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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Substance Use in Breastfeeding Parents: A Review of Safety and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	September 13, 2018
Report Length:	21 Pages

CADTH

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Cite As: Substance use in breastfeeding parents: a review of safety and guidelines. Ottawa: CADTH; 2018 Sep. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Abbreviations

ASQ-3	Ages and Stages Questionnaire, 3rd edition
CI	Confidence Interval
CRD	Centre for Reviews and Dissemination
FAS	Fetal Alcohol Syndrome
FASD	Fetal Alcohol Spectrum Disorder
GDG	Guideline Development Group
OFC	occipitofrontal circumference
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
SE	Standard error
SES	Socio-economic status
TROG	Test for the Reception of Grammar
WHO	World Health Organization

Context and Policy Issues

The benefits of breastfeeding and the use of human milk for infant feeding are well established.[1] For infants, these include decreased incidence and severity of several communicable and non-communicable diseases, decreased post-neonatal mortality rates, analgesia, and cognitive function benefits.[1] In Canada, 89% of new parents initiated breastfeeding in 2011-2012 and 26% breastfed exclusively for at least six months.[2] Breastfeeding rates tend to be low among those with substance use disorder.[3] In many cases, those who use substances are advised not to breastfeed because of concerns about adverse effects for their infants despite there being few contraindications to breastfeeding.[3]

In weighing the risks and benefits of breastfeeding by those who consume alcohol or use controlled or illicit substances, the health care provider considers several factors including the type of substance being used, the amount of the substance excreted into human milk, the extent of oral absorption by the infant, and the potential adverse effects on the infant.[3] However, our understanding of the effects of specific substances is limited as patterns of use are complex and research is lacking and difficult to perform.[4] Regarding cannabis, evidence on the effects of infant exposure to Tetrahydrocannabinol through breastfeeding alone is sparse and conflicting.[4] According to the Academy of Breastfeeding Medicine, the effects of alcohol on the breastfed infant may include fetal alcohol syndrome (FAS), birth defects, and spontaneous abortion, although this is based on low quality evidence.[4]

The purpose of this report is to identify, summarize, and critically appraise the available clinical evidence on safety and evidence-based guidelines regarding the use of controlled and illicit substances by breastfeeding parents.

Research Questions

1. What is the safety regarding the consumption of controlled and illicit substances by breastfeeding parents for the parent and infant?
2. What are the evidence-based guidelines regarding the consumption of controlled or illicit substances by breastfeeding parents?

Key Findings

The review was limited by the sparsity of evidence identified. Two non-randomized studies at high risk for bias were identified regarding the safety of parental postnatal alcohol consumption (by the breastfeeding parent) for the infant. These studies suggested that alcohol consumption by a breastfeeding parent may be associated with certain developmental markers (i.e., reduced weight centile and lower verbal IQ at ages 6-8 years, personal-social interaction developmental delay at 12 months of age), and not associated with others (i.e., no change in occipitofrontal circumference centile, palpebral fissure length centile, or total dysmorphology score at ages 6 to 8 years; communication, gross motor, fine motor, problem solving, personal-social interactions at 8 months post-partum; or communication, gross motor, fine motor, and problem solving at 12 months). For children with identified FASD, postnatal alcohol consumption by the breastfeeding parent (amount and frequency of consumption not reported) appeared to be associated with total dysmorphology score but not weight centile, OFC centile, palpebral fissure length centile, or verbal IQ score. No evidence was identified regarding the effects of using other substances on breastfed infants and no evidence regarding the safety of the breastfeeding parent was identified.

One high quality evidence based guideline regarding parents with alcohol and/or substance dependence recommends breastfeeding unless the risks clearly outweigh the benefits (conditional recommendation), advising and supporting breastfeeding parents with substance abuse or dependence who use alcohol or drugs to cease using these substances (strong recommendation), and encouraging breastfeeding for those who are stable on opioid maintenance treatment with methadone or buprenorphine unless the risks clearly outweigh the benefits (strong recommendation).

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline, PubMed, 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 used to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and August 10, 2018.

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	Breastfeeding parents ; Infants who are breastfed
Intervention	Controlled or illicit substances used during the breastfeeding period (e.g., alcohol, cannabis, opioids)
Comparator	Q1: No controlled or illicit substance use during lactation Q2: No comparator
Outcomes	Q1: Safety, harms, parental and infant exposures, Q2: Guidelines
Study Designs	Health technology assessment, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included non-randomized studies were critically appraised using the Downs and Black checklist[5] and the guideline was assessed with the AGREE II instrument.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 236 citations were identified in the literature search. Following screening of titles and abstracts, 233 citations were excluded and three potentially relevant reports from the electronic search were retrieved for full-text review. Fifteen potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, twelve publications were excluded for various reasons, and three publications met the inclusion criteria and were included in this report. These two non-randomized studies[7,8] and one evidence-based guideline.[9] Appendix 1 presents the PRISMA[10] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Of the three publications included in this review, two addressed safety and one included recommendations relevant to breastfeeding for those who use controlled or illicit substances during lactation. Detailed characteristics of the individual studies are provided in Appendix 2.

Study Design

Both studies addressing safety were non-randomized studies published in 2016 and 2014. One study was a longitudinal birth cohort study, in which women who were pregnant in 2009 to 2013 were recruited and followed.[8] The other was a controlled population based active case ascertainment study, where confirmed cases of FASD were identified from four population-based datasets of children and their mothers.[7]

The eligible guideline was produced by a national guideline development panel invited by the World Health Organization (WHO).[9] The WHO recommendations were based on evidence from systematic reviews of the literature and the quality of evidence was evaluated using the Grading Recommendations Assessment, Development and Evaluation (GRADE) framework. The included recommendations were both based on low quality evidence. One recommendation was strong, meaning that the "Guideline Development Group was confident that the quality of the evidence of effect, combined with certainty about the values, preferences, benefits and feasibility, made this a recommendation that should be done in most circumstances and settings."[9] The other recommendation was conditional, meaning "there was less certainty about the quality of the evidence and values, preferences, benefits and feasibility of this recommendation. Thus, there may be circumstances or settings in which the recommendation should not apply."[9] Recommendations were based on consensus.

Country of Origin

The non-randomized studies were conducted in South Africa[7] and Australia.[8] The guidelines apply to member states of the WHO.[9]

Patient Population

The patient populations for the non-randomized studies were breastfeeding parents and their breastfed infants.[7,8]

Specifically, parents in the birth cohort study were women (32.2 years) who did (n = 244) or did not (n = 158) report consuming alcohol during the period they were breastfeeding (N = 402 pairs).[8]

Participants in the case-control study were mothers of low socio-economic status (SES; approximately one third were from squatters communities in South Africa) who drank or did not consume alcohol while pregnant, and who did or did not consume alcohol while breastfeeding as well as their infants (N = 1047 pairs).[7] Infants in the case-control study were infants with FASD (cases) or without FASD (controls).

The evidence-based guideline was developed for use by health care providers who provide prenatal, postnatal and infant care to support care for women who are pregnant or have recently had a child, and who use alcohol or drugs or who have a substance use disorder. Highlighted recommendations apply to women who are breastfeeding or considering breastfeeding their infant.[9]

Interventions and Comparators

The two non-randomized studies addressed the safety of breastfeeding and maternal alcohol consumption.[7,8] No studies examined other substances.

The guideline presented recommendations specific to breastfeeding with maternal alcohol and / or substance use disorders, and for those stable on opioid maintenance treatment with methadone or buprenorphine.[9]

Outcomes

One non-randomized study examined infants' social, mental and motor development (i.e., communication, gross motor function, fine motor function, problem solving, personal-social interactions and social-emotional functioning) at 8 weeks and 12 months of age.[8] Developmental outcomes were assessed using the validated and reliable Ages and Stages Questionnaire (ASQ-3).[8] Response options include yes, sometimes and not yet. Age specific cut off values represent typical development for each developmental area.

The other non-randomized study examined fetal alcohol spectrum disorder (FASD) (i.e., fetal alcohol syndrome, partial fetal alcohol syndrome, alcohol-related neurodevelopmental disorders, and alcohol related birth defects) in 6 to 8 year old children.[7] Required FASD diagnostic domains are child physical growth, facial, and other dysmorphology; cognitive and behavioral testing/assessment; and maternal risk factors. Diagnoses were made by pediatric medical geneticists using revised Institute of Medicine diagnostic guidelines; the validity and reliability of the assessment was not described.[7]

Summary of Critical Appraisal

The critical appraisal of the non-randomized studies and evidence-based guidelines are summarized here. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Non-Randomized Studies

The two non-randomized studies[7,8] were assessed using the Downs and Black checklist.[5] Strengths of the studies include clear reporting of study objectives, main outcomes, participant characteristics, interventions, distributions of principal confounders, main findings, estimates of random variability, and probability values.[7,8] Regarding internal validity, statistical tests were appropriate and analyses appear to have been planned at study outside for both studies.[7,8] The study by Wilson et al. was assessed as moderate risk of bias, with clearly reported and appropriately addressed methods around recruitment, loss to follow up, and adjustment for confounding.[8] These features may increase the reliability of the recommendations as they reflect methodological rigor and reduce the potential for bias.

Limitations of both studies included the lack of a randomized recruitment strategy, meaning the included participants are not likely to have been representative of all breastfeeding parents. Furthermore, the absence of a power calculation in both studies means we cannot be certain whether no differences were reported where actual differences between groups exist.[7,8]

Evidence-Based Guidelines

The WHO[9] guideline was of high quality, however there were limitations. Strengths of the guidelines included clearly reported scope, purpose, and final guidelines, involvement of stakeholders including individuals from all relevant professional groups and the target population, rigorous development process. Limitations were related to implementation (i.e., tools to facilitate implementation and monitoring criteria were not produced) and while they may make the recommendations more difficult to implement, likely do not affect the trustworthiness of the recommendations. Finally, the funding body was identified, however it

was not explicitly reported that the views of the funding body have not influenced the content of the guideline.

Summary of Findings

Clinical Effectiveness of Breastfeeding by Women Who Use Alcohol or Substances

FASD and Related Outcomes

For infants who did not have a diagnosis of FASD, drinking milk that was produced by someone who had consumed alcohol was associated with smaller weight centile and lower verbal IQ than from those who did not consume alcohol. There was no difference between groups for OFC centile, palpebral fissure length centile, or total dysmorphology score. For infants with a diagnosis of FASD, drinking milk from those who consumed alcohol was associated with higher total dysmorphology score, while there was no difference for weight centile, OFC centile, palpebral fissure centile, or verbal IQ.[7]

In a regression model that controlled for prenatal alcohol consumption among other confounders, consuming alcohol postpartum was a significant predictor of FASD.[7] Consuming alcohol postpartum was associated with higher odds of an infant diagnosis of FASD than abstaining from alcohol.[7]

Developmental Outcomes

Infant development outcomes at eight weeks were similar between the maternal alcohol consumption and maternal alcohol abstinence groups.[8] At 12 months postpartum, lactating parents who consumed alcohol were less likely to have infants who scored below the cut-off or in the monitoring zone for developmental delay on the Personal-Social Interactions subscale of the ASQ-3 than those who abstained from alcohol. There was no difference between groups for any other 12 month developmental outcome.[8]

Guidelines

The WHO guidelines include two recommendations regarding the substance use and alcohol consumption by breastfeeding parents with substance use disorders.[9] Regarding substance use disorders, the WHO recommends that those with substance use disorders be encouraged to breastfeed unless the risks to parent and infant clearly outweigh the benefits.[9] Regarding alcohol and illicit or illegal substance use, the WHO recommends that women should be advised and supported to stop consuming alcohol or illicit or illegal substance use, and it is further specified that substance use is not necessarily a contraindication to breastfeeding.[9] Finally, the WHO recommends encouraging those who are stable on opioid maintenance treatment with methadone or buprenorphine to breastfeed unless the risks clearly outweigh the benefits.[9] No relevant guidelines regarding cannabis specifically were identified.

Appendix 4 presents a table of the main study findings and authors' conclusions.

Limitations

The included guideline was of high methodological quality (Appendix 3), however there were limitations related to gaps in the recommendations. No evidence was identified regarding other types of substances (e.g., cannabis) and breastfeeding. This was also reported within the WHO guidelines, which reported unknown effects of cannabis found in breastmilk on the infant.[9]

Regarding the clinical evidence, there were several gaps in the available evidence. Two studies examined alcohol consumptions and outcomes of importance to the breastfed infant. No studies were identified that examined other substances or outcomes regarding the breastfeeding parent.

In the identified studies that examined alcohol consumption, the non-randomized study by Wilson and colleagues included a small subsample of breastfeeding mothers who reported moderate to heavy alcohol consumption (n = 45 and n = 52 at week 8 and month 12, respectively) limiting the generalizability of these findings beyond those who report those levels of alcohol consumption.[8]

In the cohort study by May and et al., the authors described the sample participants were drawn from as being generally of very low SES and as a result, having poor nutrition, although these data were not collected. it is possible the very low the conditions experienced by the South African participants exacerbated the effects of postpartum alcohol exposure through breastmilk, potentially limiting generalizability to more advantaged populations.[7]

Importantly, both studies assessed alcohol consumption by recall, which may have biased findings. In the cohort study, parental alcohol consumption was assessed 6 to 8 years postpartum.[7] In the active case ascertainment study, the 8 week assessment assessed consumption during the past 8 weeks, while the 12 month question assessed consumption during the past month.[8] Additionally, the nature of the data collection precluded recording the timing of breastfeeding in relation to consuming alcohol.[7,8] In the study by May et al, ≥95% of women who reportedly consumed alcohol at each time point indicated using strategies to minimize the amount of alcohol consumed by the infant (e.g., waiting until after feeding, used only formula or expressed milk if drinking),[7] likely limiting the ability of the study to detect an effect of parental alcohol consumption on the breastfed infant. Potentially informative data regarding strategies employed to limit infant alcohol exposure were not analyzed in a meaningful way of relevance to this report.

Conclusions and Implications for Decision or Policy Making

Two non-randomized studies and one evidence based guideline regarding the safety of the consumption of controlled or illicit substances during the breastfeeding period were included in this review.

Overall, evidence was somewhat mixed. Alcohol consumption during the breastfeeding period by parents who breastfed for at least 12 months was associated with smaller weight centile and lower verbal IQ but not with OFC centile, palpebral fissure length centile, or total dysmorphology score in 6 to 8 year old children in one non-randomized study at high risk for bias. In another non-randomized study, postnatal alcohol consumption by breastfeeding

parents was associated with lower likelihood for infants to be identified as having a developmental delay identified by the Personal-Social Interactions subscale of the ASQ-3, or to require monitoring for a developmental delay at age 12 months. No other 12 month outcomes and no 8 week developmental outcome differences were identified.

The included studies had a moderate quality, and were subject to limitations. An important limitation of both studies is related to the lack of information around the timing of breastfeeds in relation to alcohol consumption. Evidence does exist regarding the timing of alcohol consumption and breastfeeding as it relates to the content of alcohol in breastmilk, however these studies were outside the scope of this report.

No definitive conclusions can be made regarding an effect or a dose effect of alcohol consumption on the infant based on the evidence available from the included studies. Similarly, questions remain regarding the timing and frequency of alcohol consumption during the breastfeeding period. There was no evidence identified regarding the effects of using substances other than alcohol while breastfeeding or regarding safety for the breastfeeding parent. Uncertainty would be reduced with larger, high quality studies, however, randomized studies would not be appropriate in most contexts.

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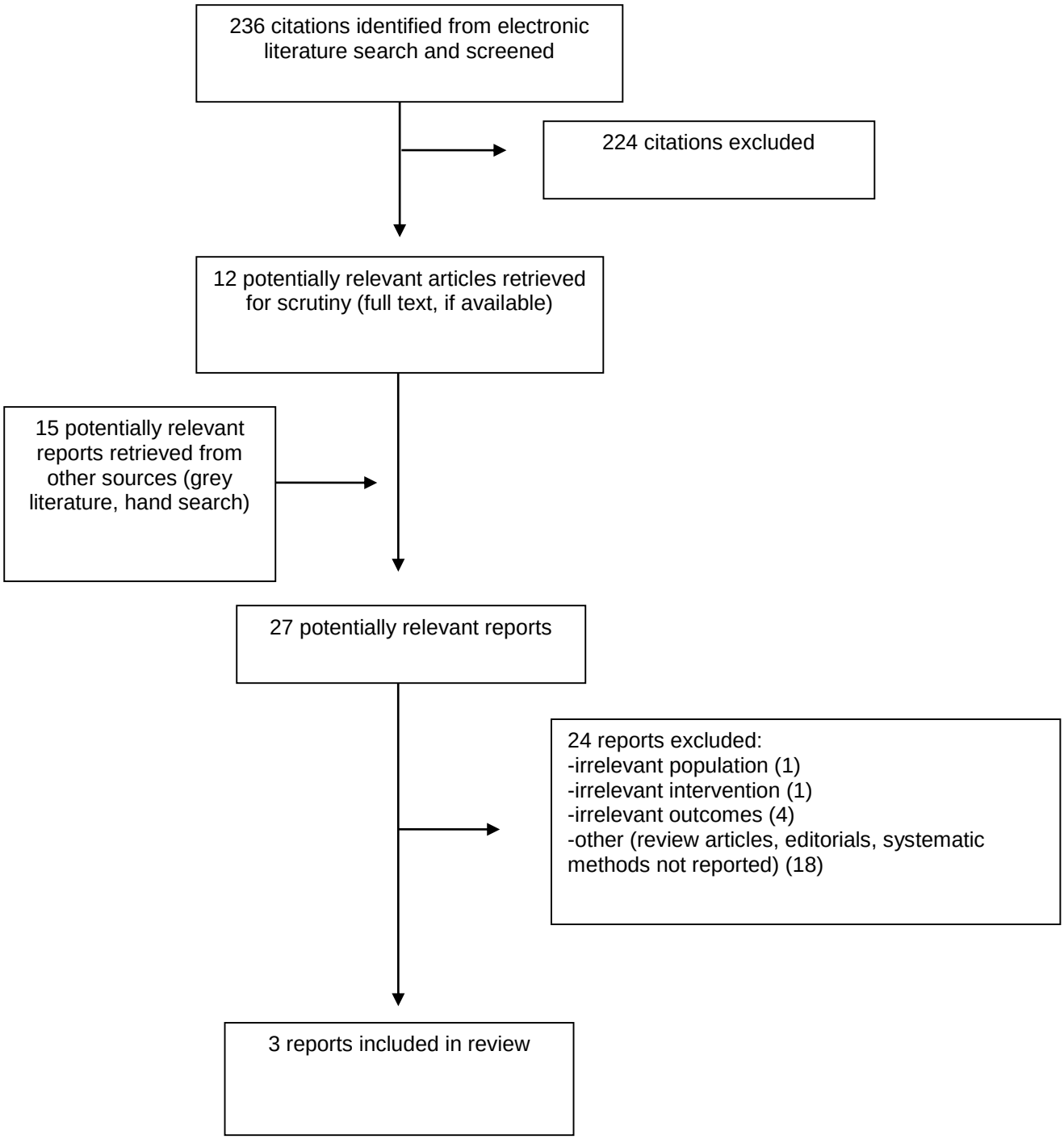
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Wilson, 2017 Australia[8]	Prospective birth cohort study. Pregnant women[a] were recruited at general prenatal clinics in public hospitals and area health services. Data were collected at 8 weeks and 12 months postnatal; the breastfeeding period was 12 months or longer.	Mother-infant pairs (N=402 pairs) Infants were assessed at 8 weeks and 12 months of age At 8 weeks postpartum, mothers who consumed alcohol vs. did not consume alcohol: Had a mean age of 33.6 (4.1) years vs 32.1 (4.9) years; Born in an English speaking country (84.5% vs 57.6%); Had weekly household income ≥2000 (75.5% vs 51.3%); and had other children under mother's care (61.9% vs 57.6%)	Alcohol consumption: Abstinence versus composite of 'low, moderate, risky and heavy drinking' 8 weeks: 39.3% abstinent (n = 158) 49.5% low (n = 199) 5.7% moderate (n = 23) 4.2% risky (n = 17) 1.2% heavy (n = 5) 12 months: 30.4% abstinent (n = 58) 42.4% low (n = 81) 8.9% moderate (n = 17) 13.1% risky (n = 25) 5.2% heavy (n = 10)	Infants' social, mental and motor development (i.e., communication, gross motor function, fine motor function, problem solving, personal-social interactions and social-emotional functioning) at 8 weeks and 12 months
May, 2016, South Africa[7]	Population-based active case ascertainment study. Children with FASD were matched with typically developing children. Participants were recruited from five communities in the Western Cape Province in South Africa	Mothers[a] and their 6 to 8 year old children (N = 1,047 pairs) Cases had a diagnosis of FASD Overall, average duration of breastfeeding = 19.9 months (20.0); Parents of FAS = 20.6; prenatally exposed controls = 19.9 (20.1); prenatally unexposed controls = 18.3 (19.5) months Reported Consuming alcohol during the breastfeeding period = 71.0%	Maternal alcohol exposure: Composite of average number of drinks per pregnancy coded as: 0 = no drinks 1 = < 3 drinks 2 = ≥3 drinks Average drinks per week: 0 = no drinks 1 = <7 drinks 2 = ≥7 drinks Days per month: 0 = no drinks 1 = <8 days	Diagnosis of FASD (i.e., fetal alcohol syndrome, partial fetal alcohol syndrome, alcohol-related neurodevelopmental disorders, and alcohol related birth defects) at ages 6 and 8

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Parents of FAS = 91.8%; prenatally exposed controls =85.7%; prenatally unexposed controls = 29.4%	2 = ≥8 days	

FAS = fetal alcohol spectrum disorders

[a] we recognize that individuals with varied gender expression and sexualities may breastfeed and reflect this in our report where possible, however, we use the language reported in the published literature to maintain accuracy and the intent of the study authors

alcohol consumption levels were: abstinent (0 drinks per week) low (≤14 standard drinks / week, and <3 drink per occasion), moderate (≤14 standard drinks per week, ≥3 to <5 standard drinks per occasion), risky drinking (≤14 standard drinks per week, ≥5 standard drinks per occasion), heavy (>14 standard drinks per week)

Table 3: Characteristics of Included Guideline

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
WHO, 2014[9]						
Health care providers who provide prenatal, postnatal and infant care	Identification and management of substance use and substance disorders in pregnancy	Healthy outcomes for pregnant individuals and their fetus or infant	A SR was conducted by four investigators to identify recent Cochrane reviews or other high quality SRs. Where none existed, a de novo SR was conducted.	GRADE	Evidence profiles and GRADE tables were presented to the GDG. Final recommendations were formulated based on the evidence	Recommendations were reviewed by an external review group, revised and finalized by the GDG

GDG = guideline development group; GRADE = The Grading of Recommendations Assessment, Development and Evaluation; SR = systematic review; WHO = World Health Organization

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Clinical Studies using Down's and Black Checklist[5]

Strengths	Limitations
Wilson, 2017[8]	
Reporting • The objectives, main outcomes, participant characteristics, interventions, distributions of principal confounders, main findings, estimates of random variability, characteristics of patients lost to follow-up, and probability values were clearly reported **External validity** • Staff, places, and facilities where the participants were treated did not differ between study participants and non-participants **Internal validity** • Statistical tests were appropriate • Analyses appear to have been planned at study outset • Follow-up length was the same for all participants • Outcome measures were valid and reliable • All patients were recruited from the same locations, over the same period of time • Analyses included adjustment for confounding • Participant losses to follow up were negligible	**External validity** • Participants were more likely to be older, employed, and primigravida than women who were informed about the study and screened but declined to participate. **Internal validity** • Participants were not recruited at random • Unclear if outcome assessors were blinded to maternal alcohol consumption status **Power** • It is not clear if power was calculated
May, 2016[7]	
Reporting • The objectives, main outcomes, participant characteristics, interventions, distributions of principal confounders, main findings, estimates of random variability, and probability values were clearly reported. **Internal validity** • Statistical tests were appropriate • Analyses appear to have been planned at study outset • Outcome measures were valid and reliable	**Reporting** • Characteristics of participants with missing data were not reported **External validity** • It is unclear if staff, places, and facilities where the participants were treated differed from those of non-participants **Internal validity** • Missing data ranged from 0-17% and reasons not reported • Follow-up length could have ranged two years, however this is unlikely to have affected the outcomes of interest • Unknown validity and reliability of outcome measures • Unclear if outcome assessors were blinded to maternal alcohol consumption status **Power** • It is not clear if power was calculated

Table 5: Strengths and Limitations of Guidelines using AGREE II[6]

Item	Guideline
	WHO, 2014[9]
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	✓
2. The health question(s) covered by the guideline is (are) specifically described.	✓
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	✓
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	✓
5. The views and preferences of the target population (patients, public, etc.) have been sought.	✓
6. The target users of the guideline are clearly defined.	✓
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	✓
8. The criteria for selecting the evidence are clearly described.	✓
9. The strengths and limitations of the body of evidence are clearly described.	✓
10. The methods for formulating the recommendations are clearly described.	✓
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	✓
12. There is an explicit link between the recommendations and the supporting evidence.	✓
13. The guideline has been externally reviewed by experts prior to its publication.	✓
14. A procedure for updating the guideline is provided.	✓
Domain 4: Clarity of Presentation	
15. The recommendations are specific and unambiguous.	✓
16. The different options for management of the condition or health issue are clearly presented.	✓

Item	Guideline
17. Key recommendations are easily identifiable.	✓
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	✓
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	x
20. The potential resource implications of applying the recommendations have been considered.	✓
21. The guideline presents monitoring and/or auditing criteria.	x
Domain 6: Editorial Independence	
22. The views of the funding body have not influenced the content of the guideline.	unclear
23. Competing interests of guideline development group members have been recorded and addressed.	✓

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Non-Randomized Studies	
Wilson (2017)[8]	
<u>Abstinent (0 average weekly drinks consumed during the past 8 weeks) vs. consumed alcohol (more than 0 average weekly drinks during the past 8 weeks) assessed at 8 weeks postpartum</u> <u>Communication</u> No difference between abstinence and consumed alcohol • OR: 0.82 (95% CI 0.45 to 1.42) p=0.47 • Adjusted OR: 0.74 (95% CI 0.42 to1.31) p=0.31 <u>Gross motor</u> No difference between abstinence and consumed alcohol • OR: 0.95 (95% CI 0.50 to 1.81) p=0.88 • Adjusted OR: 1.16 (95% CI 0.59 to 2.28) p=0.68 <u>Fine motor</u> No difference between abstinence and consumed alcohol • OR: 1.14 (95% CI 0.66 to 1.96) p=0.64 • Adjusted OR: 1.09 (95% CI 0.63 to 1.88) p=0.77 <u>Problem solving</u> No difference between abstinence and consumed alcohol • OR: 0.92 (95% CI 0.54 to 1.54) p=0.74 • Adjusted OR: 0.92 (95% CI 0.54 to 1.54) p=0.74 <u>Personal-social interactions</u> No difference between abstinence and consumed alcohol • OR: 1.36 (95% CI 0.73 to 2.53) p=0.33 • Adjusted OR: 1.32 (95% CI 0.69 to 2.55) p=0.40 <u>Abstinent (0 average weekly drinks consumed during the past month) vs. consumed alcohol (more than 0 average weekly drinks during the past month) assessed at 12-months postpartum:</u> <u>Communication</u> No difference between abstinence and consumed alcohol • OR: 0.97 (95% CI 0.53 to 1.79) p=0.93 • Adjusted OR: 0.97 (95% CI 0.53 to 1.79) p=0.93 <u>Gross motor</u> No difference between abstinence and consumed alcohol • OR: 0.89 (95% CI 0.56 to 1.44) p=0.64 • Adjusted OR: 0.87 (95% CI 0.53 to 1.42) p=0.57 <u>Fine motor</u>	Developmental outcomes were not related to consumption of alcohol at 8 weeks postpartum, before or after adjusting for potential confounders. At 12 months postpartum, 1 of 6 outcomes was significantly different between groups: "*infants of mothers who drank alcohol were significantly less likely than those whose mothers abstained to score below cut-off or within the monitoring zone*" on the ASQ-3 Personal-Social Interactions subscale (p672)

Main Study Findings	Authors' Conclusion
No difference between abstinence and consumed alcohol • OR: 1.45 (95% CI 0.82 to 2.54) p=0.20 • Adjusted OR: 1.24 (95% CI 0.67 to 2.27) p=0.50 <u>Problem solving</u> No difference between abstinence and consumed alcohol • OR: 0.91 (95% CI 0.50 to 1.65) p=0.75 • Adjusted OR: 0.70 (95% CI 0.37 to 1.32) p=0.27 <u>Personal-social interactions</u> No difference between abstinence and consumed alcohol • OR: 2.48 (95% CI 1.48 to 4.15) p=0.001 • Adjusted OR: 2.43 (95% CI 1.43 to 4.13) p=0.001 <u>Social-emotional</u> No difference between abstinence and consumed alcohol • OR: 2.90 (95% CI 0.95 to 8.84) p=0.06 • Adjusted OR: 1.11 (95% CI 0.32 to 3.90) p=0.87	
May, 2016[7]	
Mean (SD) <u>Weight centile</u> Unexposed with alcohol in breastmilk 15.9 (14.7) vs. unexposed without alcohol in breastmilk 26.8 (22.5); p=.007 FASD with alcohol in breastmilk 6.8 (9.3) vs. FASD without alcohol in breastmilk 11.4 (14.9); p=.107 <u>OFC centile</u> Unexposed with alcohol in breastmilk 22.2 (26.7) vs. unexposed without alcohol in breastmilk 30.0 (25.0); p=.185 FASD with alcohol in breastmilk 10.9 (17.2) vs. FASD without alcohol in breastmilk 16.7 (18.3); p=.090 <u>Palpebral fissure length centile</u> Unexposed with alcohol in breastmilk 20.2 (14.2) vs. unexposed without alcohol in breastmilk 26.5 (15.8); p=.077 FASD with alcohol in breastmilk 9.2 (10.9) vs. FASD without alcohol in breastmilk 10.9 (11.1); p=.434 <u>Total dysmorphology score</u> Unexposed with alcohol in breastmilk 9.7 (4.8) vs. unexposed without alcohol in breastmilk 7.7 (4.4); p=.053 FASD with alcohol in breastmilk 16.4 (4.1) vs. FASD without	"*Alcohol exposure via breastmilk in these samples are definitely associated with multiple, negative developmental traits in children by age 7 that lead to a diagnosis of FASD and to the FAS phenotype in general. They also support a conservative conclusion that women who breastfeed their children should avoid drinking alcohol during the breastfeeding period, especially in large amounts over short periods of time (binge drinking), and especially if the child was already exposed to alcohol in the prenatal period. Even though the amounts of alcohol that have been found to pass from mother to baby are proportionally low, and the effects/specific outcomes in young children are difficult to measure in a study like this one, alcohol in the breastmilk has been found to be a significant enough factor to limit or otherwise further delay a child's physical growth and neurodevelopment*." (p11) "*In case control analyses, children of MDPB were significantly lighter, had lower verbal IQ scores, and more anomalies in comparisons controlling for prenatal alcohol exposure and final FASD diagnosis. Utilizing a stepwise logistic regression model adjusting for nine confounders of prenatal drinking and other maternal risks, MDPB were 6.4 times more likely to have a child with FASD than breastfeeding mothers who abstained from alcohol while breastfeeding*." (p2)

Main Study Findings	Authors' Conclusion
alcohol in breastmilk 14.2 (5.2); p=.029 <u>Verbal IQ (TROG) Score</u> Unexposed with alcohol in breastmilk 18.2 (13.3) vs. unexposed without alcohol in breastmilk 27.6 (19.8); p=.011 FASD with alcohol in breastmilk 8.8 (12.2) vs. FASD without alcohol in breastmilk 15.9 (16.8); p=.059 <u>Logistic Regression Analysis of FASD diagnosis and breastfeeding</u> <u>Drank alcohol while breastfeeding</u> Beta = 1.863, SE = 0.729, p=.009 OR = 6.446 (95% CI 1.543 to 26.924) Short vs. long duration of breastfeeding Beta = 0.913, SE = 0.551, p = 0.97 OR = 2.493 (95% CI 0.847 to 7.338)	

ASQ-3 = Ages and Stages Questionnaire, 3rd Edition; CI = Confidence Interval; FASD = fetal alcohol spectrum disorderes; OFC = occipitofrontal circumference; OR = Odds Ratio; SE = standard error; TROG = Test for the Reception of Grammar

Table 7: Summary of Recommendations in Included Guideline

Recommendations	Strength of Evidence and Recommendations
WHO, 2014[9]	
Breastfeeding with maternal alcohol and/or substance dependence	
12.A. "*Mothers with substance use disorders should be encouraged to breastfeed unless the risks clearly outweigh the benefits*." (p.xii) 12.B. "*Breastfeeding women using alcohol or drugs should be advised and supported to cease alcohol or drug use; however, substance use is not necessarily a contraindication to breastfeeding*." (pxii)	Conditional recommendation, low quality of evidence
14. "Mothers who are stable on opioid maintenance treatment with either methadone or buprenorphine should be encouraged to breastfeed unless the risks clearly outweigh the benefits." (pxiii)	Strong recommendation, low quality of evidence

WHO = World Health Organization

Appendix 5: Additional References of Potential Interest

CADTH Reports

The diagnosis and treatment of neonatal abstinence syndrome: clinical effectiveness and guidelines. Ottawa (ON): CADTH; 2017: https://www.cadth.ca/sites/default/files/pdf/htis/2017/RB1086%20-%20NAS%20Final.pdf. Accessed Sept 12, 2018 (CADTH rapid response report: summary of abstracts).

Guidelines with Unclear Methodology

Graves et al. Breastfeeding and opiate substitution therapy: starting to understand infant feeding choices. Subst Abuse. 2016;10(S1):43-47.

Narrative Reviews

Brown RA, Dakkak H, Seabrook JA. Is breast best? Examining the effects of alcohol and cannabis use during lactation. *J Neonatal Perinatal Med*. 2018 May 23.