

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/Fentanyl/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 |

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| <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 |

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| <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 |

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| <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 <i>CYP2D6</i> , <i>OPRM1</i> , and <i>COMT</i> 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 Hoogdale 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. |

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| <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 |

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| <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) |

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| <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 |

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| | | | | | 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 | Remifentanil/Morphine | Pre-term newborns (N=34) | Pharmacogenetic analyses | Predisposition to a slow opioid response in preterm newborns carrying the <i>KCNJ6</i> -1250G.A and the <i>COMT</i> 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 | <i>COMT</i> 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 <i>UGT2B7</i> -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 |