

Pregnancy Outcomes After Exposure to Certolizumab Pegol

Updated Results From a Pharmacovigilance Safety Database

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Objective. Anti-tumor necrosis factor (anti-TNF) medications are effective in controlling chronic inflammatory diseases, but information about their use and safety in pregnancy is limited. Consequently, anti-TNF agents are often discontinued early in gestation. Certolizumab pegol (CZP), a PEGylated, Fc-free anti-TNF agent approved for the treatment of rheumatic diseases and/or Crohn's disease, has minimal to no active placental transfer. This analysis was undertaken to evaluate pregnancy outcomes in women receiving CZP, especially those exposed during early pregnancy.

Methods. Prospective and retrospective data on maternal CZP exposure were extracted from the UCB Pharma safety database through March 6, 2017. Analysis was limited to prospective reports to avoid potential bias associated with retrospective submissions. The numbers of live births, miscarriages, elective abortions, stillbirths, and major congenital malformations were ascertained.

Results. Of 1,137 prospectively reported pregnancies with maternal exposure to CZP, 528 (including 10 twin

pregnancies) had 538 known outcomes: 459 live births (85.3%), 47 miscarriages (8.7%), 27 elective abortions (5.0%), and 5 stillbirths (0.9%). There were 8 major congenital malformations (1.7%) among the 459 infants. First trimester exposure occurred in 367 (81.2%) of 452 pregnancies resulting in 459 live births. Exposure during all 3 trimesters occurred in 201 (44.5%) of 452 pregnancies.

Conclusion. This analysis represents the largest cohort of pregnant women exposed to an anti-TNF agent for management of chronic inflammatory diseases. Analysis of pregnancy outcomes does not indicate a teratogenic effect of CZP, compared to the general population, nor an increased risk of fetal death. The data are reassuring for women of childbearing age considering treatment with CZP.

For women affected by chronic inflammatory diseases, such as rheumatoid arthritis (RA), axial spondyloarthritis (SpA), psoriatic arthritis (PsA), and Crohn's disease (CD), disease onset, diagnosis, and initiation of treatment increasingly overlap with peak reproductive age (1,2). For many of these patients, disease activity during pregnancy requires effective management to maintain

Supported by UCB Pharma.

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Dr. Clowse has received consulting fees, speaking fees, and/or honoraria from UCB Pharma (more than \$10,000) and research grants from Pfizer and Janssen. Dr. Scheuerle is a contractor with UCB Pharma, INC Research, and Genentech. Dr. Chambers has received research grants from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Pfizer, Hoffmann-La Roche/Genentech, Genzyme Sanofi-Aventis, Seqirus, Takeda, and UCB Pharma. Dr. Afzali has received consulting fees, speaking fees, and/or honoraria from

AbbVie, IBD Horizons (less than \$10,000 each), UCB Pharma, and Takeda (more than \$10,000 each) and research grants from UCB Pharma. Dr. Kimball has received consulting fees, speaking fees, and/or honoraria from UCB Pharma, Dermira, Janssen (less than \$10,000 each), and AbbVie (more than \$10,000). Dr. Cush has received consulting fees, speaking fees, and/or honoraria from AbbVie, UCB Pharma, Bristol-Myers Squibb, Celgene (less than \$10,000 each), Novartis, Amgen, Genentech, Eli Lilly and Company, and Horizon (more than \$10,000 each) and research support from Pfizer, Janssen, AbbVie, Celgene, Novartis, AstraZeneca, and Genentech. Dr. Förger has received speaking fees from Mepha, Roche, and UCB Pharma (less than \$10,000 each) and research grants from UCB Pharma.

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Submitted for publication November 2, 2017; accepted in revised form March 20, 2018.

maternal health and ensure optimal fetal outcomes. Up to half of pregnant patients with rheumatic diseases and the majority of those with inflammatory bowel disease (IBD) experience active disease and need treatment (3,4). High disease activity is associated with an increased risk of pregnancy complications and adverse outcomes, including preeclampsia, preterm delivery, low birth weight, small for gestational age, and fetal loss (5–13). Adequate disease control during pregnancy is therefore paramount for fetal and maternal health, as acknowledged by recent publications (6,14–16), and the risks of untreated disease during pregnancy should be evaluated against the risks related to drug exposure of mother and fetus. However, some treatments are not used in pregnant patients, due to proven teratogenicity (for example, methotrexate) or because of concerns due to the absence of a well-established safety profile in pregnancy (16).

Clinical trial data on the effects of drugs on pregnancy outcomes are sparse, since pregnant women are generally excluded from participation in clinical studies, and women who become pregnant during a trial have treatment stopped immediately (14). Therefore, evidence generated through pharmacovigilance reporting and pregnancy registries is extremely important to help physicians and patients

make informed decisions regarding anti-tumor necrosis factor (anti-TNF) treatment for rheumatic diseases and CD during pregnancy (15,17).

The UCB Pharma safety database contained reports of 625 pregnancies exposed to certolizumab pegol (CZP) up to 2014 (18), while the 2017 data cutoff presented here includes 1,600 CZP-exposed pregnancies. With a substantial number of pregnant patients now being exposed to CZP across the different indications, more data are available to gain a better understanding of the timing of gestational exposure and its impact on maternal and infant health. In particular, exposure during the first trimester, when most organogenesis takes place, is of interest. The objective of our investigation is to provide information on pregnancy outcomes, including major congenital malformations and other adverse maternal and fetal outcomes, with a specific focus on the timing of CZP exposure.

PATIENTS AND METHODS

The methodology of pregnancy data collection and analysis has been described previously (18). Reports of CZP-exposed pregnancies were obtained from the UCB Pharma safety database from the start of CZP clinical development through the cutoff date of March 6, 2017. We report the totality of the data up

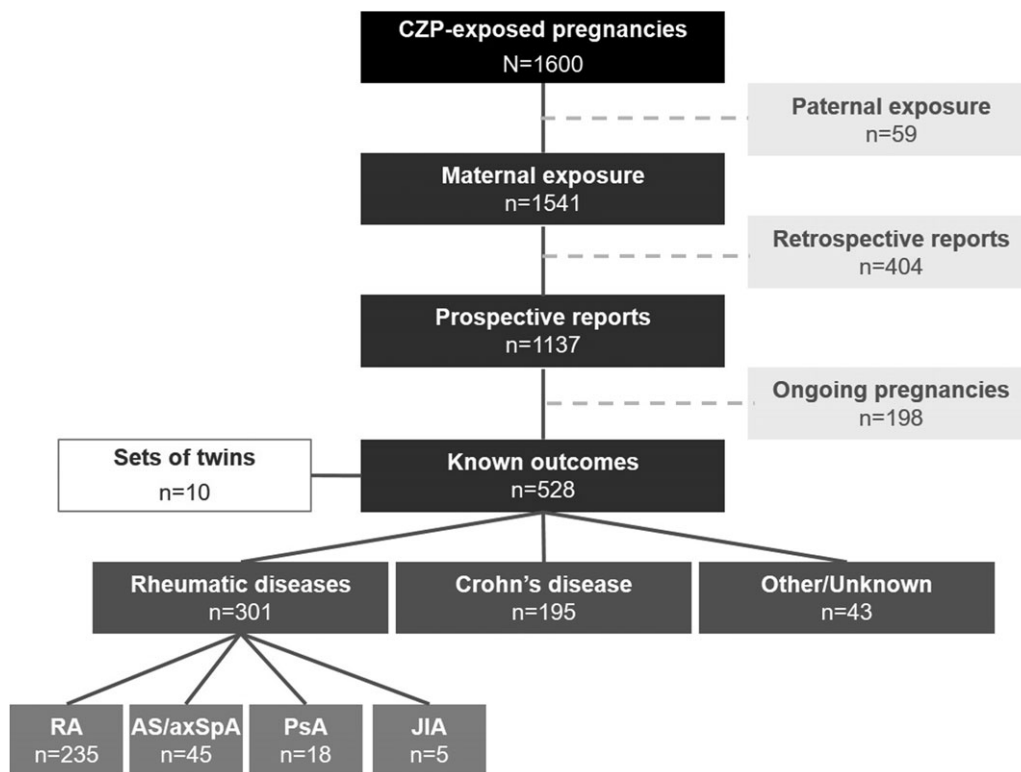


Figure 1. Overview of pregnancies exposed to certolizumab pegol (CZP). Eleven patients were included in more than 1 treatment indication category (rheumatic diseases, Crohn's disease, or other) due to multiple reported indications. RA = rheumatoid arthritis; AS = ankylosing spondylitis; axSpA = axial spondyloarthritis; PsA = psoriatic arthritis; JIA = juvenile idiopathic arthritis.

to the cutoff date, including those given in the previous data cut (18). Information on pregnancy dating, CZP exposure, congenital malformations, and other pregnancy outcomes, maternal comorbidities, and concomitant medications was extracted.

Pregnancies were classified as prospective or retrospective (19). Prospective pregnancies were those that were reported to UCB Pharma while ongoing and for which no fetal abnormalities were known. In contrast, pregnancies whose outcomes (including abnormal ultrasound results) were already known at initial notification were categorized as retrospective. The focus of this analysis was on prospectively reported pregnancies to avoid potential bias in outcome reporting rates.

Pregnancy outcomes were categorized as follows: live birth, miscarriage (non-induced 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 or after 20 weeks of gestation). Ongoing pregnancies included any pregnancy with an estimated (or calculated) due date less than 3 months before the cutoff date of March 6, 2017. If no information on pregnancy outcome was available after 3 months following the estimated pregnancy due date, it was considered lost to follow-up and reported as having an unknown outcome.

Trimesters of pregnancy were defined by time since the first day of the last menstrual period (LMP) and distinguished as first (up to 12 weeks and 6 days' gestation), second (13–28 weeks and 6 days' gestation), and third (any time at or after 29 weeks' gestation) (20). Timing of CZP exposure during pregnancy was

categorized into first, second, and third trimester by entering the exposure start, stop, and restart dates (where applicable) into an algorithm when sufficient data regarding the LMP were available.

Live birth characteristics of infants analyzed included the gestational age at delivery (i.e., the number of completed weeks starting from LMP), low birth weight ($\leq 2,500$ gm), small for gestational age (a birth weight less than the tenth percentile for infants of the same gestational age and sex), and prematurity (infants born before 37 weeks' gestation). Mothers' indications, comorbidities, adverse events, and concomitant medications were also analyzed.

Information on mother and infant was recorded in Council for International Organization of Medical Sciences forms for cases of major congenital malformations, which were reviewed by a clinical teratologist. The clinical review assessed the presence and characterization of malformations among live-born infants and the possible temporal association between malformation, organogenesis, and medication exposure.

RESULTS

Overview of pregnancies. A total of 1,600 reports of CZP-exposed pregnancies were entered in the UCB Pharma safety database from the start of CZP clinical development (earliest report July 12, 2001) through March 6, 2017, with 1,541 maternal and 59 paternal CZP exposures (Figure 1). The majority (n = 1,137) of pregnancies

Table 1. Maternal demographics by indication for CZP use in prospectively reported pregnancies with maternal CZP exposure*

	Known outcomes			Unknown outcomes (n = 411)§
	Total (n = 528)†	Rheumatic diseases (n = 301)‡	CD (n = 195)	
Report source				
Spontaneous reports¶	245 (46.4)	125 (41.5)	97 (49.7)	378 (92.0)
Clinical trials	65 (12.3)	37 (12.3)	21 (10.8)	7 (1.7)
NIS/OLEs/compassionate use#	218 (41.3)	139 (46.2)	77 (39.5)	17 (4.1)
Region				
North America	317 (60.0)	129 (42.9)	171 (87.7)	289 (70.3)
Europe	119 (22.5)	85 (28.2)	22 (11.3)	84 (20.4)
Asia	62 (11.7)	61 (20.3)	0 (0.0)	14 (3.4)
Latin America	9 (1.7)	8 (2.7)	0 (0.0)	6 (1.5)
Middle East	11 (2.1)	10 (3.3)	0 (0.0)	7 (1.7)
Australia/New Zealand	9 (1.7)	8 (2.7)	1 (0.5)	8 (2.0)
Africa	1 (0.2)	0 (0.0)	1 (0.5)	0 (0.0)
Maternal age at EDD				
Number with available data	455	254	178	200
18–34 years	332 (73.0)	169 (66.5)	146 (82.0)	154 (77.0)
<18 years	1 (0.2)	1 (0.4)	0 (0.0)	2 (1.0)
≥35 years	122 (26.8)	84 (33.1)	32 (18.0)	44 (22.0)
Median (range) years	31 (17–44)	32 (17–44)	30 (18–43)	30 (16–55)

* Except where indicated otherwise, values are the number (%). CD = Crohn's disease; NIS = non-interventional studies; OLEs = open-label extension studies; EDD = estimated due date.

† Includes pregnancy reports where the indication for treatment of the mother with certolizumab pegol (CZP) was unknown (n = 43) and excludes 11 pregnancies where more than 1 indication was reported.

‡ Includes rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis, psoriatic arthritis, and juvenile idiopathic arthritis.

§ Includes pregnancy reports where the indication for treatment (n = 50), report source (n = 9), and region (n = 3) were unknown.

¶ Including registries (but excluding Organization of Teratology Information Services), social media reports, and reports from the literature.

Includes healthy volunteers.

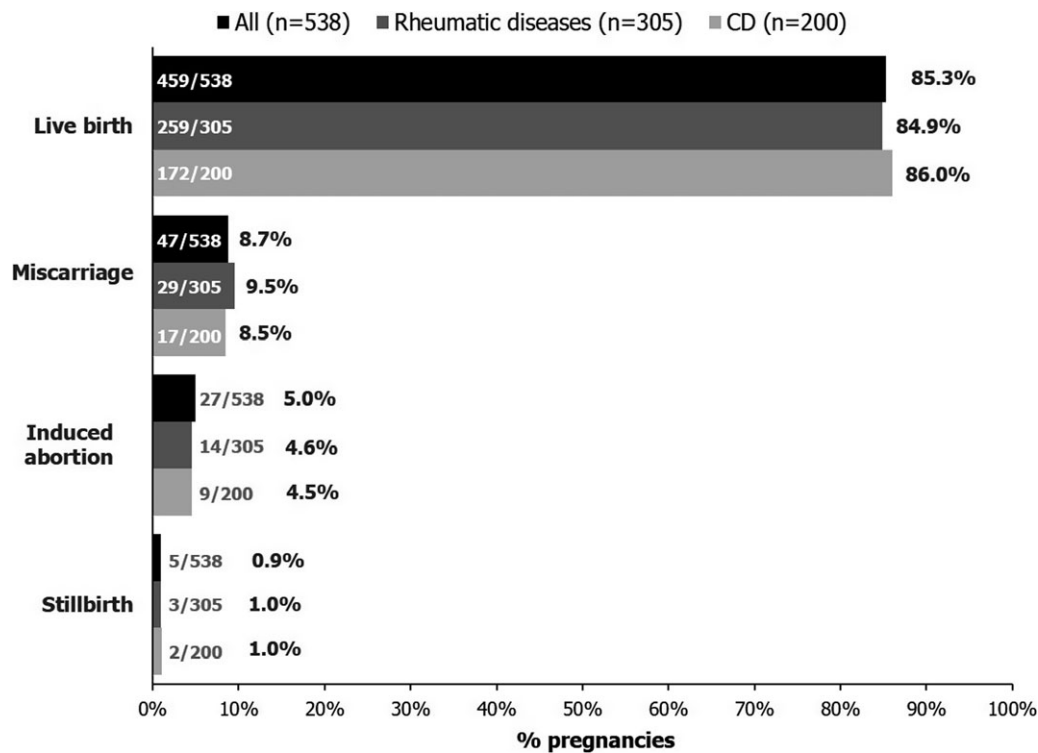


Figure 2. Known outcomes for prospectively reported pregnancies with maternal exposure to certolizumab pegol. Ten twin pregnancies are included in the total number of pregnancy outcomes (4 in mothers with rheumatic diseases, 5 in mothers with Crohn's disease [CD], and 1 in a mother with unknown indication). Miscarriage was defined as embryonic or fetal death before 20 weeks of gestation. Induced abortion includes both elective and medically indicated abortions.

with maternal exposure were prospective. Outcomes were known for 528 prospective pregnancies with maternal CZP exposure, which included 10 twin pregnancies; 198 prospective pregnancies were ongoing at the time of data cutoff (Figure 1). The outcome was not known for 411 cases.

The main indications of women with CZP exposure and known prospective pregnancy outcomes were rheumatic diseases ($n = 301$) and CD ($n = 195$). Rheumatic diseases included RA ($n = 235$), ankylosing spondylitis/axial SpA ($n = 45$), PsA ($n = 18$), and juvenile idiopathic arthritis ($n = 5$) (Figure 1). Of note, with regard to indications for treatment, 11 patients were counted more than once due to multiple reported indications.

Prospective pregnancies. Maternal demographics. Almost half (46.4%) of prospective pregnancies with maternal CZP exposure and known outcomes were spontaneous reports (including those found in the literature); the remaining 53.2% of reports came from other sources, with interventional clinical trials accounting for 12.3% of pregnancy reports (Table 1). The majority of pregnancy reports originated from North America (60.0%) and Europe (22.5%). The median age at the estimated due date (EDD) was 31 years (range 17–44 years), with 26.8% of

women age 35 years or older (Table 1). Of the women with CD, 87.7% were in North America, compared to 42.9% of those with rheumatic diseases (Table 1). Of note, more women with rheumatic diseases (33.1%) than with CD (18.0%) were older than 35 years at EDD (Table 1). The maternal demographics of prospective pregnancies with unknown outcome were also reviewed for comparison. These reports originated almost exclusively from spontaneous reporting (Table 1). Of note, the mother's age was reported for only 50% of these patients (Table 1).

Pregnancy outcomes and CZP exposure. A total of 528 pregnancies (including 10 twin pregnancies) had 538 known outcomes: 452 pregnancies resulted in 459 live births (85.3% of 538), and there were 47 miscarriages (8.7% of 538), 27 elective abortions (5.0% of 538), and 5 stillbirths (0.9% of 538) (Figure 2). Analysis of pregnancy outcomes demonstrated similar trends for women with rheumatic diseases and those with CD: live births were the most common pregnancy outcome in both indications (Figure 2). Of note, 2 cases of neonatal death were reported: 1 member of a female twin pair (born at 25 weeks), from brain damage and pneumoperitoneum; and 1 member of a female twin pair (born at 27 weeks) with a

heart defect who developed an unspecified infection of the intestines ~8 weeks after birth and underwent surgery. The infant did not survive the surgery.

Serious maternal infections occurred in 22 (4.2%) of 528 prospective pregnancies. For the 452 CZP-exposed women whose prospective pregnancies resulted in a live birth, maternal comorbidities included preeclampsia (in 5 patients [1.1%]) and gestational diabetes (in 6 patients [1.3%]).

Maternal exposure to CZP occurred during at least the first trimester for 367 (81.2%) of the 452 prospective pregnancies resulting in a live birth, including 132 (29.2%) exposed during the first trimester only

(Figure 3A). CZP exposure during all 3 trimesters of pregnancy was reported by 201 pregnant women with a live birth outcome (44.5%) (Figure 3A). Over half of the pregnant women with CD who had live births (55.6%) were exposed to CZP during all 3 trimesters, compared to 37.1% of those with rheumatic diseases (Figure 3B). More women with rheumatic diseases than women with CD were exposed to CZP during the first trimester only or during the first and second trimesters (Figure 3B), reflecting the differing clinical practice between the treatment of CD and the treatment of rheumatic diseases.

Concomitant medications were reported for only 382 pregnancies, and the type of medication was unspecified

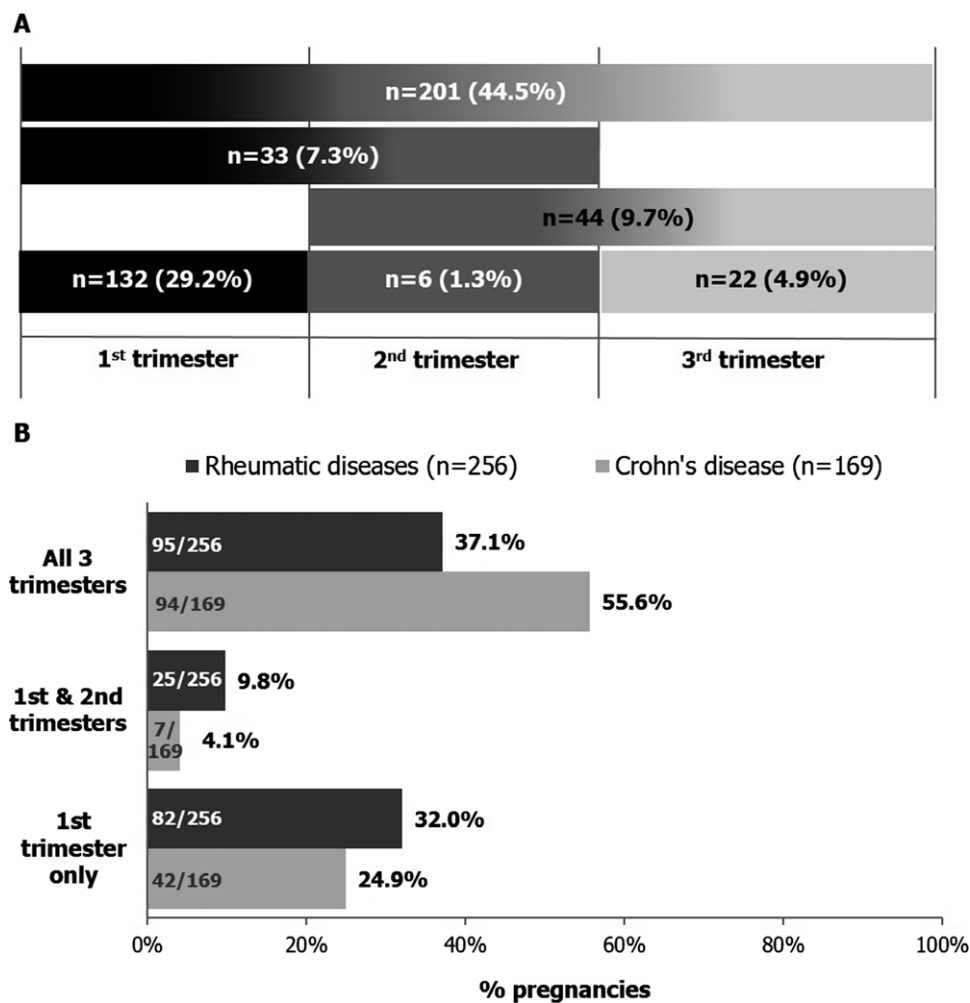


Figure 3. Trimesters of maternal certolizumab pegol (CZP) exposure for prospectively reported pregnancies resulting in a live birth. **A**, Timing of CZP exposure for all pregnancies. A total of 452 pregnancies resulted in a live birth, including those in which the mother was exposed preconception (n = 5; CZP exposure stopped >14 days and ≤70 days prior to the first trimester) and pregnancies for which the timing of exposure could not be determined (n = 8), as well as 1 patient exposed in the first and third trimesters. Black, dark gray, and light gray shading represent CZP exposure during the first, second, and third trimesters, respectively; shading gradients reflect exposure during multiple trimesters. **B**, Exposure by indication for CZP use. There were 8 live births for which the timing of exposure could not be determined (n = 2 for patients with rheumatic disease and n = 6 for patients with Crohn’s disease).

Table 2. Characteristics of live-born singletons from prospectively reported pregnancies with maternal exposure to CZP*

Characteristic	All (n = 442)†	Rheumatic diseases (n = 252)‡	CD (n = 164)‡
Cesarean section	139 (31.4)	61 (24.2)	70 (42.7)
Gestational age at birth			
Number with available data	326	195	120
20 to <32 weeks	4 (1.2)	1 (0.5)	2 (1.7)
32 to <37 weeks	35 (10.7)	22 (11.3)	12 (10.0)
≥37 weeks	287 (88.0)	172 (88.2)	106 (88.3)
Median (range) weeks	39 (27–43)	39 (27–43)	39 (31–42)
Birth weight			
Number with available data	205	145	55
Low birth weight§	24 (11.7)	17 (11.7)	7 (12.7)

* Except where indicated otherwise, values are the number (%). Of 442 singleton infants, 4 (0.9%) were small for gestational age (2 [0.8%] of 252 born to mothers with rheumatic diseases and 2 [1.2%] of 164 born to mothers with Crohn's disease [CD]). CZP = certolizumab pegol.

† Includes patients with multiple and unknown indications.

‡ Includes patients who had both rheumatic diseases and CD.

§ ≤2,500 gm.

for 3 of those pregnancies. Nonsteroidal antiinflammatory drugs and steroids were the most frequent medications used; 7 miscarriages were reported in patients who received concomitant methotrexate.

Live birth characteristics. Among women with CZP exposure, 452 prospective pregnancies resulted in 459 live births; 17 infants from 10 twin pregnancies were reported. Four twin pregnancies occurred in women with rheumatic diseases and 5 in women with CD. The indication of 1 mother of twins was unknown. Among the singleton live births, 31.4% of women had a cesarean section (24.2% of women with rheumatic diseases and 42.7% of women with CD) (Table 2). Of the live births, 11.9% were preterm, with similar proportions in the different indications; the median gestational age at birth was 39 weeks (minimum 27 weeks, maximum 43 weeks) (Table 2). Twenty-four

(11.7%) of 205 infants had low birth weight (Table 2); no differences were observed between infants of mothers with rheumatic diseases and those with CD. A low number of infants (4 [0.9%] of 442) were reported as small for their gestational age.

Major congenital malformations. Adverse events reported for the infants did not show any patterns or clusters of events suggesting a specific safety signal in newborns. Major congenital malformations were reported for 8 live-born infants (1.7%); 4 infants of mothers with RA, 1 infant of a mother with axial SpA, and 3 infants of mothers with CD (Table 3). Except for the mothers of the infants with cerebral ventricle dilatation, congenital heart disease, and hydronephrosis, all mothers of the infants with major congenital malformations were exposed to CZP at least during the first trimester. The women who had infants with accessory auricle and polydactyly were exposed during all 3 trimesters of their pregnancies (Table 3).

No discernible patterns of birth defects among the CZP-exposed infants were observed. The teratologist review concluded no temporal association with CZP exposure for the case of hydronephrosis, owing to evidence of anomalies on ultrasound prior to the initiation of medication (during the third trimester). The possibility of an association could not be ruled out for the cases of anal fistula, accessory auricle, vesicoureteric reflux, talipes, and congenital heart disease. It was not possible to assess temporality for the cerebral ventricle dilatation. It should be noted that a familial predisposition was present for the infant born with polydactyly: the father, the father's sister, and the paternal grandmother all had the same malformation at birth.

DISCUSSION

The large majority (85.3%) of CZP-exposed pregnancies evaluated in this analysis resulted in live births, and the rate of major congenital malformations for

Table 3. Major congenital malformations in live-born infants from prospectively reported pregnancies and timing of maternal CZP exposure*

Infant abnormality	Mother's indication for CZP use	CZP exposure		
		First trimester	Second trimester	Third trimester
Accessory auricle	RA	X	X	X
Anal fistula	RA	X	–	–
Congenital heart disease†	RA	–	X	X
Polydactyly	RA	X	X	X
Cerebral ventricle dilatation†	Axial SpA	–	–	X
Talipes	CD	X	–	–
Vesicoureteric reflux	CD	X	X	–
Hydronephrosis	CD	–	–	X

* A total of 452 pregnancies resulted in live births. CZP = certolizumab pegol; RA = rheumatoid arthritis; SpA = spondyloarthritis; CD = Crohn's disease.

† Premature birth.

CZP-exposed infants was similar to those reported for the general population in the US and Europe (21,22). Most pregnancies were exposed to CZP at least during the first trimester, when organogenesis primarily occurs; 201 of 452 pregnancies resulting in a live birth were exposed during all 3 trimesters. No discernible trends linking major congenital malformations to the timing of CZP exposure were observed, similar to data from other prospective studies (23–25). The frequencies of the pregnancy-associated comorbidities preeclampsia and gestational diabetes were similar to those in the general population (26,27), and no cases of eclampsia were reported. The frequency of serious infections during pregnancy was consistent with that reported in CZP-exposed patients (28–31).

Our review showed that CZP treatment during all 3 trimesters of pregnancy was more common in women with CD (55.6%) than in women with rheumatic diseases (37.1%). Spontaneous disease improvement during pregnancy is less likely in women with IBD than in women with RA and other rheumatic diseases, and many patients with IBD may require treatment throughout pregnancy, thus potentially reducing the risk of adverse outcomes, such as spontaneous miscarriage, premature birth, low birth weight, and small for gestational age (13,32,33). Compared to the incidence of low birth weight in the US general population (8.1%) (34), the incidence of low birth weight among singletons in our review (11.7%) was slightly elevated; however, this is consistent with previous reports for anti-TNF agents (35). Pregnancy outcomes, gestational age, low birth weight and small size at birth, and the rate of congenital malformations were similar for mothers with CD and their infants, compared to mothers with rheumatic diseases and their infants.

Despite the increasing evidence regarding the safety of anti-TNF therapies, patients and physicians still have concerns regarding their use during pregnancy. The potential risks to the fetus associated with the use of drugs during pregnancy are strongly related to the timing of exposure. During the first trimester, drug exposure can affect organogenesis and increase rates of miscarriage or congenital malformations. Preconception and birth control assessment is therefore important to provide information regarding the safety of anti-TNF agents before and during the time to conception, as well as during early pregnancy (36). Until December 2017, the European Union (EU) label advised women to take birth control measures for at least 5 months after the last CZP administration (37). As of January 2018, the EU label has been revised to mention that for women planning pregnancy, contraception may be considered, while taking into account their need for treatment (38). There are no contraception recommendations in place in the US label regarding CZP use (39), which

likely contributes to the majority of the pregnancy reports in this review originating in North America.

This analysis of prospective pregnancy reports from the UCB Pharma safety database represents the largest published cohort of pregnant women exposed to an anti-TNF agent for the management of chronic inflammatory diseases. It addresses the need for new and detailed studies of the impact of drug exposure during pregnancy and supports the conclusion that exposure to CZP in utero does not appear to increase the risk of major congenital malformations or fetal loss. The results are also consistent with the growing body of evidence becoming available on anti-TNF exposure during pregnancy, which indicates no association with an increased risk of adverse neonatal outcomes or congenital malformations (40).

Recent systematic reviews and meta-analyses have found no link to adverse outcomes for pregnancies with anti-TNF exposure during the first trimester (17,40,41), and more encouraging data are becoming available that support the use of these therapeutics during pregnancy (17), helping to alleviate women's and physicians' concerns regarding the impact of exposure. Exposure in late pregnancy and the resulting potential risk of postnatal infections (17) are associated with active placental drug transfer from mother to infant, mediated by binding of the Fc region to the neonatal Fc receptor (FcRn) (42). In contrast to other anti-TNF agents, the CZP molecule lacks the Fc moiety, preventing binding to placental FcRn, thus limiting placental transport (43).

Limitations to our analysis include the fact that, while the UCB safety database is an appropriate tool for standard safety evaluations, the data collection process is designed for pharmacovigilance purposes, rather than being an analysis tool for scientific pregnancy research. In addition, no untreated control group was available for comparison; therefore, a formal assessment of data by statistical analysis was not possible. However, it is acknowledged that for studies with a focus on pregnancy, inclusion of a control group is not always possible (44). Uncontrolled large data sets are still of value, in particular when assessing the frequency of rare events like congenital malformations, since this information is readily available for the general population for comparison.

Another limitation of this analysis is the fact that pregnancy outcome was unknown for a third of the cases. Missing outcomes data is an inherent issue with passive reporting of pregnancy outcomes, despite adequate follow-up attempts. In addition, the small number of available data for certain birth characteristics, such as low birth weight, impedes drawing any definite conclusions based on this information. Accurate and extrapolatable rates of miscarriage are also hard to estimate from

spontaneously reported data, since reports are received at various times throughout gestation, with a report received later on being at lower risk of spontaneous abortion than a report received earlier. Furthermore, data collected via spontaneous reporting systems are affected by reporting bias and often associated with inherent limitations, due to the passive and voluntary nature of the reporting systems. To reduce bias toward the reporting of adverse outcomes associated with retrospective data, we focused our analysis on prospective pregnancy reports to allow a quantitative assessment of outcomes and evaluation of the temporal association between CZP exposure and outcomes.

The results of our analysis represent the most comprehensive published data set for pregnancies exposed to a single anti-TNF agent to date, with a particular focus on assessment of the temporal association. The fact that 528 CZP-exposed pregnancies resulted in 459 live births, with 367 women being exposed to CZP during the first trimester, and that only 8 cases of major congenital malformations were reported, confirms and expands the known CZP safety profile. Data from other sources, such as the ongoing MotherToBaby study from the Organization of Teratology Information Specialists (45), will provide further important information to confirm the findings described here. However, these data are reassuring for women of childbearing age affected by chronic inflammatory diseases who need an anti-TNF agent to control their condition and wish to become pregnant or are pregnant during CZP treatment.

ACKNOWLEDGMENTS

The authors thank the patients and health care providers who reported data included in this analysis. The authors acknowledge Marie Teil, Cécile Ecoffet, and Simone E. Auteri (UCB Pharma, Brussels, Belgium) for publication coordination, and Julia Bárdos, PhD (Costello Medical, Cambridge, UK) for writing and editorial assistance in preparing the manuscript for publication, based on the authors' input and direction.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Clowse had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Cooney, Shaughnessy, Vanderkelen.

Acquisition of data. Cooney, Shaughnessy, Vanderkelen.

Analysis and interpretation of data. Clowse, Scheuerle, Chambers, Afzali, Kimball, Cush, Cooney, Shaughnessy, Vanderkelen, Förger.

ROLE OF THE STUDY SPONSOR

UCB Pharma sponsored the analysis and the development of this manuscript and reviewed the text to ensure that from UCB Pharma perspective, the data presented in the publication are

scientifically, technically, and medically supportable, that they do not contain any information that has the potential to damage the intellectual property of UCB Pharma, and that the publication complies with applicable laws, regulations, guidelines, and good industry practice. The authors approved the final version to be published after critically revising the manuscript/publication for important intellectual content. Publication of this article was contingent upon approval by UCB Pharma.

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