

Appendix 1. Literature Search

Databases	Years	Search Terms
Pubmed	01/1966 –	1. Analgesics, Opioid ^a / or Opioid-related Disorders ^a / or Heroin ^a / or Heroin Dependence ^a / or Morphine Dependence ^a / or Hydrocodone ^a / or Oxycodone ^a / or Oxymorphone ^a
PsycINFO	09/2016	2. Opiate ^b / or Opioid ^b / or Heroin ^b / or Morphine ^b / or Hydrocodone ^b / or Oxycodone ^b / or Oxymorphone ^b
EMBASE		3. Addict ^b / or Depend ^b / or Abuse ^b
Cochrane		4. 2 and 3
Clinicaltrials.gov		5. 1 or 4
		6. Buprenorphine ^a / or Methadone ^a / or Morphine ^a / or Inactivation, Metabolic ^a / or Narcotic Antagonists ^a / or Substance Withdrawal Syndrome ^a / or Opiate Substitution Treatment ^a
		7. Detox ^b / or Taper ^b / or Withdraw ^b / or Abstain ^b / or Abstinen ^b / or Buprenorphine ^b / or Methadone ^b / or Morphine ^b
		8. Intrauterine ^b and Withdrawal ^b and Syndrome ^b
		9. 6 or 7 or 8
		10. Pregnancy ^a / or Pregnant ^b / or Fetus ^a / or Fetus ^b / or Fetal ^b
		11. 5 and 9 and 10
		12. Labor, Obstetric ^a / or Delivery, Obstetric ^a / or Cesarean Section ^a / or Caesarean ^a / or Analgesia, Epidural ^a / or Analgesia, obstetrical ^a / or Anesthesia, Spinal ^a / or Anesthetics, Local ^a / or Anesthesia, Epidural ^a / or Anesthesia, Obstetrical ^a / or Pain, Postoperative ^a / or Postpartum Period ^a

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13. 11 not 12
14. Rats ^{a/} or Rats ^{b/} Or Rat ^{b/} or Rabbit ^{b/} or Mice ^{b/} or Mouse ^{b/} or Chick ^b
15. 13 not 14
16. 15 and Filters: Humans
17. 16 and Filters: English
18. 17 and Filters: Publication date from 1966/01/01 to 2016/12/31
19. 15 and Filters: Publication date from 2015/08/01 to 2016/12/31 (Non-indexed, “In Process” or Epub citations)
20. 18 or 19

Appendix 2. Risk of Bias Table for Evidence Regarding Opioid Detoxification During Pregnancy								
Author (year; country)	Bias Domains						Authors' Judgement	Support for Judgement
	Selection	Performance	Detection	Attrition	Reporting	Other		
Bell et al. (2016, USA)	+	+	+	+	+	+	High-risk	Non-randomized/observational design; lack of non-detox comparison population; lack of blinding; participants self-selected into detox intervention; participants who did not complete detox were excluded from analysis; participants in each group were chosen from different settings (jail and clinical settings)
Dooley et al. (2015, Canada)	+	+	+	-	-	-	High-risk	Non-randomized/observational design; lack of blinding; participants self-selected into detox intervention
Haabrekke et al. (2014, Norway)	+	+	+	+	-	+	High-risk	Non-randomized/observational design; lack of blinding; most participants self-selected into detox intervention; 5 (16%) of participants in cohort 2 were excluded from the analysis due to missing data; participants in cohorts 1 and 2 from different time periods
Stewart et. al (2013, USA)	+	-	+	+	+	-	High-risk	Non-randomized/observational design; lack of non-detox comparison population; participants self-selected into detox intervention; lost to follow-up data not reported (unclear # of patients who completed detox program, but did not deliver at study hospital)
Lund et al. (2012, USA)	+	+	+	+	-	+	High-risk	Non-randomized/observational design; lack of blinding; participants self-selected into detox intervention; 39 participants who did not complete detox and 4 with missing outcome data were excluded from analysis; data from detox arm was retrospectively collected and data from comparison arms was prospectively collected.
Jones et al. (2008, USA)	+	+	+	+	-	-	High-risk	Non-randomized/observational design; lack of blinding; participants self-selected into detox intervention; 103 patients who did not meet methadone maintenance criteria, 68 patients treated for alcohol or benzodiazepine withdrawal and 83 patients with missing data were excluded from analysis
Kahila et al. (2007, Finland)	+	+	+	-	-	-	High-risk	Non-randomized/observational design; lack of blinding; participants self-selected into detox intervention
Luty et al. (2003, UK)	+	+	+	+	+	+	High-risk	Non-randomized/observational design; lack of blinding; unclear description of proportion of participants withdrawn and lost to follow-up (only 24 (24%) with adequate obstetric records and only 10 of these completing detox; participants in experimental and control arms from different populations (control data was from "normal", non-substance using pregnant women).
Hulse et al. (2001, Australia, Portugal, UK)	+	+	+	?	+	+	High-risk	Non-randomized/observational design; lack of non-detox comparison population; lack of blinding; data from a participant who resumed opiate use excluded from analysis; unclear if participants who did not complete detox were excluded from analysis
Sinha et al. (2001, UK)	+	+	+	-	+	+	High-risk	Non-randomized/observational design; lack of blinding; participants self-selected into detox intervention (9 underwent a "self-directed cold turkey" withdrawal); unclear if detox was attempted for the entire cohort

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Dashe et al. (1998, USA)	+	+	+	+	+	-	High-risk	Non-randomized/observational design; lack blinding; lack of non-detox comparison population; participants self-selected into detox intervention; women who did not remain in the hospital > 24 hours were excluded from analysis; outcomes for patients who did not undergo detox were not reported
Kyei-Aboagye et al. (1998, USA)	+	+	+	?	-	+	High-risk	Non-randomized/observational design; lack of blinding; participants self-selected into detox intervention (80% of patients screened did not agree to residential living for 12-18 months); unclear if patients not agreeing to residential detox program were included in the comparison population; participants in experimental and control arms from different populations (30 women in control arm with cocaine abuse)
LePreau et al. (1995, USA)	+	+	+	+	+	-	High-risk	Non-randomized/observational design; lack of blinding; lack of non-detox comparison population 13 (39.4%); participants did not have outcomes available for analysis including all 10 women who did not complete the detox intervention; among 20 participants with outcomes, 14 terminated their pregnancies and 1 had a miscarriage.
Mass et al. (1990, Germany)	+	+	+	-	?	-	High-risk	Non-randomized/observational design; lack of blinding; 8 participants had not completed detox at time of delivery; lost to follow-up data not recorded; 1 participant excluded due to lack of UDS at delivery; neonatal outcomes analyzed by UDS at delivery and not by enrollment classification.
Wallach et al. (1975, USA)	+	+	+	+	+	-	High-risk	Non-randomized/observational design; lack of blinding; participants self-selected into detox intervention; 200 patients (67%) were lost to follow-up and excluded from analysis

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Appendix 3. Summary of Evidence for Adverse Maternal and Neonatal Outcomes							
Author	Completed detox, n (%)	Illicit drug use, n (%) ^a	Fetal demise, n	Fetal growth/birthweight mean (± SD) ^b	Preterm birth, n (%)	NAS, n (%) ^c	Neonatal LOS (days), mean (± SD) ^b
Bell et al.	NR	Detox 1: 25 (23.1) Detox 2: 4 (17.4) Detox 3: 57 (74.0) Detox 4: 21 (22.5)	n=2 (18 and 34 wks)	IUGR (< 5%), n=16 (5%)	Detox 1: 21 (19) Detox 2: 3 (13) Detox 3: 13 (17) Detox 4: 16 (17)	Detox 1: 20 (18.5) Detox 2: 4 (17.4) Detox 3: 54 (70.1) Detox 4: 16 (17.2)	NR
Dooley et al.	8 (9.3)	30 (34.8)	Detox: n=2 (GA NR) OUD control: n=1 (GA NR) Non-OUD control: n=4 (GA NR)	Detox: 3301 (507) g*** OUD control: 3512 (530) g Non-OUD control: 3537 (558) g	Detox: 5 (5.8) OUD control: 3 (3.8) Non-OUD control: 24 (5.5)	Detox: 11 (12.8) ^{d***} OUD control: 5 (6.2) Non-OUD control 2: 0 (0)	Detox: 2.4 (1.5) ^{e***} OUD control: 1.7 (1.1) Non-OUD control 2: 1.7 (0.9)
Haabrekke et al.	21 (100)	0 (0)	0 (0)	Detox: 3293 (428) g SUD control: 3022 (715) g Non-OUD control: 3707 (455) g Non-OUD control: 3720 (433) g	Detox: 0 (0) SUD control: 20 (25.6) Non-OUD control: 1 (1.7) Non-OUD control: 0 (0)	Detox: 0 (0) *** SUD control: 60 (76.9) Non-OUD control: 0 (0) Non-OUD control: 0 (0)	NR
Stewart et al.	76 (80)	42 (44.2)	n=3 (20 wks, GA NR for 2)	Detox only: 3065 (487) g** Detox + opioids: 2788 (516) g	Detox only: 5 (10) Detox + opioids: 7 (18)	Detox only: 5 (10)*** Detox + opioids: 33 (80)	Detox only: 3 [2, 6] ^{e***} Detox + opioids: 22 [15, 26]
Lund et al.	8 (15.7) ^e	Detox: 1 (14.3) OUD + MM control: 2 (16.7) OUD + BM control: 0 (0)	0 (0)	Detox: 3023.0 (220.9) g OUD + MM control: 2849.6 (180.4) g OUD + BM control: 2911.0 (279.4) g	Detox: 3 (37.5) OUD + MM control: 4 (25.0) OUD + BM control: 1 (20.0)	Detox: 2 (25.0) OUD + MM control: 8 (66.7) OUD + BM control: 2 (40.0)	Detox: 7.0 (3.4) OUD + MM control: 24.2 (5.1) OUD + BM control: 9 (4.8)
Jones et al.	Detox 1: 67 (89.3) Detox 2: 28 (58.3)	Detox 1: 35 (53.0)*** Detox 1 + MM: 2 (33.3) Detox 2: 16 (57.1) Detox 2 + MM: 3 (15.0) OUD + MM control: 12 (23.1)	Detox 1: 0 (0) Detox 2: n=3 (5, 10 and 26 wks) OUD + MM control: n=3 (13, 14, 20 wks)	Detox 1: 2834 (437.7) g Detox 1 + MM: 3054.1 (88.7) g Detox 2: 2823.9 (478.1) g Detox 2 + MM: 2987.0 (132.0) g OUD + MM control: 2819.1 (577.8) g	Detox 1: 18 (26.9) Detox 1 + MM: 1 (12.5) Detox 2: 10 (35.7) Detox 2 + MM: 2 (10.0) OUD + MM control: 10 (19.2)	Detox 1: 17 (25.0) Detox 1 + MM: 2 (29) Detox 2: 10 (36.0) Detox 2 + MM: 3 (15) OUD + MM control: 14 (27)	Detox 1: 9.6 (7.0) Detox 1 + MM: 7.9 (4.8) Detox 2: 8.9 (4.8) Detox 2 + MM: 6 (4.3) OUD + MM control: 12.8 (16.7)
Kahila et al.	9 (13.4)	Detox only: 4 (44.4) Detox + BM 1: 7 (33.3) Detox + BM 2: 17 (45.9)	0 (0) ^h	All detox: 3180 (503) g*** Non-OUD control: 3512 g	Detox only: 0 (0) Detox + BM 1: 1 (4.7) Detox + BM 2: 2 (5.4)	Detox only: 2 (22)*** Detox + BM 1: 21 (100) Detox + BM 2: 30 (81)	Detox only: 11.6** Detox + BM 1: 28.1 Detox + BM 2: 15.7
Luty et al.	42 (41.6)	23 (95.8)	n=1 (9 wks)	2564 g (SE=171 g)	NR	NR	NR
Hulse et al.	NR ⁱ	3 (16.7)	0 (0)	3008 (297) g	0 (0)	NR	NR
Sinha et al.	10 (19.6)	19 (37.3)	n=1 (GA NR)	Detox only: 3008 g Detox + MM: 2868 g Detox + opioids: 2754 g	NR	Detox only: 0 (0)*** Detox + MM: 17 (77)	Detox only: 7.8* Detox + MM: 10.3 Detox + opioids: 33.2

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						Detox + opioids: 13 (81)	
Dashe et al.	25 (73.5) ^j	10 (29.4)	0 (0)	Detox only: 3110 (450) g Detox + MM: 2975 (190) g Detox + opioids: 3044 (729) g	Detox only: 20% (6,44) Detox + MM: 25% (1,81) Detox + opioids: 10% (1,45)	Detox only: 15% (3,38) Detox + MM: 25% (1,81) Detox + opioids: 10% (1,45)	Detox only: 8 (7-32) Detox + MM: 31 Detox + opioids: 1
Kyei-Aboagye et al.	30 (100.0)	0 (0)	0 (0)	Detox: 3218 (596) g*** SUD control: 2806 (317) g	NR	NR	Detox: 3.0 (0.5) *** SUD control: 5.5 (2.5)
LePreau et al.	23 (69.7)	NR	n=1 (21 wks)	3008 g	NR	NR	NR
Mass et al.	17 (29.8)	32 (56.1)	0 (0) ^k	Detox only: 3070 g Detox + MM: 2625 g Detox + opioids: 2725 g OUD control: 2770 g	Detox only: 2 (11.8) Detox + MM: 4 (50) Detox + opioids: 12 (37.5) OUD control: 5 (29.4)	Detox only: 2 (11.8) Detox + MM: 6 (75.0) Detox + opioids: 24 (75.0) OUD control: 15 (88.2)	NR
Wallach et al.	NR	100 (100) ^l	Detox: n=1 (24 wks) OUD + MM control: n=9 (GA NR)	Detox: LBW, n=34 (34) OUD + MM control: 2700 (490) g	Detox: NR OUD + MM control: 30%	Detox: NR OUD + MM control: 58%	Detox: NR OUD + MM control: 15 (7-30)

Abbreviations: NR=not reported; NAS=neonatal abstinence syndrome; LOS=length of stay; IUGR=intrauterine growth restriction; GA=gestational age; SUD=substance use disorder; MM=methadone maintenance; BM=buprenorphine maintenance; SD=standard deviation; wks=weeks; g=grams

^adefined as a positive maternal urine drug screen or neonatal meconium sample at the time of delivery; ^bmean (± SD) unless otherwise specified; ^cNAS treatment rate unless otherwise specified; ^dall infants “roomed in” with their mothers; ^elength of stay does not include 7-10 day stay in outpatient facility for follow-up and NAS surveillance; ^fmedian [first quartile, third quartile]; ^gn=51 initiated detox and data for women who did not complete detox were NR; ^h2 SIDS cases (2.5 and 5 months); ⁱ2 patients were maintained on naltrexone for the remainder of their pregnancy; ^jn=4 women delivered during hospitalization for detox; ^kn=1 neonatal death; ^ln=2 women died of overdose at 2 and 6 weeks postpartum; *p<0.05; **p<0.01; ***p<0.001

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Appendix 4. Summary of Maternal and Neonatal Outcomes Reported In Included Studies

	Bell et al.	Dooley et al.	Haabrekke et al.	Stewart et al.	Lund et al.	Jones et al.	Kahila et al.	Luty et al.	Hulse et al.	Sinha et al.	Dashe et al.	Kyei-Aboagye et al.	LePreau et al.	Mass et al.	Wallach et al.
Fetal Outcomes															
Fetal demise (IUFD, SAB)	✓	✓	-	✓	-	✓	✓	✓	-	✓	✓	-	✓	-	✓
Fetal distress during detoxification	-	-	-	-	-	-	-	-	-	✓	✓	-	-	-	✓
Intrauterine growth restriction (IUGR)	✓	-	-	✓	-	-	-	-	-	✓	✓	-	-	-	-
Obstetric/Delivery Outcomes															
Induction of labor	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	-
Mode of delivery	-	✓	-	-	✓	-	✓	✓	✓	✓	✓	-	-	-	✓
Analgesia during delivery	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-
Breech/malpresentation	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	✓
Preterm birth (<37 weeks)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	-	✓	-
Preterm premature rupture of membranes (PPROM)	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	✓
Abruption	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓
Gestational age at delivery	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	-	✓	-
APGARs	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	-	-	✓
Birthweight	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Low birthweight (LBW)	-	-	-	✓	-	✓	✓	✓	✓	✓	✓	✓	-	✓	✓
Umbilical cord blood gases	-	✓	-	✓	-	-	✓	-	-	-	-	-	-	-	-
Meconium stained fluid	-	-	-	-	-	-	-	-	-	-	✓	-	-	-	✓
Postpartum hemorrhage rate	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓
Neonatal Outcomes															
NAS rate	-	✓	-	✓	-	-	✓	-	-	✓	✓	-	-	-	-
NAS treatment rate	✓	✓	✓	✓	✓	✓	✓	-	-	✓	✓	-	-	-	✓
NAS treatment duration	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-
Finnegan scores	-	✓	-	✓	✓	-	-	-	-	-	-	-	-	-	-
Neonatal length of stay	-	✓	-	✓	✓	✓	✓	-	-	✓	-	✓	-	-	✓
Neonatal length	-	✓	-	-	✓	✓	-	-	-	-	-	-	-	-	-
Neonatal head circumference (HC)	-	✓	✓	-	✓	✓	-	-	✓	-	-	-	-	✓	-
Neonatal urine toxicology	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	-
NICU admission rate	-	-	-	-	-	✓	✓	-	-	✓	-	-	-	-	-
Respiratory distress	-	-	-	-	-	-	-	-	-	-	✓	-	-	✓	-
Neonatal death	-	-	-	-	-	-	-	-	-	-	✓	-	-	-	✓
Child welfare involvement	-	-	-	-	-	-	✓	-	-	-	-	-	-	✓	-
SIDS	-	-	-	-	-	-	✓	✓	-	-	-	-	-	-	-

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Maternal outcomes															
Detoxification completion rate	-	✓	✓	✓	-	-	✓	✓	✓	✓	✓	-	✓	✓	✓
Illicit drug use/relapse rate	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	✓	✓
Prenatal care attendance	-	-	✓	-	✓	✓	-	-	-	-	-	-	-	-	-
Maternal weight gain	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-
Maternal overdose death rate	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓
Maternal length of stay during delivery	-	✓	-	-	-	-	✓	-	-	-	-	-	-	-	-

Abbreviations: IUFD=intrauterine fetal demise; NAS=neonatal abstinence syndrome; HC=head circumference; GA=gestational age; SAB=spontaneous abortion; NICU=neonatal intensive care unit; SIDS=sudden infant death syndrome

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