registry.

A subgroup of patients became pregnant during their participation in the PYRAMID registry while being treated according to the local standard of care. This provided an opportunity to collect real-world data on pregnancy outcomes in patients who had received adalimumab within 6 months prior to pregnancy and/or during pregnancy. According to the registry protocol, the decision to continue adalimumab in patients who became pregnant during their participation was solely at the discretion of the treating physician. No additional registry visits were planned when pregnancy occurred, and the scheduled data collection was maintained per protocol. In this post hoc observational analysis, we report the outcomes from 293 pregnancies with adalimumab exposure that occurred during the PYRAMID registry.

METHODS

Patients

Patients included in PYRAMID (NCT00524537) have been described previously.^{15,16} Adults with moderately to severely active CD were eligible to participate if they were naïve to adalimumab treatment, were prior participants in investigational studies with adalimumab who continued adalimumab treatment, or were currently receiving adalimumab per the local product label. All patients were treated with adalimumab in a routine clinical practice setting and were followed up during regular clinic visits every 3 months for a year, and every 6 months thereafter for up to 6 years. Pregnancies that

occurred in patients participating in PYRAMID were followed up per local standard of care from the time the pregnancy was reported until the outcome of the pregnancy was reported, with no additional registry-related visits included. Infants were followed for 70 days after delivery per protocol. Mothers with more than one pregnancy during the PYRAMID registry were counted for each pregnancy. Twin gestations were counted as one pregnancy with two pregnancy outcomes.

Demographics and disease characteristics

Maternal data recorded at entry into the registry included demographics and disease characteristics, medical history, prior and concomitant medication use, and complications of CD (selected from a predefined list: arthralgia/arthritis, iritis/uveitis, erythema nodosum, pyoderma gangrenosum, oral aphthous ulcers, anal fissure, draining fistula, perianal abscess, bowel obstruction, bowel resection, and CD surgery).

Exposure to adalimumab and other medications was also recorded throughout the registry. Other medications which were started and stopped >6 months prior to pregnancy were classified as medications used prior to the pregnancy. Other medications taken between 6 months prior to last menstrual period (LMP) date and delivery date were classified as concomitant medications to adalimumab during the pregnancy; if LMP or delivery date was missing, a 15-month window was conservatively assumed.

Complications of pregnancy

Overall safety assessments have previously been described.¹⁵ Complications of pregnancy were included based on medical and literature review,^{3,17} and defined as any event relating to the pregnancy that occurred during the interval from LMP date through to delivery date plus 3 months. Where an LMP date or delivery date was missing, a 12-month window was conservatively assumed. The events deemed relevant were: postpartum haemorrhage, pre-eclampsia/eclampsia, antepartum haemorrhage, metrorrhagia, Bartholinitis, arterial thrombosis, venous thromboembolism, gestational diabetes, abruptio placenta, chorioamnionitis, hydrops fetalis, foetal distress, infection, maternal blood transfusion, maternal death, delivery complications, premature labour, placenta previa, premature rupture of membranes, prolonged rupture of membranes, uterine contractions during pregnancy, and urine group B streptococcus.

Pregnancy outcomes

The following pregnancy outcomes were considered: live birth, spontaneous abortion (defined as a fatal pregnancy outcome at <20 weeks' gestation), stillbirth (defined as a fatal pregnancy

outcome at ≥ 20 weeks' gestation¹⁸), elective termination, or ectopic pregnancy. Information recorded for live births included congenital anomalies, gestational age, preterm birth (defined as a live birth before 37 completed weeks of gestation and subdivided into extremely preterm [gestational age <28 weeks], very preterm [gestational age ≥ 28 to <32 weeks], and moderate-to-late preterm [gestational age ≥ 32 to <37 weeks]),¹⁹ and low birth weight (defined by the World Health Organization as <2500 g²⁰).

Effectiveness measures

Effectiveness measures, used to evaluate disease activity, have been previously described.¹⁶ In brief, these included change from baseline in Physician's Global Assessment (PGA) of Disease Activity (derived from the Harvey-Bradshaw Index [HBI]), Short Quality of Life in Inflammatory Bowel Disease Questionnaire, and Work Productivity and Activity Impairment questionnaire; and clinical remission defined by HBI <5. These were collected in patients receiving adalimumab and evaluated at entry into the registry, at LMP, and at delivery date (which reflect the closest available measurement within 12 months prior to LMP date and ± 90 days around delivery date, respectively); and reported as exploratory outcomes in this patient subpopulation.

Statistical analysis

Only pregnancies with gestational adalimumab exposure were included in this analysis, defined as ≥ 1 dose of adalimumab within 6 months (≤ 183 days) prior to the LMP date and/or any time during the pregnancy. The timing of adalimumab exposure, relative to pregnancy was further classified as 'before conception only', 'first trimester only', 'after first trimester only', 'in the first and second or in the first and third trimesters', or 'throughout the pregnancy'. Due to registry data capture and study visit schedules, it was not always possible to ascertain whether the use of adalimumab was consistent throughout these time frames. Therefore, exposure in these subcategories was defined as ≥ 1 dose of adalimumab within the trimester(s) of interest. Pregnancies where the information on gestational exposure could not be retrieved from the registry database were excluded from the analyses.

An a priori sample size was not determined for this analysis and no statistical comparisons were performed. All data were summarised descriptively. Exact Clopper-Pearson 95% CIs were included for pregnancy outcomes. Complications of pregnancy were summarised by system organ class (SOC) and preferred term (PT) as the number of patients with ≥ 1 event and number of events. A patient with several reports of the same PT was only counted once per PT. A patient who reported two or more different PTs that were in the same SOC was counted only once in the SOC total.

Ethical considerations

The PYRAMID study was conducted in accordance with the International Conference on Harmonization guidelines, applicable regulations, and the Declaration of Helsinki. Study-related documents were approved by institutional ethics committees and review boards. Patients provided written informed consent at enrolment and signed a Patient Authorization for Use/Disclosure of Data form.

RESULTS

Patient demographics and disease characteristics

Overall, 5061 patients were included in the PYRAMID registry, with 57% of 5025 evaluated patients being female.¹⁵ Of the total of 356 pregnancies reported, 59 pregnancies did not have gestational adalimumab exposure (defined as having stopped adalimumab at least 6 months prior to LMP) and were excluded from this analysis. Last menstrual period date was missing for another 19/356 pregnancies, but it was possible to assign the exposure as gestational for 15 of these pregnancies since ≥ 1 dose of adalimumab was taken within 6 months of the delivery date; however, the remaining four pregnancies could not be categorised as having adalimumab exposure due to missing LMP and/or delivery date and were excluded. Thus, 293 pregnancies with gestational adalimumab exposure in 238 patients were included in this analysis, including seven twin pregnancies, resulting in 300 pregnancy outcomes (Figure 1). Of the included pregnancies, 197/293 (67.2%) were exposed to adalimumab in all three trimesters per physician's discretion within the local standard of care and the patient's decision (Table 1).

Maternal demographics and disease characteristics for pregnancies that occurred during the PYRAMID registry are summarised in Table 2, and prior biologic use and the use of concomitant medications

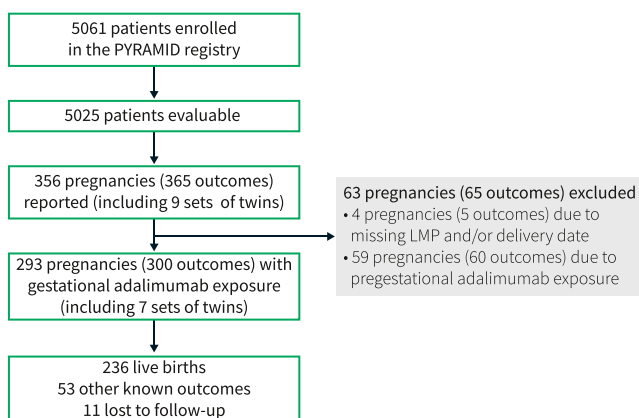


FIGURE 1 All PYRAMID maternal pregnancies. Gestational exposure was defined as adalimumab exposure within 6 months (≤ 183 days) prior to last menstrual period (LMP) date and/or any time during the pregnancy

during pregnancy are summarised in Table 3. Across the included pregnancies, mean maternal age was 31.1 years at pregnancy outcome and the mean maternal duration of CD was 8.6 years at LMP. PGA score (mean \pm standard deviation [SD]) was lower at the time of LMP (3.1 ± 4.3) or delivery date (3.2 ± 4.3) than at the time of registry entry

TABLE 1 Maternal gestational exposure to adalimumab during the PYRAMID registry

Number of pregnancies ^a	293
Gestational adalimumab exposure, n (%)	
Before conception only (≤ 6 months prior to LMP)	12 (4.1)
First trimester only	22 (7.5)
Second and/or third trimester only	1 (0.3)
First and second or first and third trimester	35 (11.9)
Throughout pregnancy ^b	197 (67.2)
Unknown exposure timing	26 (8.9)

Note: Gestational exposure was defined as adalimumab exposure within 6 months (≤ 183 days) prior to the LMP date and/or any time during the pregnancy.

Abbreviation: LMP, last menstrual period.

^aTwin gestations were counted as one pregnancy.

^b ≥ 1 dose of adalimumab within each trimester.

TABLE 2 Demographics and clinical characteristics of patients with Crohn's disease with reported pregnancies

Number of pregnancies ^a	293
Maternal age at registry entry (years)	
Mean \pm SD	28.3 \pm 4.7
Maternal age at pregnancy outcome (years)	
Mean \pm SD	31.1 \pm 4.7
Race, n (%)	
White	281 (95.9)
Black	5 (1.7)
Asian	3 (1.0)
Other	4 (1.4)
Alcohol use at registry entry, n (%)	
Current drinker	135 (47.5)
Ex-drinker	5 (1.8)
Nondrinker	144 (50.7)
Tobacco use at registry entry, n (%)	
Current smoker	79 (27.7)
Ex-smoker	46 (16.1)
Nonsmoker	160 (56.1)
CD duration at registry entry (years)	
Mean \pm SD	7.2 \pm 5.3

TABLE 2 (Continued)

CD duration at LMP (years)	<i>n</i> = 272
Mean ± SD	8.6 ± 5.4
Involved intestinal area at registry entry, <i>n</i> (%)	<i>n</i> = 293
Anal	66 (22.5)
Colon	213 (72.7)
Gastroduodenum	16 (5.5)
Ileum and other areas (excluding colon)	203 (69.3)
Jejunum	16 (5.5)
Rectum	54 (18.4)
Ileum only	49 (16.7)
Colon only	35 (11.9)
Ileum and colon	138 (47.1)
Other	9 (3.1)
Prior CD surgery, <i>n</i> (%)	<i>n</i> = 189
	46 (24.3)
CD complications history, prior to and during registry entry, <i>n</i> (%)	<i>n</i> = 189
Arthralgia/arthritis	64 (33.9)
Iritis/uveitis	0
Erythema nodosum	0
Oral aphthous ulcers	1 (0.5)
Anal fissure	2 (1.1)
Draining fistula	52 (27.5)
Internal fistula	34 (18.0)
Pyoderma gangrenosum	31 (16.4)
Perianal abscess	71 (37.6)
Bowel obstruction	31 (16.4)
Bowel resection	64 (33.9)
PGA score at registry entry	<i>n</i> = 280
Mean ± SD	4.5 ± 4.6
PGA score at LMP ^b	<i>n</i> = 241
Mean ± SD	3.1 ± 4.3
PGA score at delivery date ^c	<i>n</i> = 189
Mean ± SD	3.2 ± 4.3

Note: PGA, derived from the Harvey-Bradshaw Index, was used to assess general well-being (scored from 0 to 4), abdominal pain (scored from 0 to 3), diarrhoea (the number of semisolid/liquid stools per day during the past 7 days), blood in stool (scored from 0 to 2), abdominal mass (scored from 0 to 3), and CD-related extraintestinal manifestation (scored as 1 per complication).

Abbreviations: CD, Crohn's disease; LMP, last menstrual period; PGA, Physician's Global Assessment; SD, standard deviation.

^aTwin gestations were counted as one pregnancy.

^bLast available PGA score within 12 months prior to LMP.

^cClosest available PGA score ±90 days around delivery date.

TABLE 3 Medication use prior to or during pregnancy

Number of pregnancies	293
Prior anti-TNFs/biologics started and finished >6 months prior to LMP, > <i>n</i> (%)	
Infliximab	151 (51.5)
Certolizumab/certolizumab pegol	17 (5.8)
Investigational drug	0
Concomitant CD medications started during pregnancy (medication started or ended with ≥1 dose in a period of 6 months prior to LMP and delivery date), <i>n</i> (%)	
5-Aminosalicylates (aminosalicylic acid, sulfasalazine, mesalazine, olsalazine, balsalazide)	57 (19.5)
Azathioprine	98 (33.4)
6-Mercaptopurine	25 (8.5)
Methotrexate	15 (5.1)
Corticosteroids (prednisone, prednisolone, methylprednisolone, budesonide, hydrocortisone, beclomethasone, dexamethasone)	92 (31.4)
Antibiotics (ciprofloxacin, metronidazole, ampicillin, tetracycline)	43 (14.7)
Narcotic analgesics (fentanyl, hydrocodone, hydromorphone)	9 (3.1)

Abbreviations: CD, Crohn's disease; LMP, last menstrual period; TNF, tumour necrosis factor.

(4.5 ± 4.6). The number of pregnancies occurring in patients with a history of draining fistulas, internal fistulas, or arthralgia/arthritis were 27.5%, 18.0%, and 33.9%, respectively. For over half of the pregnancies (51.5%), patients had received infliximab prior to the pregnancy (started and stopped >6 months prior to pregnancy). Corticosteroids and thiopurines (azathioprine/6-mercaptopurine), prescribed in 31.4% and 33.4%/8.5% of pregnancies, respectively, were the most frequently administered concomitant medications to adalimumab during the pregnancy.

Complications of pregnancy

Complications occurring during the defined pregnancy time frame were reported by 20 patients (23 individual events; Table 4). The only events occurring in more than 1 patient were pre-eclampsia (3 patients) and premature labour (2 patients).

One case of hydrops fetalis was reported, caused by a parvovirus infection detected at a gestational age of 20 weeks in a 40-year-old mother. Treatment with adalimumab may have increased the susceptibility of the mother to parvovirus infection during the pregnancy due to an increased risk of infection with immunosuppressant agents.⁹ This pregnancy resulted in a stillbirth.

In addition, a 30-year-old mother, who received adalimumab in all three trimesters throughout pregnancy, delivered an infant with cerebral palsy after experiencing a uterine rupture and emergency

TABLE 4 Complications of pregnancy during the pregnancy interval^a by system organ class and preferred term

System organ class preferred term	n = 238	
	Patients, ^b n	Events, ^c n
Any pregnancy complication	20	23
Cardiac disorders	1	1
Atrial thrombosis	1	1
Infections and infestations	8	9
Candida infection	1	1
Device-related infection	1	1
Endometritis	1	1
Mastitis	1	1
Pelvic abscess	1	1
Pyelonephritis	1	1
Sialadenitis	1	1
Staphylococcal bacteraemia	1	1
Vulvovaginal mycotic infection	1	1
Injury, poisoning, and procedural complications	1	1
Uterine rupture	1	1
Pregnancy, puerperium, and perinatal conditions	9	9
Hydrops fetalis	1	1
Complication of delivery	1	1
Pre-eclampsia	3	3
Premature labour	2	2
Premature rupture of membranes	1	1
Uterine contractions during pregnancy ^d	1	1
Reproductive system and breast disorders	2	2
Bartholinitis	1	1
Metrorrhagia	1	1
Respiratory, thoracic, and mediastinal disorders	1	1
Pulmonary embolism	1	1

Abbreviation: LMP, last menstrual period.

^aThe pregnancy interval was defined from LMP date through to delivery date +3 months. If LMP date or delivery date was missing, a 12-month window was conservatively assumed. Adverse pregnancy complications were included based on medical and literature review. Pregnancy outcomes are summarised in Table 5 and not included here as complications of pregnancy.

^bA patient with several reports of the same PT is counted once per PT. The sum of the total number of patients reporting each of the preferred terms should be greater than or equal to the SOC total. A patient who reported two or more different preferred terms that were in the same SOC was counted once in the SOC total.

^cAll events were counted.

^dLikely to have been premature contractions.

caesarean section. Two days later she had a pulmonary embolism thought to have been causally related to the surgical procedure. According to the investigator, the infant's cerebral palsy and post-operative maternal pulmonary embolism were both attributed to the uterine rupture.

Pregnancy outcomes

Of the 300 foetuses with maternal adalimumab exposure included in this analysis, 289 (96.3%) had a known outcome (Table 5). Among the known outcomes, most (236/289; 81.7% [95% CI, 76.7–86.0]) were live births. There were 30 spontaneous abortions (10.4% [95% CI, 7.1–14.5]), 14 elective terminations (4.8% [95% CI, 2.7–8.0]; one case was a known foetal defect of trisomy 21 [case vignette in Supplementary Text]), eight ectopic pregnancies (2.8% [95% CI, 1.2–5.4]), and one stillbirth (0.3% [95% CI, 0.0–1.9]); this occurred in the case of hydrops fetalis reported in the previous section).

Congenital malformation was observed in one live-born infant (0.3% [95% CI, 0.0–1.9]). This event was reported in a 34-year-old patient with CD, obesity, and a cigarette smoking history of 15 pack-years who gave birth to a full-term female infant with low birth weight (1.8 kg), pulmonary valve stenosis, and tricuspid valve incompetence. The mother experienced pre-eclampsia during the pregnancy. This patient was treated with adalimumab during the first and second trimesters of pregnancy, and concomitant medications included metamizole and labetalol.

Preterm births (<37 weeks) were reported in 32/236 (13.6% [95% CI, 9.5–18.6]) live births; of these, 25 (78.1%) were moderate-

TABLE 5 Pregnancy outcomes

n = 300 ^a	
Known outcomes, n (%)	289 (96.3)
Pregnancy outcomes ^b , n (%) [95% CI]	
All live births	236 (81.7) [76.7–86.0]
Preterm (gestational age <37 weeks) ^c	32 (13.6) [9.5–18.6]
Live birth with congenital anomaly	1 (0.3) [0.0–1.9]
Spontaneous abortion	30 (10.4) [7.1–14.5]
Elective termination ^d	14 (4.8) [2.7–8.0]
Stillbirth	1 (0.3) [0.0–1.9]
Ectopic pregnancy	8 (2.8) [1.2–5.4]

Abbreviation: CI, confidence interval.

^aEach foetus was counted separately.

^bAs percentage of known outcomes (n = 289).

^cAs percentage of live births with/without congenital anomaly.

^dNot all elective terminations have analysis of foetus to determine if there were chromosomal abnormalities or foetal defects. One elective termination was reported as a chromosomal defect (see Supplementary Text).

to-late preterm (≥ 32 weeks to < 37 weeks). Very preterm (≥ 28 to < 32 weeks) and extremely preterm (< 28 weeks) births were less frequent, accounting for 5/32 (15.6%) and 2/32 (6.3%) of the total preterm births, respectively. Two of the preterm births (one extremely preterm and one very preterm [twins]) resulted in three infant deaths (case vignettes in Supplementary Text).

Of 208 live births with known birth weights, 27 infants had low birth weight (13.0%; Table S1); 12 infants with low birth weight were born preterm (44.4%).

Disease activity and patient-reported outcomes in patients who became pregnant during the PYRAMID registry are presented in Table S2 and Figures S1–3 (see Supplementary Text).

DISCUSSION

These post hoc observational data on 293 pregnancies were collected from 238 patients with CD receiving adalimumab who became pregnant while participating in the PYRAMID registry. This allowed us to observe the real-world pregnancy outcomes among those receiving adalimumab. These pregnancies generally occurred in patients in their early 30s and the mean maternal disease duration was approximately 9 years. Overall, more than 50% of pregnancies occurred in patients who were receiving their second biologic therapy; 27.5% and 18.0% of pregnancies occurred in patients who were burdened with either a draining or internal fistula, respectively. Most pregnancy outcomes (81.7% [95% CI, 76.7–86.0]) were live births, of which 13.6% (95% CI, 9.5–18.6) were preterm births, and one infant was born with a birth defect. Since 2007 when the first patient was enrolled in the PYRAMID registry, therapeutic drug monitoring (TDM) has recently emerged as the new standard of care for optimising anti-TNF therapy in CD. Therefore, it is possible that the monitoring of mother and baby may have been different then compared with standard of care today.

The rates of live births and adverse pregnancy outcomes (congenital anomalies, spontaneous abortion, preterm birth, stillbirth) reported in this analysis were generally comparable to previously published pregnancy outcomes in patients with CD receiving adalimumab (Organization of Teratology Information Services [OTIS] and Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes [PIANO] registries) or other anti-TNF inhibitors, including infliximab (The Crohn's Therapy, Resource, Evaluation, and Assessment Tool registry) and certolizumab pegol.^{13,21–24}

In this analysis, the number of infants born with birth defects was small (0.3% [95% CI, 0.0–1.9], one infant) and not higher than the rates reported in the general population, as approximately 3%–5% of all infants born in the United States have congenital anomalies.²⁵ The infant was born with pulmonary valve stenosis and tricuspid valve incompetence, which is reflective of common congenital cardiac malformations.^{25,26}

The observed rate of preterm live births in this analysis (13.6% [95% CI, 9.5–18.6]) was consistent with that reported for patients with CD or RA exposed to adalimumab (11.5%) in the OTIS registry.²¹ It was

also consistent with the rate of preterm births observed in the global general population (11.1%).²⁷ Of the 3 infants who died in this analysis, all were preterm (< 32 weeks' gestation), which is one of the leading causes of infant mortality.²⁸ Preterm births often result in low birth weight infants and, consistent with this, almost half of the infants with low birth weights were preterm births. Overall, the observed rate of pregnancies resulting in a low-birth-weight infant in this analysis (13.0%) was similar to that reported in patients with IBD exposed to TNF inhibitors (10.9%) or TNF-naïve patients with IBD (8.0%).⁴

The rate of spontaneous abortion reported in this analysis was 10.4% (95% CI, 7.1–14.5), which was consistent with the published rate in patients with CD (or RA in the OTIS registry) with nonbiologic exposure (8.9%–11.1%)^{21,22} or exposure to TNF inhibitors (12.9%–16.9%).^{21,22,29} This was also similar to background rates reported for the general population (5.2%–15.3%).^{21,29–31} The risk of spontaneous abortions increases with maternal age (> 35 years) and prior history of miscarriage,³² and almost half of the patients with spontaneous abortions in this analysis had one of these known risk factors.

The rate of stillbirths was also low in PYRAMID, with one (0.3% [95% CI, 0.0–1.9]) stillbirth noted in an infant with hydrops fetalis. Parvovirus infection occurred in this 40-year-old patient prior to 20 weeks of gestation and was found in the placenta after foetal demise. Parvovirus B19 infection may affect 1%–5% of pregnancies and has a wide range of clinical presentations ranging from uncomplicated pregnancy to severe hydrops fetalis or infant death.³³ When parvovirus infections occur before 20 weeks of gestation, there is a higher foetal loss rate compared with infections after 20 weeks (14.8% vs. 2.3%).³³ There was one elective termination resulting from a prenatal diagnosis of a chromosomal defect (trisomy 21) in a 38-year-old patient; however, alterations to chromosomal DNA cannot reasonably be attributed due to the known, nongenotoxic mechanism of adalimumab.⁹

The rate of ectopic pregnancies in this analysis (2.8% [95% CI, 1.2–5.4]) was similar to that previously reported among pregnancies in patients with CD (1.9%).³⁴ Of the 8 ectopic pregnancies, 1 patient had prior abdominal surgery (bowel resection secondary to disease-related obstruction) and another was of advanced maternal age; both risk factors are associated with ectopic pregnancy.³⁵

The most common complications of pregnancy reported included pre-eclampsia (3 patients) and premature labour (2 patients). Patients with IBD are at increased risk of severe pre-eclampsia compared with patients without IBD, with increased risk of pre-eclampsia also observed in patients with IBD receiving anti-TNF therapy.^{36,37} However, the pre-eclampsia rates (1.3%) reported in the current analysis were within the pre-eclampsia/eclampsia rates observed in patients with (2.4%) or without (1.8%) IBD.¹⁷

As IBD activity is an important contributor to adverse maternal and infant outcomes,⁷ it is crucial to control disease activity, aiming for disease remission before conception, and to maintain remission throughout the pregnancy.^{7,38–40} Current guidelines^{6,11,12,41} recommend maintaining treatment for CD during gestation, as the benefits of controlled disease may be greater than potential treatment-related risks, and discontinuation of therapy should only be

considered in patients at low risk of relapse. Indeed, in this analysis, around two-thirds of patients received adalimumab treatment throughout their pregnancies at their physician's discretion. An improvement in disease activity and quality of life outcomes, from point of registry entry to LMP or delivery was observed in this cohort of patients.

Strengths and limitations

This analysis used data from the PYRAMID registry, which is one of the largest data repositories of adult patients with CD receiving a biologic therapy in routine clinical practice. The primary objective of the registry was to evaluate the long-term safety of adalimumab; the registry also captured rare data on pregnancy outcomes and other pregnancy-related events, and therefore adds to the body of evidence observing the safety of biologic therapy in this patient population. Given the size of the registry and the broad patient populations it captures, this analysis provides a unique real-world, representative experience of the effects of adalimumab on pregnancy outcomes in patients with CD.

In relation to this post hoc, non-a priori analysis, a limitation of the registry design is that it lacked a comparator group to control for selection bias. Moreover, as PYRAMID was an open-label, non-interventional, observational registry, adalimumab treatment was administered at the discretion of the physician, including the decision of whether or when adalimumab would be discontinued after a pregnancy was reported. In addition, the study was carried out before TDM was performed routinely in clinical practice. The schedule of study visits was the same for all patients, and gaps of ≤ 70 days' treatment interruption were not considered as a break in therapy. Local treatment practices and recommendations from guidelines have been updated throughout data collection for the PYRAMID registry between 2007 and 2016. In addition, the limitations of longitudinal, noninterventional, long-term data capture, including missing data, the oversight of data entry and monitoring, and patient withdrawal from the registry, should be considered in the interpretation of these data.

Finally, infants were only followed for 70 days after delivery, so there was no long-term follow-up to assess infections, including opportunistic and serious infections, or any other adverse event reporting in this separate population.

CONCLUSIONS

Discontinuation of effective CD therapies during pregnancy due to a lack of available safety data may lead to adverse outcomes for the mother and infant. Data collected for patients with CD who became pregnant while participating in the PYRAMID registry suggested that adalimumab treatment contributed no additional adverse effects during the pregnancy course or on pregnancy outcomes.

These observational data will help inform patients with CD and their treating physicians when considering the management of CD activity prior to and during pregnancy and support the need for further clinical knowledge to improve the standard of care of pregnant patients with CD.

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CONFLICTS OF INTEREST

AH has served as consultant, advisory board member, or speaker for AbbVie, Arena, Atlantic, Bristol-Myers Squibb, Celgene, Celltrion, Falk, Ferring, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire, and Takeda; and also serves on the Global Steering Committee for Genentech. GD has received consulting and/or lecture fees from AbbVie, ActoGeniX, AIM, Boehringer Ingelheim, Centocor, Chemo Centryx, Cosmo Technologies, Elan Pharmaceuticals, enGene, Falk Pharma, Ferring, Galapagos, Giuliani SpA, Given Imaging, GlaxoSmithKline, Janssen Biologics, MSD, Neovacs, Novo Nordisk, Otsuka, PDL BioPharma, Pfizer, Receptos, Salix, Schering-Plough, SetPoint, Shire Pharmaceuticals, Takeda, Tillotts Pharma, UCB Pharma, Versant, and Vifor Pharma; research grants from AbbVie, Dr Falk Pharma, Given Imaging, Janssen, MSD, and PhotoPill; and speaking honoraria from AbbVie, Ferring, MSD, Norgine, Shire, Tillotts, Tramedico, and UCB Pharma. CHS has received speaker fees from AbbVie, Ferring, Janssen, Pfizer, Shire, and Takeda; and has served as a consultant and/or advisory board member for AbbVie, Actavis, Ferring, Janssen, Pfizer, Shire, and Takeda. EVL has received consulting fees from AbbVie, Allergan, Amgen, Arena, Boehringer Ingelheim, Bristol-Myers Squibb, Calibr, Celgene, Celltrion Healthcare, Eli Lilly, Genentech, Gilead, Iterative Scopes, Janssen, Ono Pharma, Pfizer, Scipher Medicine, Sun Pharma, Takeda, and UCB; and research support from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Genentech, Gilead, Janssen, Pfizer, Receptos, Robarts Clinical Trials, Takeda, Theravance, and UCB. RP has received consulting and/or lecture fees from AbbVie, Amgen, AstraZeneca, Axcana Pharma [now Aptalis], Biogen Idec, Bristol-Myers Squibb, Centocor, Chemo-Centryx, Eisai Medical Research Inc., Elan Pharmaceuticals, Ferring, Genentech, GlaxoSmithKline, Janssen, MSD, Ocera Therapeutics, Otsuka America Pharmaceutical, Pfizer, Prometheus Laboratories,

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AUTHOR CONTRIBUTIONS

Tricia Finney-Hayward, Mareike Bereswill: data acquisition and analysis. Tricia Finney-Hayward, Ailsa Hart, Geert D'Haens, Mareike Bereswill, Jasmina Kalabic, Gweneth Levy, Huifang Liang, Cynthia H. Seow, Edward V. Loftus, Remo Panaccione, Walter Reinisch and Jack Satsangi: interpretation of data, drafting the article, and final approval of version submitted.

DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised individual and trial-level data (analysis data sets), as well as other information (eg, protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: <https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html>.

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SUPPORTING INFORMATION

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