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.