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SUMMARY WITH CRITICAL APPRAISAL

Buprenorphine for Opioid Use Disorders during Pregnancy: A Review of Comparative Clinical Effectiveness, Safety, Cost-Effectiveness, and Guidelines

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Abbreviations

AGREE	Appraisal of Guidelines for Research and Evaluation
BC	British Columbia
DSM	Diagnostic and Statistical Manual of Mental Disorders
GRADE	Grading of Recommendation, Assessment, Development and Evaluation
OUD	opioid use disorder
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
SD	standard deviation
WHO	World Health Organization

Context and Policy Issues

Opioid use disorders (OUD) refer to non-medical uses of opioids, a class of compounds that includes heroin and opium but also includes prescribed medications such as morphine, codeine, fentanyl, oxycodone, and hydrocodone.[1] OUD rates in the US are approximately 4.2% and evidence suggests that rates are similar in Canada.[2] OUD during pregnancy has escalated in parallel with the epidemic observed in the general population.[1]

In addition to the risks associated with withdrawal and relapse, pregnant women with OUD are more likely to seek prenatal care late in pregnancy, miss appointments, acquire infection, and experience poor weight gain.[3,4] OUD during pregnancy also presents significant risks to the developing fetus including fetal growth restriction, fetal demise, and neonatal opioid withdrawal.[4] Treatment goals for this population therefore aims to reduce these maternal and infant risks. Opioid agonist therapy is the standard of care for OUD during pregnancy as opioid detoxification has been associated with a high rate of relapse.[5] As an opioid agonist, methadone has long been prescribed to pregnant women to treat OUD. More recently, buprenorphine has demonstrated similar maternal outcomes and superior neonatal outcomes in comparison to methadone.[5] Buprenorphine is available as a monoproduct in different formulations, or as a combined formulation with naloxone, an opioid antagonist. The buprenorphine monoproducts include extended-release subcutaneous injection, sublingual, implant, transdermal, and intramuscular formulations. The buprenorhpine-naloxone combination is available as a sublingual formulation taken under the tongue in which the naloxone portion of the combination is not orally active. The combination of the opioid agonist (buprenorphine) and non-orally active antagonist (naloxone) in this formulation discourages injection use or diversion since naloxone causes severe withdrawal symptoms if the combination is injected.[1] Buprenorphine monoproducts have been recommended during pregnancy to avoid prenatal exposure to naloxone.[4]

The purpose of this report is to review and appraise the evidence for the clinical effectiveness, safety, and cost-effectiveness of various buprenorphine monoproducts and buprenorphine-naloxone combination formulations for UOD during pregnancy. Additionally, this report aims to review current evidence-based guidelines regarding appropriate buprenorphine formulation use for this population.

Research Questions

1. What is the comparative clinical effectiveness of various buprenorphine or buprenorphine-naloxone formulations versus other buprenorphine formulations for the treatment of opioid use disorders during pregnancy?
2. What is the clinical evidence regarding the safety of various buprenorphine or buprenorphine-naloxone formulations for the treatment of opioid use disorders during pregnancy?
3. What is the cost-effectiveness of various buprenorphine or buprenorphine-naloxone formulations for the treatment of opioid use disorders during pregnancy?
4. What are the evidence-based guidelines regarding the use of various buprenorphine or buprenorphine-naloxone formulations for the treatment of opioid use disorders during pregnancy?

Key Findings

This report identified a lack of evidence regarding the comparative effectiveness, safety, and cost-effectiveness of various buprenorphine or buprenorphine-naloxone formulations for the treatment of opioid use disorders during pregnancy. Three relevant evidence-based guidelines were identified. Two of three guidelines contained relevant recommendations that reflected this lack of high-quality comparative evidence. These two guidelines recommended buprenorphine treatment in preference to the buprenorphine-naloxone formulation for opioid use disorders during pregnancy. One other Canadian guideline cited the same evidence to support the use of buprenorphine-naloxone as a safe and effective alternative to buprenorphine alone during pregnancy. No additional recommendations for various buprenorphine or buprenorphine-naloxone formulations during pregnancy were identified. Evidence-based treatment of pregnant patients with opioid use disorders requires further well-controlled studies for various buprenorphine and buprenorphine-naloxone formulation treatment options.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline via Ovid, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and April 8, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Pregnant and postpartum people, with opioid use disorders (i.e., Opioid Use Disorder [DSM-V], Opioid Abuse [DSM-IV], Opioid Dependence [DSM-IV]), in all settings.
Intervention	Various formulations of buprenorphine (such as: extended-release subcutaneous injection, sublingual, implant, transdermal, intramuscular) or buprenorphine-naloxone combinations.
Comparator	Q1, Q3: Various formulations of buprenorphine (e.g., extended-release subcutaneous injection, sublingual, implant, transdermal, intramuscular) or buprenorphine-naloxone combinations. Q2: No comparator; various formulations of buprenorphine (e.g., extended-release subcutaneous injection, sublingual, implant, transdermal, intramuscular) or buprenorphine-naloxone combinations;
Outcomes	Q1: Clinical effectiveness (e.g., outcomes related to OUD during pregnancy, labour, and the post-partum period; reduction in opioid consumption; prevention of OUD relapse; maintenance of abstinence; urine drug screening results; retention into OUD treatment; adherence to therapy; social functioning [e.g., return to school or work], emotional and psychological functioning [e.g., anxiety, depression, sleep]) Q2: Safety (e.g., fetal outcomes in-utero; placental pathology; outcomes during delivery; ability to breastfeed; reduction in opioid misuse and diversion; reports or evidence of abuse; overdose; all-cause mortality) Q3: Cost-effectiveness per health benefit gained Q4: Guidelines on appropriate use of different formulations and their place in treatment protocols
Study Designs	HTA/Systematic Reviews/Meta-Analyses, RCTs, non-randomized studies, economic evaluations, and guidelines

DSM = Diagnostic and Statistical Manual of Mental Disorders; HTA = health technology assessment; OUD = opioid use disorder; RCT = randomized controlled trial.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published prior to 2014.

Critical Appraisal of Individual Studies

The included guidelines were critically appraised by one reviewer using the AGREE II instrument.[6] Summary scores were not calculated for the included guidelines; rather, a review of the strengths and limitations of each included guideline were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 204 citations were identified in the literature search. Following screening of titles and abstracts, 188 citations were excluded and 16 potentially relevant reports from the electronic search were retrieved for full-text review. Six potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 22 potentially relevant articles, 19 publications were excluded for various reasons, and three evidence-based guidelines met the inclusion-criteria and were included in this report.[4,5,7] One additional case series[8] was identified by hand search; case series are not eligible for inclusion, however information on this study is provided in Appendix 5. No evidence from other study designs was identified. Appendix 1 presents the PRISMA flowchart of the study selection.[9]

Summary of Study Characteristics

Additional details regarding the characteristics of the included publications are provided in Appendix 2.

Study Design

Three identified evidence-based guidelines met the selection criteria in Table 1: one from the BC Ministry of Health, one from the Society of Obstetricians and Gynecologists of Canada, and one from the World Health Organization (WHO).[4,5,7] The most recent guideline was published in 2018 by the BC Ministry of Health and was developed by committees comprised of health authorities, academics, and other affiliations. Guideline development utilized a structured literature review and traditional evidence hierarchy to arrive at consensus for recommendations.[4] These most recent guidelines from the BC Ministry of Health were published as a supplement to more broadly focused guidelines on OUD.[10] The Society of Obstetricians and Gynecologists of Canada published evidence-based guidelines for substance use during pregnancy in 2017.[5] These guidelines were formulated by three principle authors using a structured literature search and hand search to identify relevant evidence. Evidence was ranked using the Criteria of the Canadian Task Force on Preventative Health Care; recommendations were graded according to evidence quality and reviewed by committees and professional organizations.[5] Relevant evidence-based guidelines were published by the World Health Organization (WHO) in 2014.[7] Guideline development consisted of a structured literature review and evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool. Guideline development reportedly strived for consensus but also used two-thirds majority voting to resolve disagreements.[7]

Country of Origin

Two of the identified guidelines were developed in Canada and both provide Canadian context for the OUD population and available treatment options.[4,5] The guidelines published in 2018 were developed by resources and authors located in British Columbia (BC Ministry of Heath),[4] while the three primary authors of the Society of Obstetricians and Gynecologists of Canada were located in Ontario.[5] The guideline development group and external reviewers of the WHO were of international origin and the recommendations did not provide country-specific context.

Patient Population

Guidelines focusing on OUD during pregnancy from the BC Ministry of Health are provided as a supplement to a guideline on OUD for patients of all ages.[4,10] These guidelines are intended for health care providers, policy makers, and healthcare administrators.[7] The Society of Obstetricians and Gynecologists of Canada and the WHO guidelines provided recommendations intended for health care providers of pregnant patients with substance use and substance use disorders including opioid use disorder.[5,7]

Interventions and Comparators

While the Society of Obstetricians and Gynecologists of Canada did not specify the considered interventions for OUD during pregnancy,[5] guidelines from the BC Ministry of Health and the WHO reported categories of considered interventions including withdrawal management,[4,7] long-term opioid agonist therapy,[4] opioid antagonist medications,[4] psychosocial treatment interventions,[4,7] screening,[7] detoxification,[7] dependence management,[7] and harm reduction.[4]

Outcomes

The identified guidelines did not specify outcomes of interest and instead considered all benefits and harms.[4,5,7] The guidelines from the Society of Obstetricians and Gynecologists of Canada also included costs as an outcome of interest.[5]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included guidelines, as critically appraised using the AGREE II instrument,[6] are presented in Appendix 3. Importantly the methodological details of the guidelines from the BC Ministry of Health critically appraised in this report were published in another guideline on OUD.[10]

The scope and purpose of all three guidelines presented an overall objective and described the patient population of interest. A limitation in this domain of all three guidelines was a lack of specific research questions. Target users of the guidelines were described in the guidelines,[4,5,7] however only the guidelines from the WHO also specified broad stakeholder involvement and sought views and preferences of the target population in guideline development.[7] The guidelines from the Society of Obstetricians and Gynecologists of Canada provided insufficient information on many aspects of guideline development but used a systematic literature search and considered benefits and risks when formulating recommendations.[5] Guidelines from the WHO were limited by unclear description of evidence selection criteria, however otherwise reported rigorous development methodology including tabulated study characteristics.[7] In addition to not providing a description of the strengths and weaknesses of the supporting evidence, Guidelines from the BC Ministry of Health also did not provide clear evidence selection criteria.[4] Strengths of the reported development methodology from the WHO and BC Ministry of Health guidelines also included an explicit link between recommendations and the supporting evidence, in addition to procedures for external review and guideline updating.[4,7] Guidelines from the BC Ministry of Health and the Society of Obstetricians and Gynecologists provided insufficient and unclear information on the same cited recommendation supporting studies. The supporting studies did not examine a relevant comparator which presented some disconnect between the cited evidence and the text of both guidelines.[4,5] All three guidelines provided clearly identifiable and unambiguous recommendations.[4,5,7] The guidelines from the Society of Obstetricians and Gynecologists of Canada did not provide information on recommendation applicability and implementation,[5] while provision of this information was a strength of the other guidelines.[4,7] Editorial independence was suggested by the three guidelines and disclosures of the authors were reported, however the guidelines from the Society of Obstetricians and Gynecologists of Canada did not report if any relevant disclosures were addressed. The potential influence of funding bodies on the three identified guidelines was not clear.[4,5,7]

Summary of Findings

Tabulated findings of included evidence are summarized and presented in Appendix 4.

Clinical Effectiveness of Buprenorphine or Buprenorphine-Naloxone Formulations

No relevant evidence regarding the comparative clinical effectiveness of various buprenorphine or buprenorphine-naloxone formulations versus other buprenorphine formulations for the treatment of OUDs during pregnancy was identified; therefore no summary can be provided.

Safety of Buprenorphine or Buprenorphine-Naloxone Formulations

No relevant evidence regarding the safety of various buprenorphine or buprenorphine-naloxone formulations for the treatment of OUDs during pregnancy was identified; therefore no summary can be provided.

Cost-Effectiveness of Buprenorphine or Buprenorphine-Naloxone Formulations

No relevant cost-effectiveness evidence was identified; therefore no summary can be provided.

Guidelines Regarding Buprenorphine or Buprenorphine-Naloxone Formulations

The most recent guidelines from the BC Ministry of Health recommended that buprenorphine-naloxone is as safe and effective as buprenorphine monotherapy during pregnancy. Recommendations were not graded and an evidence level was not reported in this guideline supplement for OUD during pregnancy.[4,10] The cited evidence consisted of two meta-analyses,[11,12] four retrospective cohort studies,[8,13-15], and the suboxone product monograph.[16] None of these sources met the inclusion criteria for the present report. The guidelines cited evidence that was not direct comparative evidence. The guideline did not provide a summary of study characteristics.

The Society of Obstetricians and Gynecologists of Canada recommended in 2017 that women who become pregnant while on buprenorphine-naloxone should be switched to the buprenorphine monoproduct. The guidelines continued to say that buprenorphine-naloxone treatment should be continued until the buprenorphine monoproduct alternative becomes available. Recommendations from the Society of Obstetricians and Gynecologists of Canada were not clearly linked to supporting evidence however three retrospective cohort studies also cited in the BC Ministry of Health guidelines were used to support the relevant recommendation.[8,14,15] This recommendation was assigned the highest grade and the supporting evidence was evaluated as being from well-designed controlled trials without randomization. The authors reported that the studies included a total of 71 pregnant patients treated with buprenorphine-naloxone who did not experience significant differences in maternal outcomes as compared to other studies that examined an unreported number of pregnant patients treated with burprenorphine monoproduct. The Society of Obstetricians and Gynecologists of Canada indicated that further evidence is required in order to recommend routine use of buprenorphine-naloxone during pregnancy. The authors recommend that patients who become pregnant while on buprenorphine-naloxone switch to the buprenorphine monoproduct and only switch to methadone if the buprenorphine monoproduct is unavailable.[5] No cost-effectiveness evidence was identified to aid in relevant recommendation formulation.[5]

Guidelines from the WHO included only evidence from randomized controlled trials (RCTs) to support the following recommendation: “Pregnant patients with opioid dependence should be advised to continue or commence opioid maintenance therapy with either methadone or buprenorphine.” (p. 103) The quality of the evidence to support this statement was rated as “very low”, however the strength of the recommendation was graded as “strong”. The certainty surrounding the balance of benefits and harms, certainty regarding the balance of benefits and resource consumption, and the expected values and preferences were factors in determining the strength of this recommendation. Relevant to this report, a remark related to this recommendation stated, ”In opioid-dependent pregnant women, the buprenorphine mono formulation should be used in preference to the

buprenorphine/naloxone formulation" (p. 103). The authors cite a lack of data on the safety and efficacy of the buprenorphine-naloxone combination in pregnancy.

Limitations

The lack of evidence identified in this report prevents addressing the research questions of comparative efficacy, safety, and cost-effectiveness of various buprenorphine formulations and buprenorphine-naloxone treatment options for OUD during pregnancy. The included guidelines were also supported by evidence of limited quantity and quality. Relevant comparative evidence was completely absent from the identified literature suggesting that additional research in this area is required.

Conclusions and Implications for Decision or Policy Making

A total of three guidelines were identified and included in this report. These guidelines presented conflicting recommendations regarding the use of buprenorphine and buprenorphine-naloxone during pregnancy. No additional recommendations were identified regarding the use of various other buprenorphine formulations for this population. The most recent guidelines from the British Columbia Ministry of Health concluded that buprenorphine-naloxone is a suitable first-line medication for OUD during pregnancy,[4] while guidelines from the Society of Obstetricians and Gynecologists of Canada cited the same evidence and determined it was insufficient to support routine recommendation of buprenorphine-naloxone during pregnancy and instead recommend the buprenorphine monoproduct.[5] Guidelines published by the WHO also identified a lack of efficacy and safety data for the use of buprenorphine-naloxone combinations during pregnancy and recommend the buprenorphine monoproduct.[7] The lack of consensus in the identified guidelines and the lack of relevant evidence that supported recommendations in favour of buprenorphine-naloxone use during pregnancy suggests that more comparative studies are required.

A case series cited was cited by guidelines from the BC Ministry of Health and guidelines from the Society of Obstetricians and Gynecologists of Canada were used as evidence to support recommendations.[4,5,8] This case series consisted of observations of ten perinatal women with OUD who were treated with buprenorphine-naloxone; case series studies were not eligible for inclusion in this report. The authors concluded that no obvious concerns were raised during the observation period but that further research was required.[8] A summary of study characteristics and a summary of findings are tabulated in Appendix 5.

Two guidelines provided Canadian context for OUD treatment in this population.[4,5] The British Columbia Ministry of Health points out that pregnancy was recently removed as a contraindication in the product monograph of Suboxone which is the Health Canada-approved buprenorphine-naloxone forumulation.[4] The Society of Obstetricians and Gynecologists of Canada guidelines, published in 2017, observed that the only preparation of buprenorphine readily available in Canada was a combination of buprenorphine and naloxone, but that the single agent formulation (Subutex), was available during pregnancy through Health Canada's Special Access Program.[5] The current status of these access challenges for treatment options in the Canadian healthcare system was beyond the scope of this report.

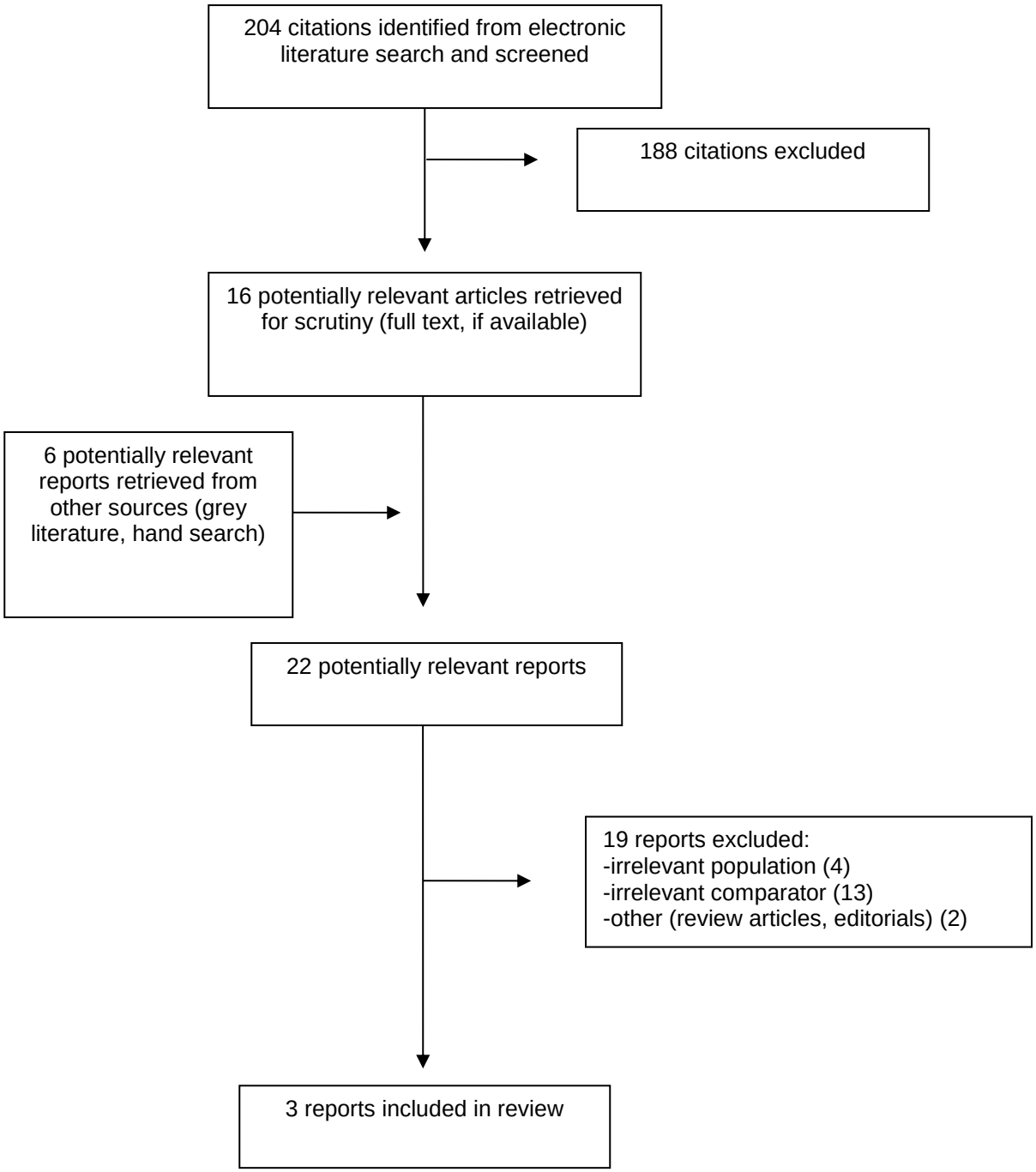
No evidence for the comparative clinical effectiveness, safety, or cost-effectiveness of various buprenorphine formulations or buprenorphine-naloxone formulations for pregnant

patients with OUD was identified in this report. Further studies are therefore required to address the research questions of this report.

References

1. Committee on Obstetric Practice. ACOG committee opinion: opioid use and opioid use disorder in pregnancy Vol 711. Washington (DC): American College of Obstetricians and Gynecologists; 2017: https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Opioid-Use-and-Opioid-Use-Disorder-in-Pregnancy. Accessed 2019 May 8.
2. Fischer B, Kurdyak P, Goldner E, Tyndall M, Rehm J. Treatment of prescription opioid disorders in Canada: looking at the 'other epidemic'? *Subst Abuse Treat Prev Policy.* 2016;11:12.
3. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. *J Addict Med.* 2015;9(5):358-367.
4. Treatment of opioid use disorder during pregnancy: guideline supplement. Vancouver (BC): British Columbia Centre on Substance Use; 2018: http://www.bccsu.ca/wp-content/uploads/2018/06/OUD-Pregnancy.pdf. Accessed 2019 Apr 10.
5. Ordean A, Wong S, Graves L. No. 349-substance use in pregnancy. *J Obstet Gynaecol Can.* 2017;39(10):922-937.e922.
6. Agree Next Steps Consortium. The AGREE II instrument. Hamilton (ON): AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2019 May 8.
7. Guidelines for the identification and management of substance use and substance use disorders in pregnancy. Geneva (CH): World Health Organization; 2014: https://apps.who.int/iris/bitstream/handle/10665/107130/9789241548731_eng.pdf?sequence=1. Accessed 2019 May 8.
8. Debelak K, Morrone WR, O'Grady KE, Jones HE. Buprenorphine + naloxone in the treatment of opioid dependence during pregnancy-initial patient care and outcome data. *Am J Addict.* 2013;22(3):252-254.
9. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
10. A guideline for the clinical management of opioid use disorder. Vancouver (BC): British Columbia Centre on Substance Use; 2017: http://www.bccsu.ca/wp-content/uploads/2018/05/BC_OUD_Guideline.pdf. Accessed 2019 May 8.
11. Lund IO, Fischer G, Welle-Strand GK, et al. A comparison of buprenorphine + naloxone to buprenorphine and methadone in the treatment of opioid dependence during pregnancy: maternal and neonatal outcomes. *Subst Abuse.* 2013;7:61-74.
12. Zedler BK, Mann AL, Kim MM, et al. Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. *Addiction.* 2016;111(12):2115-2128.
13. Wiegand SL, Stringer E., Seashore, C., et al. . 750: Buprenorphine/naloxone (B/N) and methadone (M) maintenance during pregnancy: a chart review and comparison of maternal and neonatal outcomes. *Am J Obstet Gynecol.* 2014;210(1):S368-S369.
14. Wiegand SL, Stringer EM, Stuebe AM, Jones H, Seashore C, Thorp J. Buprenorphine and naloxone compared with methadone treatment in pregnancy. *Obstet Gynecol.* 2015;125(2):363-368.
15. Dooley J, Gerber-Finn, L., Stuebe, A.M., Jones, H., Seashore, C., Thorp, J. Buprenorphine-naloxone use in pregnancy for treatment of opioid dependence: retrospective cohort study of 30 patients. *Can Fam Physician.* 2016;62(4):e194-e200.
16. Suboxone buprenorphine (as buprenorphine hydrochloride) and naloxone (as naloxone hydrochloride dihydrate): 2 mg sublingual tablets[product monograph]. Berkshire (GB): Indivior UK Limited; 2016: https://pdf.hres.ca/dpd_pm/00037755.PDF.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
BC Ministry of Health, 2018[4]						
Intended Users: Health Care Providers, policy makers, and healthcare administrators **Target Population:** Patients with OUD during pregnancy	Medically assisted withdrawal management, residential treatment, long-term opioid agonist therapy, opioid antagonist medications, psychosocial treatment interventions, harm reduction	Benefits and harms	Structured literature review with traditional evidence hierarchy using only RCT evidence when possible	GRADE tool	GRADE tool and consensus of guideline committee members [Recommendations not graded for this population]	External review
The Society of Obstetricians and Gynecologists of Canada, 2017[5]						
Intended Users: All health care providers **Target Population:** Patients with problematic substance use during pregnancy	Management of problematic substance use during pregnancy and lactation	Benefits, harms, and costs	Structured literature search and hand search	Criteria of the Canadian Task Force on Preventative Health Care	Recommendations graded according to evidence quality	Reviewed by committees and professional organizations
WHO, 2014[7]						
Intended Users: Health Care Providers **Target Population:** women from conception to birth and the post-natal period, and their infants	Screening, psychosocial, detoxification, dependence management, infant feeding, neonatal withdrawal management	Benefits and harms	Structured literature review with traditional evidence hierarchy	GRADE tool	GRADE tool and consensus or majority of guideline committee members	Values and preferences survey of health-care workers and pregnant women External review

GRADE = Grading of Recommendations, Assessment, Development and Evaluation; RCT = randomized controlled trial; WHO = World Health Organization.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Guidelines using AGREE II[6]

Item	Guideline		
	BC Ministry of Health, 2018[4]	The Society of Obstetricians and Gynecologists of Canada, 2017[5]	WHO, 2014[7]
Domain 1: Scope and Purpose			
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	No	No	No
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes
Domain 2: Stakeholder Involvement			
4. The guideline development group includes individuals from all relevant professional groups.	Not specified	No	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Not specified	No	Yes
6. The target users of the guideline are clearly defined.	Yes	Yes	Yes
Domain 3: Rigour of Development			
7. Systematic methods were used to search for evidence.	Yes	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	No	No	No
9. The strengths and limitations of the body of evidence are clearly described.	No	No	Yes
10. The methods for formulating the recommendations are clearly described.	Yes	No	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	No	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	No	Yes
14. A procedure for updating the guideline is provided.	Yes	No	Yes
Domain 4: Clarity of Presentation			
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes

Item	Guideline		
	BC Ministry of Health, 2018[4]	The Society of Obstetricians and Gynecologists of Canada, 2017[5]	WHO, 2014[7]
Domain 5: Applicability			
18. The guideline describes facilitators and barriers to its application.	Yes	No	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	No	Yes
20. The potential resource implications of applying the recommendations have been considered.	Yes	No	Yes
21. The guideline presents monitoring and/or auditing criteria.	No	No	Yes
Domain 6: Editorial Independence			
22. The views of the funding body have not influenced the content of the guideline.	Unclear	Unclear	Unclear
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Unclear if addressed	Yes

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
BC Ministry of Health, 2018[4]	
"The type of OAT to be initiated should be selected based on patients' individual circumstances and with consideration of access and availability. ***i. Methadone is traditionally recognized as the first-line option for OAT during pregnancy. (See*** *Methadone****.)*** ***ii. Buprenorphine/naloxone is an alternative first-line medication for this population. Recent studies have found this medication to be as safe and effective as methadone and buprenorphine monotherapy during pregnancy. (See*** *Buprenorphine/naloxone****.)*** ***iii. Slow-release oral morphine may be considered for patients who are not successfully retained in treatment with buprenorphine/naloxone or methadone. (See*** *Slow-release oral morphine****.)*** ***iv. Injectable opioid agonist treatment (iOAT) has not been studied in the context of pregnancy. Caution should be exercised when prescribing iOAT for individuals who are pregnant or may become pregnant. This caution should be exercised with consideration of the potential harms of denying access to iOAT for a pregnant."*** (p. 10) **Evidence:** Six studies were cited which, according to guideline authors, found no statistically significant differences between buprenorphine-only and buprenorphine-naloxone in terms of pregnancy and treatment outcomes including maternal outcomes and gestation period. ***"For patients stable on buprenorphine/naloxone prior to becoming pregnant, transition to buprenorphine monotherapy during pregnancy is not necessary."*** (p. 10) **Evidence:** The same six studies are cited as identified above.	Quality of the evidence was judged using GRADE according to the methodology but were not reported. Grades for the strength of the recommendations were not reported in the guidelines for this population.
The Society of Obstetricians and Gynecologists of Canada, 2017[5]	
"Women who become pregnant while on buprenorphine/naloxone should be switched to buprenorphine monoproduct. Combination product should be continued until the monoproduct becomes available. Women taking buprenorphine should only switch to methadone if the buprenorphine monoproduct is not accessible and/or the woman feels that she is not responding to the current treatment." (p. 932) **Evidence:** The authors cited three retrospective cohort studies examining a total of 71 pregnant women that found no significant differences in maternal outcomes between patients treated with buprenorphine, buprenorphine-naloxone, and methadone. These studies did not however directly compare these treatments. The authors suggested that a larger study is required prior to recommending routine use of buprenorphine-naloxone as an alternative treatment to buprenorphine monoproduct during pregnancy.	Evidence was from well-designed controlled trials without randomization. The recommendation is of the highest grade articulated as, *"There is good evidence to recommend the clinical preventive action."* (p. 923
WHO, 2014[7]	
"In opioid-dependent pregnant women, the buprenorphine mono formulation should be used in preference to the buprenorphine/naloxone formulation." (p. 103) This is not formulated as an independent recommendation but as a remark on the following recommendation: ***"Pregnant patients with opioid dependence should be advised to continue or commence opioid maintenance therapy with either methadone or buprenorphine."*** (p. 103)	Quality of Evidence: Very Low Strength of Recommendation: Strong

Recommendations	Strength of Evidence and Recommendations
Evidence: The authors cited three RCTs, comparing buprenorphine and methadone, one of which reported maternal outcomes. No directly relevant evidence was cited.	

GRADE = Grading of Recommendation, Assessment, Development and Evaluation; iOAT = injectable Opioid Agonist Therapy; OAT = Opioid Agonist Therapy; RCT = randomized controlled trial; WHO = World Health Organization

Appendix 5: Additional References of Potential Interest

This appendix includes one additional reference of potential interest. This case series by Debelak et al. was cited by both guidelines, however it was not included in this report as it was an ineligible study design (a case series), and was published in 2013.[8]

Table 5: Characteristics of Primary Clinical Study

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Debelak, 2013,[8] US	Case Series (n = 10)	Opioid-dependent pregnant women already on buprenorphine-naloxone (n = 8) or started on burprenorphine + naloxone (n = 2)	Continuation or initiation of buprenorphine-naloxone (Suboxone, Reckitt Benckiser Pharmaceuticals) during pregnancy No comparator	Maternal outcomes: Maternal weight gain Cesarean delivery Urine screen at delivery Maternal hospital stay Initiation of breastfeeding

Table 6: Summary of Findings of Included Primary Clinical Study

Main Study Findings		Authors' Conclusion
Debelak, 2013,[8] US		
Mean (± SD) Maternal Weight Gain Days (± SD) Maternal Hospital Stay Cesarean section Began breastfeeding after delivery Positive urine drug screen	7.1 kg (± 3.9) 4.1 days (± 4.5) 1/10 (10%) 3/10 (30%) 0/10 (0%)	"*Findings do not raise obvious concerns for clinicians who might be considering treatment of opioid-dependent pregnant women with buprenorphine + naloxone. However, these initial findings do underscore the need for future research to systematically examine its relative safety and effectiveness for mother, fetus, and child.*" (p. 254)

SD = standard deviation.