

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 CTTG (n = 7) ≥ 3 nonreactive CTTGs (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 ³ 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

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Imaz 2018 ³⁰	3 (4)	<p>M1: Physiological fetal well-being during pregnancy No congenital anomalies Birth weight 3,850 g</p> <p>M2: Fetal macrosomia detected in the 29th week of gestation No congenital anomalies Birth weight 3,660 g</p> <p>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</p> <p>M3-2: No altered physiologic parameters Birth weight 3,650 g No congenital anomalies</p>	<p>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</p>	<p>M1: Estimated gestational age 38 + 6 weeks Spontaneous vaginal delivery Apgar score (1/5/10 min): 9/10/10 No perinatal complications</p> <p>M2: Estimated gestational age 40 + 5 weeks Cesarean delivery Apgar score (1/5/10min): 9/10/10 No perinatal complications</p> <p>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</p> <p>M3-2: Estimated gestational age 39 weeks (Elective) cesarean delivery Apgar score (1/5/10 min): 9/10/10 No perinatal complications</p>	<p>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</p>
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

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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	#	#	#

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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 <i>Caenorhabditis elegans</i> 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	#

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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

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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

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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

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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= nortclozapine, OAP= other antipsychotic, OLZ= olanzapine, ROR= reporting odds ratio, SGA= small for gestational age, TSH= thyroid-stimulating hormone.