Evidence evaluation report — Substance use

Draft 22 May 2017

Contents

PROCESS OF THE REVIEW

Research questions

1. What are the maternal and perinatal outcomes associated with substance use during pregnancy?
2. How can the harms associated with substance use in pregnancy be reduced?
3. What are the additional considerations for Aboriginal and Torres Strait Islander women?

Note: Substance use includes use of amphetamines (speed), crystal methamphetamine (ice), heroin, cocaine, LSD, ecstasy, cannabis (marijuana) and non-medical use of prescription medications.

Search strategy

Two searches were conducted as the Expert Working Group requested further information on non-medical use of pharmaceuticals.

INITIAL SEARCH

Databases searched:

- MEDLINE (OVID) and PSYCHINFO (OVID) = 404
- COCHRANE LIBRARY = 20
- CINAHL = 12
- EMBASE = 475
- AUSTRALIAN INDIGENOUS HEALTHINFONET = 2

Date of searches: 07/03/2017

Dates searched: 2008 to present

Full search strategies

MEDLINE AND PSYCHINFO (OVID)

1. Meta-Analysis as Topic/
2. meta analy$.tw.
3. metaanaly$.tw.
4. Meta-Analysis/
5. (systematic adj (review$1 or overview$1)).tw.
6. exp Review Literature as Topic/
7. or/1-6
8. cochrane.ab.
9. embase.ab.
10. (psychlit or psyclit).ab.
11. (psychinfo or psycinfo).ab.
12. (cinahl or cinhal).ab.
13. science citation index.ab.
14. bids.ab.
15. cancerlit.ab.
16. or/8-15
17. reference list$.ab.
18. bibliograph$.ab.
19. hand-search$.ab.
20. relevant journals.ab.
21. manual search$.ab.
22. or/17-21
23. selection criteria.ab.
24. data extraction.ab.
25. 23 or 24
26. Review/
27. 25 and 26
28. Comment/
29. Letter/
30. Editorial/
31. animal/
32. human/
33. 31 not (31 and 32)

34. or/28-30,33
35. 7 or 16 or 22 or 27
36. 35 not 34
37. ((illicit adj1 substance$) or (illicit adj1 drug$) or (street adj1 drug$) or (designer adj1 drug$) or amphetamine$ or methamphetamine$ or ice or heroin or cocaine or LSD or (lysergic acid diethylamide) or ecstasy or cannabis or marijuana).ti.
38. Exp Street drugs/ or Exp Designer drugs/ or Exp Amphetamines/ or Exp Amphetamine-Related Disorders/ or Exp Heroin/ or Exp Opioid-Related Disorders/ or Exp Cocaine/ or Exp Cocaine-Related Disorders/ or Exp Lysergic acid diethylamide/ or Exp Cannabis/ or Exp Marijuana Abuse/ or Exp Substance Abuse, Intravenous/
39. (pregnan$ or antepart$ or prenatal$ or antenatal$ or perinatal$ or obstetric$ or maternal$).ti.
40. exp Pregnancy/ or exp Pregnancy Complications/ or exp Perinatal Care/ or exp Prenatal Care/
41. 37 or 38
42. 39 or 40
43. 36 and 41 and 42
44. Remove duplicates from 43
45. Limit 44 to 2008-Current

COCHRANE

1. ((illicit next substance*) or (illicit next drug*) or (street next drug*) or (designer next drug*) or amphetamine* or methamphetamine* or ice or heroin or cocaine or LSD or (lysergic acid diethylamide) or ecstasy or cannabis or marijuana).ti.
2. MeSH descriptor: [Street drugs] explode all trees
3. MeSH descriptor: [Designer drugs] explode all trees
4. MeSH descriptor: [Amphetamines] explode all trees
5. MeSH descriptor: [Amphetamine-Related Disorders] explode all trees
6. MeSH descriptor: [Heroin] explode all trees
7. MeSH descriptor: [Opioid-Related Disorders] explode all trees
8. MeSH descriptor: [Cocaine] explode all trees
9. MeSH descriptor: [Cocaine-Related Disorders] explode all trees
10. MeSH descriptor: [Lysergic acid diethylamide] explode all trees
11. MeSH descriptor: [Cannabis] explode all trees
12. MeSH descriptor: [Marijuana Abuse] explode all trees
13. MeSH descriptor: [Substance Abuse, Intravenous] explode all trees
14. (pregnan* or antepart* or prenatal* or antenatal* or perinatal* or obstetric* or maternal*):ti
15. MeSH descriptor: [Pregnancy] explode all trees
16. MeSH descriptor: [Pregnancy Complications] explode all trees
17. MeSH descriptor: [Perinatal Care] explode all trees
18. MeSH descriptor: [Prenatal Care] explode all trees
19. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
20. #14 or #15 or #16 or #17 or #18
21. #19 and #20
22. 2008 to current

CINAHL

1. TI ((illicit N1 substance*) or (illicit N1 drug*) or (street N1 drug*) or (designer N1 drug*) or amphetamine* or methamphetamine* or ice or heroin or cocaine or LSD or (lysergic acid diethylamide) or ecstasy or cannabis or marijuana)
2. (MH "Street drugs+") or (MH "Designer drugs+") or (MH "Amphetamines+") or (MH "Amphetamine-Related Disorders+") or (MH "Heroin+") or (MH "Opioid-Related Disorders+") or (MH "Exp Cocaine+") or (MH "Cocaine-Related Disorders+") or (MH "Lysergic acid diethylamide+") or (MH "Cannabis+") or (MH "Marijuana Abuse+") or (MH "Substance Abuse, Intravenous+")
3. TI (pregnan* or antepart* or prenatal* or antenatal* or perinatal* or obstetric* or maternal*)
4. (MH "Pregnancy+") or (MH "Pregnancy Complications+") or (MH "Perinatal Care+") or (MH "Prenatal Care+")
5. S1 or S2
6. S3 or S4
7. S5 AND S6
8. ((TI (systematic* n3 review*)) or (AB (systematic* n3 review*)) or (TI (systematic* n3 bibliographic*)) or (AB (systematic* n3 bibliographic*)) or (TI (systematic* n3 literature)) or (AB (systematic* n3 literature)) or (TI (comprehensive* n3 literature)) or (AB (comprehensive* n3 literature)) or (TI (comprehensive* n3 bibliographic*)) or (AB (comprehensive* n3 bibliographic*)) or (TI (integrative n3 review)) or (AB (integrative n3 review)) or (JN "Cochrane

Database of Systematic Reviews") or (TI (information n2 synthesis)) or (TI (data n2 synthesis)) or (AB (information n2 synthesis)) or (AB (data n2 synthesis)) or (TI (data n2 extract*)) or (AB (data n2 extract*)) or (TI (medline or pubmed or psyclit or cinahl or (psycinfo not "psycinfo database") or "web of science" or scopus or embase)) or (AB (medline or pubmed or psyclit or cinahl or (psycinfo not "psycinfo database") or "web of science" or scopus or embase)) or (MH "Systematic Review") or (MH "Meta Analysis") or (TI (meta-analy* or metaanaly*)) or (AB (meta-analy* or metaanaly*)))

9. S7 AND S8 [limit to 2008 onwards]

EMBASE

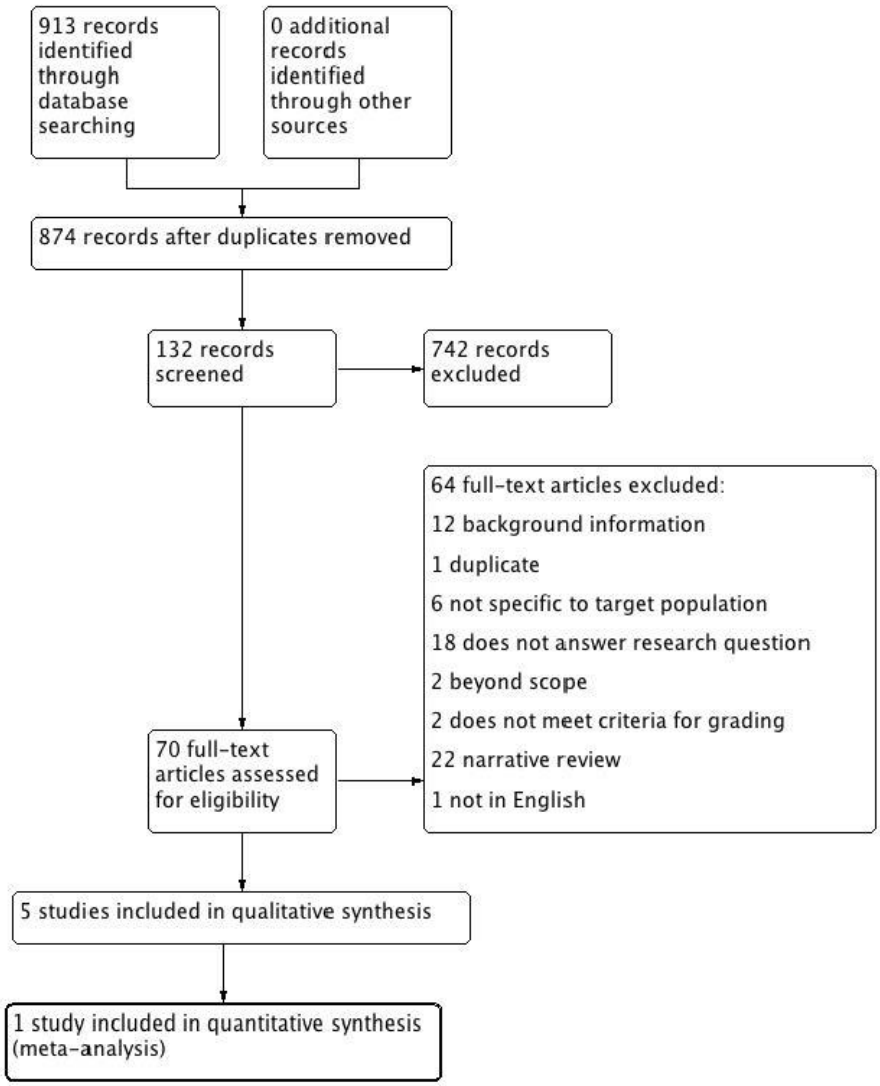
1. 'pregnancy'/exp OR 'pregnancy complication'/exp OR 'perinatal care'/exp OR 'prenatal care'/exp
2. pregnan$:ti OR antepart$:ti OR prenatal$:ti OR antenatal$:ti OR perinatal$:ti OR obstetric$:ti OR maternal$:ti
3. 'street drug'/exp OR 'designer drug'/exp OR 'amphetamine'/exp OR 'amphetamine dependence'/exp OR 'diamorphine'/exp OR 'opiate addiction'/exp OR 'cocaine'/exp OR 'cocaine dependence'/exp OR 'lysergide'/exp OR 'cannabis'/exp OR 'cannabis addiction'/exp OR 'substance abuse'/exp
4. (illicit NEXT/1 substance$):ti OR (illicit NEXT/1 drug$):ti OR (street NEXT/1 drug$):ti OR (designer NEXT/1 drug$):ti OR amphetamine$:ti OR methamphetamine$:ti OR ice:ti OR heroin:ti OR cocaine:ti OR lsd:ti OR (lysergic:ti AND acid:ti AND diethylamide:ti) OR ecstasy:ti OR cannabis:ti OR marijuana:ti
5. #1 OR #2
6. #3 OR #4
7. #5 AND #6
8. #7 AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py) AND 'review'/it
9. #8 AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py) AND ('meta analysis'/de OR 'meta analysis (topic)'/de OR 'systematic review'/de OR 'systematic review (topic)'/de)
10. #8 OR #9

AUSTRALIAN INDIGENOUS HEALTHINFONET

Title: substance AND pregnancy

Title: drug AND pregnancy

2008 to current



PRISMA flow diagram — initial review

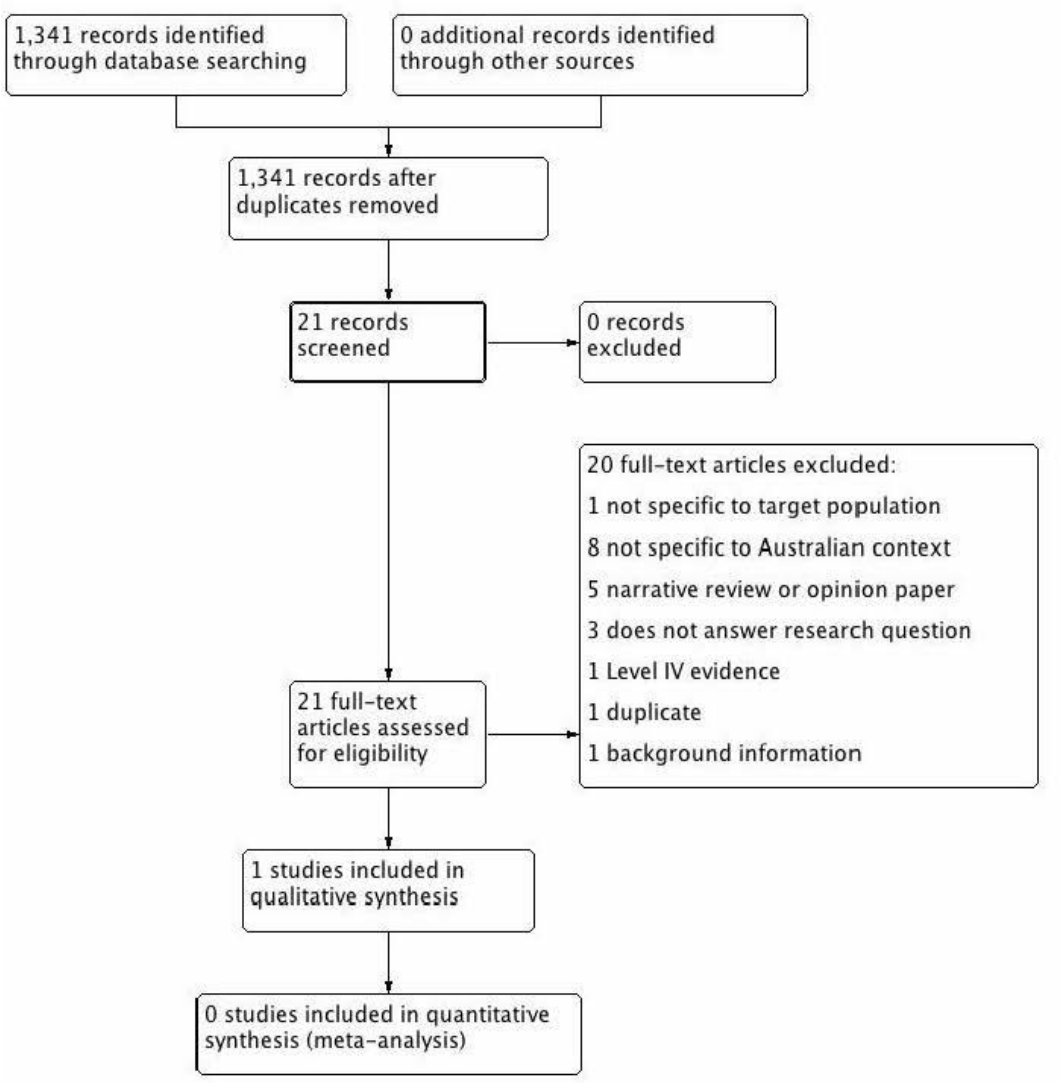
NON-MEDICAL USE OF PHARMACEUTICALS

Databases searched:

- MEDLINE = 827
- EMBASE = 514

Date of searches: 04/05/2017

Dates searched: 2008 to present



PRISMA flow diagram — non-medical use of pharmaceuticals

Full search strategy
MEDLINE (and EMBASE)

1. Prescription
2. Misuse
3. Abuse
4. Drugs
5. Pregnancy
6. Prescription or Drugs
7. Misuse or Abuse
8. Pregnancy
9. 6 and 7 and 8
10. Limit 9 to 2008-Current

Exclusion criteria

As outlined in the PRISMA flow diagrams above, the exclusion criteria applied to studies were:

- background information
- duplicate
- not specific to target population (eg specific to non-pregnant women or high-risk women) or health care setting
- does not answer research question

- beyond scope of guidelines
- does not meet criteria for grading (eg no outcomes reported or reporting too limited to establish risk of bias, conference abstract, study protocol)
- narrative review or opinion paper (editorial, letter, summary, comment, interview)
- not in English

No studies specific to outcomes or interventions among Aboriginal and Torres Strait Islander women were identified.

Assigning level of evidence

Levels of evidence were assigned using the NHMRC levels and the following definitions.

Level	Intervention
I	Systematic review of level II studies
II	A randomised controlled trial
III-1	Pseudo-randomised trial
III-2	A comparative study with concurrent controls: • Non-randomised experimental trial • Cohort study • Case-control study • Interrupted time series with control group
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study ▪ Interrupted time series without parallel control
IV	Case series with either post-test or pre-test/post-test outcomes

Study design definitions

- **All or none** — all or none of a series of people (case series) with the risk factor(s) experience the outcome. The data should relate to an unselected or representative case series, which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination. This is a rare situation.
- **Case series** — a single group of people exposed to the intervention (factor under study). **Post-test** – only outcomes after the intervention (factor under study) are recorded in the series of people, so no comparisons can be made. **Pre-test/post-test** – measures on an outcome are taken before and after the intervention is introduced to a series of people and are then compared (also known as a 'before- and-after study').
- **Case-control study** — people with the outcome or disease (cases) and an appropriate group of controls without the outcome or disease (controls) are selected and information obtained about their previous exposure/non-exposure to the intervention or factor under study.
- **Cross-sectional study** — a group of people are assessed at a particular point (or cross-section) in time and the data collected on outcomes relate to that point in time ie proportion of people with asthma in October 2004. This type of study is useful for hypothesis-generation, to identify whether a risk factor is associated with a certain type of outcome, but more often than not (except when the exposure and outcome are stable eg. genetic mutation and certain clinical symptoms) the causal link cannot be proven unless a time dimension is included.
- **Historical control study** – outcomes for a prospectively collected group of people exposed to the intervention (factor under study) are compared with either (1) the outcomes of people treated at the same institution prior to the introduction of the intervention (ie. control group/usual care), or (2) the outcomes of a previously published series of people undergoing the alternate or control intervention.

- **Interrupted time series with a control group** – trends in an outcome or disease are measured over multiple time points before and after the intervention (factor under study) is introduced to a group of people, and then compared to the outcomes at the same time points for a group of people that do not receive the intervention (factor under study).
- **Interrupted time series without a parallel control group** – trends in an outcome or disease are measured over multiple time points before and after the intervention (factor under study) is introduced to a group of people, and compared (as opposed to being compared to an external control group).
- **Non-randomised, experimental trial** - the unit of experimentation (eg. people, a cluster of people) is allocated to either an intervention group or a control group, using a non-random method (such as patient or clinician preference/availability) and the outcomes from each group are compared. This can include:
  - **a controlled before-and-after study**, where outcome measurements are taken before and after the intervention is introduced, and compared at the same time point to outcome measures in the (control) group.
  - **an adjusted indirect comparison**, where two randomised controlled trials compare different interventions to the same comparator ie. the placebo or control condition. The outcomes from the two interventions are then compared indirectly.
- **Prospective cohort study** — where groups of people (cohorts) are observed at a point in time to be *exposed or not exposed* to an intervention (or the factor under study) and then are followed prospectively with further outcomes recorded as they happen.
- **Pseudo-randomised controlled trial** - the unit of experimentation (eg. people, a cluster of people) is allocated to either an intervention (the factor under study) group or a control group, using a pseudo-random method (such as alternate allocation, allocation by days of the week or odd-even study numbers) and the outcomes from each group are compared.
- **Randomised controlled trial** — the unit of experimentation (eg. people, or a cluster of people4) is allocated to either an intervention (the factor under study) group or a control group, using a random mechanism (such as a coin toss, random number table, computer-generated random numbers) and the outcomes from each group are compared.
- **Retrospective cohort study** — where the cohorts (groups of people exposed and not exposed) are defined at a point of time in the past and information collected on subsequent outcomes, eg. the use of medical records to identify a group of women using oral contraceptives five years ago, and a group of women not using oral contraceptives, and then contacting these women or identifying in subsequent medical records the development of deep vein thrombosis.
- **Systematic literature review** — systematic location, appraisal and synthesis of evidence from scientific studies.
- **Two or more single arm study** – the outcomes of a single series of people receiving an intervention (case series) from two or more studies are compared.

Source: NHMRC (2009) *NHMRC levels of evidence and grades of recommendations for developers of guidelines.*

Selection of outcomes for GRADE analysis

Outcomes considered for inclusion factors associated with substance use in pregnancy. Outcomes were selected on the basis of clinical impact.

Outcome	Importance	Inclusion
Maternal outcomes		
Retention of women in treatment	7	☑
Continued substance use	9	☑
Anaemia	8	
Perinatal outcomes		
Low birth weight	9	☑
Preterm birth	9	☑
Growth restriction	9	
Apgar score	8	☑
Neonatal abstinence syndrome	9	☑
Perinatal mortality	9	
Neurobehavioural function in the infant	9	

Key: 1 – 3 less important; 4 – 6 important but not critical for making a decision; 7 – 9 critical for making a decision

Evidence tables

1. What are the maternal and perinatal outcomes associated with substance use during pregnancy?

The evaluation of the evidence for outcomes associated with illicit substance use in pregnancy was limited to systematic reviews. Studies included in the identified reviews were observational. A cohort study that provided information on outcomes associated with misuse of opioids was also included.

Maternal outcomes

- *Marijuana use in pregnancy* — A review (that did not adjust for confounders) found an increase in risk of anaemia (OR 1.36: 95%CI 1.10 to 1.69) (Gunn et al 2016).

Perinatal outcomes

- *Amphetamine use in pregnancy* — Significant increases in unadjusted risks of preterm birth (OR 4.11; 95%CI, 3.05 to 5.55), low birthweight (OR 3.97; 95%CI, 2.45 to 6.43), and small for gestational age (OR 5.79; 95%CI 1.39 to 24.06) were identified and mean birthweight was significantly lower (MD –279 g; 95% CI, –485 to -74 g) (Ladhani et al 2011).
- *Cocaine use in pregnancy* — There was an association with significantly higher risk of preterm birth (OR 3.38; 95%CI 2.72 to 4.21), low birthweight (OR 3.66; 95%CI 2.90 to 4.63), and small for gestational age infants (OR 3.23; 95%CI 2.43 to 4.30), as well as shorter gestational age at delivery (–1.47 wk; 95%CI –1.97 to –0.98 wk) and reduced birthweight (–492 g; 95%CI –562 to –421 g) (Gouin et al 2011).
- *Marijuana use in pregnancy* — One review (n=31) found an association with increased risk of low birth weight (RR 1.43, 95%CI 1.27 to 1.62) and preterm delivery (RR 1.32, 95%CI 1.14-1.54) but, when pooled data were adjusted for tobacco use and other confounding factors, there was no statistically significant difference (birth weight RR 1.16, 95%CI 0.98 to 1.37; preterm birth RR 1.08, 95%CI 0.82 to 1.43) (Conner et al 2016). Another review that did not adjust for confounders found an increase in risk of low birth weight (OR 1.77; 95%CI 1.04 to 3.01; MD 109.42 g: 38.72 to 180.12 g) (Gunn et al 2016).
- *Opioid dependence in pregnancy* — A review of neurobehavioural function in infants found non-significant mean effect sizes in favour of non-opioid exposed controls for cognition (0.24, Z=1.41, p=0.16, 95%CI −0.09 to 0.58), psychomotor function (0.28, Z=1.67, p=0.09, 95%CI −0.05 to 0.61) and behaviour (corrected mean 1.21, Z=1.30, p=0.19; 95%CI −0.61 to 3.03) (Baldacchino et al 2014).

A cohort study (Maeda et al 2014) found that births associated with maternal opioid abuse or dependence compared with those without opioid abuse or dependence were associated with an increased odds of maternal death during hospitalisation (aOR 4.6; 95%CI 1.8 to 12.1; cardiac arrest (aOR 3.6; 95% CI 1.4 to 9.1), intrauterine growth restriction (aOR 2.7; 95%CI, 2.4 to 2.9), placental abruption (aOR 2.4; 95%CI 2.1 to 2.6), length of stay >7 days (aOR 2.2; 95%CI 2.0 to 2.5), preterm labor (aOR 2.1; 95%CI 2.0 to 2.3), oligohydramnios (aOR 1.7; 95%CI 1.6 to 1.9), transfusion (aOR 1.7; 95% CI 1.5 to 1.9), stillbirth (aOR 1.5; 95%CI 1.3 to 1.8), premature rupture of membranes (aOR 1.4; 95%CI 1.3 to 1.6) and cesarean section (aOR 1.2; 95%CI 1.1 to 1.3).

No studies were identified that investigated outcomes associated with the use of crystal methamphetamine, LSD or ecstasy in pregnancy.

Background information

Prevalence of illicit substance use in Australia

The National Drug Survey reported that in Australia in 2013 (AIHW 2014):

- among pregnant women, a small minority had used illicit drugs — 2.4% before knowledge of their pregnancy and 1.6% after they knew they were pregnant
- regardless of whether women knew they were pregnant or not, 2.2% had used an illicit drug such as marijuana and 0.9% had misused prescription analgesics.

International recommendations on screening for substance use in pregnancy

The World Health Organization has developed recommendations on screening for substance use in pregnancy using GRADE processes (WHO 2014). However, their relevance to this review is limited as the analysis included only one study (n=30) that was specific to substances other than alcohol and it involved women in the postnatal period.

The recommendations and commentary are given below.

1 Health-care providers should ask all pregnant women about their use of alcohol and other substances (past and present) as early as possible in the pregnancy and at every antenatal visit (strong recommendation; low quality evidence).

- Asking at every visit is important as some women are more likely to report sensitive information only after a trusting relationship has been solidly established.
- Pregnant women should be advised of the potential health risks to themselves and to their babies posed by alcohol and drug use.
- Validated screening instruments for alcohol and other substance use and use disorders are available.
- Health-care providers should be prepared to intervene or refer all pregnant women who are identified as using alcohol and/or drugs (past and present).
- It was decided that despite the low quality of evidence of effect, the benefit – potential reduction of alcohol and substance use – outweighed any potential harms of a brief psychosocial intervention, which were considered minimal. Therefore the balance of benefits versus harms was clearly positive despite uncertainty about the degree of benefit. In addition, the burden of implementation was minimal.

2 Health-care providers should offer a brief intervention to all pregnant women using alcohol or drugs (strong recommendation; low quality evidence).

- Brief intervention is a structured therapy of short duration (typically 5–30 minutes) offered with the aim of assisting an individual to cease or reduce the use of a psychoactive substance. It is designed in particular for general practitioners and other primary health-care workers.
- Health-care providers should be given appropriate training and resource materials.
- The brief intervention should be individualised, and include feedback and advice on ceasing or reducing alcohol and other substance use during pregnancy. There may need to be follow-up with the patient, with the possibility of referral to treatment for those patients who are unable to reduce or eliminate such use.
- The approach/attitude of health-care providers is an important contributor to the effectiveness of brief interventions.
- As for recommendation 1, it was decided that despite the low quality of evidence of effectiveness, this should be a strong recommendation because the potential benefit – reduction of alcohol and/other substance use – likely outweighs any potential harms of a brief psychosocial intervention which were considered minimal. Therefore the balance of benefits versus harms was clearly positive, although there was uncertainty about the degree of benefit. In addition the burden of implementation was minimal.

Advice to the EWG

- Include information on outcomes from the evidence evaluation in the narrative.
- Consider including the following consensus-based recommendation and including other relevant information from the WHO guidelines in the narrative.

Consensus-based recommendation

Early in pregnancy, assess a woman's use of illicit substances and provide advice about the associated harms.

- Include in the narrative relevant information from background studies and guidelines.

1.1 Amphetamines (speed)

Study ref	Study design	LoE	Sample size	Aim/methods	Findings	Comments
(Ladhani et al 2011)	SLR	IV	10 cohort studies	**Aim**: to systematically review the relationship between amphetamine exposure in pregnancy and birth outcomes. **Methods**: Electronic databases were searched to identify relevant studies. Data from included studies were extracted by 2 reviewers. Summary odds ratio (OR) and confidence intervals (Cis) were calculated using the random effects model.	Significant increases in unadjusted risks of preterm birth (OR 4.11; 95%CI, 3.05 to 5.55), low birthweight (OR 3.97; 95%CI, 2.45 to 6.43), and small for gestational age (OR 5.79; 95%CI 1.39 to 24.06) were identified among women exposed to amphetamines in pregnancy. Mean birthweight was significantly lower among amphetamine-exposed pregnancies (MD –279 g; 95% CI, –485 to -74 g). Two studies provided adjusted estimates on different outcomes, and their results were consistent with the findings from the unadjusted data.	

1.2 Opioids

Study ref	Study design	LoE	Sample size	Aim/methods	Findings	Comments
(Baldacchino et al 2014)	SLR	IV	5 case-control studies 33–143 subjects 45–85 controls	**Aim**: To determine whether infants (mean age 14.1 mth) and children born to opioid dependent mothers have impaired neurobehavioral function. **Methods**: Quantitative and systematic review of the literature on the consequences of chronic maternal opioid use during pregnancy on neurobehavioral function of children was conducted. We searched Cinahl, EMBASE, PsychINFO and MEDLINE between the periods of January 1995 to January 2012.	*Cognition*: Pooling of results (4 studies; n=251 exposed; n=315 non-exposed) revealed a non-significant effect size of 0.24 in favour of non-opioid exposed controls (Z=1.41, p=0.16, 95%CI −0.09 to 0.58). *Psychomotor*: Pooling of results (4 studies; n=251 exposed; n=315 non-exposed) revealed a non-significant effect size of 0.28 in favour of non-opioid exposed controls (Z=1.67, p=0.09, 95%CI −0.05 to 0.61). *Behaviour*: Pooling of results (3 studies; n=145 exposed; n=216 non-exposed) revealed a non-significant effect size of 0.40 in favour of non-opioid exposed controls (Z=1.25, p=0.20). However, as there was significant evidence of heterogeneity (Q=7.13, p<0.03, I_2=71.93), additional analysis was performed to correct for random effects. The corrected mean effect size was 1.21 (Z=1.30, p=0.19; 95%CI; −0.61 to 3.03).	The findings of this review are limited by the small number of studies analysed, the heterogenous populations and small numbers within the individual studies.

Study ref	Study design	LoE	Sample size	Aim/methods	Findings	Comments
(Maeda et al 2014)	Cohort	III-2	—	**Aim**: to investigate nationwide trends in opioid abuse or dependence during pregnancy and assess the impact on maternal and obstetrical outcomes in the United States. **Methods**: Hospitalisations for childbirth were extracted from the Nationwide Inpatient Sample from 1998 to 2011. Temporal trends were assessed and logistic regression was used to examine the associations between maternal opioid abuse or dependence and obstetrical outcomes adjusting for relevant confounders.	Births associated with maternal opioid abuse or dependence compared with those without opioid abuse or dependence were associated with an increased odds of maternal death during hospitalisation (aOR 4.6; 95%CI 1.8 to 12.1; cardiac arrest (aOR 3.6; 95% CI 1.4 to 9.1), intrauterine growth restriction (aOR 2.7; 95%CI, 2.4 to 2.9), placental abruption (aOR 2.4; 95%CI 2.1 to 2.6), length of stay >7 days (aOR 2.2; 95%CI 2.0 to 2.5), preterm labor (aOR 2.1; 95%CI 2.0 to 2.3), oligohydramnios (aOR 1.7; 95%CI 1.6 to 1.9), transfusion (aOR 1.7; 95% CI 1.5 to 1.9), stillbirth (aOR 1.5; 95%CI 1.3 to 1.8), premature rupture of membranes (aOR 1.4; 95%CI 1.3 to 1.6) and cesarean section (aOR 1.2; 95%CI 1.1 to 1.3).	

1.3 Cocaine

Study ref	Study design	LoE	Sample size	Aim/methods	Findings	Comments
(Gouin et al 2011)	SLR	IV	31 cohort studies	**Aim**: To review systematically maternal antenatal cocaine exposure and adverse perinatal outcomes. **Methods**: Medline, Embase, CINAHL and secondary references in relevant studies were searched. English language studies of antenatal cocaine exposure and pregnancy outcomes published from 1966 to July 2009 were included. Metaanalyses were performed using the random effects model.	Cocaine use during pregnancy was associated with significantly higher odds of preterm birth (OR 3.38; 95% confidence interval [CI], 2.72-4.21), low birthweight (OR, 3.66; 95% CI, 2.90-4.63), and small for gestational age infants (OR, 3.23; 95% CI, 2.43-4.30), as well as shorter gestational age at delivery (-1.47 week; 95% CI, -1.97 to -0.98 week) and reduced birthweight (-492 g; 95% CI, -562 to -421 g).	

1.4 Cannabis (marijuana)

Study ref	Study design	LoE	Sample size	Aim/methods	Findings	Comments
(Conner et al 2016)	SLR	IV	31 cohort and case-control studies	**Aim**: To estimate whether marijuana use in pregnancy increases risks for adverse neonatal outcomes and clarify if any increased risk is attributable to marijuana use itself or to confounding factors such as tobacco use. **Methods**: Two authors performed a search of the data through August 2015 utilizing PubMed, Embase, Scopus, Cochrane reviews, ClinicalTrials.gov, and Cumulative Index to Nursing and Allied Health. Observational studies that compared rates of prespecified adverse neonatal outcomes in women who used marijuana during pregnancy with women who did not were 16linique. Primary outcomes were low birth weight (<2,500 g) and preterm delivery <37 weeks. Secondary outcomes were birth weight, gestational age at delivery, small for gestational age, level II or greater nursery admission, stillbirth, spontaneous abortion, low Apgar score, placental abruption, and perinatal death.	Based on pooled unadjusted data, marijuana use during pregnancy was associated with an increased risk of low birth weight (15.4% compared with 10.4%, pooled relative risk [RR] 1.43, 95%CI 1.27 to 1.62) and preterm delivery (15.3% compared with 9.6%, pooled RR 1.32, 95%CI 1.14-1.54). However, pooled data adjusted for tobacco use and other confounding factors showed no statistically significant increased risk for low birth weight (pooled RR 1.16, 95%CI 0.98 to 1.37) or preterm delivery (pooled RR 1.08, 95%CI 0.82 to 1.43). Maternal marijuana use during pregnancy is not an independent risk factor for adverse neonatal outcomes after adjusting for confounding factors. The association between maternal marijuana use and adverse outcomes appears attributable to concomitant tobacco use and other confounding factors.	

Study ref	Study design	LoE	Sample size	Aim/methods	Findings	Comments
(Gunn et al 2016)	SLR	I	24 cohort, case-control and cross-section studies	**Aim**: To assess the effects of use of cannabis during pregnancy on maternal and fetal outcomes. **Methods**: Seven electronic databases were searched from inception to 1 April 2014. Case-control studies, cross-sectional and cohort studies that investigated the effects of use of cannabis during pregnancy on maternal and fetal outcomes were included. Data synthesis was undertaken via systematic review and meta-analysis of available evidence. Meta-analyses were conducted on variables that had three or more studies that measured an outcome in a consistent manner, these included: anaemia, birth weight, low birth weight, neonatal length, placement in the neonatal intensive care unit, gestational age, head circumference and preterm birth.	Women who used cannabis during pregnancy had an increase in the odds of anaemia (pooled OR (pOR) 1.36: 95%CI 1.10 to 1.69) compared with women who did not. Infants exposed to cannabis in utero had a decrease in birth weight (low birth weight pOR 1.77: 95% CI 1.04 to 3.01; pooled mean difference (pMD) for birth weight 109.42 g: 38.72 to 180.12) compared with infants were not. Infants exposed to cannabis in utero were also more likely to need placement in the neonatal intensive care unit compared with infants whose mothers did not use cannabis during pregnancy (pOR=2.02: 1.27 to 3.21). As use of cannabis gains social acceptance, pregnant women and their medical providers could benefit from health education on potential adverse effects of use of cannabis during pregnancy.	

1.5 Excluded studies

Background papers

Background information will inform revision of the narrative.

(Fraser & Walker 2016)	In Australia, the use of illicit substances is on the rise, with as many as two in five people admitting to having ever used an illicit substance. As illicit drug availability is becoming ever more readily available, it has been argued that maternal substance use is increasing the demands of neonatal intensive care units and special care nurseries Australia wide. Cocaine causes miscarriage due to its vasoconstrictive effects on the blood supply of the developing foetus when used during the first trimester of pregnancy. Furthermore there is an increased risk of the foetus developing congenital anomalies and insufficient intracranial growth all due to the vasoconstrictive teratogenic effects of cocaine. Within this paper, common teratogenic effects of prenatal cocaine use are explored and further supplemented with the documented associated short and long term effects of such illicit drug use as reported in recent literature. The most common short term effect of maternal substance use on the neonate is neonatal abstinence syndrome (NAS) being one of the most common reasons and possibly unavoidable for admission to a neonatal intensive care unit (NICU).
(Committee on Health Care for Underserved Women & Gynecologists 2012)	All women should be screened early during pregnancy for substance use, including prescription drug abuse, with a validated questionnaire.

Other exclusions

Study	**Reason for exclusion**
Ackerman, J. P., et al. (2010). "A review of the effects of prenatal cocaine exposure among school-aged children." Pediatrics 125(3): 554-565.	Does not answer research question
Alpár, A., et al. (2016). "At the tip of an iceberg: Prenatal marijuana and its possible relation to neuropsychiatric outcome in the offspring." Biological Psychiatry 79(7): e33-e45.	Does not answer research question
Bandstra, E. S., et al. (2010). "Prenatal drug exposure: Infant and toddler outcomes." Journal of Addictive Diseases 29(2): 245-258.	Does not answer research question
Barthelemy, O. J., et al. (2016). "Prenatal, perinatal, and adolescent exposure to marijuana: Relationships with aggressive 18linique18." Neurotoxicology and Teratology 58: 60-77.	Narrative review
Behnke, M. and V. C. Smith (2013). "Prenatal substance abuse: Short- and long-term effects on the exposed fetus." Pediatrics 131(3): e1009-e1024.	Narrative review

Study	Reason for exclusion
Bhuvaneswar, C. and G. Chang (2009). "Substance use in pregnancy." 432-452. Book chapter : Women and addiction: a comprehensive handbook	Narrative review
Brogly, S. B., et al. (2014). "Prenatal buprenorphine versus methadone exposure and neonatal outcomes: systematic review and meta-analysis." American Journal of Epidemiology 180(7): 673-686.	Does not answer research question
Buckingham-Howes, S., et al. (2013). "Systematic review of prenatal cocaine exposure and adolescent development." Pediatrics 131(6): e1917-1936.	Does not answer research question
Calvigioni, D., et al. (2014). "Neuronal substrates and functional consequences of prenatal cannabis exposure." European Child & Adolescent Psychiatry 23(10): 931-941.	Narrative review
Correa, F., et al. (2016). "Endocannabinoid system and pregnancy." Reproduction 152(6): R191-R200.	Narrative review
De Bortoli, L., et al. (2014). "Linking illicit substance misuse during pregnancy and child abuse: What is the quality of the evidence?" Child & Family Social Work 19(2): 136-148.	Does not answer research question
De Giovanni, N. and D. Marchetti (2012). "Cocaine and its metabolites in the placenta: a systematic review of the literature." Reproductive Toxicology 33(1): 1-14.	Does not answer research question
Dixon, D. R., et al. (2008). "A systematic review of challenging behaviors in children exposed prenatally to substances of abuse." Research in Developmental Disabilities 29(6): 483-502.	Does not answer research question
Dow-Edwards, D. (2011). "Translational issues for prenatal cocaine studies and the role of environment." Neurotoxicology and Teratology 33(1): 9-16.	Does not answer research question
Dow-Edwards, D. and A. Torres-Reveron (2012). "Sex differences in the effects of cocaine exposure on dopaminergic systems during brain development." In: Dow-Edwards, Diana; Torres-Reveron, Annelyn Lewis, Michael (Ed); Kestler, Lisa (Ed). (2012). *Gender differences in prenatal substance exposure*. Washington, DC, US: American Psychological Association, pp55-76.	Does not answer research question
Higuera-Matas, A., et al. (2015). "Long-term consequences of perinatal and adolescent cannabinoid exposure on neural and psychological processes." Neuroscience and Biobehavioral Reviews 55: 119-146.	Does not answer research question
Hill, M. and K. Reed (2013). "Pregnancy, breast-feeding, and marijuana: A review article." Obstetrical and Gynecological Survey 68(10): 710-718.	Narrative review
Holley, M. F. (2009). "Fetal, neonatal, and early childhood effects of prenatal methamphetamine exposure." In: Angela Browne-Miller (Ed). *The Praegar International Collection on Addictions: Characteristics and Treatment Perspectives*. Barnes and Noble.	Narrative review

Study	Reason for exclusion
Huizink, A. (2014). "Prenatal cannabis exposure and infant outcomes: Overview of studies." Progress in Neuro-Psychopharmacology & Biological Psychiatry 52: 45-52.	Narrative review
Huizink, A. C. (2012). "Prenatal substance use, prenatal stress and offspring behavioural outcomes: Considerations for future studies." Nordic Journal of Psychiatry 66(2): 115-122.	Does not answer research question
Huizink, A. C. (2015). "Prenatal maternal substance use and offspring outcomes: Overview of recent findings and possible interventions." European Psychologist 20(2): 90-101.	Narrative review
Irner, T. B. (2012). "Substance exposure in utero and developmental consequences in adolescence: a systematic review." Child Neuropsychology 18(6): 521-549.	Does not answer research question
Kwiatkowski, M. A., et al. (2014). "Effects of prenatal methamphetamine exposure: A review of cognitive and neuroimaging studies." Metabolic Brain Disease 29(2): 245-254.	Narrative review
Lambert, B. L. and C. R. Bauer (2012). "Developmental and clinical consequences of prenatal cocaine exposure: A review." Journal of Perinatology 32(11): 819-828.	Narrative review
Lamy, S., et al. (2015). "Consequences of tobacco, cocaine and cannabis consumption during pregnancy on the pregnancy itself, on the newborn and on child development: A review." L'Encephale: Revue de psychiatrie 20linique biologique et therapeutique 41(Suppl 1): S13-S20.	Not in English
Lassi, Z. S., et al. (2014). "Preconception care: Caffeine, smoking, alcohol, drugs and other environmental chemical/radiation exposure." Reproductive Health 11.	Does not answer research question (preconception)
Metz, T. D. and E. H. Stickrath (2015). "Marijuana use in pregnancy and lactation: A review of the evidence." American Journal of Obstetrics and Gynecology 213(6): 761-778.	Narrative review
Shah, P., et al. (2011). "Amphetamine exposure and birth outcomes: A systematic review and meta-analyses." American Journal of Obstetrics and Gynecology 204(1): S240.	Does not meet criteria for grading (abstract only)
Smith, L. M. and L. S. Santos (2016). "Prenatal exposure: The effects of prenatal cocaine and methamphetamine exposure on the developing child." Birth Defects Research Part C – Embryo Today: Reviews 108(2): 142-146.	Does not answer research question

Exclusions for non-medical use of pharmaceuticals

Study	Reason for exclusion
Casati A, Sedefov R, Pfeiffer-Gerschel T (2012) Misuse of medicines in the European Union: a systematic review of the literature. *Eur Addict Res* 18(5): 228-45.	Not specific to target population

Study	Reason for exclusion
Committee on Health Care for Underserved Women TACoO & Gynecologists (2012) Committee opinion no. 538: nonmedical use of prescription drugs. *Obstet Gynecol* 120(4): 977-82.	Background
Epstein RA, Bobo WV, Martin PR et al (2013) Increasing pregnancy-related use of prescribed opioid analgesics. *Ann Epidemiol* 23(8): 498-503.	Not relevant to Australian context
Forray A (2016) Substance use during pregnancy. *F1000Res* 5.	Duplicate
Hemsing N, Greaves L, Poole N et al (2016) Misuse of Prescription Opioid Medication among Women: A Scoping Review. *Pain Res Manag* 2016: 1754195.	Not relevant to Australian context
Hoeke H, Roeder S, Bertsche T et al (2016) Assessment of maternal drug intake by urinary bio monitoring during pregnancy and postpartally until the third perinatal year. *Pharmacoepidemiol Drug Saf* 25(4): 431-7.	Not relevant to Australian context
Kozhimannil KB, Graves AJ, Levy R et al (2017) Nonmedical Use of Prescription Opioids among Pregnant U.S. Women. *Womens Health Issues*.	Not relevant to Australian context
Kreshak A, Villano J, Clark A et al (2016) A descriptive regional study of drug and alcohol use in pregnant women using results from urine drug testing by liquid chromatography-tandem mass spectrometry. *Am J Drug Alcohol Abuse* 42(2): 178-86.	Not relevant to Australian context
Lund IO, Skurtveit S, Engeland A et al (2013) Prescription drug use among pregnant women in opioid Maintenance Treatment. *Addiction* 108(2): 367-76.	Not relevant to Australian context
Martin CE, Longinaker N, Terplan M (2015) Recent trends in treatment admissions for prescription opioid abuse during pregnancy. *J Subst Abuse Treat* 48(1): 37-42.	Not relevant to Australian context
Smith MV, Costello D, Yonkers KA (2015) Clinical correlates of prescription opioid analgesic use in pregnancy. *Matern Child Health J* 19(3): 548-56.	Does not answer research question
Smith K & Lipari RN (2017) *Women of childbearing age and opioids. The CBHSQ Report: January 17, 2017.* Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.	Not relevant to Australian context
Stover MW & Davis JM (2015) Opioids in pregnancy and neonatal abstinence syndrome. *Semin Perinatol* 39(7): 561-5.	Narrative review
United States Department of Health and Human Services. Substance Abuse and Mental Health Services Administration. Center for Behavioral Health Statistics and Quality. National Survey on Drug Use and Health, 2014. ICPSR36361-v1. Ann Arbor, MI: Inter-university Consortium for Political and Social Research.	Does not answer research question
Wendell AD (2013) Overview and epidemiology of substance abuse in pregnancy. *Clin Obstet Gynecol* 56(1): 91-6.	Narrative review

Study	Reason for exclusion
Wexelblatt SL, Ward LP, Torok K et al (2015) Universal maternal drug testing in a high-prevalence region of prescription opiate abuse. *J Pediatr* 166(3): 582-6.	Does not answer research question
Whiteman VE, Salemi JL, Mogos MF et al (2014) Maternal opioid drug use during pregnancy and its impact on perinatal morbidity, mortality, and the costs of medical care in the United States. *J Pregnancy* 2014: 906723.	Level IV evidence
Wilder CM & Winhusen T (2015) Pharmacological Management of Opioid Use Disorder in Pregnant Women. *CNS Drugs* 29(8): 625-36.	Narrative review
Yazdy MM, Desai RJ, Brogly SB (2015) Prescription Opioids in Pregnancy and Birth Outcomes: A Review of the Literature. *J Pediatr Genet* 4(2): 56-70.	Narrative review
Young JL & Martin PR (2012) Treatment of opioid dependence in the setting of pregnancy. *Psychiatr Clin North Am* 35(2): 441-60.	Narrative review

2 How can the harms associated with substance use in pregnancy be reduced?

Evidence summary

Psychosocial or psychological intervention

No systematic reviews were identified that investigated the effectiveness of psychosocial or psychological intervention in the antenatal care setting in reducing harms associated with illicit substance use in pregnancy.

Pharmaocological intervention

A Cochrane review on maintenance agonist treatments for women with opioid dependence in pregnancy was identified (Minozzi et al 2013). The review did not find sufficient significant differences between methadone and buprenorphine or slow-release morphine to allow conclusions to be drawn on whether one treatment is superior to another for all relevant outcomes. While methadone seems superior in terms of retaining women in treatment, buprenorphine seems to lead to less severe neonatal abstinence syndrome.

Background information

A background search identified WHO guidelines on identifying and managing substance use and substance use disorders in pregnancy (WHO 2014). Many of the studies specific to psychosocial intervention were either conducted in specialised treatment settings or related to the postnatal period. The summary of findings table (see page 24) is based on one study conducted in a generalised setting in the antenatal and postnatal periods (from intake until 3 months postpartum).

Advice to EWG

Incorporate evidence into the narrative.

Summary of findings

Cognitive behavioural therapy compared to control for pregnant or postpartum women with problematic substance use

Patient or population: Pregnant or postpartum women with problematic substance use
Setting: General treatment settings
Intervention: Cognitive behavioural therapy
Comparison: Control (brief advice)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	
	Assumed risk	Corresponding risk				
	Control	Cognitive behavioural therapy				
Maternal treatment retention participants attending at least one session Follow-up: 6–24 wk	934 per 1,000	**850 per 1,000** (766 to 943)	**RR 0.91** (0.82 to 1.01)	183 (1 study)	⊕⊕◯◯ LOW [1,2]	
Maternal substance use % days used drugs or alcohol in past month measured at birth Follow-up: mean 12 wk[3]		The proportion of days with drug or alcohol use in the intervention group was **1% higher** (5.05 lower to 7.05 higher)		163 (1 study)	⊕⊕◯◯ LOW [4]	Mixed effects negative binomial regression test for group by time interaction found no significant differences between groups at birth and 3 mth postpartum
Low birth weight <2,500 g Medical records	202 per 1,000	**146 per 1,000** (73 to 289)	**RR 0.72** (0.36 to 1.43)	160 (1 study)	⊕⊕◯◯ LOW [4,5]	
Preterm birth <37 wk Medical records	202 per 1,000	**101 per 1,000** (47 to 221)	**RR 0.5** (0.23 to 1.09)	163 (1 study)	⊕⊕◯◯ LOW [4,5]	

* The basis for the assumed risk is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1 Risk of bias: Rated as Serious: A likely lack of blinding for providers and participants may have introduced performance bias.
2 Indirectness: Rated as Serious. The measurement for treatment retention used in the analysis is a proxy measure — attending at least one of 6 sessions during the entire study period which continued to 3 months postpartum.
3 Inclusion criteria was women of < 28 weeks pregnant. The mean duration of follow-up was calculated as from 28 weeks to delivery although women may have been in treatment for longer if enrolled before 28 weeks.
4 Risk of Bias: Rated as Serious. This well-conducted trial was down-graded on the basis of a likely lack of blinding which may have introduced performance bias.
5 Imprecision: The event rate is very low < 300.

Source: Adapted from (WHO 2014).

Methadone compared to buprenorphine for opiate-dependent pregnant women

Patient or population: Opiate-dependent pregnant women
Setting: Austria, Canada, United States
Intervention: methadone
Comparison: buprenorphine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Buprenorohine	Methadone			
Drop out Objective Follow-up: 15–18 wk	**Study population**		**RR 0.64** (0.41 to 1.01)	223 (3 studies)	⊕⊕◯◯ LOW [1,2,]
	318 per 1,000	**204 per 1,000** (130 to 321)			
	Moderate				
	326 per 1,000	**209 per 1,000** (134 to 321)			
Use of primary substance Objective Follow-up: 15–18 wk	**Study population**		**RR 1.81** (0.7 to 4.69)	151 (2 studies)	⊕⊕◯◯ LOW [1,2,]
	75 per 1,000	**135 per 1,000** (52 to 350)			
	Moderate				
	43 per 1,000	**78 per 1,000** (30 to 202)			
Birth weight Objective Follow-up: mean 18 wk	The mean birth weight ranged across control groups from 3,530 to 3,093 g	The mean birth weight in the intervention groups was **224.91 g lower** (248.46 to 201.36 lower)		150 (2 studies)	⊕⊕◯◯ LOW [1,2,3,4]
APGAR score Objective. Scale from 0 to 10 Follow-up: mean 18 wk	The mean APGAR score ranged across control groups from 8.9 to 9.0	The mean APGAR score in the intervention groups was **0 higher** (0.03 lower to 0.03 higher)		163 (2 studies)	⊕⊕◯◯ LOW [1,2]
Number treated for NAS Objective Follow-up: 15–18 wk	**Study population**		**RR 1.22** (0.89 to 1.67)	166 (3 studies)	⊕◯◯◯ VERY LOW [1,2,5]
	447 per 1,000	**546 per 1,000** (398 to 747)			
	Moderate				
	466 per 1,000	**569 per 1,000** (415 to 778)			

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
APGAR score: Activity, Pulse, Grimace, Appearance and Respiration score; CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1 For incomplete outcome data, we judged the studies at high risk of attrition bias because the attrition rate was high and unbalanced between groups.
2 Small sample size.
3 Statistically significant heterogeneity.
4 No explanation was provided.
5 Variability in results.
Source: (Minozzi et al 2013)

Methadone compared to oral slow-release morphine for opiate-dependent pregnant women

Patient or population: Opiate-dependent pregnant women
Setting:
Intervention: methadone
Comparison: oral slow-release morphine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Oral slow-release morphine	Methadone			
Use of substance Objective Follow-up: 15 wk	**Study population**		**RR 2.4** (1 to 5.77)	48 (1 study)	⊕⊕⊕◯ MODERATE [1]
	208 per 1,000	**500 per 1,000** (208 to 1,000)			
	Moderate				
	208 per 1,000	**499 per 1,000** (208 to 1,000)			
Birth weight Objective Follow-up: 15 wk	The mean birth weight in the control groups was 2,912 g	The mean birth weight in the intervention groups was **124 g higher** (186.94 lower to 434.94 higher)		48 (1 study)	⊕⊕⊕◯ MODERATE [1]

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
APGAR score: Activity, Pulse, Grimace, Appearance and Respiration score; CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1 Only one study with small sample size.

Source: (Minozzi et al 2013)

2.1 Pharmacological interventions

Methadone vs buprenorphine for opioid dependence

Study ref	Design	LoE	N	Aim/setting/population/methods	Results	Comments
(Minozzi et al 2013)	SLR	I	1 RCT 48 women	**Aim**: To assess the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial interventions for child health status, neonatal mortality, retaining pregnant women in treatment and reducing the use of substances. **Methods**: We searched the Cochrane Drugs and Alcohol Group Trials Register (September 2013), PubMed (1966 to September 2013), CINAHL (1982 to September 2013), reference lists of relevant papers, sources of ongoing trials, conference proceedings and national focal points for drug research. Randomised controlled trials assessing the efficacy of any maintenance pharmacological treatment for opiate-dependent pregnant women were included.	The drop-out rate from treatment was lower in the methadone group (RR 0.64, 95%CI 0.41 to 1.01, 3 studies, n=223). There was no statistically significant difference in the use of primary substance between groups (RR 1.81, 95% CI 0.70 to 4.69, 2 studies, n=151). Birth weight was higher in the buprenorphine group (MD –365.45 g (95% CI -673.84 to -57.07), 2 studies, n=150). There was no significant difference between groups in APGAR score or number of newborns treated for neonatal abstinence syndrome. Only one study reported side effects — for the mother there was no statistically significant difference; for the newborns in the buprenorphine group there were significantly fewer serious side effects.	

Methadone vs oral slow-release morphine for opioid dependence

Study ref	Design	LoE	N	Aim/setting/population/methods	Results	Comments
(Minozzi et al 2013)	SLR	I	1 RCT 48 women	**Aim**: To assess the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial interventions for child health status, neonatal mortality, retaining pregnant women in treatment and reducing the use of substances. **Methods**: We searched the Cochrane Drugs and Alcohol Group Trials Register (September 2013), PubMed (1966 to September 2013), CINAHL (1982 to September 2013), reference lists of relevant papers, sources of ongoing trials, conference proceedings and national focal points for drug research. Randomised controlled trials assessing the efficacy of any maintenance pharmacological treatment for opiate-dependent pregnant women were included.	There was no drop-out in either group. Oral SR morphine seemed superior to methadone for abstinence from heroin use during pregnancy (RR 2.40, 95%CI 1.00 to 5.77, 1 study, n=48). No side effects were reported for the mother, whereas one child in the methadone group had central apnoea and one child in the morphine group had obstructive apnoea.	

2.2 Excluded studies

Background studies and guidelines

Study	
Guidelines	
(ACOG 2011)	Drug enforcement policies that deter women from seeking prenatal care are contrary to the welfare of the mother and fetus. Incarceration and the threat of incarceration have proved to be ineffective in reducing the incidence of alcohol or drug abuse. Obstetrician-gynecologists should be aware of the reporting requirements related to alcohol and drug abuse within their states. They are encouraged to work with state legislators to retract legislation that punishes women for substance abuse during pregnancy.
(SOGC 2011)	1. All pregnant women and women of childbearing age should be screened periodically for alcohol, tobacco, and prescription and illicit drug use. (III-A) 2. When testing for substance use is clinically indicated, urine drug screening is the preferred method. (II-2A) Informed consent should be obtained from the woman before maternal drug toxicology testing is ordered. (III-B) 3. Policies and legal requirements with respect to drug testing of newborns may vary by jurisdiction, and caregivers should be familiar with the regulations in their region. (III-A) 4. Health care providers should employ a flexible approach to the care of women who have substance use problems, and they should encourage the use of all available community resources. (II-2B) 5. Women should be counselled about the risks of periconception, antepartum, and postpartum drug use. (III-B) 6. Smoking cessation counselling should be considered as a first-line intervention for pregnant smokers. (I-A) Nicotine replacement therapy and/or pharmacotherapy can be considered if counselling is not successful. (I-A) 7. Methadone maintenance treatment should be standard of care for opioid-dependent women during pregnancy. (II-IA) Other slow-release opioid preparations may be considered if methadone is not available. (II-2B) 8. Opioid detoxification should be reserved for selected women because of the high risk of relapse to opioids. (II-2B) 9. Opiate-dependent women should be informed that neonates exposed to heroin, prescription opioids, methadone, or buprenorphine during pregnancy are monitored closely for symptoms and signs of neonatal withdrawal (neonatal abstinence syndrome). (II-2B) Hospitals providing obstetric care should develop a protocol for assessment and management of neonates exposed to opiates during pregnancy. (III-B) 10. Antenatal planning for intrapartum and postpartum analgesia may be offered for all women in consultation with appropriate health care providers. (III-B) 11. The risks and benefits of breastfeeding should be weighed on an individual basis because methadone maintenance therapy is not a contraindication to breastfeeding. (II-3B)

Study	
(ACOG 2012)	The current standard of care for pregnant women with opioid dependence is referral for opioid-assisted therapy with methadone, but emerging evidence suggests that buprenorphine also should be considered. Medically supervised tapered doses of opioids during pregnancy often result in relapse to former use. Abrupt discontinuation of opioids in an opioid-dependent pregnant woman can result in preterm labor, fetal distress, or fetal demise.
(NSW Health)	The guidelines emphasise the importance of establishing a sound therapeutic relationship with the woman based on respect and non-judgmental attitudes, of engaging the woman into adequate antenatal care through this relationship, and of maintaining continuity of care and of carers throughout the pregnancy and postnatal period. The guidelines recommend that pregnant women with significant problematic substance use will benefit from an appropriate referral for specialist drug and alcohol assessment (in addition to midwifery and obstetric care), appointment of a consistent and continuous case manager and care team who use effective communication systems, and specific treatments for their substance use, which may include counselling, pharmacotherapies and relapse prevention strategies.
(Reinsperger et al 2015)	Among 16 guidelines, developed by 9 institutions from Europe, the United States, Canada and Australia, there was no consensus concerning assessment for illicit drug use. Three guidelines recommended screening (NB one of these was Module I, which not specifically recommend screening), whereas the USPSTF stated that there was insufficient evidence to assess the balance of benefits and harms. Moreover, there is uncertainty about the best screening method.
Background	
(Albright & Rayburn 2009)	Substance abuse poses significant health risks to reproductive age women in the United States and, for those who become pregnant, to their children. Substance use or dependence is defined as a maladaptive pattern of substance use marked by recurrent and significant negative consequences related to the repeated use of substances. Alcohol is the most prevalent substance consumed by childbearing-aged women, followed by tobacco and various illicit drugs. Substance use in the preconception period predicts continued but often limited substance use during the prenatal period. Providers must be aware of reproductive age women's unique physiologic, psychological, and social needs and the related legal and ethical ramifications surrounding substance abuse before referral to a community-based multidisciplinary team for often long-term treatment.

Study	
(Arunogiri et al 2013)	Engaging a woman in treatment through a non-judgemental approach, empathic listening and careful exploration of her specific concerns is a starting point to forming a therapeutic alliance Accurate information provision is essential in supporting a patient in making an informed decision Respecting the patient's choice and supporting her decision-making provides an opportunity for her to remain engaged in treatment for ongoing monitoring and follow-up Referring her to a specialist drug and alcohol service for a second opinion and secondary consultation may be beneficial Facilitating the patient's linkage with the appropriate antenatal service may provide additional support Regular communication between the general practitioner, antenatal service and drug and alcohol service is crucial to providing holistic and integrated care
(Heberlein et al 2012)	Regarding opioid dependence, current results suggest that factors like the health status of the mother, the need for additional medications (e.g. treatment for HIV), comorbid drug dependence, and concurrent drug use need to be considered in order to find the 'best opioid substitute
(Jumah et al 2015)	Methadone has important logistical limitations that prohibit its use in resource-limited locations [in Canada]. Methadone can only be prescribed by physicians who hold a special license. Because of the high risk of overdose at the start of treatment, methadone must be dispensed daily and ingested under the observation of a licensed pharmacist at a registered pharmacy. Because many rural and remote communities are unable to provide this service, methadone is not offered.
(Jumah 2016)	This review has shown that the nature, impact, and treatment of opioid use during pregnancy in rural settings differ from those in urban centers. Because the majority of studies included in this review were observational, it is not possible to draw strong conclusions based on the findings. One exception is the use of buprenorphine for the treatment of opioid dependence during pregnancy in rural settings, which is supported by strong evidence. Accessibility and availability were identified as the two biggest barriers to receiving treatment among rural, opioid-using pregnant women. Rural, community-based programs that addressed these two issues reported increased enrollment in treatment programs and keeping birth in communities.

Study	
(Saia et al 2016)	Pregnant women with opioid use disorder face numerous barriers to care, including limited access to treatment, stigma, and fear of legal consequences. Recommendations for health care systems to provide to pregnant women with opioid use disorder • Access to opioid agonist treatment options — Methadone or buprenorphine • Access to obstetric care — Recovery-affirming and trauma-informed; Comprehensive obstetric and addiction medicine services; Group prenatal care as an option • Access to psychiatry consultation: assessment and treatment options for co-occurring disorders • Access to behavioral health counseling: weekly individual or group counseling • Resource guides for community-based relapse prevention — Mutual aid support groups; Mothers-in-recovery groups • Development of enhanced postpartum care: program development to intensify recovery support potentially utilizing peer supports; Close follow-up (<2 weeks from delivery); Allow for multiple postpartum visits; Consider visits every 2 weeks for 3–6 visits; Breastfeeding/lactation support; Screening/treatment for postpartum depression; Transition to a primary care provider familiar with opioid use disorder and its treatment

Other exclusions

Study	Reason for exclusion
Alharbi, F. F. and N. el-Guebaly (2014). "Exploring the management of cannabis use among women and during pregnancy." Addictive Disorders & Their Treatment 13(2): 93-100.	Narrative review
Alinejad, S., et al. (2015). "A systematic review of the cardiotoxicity of methadone." EXCLI Journal 14: 577-600.	Does not answer research question
Buckley, D. N. and M. Ibrahim (2014). "Brief review: Obstetric care and perioperative analgesic management of the addicted patient." Canadian Journal of Anesthesia 61(2): 154-163.	Does not answer research question
Cleary, B. J., et al. (2010). "Methadone dose and neonatal abstinence syndrome-systematic review and meta-analysis." Addiction 105(12): 2071-2084.	Beyond scope of guidelines
Doab, A., et al. (2015). "Factors that influence mother-child reunification for mothers with a history of substance use: A systematic review of the evidence to inform policy and practice in Australia." International Journal of Drug Policy 26(9): 820-831.	Not specific to target population
Farr, S. L., et al. (2014). "Brief interventions for illicit drug use among peripartum women." American Journal of Obstetrics & Gynecology 211(4): 336-343.	Not specific to target population

Study	Reason for exclusion
Floyd, R. L., et al. (2008). "The clinical content of preconception care: alcohol, tobacco, and illicit drug exposures." American Journal of Obstetrics and Gynecology 199(6 SUPPL. B): S333-S339.	Does not answer research question
Forray, A. (2016). "Substance use during pregnancy [version 1; referees: 2 approved]." F1000Research 5.	Narrative review
Fullerton, C. A., et al. (2014). "Medication-assisted treatment with methadone: assessing the evidence." Psychiatric Services 65(2): 146-157.	Narrative review
Hull, L., et al. (2010). "Treatment of cocaine abuse during pregnancy: Translating research to clinical practice." Current Psychiatry Reports 12(5): 454-461.	Narrative review
Jones, H. E., et al. (2012). "Buprenorphine treatment of opioid-dependent pregnant women: a comprehensive review." Addiction (Abingdon, England) 107 Suppl 1: 5-27.	Narrative review
Jones, H. E., et al. (2012). "Methadone and buprenorphine for the management of opioid dependence in pregnancy." Drugs 72(6): 747-757.	Narrative review
Konijnenberg, C. and A. Melinder (2011). "Prenatal exposure to methadone and buprenorphine: A review of the potential effects on cognitive development." Child Neuropsychology 17(5): 495-519.	Narrative review
Minozzi, S., et al. (2013). "Maintenance agonist treatments for opiate-dependent pregnant women." Cochrane Database of Systematic Reviews(12): CD006318.	Duplicate
Mitchell, A. M., et al. (2010). "An overview of opiate use during pregnancy: An evidence-based approach to treatment." Minerva Psichiatrica 51(4): 271-280.	Narrative review
Newman, R. G. and S. G. Gevertz (2011). "Efficacy versus effectiveness of buprenorphine and methadone maintenance in pregnancy." Journal of Addictive Diseases 30(4): 318-322.	Editorial
Niccols A, Milligan K, Sword W et al (2010) Maternal mental health and integrated programs for mothers with substance abuse issues. *Psychol Addict Behav* 24(3): 466-74.	Not specific to target population
Niccols A, Milligan K, Smith A et al (2012a) Integrated programs for mothers with substance abuse issues and their children: a systematic review of studies reporting on child outcomes. *Child Abuse Negl* 36(4): 308-22.	Not specific to target population
Niccols A, Milligan K, Sword W et al (2012b) Integrated programs for mothers with substance abuse issues: A systematic review of studies reporting on parenting outcomes. *Harm Reduct J* 9: 14.	Not specific to target population
Ricks, N., et al. (2017). "Substance use and preconception care: A review of the literature." International Journal of Women's Health and Reproduction Sciences 5(1): 3-10.	Not specific to target population

Study	Reason for exclusion
Shah, P. S., et al. (2010). "Maternal cocaine use and effects of intervention for reducing or eliminating cocaine use on pregnancy outcomes: A systematic review and meta-analysis." Paediatrics and Child Health 15: 24A.	Does not meet criteria for grading (abstract only)
Shiu, J. R. and M. H. H. Ensom (2012). "Dosing and monitoring of methadone in pregnancy: Literature review." Canadian Journal of Hospital Pharmacy 65(5): 380-386.	Beyond scope of guidelines
Soyka, M. (2013). "Buprenorphine use in pregnant opioid users: A critical review." CNS Drugs 27(8): 653-662.	Narrative review

3 What are the additional considerations for Aboriginal and Torres Strait Islander women?

Evidence summary

No evidence was identified through the systematic review.

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