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ORIGINAL ARTICLE



Safety of cetirizine in pregnancy

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ABSTRACT

Managing symptoms of allergic rhinitis (AR) and urticaria in pregnant women is important to reduce complications and negative outcomes. The objective of this study was to provide information on the pregnancy outcomes of women exposed to the antihistamine cetirizine (CTZ). The UCB Pharma Patient Safety Database was searched for pregnancies up to 28 February 2015. Maternal CTZ exposure reports were extracted, and pregnancy outcomes were examined, including exposure, comorbidities and infant events. 228 of 522 pregnancies with maternal CTZ exposure had available outcomes; 49 were prospective. The majority (83.7%) resulted in live births; four spontaneous miscarriages, three induced abortions and one stillbirth were reported. Most pregnancies were exposed during the first trimester. Two congenital malformations were reported. The results suggest that CTZ exposure is not associated with adverse pregnancy outcomes above the background rates. While reassuring, the strengths and limitations of a safety database study need to be considered.

IMPACT STATEMENT

- **What is already known on this subject?** AR and urticaria can substantially affect pregnant women, and adequately managing their symptoms is important to reduce maternal and foetal complications. Antihistamines are efficacious, however, there is still a lack of data regarding use during pregnancy. Although current evidence indicates that antihistamines are well-tolerated during pregnancy, data regarding foetal safety are inconclusive.
- **What do the results of this study add?** Our study suggests that CTZ exposure during pregnancy is not linked to an increase in adverse outcomes. CTZ exposure mainly happened during the first trimester only, when most organogenesis takes place. Most of the maternally exposed, prospective pregnancies resulted in live births (83.7%). Congenital malformations occurred in 2/41 live births from the CTZ-exposed pregnancies.
- **What are the implications of these findings for clinical practice and/or further research?** Our study presents a detailed data analysis from a large number of CTZ-exposed pregnancies, and its results are in line with those from previous reports. While the limitations of a safety database study need to be considered, the results shown here are reassuring. Further prospectively reported pregnancies are required, before definite conclusions on the risks of CTZ exposure during pregnancy can be drawn.

KEYWORDS

Antihistamine; cetirizine; foetal safety; pregnancy; pregnancy outcomes

Introduction

It has been estimated that approximately 20–30% of women of childbearing age suffer from allergic conditions, such as rhinitis, asthma, allergic conjunctivitis, acute urticaria, anaphylaxis, and food and drug allergies. Studies suggest that as many as 10–30% of pregnant women with known allergies will experience increasing allergy symptoms during their pregnancy (Incaudo 2004; Pali-Schöll et al. 2016).

Allergic rhinitis (AR) is one of the most common causes for allergy symptoms in pregnant women; its symptoms include nasal obstruction and discharge, sneezing and itching (Keles 2004; Pali-Schöll et al. 2016). The prevalence of AR is closely linked with that of asthma: 20–50% of adult AR patients also have asthma, and AR is considered a risk factor for developing or aggravating asthma (Bousquet et al. 2003; Giavina-Bianchi et al. 2016). Asthma episodes in pregnant women are

of particular concern, as they are associated with maternal complications (including pre-eclampsia, vaginal haemorrhage and complicated labour), as well as adverse foetal outcomes, such as perinatal mortality, intrauterine growth restriction, pre-term birth, low birth weight and neonatal hypoxia (Yawn and Knudtson 2007). Furthermore, rhinitis has been linked to snoring and an increased risk for hypertension (Corbo et al. 2006), and pregnancy-onset snoring is associated with gestational hypertension and pre-eclampsia (O'Brien et al. 2012).

Similarly, urticaria can occur in all stages of pregnancy, presenting with raised, itching and/or painful wheals on various body parts, often accompanied by angioedema (Lawlor 2014). Most episodes last fewer than 6 weeks and are diagnosed as acute urticaria, whereas chronic urticaria occurs intermittently or continuously for at least 6 weeks. Its symptoms can have a detrimental effect on the patient's quality of life, as they are often associated with sleep deprivation,

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anxiety, depression and reduced performance at work and in their private life (Zuberbier et al. 2014).

Although not directly associated with adverse perinatal or maternal outcomes as such, both AR and urticaria can substantially affect the well-being of pregnant women. Adequately managing AR and urticaria symptoms during pregnancy is important to reduce maternal complications, as well as to prevent negative foetal outcomes (Goldstein and Govindaraj 2012; Namazy and Schatz 2016).

Antihistamines are efficacious therapies for the treatment of AR and urticaria (Hoyte and Katial 2011), and approximately 10–15% of women take an antihistamine drug for the relief of nausea and vomiting, allergy and asthma symptoms or indigestion (Gilboa et al. 2014) during pregnancy. However, special consideration regarding the antihistamine choice and dosing for pregnant women is required; concerns about the safety of different available agents centre around their potential to cause pregnancy complications and have adverse effects on the foetus (Kar et al. 2012). Similarly, uncertainties exist regarding the effects following inadvertent exposures, i.e. medications taken prior to pregnancy recognition and those prescribed for chronic illness. A better understanding of medication utilisation during pregnancy could help improve the safe and effective treatment of pregnant women (Wyszynski and Shields 2016).

Although current evidence indicates that antihistamines used to treat AR and urticaria are well-tolerated during pregnancy, the data regarding foetal safety are inconclusive. Second-generation antihistamines, such as cetirizine (CTZ) and loratadine, are considered safe in pregnancy and are not associated with an increased risk for major congenital malformations (Li et al. 2013; Gonzalez-Estrada and Geraci 2016). Isolated cases of antihistamine use during pregnancy having adverse effects on outcomes have been described: one analysis found a strong, but very imprecise association of the maternal use of meclizine and a major congenital birth defect (cleft palate; posterior odds ratio: 6.16, 95% posterior confidence interval: 1.78, 21.33), however, these results warrant further investigations and interpretation (Gilboa et al. 2009).

Cetirizine, an active metabolite of hydroxyzine, is a second-generation antihistamine used for the symptomatic relief of allergic conditions, such as AR and urticaria (Zhang et al. 2013). Studies have demonstrated that exposure to CTZ during pregnancy does not appear to be associated with an increased safety risk for mothers and infants (Einarson et al. 1997; Weber-Schoendorfer and Schaefer 2008; Etwel et al. 2014). The American College of Obstetricians and Gynecologists and the American College of Allergy, Asthma and Immunology (ACOG-ACAAI) recommend CTZ for pregnant women who would benefit from antihistamine treatment (Blais 2003).

The objective of this study was to provide information on the pregnancy outcomes and demographics, including information on exposure to CTZ of women and infants, in a retrospective analysis of the pregnancy case reports in the UCB Pharma Patient Safety Database. As UCB Pharma is the market authorisation holder for CTZ (Zyrtec®), its safety database is the primary source of pregnancy data on this drug.

Materials and methods

Data sources and collection processes

The UCB Pharma Patient Safety Database was searched for reports of CTZ-exposed pregnancies up to 28 February 2015. The pregnancy reports captured in the database were obtained from interventional clinical trials, non-interventional studies and spontaneous reports from patients or healthcare providers. Reports from the literature were not included in this analysis, as it was not possible to validate the data from these sources.

This analysis includes data from pregnancies with maternal exposure (mother received CTZ), the data on paternal exposure (father received CTZ) was not included. Amongst other covariates, the information sought regarding exposed pregnancies included the first date of last menstrual period (LMP) and the estimated date of delivery (EDD); the details of exposure during pregnancy; the results of prenatal investigations; maternal characteristics, including age, weight and concomitant diseases. Information on the course of the pregnancy (including adverse events experienced by the mother) was also requested.

The information collected on drug exposure (exposure start/stop/re-start dates) was utilised to specify exposure timing by the first, second and third trimesters (including the earliest exposure), if sufficient data to date from the start of the pregnancy were available. Pregnancy dating was carried out using LMP, EDD, pregnancy outcome dates and gestational age at pregnancy outcome, based on the available information and ranked according to the reliability of the reports. A pregnancy outcome was categorised and defined as follows: a live birth, a miscarriage (non-induced embryonic or foetal death or passage of products of conception before 20 weeks of gestation), an induced abortion (medically indicated or elective) and a stillbirth (a foetal death occurring at 20 weeks of gestation or after). If no information on pregnancy outcome was available by the cut-off date, it was considered unknown. The congenital malformations, delivery complications and newborn complications were also recorded.

Data review

The information on exposed pregnancies was extracted from case reports by two separate reviewers, with reconciliations for discrepancies performed by a third independent reviewer when necessary.

The pregnancy dating was based on the available information in a hierarchy of data, according to reliability: gestational age at pregnancy outcome and the pregnancy outcome date (if reported) were utilised first. If these dates were not available, the EDD was used; the LMP date was used as a final option for dating the pregnancy. The trimesters of pregnancy were distinguished as the first trimester up to 12 weeks and 6 days, the second trimester from 13 weeks to 28 weeks and 6 days and the third trimester was any time including and after 29 weeks (NICHD 2016). The earliest trimester of exposure was determined using the start and stop dates of

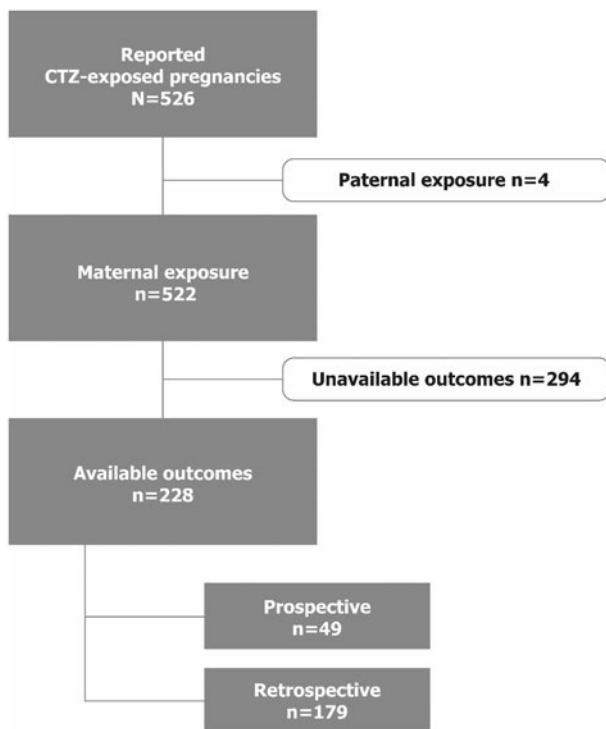


Figure 1. Distribution of pregnancy reports. CTZ: cetirizine.

exposure to CTZ, as reported in the case narrative or corresponding to the dates of the pregnancy, calculated from the hierarchy of pregnancy dates described above.

Pregnancies were classified as retrospective or prospective; the prospective pregnancies are pregnancies that were ongoing at the time of reporting and where no foetal abnormalities were reported at initial notification, whereas the pregnancies whose data originated from reports where the outcome (including abnormal results) was already known were classed as retrospective. The focus of this manuscript is on the data from the prospective pregnancies, as these are the most scientifically valid.

Results

Overview of maternal CTZ-exposed pregnancy reports

In total, 526 CTZ-exposed pregnancies were reported in the UCB Pharma Safety Patient Database, of which 522 had maternal and 4 paternal exposures. The earliest pregnancy report was received in 1995. Outcomes were available for 228 of the maternally exposed pregnancies; 49 of these reports were prospective, 179 retrospective (Figure 1).

The data for the majority of maternal-exposed pregnancies originated from spontaneous reports (prospective: 100.0%; retrospective: 85.5%); other sources included interventional and non-interventional UCB studies (Table 1). Most prospective pregnancy reports originated from Europe (83.7%) (Table 1). No pregnancies were reported for women aged <18 years at EDD; most prospective reports (95.7%) originated from women aged 18–34 years, and one mother was ≥35 years old (Table 1).

No multiple gestations occurred for prospective reports; maternal comorbidities (including asthma, placental issues

Table 1. Characteristics of maternal CTZ-exposed pregnancy reports with known outcome (prospective and retrospective reports; $n = 228$).

Characteristic	Prospective reports ($n = 49$) n (%)	Retrospective reports ($n = 179$) n (%)
Report source		
Spontaneous	49 (100.0)	153 (85.5)
UCB interventional study	0	1 (0.6)
UCB non-interventional study	0	25 (14.0)
Region		
North America	5 (10.2)	55 (30.7)
Europe	41 (83.7)	115 (64.2)
Asia	2 (4.1)	8 (4.5)
Latin America	1 (2.0)	0
Africa	0	1 (0.6)
Maternal age at EDD, years		
Number reported	23	24
<18	0	0
18–34	22 (95.7)	17 (70.8)
≥35	1 (4.3)	7 (29.2)
Mean, years (SD)	28.3 (4.4)	31.7 (5.1)
Multiple gestation		
Yes	0	3
Maternal comorbidities		
Yes	6	30

EDD: estimated delivery date; SD: standard deviation.

and thyroid issues) were reported in six of the maternally CTZ-exposed prospective pregnancies (Table 1).

Pregnancy outcomes and live birth characteristics of maternal CTZ-exposed pregnancies: Prospective reports

The majority of the 49 prospective maternal CTZ-exposed pregnancies (83.7%) resulted in a live birth (Figure 2). There were four reported spontaneous miscarriages (before 20 weeks of gestation), three induced abortions, and one stillbirth (Figure 2).

Of the prospective pregnancies for which the earliest trimester of exposure could be determined, earliest exposure to CTZ was during the first trimester for most pregnancies (76.5%) resulting in live births (Table 2). For the majority (50.0%) of prospective pregnancies, the exposure was limited to this trimester only. One woman was exposed to CTZ for her entire pregnancy, resulting in a live birth (Table 2).

Less than 20% of the live births were via caesarean section, and the majority of the infants from prospectively reported pregnancies were born at term (90.0%) and had normal birth weight (92.6%) (Table 3).

Congenital malformations were reported for 2/41 live births (Table 3); the reported congenital malformations were cleft lip syndrome ($n = 1$) and a missing ventricular septum ($n = 1$) (Table 4).

Pregnancy outcomes and live birth characteristics of maternal CTZ-exposed pregnancies: Retrospective reports

Of the 179 retrospective maternally CTZ-exposed pregnancies, 121 reported live births. There were 32 reports of spontaneous miscarriage, 18 induced abortions, 1 abortion unspecified and 7 stillbirths. 28 infants had congenital malformations (Table 4).

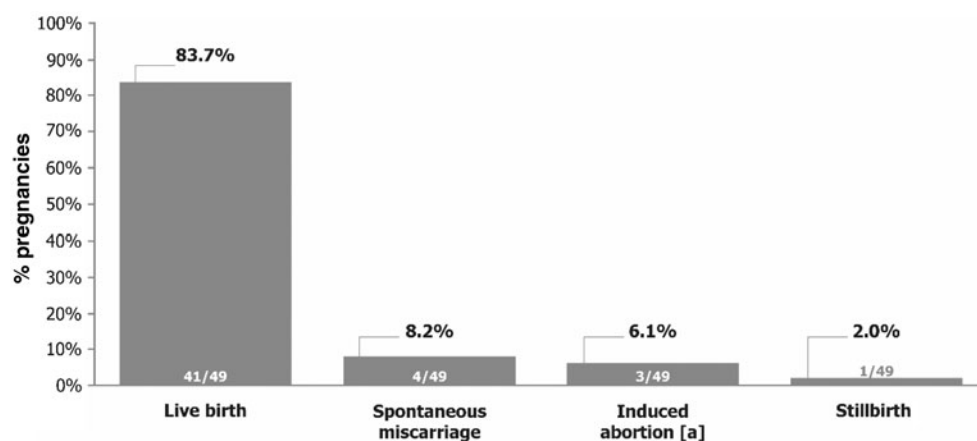


Figure 2. Known outcomes of maternal CTZ-exposed pregnancies (prospective reports; $n = 49$). [a] Includes elective and medically indicated.

Table 2. Maternal exposure to CTZ (prospective reports; $n = 49$).

	Live birth $n = 41$	Spontaneous miscarriage $n = 4$	Induced abortion $n = 3$	Abortion unspecified $n = 0$	Stillbirth $n = 1$
<i>Earliest trimester exposed n (%)</i>					
First ($n = 34$)	26 (76.5)	4 (11.8)	3 (8.8)	0	1 (2.9)
Second ($n = 8$)	8 (100.0)	0	0	0	0
Third ($n = 2$)	2 (100.0)	0	0	0	0
Unknown ($n = 5$)	5 (100.0)	0	0	0	0
<i>Trimesters exposed n (%)</i>					
1 only ($n = 8$)	4 (50.0)	3 (37.5)	1 (12.5)	0	0
2 only ($n = 3$)	3 (100.0)	0	0	0	0
3 only ($n = 2$)	2 (100.0)	0	0	0	0
1 and 2 ($n = 1$)	0	1 (100.0)	0	0	0
2 and 3 ($n = 1$)	1 (100.0)	0	0	0	0
1, 2 and 3 ($n = 1$)	1 (100.0)	0	0	0	0
Unknown ($n = 33$)	30 (90.9)	0	2 (6.1)	0	1 (3.0)

Table 3. Live birth characteristics of maternal CTZ-exposed pregnancies (prospective reports; $n = 41$).

Live birth characteristics	Prospective reports ($n = 41$) n (%)
Caesarean section	
Yes	7 (17.1)
Gestational age at birth (weeks)	
Number reported	20
<32 (early pre-term)	0
32 to <37 (pre-term)	2 (10.0)
≥37 (term)	18 (90.0)
Birth weight (grams)	
Number reported	27
<1500 (very low)	0
1500–2499 (low)	2 (7.4)
≥2500 (normal)	25 (92.6)
Mean, grams (SD)	3306.4 (538.3)
Congenital malformations	
Yes	2 (4.9)

SD: standard deviation.

Discussion

Utilising pregnancy case reports from the UCB Pharma Patient Safety Database, we performed a detailed analysis of demographics, pregnancy outcomes, exposure timing and length and birth characteristics of pregnant women exposed to CTZ and their infants. The large majority of prospectively reported pregnancies resulted in live births (83.7%). Congenital malformations occurred in 2 of the 41 CTZ-exposed prospective pregnancies which resulted in a live birth. Our analysis found that exposure to CTZ mostly

happened during the first trimester only, when the majority of organogenesis takes place. For comparison, it has been estimated that in the US, 64.5% of pregnancies result in live births, 16.9% in spontaneous miscarriage and stillbirth, and 18.4% in induced abortions (Ventura et al. 2012). Major birth defects affect approximately 2–4% of births in the US (Kucik et al. 2008) and in Europe (EUROCAT 2017).

This study summarises data from 49 prospectively reported pregnancies exposed to CTZ. Its results support the expectation that exposure to CTZ in pregnant women is not linked to adverse effects and outcomes and are in line with those from previous reports. Prospective, observational studies of 39 (Einarson et al. 1997) and 196 (Weber-Schoendorfer and Schaefer 2008) pregnant women exposed to CTZ during the first trimester, respectively, concluded that use of CTZ in early pregnancy does not appear to be associated with increased rates of adverse pregnancy outcomes. Similarly, data from the Swedish Medical Birth Registry, which included 917 women who had taken CTZ during their pregnancy, showed no association with malformations or adverse delivery outcomes, compared to the general population (Källén 2002). A cohort study involving 78 pregnant women exposed to CTZ in the first, and 56 in the second or third trimester demonstrated no increased risk of major malformations or spontaneous abortions when CTZ was taken during organogenesis, compared to the control group of women taking non-teratogenic agents (Etwel et al. 2014). Similarly, a meta-analysis of 10 studies involving 1293 pregnant women reported no

Table 4. Congenital malformations (live births, prospective and retrospective reports; $n = 162$).

	<i>n</i>
Prospective reports ($n = 41$)	
Cleft lip syndrome	1
No ventricular septum	1
Retrospective reports ($n = 121$)	
Additional hypoplastic thumb-like finger on radial side of left hand	1
Atrial septal defect, peripheral pulmonary stenosis	1
Cervical spine malformations at 12 months; hemi-vertebrae and spinal fusion	1
Chiari malformation, congenital adrenal hyperplasia	1
Cleft lip/palate	1
Coarctation of aorta	1
Coarctation of aorta and left ventricular hypoplasia	1
Coarctation of artery	1
Congenital anal atresia without fistula	1
DiGeorge syndrome; thymic agenesis, aplasia and hypoplasia; thymic ectopia; supernumerary thymus; interatrial septal defect; chromosomal deletion (22q11); palate cleft and mongoloid palpebra	1
Ear tags, cleft lip and palate, mitral valve prolapse, Eustachian tube disorder	1
Fused fingers and toes bilaterally	1
Hydronephrosis	1
Hypertrophic pyloric stenosis	1
Hypoplastic left heart syndrome; Turner Syndrome	1
Hypoplastic left heart	1
Lymphangioma	1
Malformation of hand	1
Malformation of mouth	1
Micropenis, narrow and displaced urethra	1
One umbilical artery, bilateral cleft palate	1
One umbilical artery, spina bifida	1
Pierre Robbins syndrome, cardiac malformations, renal malformations, upper respiratory malformations	1
Radiologic spinal malformations TH12 and L1	1
Trisomy 18	1
Trisomy 21	2
Undescended testicles	1

increased risk of major malformations or other adverse foetal outcomes following hydroxyzine or CTZ exposure, compared to the unexposed controls (Etwel et al. 2014).

The limitations of the analysis include that the UCB Pharma Patient Safety Database is a surveillance reporting tool for adverse events, rather than an analysis tool, and the data collection process is tailored to pharmacovigilance purposes. Since the reports from the safety database relate to patients receiving CTZ, no untreated control group was available for comparison, and a formal assessment of data by statistical analysis was therefore not possible. Although it is desirable to identify a relevant control group to allow for a higher level of certainty for risk assessments, it has been acknowledged that it is not always possible to find such a group for studies with focus on pregnancy and/or foetal safety. The frequency of major congenital malformations is relatively well documented for the general population, and uncontrolled data are therefore also of value (EMA 2008).

Another limitation is the limited data available due to the nature of the database and the reporting process. It should be noted that, compared to the prospective reports, retrospective pregnancy reports are biased towards reporting of adverse pregnancy outcomes (FDA 2002; EMA 2005). To avoid this, we focussed on prospective pregnancy reports with known outcomes, allowing a quantitative assessment, but thereby reducing the amount of data that could be included in the analyses.

Since the data utilised for this study was provided by the safety database, comparisons to pregnancy outcomes in the general population are inappropriate and should be done with caution, and only for prospectively reported pregnancies. The majority of the data used for this study originated from spontaneous reports, which, although essential for post-marketing pharmacovigilance surveillance, are affected by bias. The limitations of this reporting method include under-representation of exposed pregnancies, variable quality and completeness of the data and lack of information on exposure. However, since women who are pregnant or may become pregnant are almost always excluded from clinical drug trials because of concerns about safety and liability, it can be argued that this limitation applies to most, if not all, pregnancy-related data in clinical research. Importantly, although data availability and therefore generalisability of the results were limited, our analysis included data about CTZ exposure during all three trimesters of pregnancy, allowing investigation of outcomes in women who had been exposed for only 1 or 2 trimesters, as well as for the whole duration of their pregnancies. In comparison, previous studies reported on the CTZ exposure during the first trimester only (Einarson et al. 1997; Weber-Schoendorfer and Schaefer 2008).

However, these limitations are inherent to most safety databases, and the UCB Pharma Safety Database nevertheless provides valuable information for studies like the one presented here. To our knowledge, our study represents the most comprehensive dataset for the CTZ-exposed pregnancies to-date. Future studies will increase data availability and allow to obtain more detailed information on the pregnancies and their outcomes.

Conclusions

This study represents a large number of pregnancies exposed to CTZ and suggests that exposure to CTZ during pregnancy is not associated with adverse outcomes above background rates. While the results are reassuring and add to the growing body of literature, they must be interpreted within the context of the strengths and limitations of a safety database study. Further prospectively reported pregnancies are required before definite conclusions can be drawn on the risks of CTZ exposure during pregnancy.

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