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ORIGINAL REPORT

Safety of clozapine use during pregnancy: Analysis of international pharmacovigilance data

Marieke M. Beex-Oosterhuis[1,2] | Amadou Samb[3] | Eibert R. Heerdink[3,4,5] | Patrick C. Souverein[3] | Arthur R. Van Gool[6] | Ronald H. B. Meyboom[3] | Rob J. van Marum[2,7]

[1]Department of Clinical Pharmacy, Albert Schweitzer Hospital, Dordrecht, The Netherlands

[2]Department of General Practice and Elderly Care Medicine, EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands

[3]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

[4]Department of Clinical Pharmacy, Utrecht University Medical Center, Utrecht, The Netherlands

[5]Research Group Innovation of Pharmaceutical Care, University of Applied Sciences Utrecht, Utrecht, The Netherlands

[6]Emergis, Goes, The Netherlands

[7]Geriatric Department and Center for Clinical Pharmacology, Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands

Correspondence
Marieke M. Beex-Oosterhuis, Department of Clinical Pharmacy, Albert Schweitzer Hospital, Albert Schweitzerplaats 25, 3318 AT Dordrecht, The Netherlands.
Email: m.oosterhuis@asz.nl

Abstract

Purpose: Safety data on clozapine use during pregnancy are limited. The aim of this study was to determine disproportionality in case safety reports on adverse pregnancy outcomes between clozapine and other antipsychotics (OAP) used during pregnancy.

Methods: We included all reports of suspected adverse drug reactions (ADRs) to antipsychotics registered in the World Health Organization global individual case safety report (ICSR) database (VigiBase) in children younger than 2 years and women aged 12-45 years. A case/non-case approach was used to evaluate the association between several pregnancy-related ADRs and clozapine exposure during pregnancy, using 2×2 contingency tables to investigate disproportionality and Standard MedDRA Queries to select cases. Clozapine exposure was defined as all ICSR-ADR combinations with clozapine as (one of) the suspected drug(s). Non-exposure was defined as all ICSR-ADR combinations with OAP as (one of) the suspected drug(s).

Results: We identified 42 236 unique ICSR-ADR combinations related with clozapine exposure and 170 710 with OAP exposure. Of these, 494 and 4645 ICSR-ADR combinations involved adverse pregnancy outcomes related with clozapine exposure and OAP exposure respectively. Overall, no signal of disproportionate reporting associating clozapine with the studied adverse pregnancy outcomes was found compared with OAP exposure.

Conclusion: Based on global pharmacovigilance data, we did not find any evidence that clozapine is less safe during pregnancy than OAP. Although this is not automatically equivalent to the relative safety of clozapine during pregnancy, these findings add to the convergence of proofs to allow final conclusions and decisions regarding the treatment of pregnant women with clozapine.

KEYWORDS

clozapine, pharmacoepidemiology, pharmacovigilance, pregnancy

Disclaimer: The information in this article does not represent the opinion of the World Health Organization, the Uppsala Monitoring Centre, or the opinion of the national pharmacovigilance centres.

1 | INTRODUCTION

The atypical antipsychotic drug clozapine is currently the only drug proven to be effective in patients with treatment-refractory schizophrenia. While it used to be under-prescribed and with a delayed onset of treatment,[1,2] the importance of starting clozapine as soon as possible is gradually being recognized,[3-5] and prescription rates have increased in recent years.[6-8] In the Netherlands, approximately one third of clozapine users are women of childbearing age.[8] Although fertility rates are generally lower in patients with schizophrenia than in healthy individuals of the same age,[9] the fertility rate is increasing,[10,11] reflected by the growing number of pregnancies in women taking atypical antipsychotics.[12] Safety data on the use of the other atypical antipsychotics quetiapine, olanzapine, and aripiprazole during pregnancy do not suggest that their use is associated with a clinically meaningful increased risk of congenital malformation.[13] However, there are few data on the risk of using clozapine during pregnancy.[13] Some anecdotal cases of congenital anomalies have been reported in association with clozapine use during pregnancy, such as a baby with gastroschisis and a horseshoe kidney[14] and a baby with a missing testicle,[15] but specific patterns of anomalies have not been detected.[16]

The increased prescription of clozapine and the improved fertility of women with schizophrenia make it essential to have additional pregnancy safety data. Reported adverse drug reactions (ADRs) are a valuable source of additional information about drug safety. Therefore, this study compared the frequency of reported adverse pregnancy outcomes after the use of clozapine vs other antipsychotics (OAP) during pregnancy, using the World Health Organization (WHO) global individual case safety report (ICSR) database, VigiBase.[17]

KEY POINTS

- Pharmacovigilance data provide a valuable source of safety information about a given drug.
- No signal of disproportionate reporting associating clozapine with the studied adverse pregnancy outcomes was found compared with OAP exposure.

2 | METHODS

2.1 | Data source

The Uppsala Monitoring Centre, in its role as the WHO Collaborating Centre for International Drug Monitoring, collects reports of suspected ADRs from national centres in countries participating in the WHO pharmacovigilance network. The information is stored in VigiBase, the world's largest pharmacovigilance database. The size and worldwide coverage of this database makes it particularly appropriate for exploring signals for comparatively rare events such as teratogenic events, stillbirths and abortions. As of November 2017, VigiBase contained more than 16 million ICSRs from 130 collaborating countries and 26 associate countries.[17,18] ICSRs may be submitted by health professionals, patients, and manufacturers, depending on the reporting strategies of the national pharmacovigilance centres and include information on patient characteristics, suspected ADRs, country of origin, and the drugs involved. An ICSR may contain information about multiple suspected drugs and multiple suspected ADRs, hence there are more drug-ADR combinations than ICSRs in the database. ADRs are coded according to the Medical Dictionary for Regulatory Authorities (MedDRA) terminology, which was developed to standardize the international medical terminology for regulatory activities.[17,19] MedDRA is a hierarchical system, starting with a very general level (the system organ classes) and ending with the more detailed preferred terms (PTs) which in turn are divided into the most specific level, namely, low-level terms (LLTs).[19]

2.2 | Study population

We included all ICSRs registered in VigiBase since its establishment in 1968 until January 2018 concerning children younger than 2 years and women aged 12-45 years in which an antipsychotic drug was a suspected drug (ATC code N05A, excluding lithium [N05AN01], since lithium is not an antipsychotic and is not indicated for the treatment of schizophrenia and therefore lithium-users would represent another population). This age and gender selection were based on selection of either the affected child or the affected mother, since pregnancy outcomes can be reported for both the mother and the child in pharmacovigilance databases.

2.3 | Case/non-case identification and exposure definition

In this study, a case/non-case approach was used to evaluate the association between several pregnancy-related adverse events and clozapine exposure during pregnancy. To facilitate the identification and retrieval of safety data, the International Conference of Harmonization has developed so-called Standardized MedDRA Queries (SMQs).[20] In general, SMQs consist of preferred terms that have been grouped together, based on consistency with an overall medical condition or area of interest.[20] We used the following SMQs to select our cases: “Pregnancy, labour and delivery complications and risk factors (excl. abortion and stillbirth)” (SMQ 20000186), “Termination of pregnancy and risk of abortion” (SMQ 20000192), “Foetal disorders” (SMQ 20000190), “Congenital, familial and genetic disorders” (SMQ 20000077), and “Neonatal disorders” (SMQ 20000191). Since the SMQ “termination of pregnancy and risk of abortion” contains both the preferred terms “spontaneous abortion” and “induced abortion”, we also used a modified MedDRA query, including only terms referring to spontaneous abortions.

In the included ICSRs, in which an antipsychotic was reported as a suspected drug, a case was defined as an ICSR-ADR combination with an ADR (a preferred term or low-level term) included in one of the SMQs mentioned above. Non-cases were all included ICSR-ADR combinations without ADRs of the SMQs of interest.

In addition, all ICSR-ADR combinations with an ADR included in the SMQ "Congenital, familial and genetic disorders" were analyzed at the PT/LLT level for each ADR reported. Some ADRs included in this SMQ, such as haemoglobinopathy or dolichocolon, are not unambiguously related to a pregnancy, but are also used to report an adverse event in the actual user. Therefore, when reported for a woman aged 12-45 years, other characteristics of the individual ICSR were studied in more detail to determine final case selection.

Clozapine exposure was defined as all ICSR-ADR combinations in which the reporter had designated clozapine as (one of) the suspected drug(s). Other antipsychotic exposure was defined as all ICSR-ADR combinations with OAPs as suspected drugs. ICSRs with both clozapine and OAP as suspected drugs were defined as clozapine-exposed ICSRs.

2.4 | Data analysis

Demographic data for the ICSRs were analyzed using descriptive statistics.

In general, if the proportion of an ADR is greater in patients exposed to a drug or group of drugs than in patients not exposed to this drug, this suggests an association between the specific drug and the reaction and is a signal for a potential safety issue. In our study, the unit of analysis was the unique combination of the report (ICSR) and the reported suspected ADR (MedDRA code). To identify ICSR-ADR pairs with the adverse pregnancy outcomes of interest that were reported more frequently for ICSRs with clozapine as (one of) the suspected drug(s) than for ICSRs with OAP (one of) the suspected drug(s), the reporting odds ratio (ROR) was used as a measure of disproportional reporting by assessing 2×2 contingency tables[21] (Figure 1). This is a validated method of safety signal detection[22] and, in this study, it provided an estimate of the extent to which adverse pregnancy outcomes were reported in association with clozapine exposure compared with exposure to other antipsychotics. The ROR was defined as the ratio between proportions of reports in the "case" (reports containing the adverse pregnancy outcomes of interest) and in the "non-case" (reports containing other ADRs, without the outcomes of interest) group that are associated with clozapine exposure and with OAP exposure. A signal of disproportionate reporting was defined when the lower limit of the 95% two-sided CI for the ROR exceeded the threshold value of 1.[21] The results are presented as the RORs with the corresponding 95% confidence intervals (95%CI).

	Case	Non-case
Clozapine as (one of) the suspected drug(s)	a	b
OAP as (one of) the suspected drug(s)	c	d

FIGURE 1 2×2 contingency table for calculation of the ROR as a measure of disproportional reporting using the following formula: ROR = (a/b)/(c/d). In the analysis based on SMQs, cases are defined as ICSR-ADR pairs with an ADR included in one of the SMQs of interest. In the second analysis, cases are defined as ICSR-ADR pairs with an ADR included in the SMQ "Congenital, familial and genetic disorders"

The detection of a signal of disproportionate reporting can be hampered by high frequencies of reports of events known to be strongly associated with a drug. Since clozapine was temporarily taken off the market in most European countries in 1975 after reports of life-threatening agranulocytosis in Finland shortly after it had been introduced on the Finnish market,[23] it is conceivable that there is a greater alertness to adverse reactions with clozapine use in general and specifically with regard to reports of blood dyscrasia. Hence, in our study, when there is a large number of reports related to for example leukopenia, the reporting rate for other events for clozapine is mathematically reduced. To circumvent this potential masking effect, we first identified the adverse events that defined approximately 10% of the total number of ICSR-ADR combinations for clozapine. Then we removed these ICSR-ADR combinations and recalculated the RORs based on the SMQs. The same was done for the adverse events defining approximately 10% of the total number of ICSR-ADR combinations for OAP exposure.

Taking into account the complex marketing history of clozapine, a sensitivity analysis restricted to cases reported to VigiBase from 1990, the year in which clozapine was granted access to the United States' market, and onwards has also been performed.

To search for possible trends in the extent to which a specific ADR of the SMQ "Congenital, familial, and genetic disorder" had been reported in association with clozapine exposure, the RORs of the reported ADRs were also calculated with their 95%CIs.

All statistical analyses were conducted using SPSS Statistics version 24.0.

3 | RESULTS

3.1 | All reports

We identified a total of 18 448 unique ICSRs in which clozapine was (one of) the suspected drug(s), and 67 991 unique ICSRs in which an OAP was (one of) the suspected drug(s) (Table 1), with on average 2.3 ADRs reported per ICSR with clozapine as (one of) the suspected drug(s) and 2.5 ADRs per ICSR with OAP as (one of) the suspected drug(s). Most of the reports originated from Europe, followed by the Americas. Few reports with clozapine as (one of the) suspected drug(s) originated from before 1990, the year when clozapine was introduced in the United States.

TABLE 1 Characteristics of the unique individual case safety reports with clozapine or other antipsychotics as (one of the) suspected drug(s)

	Children aged <2 y		Women aged 12-45 y	
	CLZ (N [%])	OAP (N [%])	CLZ (N [%])	OAP (N [%])
Total number of unique ICSRs	125	1426	18 323	66 565
Total number of unique ICSR-ADR combinations	422	4214	41 814	166 496
Mean number of ADRs per ICSR	3.4	3.0	2.3	2.5
Gender				
Male	59 (47%)	735 (52%)	n.a.	n.a.
Female	53 (42%)	550 (39%)	18 323 (100%)	66 565 (100%)
Missing	13 (10%)	141 (10%)	n.a.	n.a.
Age group				
0-28 d	60 (48%)	827 (58%)	n.a.	n.a.
28 d - 23 mo	65 (52%)	599 (42%)	n.a.	n.a.
12-17 y	n.a.	n.a.	636 (3%)	5631 (8%)
18-45 y	n.a.	n.a.	17 687 (97%)	60 934 (92%)
Reporting region				
European region	82 (66%)	789 (55%)	7809 (43%)	21 538 (32%)
Region of the Americas	24 (19%)	349 (24%)	7040 (38%)	29 152 (44%)
Western Pacific region	16 (13%)	260 (18%)	3169 (17%)	10 778 (16%)
South-East Asia region	1 (1%)	17 (1%)	268 (1%)	4235 (6%)
African region	1 (1%)	3 (0%)	23 (0%)	564 (1%)
Eastern Mediterranean region	1 (1%)	8 (1%)	14 (0%)	298 (0%)
Reporting period				
<1990	0 (0%)	70 (5%)	122 (1%)	4789 (7%)
1990-2000	10 (8%)	81 (6%)	4497 (25%)	5971 (9%)
2000-2010	31 (25%)	246 (17%)	5741 (31%)	15 299 (23%)
>2010	84 (67%)	1029 (72%)	7963 (43%)	40 506 (61%)

Abbreviations: ADR, adverse drug reaction; CLZ, clozapine; ICSRs, individual case safety reports; n.a., not applicable; OAP, other antipsychotics.

In only 6.3% (n = 2660) of the 42 236 unique ICSR-ADR combinations in which clozapine was reported as suspected drug, there was also an OAP reported as a suspected drug.

3.2 | Pregnancy-related adverse events

The associations between the SMQs of interest and exposure to clozapine or an OAP are presented in Table 2. In total, 494 ICSR-ADR combinations were found involving adverse pregnancy outcomes with clozapine as (one of) the suspected drug(s) and 4645 ICSR-ADR combinations with OAP as suspected drug(s). Overall, no signal of disproportionate reporting associating clozapine exposure with "Pregnancy, labour and delivery complications and risk factors," "Termination of pregnancy and risk of abortion," "Foetal disorders," "Congenital, familial and genetic disorders," and "Neonatal disorders" was found compared with OAP exposure. Moreover, in the combined population of children younger than 2 years and women aged 12-45 years, clozapine was statistically significantly less often associated with all the pregnancy-related adverse outcomes than OAP exposure.

To circumvent a potential masking effect resulting from high frequencies of reports of events known to be strongly associated with clozapine treatment, the adverse events that defined approximately 10% of the total number of ICSR-ADR combinations for clozapine were identified: Leukopenia (4.6%), Neutropenia (3.8%), Tachycardia (3.1%) and Granulocytopenia (2.4%). No signal of disproportionate reporting associating clozapine with one of the adverse pregnancy events was unmasked after removal of these ICSR-ADR combinations. The same was done for the adverse events defining approximately 10% of the total number of ICSR-ADR combinations for OAP exposure (ie, Extrapyramidal disorder (1.6%), Somnolence (1.4%), Dystonia (1.3%), Tremor (1.1%), Weight increased (1.1%), Suicide attempt (1.0%), Diabetes mellitus (1.0%) and Insomnia (1.0%)). This did not influence our findings either.

The results of the sensitivity analysis restricted to ICSRs reported since 1990 are presented in Table 3. The results are almost identical to the analysis of the ICSRs reported to VigiBase since its establishment in 1968 and onwards.

TABLE 2 Number of individual case safety report – adverse drug reaction combinations for adverse pregnancy outcomes grouped by Standard MedDRA Query, with reporting odds ratios for ICSR-ADR combinations with clozapine vs other antipsychotics as suspected drug(s)

	Children aged <2 y				Women aged 12-45 y				Combined population (children aged <2 y and women aged 12-45 y)			
Standard MedDRA Queries (SMQ)	CLZ (n^a = 422)	OAP (n^a = 4214)	ROR	(95% CI)	CLZ (n^a = 41 814)	OAP (n^a = 166 496)	ROR	(95% CI)	CLZ (n^a = 42 236)	OAP (n^a = 170 710)	ROR	(95% CI)
Pregnancy, labour and delivery complications and risk factors (excl. abortions and stillbirth) (20000186)	34	405	0.82	0.57-1.19	206	1770	0.46	0.40-0.53	240	2175	0.44	0.39-0.51
Termination of pregnancy and risk of abortion (20000192)	0	21	n.a.		64	440	0.58	0.45-0.75	64	461	0.56	0.43-0.73
Modified MedDRA query based on Termination of pregnancy and risk of abortion	0	17	n.a.		63	396	0.63	0.49-0.83	63	413	0.62	0.47-0.80
Foetal disorders (20000190)	14	123	1.14	0.65-2.00	24	103	0.93	0.60-1.45	38	226	0.68	0.48-0.96
Congenital, familial and genetic disorders (20000077)	38	511	0.72	0.51-1.01	38	313	0.48	0.35-0.68	76	824	0.37	0.29-0.47
Neonatal disorders (20000191)	57	856	0.61	0.46-0.82	19	103	0.73	0.45-1.20	76	959	0.32	0.25-0.40

Abbreviations: ADR, adverse drug reaction; CLZ, clozapine; ICSRs, individual case safety reports; n.a., not applicable; OAP, other antipsychotics; SMQ, Standard MedDRA Queries.
[a]n, total number of unique ICSR-ADR combinations.

TABLE 3 Number of individual case safety report – adverse drug reaction combinations for adverse pregnancy outcomes grouped by Standard MedDRA Query reported in VigiBase from 1990 onwards, with reporting odds ratios for ICSR-ADR combinations with clozapine vs other antipsychotics as suspected drug(s)

	Children aged <2 y				Women aged 12-45 y				Combined population (children aged <2 y and women aged 12-45 y)			
Standard MedDRA Queries (SMQ)	CLZ (n^a = 422)	OAP (n^a = 4094)	ROR	(95% CI)	CLZ (n^a = 41 628)	OAP (n^a = 158 415)	ROR	(95% CI)	CLZ (n^a = 42 050)	OAP (n^a = 162 509)	ROR	(95% CI)
Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (20000186)	34	405	0.80	0.55-1.15	206	1769	0.44	0.38-0.51	240	2174	0.42	0.37-0.48
Termination of pregnancy and risk of abortion (20000192)	0	21	n.a.		63	427	0.56	0.43-0.73	63	448	0.54	0.42-0.71
Modified MedDRA query based on Termination of pregnancy and risk of abortion	0	17	n.a.		62	383	0.62	0.47-0.81	62	400	0.60	0.46-0.78
Foetal disorders (20000190)	14	123	1.11	0.63-1.94	24	101	0.90	0.58-1.41	38	224	0.66	0.47-0.92
Congenital, familial and genetic disorders (20000077)	38	501	0.71	0.50-1.00	38	221	0.65	0.46-0.92	76	722	0.41	0.32-0.51
Neonatal disorders (20000191)	57	849	0.60	0.45-0.80	19	95	0.76	0.47-1.25	76	944	0.31	0.25-0.39

Abbreviations: ADR, adverse drug reaction; CLZ, clozapine; ICSRs, individual case safety reports; n.a., not applicable; OAP, other antipsychotics; SMQ, Standard MedDRA Queries.
[a]n, total number of unique ICSR-ADR combinations.

TABLE 4 Identity, number reported, and reporting odds ratios of the adverse drug reactions of Standard MedDRA Query "*Congenital, familial and genetic disorders*" grouped by preferred term

Preferred term	Reported number		ROR	95%CI	Note
	CLZ (N)	OAP (N)			
Atrial septal defect	8	75	0.43	0.21-0.89	• 2 clozapine-exposed ICSRs also reported a ventricular septal defect, of which 1 also reported anal atresia, cryptorchism and vitello-intestinal duct remnant and the other also reported citalopram and lithium as suspected drugs. • In 1 clozapine-exposed ICSR levetiracetam and lamotrigine were also reported as suspected drugs. • In 1 clozapine-exposed ICSR clomipramine was also reported as a suspected drug. • 2 clozapine-exposed ICSRs also reported the following ADRs not included in the SMQ "Congenital, familial and genetic disorders": increased drug level, agitation, arrhythmia, cardiomegaly and confusional state, possibly referring to ADRs in a female user and not in a newborn child. In these ICSRs, topiramate was also reported as a suspected drug. Since the information in these 2 ICSRs were exactly the same, these ICSRs were regarded as duplicate ICSRs. • In 1 clozapine-exposed ICSR coarctation of the aorta, aorta hypoplasia and patent ductus arteriosus were also reported • In 1 clozapine-exposed ICSR patent ductus arteriosus was also reported
Congenital anomaly	7	39	0.73	0.32-1.62	In 3 of the 7 clozapine-exposed ICSRs the anomaly was also specified by one or more other MedDRA code(s): 1 ICSR also reported ear malformation; 1 ICSR also reported hypospadias, congenital foot malformation and congenital hand malformation; 1 ICRS also reported cleft palate.
Ventricular septal defect	6	42	0.58	0.25-1.36	• 2 clozapine-exposed ICSRs also reported an atrial septal defect, of which 1 also reported anal atresia, cryptorchism and vitello-intestinal duct remnant and the other also reported citalopram and lithium as suspected drugs. • 1 clozapine-exposed ICSR also reported VACTERL syndrome • 1 clozapine-exposed ICSR also reported amitriptyline as a suspected drug • 1 clozapine-exposed ICSR also reported aripiprazole as a suspected drug
Dysmorphism	4	18	0.90	0.30-2.65	3 of the 4 reported dysmorphisms referred to the same ICSR, reporting Dysmorphism as a PT, but also as the related LLTs "Facial dysmorphism" and "Flat philtrum". In this ICSR valproic acid and propranolol were also reported as one of the suspected drugs and cryptorchism was also reported as an ADR. The other clozapine-exposed ICSR also reported abnormal palmar/plantar creases as an ADR and quetiapine, opipramol, simvastatin, pantoprazole and ziprasidone as suspected drugs.
Cryptorchism	3	9	1.35	0.36-4.98	In 1 clozapine-exposed ICSR dysmorphism was also reported.
Patent ductus arteriosus	3	14	0.87	0.25-3.01	In 1 clozapine-exposed ICSR atrial septal defect was also reported. In 1 clozapine-exposed ICSR coarctation of the aorta, aorta hypoplasia atrial septal defect were also reported
Huntington's disease[a]	2[a]	2	4.04	0.57-28.70	
Congenital foot malformation	2	6	1.35	0.27-6.68	In 1 clozapine-exposed ICSRS carbamazepine was also reported as one of the suspected drugs

TABLE 4 (Continued)

Preferred term	Reported number		ROR	95%CI	Note
	CLZ (N)	OAP (N)			
Microcephaly	2	8	1.01	0.21-4.76	In 1 clozapine-exposed ICSR valproic acid was also reported as one of the suspected drugs
Sickle cell anemia with crisis[a]	2[a]	2	4.04	0.57-28.69	• 1 clozapine-exposed ICSR also reported the following ADR not included in the SMQ "Congenital, familial and genetic disorders": gastrointestinal pain • 1 clozapine-exposed ICSR also reported the following ADRs not included in the SMQ 'Congenital, familial and genetic disorders': neutrophil count increased and white blood cell count increased
Cleft palate	2	24	0.34	0.08-1.43	1 clozapine-exposed ICSR also reported "congenital anomaly" as an ADR
Aorta hypoplasia	2	1	8.08	0.73-89.16	• 1 clozapine-exposed ICSR also reported coarctation of the aorta, atrial septal defect and patent ductus arteriosus • 1 clozapine-exposed ICSR also reported bicuspid aorta valve
Vascular malformation	2	2	4.04	0.57-28.70	
Abnormal palmar/plantar creases	1	1	4.04	0.25-64.62	The clozapine-exposed ICSR also reported dysmorphism as an ADR and quetiapine, opipramol, simvastatin, pantoprazole and ziprasidone as suspected drugs.
Melkersson-Rosenthal syndrome[a]	1[a]	0	n.e.	n.e.	The clozapine-exposed ICSR also reported the following ADRs not included in the SMQ "Congenital, familial and genetic disorders": apathy, claustrophobia, depressed mood, drooling, increased appetite, malaise, thinking abnormal and weight abnormal.
Pulmonary hypoplasia	1	2	2.02	0.18-22.29	The clozapine-exposed ICSR also reported renal aplasia and renal hypoplasia
Hypospadias	1	16	0.25	0.03-1.90	The clozapine-exposed ICSR also reported congenital anomaly, congenital foot malformation and congenital hand malformation
Renal aplasia	1	4	1.01	0.11-9.04	The clozapine-exposed ICSR also reported pulmonary hypoplasia and renal hypoplasia
Renal hypoplasia	1	0	n.e.	n.e.	The clozapine-exposed ICSR also reported renal aplasia and pulmonary hypoplasia
Hepato-lenticular degeneration[a]	1[a]	0	n.e.	n.e.	The clozapine-exposed ICSR also reported the following ADRs not included in the SMQ "Congenital, familial and genetic disorders": anemia, choreoathetosis, constipation, movement disorder, thrombocytopenia.
Congenital hydrocephalus	1	1	4.04	0.25-64.62	
Congenital nystagmus	1	2	2.02	0.18-22.29	
Congenital hand malformation	1	10	0.40	0.05-3.16	
Talipes	1	42	0.10	0.01-0.70	The clozapine-exposed ICSR also reported flupentixol, sertraline and promethazine as suspected drugs
Scaphocephaly	1	0	n.e.	n.e.	The clozapine-exposed ICSR also reported cyamemazine and oxazepam as suspected drugs
Congenital musculoskeletal anomaly	1	15	0.27	0.04-2.04	
Porphyria[a]	1[a]	3	1.35	0.14-12.95	
Sickle cell trait[a]	1[a]	0	n.e.	n.e.	The clozapine-exposed ICSR also reported the following ADRs not included in the SMQ "Congenital, familial and genetic disorders": iron deficiency, serum ferritin decreased and viral infection
Anal atresia	1	3	1.35	0.14-12.95	The clozapine-exposed ICSR also reported atrial septum defect, cryptorchism, ventricular septal defect and vitello-intestinal duct remnant.

(Continues)

TABLE 4 (Continued)

Preferred term	Reported number		ROR	95%CI	Note
	CLZ (N)	OAP (N)			
Gastroschisis	1	2	2.02	0.18-22.29	The clozapine-exposed ICSR also reported paroxetine as a suspected drug
Dolichocolon[a]	1[a]	0	n.e.	n.e.	The clozapine-exposed ICSR also reported the following ADRs not included in the SMQ "Congenital, familial and genetic disorders": volvulus, abdominal pain, constipation and megacolon.
Vitello-intestinal duct remnant	1	0	n.e.	n.e.	
Gastrointestinal malformation	1	4	1.01	0.11-9.04	The clozapine-exposed ICSR also reported lithium as a suspected drug
Color blindness	1	3	1.35	0.14-12.95	
Ear malformation	1	10	0.40	0.05-3.16	The clozapine-exposed ICSR also reported "congenital anomaly" as an ADR
VACTERL syndrome	1	0	n.e.	n.e.	The clozapine-exposed ICSR also reported ventricular septum defect as an ADR
Trisomy 21	1	9	0.45	0.06-3.55	
Heart disease congenital	1	23	0.18	0.02-1.30	
Atrioventricular septal defect	1	1	4.04	0.25-64.62	
Hypertrophic cardiomyopathy	1	0	n.e.	n.e.	
Bicuspid aortic valve	1	0	n.e.	n.e.	The clozapine-exposed ICSR also reported aorta hypoplasia
Coarctation of the aorta	1	4	1.01	0.11-9.04	The clozapine-exposed ICSR also reported aorta hypoplasia, atrial septal defect and patent ductus arteriosus
Haemoglobinopathy[a]	1[a]	0	n.e.	n.e.	The clozapine-exposed ICSR also reported the following ADRs not included in the SMQ "Congenital, familial and genetic disorders": neutrophil count decreased, neutropenia and white blood cell count decreased.
Thalassaemia[a]	1[a]	0	n.e.	n.e.	The clozapine-exposed ICSR also reported the following ADRs not included in the SMQ "Congenital, familial and genetic disorders": lymphocyte count increased, mean cell hemoglobin, platelet count increased, red blood cell count increased and red cell distribution width increased.

Abbreviations: ADR, adverse drug reaction; CI, confidence interval; CLZ, clozapine; ICSRs, individual case safety reports; n.e., not executable (due to 0 ICSR-ADR combinations for OAP ICSRs); OAP, other antipsychotics; ROR, reporting odds ratio; SMQ, Standard MedDRA Queries.
[a]Possible misclassification due to inclusion of an ADR or condition in a clozapine user / not applicable to perinatal use.

3.3 | Congenital, familial and genetic disorders

Table 4 lists the identity, number of reports, and RORs of the 76 ADRs of the SMQ "Congenital, familial and genetic disorders" grouped by preferred term. These ADRs were reported in 54 unique ICSRs.

On closer inspection, 11 of the 76 ICSR-ADR pairs that were associated with clozapine exposure reporting ADRs of the SMQ "Congenital, familial and genetic disorders" were thought to be related to adverse events observed in a clozapine user or related to events for which clozapine was indicated, rather than an effect seen in the offspring of a clozapine user due to perinatal exposure. Two duplicate safety reports were identified, both describing "atrial septal defect". These two duplicate ICSRs were also thought to refer to ADRs in a female user instead of in an infant exposed to clozapine during pregnancy.

Atrial septal defect (ASD) (n = 8), *Congenital anomaly* (n = 7), and *Ventricular septal defect (VSD)* (n = 6) were the most frequently reported ADRs for ICSRs with clozapine as (one of) the suspected drug(s), but these ADRs were relatively equally (congenital anomaly and VSD) or even more (ASD) often associated with OAP exposure.

4 | DISCUSSION

This study provides an overview of all spontaneously reported ADRs worldwide (1968-2018) that are associated with antipsychotic use during pregnancy. Our main finding is that, based on data from this large pharmacovigilance database, we did not detect any signal of disproportionate reporting of pregnancy-related adverse events associated with clozapine exposure compared with exposure to other

antipsychotics. We used SMQs, which combine multiple ADRs related to one specific topic, to select safety reports about pregnancy, labour, and delivery complications, foetal and neonatal disorders, risk of stillbirth and abortion, and congenital disorders. SMQs provide a standard and validated tool for signal detection.[20] To look for possible trends and patterns in the reporting of specific ADRs regarding congenital anomalies, we also examined these related ICSRs in more detail. Again, we did not detect an increased frequency of safety reports with clozapine rather than an OAP as (one of the) suspected drugs(s). In fact, in the combined population of children younger than 2 years and women aged 12-45 years, we even found statistically significant lower frequencies of reports with clozapine than with OAP as suspected drug(s) for all six pregnancy related SMQs, suggesting that clozapine is less likely than other antipsychotic drugs to be related to adverse pregnancy outcomes. These lower reporting frequencies cannot be explained by a mathematical reduction in the number of reports of pregnancy-related adverse events by other adverse events with high reporting frequencies, since we have excluded this possible masking effect. Yet, it is important to emphasize that, unlike an odds ratio (OR), the ROR is not a direct risk measurement, but rather reflects imbalance in reporting frequency of a drug-associated adverse event in comparison with other events associated with the same drug. Thus, when interpreting the value of the reporting odds ratio, one should bear in mind that the true number of "exposed" and "non-exposed" patients is not available and instead the number of reports is being used as nominator and denominator, which is subject to reporting bias. In general, the number of reports associated with a drug may be influenced by the extent of its use, publicity, the nature of the reactions, and other factors. Due to clozapine's reputation as a useful but potentially harmful medicine,[6] it is possible that clozapine has been used in fewer pregnancies than OAP, which could be an explanation for the significantly lower reporting frequencies of adverse pregnancy events associated with clozapine exposure. On the other hand, while we do not know if women using clozapine are more likely to have more unplanned pregnancies than women using OAP, we do know that women with psychotic disorders in general are likely to have more unplanned pregnancies than women without psychotic disorders[24,25] and thus may not consciously weigh the risks of using a potentially harmful drug. In addition, the relatively large number of ICSRs with clozapine as a suspected drug (n = 18 448) compared to the total number of ICSRs with OAP as a suspected drug (n = 67 991), does not correspond to the small proportion of actual clozapine users compared to OAP users worldwide. Owing to clozapine's stigma, there is a great awareness and willingness to report case safety data for clozapine. Thus, although we cannot completely rule out that a smaller number of pregnancies exposed to clozapine may have influenced our findings, we believe that if this is the case, this will be, at least partly, compensated by the higher willingness to report safety data of clozapine.

Nevertheless, these lower RORs could be subject to further investigation in direct comparative studies. Our findings are in concordance with the conclusions of Mehta and Van Lieshout, who could not detect specific patterns of anomalies.[16] They concluded that, although the evidence regarding the safety and efficacy of clozapine use during pregnancy is still very limited, the risk of congenital anomalies did not appear to exceed that of the general population.

Although disproportionality analysis of pharmacovigilance data is able to give valuable information on rare and/or nonspecific ADRs and drug safety,[22] there are some important precautions. In addition to the aforementioned possibility of reporting bias, it should be borne in mind that the reports submitted to pharmacovigilance centres generally describe no more than a suspicion arisen from an observation of an unexpected or unwanted event. The reports may be incomplete and the evidence for the causality of associations is not the same in all reports and is often even lacking. So, results should be interpreted with caution, which makes it difficult to draw definite conclusions. Also, the available information about the reports is not unlimited. In our study, it would have been informative to distinguish between adult women (aged 18-45 years) and adolescent women (aged 12-18 years), but unfortunately nowadays VigiBase only provides the variable age as age-categories. In any case, we believe that the use of this age category, including adolescents is meaningful because adolescent women can become pregnant as well. Also, this study method did not allow for adjustment for other confounding factors. Exposure to antipsychotics during pregnancy is inevitably linked with exposure to maternal illness, and schizophrenia as such has also been associated with several adverse obstetric complications and pregnancy outcomes.[26] Other concomitant factors, such as low dietary vitamin intake, poor nutrition, reduced serum folate levels related to poor antenatal care, smoking, and alcohol and drug abuse, make it extremely difficult to separate the contribution of antipsychotics from the influence of these potentially confounding factors.[27,28] To reduce the impact of these concomitant factors as much as possible, we explicitly selected exposure to OAP as our comparator group, thereby creating a comparator group exposed to conditions that are most similar to those of patients in the clozapine-exposed ICSRs. Moreover, due to clozapine's position in the treatment algorithm, clozapine is used by the severely ill and is almost always the drug of last resort. Consequently, it is not a question of whether or not to treat the pregnant mother, but what is the least harmful treatment in this situation for both the mother and the unborn child. Therefore, the comparator group did not consist of all other reports in VigiBase for our population, but of the theoretically available alternative of treatment with other antipsychotics.

Finally, as can be seen from Table 4, some ICSR-ADR combinations may have been erroneously selected as cases, owing to the inclusion of preferred terms in the SMQ "Congenital, familial and genetic disorder" that are not unambiguously related to a pregnancy. In other words, when reported for a woman aged 12-45 years, some ADRs of this SMQ may refer to an adverse event (such as dolichocolon) associated with use of the drug rather than a congenital disorder due to in utero exposure to the drug. Since we studied the 76 ICSR-ADR combinations potentially associated with clozapine exposure in detail, but not the 824 ICSR-ADR combinations potentially associated with OAP exposure, we could not calculate an adjusted ROR. However, based on the ROR for the population of

children <2 years, it seems justified to expect that adjustment for inclusion of ICSRs related to observed adverse events in the actual users will not essentially change our results.

The therapeutic benefit of clozapine in treatment-resistant schizophrenia, is beyond doubt. However, little is known about the safety of using various neuroleptic agents during pregnancy, since this information is, understandably, lacking from randomized controlled trials. As with all pregnant women or women who are contemplating pregnancy, the risks and benefits of medical treatment have to be weighed carefully, and perhaps particularly so in women on clozapine, for whom it is likely that they have not responded adequately to other antipsychotic drugs and are unlikely to be able to do without them. Discontinuing clozapine could risk her not being able to effectively parent her child, with all the consequences that this entails.

To the best of our knowledge, this is the first study to use global pharmacovigilance data to estimate the extent to which pregnancy-related adverse events have been reported in association with clozapine as (one of the) designated suspected drug(s) compared with reports with an OAP as suspected agent. Despite its inherent limits, disproportionality analysis in pharmacovigilance databases is a valuable tool for drug safety research and surveillance, although this kind of approach should only be considered as exploratory to generate signals. Finding of a disproportionality ratio for a drug does not imply a higher risk of ADR occurrence in absolute terms and should lead to further investigation. Vice versa, in our study, the absence of a higher proportional reporting frequency is not automatically equivalent to the relative safety of clozapine during pregnancy. On the other hand, we did not find any evidence that clozapine is less safe during pregnancy than the other antipsychotics either. This summary of pharmacovigilance data is of added value for the convergence of proofs to allow final conclusions and decisions regarding the treatment of pregnant women with clozapine.

ETHICS STATEMENT

The authors state that no ethical approval was needed' will be set accordingly.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest.

ORCID

Marieke M. Beex-Oosterhuis https://orcid.org/0000-0002-3070-3626

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