

**Table S1.** Studies on opioid exposure during pregnancy.

Article	Article type	Opioid class	Sample size	Issue of interest	Main findings
<i>Kaltenbach et al. [1]</i>	Review	Metahdone, heroin	/	Foetus and infant cause of death	Overview of the main fetal and infant complications
<i>Sithisarn et al. [2]</i>	Review	Opiates	/	Foetus and infant cause of death	Overview of the main infant complications
<i>Bertaso et al. [5]</i>	Retrospective study	Morphine, methadone	51	Toxicological analyses	Assessment of in utero exposure to drugs
<i>Friguls et al. [6]</i>	Experimental study	Opiates	107	Foetus and infant cause of death	Assessment of in utero exposure to drugs
<i>Lam et al. [9]</i>	Retrospective study	Methadone, heroin	51	Foetus and infant cause of death	Overview of the main fetal and infant complications
<i>Fishman et al. [11]</i>	Retrospective study	Propoxyphene, codeine, tramadol, oxycodone, fentanyl	3003	Foetus and infant cause of death	Analysis for total major malformations and for spina bifida
<i>Pötsch et al. [12]</i>	Case report	Heroin metabolites, morphine	1	Toxicological analyses	All the fetal specimens were investigated
<i>Rausgaard et al. [14]</i>	Retrospective study	Codeine, tramadol, oxycodone, morphine	10878 pregnant women	Foetus and infant cause of death	Trend modifications in opioid prescriptions in pregnancy in the period 1997-2016 and intrauterine effects of exposition
<i>Bhatt-Mehta et al. [15]</i>	Retrospective study	Methadone	11 opioid-dependent mother-infant dyads	Toxicological analyses	Evaluate maternal and umbilical cord plasma concentrations of methadone and EDDP
<i>Bashore et al. [16]</i>	Review	Heroin	/	Foetus and infant cause of death	Overview of the main fetal and infant complications
<i>Anbalagan et al. [17]</i>	Review	Methadone, heroin, buprenorphine	/	Foetus and infant cause of death	Neonatal abstinence syndrome
<i>Ryan et al. [18]</i>	Review	Methadone, heroin, buprenorphine	/	Foetus and infant cause of death	Overview of the main fetal and infant complications
<i>Esposito et al. [19]</i>	Retrospective study	Prescription opioid in pregnancy (except opioid replacement therapy)	1,833,871 pregnant women	Foetus and infant cause of death	Overview of the main fetal and infant complications
<i>Borrelli et al. [20]</i>	Experimental study	Methadone/Fentanil/Buprenorphine	40	Epigenetic analyses	Prenatal opioid exposure and placental epigenetic changes lead to abnormal fetal brain development and NOWS
<i>Little et al. [21]</i>	Research study	Heroin	24	Foetus and infant cause of death	Overview of the main fetal and infant complications
<i>O'Donnell et al. [22]</i>	Communication	Heroin	/	Foetus and infant clinical complications	Overview on management of opioid use disorder in pregnancy
<i>Kandall et al. [23]</i>	Retrospective study	Methadone, heroin	337 newborns	Foetus and infant cause of death	Birth weight analysis

<i>Wolff et al. [24]</i>	Communication	Heroin, methadone	/	Foetus and infant clinical complications	Opioid Neonatal Abstinence Syndrome
<i>Athanasakis et al [25]</i>	Review	Opiates	/	Foetus and infant cause of death	Contributing factors to SIDS
<i>Maguire et al. [26]</i>	Meta-analysis	Methadone, buprenorphine	/	Foetus and infant clinical complications	Long-term outcomes of the prenatal exposure
<i>Benck et al. [27]</i>	Retrospective study	Methadone, buprenorphine	371	Foetus and infant clinical complications	Care of pregnant incarcerated persons with opioid use disorder
<i>Burns et al. [28]</i>	Retrospective study	Methadone	675310 liveborn infants	Foetus and infant cause of death	Risk of in infant death in methadone maintenance therapy
<i>Caritis et al. [29]</i>	Communication	Morphine, methadone	/	Foetus and infant clinical complications	Implication on fetal brain
<i>Cohen et al. [30]</i>	Research article	Heroin, methadone	138 neonatal autopsies	Infant cause of death	SIDS association
<i>Conradt et al. [31]</i>	Review	Morphine, methadone, buprenorphine	/	Foetus and infant clinical complications	Neurodevelopmental consequences
<i>Concheiro et al. [32]</i>	Research study	Opioids, methadone	727 mother–infant dyads	Toxicological analyses	Maternal hair resulted as the most sensitive specimen to detect drug exposure during pregnancy
<i>de Castro et al. [33]</i>	Research study	Methadone	19	Toxicological analyses	Umbilical cord methadone concentrations were correlated to methadone doses
<i>Dryden et al. [34]</i>	Retrospective study	Methadone	450	Foetus and infant clinical complications	Development of neonatal abstinence syndrome
<i>Duska et al. [35]</i>	Retrospective study	Methadone, naloxone	12	Foetus and infant cause of death	Provide a framework for other Ob/Gyn clinics to use in implementing similar naloxone distribution programs
<i>Epstein et al. [36]</i>	Retrospective study	Morphine, methadone, buprenorphine	14448	Foetus and infant clinical complications	Prevalence of prescribed opioid analgesics among pregnant women from 1995 to 2009
<i>Galli et al. [37]</i>	Case series	Methadone	2	Foetus and infant clinical complications	Long-Term Visual and Neurodevelopmental Outcomes
<i>Garrison et al. [38]</i>	Retrospective study	Morphine, methadone	59	Foetus and infant clinical complications	Fetal Growth Outcomes
<i>Irnes et al. [39]</i>	Retrospective study	Morphine, methadone	16	Foetus and infant clinical complications	Brain morphology with magnetic resonance imaging
<i>Kandall et al. [40]</i>	Review	Heroin, methadone	/	Foetus and infant cause of death	Association between opiates and SIDS
<i>Kandall et al. [41]</i>	Retrospective study	Heroin, methadone	1760 SIDS cases analyzed	Foetus and infant cause of death	Association between opiates and SIDS
<i>Kushmir et al. [42]</i>	Retrospective study	Methadone, buprenorphine	290	Foetus and infant clinical complications	Different between prenatally exposed to methadone or buprenorphine

<i>McCarthy et al. [43]</i>	Communication	Methadone, buprenorphine	/	Foetus and infant clinical complications	Buprenorphine versus Methadone in Pregnancy
<i>López et al. [44]</i>	Case report	Codeine	1	Toxicological analyses	levels of drugs disappeared by the third day
<i>McGlone et al. [45]</i>	Retrospective study	Methadone	81	Foetus and infant clinical complications	Abnormal visual electrophysiology
<i>Monnelly et al. [46]</i>	Meta-analysis	Methadone	/	Foetus and infant clinical complications	Childhood neurodevelopment
<i>Montanari et al. [47]</i>	Case report	Methadone	1	Foetus and infant cause of death	Methadone contribution to IUFD
<i>Montanari et al. [48]</i>	Case report	Methadone	1	Foetus and infant cause of death	Genetic assessment of methadone fetal clearance
<i>Newbury et al. [49]</i>	Retrospective study	Methadone	80	Foetus and infant clinical complications	Social adversity, caregiver psychological factors, and language outcomes
<i>Pandya et al. [50]</i>	Retrospective study	Morphine	175000	Toxicological analyses	Assessment of the most common drug combination in meconium
<i>Ordean et al. [51]</i>	Retrospective study	Buprenorphine	/	Toxicological analyses	buprenorphine-naloxone is a safe and effective opioid agonist treatment for pregnant people
<i>Ostrea et al. [52]</i>	Research study	Opiates	58	Toxicological analyses	Estimates of illicit drug use during pregnancy by hair analysis and meconium analysis
<i>Parikh et al. [53]</i>	Research study	methadone	36	Toxicological analyses	Newborns exposed to methadone are at risk of cardiac rhythm disturbances
<i>Ramirez et al. [54]</i>	Retrospective study	Methadone	56	Foetus and infant clinical complications	Intrapartum fetal heart rate patterns
<i>Robert et al. [55]</i>	Research study	Buprenorphine	9 mothers 4 infants	Toxicological analyses	Significant positive association between concentrations of buprenorphine and norbuprenorphine in maternal hair and a trend for this association in infant hair
<i>Ross et al. [56]</i>	Review	Opiates	/	Toxicological analyses	Drugs effect on developing nervous system
<i>Serra et al. [57]</i>	Retrospective study	Methadone, buprenorphine	86 (buprenorphine) + 268 (methadone) exposed placentas	Foetus and infant cause of death	Placental histological examination
<i>Spowart et al. [58]</i>	Retrospective study	Methadone	153	Foetus and infant clinical complications	Executive functioning, behavioural, emotional, and cognitive difficulties
<i>Ward et al. [59]</i>	Retrospective study	Opiates	497 infants	Foetus and infant cause of death	Effects of opiates on the fetus and the infant

<i>Towers et al. [60]</i>	Retrospective study	Morphine, methadone	429	Foetus and infant clinical complications	Head circumference in neonatal abstinence syndrome
<i>Whiteman et al. [61]</i>	Retrospective study	Opioid	138,224 pregnant women	Foetus and infant cause of death	Effects of opiates on the fetus and the infant
<i>Walhovd et al. [62]</i>	Research study	opiates	14	Toxicological analyses	Myelin may be particularly vulnerable to prenatal substance exposure
<i>Wurst et al. [63]</i>	Research study	Buprenorphine, methadone	176 (buprenorphine) + 52 (methadone) pregnant women	Foetus and infant cause of death	Effects of opiates on the fetus and the infant
<i>Zedler et al. [64]</i>	Review	Buprenorphine, methadone	/	Toxicological analyses	Evidence of lower risk of preterm birth, greater birth weight and larger head circumference with buprenorphine treatment during pregnancy compared with methadone treatment
<i>Zipursky et al. [65]</i>	Review	Opioids	/	Toxicological analyses	Opioid use in pregnancy and how this relates to maternal and neonatal health outcomes
<i>Crews et al. [66]</i>	Review	Codeine, tramadol, hydrocodone, oxycodone, methadone	/	Pharmacogenetic analyses	Implementation Consortium Guidelines for opioids therapy and CYP2D6, OPRM1, and COMT genotyping
<i>CPIC Guideline [67]</i>	Guidelines	Drugs	/	Pharmacogenetic analyses	Pharmacogenetic test and drug therapy
<i>Yalçın et al. [68]</i>	Review	Morphine, methadone, tramadol, sufentanil, midazolam	/	Pharmacogenetic analyses	Pharmacogenetics in infants and neonates
<i>Madaadi et al. [69]</i>	Review	Morphine, synthetic and semi-synthetic opioids	/	Pharmacogenetic analyses	Pharmacogenetics variants and pregnancy
<i>McPhail et al. [71]</i>	Review	Methadone, buprenorphine, morphine	/	Foetus and infant clinical complications	Pharmacokinetic and pharmacodynamic of opioids in infants with NOWS: challenges and future approaches
<i>Liu et al. [72]</i>	Clinical trial study	Morphine	34	Pharmacokinetic model analysis	Description of the population PK of morphine in NAS
<i>van Hoogdaem et al. [73]</i>	Review	Buprenorphine, clonidine, methadone, morphine	/	Pharmacogenetic analyses	Influence of gestational age, postnatal age, and pharmacogenetics on the pharmacokinetics of drug therapies used in NOWS.

<i>Wachman et al. [74]</i>	Multicenter cohort study	Methadone, buprenorphine	86	Pharmacogenetic analyses	OPRM1 and COMT gene variants were associated with a shorter length of hospital stay
<i>Albano et al. [75]</i>	Review	Opioids	/	Toxicological analyses	Evidence-based approach for managing neonatal exposure to opioids
<i>Kintz et al. [76]</i>	Research study	Heroin, methadone	24	Toxicological analyses	Interpretation issue in assessing neonatal drug exposure
<i>Baldo et al. [90]</i>	Review	Methadone, buprenorphine, morphine	/	Pharmacogenetic analyses	Pharmacogenomics of NOWS and respiratory depression
<i>Wachman et al. [93]</i>	Experimental study	Methadone, buprenorphine	86	Epigenetic analyses	Increased methylation within the OPRM1 promoter is associated with worse NAS outcomes

**Table S2.** Fetal and infant outcomes associated with maternal opioid use.

Article	Opioid class	Outcomes
<i>Kaltenbach et al. [1]</i>	Methadone, heroin	Spontaneous abortion, IUFD, IUGR, preeclampsia, premature labor/delivery, PROM, abruptio placentae, intrauterine passage of meconium, low Apgar scores
<i>Sithisarn et al. [2]</i>	Opiates	SGA, altered neurobehavioral in infancy
<i>Huestis et al. [8]</i>	Methadone, heroin	Increased risk of abortion in case of sudden withdrawal, IUGR, SGA, NOWS; increased risk of SIDS
<i>Lam et al. [9]</i>	Methadone, heroin	Prematurity, SGA, antepartum hemorrhage, NOWS
<i>Fishman et al. [11]</i>	Propoxyphene, codeine, tramadol, oxycodone, fentanyl	propoxyphene and codeine: perinatal death, low birth weight, SGA, low Apgar score (<8) at 1 and 5 minutes after birth; codeine: increased risk of spina bifida; third trimester exposition of opioids: low birth weight, perinatal death.
<i>Rausgaard et al. [14]</i>	Codeine, tramadol, oxycodone, morphine	No variations in prescription drugs and no difference in livebirth or stillborn babies
<i>Bashore et al. [16]</i>	Heroin	Preeclampsia, IUGR, IUFD, NOWS
<i>Anbalagan et al. [17]</i>	Methadone, heroin, buprenorphine	NOWS, neurodevelopmental delays, behavioral problems, death
<i>Ryan et al. [18]</i>	Methadone, heroin, buprenorphine	placental insufficiency, preterm birth, NOWS, low birth weight, SGA
<i>Esposito et al. [19]</i>	Prescription opioids in pregnancy (except opioid replacement therapy)	minimal increased risk of placental abruption, preterm birth, and SGA
<i>Little et al. [21]</i>	Heroin	Preterm birth, SGA, low birth weight infants
<i>O'Donnell et al. [22]</i>	Heroin	Neonates exposed to opioids in utero have a risk of neonatal abstinence syndrome (NAS) that is as high as 90%
<i>Kandall et al. [23]</i>	Methadone, heroin	IUGR, low birth weight

<i>Wolff et al. [24]</i>	Heroin, methadone	Generalized motor seizures and myoclonic jerks rates of occurrence ranging from 2% to 10% for infants withdrawing from opioids
<i>Athanasakis et al [25]</i>	Opiates	Pregnancy exposition contribute to SIDS
<i>Maguire et al. [26]</i>	Methadone, buprenorphine	Worse outcomes for impaired vision
<i>Benck et al. [27]</i>	Methadone, buprenorphine	Accessing medications prevent erratic fetal opioid level withdrawals, fetal and neonatal morbidity and mortality
<i>Burns et al. [28]</i>	Methadone	Higher infant death rate, mainly SIDS, in methadone maintenance therapy
<i>Caritis et al. [29]</i>	Morphine, methadone	Alterations in white matter of the centrum ovale, longitudinal fasciculi, and capsules
<i>Cohen et al. [30]</i>	Heroin, methadone	SIDS
<i>Conradt et al. [31]</i>	Morphine, methadone, buprenorphine	Alterations in IQ, neurologic performance and language performance
<i>Dryden et al. [34]</i>	Methadone	Smaller birthweight and head circumference
<i>Epstein et al. [36]</i>	Morphine, methadone, buprenorphine	Birth defects with early fetal exposure and neonatal abstinence syndrome with later fetal exposure
<i>Galli et al. [37]</i>	Methadone	In all cases ophthalmologic, oculomotor, and perceptive problems
<i>Garrison et al. [38]</i>	Morphine, methadone	49.2% incidence of microcephaly
<i>Irnes et al. [39]</i>	Morphine, methadone	6.5% smaller basal ganglia, 9.2% caudate, 7.6% thalamus and 10.3% cerebellar white matter
<i>Kandall et al. [40]</i>	Heroin, methadone	Weak association between SIDS and opiate use
<i>Kandall et al. [41]</i>	Heroin, methadone	Opiate contribution to SIDS cause
<i>Kushnir et al. [42]</i>	Methadone, buprenorphine	birth weight between groups (neonates in the Bup/Bup+ being significantly heavier than the Met/Met+ ones)
<i>McCarthy et al. [43]</i>	Methadone, buprenorphine	Buprenorphine is associated with a lower risk of adverse out-comes than methadone concerning behavioural, emotional and cognitive regulation
<i>McGlone et al. [45]</i>	Methadone	40% failed clinical visual assessment; relative risk of abnormal assessment was 5.1
<i>Monnelly et al. [46]</i>	Methadone	Mental Development Index weighted mean difference of children -4.3
<i>Montanari et al. [47]</i>	Methadone	IUFD high likely due to chronic fetal MTD intoxication, placental delayed villous maturation, and chorionic thrombosis
<i>Montanari et al. [48]</i>	Methadone	Abnormal genetic profile of <i>CYP2B6</i> , <i>ABCB1</i> and <i>OPRM1</i> reducing methadone clearance
<i>Newbury et al. [49]</i>	Methadone	At age 9.5 years lower language scores than the non-exposed children
<i>Ramirez et al. [54]</i>	Methadone	Severe variable or late decelerations during the second stage of labor (44.2%)
<i>Serra et al. [57]</i>	Methadone, buprenorphine	Increased incidence of delayed villous maturation in the exposed placentas
<i>Spowart et al. [58]</i>	Methadone	Children had birthweights 236 g lighter on average and had smaller birth OFC by an average of 0.8 cm
<i>Ward et al. [59]</i>	Opiates	SIDS and cleft palate
<i>Towers et al. [60]</i>	Morphine, methadone	Head circumference for was 33.04 cm ( $\pm 1.9$ cm)

<i>Whiteman et al. [61]</i>	Prescription opioid in pregnancy	Preterm labor, PROM, IUGR, IUFD
<i>Wurst et al. [63]</i>	Methadone, buprenorphine	Reduced risk of NOWS in buprenorphine, in methadone higher frequency of preterm birth and congenital malformations

**Table S3.** Forensic techniques for detecting and quantifying opioids in maternal and infant samples.

Article	Analytical techniques
<i>Bertaso et al. [5]</i>	LC-MS/MS
<i>Pötsch et al. [12]</i>	GC-MS
<i>Concheiro et al. [32]</i>	LC-MS/MS
<i>de Castro et al. [33]</i>	LC-MS/MS
<i>López et al. [44]</i>	GC-MS
<i>Pandya et al. [50]</i>	LC-MS/MS
<i>Ordean et al. [51]</i>	/
<i>Ostrea et al. [52]</i>	GC-MS
<i>Parikh et al. [53]</i>	/
<i>Robert et al. [55]</i>	LC-MS/MS
<i>Ross et al. [56]</i>	/
<i>Walhovd et al. [62]</i>	/
<i>Zedler et al. [64]</i>	/
<i>Zipursky et al. [65]</i>	/
<i>Albano et al. [75]</i>	/
<i>Kintz et al. [76]</i>	LC-MS/MS

**Table S4.** Genetic and epigenetic factors associated with opioid-related adverse outcomes.

Article	Article type	Opioid class	Sample size	Issue of interest	Main findings
<i>Montanari et al [48]</i>	Experimental research	Methadone	Stillborn (N=1)	Pharmacogenetic analyses	Association between CYP2B6 variant alleles and stillborn methadone intoxication
<i>Mactier et al. [70]</i>	Observational cohort study	Methadone	MMOD mother and their newborns (N=21)	Pharmacogenetic analyses	Higher frequency of homozygous allele at 516 and 785 regions of CYP2B6

					gene in treated infants leading to severity of NAS
<i>Wachman et al. [74]</i>	Cohort study	Morphine/ Buprenorphine	Mother/infant pairs (N=113)	Genetic analyses	Infants with the rs1799971 AG or GG genotypes experience shorter hospital stays for the treatment of NAS in comparison to those with the AA genotype.
<i>Koren et al [77]</i> <i>Madadi, et al [78]</i> <i>Friedrichsdorf, et al. [79]</i> <i>Madadi, et al [80]</i> <i>Sistonen, et al [81]</i>	Case and cohort studies	Morphine/ Methadone	Mother-infant pairs (Total N=188)	Pharmacogenetic analyses	High risk of opioid toxicity in breastfed infant associated with <i>CYP2D6</i> and <i>ABCB1</i> mother's genetic polymorphism
<i>Claessens et al [82]</i>	Experimental study	Clonidine	Pregnant women (N=17)	Pharmacogenetic analyses	Increase in clonidine oral clearance in pregnant women primarily mediated by <i>CYP2D6</i>
<i>Badaoui et al [83]</i>	Pharmacokinetic modelling	Codeine/Morphine	Pregnant females/foetus (N=250)	Pharmacogenetic analyses	Higher risk to foetal morphine exposure in the first trimester of pregnancy
<i>Pogliani et al [84]</i>	Case report	Morphine	Pre-term newborn (N=1)	Pharmacogenetic analyses	Opioid-induced urinary retention linked to a homozygous for the C3435T polymorphism in the <i>ABCB1</i> gene
<i>Elens et al [85]</i>	Experimental study	Remifentanyl/Morphine	Pre-term newborns (N=34)	Pharmacogenetic analyses	Predisposition to a slow opioid response in preterm newborns carrying the KCNJ6 -1250G.A and the COMT c.472G.A alleles
<i>Matic et al [86]</i>	Cohort study	Morphine	Pre-term newborns (N=34)	Pharmacogenetic analyses	The combined <i>OPRM1/COMT</i> 'high-risk' genotype led to a significant association with the need for rescue
<i>Hronová et al [87]</i>	Retrospective study	Sufentanil	Newborns (N=30)	Pharmacogenetic analyses	COMT and <i>ABCB1</i> polymorphism influence the sufentanil dosing
<i>Matic et al [88]</i>	Cohort study	Morphine	Pre-term newborns (N=15)	Pharmacogenetic analyses	The UGT2B7 -900G>A polymorphism significantly alters morphine pharmacokinetics in preterm infants.
<i>Matic et al. [89]</i>	Retrospective study	Methadone	Pre-term ill newborns and infants (N=50)	Pharmacogenetic analyses	Combination of <i>CYP2D6</i> and <i>SLC22A1/OCT1</i> polymorphism influence O-desmethyltramadol PK
<i>Dennis et al [91]</i>	Review	Methadone	/	Pharmacogenetic analyses	Methadone metabolism is significantly slower in *6 homozygous carriers
<i>Wachman al. [92]</i>	Cohort study	Methadone or buprenorphine	Infants treated for NOWS (N=68)	Epigenetic analyses	High levels of <i>OPRM1</i> methylation at specific CpG sites influence the increased NAS severity