Pregnancy Outcomes in Subjects Exposed to Certolizumab Pegol

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ABSTRACT. ***Objective.*** To provide information on pregnancy outcomes in women receiving certolizumab pegol (CZP).

Methods. The UCB Pharma safety database was searched for pregnancies through to September 1, 2014. Reports for maternal and paternal CZP exposure were included and outcomes examined, and data on CZP exposure, pregnancy, comorbidities, and infant events were extracted by 2 independent reviewers. Concomitant medications and disease activity were reviewed for clinical trial patients.

Results. Of 625 reported pregnancies, 372 (59.5%) had known outcomes. Paternal exposure pregnancies (n = 33) reported 27 live births, 4 miscarriages, 1 induced abortion, and 1 stillbirth. Maternal exposure pregnancies (n = 339) reported 254 live births, 52 miscarriages, 32 induced abortions, and 1 stillbirth. Almost all reported pregnancies had exposure to CZP in the first trimester, when organogenesis takes place, and a third of them continued the drug into the second and/or third trimesters. The most frequent indications for maternal CZP use were Crohn disease (192/339) and rheumatic diseases (118/339). Twelve cases of congenital malformation and a single neonatal death were reported.

Conclusion. Analysis of pregnancy outcomes after exposure to CZP supports previous reports, suggesting a lack of harmful effect of maternal CZP exposure on pregnancy outcomes. However, additional data from a larger number of outcomes after exposure and studies including an unexposed comparison group are required to fully evaluate CZP safety and tolerability in pregnancy. (J Rheumatol First Release November 1 2015; doi:10.3899/jrheum.140189)

Key Indexing Terms:
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Inflammatory diseases, including rheumatoid arthritis (RA) and Crohn disease (CD), often affect women of reproductive age. Evidence suggests that the risk of adverse pregnancy outcomes is correlated with maternal disease activity and that active disease complicates pregnancy outcomes[1,2,3,4]. Discontinuation of medication because of pregnancy has also been associated with delivery at an earlier gestational age[5]. Therefore, to achieve the best fetal and maternal outcomes, there is a need for optimum maternal health and adequate disease control during pregnancy.

Antitumor necrosis factor (anti-TNF) medications are often used for the treatment of inflammatory diseases; however, only a few immunosuppressive drugs are considered safe during pregnancy by regulatory authorities[6]. Several updated reviews, including a systematic literature review, have investigated the safety of anti-TNF therapy use during pregnancy and breastfeeding[7,8,9]. These reports suggest that anti-TNF can be useful for controlling disease activity during pregnancy with no obvious effect on pregnancy outcomes to date, although treatment decisions need to be made on a case-by-case basis to evaluate potential toxic effects against the harm of high maternal disease activity on pregnancy outcomes. They also acknowledge that

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data regarding the effect of such therapies on pregnancy outcomes are currently limited, and thus safety during pregnancy cannot be adequately assessed. Based on the available data, guidelines from expert physicians advise continuation of anti-TNF therapy in CD during pregnancy at least through the second trimester when justified by maternal disease activity[10,11]. In RA, anti-TNF can be continued during pregnancy if warranted by maternal disease[12]. It is recommended that anti-TNF therapy be discontinued during the third trimester to limit fetal transfer of these drugs close to term.

Certolizumab pegol (CZP) is a PEGylated Fc-free anti-TNF therapy approved in over 50 countries for the treatment of RA, ankylosing spondylitis, axial spondyloarthritis, psoriatic arthritis, and CD[13]. CZP differs from other anti-TNF because it lacks an antibody Fc-region, which is known to play a key role in active materno-fetal placental transfer by binding to the neonatal Fc receptor (FcRn)[14]. Because of the absence of an Fc-region, CZP does not bind human FcRn and consequently does not undergo FcRn-mediated transfer across the placenta[15]. Lack of FcRn binding may also explain the absence of placental transfer in an *in vivo* rodent model, an *ex vivo* human placental transfer model, and in an observational clinical study[16,17,18]. However, clinical data are limited, and the US Food and Drug Administration (FDA) prescribing information indicates that CZP should be used during pregnancy only if clearly needed[19], while the European Medicines Agency's Summary of Product Characteristics states that CZP is not recommended during pregnancy[20].

The objective of our investigation was to provide information on the pregnancy outcomes of women and infants exposed to CZP in a retrospective analysis of pregnancy case reports in the Union Chimique Belge (UCB) Pharma safety database up to September 1, 2014. Data were also collected on pregnancies where a male partner reported exposure around the time of conception. Our study reports pregnancy outcomes and maternal demographics, including information on trimesters of CZP exposure, maternal disease activity, and concomitant medication usage, for the largest count of CZP-exposed pregnancies to date.

MATERIALS AND METHODS

The UCB Pharma drug safety database was searched for all CZP-exposed pregnancy reports. Pregnancy data were obtained from several sources, such as spontaneous reports, where information was received directly from healthcare professionals (e.g., physicians, pharmacists, and nurses) or consumers (e.g., patients, family members, and lawyers) as well as interventional and noninterventional studies (NIS). Reports from the literature were not included because it was not possible to validate the data from those sources.

FDA guidelines for evaluating the risks of drug exposure in human pregnancies were followed[21]. When notification of a pregnancy report was received, it triggered targeted followup with the reporter using a specialized pregnancy reporting form. Among other covariates, information sought from the reporter included first date of last menstrual period and estimated date of delivery; details of exposure to CZP and concomitant drugs within 3 months prior to conception and during pregnancy; results of prenatal investigations; maternal characteristics including age, weight, and comorbid diseases; and the woman's obstetric history. Information on the course of the pregnancy (including adverse events experienced by the mother) was also requested. In paternal exposure pregnancies, information on exposure date, maternal medical history, and maternal concomitant medications was sought.

Outcomes were considered for pregnancies after paternal (father received CZP) and maternal exposures (mother received CZP). Data were collected from both prospective and retrospective reports; a prospective pregnancy was defined as a pregnancy for which there was no prenatal diagnosis of a fetus with a congenital defect and the pregnancy was still ongoing at the time of the initial report to UCB Pharma. A retrospective pregnancy constituted either a pregnancy with a prenatal diagnosis of a congenital defect or a pregnancy that had already been completed at the time of the report. Pregnancies were reported from the start of CZP clinical development (earliest report dated July 12, 2001) and continued postmarketing. For our manuscript, the cutoff date for data collection from the safety database was September 1, 2014. Data on exposure, pregnancy dating, maternal comorbidities, and infant events were extracted from case reports by 2 independent reviewers; reconciliation for discrepancies was performed by a third independent reviewer when necessary.

Pregnancy dating was based on available information in a hierarchy of data, according to reliability; gestational age at pregnancy outcome and the pregnancy outcome date (if reported) were used first. If these dates were not available, the estimated date of delivery was used and/or the last menstrual period date was used as a final option to date the pregnancy. Trimesters of pregnancy were determined using the above algorithm and distinguished as first trimester up to 12 weeks and 6 days, second trimester from 13 weeks to 28 weeks and 6 days, and third trimester as any time including and after 29 weeks[22]. Earliest trimester of exposure was determined by using the start and stop dates of exposure to the drug as reported in the case narrative and corresponding to the dates of the pregnancy as calculated from the hierarchy of pregnancy dates described above. For cases where these dates were incomplete or unclear, a separate review by 2 independent reviewers was conducted to determine when exposure occurred.

Pregnancy outcome was categorized and defined as follows: live birth, miscarriage (noninduced embryonic or fetal death or passage of products of conception before 20 weeks of gestation), induced abortion (medically indicated or elective), and stillbirth (a fetal death occurring at ≥ 20 weeks of gestation). Outcomes were followed up with the case reporter (predominantly the treating physician), including both written and telephone contact attempts, starting within 30 days of estimated delivery date (EDD) and continuing over several months. When an EDD was not available, it was automatically calculated as 9 months after the date of the pregnancy report. If no information on pregnancy outcome was available by the cutoff date, the pregnancy outcome was considered unknown. Ongoing pregnancies included any pregnancy with an estimated (or calculated) due date after August 31, 2014. All other reports with an unknown outcome were considered lost to followup.

Disease activity information was retrieved for patients within clinical trials until the trial exit because of pregnancy. Data presented here are from a previous 2013 data cut, not updated because of a limited number of new cases. Because data originated from a variety of clinical trials, disease activity was reported with multiple clinical measures. The clinical measures used for the majority of subjects were the Crohn's Disease Activity Index (CDAI) for CD and the Disease Activity Score in 28 joints (DAS28) with erythrocyte sedimentation rate (ESR) for RA. Disease activity was obtained at trial baseline (study entry) and the visit prior to the pregnancy report, and was stratified by pregnancy outcome.

Concomitant medications were identified as those taken between the most recent visit prior to pregnancy report and pregnancy report date (excluding those that ended before start of pregnancy report visit and those that started after pregnancy report date). Concomitant medication start date

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was available for most patients in clinical trials; however, because patients were withdrawn from the clinical trial at the point where pregnancy was reported, the information available for concomitant medication end dates may be unreliable or sometimes absent. Summarized concomitant medication analysis was thus restricted to patients for whom the concomitant medication end date was available. Missing data were imputed.

RESULTS

At the September 1, 2014 cutoff date, 625 pregnancies were reported, of which 579 (92.6%) and 46 (7.4%) occurred following maternal and paternal CZP exposures, respectively (Figure 1).

Overview of all reported maternal pregnancy reports. Among the 579 maternal pregnancy reports, outcomes were available for 339 pregnancies with the majority of the pregnancies with unknown outcome being considered lost to followup (176/240, 73.3%; Figure 1). Pregnancies with unknown outcomes were more likely to be spontaneous reports (87.5% vs 64.0%, respectively) and prospective (97.5% vs 66.7%, respectively) compared with pregnancies with available outcomes. There were no differences by country or indication (data not shown).

Of the 339 maternal exposure pregnancies with known outcomes, 226 (66.7%) and 113 (33.3%) arose from prospective and retrospective reports, respectively (Figure 1). The majority of pregnancies occurred in North America (72.0%) and Europe (22.1%). Report sources were spontaneous (64.0%), clinical trials (9.1%), and other studies (26.8%), which included NIS, healthy volunteer studies, open-label extensions, and compassionate use. The majority of pregnancies were in women with CD. Overall, 254 (74.9%) live birth pregnancies, 52 (15.3%) miscarriages, 32 (9.4%) induced abortions, and 1 stillbirth were reported (Table 1). Differences in pregnancy outcomes were noted between retrospectively and prospectively reported pregnancies, with retrospective pregnancies resulting in substantially more miscarriages (Table 1). Retrospective reports can be biased toward the reporting of more unusual and severe outcomes, suggesting that it is important to characterize these pregnancies separately.

Prospective maternal pregnancy reports. Of the 226 prospective maternal CZP exposure pregnancies with available outcomes, 135 (59.7%) arose from spontaneous reports and 23 (10.2%) were reported for patients enrolled in CZP clinical trials. Most prospective pregnancy reports originated in North America (73.5%) and were reported in women with CD (58.4%; Table 1).

CZP exposure during pregnancy. Most pregnancies were exposed during the first trimester when the majority of fetal organ and organ system development takes place (Table 2). For the 132 pregnancies where trimester of exposure could be determined, 63 women stopped CZP in the first trimester (of which 34 had live births, 16 a miscarriage, and 13 an induced abortion); 48 continued CZP beyond the first trimester, and 16 started CZP in the second or third trimesters. Notably, 41 pregnancies were exposed to CZP in all 3 trimesters (Table 2).

Pregnancy and infant outcomes. Of the 226 pregnancies reported prospectively with available pregnancy outcomes, 182 (80.5%) live births, 21 (9.3%) miscarriages, and 22 (9.7%) induced abortions were described; 1 pregnancy resulted in stillbirth. Cesarean deliveries were reported in

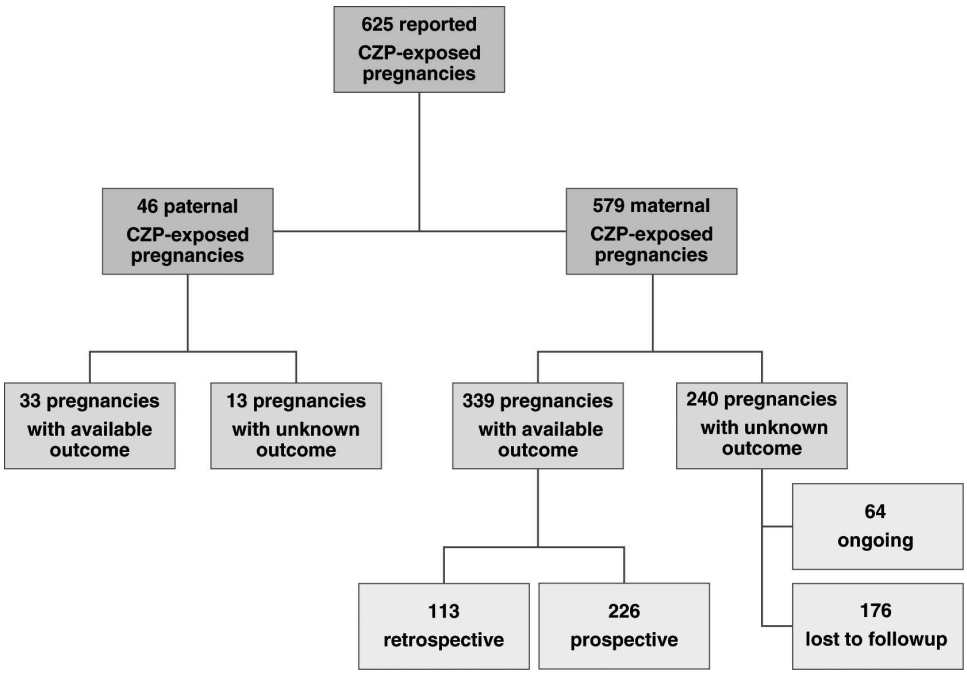

Figure 1. Distribution of pregnancy reports. CZP: certolizumab pegol.

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Table 1. Characteristics of maternal CZP-exposed pregnancies with known outcome by report type. Values are n (%) unless otherwise specified.

Characteristics	Prospective, n = 226	Retrospective, n = 113	Total, n = 339
Report source			
Spontaneous	135 (59.7)	82 (72.6)	217 (64.0)
Clinical trial	23 (10.2)	8 (7.1)	31 (9.1)
Other clinical study*	68 (30.1)	23 (20.4)	91 (26.8)
Region			
North America	166 (73.5)	78 (69.0)	244 (72.0)
Europe	47 (20.8)	28 (24.8)	75 (22.1)
Asia	7 (3.1)	2 (1.8)	9 (2.7)
Latin America	3 (1.3)	3 (2.7)	6 (1.8)
Africa	1 (0.4)	1 (0.9)	2 (0.6)
Oceania	2 (0.9)	1 (0.9)	3 (0.9)
Indication			
Rheumatic disease**	78 (34.5)	40 (35.4)	118 (34.8)
Crohn disease	132 (58.4)	60 (53.1)	192 (56.6)
Other	16 (7.1)	13 (11.5)	29 (8.6)
Pregnancy outcome			
Live birth	182 (80.5)	72 (63.7)	254 (74.9)
Miscarriage	21 (9.3)	31 (27.4)	52 (15.3)
Induced abortion	22 (9.7)	10 (8.8)	32 (9.4)
Stillbirth	1 (0.4)	0	1 (0.3)
Maternal age at EDD, yrs, mean (SD)			
No. reported	188	40	228
< 18	1 (0.5)	0	1 (0.4)
18–34	137 (72.9)	23 (57.5)	160 (70.2)
≥ 35	50 (26.6)	17 (42.5)	67 (29.4)
Multiple gestation			
Yes	3 (1.3)	2 (1.8)	5 (1.5)
Live birth characteristics	**Prospective, n = 182**	**Retrospective, n = 72**	**Total, n = 254**
Gestational age at birth, weeks			
No. reported	133	28	161
< 32, early preterm	5 (3.8)***	0	5 (3.1)***
32 to < 37, preterm	15 (11.3)†	7 (25.0)	22 (13.7)†
≥ 37, term	113 (85.0)	21 (75.0)	134 (83.2)
Birth weight, g			
No. reported	120	24	144
< 1500, very low	0	0	0
1500–2499, low	12 (10.0)	2 (8.3)	14 (9.7)
≥ 2500, normal	108 (90.0)	22 (91.7)	130 (90.3)
Cesarean delivery	63 (34.6)‡	17 (23.6)	80 (31.5)

* Other study includes noninterventional studies, healthy volunteer, open-label extensions, and compassionate use. ** Rheumatic disease includes rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, and juvenile idiopathic arthritis. *** Includes 2 sets of twins. † Includes 1 set of twins. ‡ Includes all 3 sets of twins. CZP: certolizumab pegol; EDD: estimated delivery date.

34.6% of the 182 pregnancies resulting in live births (Table 1). Among the 133 pregnancies with available gestational age at birth, 113 (85.0%) were considered term (≥ 37 weeks of gestation); 5 pregnancies were considered early preterm (< 32 weeks of gestation), including 2 sets of twins; and 15 were preterm (between 32 and 37 weeks of gestation), including 1 set of twins. There were 3 sets of twins within the 182 live birth pregnancies, resulting in a total of 185 infants born (Table 1). Among the 120 live births with birth weight available, 90% (n = 108) were of normal birth weight and 10% had low birth weight (between 1500 and 2499 g; Table 1). Birth weight was not available for any of the twin live births. There was 1 infant reported to be small for gestational age (data not shown).

There were some differences in pregnancy outcomes by report source: spontaneously reported pregnancy or pregnancies reported in women participating in other study types (e.g., NIS) were more likely to result in live births (86.7% and 76.5%, respectively) than pregnancies reported in clinical trial patients (56.5%), which were more likely to

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Table 2. Characteristics of maternal CZP-exposed pregnancies with known outcome by pregnancy outcome. Values are n (%) unless otherwise specified.

Characteristics	Live Birth	Miscarriage	Induced Abortion	Stillbirth
Prospective, n	182	21	22	1
Report source				
Spontaneous, n = 135	117 (86.7)	10 (7.4)	7 (5.2)	1 (0.7)
Clinical trial, n = 23	13 (56.5)	4 (17.4)	6 (26.1)	0
Other clinical study, n = 68*	52 (76.5)	7 (10.3)	9 (13.2)	0
Indication				
Rheumatic disease, n = 78**	57 (73.1)	9 (11.5)	11 (14.1)	1 (1.3)
Crohn disease, n = 132	113 (85.6)	12 (9.1)	7 (5.3)	0
Other, n = 16	12 (75.0)	0	4 (25.0)	0
Maternal age at EDD, yrs				
No. reported	155	19	13	1
< 18, n = 1	1 (100.0)	0	0	0
18–34, n = 137	121 (88.3)	9 (6.6)	7 (5.1)	0
≥ 35, n = 50	33 (66.0)	10 (20.0)	6 (12.0)	1 (2.0)
Multiple gestation				
Yes, n = 3	3 (100.0)	0	0	0
Earliest trimester of CZP exposure				
Pre-conception only, n = 6†	5 (83.3)	0	1 (16.7)	0
1, n = 164	125 (76.2)	19 (11.6)	19 (11.6)	1 (0.6)
2, n = 17	17 (100.0)	0	0	0
3, n = 4	4 (100.0)	0	0	0
Indeterminable, n = 35‡	31 (88.6)	2 (5.7)	2 (5.7)	0
Trimester(s) of CZP exposure				
Preconception only, n = 6†	5 (83.3)	0	1 (16.7)	0
1, n = 63	34 (54.0)	16 (25.4)	13 (20.6)	0
2, n = 1	1 (100.0)	0	0	0
3, n = 3	3 (100.0)	0	0	0
1 & 2, n = 7	5 (71.4)	2 (28.6)	0	0
2 & 3, n = 12	12 (100.0)	0	0	0
1, 2, & 3, n = 41	41 (100.0)	0	0	0
Indeterminable, n = 93‡	81 (87.1)	3 (3.2)	8 (8.6)	1 (1.1)
Retrospective, n	72	31	10	0
Report source				
Spontaneous, n = 82	62 (75.6)	18 (22.0)	2 (2.4)	0
Clinical trial, n = 8	3 (37.5)	1 (12.5)	4 (50.0)	0
Other clinical study, n = 23*	7 (30.4)	12 (52.2)	4 (17.4)	0
Indication				
Rheumatic disease, n = 40**	26 (65.0)	8 (20.0)	6 (15.0)	0
Crohn disease, n = 60	37 (61.7)	20 (33.3)	3 (5.0)	0
Other, n = 13	9 (69.2)	3 (23.1)	1 (7.7)	0
Maternal age at EDD, yrs				
No. reported	22	14	4	0
< 18, n = 0	0	0	0	0
18–34, n = 23	16 (69.6)	7 (30.4)	0	0
≥ 35, n = 17	6 (35.3)	7 (41.2)	4 (23.5)	0
Multiple gestation				
Yes, n = 2	0	2 (100.0)	0	0
Earliest trimester of CZP exposure				
Preconception only, n = 0†	0	0	0	0
1, n = 32	14 (43.8)	14 (43.8)	4 (12.5)	0
2, n = 6	6 (100.0)	0	0	0
3, n = 4	4 (100.0)	0	0	0
Indeterminable, n = 71‡	48 (67.6)	17 (23.9)	6 (8.5)	0
Trimester(s) of CZP exposure				
Preconception only, n = 0†	0	0	0	0
1, n = 22	4 (18.2)	14 (63.6)	4 (18.2)	0
2, n = 0	0	0	0	0
3, n = 4	4 (100.0)	0	0	0
1 & 2, n = 2	2 (100.0)	0	0	0
2 & 3, n = 5	5 (100.0)	0	0	0
1, 2, & 3, n = 6	6 (100.0)	0	0	0
Indeterminable, n = 74‡	51 (68.9)	17 (23.0)	6 (8.1)	0

* Other study includes noninterventional studies, healthy volunteer, open-label extensions, and compassionate use. ** Rheumatic disease includes rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, and juvenile idiopathic arthritis. † Preconception only refers to cases where it is known that exposure stopped more than 14 and not more than 70 days prior to the first trimester. ‡ Cases where it was not possible to date CZP exposure and/or the pregnancy. CZP: certolizumab pegol; EDD: estimated delivery date.

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have an induced abortion (26.1%) or miscarriage (17.4%; Table 2).

The majority of women (72.9%) were between the ages of 18 and 34 years at EDD; 26.6% of pregnancies occurred in women 35 and older (Table 1). Nineteen percent of prospective maternal pregnancies reported pregnancy complications, including preeclampsia/hypertension (n = 6), placental abnormalities (n = 4), infection (n = 5), disease flare (n = 10), and gestational diabetes (n = 5).

Congenital malformations. Eight cases of congenital malformation were reported in the 185 infants born, 3 delivered from mothers with RA and 5 delivered from mothers with CD (Table 3). One baby had 22q11.2 deletion syndrome, unilateral right kidney, hypospadias, and inguinal hernia. The remaining 7 babies were born with individual cases of anal fistula, left-sided vesico-ureteric reflux, pyloric stenosis, club foot, polydactyly (left hand, pinky side), renal cyst (no treatment required), and ankyloglossia.

The death of a single neonate from brain damage and pneumo-peritoneum (report originating in the United States) after maternal CZP exposure during pregnancy was reported. The neonatal death was 1 of female twins born at 25 weeks and 6 days gestation by preterm Caesarean section, which was performed because of sustained fetal bradycardia in both babies. The maternal information for this case was very limited: indication for CZP, timing of exposure in pregnancy, concomitant medications, and maternal age were not reported. Age of the neonate at death was not reported, and all attempts to followup with the reporting physician failed.

Disease activity in clinical trial pregnancy reports. Disease activity at the time of pregnancy detection was examined for subjects reporting pregnancy during clinical trials; information on disease activity was unavailable after the pregnancy was detected because pregnant patients were required to exit the clinical trials. CDAI and DAS28-ESR data for patients with CD and RA, respectively, at baseline visit prior to pregnancy report and change from baseline stratified by pregnancy outcome are presented in Table 4. CD subjects had moderate (median CDAI 288.8) to low (median CDAI 175.8) disease activity at study entry and at the visit prior to the pregnancy report, respectively, with lowest median CDAI observed in the subjects who reported miscarriages and highest median CDAI reported in subjects who had induced abortions (Table 4). RA disease activity (median DAS28-ESR 6.2) was high at baseline (study entry), whereas low disease activity was reported at the visit prior to the pregnancy report for subjects with pregnancies resulting in live births and DAS28-ESR remission or moderate disease activity for subjects whose pregnancies resulted in miscarriage and induced abortion, respectively (Table 4). It should be noted that because disease activity data were available only for a small number of pregnancy reports (12 CD and 14 RA), results are to be interpreted with caution.

For pregnancies in clinical trials, the concomitant medications around the time of pregnancy are presented in Table 5. Nonsteroidal antiinflammatory drugs and corticosteroids were the most frequent medications used. Five patients with a miscarriage used concomitant methotrexate (contraindicated in pregnancy, FDA category X).

Retrospective maternal pregnancy reports. Of the 113 pregnancies that arose from retrospective reports, 72 (63.7%) live births, 31 (27.4%) miscarriages, and 10 (8.8%) induced abortions were reported (Table 1). No preconception CZP exposure was reported for the retrospective pregnancies; 22 pregnancies were exposed to CZP in the first trimester only, of which 14 resulted in miscarriage, 4 live births, and 4

Table 3. Description of congenital malformations.

Abnormality	Report Type	Region	Study Type	Indication for CZP Use
Left sided vesico-ureteric reflux	Prospective	Africa	Open-label extension	CD
Club foot	Prospective	North America	Noninterventional study	CD
22Q11.2 deletion syndrome, unilateral right kidney, hypospadias, and inguinal hernia	Prospective	North America	Clinical trial	CD
Pyloric stenosis	Prospective	North America	Clinical trial	CD
Posterior ankyloglossia	Prospective	North America	Spontaneous	CD
Polydactyl, left hand, pinky side	Prospective	North America	Spontaneous	RA
Renal cyst, no treatment required	Prospective	North America	Clinical trial	RA
Anal fistula	Prospective	Europe	Spontaneous	RA
Cleft palate	Retrospective	North America	Spontaneous	CD
Congenital diaphragmatic hernia	Retrospective	North America	Spontaneous	CD
Congenital morbus hirschsprung and club feet	Retrospective	Europe	Spontaneous	RA
Right aortic arch with aberrant left subclavian	Retrospective	Europe	Spontaneous	RA

CZP: certolizumab pegol; CD: Crohn disease; RA: rheumatoid arthritis.

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Table 4. Maternal disease activity by outcome for pregnancies from clinical trial reports: CD and RA subgroups*. Range of CDAI index: 0–600, remission < 150, low disease activity 150–219, moderate disease activity 220–450, and high disease activity > 450. Range of DAS28-ESR index: 0–10, remission ≤ 2.6, low disease activity > 2.6 to ≤ 3.2, moderate disease activity > 3.2 to ≤ 5.1, and high disease activity > 5.1.

CD	Live Birth, n = 6	Miscarriage, n = 2	Induced Abortion, n = 4	Total, n = 12
CDAI at baseline, CD study entry				
Mean (SD)	280.3 (42.0)	296.0 (7.2)	320.1 (47.8)	296.2 (42.1)
Median	275.4	296.0	304.9	288.8
Min, max	223, 347	291, 301	284, 387	223, 387
CDAI at visit prior to pregnancy report				
Mean (SD)	180.5 (100.9)	151.4 (2.3)	168.8 (99.3)	171.7 (86.2)
Median	200.3	151.4	163.2	175.8
Min, max	34, 304	150, 153	72, 277	34, 304
CDAI change from baseline				
Mean (SD)	–99.9 (74.1)	–144.6 (9.6)	–151.3 (84.7)	–124.5 (71.6)
Median	–86.2	–144.6	–147.9	–123.9
Min, max	–189, 1	–151, –138	–251, –58	–251, 1
RA	**Live Birth, n = 7**	**Miscarriage, n = 4**	**Induced Abortion, n = 3**	**Total, n = 14**
DAS28-ESR at baseline, RA study entry				
Mean (SD)	6.4 (0.8)	6.1 (0.7)	6.6 (0.9)	6.4 (0.8)
Median	6.2	6.1	6.6	6.2
Min, max	5.1, 7.3	5.4, 7.0	5.8, 7.6	5.1, 7.6
DAS28-ESR at visit prior to pregnancy report				
Mean (SD)	3.5 (1.7)	2.4 (1.4)	4.4 (1.1)	3.4 (1.6)
Median	2.7	1.9	4.2	2.9
Min, max	2.2, 6.3	1.3, 4.5	3.4, 5.6	1.3, 6.3
DAS28-ESR change from baseline				
Mean (SD)	–2.9 (1.6)	–3.7 (1.6)	–2.2 (0.8)	–3.0 (1.5)
Median	–3.0	–4.0	–2.1	–3.0
Min, max	–4.7, –0.6	–5.2, –1.6	–3.1, –1.6	–5.2, –0.6

* Includes pregnancies collected between July 12, 2001 and March 28, 2013. CD: Crohn disease; RA: rheumatoid arthritis; CDAI: Crohn's Disease Activity Index; DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate.

Table 5. Summary of concomitant medications taken at the time of pregnancy report. Values are n (%).

Medication	Live Birth, n = 39	Miscarriage, n = 10	Induced Abortion, n = 17	Unknown, n = 12	All, n = 78
Any	37 (94.9)	10 (100.0)	17 (100.0)	10 (83.3)	74 (94.9)
Methotrexate	7 (17.9)	5 (50.0)	4 (23.5)	1 (8.3)	17 (21.8)
Azathioprine	7 (17.9)	2 (20.0)	1 (5.9)	1 (8.3)	11 (14.1)
Mesalazine	10 (25.6)	2 (20.0)	3 (17.6)	0	15 (19.2)
NSAID	13 (33.3)	4 (40.0)	8 (47.1)	3 (25.0)	28 (35.9)
Steroids	12 (30.8)	3 (30.0)	6 (35.3)	4 (33.3)	25 (32.1)
Cyclosporine	0	0	1 (5.9)	0	1 (1.3)
Sulfasalazine	3 (7.7)	1 (10.0)	2 (11.8)	2 (16.7)	8 (10.3)

NSAID: nonsteroidal antiinflammatory drug.

women had induced abortions. Eight pregnancies continued CZP beyond the first trimester, and 9 pregnancies started CZP in the second and/or third trimesters; 6 pregnancies were exposed to CZP in all 3 trimesters (Table 2). There were 2 sets of twins, both resulting in miscarriage (Table 2). Four cases of congenital malformations were reported, 2 to mothers with RA and 2 to mothers with CD. One baby had congenital morbus hirschsprung and club feet, 1 had cleft palate, 1 had a right aortic arch with aberrant left subclavian, and 1 had a congenital diaphragmatic hernia (Table 3).

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Paternal pregnancy reports. Among the 46 paternal-exposed pregnancies, outcomes were available for 33 pregnancies (Figure 1). Reports with unavailable or unknown pregnancy outcomes were more likely to be from NIS, have CD, and be reported in North America than those with outcomes available. The majority of paternal pregnancy reports originated in North America (65.2%) and Europe (17.4%; data not shown).

Of the 33 pregnancies following paternal exposure, 27 resulted in live birth, 4 miscarriage, 1 induced abortion, and 1 stillbirth.

DISCUSSION

To our knowledge, this is the largest cohort to date of pregnancies exposed to an anti-TNF medication. Most of the pregnancies had first-trimester CZP exposure, and up to a third of prospectively collected pregnancies continued drug use into the second and/or third trimesters. The large majority of prospectively collected pregnancies resulted in positive outcomes with low rates of miscarriage, preterm birth, and congenital anomalies. Prior reports of anti-TNF medications have not found increased rates of congenital malformations following exposure during pregnancy[23,24,25,26,27], although data from large cohorts are not yet available[7,8,9]. Reports based on small numbers of pregnancies or case studies have suggested that the use of anti-TNF, such as adalimumab (ADA), infliximab (IFX), and etanercept, do not increase the risk of adverse pregnancy outcomes, and the data in our large single anti-TNF study confirms these reports[24,28,29,30,31].

Published data from 31 patients with inflammatory bowel disease, 10 of whom received CZP during pregnancy, demonstrated low levels of CZP placental transfer to neonates (3.9% of the plasma concentration measured in the mother) at birth[16]. In comparison, concentrations of IFX and ADA were higher in cord blood at birth compared with maternal plasma concentrations (160% and 153%, respectively). IFX and ADA concentrations were higher in infants than mothers and were detectable for weeks to months after birth[16]. The neonatal FcRn is involved in the maternal-fetal transfer of antibodies (γ globulin, immunoglobulin G), and the absence of the Fc portion in CZP likely interferes with binding to the FcRn and significantly reduces placental transfer[32]. *Ex vivo* placental transfer and animal model data also support low levels of CZP placental transfer[17,33]. Together, these results suggest that because of its unique lack of an Fc region, use of CZP during pregnancy may offer reduced exposure risk to the fetus after placental formation.

While our current study suggests that neonatal CZP exposure early in pregnancy is not associated with an increase in adverse pregnancy outcomes, there are important limitations to the analysis. For example, the drug safety database is designed as a surveillance reporting tool for adverse events, rather than an analysis tool; further, almost all reports within this database relate to patients receiving CZP therapy, and thus do not provide an untreated control group for comparison. In addition, although our analysis includes a large number of pregnancy outcomes in patients receiving an anti-TNF, the numbers are still relatively small for less common events of interest, and information regarding disease activity and concomitant medications at conception/during pregnancy is limited. Similarly, because of the biased structure of the retrospective cohort, comparability of the frequency of congenital malformations reported in our study with that of the general population should be limited to the prospective cohort. Estimates of major birth defects are similar in the European Union (2.6%)[34] and the United States (2.8%)[35]. Limited data availability because of the structure of the database and the reporting process also need to be considered; for example, regarding the timing of CZP exposure and concomitant medications taken during pregnancy.

An acknowledged limitation is also that the majority of the data originated from spontaneous postmarketing reports. While spontaneous reporting systems are recognized as essential elements for postmarketing pharmacovigilance surveillance, the data collected are affected by bias and often associated with inherent limitations, partly because of the passive and voluntary characteristic of the reporting systems. The differences in pregnancy outcomes between the prospective and retrospective pregnancy cohorts in our study highlight the difficulties of this reporting system. Limitations include recognized and extensive underreporting, variable quality and completeness of the data reported, and lack of information on drug exposure[36,37,38,39]. Incomplete reports were followed up repeatedly through written and telephone attempts for several months after expected delivery date. However, despite this, further data were unavailable for a proportion of pregnancy reports; this issue mostly affected spontaneous postmarketing reports. Incomplete reporting was a predominant limitation within our current study, and thus the results presented may not be representative of all CZP-exposed pregnancies.

Current data regarding CZP exposure before and during pregnancy are encouraging and suggest CZP exposure *in utero*, including first trimester exposure, does not adversely affect pregnancy outcomes. Our analysis represents a uniquely large number of pregnancies exposed to a single anti-TNF; further prospective data from increased numbers of pregnant women exposed to CZP will continue to be collected to comprehensively assess CZP safety and tolerability in pregnancy.

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