Clozapine Treatment During Pregnancy and the Postpartum Period: A Systematic Literature Review

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ABSTRACT

Objective: The objective of this systematic review was to provide a critical appraisal of the evidence related to the safety of clozapine for schizophrenia during pregnancy and lactation.

Data Sources: PubMed/MEDLINE, Embase, and the Cochrane Library were searched from inception through December 2020. Reference lists of included studies were hand-searched. The International Clinical Trials Registry Platform and ClinicalTrials.gov were searched for unpublished trials, and PROSPERO was searched for unpublished reviews. The current marketing authorization holder of the originator brands Clozaril and Leponex was also contacted for pharmacovigilance data.

Study Selection: Original reports published in English, German, French, or Dutch containing clinical and preclinical data were included if they provided data on maternal, fetal, and neonatal outcomes after clozapine exposure during pregnancy or lactation.

Data Extraction: Two reviewers independently extracted relevant data.

Results: A total of 860 records were identified, and the full texts of 117 articles were reviewed. Forty-two studies met the inclusion criteria. Data on perinatal clozapine exposure are of limited quality and quantity. Although clozapine demonstrates partial placental passage, data thus far do not support that clozapine is teratogenic; that it increases the risk of stillbirth, abortion, or fetal disorders; or that it increases the risk of delivery complications or premature birth. Information about clozapine exposure through breast milk is scarce, but based on its chemical properties, it is likely that clozapine enters the breast milk of nursing mothers taking clozapine.

Conclusions: When weighing the risks and benefits of clozapine continuation during pregnancy and lactation versus switching to another antipsychotic, one should include severity of illness and treatment history but also be aware of the limitations of the available safety data regarding perinatal clozapine use, including the fact that there are few studies.

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Clozapine is the prototype of what has become the group of so-called atypical antipsychotics.[1] Although the number of atypical antipsychotics available has increased over the past decades, clozapine remains the only one with proven efficacy for treatment-resistant schizophrenia.[2,3] However, concerns over its side effects, which include agranulocytosis, cardiomyopathy, bowel obstruction, weight gain, sialorrhea, and sedation, have limited its use and have led to clozapine being considered the treatment of "last resort." To ensure that the benefits of clozapine outweigh the risk of severe neutropenia, the US Food and Drug Administration has established a program called the Clozapine Risk Evaluation and Mitigation Strategy that defines the conditions for prescribing, dispensing, and using clozapine, including mandatory testing of the white blood cell count.[4]

Yet, in recent years there is a growing perception that clozapine is underused, and the number of patients using clozapine is increasing.[5–8] Since schizophrenia has a peak age at onset among women in their childbearing years,[9] it can be expected that, over time, the number of pregnant women treated with clozapine will increase. Although clozapine can pass the placental barrier, exposing the fetus to the drug, not treating psychosis during pregnancy and postpartum may prove harmful to both mother and child.[10–12]

While safety data suggest that antipsychotics in general are safe in pregnancy,[10,13,14] there is little literature on the safety of clozapine use during pregnancy and the postpartum period.[15] Switching to another antipsychotic for which more safety data are available is rarely an option. The objective of this study was to provide a critical appraisal of the evidence related to the safety of clozapine for schizophrenia during pregnancy and lactation, focusing on maternal, fetal, and neonatal outcomes.

METHODS

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[16] following a protocol registered with PROSPERO (registration number CRD42015032475).

Inclusion Criteria

Eligible studies were original reports containing clinical data, including case series and case reports,

Clinical Points

- Since the number of patients using clozapine is increasing, over time, the number of pregnant women treated with clozapine is likely to increase.
- When considering a switch to another antipsychotic with more robust pregnancy data, one should include severity of illness and treatment history but also be aware of the limitations of the available safety data regarding perinatal clozapine use.
- Available data do not indicate that clozapine is a teratogenic drug nor a drug that, compared to other antipsychotics, increases the risk of stillbirth, abortion, fetal disorders, delivery complications, or premature birth.

on clozapine treatment during pregnancy and lactation. Animal studies describing prenatal exposure to clozapine were also eligible for inclusion. Review articles were used for cross-reference checks only. Articles not written in English, German, French, or Dutch were excluded. No year limits were applied.

Search Strategy

An electronic literature search was performed in PubMed/MEDLINE, Embase, and the Cochrane Library in February 2019 and updated in December 2020. The PubMed/MEDLINE search strategy has been included as an appendix (Supplementary Appendix 1) and was adapted accordingly for use in the other databases.

Two authors (M.M.B. and A.R.V.) independently reviewed all titles and abstracts identified by the electronic searches. Articles were selected for full-text review if the two authors agreed that the inclusion criteria were met or if there was uncertainty about this. Again, full-text articles not fulfilling the inclusion criteria were removed. The reference lists of the included articles were searched for any further literature not identified in the initial database search. Additionally, the International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov were searched for unpublished trials and PROSPERO for unpublished reviews. Lastly, the current marketing authorization holder of the originator brands Clozaril and Leponex (Mylan Products Ltd) was contacted for pharmacovigilance data.

Data Extraction

Data on study design, eligibility criteria, number of patients (ie, number of fetuses or neonates or mothers), demographic information of the mother, exposure information, follow-up period, and reported maternal, fetal, or neonatal outcomes were extracted.

RESULTS

The search yielded 262 articles from PubMed, 771 from Embase, 1 from the Cochrane Library, and 9 from the reference list check. After the elimination of duplicate studies, 860 articles remained. Of these, 117 articles were considered eligible for full-text screening; 75 articles were subsequently excluded (see flow diagram in Figure 1[16]). Forty-two articles were used for data extraction: 5 cohort studies, 2 case/non-case studies, 2 observational studies, 3 preclinical studies, and 30 case series, case reports, or letters to the editor (Table 1). The ICTRP search portal, ClinicalTrials.gov, and PROSPERO did not reveal any ongoing or recently completed trials or reviews, and the contacted manufacturer did not provide additional pharmacovigilance data. The findings are presented below in outcomes related to the mother, fetus (including delivery), and neonate.

See end of article for Table 1.

Mother

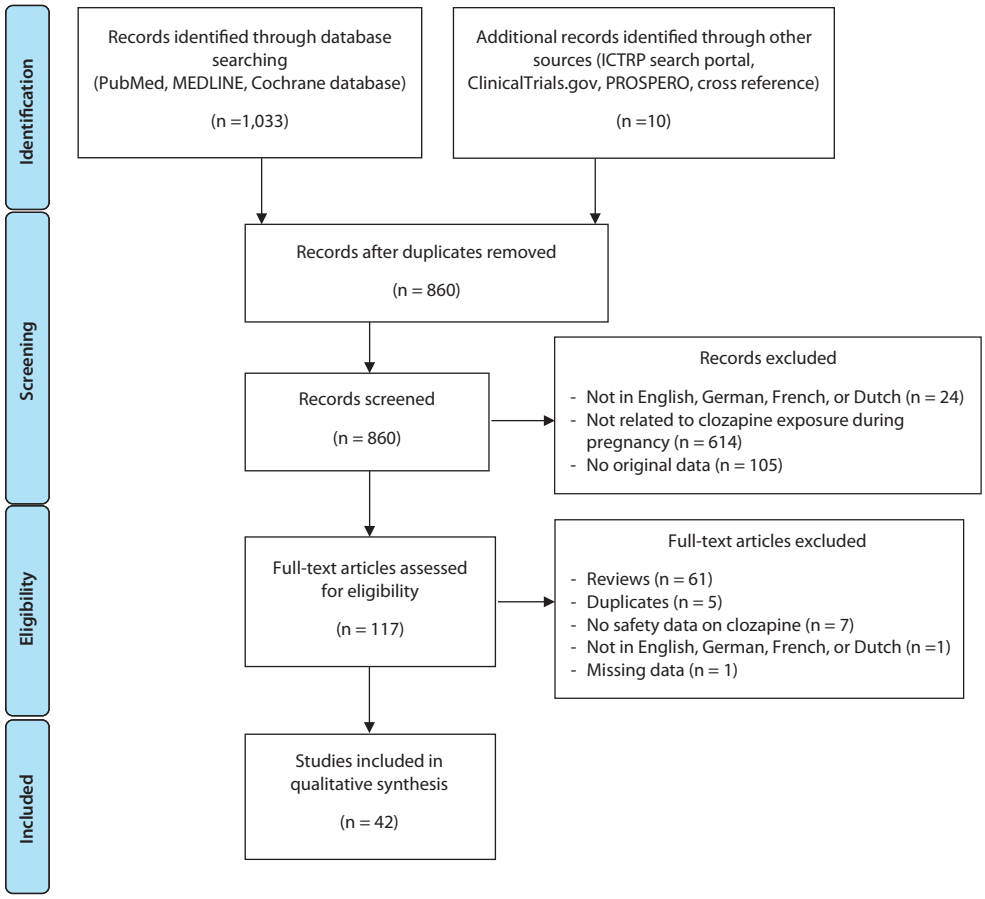
Pharmacokinetics during pregnancy. Several physiologic changes occur during pregnancy with the potential of altering the pharmacokinetics of clozapine in the mother. Clozapine metabolism is largely dependent on the activity of CYP1A2, a hepatic cytochrome P450 (CYP) enzyme. Studies indicate that CYP1A2 activity decreases during pregnancy, by 33% (±23%) in the first trimester, 48% (±27%) in the second trimester, and 65% (±15%) in the third trimester,[59] as a result of the inhibitory effects of female sex hormones.[60,61] Decreased CYP1A2 activity will prolong clozapine clearance in pregnant women. CYP1A2 is also susceptible to changes in tobacco and caffeine use, so that if expectant mothers stop or reduce their use of tobacco- and caffeine-containing products, clozapine clearance will decrease further. However, hepatic perfusion increases during pregnancy, potentially leading to a higher hepatic clearance of clozapine.

Only 1 retrospective cohort study has investigated to what extent pregnancy affects serum levels of various antipsychotics.[17] This study reported no or little change in clozapine serum concentrations during pregnancy (−23% [95% CI, −46% to 9%]). However, only 10 clozapine measurements were taken, information on smoking habits was not available, and treatment adherence was unknown (Table 2).

One case series[29] reported clozapine levels for 3 of the 8 women included. In one woman, concentrations were more or less stable; in the second woman, there was a 4-fold increase in clozapine concentration between gestational day 50 and day 200, with a nearly 2-fold decrease in the last trimester; and in the third woman levels fluctuated, but particularly in the last trimester. Again, there was no information about tobacco use, treatment adherence, or the use of potentially interacting comedication.

One case report[57] described maternal plasma levels of 38–55 ng/mL in the first 32 weeks of pregnancy in a mother who took 100 mg clozapine per day. Although the dose was halved in the 32nd week, the concentrations found in the third trimester, at the day of delivery, and the day after were less than half of the concentrations found in the first 32 weeks. Unfortunately, this report also did not provide information about treatment adherence, comedication, and smoking and did not distinguish between concentrations measured in the first 2 pregnancy trimesters.

Figure 1. Flow Diagram of Study Selection[16]



Abbreviation: ICTRP = International Clinical Trials Registry Platform.

In summary, there is too little information about how clozapine concentrations change during pregnancy to define a net effect, and the available data are probably influenced by modifying factors.

Maternal outcomes. A few cases have reported worsening of psychiatric symptoms during pregnancy in women using clozapine, but none provided information on clozapine levels (Table 3).[24,30,35,54]

A retrospective cohort study found that the risk of gestational diabetes mellitus (GDM) was not increased in women who used olanzapine and/or clozapine (n = 169) or other antipsychotics (n = 338) compared with the risk in women who had not been exposed to antipsychotics.[20] The actual impact of clozapine, however, was too small to draw conclusions, since only 11 of the 507 women used clozapine. While several reports mention the development of GDM in women treated with clozapine,[18,24,29,30,32,33,37,38,48,50,58] an equal number found no such development of GDM.[29,30,35,39,41,43–45,49,50] Unfortunately, many reports do not mention the mother's pre-pregnancy body mass index (BMI) or provide information about the presence or absence of earlier glucose intolerance.[18,24,33,37,38,48,58]

Since most data come from case reports and the number of clozapine users in the only available cohort study[20] was small, it is not possible to draw conclusions about the risk of GDM in women using clozapine. An increased BMI early in pregnancy, whether or not due to the use of antipsychotics, may be a better predictor of the development of GDM than the use of antipsychotics as such.[20]

Beside some anecdotal reports[24,47] of pregnancy-induced hypertension in mothers using clozapine during pregnancy, we did not find any studies that investigated the risk of clozapine-associated pregnancy-induced hypertension.

Fetus

Placental passage of clozapine. In general, the placental passage of a drug is governed by its molecular size, lipid solubility, and extent of plasma protein binding in the maternal system as well as by patient-specific factors, such as placenta transporter proteins.[62] Only the unbound fraction of a drug is able to cross membranes,[63] provided the molecule is smaller than 600 Daltons.[64] Clozapine and norclozapine, the main metabolite of clozapine, are small enough to pass the placental barrier, but under "non-pregnant" circumstances both are highly protein bound in blood, mainly to α_1-acid glycoprotein (AGP).[65,66] It is noteworthy that the concentration of AGP decreases by 20%–30% in the third trimester of pregnancy.[67,68] Thus, toward the end of pregnancy, theoretically more drug is available to cross the placental barrier.[63] However, we did not find any literature on

Table 2. Studies Describing Neonatal and Maternal Clozapine Concentrations as Well as Clozapine Concentrations in Breast Milk

First author and year of publication	Number of mothers (number of pregnancies)	Maternal CLZ concentrations (mean ng/mL)					Amniotic fluid concentration (ng/mL)	Umbilical cord concentration (ng/mL)	Concentration in breast milk (ng/mL)	Neonatal concentration (ng/mL)	
		Pre-pregnancy	1st Trimester	2nd Trimester	3rd Trimester	Since delivery					
Nguyen 2020[29]	N = 3 (3)	#	Day 50: M1: ± 200 M2: ± 200 M3: #	Day 100: M1: # M2: # M3: ± 300 and ± 200	Day 200: M1: ± 800 M2: # M3: ± 200 Day 250: M1: # M2: ± 300 M3: ± 500 Day 260: M1: # M2: # M3: ± 300	Day 0: M1: ± 500 M2: ± 200 M3: ± 800 Day 10: M1: ± 1,400 M2: # M3: #	#	#	#	#	
Westin 2018[17]	N = 4 (4)	418.6	399.7	358.8	322.1	#	#	#	#	#	
Imaz 2018[30]	N = 3 (4)	#	#	#	#	Day 0: M1: CLZ: 198 NorCLZ: 200 M2: CLZ: 122 NorCLZ: 79 M3-1: CLZ: 194 NorCLZ: 114 M3-2: CLZ: 148 NorCLZ: 149	M1: CLZ: 61 NorCLZ: 39 M2: CLZ: # NorCLZ: # M3-1: CLZ: 67 NorCLZ: 52 M3-2: CLZ: # NorCLZ: #	M1: CLZ: 77 NorCLZ: 56 M2: CLZ: 68 NorCLZ: 26 M3-1: CLZ: 113 NorCLZ: 42 M3-2: CLZ: 67 NorCLZ: 32	#	**Concentrations derived from Figure 1[30]:** M1 0 hours post-delivery: CLZ: 78 NorCLZ: 52 M1 ± 12 hours post-delivery: CLZ: 40 NorCLZ: 38 M1 ± 80 hours post-delivery: CLZ: 12 NorCLZ: 18 M1 ± 280 hours post-delivery: CLZ: 10 NorCLZ: 15 M1 $T_{1/2}$: CLZ: 99 hours NorCLZ: 161 hours M2: CLZ: # NorCLZ: # M2 $T_{1/2}$: CLZ: # NorCLZ: #	M3-1 0 hours post-delivery: CLZ: 115 NorCLZ: 42 M3-1 ± 50 hours post-delivery: CLZ: 110 NorCLZ: 38 M3-1 ± 245 hours post-delivery: CLZ: 20 NorCLZ: 20 M3-1 $T_{1/2}$: CLZ: 71 hours NorCLZ: 187 hours M3-2 0 hours post-delivery: CLZ: 68 NorCLZ: 32 M3-2 ± 75 hours post-delivery: CLZ: 30 NorCLZ: 22 M3-2 ± 245 hours post-delivery: CLZ: 18 NorCLZ: 10 M3-2 $T_{1/2}$: CLZ: 107 hours NorCLZ: 131 hours M2 Day 2 (33 hours postpartum): CLZ infant/maternal plasma concentration ratio: 6.5%, under mixed breastfeeding.
Coston 2012[38]	N = 1 (1)	#	#	#	#	#	#	#	#	Day 4: CLZ: 54	

(continued)

Table 2 (continued).

First author and year of publication	Number of mothers (number of pregnancies)	Maternal CLZ concentrations (mean ng/mL)					Amniotic fluid concentration (ng/mL)	Umbilical cord concentration (ng/mL)	Concentration in breast milk (ng/mL)	Neonatal concentration (ng/mL)
		Pre-pregnancy	1st Trimester	2nd Trimester	3rd Trimester	Since delivery				
Moreno-Bruna 2012[39]	N = 1 (1)	#	At 2 months pregnancy: CLZ: 370 NorCLZ: 215	#	#	#	#	#	#	Day 5: CLZ: 103 NorCLZ: 47 Day 8: CLZ: 45 NorCLZ: 26
Klys 2007[42]	N = 1 (1)	#	#	#	#	#	#	#	#	**1 day after admission:** Postmortem blood: CLZ: 7,300 NorCLZ: 2,600 CLZ-*N*-oxide: 500 Liver: CLZ: 28,000 NorCLZ: 17,100 CLZ-*N*-oxide 31,100 Kidney: CLZ: 10,100 NorCLZ 6,100 CLZ-*N*-oxide 5,800
Barnas 1994[57]	N = 1 (1)	#	38–55[a]		15.4	Day 0: 14.1 Day 1: 14.7 Day 7: 41.4	11.6	#	Day 1: 63.5 Day 7: 115.6	Day 0: 27

[a]Article does not distinguish between first and second trimester and only mentions this plasma concentration range as measured when the mother used 100 mg/d. This dose regimen was used during the first 2 trimesters.
#No information.
Abbreviations: CLZ = clozapine, M1 = mother 1 (and so on), M2-1 = mother 2, pregnancy 1 (and so on), NorCLZ = norclozapine.

maternal concentrations of unbound clozapine during pregnancy, so it remains unknown whether decreasing concentrations of AGP affect the extent to which clozapine crosses the placenta.

One case series[30] describing 4 pregnancies in 3 women reported the placental passage of clozapine and norclozapine as the ratio of umbilical cord blood to maternal plasma concentrations (UCB/MP ratio [%]). The UCB/MP ratio ranged between 39% and 58% for clozapine and between 28% and 37% for norclozapine, indicating (partial) placenta passage of clozapine toward the end of a full-term pregnancy (Table 2). Since fetal CYP1A2 has negligible activity,[69] norclozapine detected in the fetal system probably comes from the mother rather than arising from fetal metabolism.

Two other case reports[38,57] also showed detectable clozapine concentrations in 2 newborns. In one,[57] the neonatal concentration at delivery was almost twice as high as the concentration in the mother on the day of delivery.

Another report[42] described an infant that died after its mother ingested 100–200 tablets (100 mg) of clozapine when she was 9 months pregnant. The high concentrations of clozapine and its metabolites in the neonate's blood, taken 1 day after admission of the mother, again reflect the placental passage of clozapine and norclozapine.

Neurodevelopment. Since antipsychotics block dopamine and serotonin receptors and these neurotransmitters are involved in neural development,[70,71] prenatal exposure to antipsychotics may affect neural development. A preclinical study[26] examined the effects of intrauterine exposure to various antipsychotics (clozapine, haloperidol, thioridazine, sulpiride, chlorprothixene, fluphenazine, and chlorpromazine) on learning and memory in rats. The authors concluded that prenatal exposure to these antipsychotics may negatively affect problem-solving ability, rather than specifically affecting learning and memory, in adult animals.

Intrauterine exposure to clozapine during sensitive periods of brain development produced longer lasting changes in cognitive function and locomotor activity in mice pups than did similar exposure to haloperidol.[28] Clozapine induced hyperlocomotion, an effect that lasted more than 3 weeks after exposure was discontinued. In contrast to the findings of Oltulu and colleagues,[26] chronic clozapine or

Table 3. Studies Describing Maternal Outcomes of Clozapine Treatment During Pregnancy

First author and year of publication	Number of mothers (number of pregnancies/infants)	Maternal outcomes
Nguyen 2020[29]	N = 8 (9)	No psychotic relapse during the course of the 9 pregnancies Constipation: n = 5 (55.5%), including 1 fecal impaction during labor Symptomatic orthostatic hypotension, at 34 weeks' gestation, with conservative management until delivery: n = 1 Persistent tachycardia (4 days postpartum): n = 1 (patient had been on a stable dose of 400 mg of CLZ for 1.5 years prior to conception) Preeclampsia: n = 0 (0%) GDM: n = 6 (66.7%) (all with pre-pregnancy BMIs in the overweight or obese range) Medication controlled: n = 2 (22.2%) Diet controlled: n = 4 (44.4%)
Narayanaswamy 2018[32]	N = 1 (1)	GDM at the 36th week (normal pre-pregnancy BMI)
Uygur 2019[33]	N = 1 (2)	Pregnancy 1: # Pregnancy 2: GDM in the 18th week (unknown pre-pregnancy BMI, but no family history of diabetes), with successful dietary control No psychotic exacerbation
Imaz 2018[30]	N = 3 (4)	M1: No complications M2: GDM from week 14 Brief psychiatric hospitalization 5 days after delivery due to a relapse of manic psychotic symptoms, with rapid response to an increase in CLZ to 200 mg/d M3-1: Psychiatric hospitalization in week 26 until the end of pregnancy M3-2: Psychiatric hospitalization at 6 weeks of pregnancy after alterations in the mother's behavior, without evidence of a relapse in schizoaffective disorder
Hatters Friedman 2016[18]	N = 1 (1)	GDM in the single pregnancy exposed to CLZ (unknown pre-pregnancy BMI)
Köse Çinar 2016[35]	N = 1 (1)	Clinical admission with paranoid and persecution delusions at week 33 No metabolic diseases during pregnancy with normal pre-pregnancy BMI
Guyon 2015[37]	N = 1 (1)	GDM at the 26th week, with successful dietary management (unknown pre-pregnancy BMI)
Shao 2015[24]	N = 33 (33)	Psychotic relapse in 3 CLZ-using mothers GDM in 2 CLZ-using mothers Pregnancy-induced hypertension in 2 CLZ-using mothers
Bodén 2012[20]	Group 1: N = 169 CLZ- and/or olanzapine-exposed mothers (169) Group 2: N = 388 OAP-exposed mothers (388)	Risk of GDM compared to nonexposed women: Group 1: OR 2.44 (95% CI, 1.14–4.24) Group 2: OR 2.53 (95% CI, 1.48–4.34) Risk of GDM compared to nonexposed women after adjustment for early pregnancy BMI: Group 1: OR 1.46 (95% CI, 0.84–2.53) Group 2: OR 1.71 (95% CI, 0.82–3.56) Increased early pregnancy BMI seemed to be the major cause of GDM
Coston 2012[38]	N = 2 (2)	M1: GDM (unknown pre-pregnancy BMI) M2: GDM (unknown pre-pregnancy BMI)
Moreno-Bruna 2012[39]	N = 1 (1)	No known GDM, but a weight gain of 16 kg
Duran 2008[41]	N = 2 (3)	M1-1: No psychotic exacerbation Normal fasting blood glucose levels Normal lipid profile Normal hemoglobin A_{1c} levels No history of GDM in the medical records (normal pre-pregnancy BMI M1-2: No history of GDM in the medical records (no pre-pregnancy BMI information) M2: No history of GDM in the medical records (normal pre-pregnancy BMI)
Mendhekar 2007[43]	N = 1 (1)	Good nutritional care No exacerbation throughout the pregnancy Normal routine laboratory investigations (including blood glucose, hemoglobin, and white blood cell count)
Doherty 2006[45]	N = 1 (1)	BMI 34 mg/kg^2 at delivery Normal blood sugar at regular antenatal visits
Sethi 2006[44]	N = 1 (1)	No GDM (unknown pre-pregnancy BMI)
Gupta 2004[47]	N = 1 (2)	Pregnancy induced hypertension in both pregnancies
Karakula 2004[48]	N = 1 (1)	GDM (unknown pre-pregnancy BMI)
Mendhekar 2003[49]	N = 1 (1)	Normal routine laboratory investigations, including glucose monitoring No GDM (unknown pre-pregnancy BMI)
Nguyen 2003[50]	N = 1 (2)	Pregnancy 1: GDM (unknown pre-pregnancy BMI) Pregnancy 2: no GDM (normal pre-pregnancy BMI) No psychiatric exacerbations during in both pregnancies
Stoner 1997[54]	N = 2 (2)	M1 and M2: Psychiatric symptoms intensified during pregnancy M1 and M2: Uncooperative during labor
Waldman 1993[58]	N = 1 (1)	GDM in the second trimester (unknown pre-pregnancy BMI) Otherwise uneventful No exacerbation of psychiatric illness throughout gestation, labor, and delivery

#No information.

Abbreviations: BMI = body mass index, CLZ = clozapine, NorCLZ = norclozapine, GDM = gestational diabetes mellitus, M1 = mother 1 (and so on), M2-1 = mother 2, pregnancy 1 (and so on), OAP = other antipsychotics, OR = odds ratio.

clozapine withdrawal for 1 and 3 weeks tended to improve memory in mice pups.

Another preclinical study[27] using an invertebrate model organism (*Caenorhabditis elegans*) found that clozapine and fluphenazine produced greater deficits in neuronal development in *C. elegans* than did haloperidol, quetiapine, olanzapine, risperidone, or aripiprazole.

The cross-species validity, however, is one of the major limitations of the animal studies since animal models lack the underlying disease.

One prospective case-control study[24] investigated the developmental effects of fetal exposure to clozapine and other antipsychotics. More infants exposed to clozapine as a fetus had delayed development of adaptive behavior at 2 and 6 months of age than did infants exposed to other antipsychotics, and more infants exposed to clozapine had disturbed sleep and "labile state" (depending on parents' reports) at 2 months of age. However, these differences disappeared after 6 months of age. The groups had a similar performance on cognitive, motor, social-emotional, and language scales.

A few cases[30,43,48] of neurodevelopmental delay after in utero exposure to clozapine have been reported, but it is not known whether objective instruments or parental report were used to assess the neurodevelopmental delay. One report[43] described an infant exposed to clozapine in utero as a result of an unplanned pregnancy. The child gained normal fluent speech only after 5 years. In a case series,[30] 1 infant had neurodevelopmental delay at 18 months and 1 showed symptoms of attention-deficit/hyperactivity disorder, without fulfilling the diagnostic criteria at 6 years of age; the other 2 infants had normal neurodevelopment at 6 and 32 months. One case report[48] described a neonate admitted to the neonatal intensive care unit shortly after delivery for convulsions, respiratory insufficiency, and an abnormal heart shape. After 7 months, the baby could only raise its head. The mother had been using clozapine during gestation and the father had been dependent on alcohol. Several case reports describe normal neurodevelopment after different follow-up periods,[33,39,41,44,47,50,53,54,57] but these reports are generally of limited quality and, again, it is not known how the neurodevelopment of these infants had been assessed.

In summary, it remains unclear whether early developmental exposure to clozapine results in permanent changes in the brain that affect cognitive function or behavior in both the short and long term.

Fetal disorders. In our study[22] using global pharmacovigilance data, we compared the frequency of reported adverse pregnancy outcomes associated with the use of clozapine compared with other antipsychotics during pregnancy. We found that in utero exposure to clozapine was not associated with more "fetal disorders" than exposure to other antipsychotics during pregnancy (Table 4). However, several case reports[29,34,37,38,40,45,51] mention cardiotocography findings of reduced or absent fetal heart rate variability in the unborn infant. Unfortunately, none of the reports have provided information about clozapine concentrations. Cardiotocography is commonly used to detect changes in fetal heart rate patterns in response to hypoxia, but in the case of maternal clozapine treatment, clozapine is thought to reduce fetal heart rate variability by blocking the cholinergic and adrenergic receptors of the fetal nervous system. Misleadingly, this could mimic the symptoms of potential asphyxia.

See end of article for Table 4.

Stillbirth and abortion. In our pharmacovigilance study,[22] we did not find evidence that clozapine exposure was associated with "termination of pregnancy and risk of abortion" either (Table 4). In fact, clozapine was even statistically significantly less often associated with this endpoint than exposure to other antipsychotics.

Beside the aforementioned fatal poisoning of a neonate in the final stage of gestation after the mother had taken a clozapine overdose[42] and some anecdotal reports of stillbirth[49,50] and abortion[56] after fetal exposure to clozapine, we did not find additional studies associating the risk of stillbirth and abortion with clozapine exposure during pregnancy.

Congenital malformations. In our pharmacovigilance study,[22] we found 76 adverse drug reactions (ADRs) categorized as "congenital, familial, and genetic disorders" with clozapine as one of the suspected drugs. "Atrial septal defect" (ASD) (n = 8) and "ventricular septal defect" (n = 6) were the most frequently reported ADRs. But relative to other antipsychotics, clozapine was equally (ventricular septal defect) or even less (atrial septal defect) often associated with these ADRs. Again, we did not find any evidence that clozapine is less safe during pregnancy than other antipsychotics in terms of "congenital, familial, and genetic disorders."

In a cohort study[21] comparing the pregnancy outcomes of 570 women with self-reported use of antipsychotics in the first trimester with the outcomes of unexposed pregnancies, atrial and ventricular septal defects were the most frequently reported congenital malformations after exposure to antipsychotics. Among the 18 women who used clozapine, only 1 malformation (ectopic anus) was reported.

Of 41 cases of cleft palate associated with the use of at least 1 antipsychotic drug reported in another case/non-case study,[23] based on global pharmacovigilance data, 2 cases of cleft palate were associated with fetal exposure to clozapine.

In a cohort study[19] including 11 pregnancies of mothers exposed to clozapine in the first trimester, 2 major malformations after exposure to clozapine were reported: hypospadias and hypertelorism in one baby and gastroschisis and horseshoe kidney in the other baby. Unfortunately, no additional information about these 2 cases was available.

A number of case reports and case series[29,30,32,46,48,54,56] report various malformations but often lack information regarding possible confounders, and there does not seem to be a clear pattern of malformations. Moreover, there are at least as many reports[18,24,31,33,35,41,43,44,47,50,53,54,57] describing uncomplicated pregnancies and healthy offspring without

malformations after fetal exposure to clozapine, of including 1 uncomplicated triplet[36] and 1 twin[41] pregnancy.

In summary, although the available data are limited in terms of quality and quantity, clozapine does not appear to be a teratogenic agent.

Prematurity. In a study[20] of the risk of preterm birth after maternal use of antipsychotics, 5.1% of unexposed infants were born preterm, compared with 8.0% of the infants exposed to olanzapine and/or clozapine and 9.5% exposed to other antipsychotics. This difference was not statistically significant. The study design did not permit a distinction to be made between clozapine and olanzapine (Table 4).

In a prospective study[24] investigating 33 infants exposed to clozapine in utero compared to 30 infants exposed to other antipsychotics (risperidone, olanzapine, or quetiapine), there was no significant difference in gestational age at birth between the two groups.

Delivery complications. The abovementioned prospective study[24] did not find a significant difference in the Apgar score at 5 minutes after birth between clozapine-exposed and other antipsychotic–exposed infants. The Apgar score at 1 minute was even slightly higher in the clozapine group than in the other antipsychotic group (8.6 vs 8.3, $P = .030$) (Table 4).

In our pharmacovigilance study,[22] we also calculated reporting odds ratios for ADRs related to "pregnancy, labor, and delivery complications and risk factors," a group of diverse ADRs including, for instance, breech presentation, cesarean section, eclampsia, GDM, and placental problems. The relative number of reports associating clozapine with these ADRs was significantly lower than the relative number of reports associating other antipsychotics with these ADRs.

In a case series[29] of 9 pregnancies, 8 infants required resuscitation at birth, including suction, oxygen therapy, continuous positive airway pressure, bag and mask, intubation, external cardiac massage, or other; 4 of these infants required admission to special care nursery, without further specification. Six of the 9 mothers were obese (BMI > 30 mg/kg^2), 6 developed GDM, and 4 used other psychotropic medications concurrently.

Shoulder dystocia has been reported in 3 case reports[32,52,58]: a mother with pre-pregnancy diabetes[52] and a mother with a normal pre-pregnancy BMI who developed diabetes during pregnancy[32]; unfortunately, there was no information about weight and metabolic issues in the third case report.[58]

Birth weight and height. In a previously mentioned prospective study,[24] there were no significant differences in the percentages of low birth weight (< 2.5 kg), mean birth weight, and birth length between infants exposed to clozapine or other antipsychotics (Table 4).

Exposure to olanzapine and/or clozapine was not associated with an increased risk of being born small or large for gestational age.[20] However, there was an increased risk of being born with a large head circumference after exposure to olanzapine and/or clozapine (adjusted OR = 3.02 [95% CI, 1.60 to 5.71]). None of these neonates had hydrocephalus.

A possible association between fetal exposure to atypical antipsychotics and increased infant birth weight and length, particularly with use of clozapine and olanzapine, was suggested in another prospective comparison study.[25] However, only 3 of 16 infants exposed to either clozapine or olanzapine were actually exposed to clozapine, which also complicates the interpretation of clozapine's contribution to the results.

Lastly, in a preclinical study,[28] the average weight of mice prenatally and postnatally exposed to clozapine increased more slowly than did that of control pups at a young age but not later.

Neonate

Neonatal pharmacokinetics of clozapine. Since some pharmacokinetic parameters, such as clearance, volume of distribution, and bioavailability, are age-related, the pharmacokinetics of clozapine in neonates may be different from those in adults.[72] In a case series[30] describing 4 neonates, a mean half-life value of clozapine of 92 (± 18) hours was calculated for neonates, whereas it is 9–17 hours in adults (Table 2).[73]

Another case report[36] described a prolonged elimination half-life in neonates of approximately 2.5 days for clozapine and 3 days for norclozapine.

Available data are too limited to define an elimination half-life of clozapine and norclozapine in neonates, but the delayed clearance reported above is in line with the fact that CYP1A2 activity attains its adult level 7–8 months after birth.[69]

Neonatal outcomes. On the basis of the above and the assumption that it takes 5 elimination half-lives to eliminate a drug, it would take approximately 15 days to eliminate clozapine from the neonate after delivery. Thus, it is conceivable that clozapine exerts pharmacodynamic effects in the first 2–3 weeks after birth if the neonate has been exposed to clozapine in utero.

In our previous study,[22] we also calculated the reporting odds ratio for ADRs related to "neonatal disorders." Again, the relative number of reports associating clozapine with these ADRs was lower than the relative number of reports referring to other antipsychotics as suspected drug(s) (Table 4).

One case report[39] described an infant with diminished peristalsis and vomiting whose mother had been using 100 mg clozapine per day at term. The authors attributed the peristalsis and vomiting to the anticholinergic properties of clozapine.

Two cases[48,55] of floppy infant syndrome have been described. In one, the infant had also been exposed to high doses of lorazepam.[55]

Infant exposure to clozapine through breast milk. Theoretically, infants can be exposed to clozapine via breast milk, but there have been few studies of this. Clozapine concentrations in breast milk have been reported in only 1 study (Table 2).[57] The day after delivery, when the mother was using clozapine 50 mg/d, the clozapine level was 14.7

ng/mL in plasma and 63.5 ng/mL in the first "portion" of breast milk. One week later, when the clozapine dose had been increased to 100 mg/d, the breast milk concentration was 115.6 ng/mL, and the maternal plasma level was 41.4 ng/mL. No additional data regarding neonatal clozapine concentrations were presented.

Dev and Krupp[56] only briefly refer to 4 breastfed babies from mothers taking clozapine. One baby was extremely sleepy, and another developed agranulocytosis, which disappeared spontaneously when breastfeeding was discontinued. The other 2 babies had no apparent adverse effects.

In summary, there is very little information about clozapine in breast milk, but the lipophilicity and low molecular weight of the drug make it likely that it will enter the breast milk of nursing mothers taking clozapine.

DISCUSSION

In this review, we summarized current knowledge on the use of clozapine during pregnancy and lactation (Table 5). Although data on perinatal clozapine exposure are of limited quality and quantity, available data show that clozapine and norclozapine pass the placental barrier and that the fetus will be exposed to clozapine and norclozapine if a mother uses clozapine during pregnancy. However, clozapine appears to cross the placental barrier to a lesser extent than olanzapine but to a similar extent as risperidone.[30,62] Although it is not known at which stage of pregnancy clozapine enters the fetal system, data thus far do not support that clozapine is teratogenic or, compared to other antipsychotics, that it increases the risk of stillbirth, abortion, or fetal disorders or increases the risk of delivery complications or premature birth.

With exposure in the last trimester, newborns are potentially at risk of all clozapine-related adverse events postpartum, including agranulocytosis. The limited data on clozapine pharmacokinetics in neonates suggest that the elimination rate is slower, so that the neonate is exposed to clozapine for 2–3 weeks postpartum and even longer if the infant is breastfed. We did not find any reports of neonatal agranulocytosis after in utero exposure, but the incidence of agranulocytosis in adults is rare anyway.[74] Nonetheless, we recommend close antenatal monitoring of decreased white blood cell/absolute neutrophil count and other potential adverse events of clozapine, including diminished peristalsis, or possible withdrawal effects in the neonate during the first month after birth.

Yet, agranulocytosis has been reported in a breastfed infant.[56] A lack of additional information, however, means that we do not know whether the mother also used clozapine at term and whether the symptoms developed within 2–3 weeks postpartum. Information on clozapine concentrations in breast milk is limited to a single observation, but based on the physical chemical properties of the drug, clozapine exposure through breastfeeding is highly probable. Again, all adverse events associated with clozapine exposure can be

Table 5. Summary of Findings: Take-Home Messages

Mother	
Maternal pharmacokinetics during pregnancy	• Several physiologic changes occur during pregnancy with the potential of altering the pharmacokinetics of clozapine in the mother. • The available data about how clozapine concentrations change during pregnancy are too limited to define a net effect, and the available data are probably influenced by modifying factors.
Maternal outcomes	• No reliable data exist about the relationship between pregnancy, course of psychiatric symptoms, and changes in clozapine concentrations during pregnancy. • The relationship between GDM and clozapine treatment is not clear. An increased body mass index early in pregnancy may be a better predictor of the development of GDM than the use of antipsychotics. • The relationship between maternal clozapine treatment and pregnancy-induced hypertension is unknown.
Fetus	
Placental passage of clozapine	• Clozapine partially passes the placenta. • It is unknown whether decreasing concentrations of AGP during pregnancy affect the extent to which clozapine crosses the placenta.
Neurodevelopment	It is unclear whether early developmental exposure to clozapine results in permanent changes in the brain that affect cognitive function or behavior in both the short and long term.
Fetal disorders	• Data thus far do not support that in utero exposure to clozapine is associated with more "fetal disorders" than exposure to other antipsychotics during pregnancy. • In utero exposure to clozapine appears to be able to cause reduced or absent fetal heart rate variability in the unborn infant, which, misleadingly, could mimic the symptoms of potential asphyxia.
Stillbirth and abortion	Data thus far do not support that in utero exposure to clozapine is associated with an increased risk of termination of pregnancy and risk of abortion.
Congenital malformations	Although the available data are limited in terms of quality and quantity, clozapine does not appear to be a teratogenic agent.
Prematurity	Data thus far do not support that there is a significant difference in gestational age at birth between clozapine-exposed infants and infants exposed to other antipsychotics.
Delivery complications	Data thus far do not support that there is a significant difference in "pregnancy, labor, and delivery complications and risk factors" between clozapine-exposed infants and infants exposed to other antipsychotics.
Birth weight and height	• The risk of increased infant birth weight after maternal clozapine use during pregnancy is unclear. • The risk and implications of the larger head circumference seen with clozapine compared with other antipsychotics remain to be elucidated.
Neonate	
Neonatal pharmacokinetics of clozapine	The elimination half-lives of clozapine and norclozapine appear to be prolonged compared to the half-lives in adults. Available data are too limited, however, to define an elimination half-life of clozapine and norclozapine in neonates.
Neonatal outcomes	• It is conceivable that clozapine exerts pharmacodynamic effects in the first 2–3 weeks after birth if the neonate has been exposed to clozapine in utero. • Data thus far do not support that there is a significant difference in neonatal disorders between clozapine-exposed infants and infants exposed to other antipsychotics.
Infant exposure to clozapine through breast milk	There is little information about clozapine in breast milk, but the chemical properties of the drug make it likely that clozapine enters the breast milk of nursing mothers taking clozapine.

Abbreviations: AGP = α_1-acid glycoprotein, GDM = gestational diabetes mellitus.

expected if an infant is being breastfed by a mother who is using clozapine.

The physiologic changes during pregnancy, the pharmacokinetic properties of clozapine, and possible changes in tobacco and caffeine use during pregnancy make it plausible that maternal clozapine concentrations change despite stable dosing. We conclude that the net result of these changes cannot be predicted, thereby emphasizing the need for close monitoring of clozapine concentrations during pregnancy in order to keep the mother's psychiatric condition stable during this period. There remains a need for well-designed, prospective studies linking maternal clozapine levels, including unbound concentrations, and dose regimens in the last trimester with the pharmacokinetics and pharmacodynamics of clozapine in neonates.

Although based on anecdotal reports, clozapine exposure might be related to an increased frequency of reduced or absent fetal heart rate variability in the unborn infant, thereby mimicking signs of fetal stress on the cardiotocography. It is unknown whether this effect is accompanied by an elevated clozapine concentration in the mother or the fetus.

The effects of maternal clozapine use during pregnancy on GDM remain unclear, as is the risk of increased infant birth weight. In the study by Bodén et al,[20] the lower BMI at baseline in the group of clozapine- and/or olanzapine-treated mothers compared to the group of mothers treated with other antipsychotics could be based on selective non-prescribing of clozapine and olanzapine to overweight women. We cannot exclude that this possible selection process could have masked a pharmacologic effect that increased the risk of GDM. An increased BMI in early pregnancy, regardless of whether it is due to the use of antipsychotics, may be a better predictor of the development of GDM than the use of antipsychotics as such. Also, the risk and implications of the larger head circumference seen with clozapine compared with other antipsychotics remain to be elucidated.[20] Lastly, more information is needed to ascertain whether prenatal clozapine exposure results in permanent changes in the brain and how this affects the child in the short and long term. The results of preclinical studies suggest that clozapine might affect neurodevelopment, and the only available clinical data suggest that clozapine affects the development of adaptive behavior to a greater extent than do other antipsychotics, at least in the short term.

Studies of the safety of drugs in pregnancy rarely meet the gold standard of randomized controlled trial data. As a result, the best available data in this area tend to come from observational studies, and the majority of data come from case series and case reports in which publication bias can be expected. Nevertheless, in the absence of more controlled studies, every case report on the use of clozapine in the perinatal period contributes to the accumulation of knowledge on this subject.

Another limitation of the studies included in this review is that there was often no information available about smoking and substance use during pregnancy, the use of comedication, vitamin status, maternal age, planned or unplanned pregnancy, and pre-pregnancy BMI. In addition, exposure to clozapine is a consequence of severe maternal illness, and schizophrenia as such has also been associated with a number of adverse obstetric complications and pregnancy outcomes.[75] In the absence of a control group, it is not possible to differentiate between the risks associated with drug exposure and those of the mental illness and its associated physical health problems and lifestyle factors.

In addition, given the estimated baseline population rate for malformation in the general population of 1%–3%,[76] large numbers of exposed fetuses are needed to detect differences in the incidence of malformations, and an even larger number is needed to control for confounders.

In general, when a clinician is consulted by a woman using clozapine who seeks preconception advice or who is already pregnant, one might prefer an agent with more robust pregnancy data. As a consequence, the clinician might consider a switch to another antipsychotic. However, every switch confers a risk, and a risk-benefit analysis should be made, taking into account, on the one hand, the available data and the level of evidence and, on the other hand, the timing of counseling (pre- or post-conception), lactation plans, and the severity of illness and response to medication in the past. With regard to timing, the exposure to clozapine covers more developmental stages of the fetus in case a woman presents for preconception counseling on clozapine, compared with the situation that conception has already taken place or in the case of an advanced pregnancy.

In the first situation, there is more time to gather information, make a thorough decision, and, in some cases, involve family members. Also, when the mother plans to breastfeed the child after birth, the scarce safety data regarding clozapine exposure through breast milk in combination with probable neonatal exposure based on its chemical properties should be considered.

On the other hand, given clozapine's place in the treatment algorithm of schizophrenia, it is likely that a woman has been diagnosed with treatment-resistant schizophrenia when she uses clozapine and thus has not responded adequately to other antipsychotics. One should know if previous psychotic episodes were associated with danger to the patient (eg, suicidal behavior) or to others and if previous antipsychotic drugs were associated with serious side effects (eg, severe akathisia or parkinsonism) before deciding if stopping or changing clozapine would outweigh the risk of relapse in this context.

In summary, at some point, clinicians can be faced with the challenge of planned and unplanned pregnancies in their clozapine-treated patients. When carefully weighing the risks and benefits of clozapine continuation during pregnancy versus switching to another antipsychotic, one should include severity of illness and treatment history, but also be aware of the limitations of the available safety data regarding perinatal clozapine use, including the fact that there are few studies.

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Table 1. Summary of the Main Characteristics of the Included Studies of Clozapine Treatment During Pregnancy and Lactation

First author and year of publication	Study design	Aim	Cases	Exposure	Major limitations	Reported outcomes
Westin 2018[17]	Retrospective cohort study	To elucidate to what extent pregnancy affects serum concentrations of APs in a large target population in a naturalistic setting	103 women with 110 pregnancies; 4 were CLZ-using mothers with 4 pregnancies Number of serum CLZ concentration measurements at baseline: 114 Number of serum CLZ concentration measurements during pregnancy: 10 Number of serum CLZ concentration measurements first 12 weeks following delivery: 2	Measured serum concentrations divided by the daily dose used by the woman at the time of sampling, providing a serum concentration/dose ratio, and then multiplied by the defined daily dose of the drug (ie, 300 mg for CLZ) Concomitant use of "interacting drugs" was used as an exclusion criterion No information about smoking, alcohol use, or substance use	No data about smoking Limited generalizability of the findings due to the small number of CLZ samples No information about treatment adherence Possible varying time intervals between last dose to sampling	Maternal pharmacokinetics
Hatters Friedman 2016[18]	Retrospective cohort study	To describe pregnancy outcomes for women prescribed atypical APs during pregnancy	45 pregnancies exposed to the following: 21 quetiapine 19 olanzapine 7 risperidone 6 aripiprazole 1 CLZ	No data regarding planned or unplanned pregnancies No individual drug data regarding drug exposure (dosage, dose interval, timing of exposure, drug concentration) No individual drug data regarding comedication ("64% being exposed to more than a single agent") Smoking during pregnancy 31% Alcohol use during pregnancy 20% Substance use during pregnancy 13% No data regarding maternal pre-pregnancy BMI	Information about drug exposure based on prescriptions Study outcomes considered for all APs as a group, possibly masking divergent frequencies among the single APs Potential determinants only provided for the group of mothers and not specifically for the single CLZ-using mother No adjustments for potential confounders Exposure to more than a single psychotropic agent in 64% of the mothers Single report of GDM without information about the mother's pre-pregnancy BMI	Maternal outcomes Fetal outcomes Delivery
Kulkarni 2014[19]	Observational cohort study	Not clearly specified (in the Discussion paragraph: "to identify the safest AP for use in pregnancy")	147 pregnancies exposed to APs in the first trimester; 11 of these pregnancies were exposed to CLZ (7.5%)	No data regarding planned or unplanned pregnancies No individual drug data regarding drug exposure (dosage, dose interval, timing of exposure, drug concentration) No individual drug data regarding comedication Smoking during pregnancy 35% Alcohol use during pregnancy 26% Substance use during pregnancy 12% No individual drug data regarding maternal pre-pregnancy BMI	Study outcomes considered for all APs as a group, possibly masking divergent frequencies among the single APs Unknown distribution of possible confounders among the different drugs Absence of a control group No additional information regarding the 2 reported anomalies	Fetal outcomes

(continued)

Table 1 (continued).

First author and year of publication	Study design	Aim	Cases	Exposure	Major limitations	Reported outcomes
Bodén 2012[20]	Retrospective cohort study	To investigate the effects of maternal use of APs during pregnancy on gestational diabetes and fetal growth	Neonates exposed to (n (%): Olanzapine 159 (31.4) CLZ 11 (2.2) OAP 338 (66.7): Quetiapine 90 (17.8) Risperidone 72 (14.2) Flupenthixol 58 (11.4) Haloperidol 52 (10.3) Aripiprazole 38 (7.5) Perphenazine 35 (6.9) Zuclopenthixol 30 (5.9) Ziprasidone 18 (3.6) Chlorprothixene 9 (1.8) Fluphenazine 2 (0.4) Pimozide 1 (0.2) Some of the APs were used concomitantly	No data regarding planned or unplanned pregnancies Exposure defined as "filling a prescription for an AP from last menstrual period to partition" No individual drug data regarding drug exposure (dosage, dose interval, timing of exposure, drug concentration) No individual drug data regarding comedication Maternal smoking in early pregnancy: 22.5% for olanzapine/CLZ exposure 31.7% for OAP exposure 6.7% for nonexposure No information about alcohol or substance use Maternal early pregnancy BMI: < 18.5 kg/m^2: • 3% for olanzapine/CLZ • 2.1% for OAP • 2.2% for nonexposure 18.5–24.9 kg/m^2: • 39.6% for olanzapine/CLZ • 40.5% for OAP • 55.7% for nonexposure 25.0–29.9 kg/m^2: • 34.9% for olanzapine/CLZ • 25.1% for OAP • 22.4% for nonexposure > 30.0 kg/m^2: • 14.2% for olanzapine/CLZ • 23.4% for OAP • 10.7% for nonexposure	Information about drug exposure based on filled prescriptions No information about drug compliance/unknown if exposure to AP has been continued during pregnancy No information about alcohol or substance use 19.5% of the CLZ/olanzapine group also used 1 or more OAP throughout the pregnancy period Possible selective prescribing of olanzapine and CLZ	Maternal outcomes Fetal outcomes
Reis 2008[21]	Retrospective cohort study	To describe the delivery outcomes after the use of typical and atypical APs during the first trimester of pregnancy, with special emphasis on the risk for congenital malformations in the offspring	570 women with reported use of APs in early pregnancy, of which 18 were women with reported use of CLZ	No data regarding planned or unplanned pregnancies No individual drug data regarding drug exposure (dosage, dose interval, timing of exposure, drug concentration) No individual drug data regarding comedication No individual drug data regarding smoking No information about alcohol or substance use No individual drug data regarding maternal pre-pregnancy BMI	Not possible to distinguish chronic drug users from women who used the drugs only temporarily or women who used high doses from women who used low doses No information about the contribution of CLZ to the study outcomes since this study focused on the effect of AP as a group Potential determinants provided only for the group of mothers and not specifically for the single malformation reported after CLZ exposure	Fetal outcomes
Beex-Oosterhuis 2020[22]	Case/non-case study	To compare the frequency of reported adverse pregnancy outcomes after the use of CLZ versus OAP during pregnancy, using data from Vigibase	494 individual case safety report–adverse drug reaction pairs involved adverse pregnancy outcomes related with CLZ exposure and 4,645 related with OAP exposure	No information about planned or unplanned pregnancies No individual drug data regarding drug exposure (dosage, dose interval, timing of exposure, drug concentration) No information about comedication No information about smoking, alcohol use, or substance use No pre-pregnancy BMI information	Risk of bias if the true number of pregnancies exposed to CLZ is relatively smaller than the number of pregnancies exposed to OAP Case safety reports only describe a suspicion and evidence for causality of associations is not the same in all reports and often even lacking No adjustment for other confounding factors	Fetal outcomes Delivery Neonatal outcomes

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Table 1 (continued).

First author and year of publication	Study design	Aim	Cases	Exposure	Major limitations	Reported outcomes
Montastruc 2016[23]	Case/non-case study	To research a signal between AP use and gastrointestinal congenital disorders by using data from Vigibase, taking into account competition biases	41 safety reports of cleft palate related to in utero exposure to AP; 2 case safety reports in Vigibase of cleft palate related to in utero exposure to CLZ	No information about planned or unplanned pregnancies No individual drug data regarding drug exposure (dosage, dose interval, timing of exposure, drug concentration) Benztropine used as comedication in the 2 CLZ cases No information about smoking, alcohol use, or substance use No pre-pregnancy BMI information	The study was designed for detection of safety signals for AP as a group and therefore only adds 2 casuistic reports to our data in absence of additional information about potential confounders	Fetal outcomes
Shao 2015[24]	Prospective observational study	To investigate the developmental effects of CLZ and other atypical APs on infants who were exposed to as fetus	CLZ (n = 33) Risperidone (n = 16) Olanzapine (n = 8) Quetiapine (n = 6)	Unplanned pregnancy CLZ 54.5% OAP 50.0% (P = .718) Minimum CLZ dosage: 75 mg Maximum CLZ dosage: 450 mg Mean CLZ dosage (SD): 178.03 mg (70.37) No benzodiazepines and no mood stabilizers (all 63 women) No vitamin or folic acid taken during pregnancy: 8 CLZ-using mothers (24.2%) 7 OAP-using mothers (23.3%) (P = .933) No information about alcohol or substance use Smoking during pregnancy: 1 CLZ-using mother (3.0%) 1 OAP-using mother (3.3%) (P = .945) Pre-pregnancy BMI > 23.9 mg/kg^2: CLZ 54.5% OAP 26.% (P = .025)	This study used data from a previous study. Unlike in the previous study, the 13 sulpiride-exposed infants are not included in the current study, without provision of clarification No information about alcohol or substance use Unknown how the infant's sleep and mental state have been assessed Uncertain generalizability of the study results, since, according to the authors, and unlike in western countries, CLZ is popularly used for female patients with schizophrenia in China Reports of GDM without individual information about the mothers' pre-pregnancy BMI. Moreover, diabetes mellitus during pregnancy was used as an exclusion criterion	Maternal outcomes Fetal outcomes Developmental outcomes Delivery Neonatal outcomes
Newham 2008[25]	Prospective, observational study	To determine whether atypical and typical APs differ in their effects on birth weight after maternal exposure during pregnancy	56 pregnancies exposed to typical APs and 30 to atypical APs Exclusion of 9 infants exposed to typical (16%) and 5 exposed to atypical (17%) APs owing to premature birth Exclusion of 2 infants exposed to typical APs (4%) for postdatism	No information about planned or unplanned pregnancy No individual drug data regarding drug exposure (dosage, dose interval, timing of exposure, drug concentration) No information about smoking, alcohol use, or substance use No pre-pregnancy BMI information	Data regarding potential confounders are not presented, and thus little is known about efforts addressing potential confounders Unknown if exclusion of infants owing to premature birth or postdatism could have affected the results	Fetal outcomes
Oltulu 2016[26]	Preclinical study	To examine the effects of prenatal exposure to various APs on learning and memory in adult rats	4 pregnant rats receiving CLZ	40 mg/kg CLZ as water suspension once a day during the gestation period until partition compared with: 2 mg/kg haloperidol 100 mg/kg thioridazine 200 mg/kg sulpiride 20 mg/kg chlorprothixene 10 mg/kg fluphenazine 20 mg/kg chlorpromazine A control group receiving water by intragastric gavage	Unknown how the administered (relative) doses of the AP in rats relate to human doses The study seems to be designed to test the influence of the different AP chemical classes, but the conclusions refer to AP in general Preclinical study, thus the results are, at most, hypothetical, for the effects in humans	Developmental outcomes

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Table 1 (continued).

First author and year of publication	Study design	Aim	Cases	Exposure	Major limitations	Reported outcomes
Donohoe 2008[27]	Preclinical study	To test the hypothesis that APs affect neurodevelopment through their actions on known signaling pathways, including dopamine and serotonin receptors, and calmodulin using the model organism *Caenorhabditis elegans*	Unknown	Model organisms in the fourth larval stage (prior to reproductive maturation) placed on control (solvent alone) or drug plates and allowed to mature and lay eggs, ensuring developing embryos exposed to drug Progeny developing to the third larval stage and then mounted on microscope slides	Study conducted in an invertebrate model organism. Unknown whether, and how, the findings of this study are likely to translate to a vertebrate nervous system No information about the number of experimental and control groups	Developmental outcomes
Wang 2006[28]	Preclinical study	To evaluate the behavioral effects of chronic haloperidol and CLZ during gestation and postnatal development in mouse offspring at different ages, compared with transient treatments that stopped 1–3 weeks before the test, to know whether prenatal chronic administrations of these APs permanently or temporally influence the behavior in offspring, particularly compared with drug withdrawal	Unknown	Pregnant mice, 1 or 2 in each cage, housed under standard conditions with food and normal vehicle or vehicle containing 6 mg/L of haloperidol, 90 mg/L or 180 mg/L of CLZ	No information about the total number of animals used in each experiment and the number of animals in each experimental group Unknown how the administered (relative) doses of the AP in mice relate to human doses Unknown whether, and how, the findings of this study are likely to translate to human biology	Developmental outcomes
Nguyen 2020[29]	Case series	To document any specific findings of obstetric, neonatal, and psychiatric outcomes for pregnant women taking CLZ	n = 8 mothers, 9 pregnancies	No information about planned or unplanned pregnancy CLZ dose range: 100–400 mg/d Mean daily CLZ dose (SD) 258.3 mg (98.4) No change in dosing for the individual women during pregnancy Other concurrent psychotropic medications: 44.4% (such as fluvoxamine, clonazepam, aripiprazole, reboxetine, and venlafaxine) Smoking 44.4% No information about alcohol or substance use Obesity at booking visit (BMI > 30 kg/m^2): 66.7% Gestational diabetes: 66.7%	The pharmacokinetic data are too limited to draw final conclusions No information regarding timing between last dose and sampling No individual information about treatment adherence, comedication, and "smoking adherence" Little additional information about the individual cases	Maternal pharmacokinetics Maternal outcomes Fetal outcomes Delivery Neonatal outcomes

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Table 1 (continued).

First author and year of publication	Study design	Aim	Cases	Exposure	Major limitations	Reported outcomes
Imaz 2018[30]	Case series	To provide new information on the features of CLZ pharmacokinetics that determine its placental and lactation passage, as well as the neonatal CLZ elimination half-life and neonatal and infant/child outcomes	n = 3 mothers, 4 pregnancies	M1: planned pregnancy M2: planned pregnancy M3-1: unplanned pregnancy M3-2: unknown Clozapine exposure: M1: 550 mg/d when pregnancy was confirmed and titrated down to 350 mg/d M2: 200 mg/d when pregnancy was confirmed and titrated down to 100 mg/d from the 19th week of pregnancy M3-1: 200 mg/d when pregnancy was confirmed, discontinued at week 16 and reintroduced (200 mg/d) at week 21. Hospitalization in week 26, until delivery with CLZ increase to 300 mg/d M3-2: 200 mg/d when pregnancy was confirmed until delivery Comedication: M1: Risperidone 50 mg/mo (long-acting injection) week 0–delivery M2: No comedication M3-1: diazepam 15 mg/d week 30–37 M3-2: sertraline 100 mg/d week 35–delivery Smoking/alcohol/substance use: M1: 18 cigarettes/d when pregnancy was confirmed and then reduced by 50% M2: no M3-1: alcohol, cocaine, and cannabis during first 5 months of pregnancy, tobacco use daily M3-2: tobacco use daily Pre-pregnancy BMI: M1: 31.84 kg/m^2 M2: 27.78 kg/m^2 M3-1: 24.90 kg/m^2 M3-2: 28.09 kg/m^2	Very limited number of TDM measurements Assumed linear neonatal pharmacokinetics, while from the presented individual neonatal concentrations, this linear pharmacokinetics is uncertain Unknown if the follow-up information has been based on structured tools to assess the development of the infants or on parents' reports	Maternal outcomes Fetal outcomes Developmental outcomes Delivery Neonatal pharmacokinetics Neonatal outcomes
Molins 2019[31]	Letter to the editor/case report	Not specified	n = 1 mother, 1 pregnancy	Unplanned pregnancy CLZ exposure: Only started at the 24th pregnancy week along with electroconvulsive therapy Dose increased up to 250 mg/d (plasma CLZ level: 495 ng/mL), > week 33: reduction to 200 mg/d because of drowsiness and dizziness Although not clearly stated, the mother probably used aripiprazole 10 mg/d at conception At the time of admission (17 weeks pregnancy), she was using only tobacco Pre-pregnancy BMI of 24.7 kg/m^2	Single observation	Fetal outcomes Delivery Neonatal outcomes

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Table 1 (continued).

First author and year of publication	Study design	Aim	Cases	Exposure	Major limitations	Reported outcomes
Narayanaswamy 2018[32]	Case report	To present a case in which a woman on CLZ along with folic acid supplementation gave birth to an infant with neural tube defect	n = 1 mother, 1 pregnancy	No information about planned or unplanned pregnancy CLZ exposure: When the mother was found to be pregnant after 4 months of amenorrhea: 225 mg/d (dose frequency unknown) Then CLZ stopped and haloperidol 10 mg/d CLZ restarted within a month and maintained at 150 mg/d until delivery Comedication: haloperidol 2.5 mg/d, multivitamin tablets (containing vitamin A 2,500 IU, vitamin D_3 200 IU, vitamin B_1 2 mg, vitamin B_2 2 mg, vitamin B_6 0.5 mg, niacinamide 25 mg, calcium pantothenate 10 mg, vitamin C 50 mg, and folic acid 0.2 mg) Insulin for GDM from gestational week 36 No information about smoking, alcohol use, or substance use Pre-pregnancy BMI 23 kg/m^2	Single observation Report lacks relevant information about smoking, alcohol use, or substance use throughout the pregnancy Pregnancy was discovered only after 4 months	Maternal outcomes Fetal outcomes Delivery Neonatal outcomes
Uygur 2019[33]	Case report	To present growth and neurodevelopmental outcomes of an infant exposed to CLZ during pregnancy and exposed to CLZ plus olanzapine during the lactation period	n = 1 mother, 2 pregnancies of which the most information is available for the second pregnancy	M1-1: unplanned M1-2: no information about planned or unplanned pregnancy CLZ exposure: M1-1: unknown CLZ dose M1-2: 300 mg/d when pregnancy was confirmed. Dose reduction to 100 mg/d at the third trimester No information about comedication No information about smoking, alcohol use, or substance use No information about pre-pregnancy BMI, but "no family history of diabetes"	Two single observations with little additional information Report of GDM without information about the mother's pre-pregnancy BMI	Maternal outcomes Fetal outcomes Developmental outcomes Delivery Neonatal outcomes
Hodge 2016[34]	Case report	To present a case of fetal and neonatal CTG abnormalities due to CLZ use	n = 1 mother, 1 pregnancy	No information about planned or unplanned pregnancy No data regarding CLZ exposure (dosage, dose interval, timing of exposure, drug concentration) The mother was on "multidrug therapy" (not further specified) No information about smoking, alcohol use, or substance use No pre-pregnancy BMI information	Single observation with too limited data to draw conclusions	Fetal outcomes Delivery Neonatal outcomes
Köse Çinar 2016[35]	Case report	To present a case of 2 uncomplicated deliveries of healthy infants of a mother using olanzapine during her first pregnancy and CLZ during her second pregnancy	n = 1 mother, 1 pregnancy	Unplanned and unwanted pregnancy CLZ exposure: When pregnancy was confirmed: 750 mg/d From week 33: 350 mg/d No information about comedication, smoking, alcohol use, or substance use Normal BMI (18.5–25 kg/m^2)	Single observation, with no information about comedication, smoking, alcohol use, or substance use	Maternal outcomes Fetal outcomes Delivery Neonatal outcomes

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Table 1 (continued).

First author and year of publication	Study design	Aim	Cases	Exposure	Major limitations	Reported outcomes
Sreeraj 2016[36]	Case report	To present a case of a women diagnosed with schizophrenia giving birth to triplets while on CLZ	n = 1 mother, with a triplet pregnancy	Planned pregnancy CLZ exposure: During the first trimester: reduction from 400 to 200 mg/d Comedication prior to conception: treatment with human menopausal gonadotropin 150 mg, human chorionic gonadotropin 5,000 IU, pregnanolone 10 mg, folic acid, and other vitamin supplementation in view of infertility No information about other comedication prior to and during pregnancy No information about smoking, alcohol use, or substance use No information about pre-pregnancy BMI	Single observation Report of an infant with a macrocephaly, without information about other comedication prior to and during pregnancy or information about smoking, alcohol use, or substance use	Fetal outcomes Delivery Neonatal outcomes
Guyon 2015[37]	Case report	To present a case of alteration of the fetal heart rate in a woman treated with CLZ	n = 1 mother, 1 pregnancy	No information about planned or unplanned pregnancy CLZ 125 mg/d for 9 years Levothyroxine 25 µg/d for mild goiter No information about smoking, alcohol use, or substance use No pre-pregnancy BMI information	Single observation, with little additional data Report of GDM without information about the mother's pre-pregnancy BMI	Maternal outcomes Fetal outcomes Delivery Neonatal outcomes
Coston 2012[38] (French)	Case report	To report 2 cases of absence of fetal heart rate variability in fetus exposed to CLZ in utero and to show the limitations of the analysis of the fetal heart rate under CLZ by computerized CTG	n = 2 mothers, 2 pregnancies	No information about planned or unplanned pregnancy CLZ M1: 300 mg/d CLZ M2: 300 mg/d M1: no other drugs M2: aripiprazole 10 mg/d No information about smoking, alcohol use, or substance use No pre-pregnancy BMI information	Two single observations with little additional information Report of GDM without information about the mother's pre-pregnancy BMI	Maternal outcomes Fetal outcomes Delivery
Moreno-Bruna 2012[39] (in French)	Case report	To present a case of neonatal delayed peristalsis and macrosomia after in utero exposure to CLZ	n = 1 mother, 1 pregnancy	No information about planned or unplanned pregnancy CLZ: 325 mg/d with CLZ and NorCLZ drug concentrations at 2 months pregnancy of 370 mg/L and 215 mg/L, respectively. CLZ dose decreased to 100 mg/d at term No comedication No information about smoking, alcohol use, or substance use Pre-pregnancy BMI 25 kg/m^2	Single observation Very limited number of TDM measurements Unknown if the follow-up information is based on structured tools to assess the development of the infants or on parents' reports	Maternal outcomes Fetal outcomes Developmental outcomes Delivery Neonatal outcomes Neonatal pharmacokinetics
Novikova 2009[40]	Case report	To report a case of a young woman who poisoned herself with 10 g of CLZ late in pregnancy	n = 1 mother, 1 pregnancy	Intentional acute intoxication with approximately 10 g CLZ prescribed for someone else at 32 weeks' gestation of an unplanned pregnancy	Single observation of an attempted suicide, without additional therapeutic drug monitoring data	Fetal outcomes Delivery Neonatal outcomes

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Table 1 (continued).

First author and year of publication	Study design	Aim	Cases	Exposure	Major limitations	Reported outcomes
Duran 2008[41]	Case report	To present 2 cases of pregnant women receiving CLZ treatment	n = 2 mothers, 3 pregnancies (M1: 2 pregnancies; M2: 1 twin pregnancy)	Planned pregnancies CLZ exposure: M1-1: probably 200 mg/d M1-2: 200 mg/d M2: conception under a not clearly specified dose, but probably between 200–400 mg/d. Delivery under 200 mg/d No information about comedication, smoking, alcohol use, or substance use M1-1: pre-pregnancy BMI 23.6 kg/m^2 M1-2: no pre-pregnancy BMI information M2: 24.1 kg/m^2	Three single observations Unknown if the follow-up information is based on structured tools to assess the development of the infants or on parents' reports	Maternal outcomes Fetal outcomes Developmental outcomes Delivery Neonatal outcomes
Klys 2007[42]	Case report	To describe a case of the death of a neonate after intrauterine CLZ poisoning due to ingestion by the then 9-months-pregnant mother with the aim of committing suicide	n = 1 mother, 1 pregnancy	No information about planned or unplanned pregnancy CLZ discontinuation in the first trimester, and the patient was on valproate, promethazine, risperidone, and fluoxetine According to the medical record, at 9 months pregnancy: "the patient ingested Klozapol 100 mg, in the amount of 100–200 tablets, with the aim of committing suicide" The mother did not smoke or drink alcoholic beverages No information about other substance use	Single observation of an attempted suicide, without additional therapeutic drug monitoring data	Fetal outcomes Delivery
Mendhekar 2007[43]	Letter to the editor/case report	To report a case of a woman with schizophrenia who continued CLZ treatment throughout her 9 months of pregnancy and during lactation	n = 1 mother, 1 pregnancy	Unplanned pregnancy CLZ 100 mg /d No comedication No information about smoking, alcohol use, or substance use No pre-pregnancy BMI information	Single observation in an unplanned pregnancy (not known when pregnancy was detected) No information about smoking, alcohol use, or substance use Unknown if the follow-up information is based on structured tools to assess the development of the infants or on parents' reports	Maternal outcomes Fetal outcomes Developmental outcomes Delivery Neonatal outcomes
Sethi 2006[44]	Case report	Not specified	n = 1 mother, 1 pregnancy	Pregnancy disclosure at the end of the first trimester, despite repeated advice to practice contraception CLZ continued at the same dose throughout the gestational period: 250 mg/d No information about comedication, smoking, alcohol use, or substance use No information about pre-pregnancy BMI	Single observation, with little additional information Unknown if the follow-up information is based on structured tools to assess the development of the infants or on parents' reports	Maternal outcomes Fetal outcomes Developmental outcomes Delivery
Doherty 2006[45]	Case report	To represent the first recorded usage of CLZ in Northern Ireland during pregnancy and labor	n = 1 mother, 1 pregnancy	No information about planned or unplanned pregnancy CLZ treatment continued throughout pregnancy. Last dose taken on the morning of admission for the cesarean section. "Drug levels had been monitored at regular monthly intervals and were within the therapeutic range" No information about comedication, smoking, alcohol use, or substance use No pre-pregnancy BMI information, BMI at delivery 34 kg/m^2	Single observation, with little additional data	Maternal outcomes Fetal outcomes Delivery
Walch 2005[46] (in German)	Case report	Not specified	n = 1 mother, 1 pregnancy	Planned pregnancy CLZ: 6–12.5 mg/d No information about comedication and smoking No alcohol or substance use during pregnancy No information about pre-pregnancy BMI	Single observation No information about comedication	Fetal outcomes Delivery Neonatal outcomes

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Table 1 (continued).

First author and year of publication	Study design	Aim	Cases	Exposure	Major limitations	Reported outcomes
Gupta 2004[47]	Letter to the editor/case report	To describe a case wherein CLZ therapy was continued successfully over 2 consecutive pregnancies	n = 1 mother, 2 pregnancies	Planned pregnancies CLZ exposure: Pregnancy 1: 200 mg/d Pregnancy 2: 100 mg/d Pregnancy 1: Folic acid started at the 10th week of pregnancy No information about other comedication is given for both pregnancies No information about smoking, alcohol use, or substance use No pre-pregnancy BMI information	Two single observations Unknown if the follow-up information is based on structured tools to assess the development of the infants or on parents' reports	Maternal outcomes Fetal outcomes Developmental outcomes Delivery
Karakula 2004[48]	Case report	To describe the case of a neonate who had been exposed to CLZ in utero	n = 1 mother, 1 pregnancy	No information about planned or unplanned pregnancy CLZ 200 mg/d No information about comedication, smoking, alcohol use, or substance use. The father had been dependent on alcohol No pre-pregnancy BMI information	Single observation with too limited data to draw conclusions Report of GDM without information about the mother's pre-pregnancy BMI	Maternal outcomes Fetal outcomes Developmental outcomes Delivery Neonatal outcomes
Mendhekar 2003[49]	Letter to the editor/case report	To describe a case in which CLZ was continued as monotherapy during pregnancy	n = 1 mother, 1 pregnancy	No information about planned or unplanned pregnancy Pregnancy not detected until the end of first trimester CLZ 75 mg/d, with unsuccessful attempts to reduce the dose to 50 mg in the first and to 62.5 mg in second trimester No comedication ("CLZ monotherapy") No information about smoking, alcohol use, or substance use No pre-pregnancy BMI information	Single observation, lacking information about alcohol use, smoking, and substance use	Maternal outcomes Fetal outcomes Delivery
Nguyen 2003[50] (in French)	Case report	To survey the questions regarding perinatal CLZ use and to present a case of CLZ use during 2 consecutive pregnancies	n = 1 mother, 2 pregnancies	Planned pregnancy CLZ 350 mg/d Pregnancy 1: doxylamine used for nausea (unknown period and dose) and insulin for GDM since the 27th week of gestation. Pregnancy 2: no information about comedication The mother continued smoking during the pregnancies (1 pack of cigarettes a day) No drugs or alcohol use during the pregnancies Pregnancy 1: pre-pregnancy BMI unknown (30.4 kg/m^2 at 27th gestational week) Pregnancy 2: 23.7 kg/m^2 at the beginning of the pregnancy	Two single observations Unknown if the follow-up information is based on structured tools to assess the development of the infants or on parents' reports	Maternal outcomes Fetal outcomes Developmental outcomes Delivery
Yogev 2002[51]	Case report	Not specified	n = 1 mother, 1 pregnancy	No information about planned or unplanned pregnancy No information about CLZ dose and duration and timing of exposure No information about comedication No information about smoking, alcohol use, or substance use No information about pre-pregnancy BMI	Single observation with little additional information	Fetal outcomes Delivery

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Table 1 (continued).

First author and year of publication	Study design	Aim	Cases	Exposure	Major limitations	Reported outcomes
Dickson 1998[52]	Case report	Not clearly specified	n = 1 mother, 1 pregnancy	Planned pregnancy CLZ: 450 mg at conception, then reduced to 200 to 250 mg/d during the second trimester and to 150 mg/d during the last 2 months of the pregnancy Metformin was discontinued when pregnancy was confirmed at 7 weeks of gestational age and insulin injections were initiated No information about smoking, alcohol use, or substance use No pre-pregnancy BMI information	Single observation In the light of shoulder dystocia, the weight and length of the child would have been informative as well as the mother's BMI	Delivery
Tënyi 1998[53]	Case series	Not specified	n = 4 mothers, 6 children	M1-1: no information about planned or unplanned pregnancy M1-2: unplanned (during use of an IUD) M1-3: unknown M2, M3, and M4: unknown CLZ exposure M1-1: 100 mg/d (1–12 weeks), 50 mg/d (12–40 weeks) M1-2: 25 mg/d M1-3: 25 mg/d M2: 300 mg/d (14–19 weeks), 150 mg/d (20–34 weeks), 50 mg/d (34–37 weeks) M3: 75 mg/d (week 20–38) M4: 25 mg/d (week 16–39) No information about comedication No information about smoking, alcohol use, or substance use No information about pre-pregnancy BMI	Six single observations with little additional information Unknown if the follow-up information has been based on structured tools to assess the development of the infants or on parents' reports	Fetal outcomes Delivery Developmental outcomes
Stoner 1997[54]	Case report	To report the cases of 2 women with treatment-resistant schizophrenia who received CLZ during all 3 trimesters and delivered at term	n = 2 mothers, 2 pregnancies	No information about planned or unplanned pregnancy CLZ exposure: M1: conception–week 23: 300 mg/d, but (at least) noncompliant between week 21 and 23. After week 23, CLZ was titrated up to 350 mg/d M2: conception–delivery 600–625 mg/d. Only partial compliance before conception Comedication: M1: lithium during the first trimester (unknown dose), during hospitalization after week 23 at least 1 dose of lorazepam, haloperidol, acetaminophen with and without codeine, guaifenesin, magaldrate, aluminium-magnesium hydroxide, cephalexin, metronidazole, multivitamin with folate M2: lithium prior to learning of the pregnancy and stopped during the first trimester No information about smoking, alcohol use, or substance use No information about pre-pregnancy BMI	Two single observations Clozapine concentrations in the neonate would have been informative in the light of the seizures Unknown if the follow-up information has been based on structured tools to assess the development of the infants or on parents' reports (absent information in the second child)	Maternal outcomes Fetal outcomes Developmental outcomes Delivery Neonatal outcomes

(continued)

Table 1 (continued).

First author and year of publication	Study design	Aim	Cases	Exposure	Major limitations	Reported outcomes
Di Michele 1996[55]	Case report	To describe a successful pregnancy in a woman undergoing treatment with CLZ and lorazepam, but whose baby developed transient floppy infant syndrome	n = 1 mother, 1 pregnancy	Planned pregnancy CLZ exposure from partition until delivery CLZ 200 mg/d, with increase up to 300 mg/d 3 times during the pregnancy, due to the mother's clinical condition Comedication: lorazepam 2.5 mg 3 times daily, and frequently increased up to 5 tablets a day No information about smoking, alcohol use, or substance use No pre-pregnancy BMI information	Single observation No information about several important factors, such as alcohol use, smoking, substance use, CLZ concentrations during pregnancy, and CLZ concentrations in the neonate, which would have been informative in the light of the floppy infant syndrome, although this syndrome is mainly attributed to the use of high doses of lorazepam	Fetal outcomes Delivery Neonatal outcomes
Dev 1995[56]	"Review"/ case overview	Not clearly specified	102 pregnancies exposed to CLZ	No information about planned or unplanned pregnancy No information about CLZ dose and duration and timing of exposure No information about smoking, alcohol use, or substance use No pre-pregnancy BMI information	Very limited data as any additional information such as maternal age, pre-pregnancy BMI, comedication, smoking, alcohol use, or substance use during pregnancy, CLZ dose, and timing of exposure is absent Authors worked at Sandoz Pharma, but the source of the data is not defined	Fetal outcomes Neonatal outcomes Lactation
Barnas 1994[57]	Case report	Not clearly specified	n = 1 mother, 1 pregnancy	Planned pregnancy CLZ exposure: Conception–week 32: 100 mg/d Week 32–delivery: 50 mg/d Day 3 after delivery: 100 mg/d No information about pre-pregnancy BMI, comedication, smoking, alcohol use, or substance use	Single observation, with little additional information Pharmacokinetic data are too limited to draw final conclusions No information regarding timing between last dose and sampling No information about treatment adherence, comedication, and smoking Unknown if the follow-up information has been based on structured tools to assess the development of the infants or on parents' reports	Maternal pharmacokinetics Fetal outcomes Developmental outcomes Deivery Lactation
Waldman 1993[58]	Letter to the editor/case report	Not specified	n = 1 mother, 1 pregnancy	No information about planned or unplanned pregnancy No information about CLZ dose and duration and timing of exposure No information about comedication No information about smoking, alcohol use, or substance use No information about pre-pregnancy BMI	Single observation with little additional information Report of GDM without information about the mother's pre-pregnancy BMI	Maternal outcomes Fetal outcomes Delivery Neonatal outcomes

Abbreviations: AP = antipsychotic, BMI = body mass index, CLZ = clozapine, CTG = cardiotocograph, GDM = gestational diabetes mellitus, M1 = mother 1 (and so on), M2-1 = mother 2, pregnancy 1 (and so on), NorCLZ = norclozapine, OAP = other antipsychotics.

Table 4. Studies Describing Fetal and Neonatal Outcomes, Including Delivery Outcomes, After In Utero Exposure to Clozapine

First author and year of publication	Number of mothers (number of pregnancies)	Fetal outcomes	Developmental outcomes	Delivery outcomes	Neonatal outcomes
Beex-Oosterhuis 2020[22]	494 ICSR-ADR pairs with adverse pregnancy outcomes related with CLZ exposure 4,645 ICSR-ADR pairs with adverse pregnancy outcomes related with OAP exposure	Fetal disorders: ROR = 0.68 (95% CI, 0.48–0.96) for CLZ vs OAP Termination of pregnancy and risk of abortion: ROR = 0.56 (95% CI, 0.43–0.73) for CLZ vs OAP	#	Pregnancy, labor, and delivery complications and risk factors: ROR = 0.44 (95% CI, 0.39–0.51) for CLZ vs OAP	Neonatal disorders: ROR = 0.32 (95% CI, 0.25–0.40) for CLZ vs OAP Congenital, familial, and genetic disorders: ROR = 0.37 (95% CI, 0.29–0.47) for CLZ vs OAP
Nguyen 2020[29]	8 (9)	≥ 1 nonreactive CTG (n = 7) ≥ 3 nonreactive CTGs (n = 5) Mean (SD) birth weight: 3,396 (188.7) g	#	Premature rupture of membranes (n = 1; 11.1%) Antepartum hemorrhage (n = 1; 11.1%) Unassisted vaginal delivery (n = 4; 44.4%) Assisted instrumental delivery (n = 1; 11.1%) Emergency cesarean (n = 1; 11.1%) Elective cesarean (n = 3; 33.3%) Mean gestation at birth (weeks + days, SD) 38 + 2 (6.58 days) Any resuscitation at birth (including suction, oxygen therapy, CPAP, bag and mask, intubation, external cardiac massage, or other): n = 8 (88.9%) Special care nursery admission: n = 4 (44.4%)	2 birth defects (1 pulmonary artery stenosis and atrial septal defect and 1 pyloric stenosis) 5 neonates with full blood counts taken within 7 days of birth with no evidence of agranulocytosis
Molins 2019[31]	1 (1)	No malformations Birth weight 3,590 g	#	Forceps-assisted vaginal delivery at 38 weeks with no perinatal complications Apgar scores of 9-10-10	Normal white blood cell count No seizures No withdrawal syndrome No other neonatal complications
Narayanaswamy 2018[32]	1 (1)	Fetal ventriculomegaly noticed on ultrasonography in the 5th month and at term Neural tube defect in a mother who used CLZ and haloperidol and found to be pregnant after the critical period of organogenesis Birth weight 3,490 g Birth height 46 cm Birth head circumference 34.5 cm	#	Shoulder dystocia during labor Delivery at term Low Apgar score at 1 and 9 minutes (not further specified	Admission in the intensive care unit for further care
Uygur 2019[33]	1 (2)	Pregnancy 1: # Pregnancy 2: Normal ultrasound examinations	No reports of negative effects of the treatment on the infant in the first pregnancy No neurocognitive or motor delays* at 2 years follow-up[a] of the second pregnancy	Pregnancy 1: # Pregnancy 2: Delivery at 38 weeks' gestation by cesarean section Apgar scores of 7 and 9	Pregnancy 1: "The mother and her family did not report any negative effects of the treatment on the infant" Pregnancy 2 No perinatal complications No agranulocytosis, seizures, or other neonatal complications

(continued)

Table 4 (continued).

First author and year of publication	Number of mothers (number of pregnancies)	Fetal outcomes	Developmental outcomes	Delivery outcomes	Neonatal outcomes
Imaz 2018[30]	3 (4)	M1: Physiological fetal well-being during pregnancy No congenital anomalies Birth weight 3,850 g M2: Fetal macrosomia detected in the 29th week of gestation No congenital anomalies Birth weight 3,660 g M3-1: Type I intrauterine growth restriction in the 28th week of gestation Breech presentation at delivery Birth weight 2,498 g Left inguinal hernia and left cryptorchidism M3-2: No altered physiologic parameters Birth weight 3,650 g No congenital anomalies	M1: symptoms, but no diagnostic criteria, of ADHD* at 6 years follow-up M2: no neurodevelopmental disorders* at 32 months of age M3-1: generalized neurodevelopmental delay* at 18 months M3-2: no neurodevelopmental disorders* at 6 months of age	M1: Estimated gestational age 38 + 6 weeks Spontaneous vaginal delivery Apgar score (1/5/10 min): 9/10/10 No perinatal complications M2: Estimated gestational age 40 + 5 weeks Cesarean delivery Apgar score (1/5/10min): 9/10/10 No perinatal complications M3-1: Estimated gestational age 38 + 6 weeks Cesarean delivery due to breech presentation Apgar score (1/5/10 min): 6/10/10 Resuscitation procedure (positive pressure ventilation) due to decreased Apgar min 1 score M3-2: Estimated gestational age 39 weeks (Elective) cesarean delivery Apgar score (1/5/10 min): 9/10/10 No perinatal complications	M1: no agranulocytosis, seizures, or other neonatal complications M2: no agranulocytosis, seizures, or other neonatal complications M3-1: No agranulocytosis, seizures, or other neonatal complications Urine drug test positive for benzodiazepines M3-2: no agranulocytosis, seizures, or other neonatal complications
Hatters Friedman 2016[18]	1 (1)	No malformations Birth weight of 3,095 g	#	Delivery at 38 weeks of gestation	#
Hodge 2016[34]	1 (1)	Reduced FHR variability and absence of accelerations in a mother using multiple drugs resulting in an emergency cesarean section Normal weight	#	Emergency cesarean section Normal Apgar scores	CRP increase over the first 48 hours of life with no other concerns
Köse Çinar 2016[35]	1 (1)	Birth weight 3,090 g Birth height 50 cm Head circumference 34.5 cm	#	Cesarean section without any complications Apgar score of 10-10	Healthy baby
Montastruc 2016[23]	2 (2)	Cleft palate (2x)	#	#	#
Oltulu 2016[26]	NA	#	Deterioration of learning performance in the Morris water maze task in rats with prenatal exposure to clozapine, haloperidol, sulpiride, chlorprothixene, and chlorpromazine. These rats also showed an increase in thigmotaxis	#	#
Sreeraj 2016[36]	1 (3) (triplet pregnancy)	Macrocephaly (34.5 cm) (1x) No congenital abnormalities or major physical problems in the other 2 children	#	Premature rupture of membranes at term Delivery by cesarean section Male monozygotic triplets with Apgar scores of 8-9-9	Transient tachypnea of newborn that settled within 12 hours of delivery in the second baby born

(continued)

Table 4 (continued).

First author and year of publication	Number of mothers (number of pregnancies)	Fetal outcomes	Developmental outcomes	Delivery outcomes	Neonatal outcomes
Guyon 2015[37]	1 (1)	Low variability in FHR with a normal baseline and accelerations at week 32 of pregnancy, which normalized from week 38 of pregnancy to term	#	Vaginal delivery at 40 + 5 weeks Apgar score (1/5 min): 9/10	Normal pediatric evaluation 5 and 10 days after birth. No further cardiac investigation needed Negative systematic screening for neonatal metabolic disorders, including hypothyroidism
Shao 2015[24]	CLZ: 33 (33) Comparator group consisting of risperidone [n = 16 (16)], OLZ [n = 8 (8)], or quetiapine [n = 6 (6)]	No significant differences between the CLZ group and the comparator group in: Percentage of low birth weight (less than 2.5 kg) (9.0% vs 16.7%, $P = .367$) Mean birth weight (3.2 kg vs 3.3 kg, $P = .409$) Height at birth (51.2 cm vs 50.8 cm, $P = .195$) No malformations (not in the CLZ-exposed group and not in the comparator group)	Lower mean adaptive-behavior scores of Bayley-III in CLZ-exposed infants compared with OAP-exposed infants at 2 (89.1 vs 96.3, $P = .001$) and 6 (94.8 vs 100.5, $P = .011$) months of age, but these differences disappeared at 12 months of age (98.3 vs 96.3, $P = .712$) Significantly more CLZ-exposed infants with delayed development (score < 85) in the adaptive-behavior domain compared with OAP-exposed infants at 2 (54.5% vs 16.7%, $P = .002$) and 6 (30.3% vs 10.0%, $P = .047$) months of age, but these differences disappeared at 12 months of age (21.2% vs 6.7%, $P = .099$) More CLZ-exposed infants had disturbed sleep and labile state than OAP-exposed infants at 2 months of age (75.8% vs 26.7%, $P < .001$) No differences in weight and height development between CLZ- and OAP-exposed infants during the first year of life	No significant differences between the CLZ group and the comparator group in the Apgar score at 5 minutes after birth (9.6 vs 9.4, $P = .176$) Higher Apgar score at 1 minute in the CLZ group than in the comparator group (8.6 vs 8.3, $P = .030$) No significant differences between the CLZ group and the comparator group: in the mean gestational age at birth (39.0 vs 38.9 weeks, $P = .430$) in complications during delivery	No significant differences between the CLZ group and the comparator group in the rates of neonatal complications between the two groups
Kulkarni 2014[19]	CLZ: 11 pregnancies N = 147 pregnancies exposed to antipsychotics in the first trimester	Two infants with major congenital anomalies: Hypospadias and hypertelorism in 1 baby Gastroschisis and horseshoe kidney in the other baby	#	Not specified for the individual drugs	#
Bodén 2012[20]	CLZ: 11 neonates OLZ: 159 neonates Group 1: OLZ and/or CLZ (n = 169) Group 2: OAP (n = 338) Group 3: no antipsychotics (n = 357 696)	OR for being born preterm: 1.58 (95% CI, 0.91–2.73) for OLZ/CLZ-exposed infants compared with nonexposed infants and 1.94 (95% CI, 1.37–2.77) for infants exposed to OAP No statistically significant difference regarding the risk of being SGA or LGA for weight and length for group 1 or 2 after adjusting for confounders Exposure to OLZ and/or CLZ was associated with being LGA for head circumference with an adjusted OR of 3.02 (95% CI, 1.60–5.71), but none of the neonates had a hydrocephalus diagnosis	#	#	#

(continued)

Table 4 (continued).

First author and year of publication	Number of mothers (number of pregnancies)	Fetal outcomes	Developmental outcomes	Delivery outcomes	Neonatal outcomes
Coston 2012[38]	2 (2)	M1: Physiological fetal well-being during pregnancy Absence of FHR variability/flattening of the FHR detected at pregnancy week 34 + 5 M2: Absence of FHR variability at pregnancy week 38 + 5 Infant weight 3,330 g	#	M1: Estimated gestational age 39 + 2 weeks Eutrophic neonate "Perfect Apgar scores" Arterial pH 7.33 M2: Cesarean delivery due to insufficient cervical dilatation and moderate fetal tachycardia with late decelerations "Perfect Apgar score" Arterial pH 7.30 and venous pH 7.32	#
Moreno-Bruna 2012[39]	1 (1)	Normal ultrasounds during pregnancy Macrosomia (4,060 g)	No neurodevelopmental disorders and normal growth at 2-year follow-up*	Uncomplicated vaginal delivery at term (40 + 5) Apgar score (1/5 min): 10/10	Delayed peristalsis with vomiting
Novikova 2009[40]	1 (1)	Absence of FHR variability without acidosis at 32 weeks' gestation	#	Cesarean delivery due to the critical maternal condition and fetal distress Apgar score of 7 at 5 minutes Placental pH 7.19	Delayed peristalsis
Donohoe 2008[27]	NA	#	Deficits in the migration of neuroblasts and axonal growth in neurons in comparison to control animals in *Caenorhabditis elegans* organisms exposed to clozapine or fluphenazine during embryonic development	#	#
Duran 2008[41]	2 (4) 2 mothers (M1: 2 pregnancies; M2: 1 twin pregnancy)	M1, pregnancy 1: Birth weight 2,900 g Birth height 52 cm M1, pregnancy 2: Birth weight 3,000 g Birth height 50 cm M2 (twins): Birth weights of 3,100 and 2,940 g Birth heights of 51 and 49 cm	All 4 children with normal motor and mental development and hematologic examinations (unknown follow-up period)*	M1, pregnancy 1: Term, uncomplicated vaginal delivery Apgar scores of 9-10 Normal white blood cell count M1, pregnancy 2: Term, uncomplicated vaginal delivery Apgar scores of 10-10 M2 (twins): Apgar scores of 10-10 and 9-10	M1, pregnancy 1: Normal white blood cell count No neonatal seizures M1, pregnancy 2: # M2 (twins): no positive records on seizure or agranulocytosis
Newham 2008[25]	3 (3)	Two of the 3 CLZ-exposed babies seemed to be LGA for weight	#	#	#
Reis 2008[21]	18 (18)	Ectopic anus	#	#	#
Klys 2007[42]	1 (1)	Neonatal death shortly after delivery after 39 weeks' gestation due to an acute clozapine overdose by the mother Birth weight 4,050 g	#	Spontaneous delivery 1 day after the suicide attempt, following vacuum extraction Apgar score of 1, with single isolated heartbeats	
Mendhekar 2007[43]	1(1)	Birth weight 2,950 g	Normal development, except for speech. By the end of 5 years, the infant gained normal fluent speech*	Delivery at 9 months and 2 days of gestation	No perinatal complications
Doherty 2006[45]	1 (1)	Late fetal decelerations on the cardiotocograph Morphologically normal infant	#	Emergency cesarean section at 40 weeks Apgar scores of 9 and 10	#

(continued)

Table 4 (continued).

First author and year of publication	Number of mothers (number of pregnancies)	Fetal outcomes	Developmental outcomes	Delivery outcomes	Neonatal outcomes
Sethi 2006[44]	1 (1)	Child showed no congenital anomaly	No developmental delay at 2-year follow-up*	No complication during labor and delivery	#
Wang 2006[28]	NA	#	Pups exposed to HAL/CLZ increased in body weight more slowly than control pups at the beginning of the development. After 6 weeks, neither the HAL- nor CLZ-treated mice differed in body weight CLZ and CLZ-withdrawal increased locomotor activity Chronic clozapine treatment and transient withdrawal caused no impairment in the acquisition of memory. Moreover, it tended to improve memory	#	#
Walch 2005[46]	1 (1)	Gestational week 33: fetal retardation and oligohydramnios Birth weight 2,400 g Birth length 49 cm Head circumference 31 cm Trisomy 21	#	Cesarean delivery at week 37	Sound conduction disorder At day 4: slightly increased TSH (23 mU/L) At day 10: increased TSH (62 mU/L) At day 23: Muscular hypotonia Poor feeding Increased drowsiness Hypothermia Enlarged thyroid
Gupta 2004[47]	1 (2)	No congenital malformations detected with ultrasonography at the 10th week and repeating occasions during the first pregnancy	No neurodevelopmental disorders at 20 months and 6 months follow-up*	First pregnancy: Delivery with episiotomy at 39 weeks Apgar scores of 8-9 Second pregnancy: Cesarean section at 39 weeks Breech presentation Apgar scores of 7-9	#
Karakula 2004[48]	1 (1)	Birth weight 4,000 g Head circumference 36 cm Birth length 56 cm	Major developmental delay at 7 months follow-up	Cesarean section due to fetal arrhythmia and threat of fetal asphyxiation at week 28(?) Apgar scores (1-3-5-10 min): 7-8-8-8 Last CLZ dose 10 hours before delivery	14 hours after delivery: clonic-tonic convulsions, opisthotonus, lockjaw, apnea following tracheal intubation and administration of phenobarbital, without significant improvement, abnormal heart shape 17 hours after delivery: admission to the neonatal intensive care unit At day 3(?): diagnosis of "encephalopathy as side effect of medication with convulsions and coma, respiratory insufficiency" At day 10: mandibular recess, decreased muscle tone, periodic convulsions in upper extremities, flaccid chest, dyspnea, hernia of the linea alba, left testicle not palpable At day 15: deflection of the head, hypersomnia, increased muscle flaccidity after deflection

(continued)

Table 4 (continued).

First author and year of publication	Number of mothers (number of pregnancies)	Fetal outcomes	Developmental outcomes	Delivery outcomes	Neonatal outcomes
Mendhekar 2003[49]	1 (1)	The mother never reported fetal movements Stillborn baby of 2,200 g with no gross congenital malformations	#	Delivery at 9 months and 9 days	#
Nguyen 2003[50]	1 (3)	Pregnancies 1 and 2: normal ultrasounds and amniocenteses (unknown in which trimester[s]) Pregnancy 1: Birth weight 3,460 g Functional heart murmur at cardiac auscultation, without signs of any cardiomyopathy on the ultrasounds Pregnancy 2: birth weight 3,470 g	No neurodevelopmental disorders at 5- and 3-year follow-up* One of the children had an average weight, height, and cranial parameter. The other child was on the lower part of the curves for weight, height, and cranial parameter at 5- and 3-year follow-up*	Pregnancy 1: At term Emergency cesarean section because of fetal distress (late deceleration) and due to decreased progression of delivery Apgar scores of 8-9-9 Pregnancy 2: Vaginal delivery at 40 weeks using forceps because of a prolonged second stage Apgar scores of 8-9-9	#
Yogev 2002[51]	1 (1)	Unremarkable pregnancy follow-up Reduced FHR variability on all fetal surveillance tests before labor and during all stages of labor without specific time correlation to drug administration Birth weight of 3,420 g	#	Normal delivery at week 37 Normal fetal assessment by biophysical score Apgar score of 9–10 Normal umbilical artery pH	#
Dickson 1998[52]	1 (1)	No information regarding birth weight and length	#	Induced delivery at 38 weeks' gestation Complicated delivery due to shoulder dystocia assisted by low mid forceps	Healthy baby was born

(continued)

Table 4 (continued).

First author and year of publication	Number of mothers (number of pregnancies)	Fetal outcomes	Developmental outcomes	Delivery outcomes	Neonatal outcomes
Tenyi 1998[53]	4 (6)	No embryotoxic disturbances in all 6 pregnancies M1, pregnancy 1: Birth weight 4,300 g Birth length 59 cm Head circumference 35 cm No teratogenic disturbances M1, pregnancy 2: Birth weight 3,800 g Birth length 56 cm Head circumference 35 cm No teratogenic disturbances M1, pregnancy 3: Birth weight 3,500 g Birth length 52 cm Birth head circumference 35 cm No teratogenic disturbances M2: Birth weight 2,800 g Birth length 49 cm Birth head circumference 33 cm No teratogenic disturbances M3: Birth weight 3,090 g Birth length 48 cm Birth head circumference: 33 cm No teratogenic disturbances M4: Birth weight 3,570 g Birth length 50 cm Head circumference: 33 cm No teratogenic disturbances	3 children (of 1 mother) with normal (psychomotor) development at 6 years, 3½ years, and 1½ years follow-up.* Follow-up of the other 3 infants also showed no disturbances	M1, pregnancy 1: Cesarean section at 40 weeks due to relative spatial disproportion Apgar scores of 9 and 10 M1, pregnancy 2: Cesarean section at 40 weeks due to relative spatial disproportion Apgar scores of 6 and 9 M1, pregnancy 3: Cesarean section at 40 weeks' gestation Apgar score of 7 and 9 M2: Delivery at 37 weeks' gestation Apgar scores of 9 and 10 M3: Delivery at 38 weeks' gestation Apgar scores of 9 and 9 M4: Delivery at 39 weeks' gestation Apgar scores of 9 and 10	#
Stoner 1997[54]	2 (2)	M1: birth weight 3,800 g M2: birth weight 2,510 g	M1: no physical disorders at 2-year follow-up* M2: no follow-up information	M1: Delivery with vacuum extraction at 39 weeks due to lack of cooperation Temperature of 36.9°C Pulse 128 bpm 16 respirations/min Apgar scores of 8-9 Arterial cord pHs of 7.27 and 7.30 M2: Delivery at 40 weeks Apgar scores of 8 and 9	M1: Abnormal findings at birth: Cephalhematoma (resolved between 2 days after delivery) Hyperpigmentation folds (resolved between 2 days after delivery) Coccygeal dimple (resolved between 2 days after delivery) 1 seizure at day 8 after delivery Possible mild gastroesophageal reflux No long-term sequelae from the seizure and no further seizure activity M2: No abnormalities; the baby developed low grade fever postpartum that resolved prior to discharge

(continued)

Table 4 (continued).

First author and year of publication	Number of mothers (number of pregnancies)	Fetal outcomes	Developmental outcomes	Delivery outcomes	Neonatal outcomes
Di Michele 1996[55]	1 (1)	Uneventful pregnancy under obstetric supervision Birth weight 3,300 g	#	Cesarean section at 37 weeks Apgar scores of 7 and 9 Arterial cord pH of 7.3	Benign tachypnea Mild floppy infant syndrome; with hypotonia resolving 5 days after delivery Normal cerebral ultrasound, electroencephalography, abdominal ultrasound, and lung x-ray
Dev 1995[56]	102 pregnancies Outcome of pregnancy in 22 patients is unknown	8 non-elective and 13 elective abortions 5 infants with malformations (in some instances, mothers were also taking other drugs that may have caused these malformations). Not described if these were minor or major malformations	#	#	Of the 61 babies (59 pregnancies): 51 healthy infants 5 infants with (undefined) problems during the postnatal period
Barnas 1994[57]	1 (1)	Uneventful pregnancy with regular ultrasonography to confirm normal fetal growth Birth weight of 3,600 g	No psychomotor disorders at 6 months follow-up*	Delivery with vacuum extraction at 41 weeks of pregnancy Apgar scores of 5 and 8 Arterial cord pH of 7.34	#
Waldman 1993[58]	1 (1)	Birth weight of 3,700 g	#	Induced delivery with prostin gel at 38 weeks, due in part to the mother's inability to comply satisfactorily with diabetic dietary restrictions Uncomplicated delivery except for shoulder dystocia Apgar scores of 7 and 9	Healthy baby

#No information.
*Unknown if this is based on structured tools to assess the development of the infants or on parents' reports.
Abbreviations: 95% CI = 95% confidence interval, ADHD = attention-deficit/hyperactivity disorder, CLZ = clozapine, CPAP = continuous positive airway pressure, CRP = C reactive protein, CTG = cardiotocograph, FHR = fetal heart rate, ICSR-ADR= individual case safety report adverse drug reaction, LGA = large for gestational age, NA = not applicable, NorCLZ = norclozapine, OAP = other antipsychotic, OLZ = olanzapine, ROR = reporting odds ratio, SGA = small for gestational age, TSH = thyroid-stimulating hormone.

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Supplementary Material

Article Title: Clozapine Treatment During Pregnancy and the Postpartum Period: A Systematic Literature Review

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List of Supplementary Material for the article

1. **Appendix 1** Search Strategy PubMed/MEDLINE

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Appendix I: Search strategy Pubmed/ Medline

((("clozapine"[MeSH Terms] OR "clozapine"[All Fields] OR "leponex"[All Fields] OR "clozaril"[All Fields])) AND (((((((Pregnancy[Mesh] OR pregnan*[tiab] OR gestation*[tiab])) OR ("Maternal Exposure"[Mesh] OR maternal[tiab] OR "in utero"[tiab] OR prenatal*[tiab])) OR (Fetus[Mesh] OR fetus*[tiab] OR fetal[tiab] OR foetus*[tiab] or foetal[tiab])) OR ("infant, newborn"[MeSH Terms] OR "infant"[All Fields] OR "newborn"[All Fields] OR "newborn infant"[All Fields] OR "neonate"[All Fields] OR neonat*[All fields] OR offspring[All fields])) OR (("lactation"[MeSH Terms] OR "lactation"[All Fields] OR "breast feeding"[MeSH Terms] OR ("breast"[All Fields] AND "feeding"[All Fields]) OR "breast feeding"[All Fields])))