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Management and monitoring of opioid use in pregnancy

Nete Lundager Klokker RAUSGAARD, Inge Olga IBSEN, Jan Stener JØRGENSEN, Ronald Francis LAMONT, Pernille RAVN

Department of Gynecology and Obstetrics, University of Southern Denmark, Odense University Hospital, Odense, Denmark

Corresponding author:
Nete Lundager Klokker Rausgaard
Research Unit of Obstetrics and Gynecology, Clinical Institute, University of Southern Denmark, Department of Gynecology and Obstetrics, Odense University Hospital, Boulevard 29, Indgang 55, 5000 Odense C, Denmark
Email: neterausgaard@gmail.com

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ABSTRACT

Opioid use during pregnancy has serious consequences for mother and baby. The true extent of the problem is unknown and there is a need for better screening. Existing guidelines with respect to the management of pregnant women with opioid use are based on limited evidence. To improve recommendations for optimal identification, management and treatment, publications on opioids in pregnancy were reviewed. Published literature from 2007 to 2017 was searched in PubMed, Cochrane and Embase Databases. The review employed 60 publications from 210 studies identified, that were of varying quality and included randomized controlled trials, systematic reviews, meta-analyses and Cochrane reviews. The prevalence of opioid use in pregnancy is underestimated. Screening by urine testing and self-reporting is acceptable to identify fetal exposure. To minimize risk, opioid agonist pharmacotherapy should replace the continued use of opioids or detoxification. Current guidelines recommend methadone and buprenorphine equally. However, recent studies indicate that buprenorphine has advantages over methadone. Accordingly, we suggest buprenorphine as first-line therapy. Future studies should elaborate on better objective screening methods to prevent the consequences of fetomaternal opioid exposure.

Keywords
Buprenorphine, methadone, neonatal abstinence syndrome, opioid, opioid abuse, opioid use disorder, pregnancy, substance abuse.

Abbreviations
ACOG American College of Obstetrics and Gynecology
MOTHER Maternal Opioid Treatment: Human Experimental Research study
NAS neonatal abstinence syndrome
OUD opioid use disorder / opioid use
SAMHSA Substance Abuse and Mental Health Services Administration
SUD substance use disorder / substance use
WHO World Health Organization
Key Message
We suggest a change to the standard recommendation of opioid agonist pharmacotherapy in pregnancy of buprenorphine over methadone. Furthermore, we propose a model of screening for substance use in early antenatal care by repeated self-reporting and maternal urine analyses.

1. INTRODUCTION

1.1 Definition and Nomenclature
Controversy exists with respect to terminology of substance “use” versus “abuse”. The term “abuse” is a Medical Subject Heading (MeSH, used by PubMed/Medline) term and hence, used widely in the published literature. In contrast, Substance Abuse and Mental Health Services Administration (SAMHSA) uses the term “substance use disorder” (SUD). The definition of pregnant women with SUD covers all use of substances regardless of indication. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) combines the previous terms “opioid abuse” and “opioid dependence” into the all-encompassing term “opioid use disorder” (OUD) (1). The term “use” does not stigmatize individuals and is favoured and recommended in daily clinical practice in our Family Clinics, Denmark. For the purpose of this review we will use the term “use”.

There is also a global discrepancy in the distinction between opioids and opiates. Opiates are either natural or semi-synthetic. Natural opiates are synthesized from the naturally occurring compound opium. Semi-synthetic opiates are not present in opium, but can be produced from the natural opiates. Somewhat confusingly, naturally occurring opiates can also be produced synthetically. Opioids are drugs that act like morphine, however, there remains some overlap between opiates and opioids. In this review we follow earlier recommendations and apply the term opioids to all. With respect to opioids, SAMHSA divides pregnant women who use opioids into four groups: i) those receiving pain management, ii) those undergoing treatment for OUD, iii) misusing or abusing opioid pain medications with or without prescription, and iv) using or abusing illicit opioids (2). Ideally, these groups should be considered separately, but much of the published literature pools the data.

1.2 Current Management
Existing guidelines with respect to the management of pregnant women with SUD are based on evidence that is either sparse or is not robust. Identification of pregnant women with SUD is complex, and since there is no gold-standard, screening methods need to be updated, though pregnant women with SUD are generally reluctant to participate in antenatal care programmes (3). Without universal screening methods, there is a risk of stigmatizing women and overlooking cases (4). Identification of OUD is mainly dependent on maternal self-reporting, and improved methods of identification are likely to help healthcare professionals to detect relevant cases and to target specialized, supportive obstetric care.

1.3 Extent of the problem

According to the SAMHSA and the National Institute on Drug Abuse, the overall prevalence of SUD in pregnant women in the USA is 4–5%, and about 21% among 15 to 17 year olds (5). During the period 2000-2009, the prevalence of antepartum OUD increased nearly 5-fold from 1.19 to 5.63/1000 births (6). Recent data from the Region of Southern Denmark showed an overall prevalence of SUD of 3.6% among pregnant women, 79% of which was due to OUD, which was higher than expected (7).

1.4 Purpose of this review

This manuscript reviews the existing literature on the management of OUD in pregnancy and methods for identification of pregnant women with SUD and exposed fetuses. The aim was to improve recommendations that will optimize identification, management and treatment.

2. MATERIAL AND METHODS

2.1 Description of search

The literature search was limited to the period: 01/01/2007 to 01/01/2017, to the five languages we understand: English, Danish, German, Norwegian and Swedish. The databases used were PubMed, Embase Record and Cochrane Library. The database search terms were: exp pregnancy combined with exp drug abuse, exp substance abuse, exp opiate and opioid.mp (Figure 1). The searches in PubMed and Embase Record were limited to the following study designs: i) clinical trials; ii) randomized controlled trials; iii) controlled clinical trials; iv) meta-analyses; v) systematic reviews and vi) reviews. The search in Cochrane Library comprised: i) Cochrane reviews; ii) other reviews; iii) trials; iv) methodological studies; v) technology assessments; vi) economic evaluations and vii) Cochrane groups. Identical searches were carried out four times,
the most recent being January 2017. Similar searches were carried out for cocaine, amphetamines, ecstasy, cannabis and benzodiazepines (including synonyms), but these substances will be the subjects of separate reports. We did not include alcohol and tobacco in our search, because their role in pregnancy is well understood and covered by excellent reviews elsewhere. The focus of the literature search was management of pregnant women with OUD. Perinatal risks of OUD (obstetric, fetal and neonatal outcomes until the first 28 days of life) will be reviewed as part of a separate manuscript. If an abstract was deemed relevant, the article was read in full. Due to the heterogeneity of articles, all articles within the focus criteria, regardless of quality, were reviewed and evaluated (Figure 1). Retrieved articles were hand searched for additional references. Abstracts presented at conferences were excluded.

2.2 Guidelines/policies
During the designated search period, four guideline/policy documents were produced (2, 8-10), and two additional relevant guidelines were published thereafter (4, 11).

2.3 Clinical studies
In total, 86 individual studies were published during the designated search period. The focus of these studies varied: i) prevalence of SUD; ii) teratogenicity of opioids; iii) effects of opioids; iv) comparison of methadone and buprenorphine, and v) detection of substance use (Supporting Information Tables S1a-j).

2.4 Systematic reviews and meta-analyses
One systematic review was carried out that focussed on tramadol in pregnancy (12). In addition, four systematic reviews with meta-analyses were published, focusing on methadone and i) the risk of the neonatal abstinence syndrome (NAS); ii) comparison of methadone and buprenorphine and iii) integrated treatment programmes for pregnant women with SUD (3, 13-15).

2.5 Cochrane reviews
During the designated search period, one Cochrane review was published that covered treatment of opioid dependence in pregnancy (5).

2.6 Reviews

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In total, 109 reviews of varying quality were published. The topics varied from: i) effects of opioids including methadone and buprenorphine; ii) NAS; iii) intrauterine abstinence syndrome (IAS) and iv) detection of SUD.

2.7 Selection of articles
All articles were read and contributed to the manuscript, except from reviews, where only a few merited inclusion. Guidelines, best-quality articles (such as systematic reviews, meta-analyses, Cochrane reviews) and the most recent articles received the greatest emphasis. As per journal instructions, the reference list was restricted to 60 references, but a full reference list can be provided on request.

2.8 Supporting Information tables
For more information, see Supporting Information Tables S1a-j for a detailed report of findings in the studies and meta-analyses that were included.

3. RESULTS

3.1 Management
The different strategies are discussed below with respect to: i) continued opioid use; ii) detoxification (Alternative 1) and iii) Opioid Agonist Pharmacotherapy with either methadone (Alternative 2) or buprenorphine (Alternative 3) (Figure 2). The term “continued use” in this review refers to self-administered, uncontrolled use of illegal or unprescribed opioids that do not have any medical advantages. The disadvantages include a wide spectrum of obstetric, fetal and neonatal complications, which will be covered in a separate review.

3.1.1 Alternative 1: Detoxification
To prevent NAS, several clinicians have suggested opioid detoxification (16-19). One study found better NAS-outcomes after detoxification from buprenorphine compared to continued treatment (16) (Supporting Information Table S1a). Some studies defined tapering off opioid-agonist pharmacotherapy as “detoxification”. Others defined detoxification as an abrupt discontinuation. One study compared different definitions of detoxification, and concluded that detoxification (with tapering off buprenorphine) did not appear to harm the fetus, and that the incidence of NAS, and the potential risk of relapse can be reduced with long-term behavioral management (18). The study has subsequently been criticized for overlooking fatal maternal and

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neonatal risks (20). Another smaller study defined successful detoxification as “no illicit drug supplementation at delivery” regardless of continued use or tapered-off methadone (19), and found benefit of detoxification, when focusing on a few, specific neonatal outcomes. One study investigated the effect of methadone pharmacotherapy after tapering off methadone, and indicated a neutral effect on adverse obstetric or fetal outcomes, but poorer maternal outcomes (21). A further study found a significantly larger head circumference among infants exposed to the combination of buprenorphine plus naloxone compared to methadone-assisted withdrawal, but a neutral effect on other neonatal outcomes (22). Detoxification carried the risk of fluctuating concentrations of opioids during cycles of abstinence, which increased the risk of complications (Figure 2). Accordingly, detoxification is generally not recommended during pregnancy. This recommendation is supported by SAMHSA (11) and the World Health Organization (WHO): “pregnant women dependent on opioids should be encouraged to use opioid maintenance treatment whenever available, rather than to attempt opioid detoxification” (8).

3.1.2 Alternative 2: Methadone
Methadone has been described as the standard Opioid Agonist Pharmacotherapy among pregnant women (2). Methadone reduces the adverse effects of opioids even though it is also an opioid (Figure 2). The American College of Obstetrics and Gynecology (ACOG) highlights that Opioid Agonist Pharmacotherapy improves participation in antenatal care and addiction treatment programmes (4). Methadone has a long half-life and must be administered less frequently than opioids such as heroin to maintain therapeutic concentrations of opioid (5). This minimizes the risk of withdrawal and reduces the risk of complications, including low compliance to antenatal care and maternal risk behavior, compared to continued use of other opioids (Figure 2). For ethical reasons, it is not possible to determine whether this is due to the treatment itself or the associated improvements in antenatal care. Although methadone still causes NAS that may be worse than after exposure to continued use of other opioids (Figure 2), the less harmful effects of methadone are thought to outweigh the risks of untreated OUD (11).

3.1.3 Alternative 3: Buprenorphine
Buprenorphine is marketed with or without naloxone. When administered intravenously or intranasally, but not sublingually, naloxone precipitates withdrawal from opioids. It is added as a deterrent to buprenorphine sublingually to limit misuse (23). Due to lack of data, the WHO recommends the mono-product of buprenorphine before buprenorphine plus naloxone (23). In contrast, the ACOG recommends the mono-product due to the risk of inducing immediate fetal
withdrawal with buprenorphine plus naloxone (24). Two studies compared the use of buprenorphine plus naloxone with either no opioid use, or illegal opioid use, other than buprenorphine plus naloxone (23, 25). Both studies supported the safety of buprenorphine plus naloxone. Furthermore, the study indicated that women treated with buprenorphine plus naloxone, reduced or stopped their use of other substances compared to women with ongoing illicit opioid use (23, 25). Another study, which extracted data from seven published studies, compared the use of buprenorphine plus naloxone with both buprenorphine and methadone, and found that birth parameters were within the normal range, but concluded that more research was needed (22).

There is a paucity of information with respect to the combination of buprenorphine plus naloxone compared to buprenorphine alone. SAMHSA concluded that experts did not agree on whether or not a woman on buprenorphine plus naloxone for OUD, who intended to become pregnant, or were in the early stages of pregnancy, should be changed from the combination of buprenorphine plus naloxone to the buprenorphine-only product (11).

3.1.4 Methadone vs buprenorphine
The Maternal Opioid Treatment: Human Experimental Research study (MOTHER) trial (26), investigated Opioid Agonist Pharmacotherapy with buprenorphine or methadone. There were no significant differences in the primary outcomes: i) NAS incidence requiring treatment; ii) NAS peak score or iii) head circumference, on neonatal outcomes such as birth weight, birth length, preterm birth, gestational age, Apgar score or maternal outcomes (Supporting Information Table S1b). Nevertheless, the MOTHER trial showed significantly better effects of buprenorphine compared to methadone with respect to infant need of morphine, hospital stay and duration of treatment. The authors suggested that buprenorphine should be considered first choice for Opioid Agonist Pharmacotherapy. Twenty-two studies (3, 5, 14, 22, 26-40) including the MOTHER trial, a Cochrane-review with meta-analysis and two systematic reviews with meta-analyses, confirmed the safety of buprenorphine (Supporting Information Table S1b). The studies indicated similar or better results for buprenorphine on stillbirth, malformations, miscarriages, preterm birth, mode of delivery, anthropometric measurements at birth, NAS variables, duration of hospitalization, Apgar scores, arterial cord blood pH, respiratory distress, gestational age at birth, cardiac measures and gender distributions, compared to methadone. In addition, a systematic review and meta-analysis concluded that buprenorphine had advantages compared to methadone with respect to risk of relapse (14).
It has been suggested that infants of buprenorphine-maintained mothers are exposed to a reduced maternal dose of buprenorphine compared to methadone (41). This would explain the reduced severity of withdrawal symptoms observed in buprenorphine-exposed infants. The ACOG and the American Society of Addiction Medicine have jointly acknowledged that “emerging evidence supports the use of buprenorphine for opioid-assisted treatment during pregnancy” (4). In addition, WHO recommends, “opioid-dependent pregnant women who are already taking opioid maintenance therapy with methadone, should not be advised to change to buprenorphine due to the risk of opioid withdrawal” (8), a recommendation that is confirmed by ACOG (4). WHO continues, “pregnant opioid-dependent women taking buprenorphine should not be advised to switch to methadone unless they are not responding well to their current treatment” (8). In summary, buprenorphine appears to be as safe as, and has advantages over, methadone (Figure 2).

3.1.5 Dose-response-relationship between opioid agonist pharmacotherapy and NAS

A reduction in dose can cause withdrawal symptoms and relapse into SUD (42) (Supporting Information Table S1c). Similarly, pregnant women maintained on methadone on lower doses, have higher concomitant use of opioids compared to women on higher doses (43). According to NAS variables, reduction in buprenorphine dosage did not harm the fetus (16). This raises the question of whether high doses should be recommended to minimize withdrawal and illicit use. The majority of studies (13, 26, 30, 31, 34, 40, 41, 44-53) including the MOTHER trial and a systematic review and meta-analysis, found no dose-response relationship between methadone, buprenorphine or prescribed non-maintenance opioids and NAS variables or other neonatal outcomes (Supporting Information Table S1d). Only a few studies (42, 54-56) found a positive dose-response relationship and three studies found inconsistent results (57) (Supporting Information Table S1d).

When considering the effects of dosage on NAS, the method to assess NAS is relevant. Some studies focus on NAS incidence (13, 34, 45, 56), some use the ICD-9 classification of NAS (56), and others only use the term when symptoms require treatment (48, 49, 54, 57). Generally, pediatricians use the Finnegan scoring system designed for full-term infants. Accordingly, the use in preterm infants is problematic due to immaturity of the central nervous system (54).

Some studies with negative dose-response findings are interrelated: The MOTHER trial (26) serves as a parent study for several substudies (48, 51, 53), and some studies are retrospective (45, 50, 52). However, other studies with positive dose-response findings were of small sample size (55, 57), of retrospective design (54, 57), used dose-based calculations of prescribed

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opioids, and did not take into account other opioid use (56), or included maternal self-report (55). The conclusion is that the dose does not appear to affect NAS, and as ACOG and SAMHSA also recommend, dose adjustments should be advised to prevent withdrawal and relapse into OUD (4, 11).

3.1.6 Duration of treatment and timing of initiation of opioid agonist pharmacotherapy and NAS variables

There is consensus that dosage does not affect the severity of NAS, but the timing of initiation, and duration of treatment, may influence NAS variables. One study found a higher risk of NAS among infants exposed to prescribed non-maintenance opioids in late pregnancy, compared to use in early pregnancy, and among infants exposed to long term opioid use, compared to short term use (56) (Supporting Information Table S1e). Another study (29) found that initiation of buprenorphine prior to conception, compared to post-conception, reduced NAS variables. However, most studies have failed to confirm the influence of timing of initiation or duration of treatment (44-50). It has been proposed that associations between greater duration of maternal medication and better neonatal outcomes occur because of a longer time in antenatal care and hence reduced concomitant substance use (48). Methadone and buprenorphine have a ceiling effect (defined as the optimal potential effect) on analgesia and euphoria (2, 13), which makes these substances favorable for treatment of OUD. It is assumed that buprenorphine has a lower ceiling of opioid effect than methadone (26). A shift from high doses of opioids to buprenorphine will cause withdrawal symptoms, since buprenorphine blocks the effect of other opioids (2). This explains why dose reduction is fruitless if previous use exceeds that ceiling. A change from buprenorphine to methadone should follow the usual methadone induction procedures (11), whereas a change from methadone to buprenorphine should follow methadone tapering and several days of abstinence (11). Buprenorphine has a high affinity for the opioid receptor, so is a competitive inhibitor that minimizes the risk of overdose (4, 9, 11). In general, drug metabolism increases during pregnancy (4, 9, 11), and this also applies to buprenorphine (58) (Supporting Information Table S1g). To prevent withdrawal and relapse into substance use, split dosing must be optimized and a significantly more reassuring fetal heart rate, better variability and motor activity, have been reported with this approach (4, 11, 44). It is likely that the severity of NAS depends more on the use of other substances and/or fetal and neonatal clearance rates.

3.2 Monitoring of substance use

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3.2.1 Fetal monitoring

Transition from methadone to buprenorphine can cause maternal and fetal withdrawal symptoms, which can be life threatening for the fetus. The MOTHER trial has been criticized for not addressing whether or not the fetus suffered from withdrawal during the induction with buprenorphine (17, 59), albeit that no validated methods to monitor fetal withdrawal have been described (17, 59). The ACOG recommends fetal monitoring between 32 and 34 weeks gestation (10). Only three studies have attempted to monitor fetal withdrawal using fetal heart rate, variability, motor activity, movement, stress test and biophysical profile. Two studies confirmed the finding of fetal wellbeing (33, 35). The third study found changes in fetal neurobehavioral measures, without concurrent changes in measures of maternal wellbeing (44) (Supporting Information Table S1). Accordingly, it might be possible to monitor the effects on fetal wellbeing, when we have a suspicion of failure to thrive, but whether this reflects fetal withdrawal remains unclear. In the absence of validated methods, it has been suggested that fetal withdrawal should be linked exclusively to maternal withdrawal symptoms (17, 59).

3.2.2 Exposure monitoring

The assessment of fetal risks of antenatal substance use, including fetal withdrawal, relies on estimates of fetal exposure. Candidate specimens include: i) meconium; ii) cord blood; iii) maternal and neonatal hair; iv) nails; v) gastric fluids; vi) maternal and neonatal urine; vii) placenta; viii) saliva; ix) sweat and x) amniotic fluid. Each choice of specimen has its pros and cons, and results depend on the substance and specimen chosen. In general, biological specimens from pregnant women supply little information on true fetal exposure, whereas neonatal specimens are more closely related to actual exposure in utero. Meconium, amniotic fluid and maternal and neonatal hair have the longest windows of detection and reflect long-term accumulation. Meconium may be delayed or be missing (if discharged before delivery), and may also reflect substance administration directly to the newborn child. Neonatal hair, placenta and the umbilical cord are all accessible immediately after delivery. Analysis of samples of neonatal hair cannot distinguish between environmental exposure and maternal use, and hair may be sparse. Meconium forms in the second trimester and neonatal hair in the third trimester, so these components do not reflect exposure in early pregnancy. In contrast, maternal hair, placenta and amniotic fluid reflect use in early fetal life, but the collection of amniotic fluid is difficult. Placenta and cord blood have even shorter windows of detection than meconium, hair and urine.
Self-reporting is non-invasive and is cost effective. Self-reporting also gives information about timing and amount of exposure during pregnancy, but the method is vulnerable due to reliance on trust, and is also influenced by recall bias (15). Blood and urine samples have short detection windows, which emphasizes that valid monitoring of SUD requires repeated screening during pregnancy. Several reports have investigated the validity of maternal self-reporting, maternal saliva, maternal sweat, samples from neonatal or maternal urine, meconium, placenta, umbilical cord, and maternal or neonatal hair (Supporting Information Table S1j) (31, 41-43). All reports concluded that, to a greater or lesser extent, most biological specimens can detect substance exposure and/or predict the severity of NAS. The ACOG recommends universal screening at the first antenatal visit using screening tools such as validated questionnaires (4). WHO recommends that “healthcare professionals ask all pregnant women about their use of alcohol and other substances … as early as possible in the pregnancy and at every follow-up visit” (8). SAMHSA states that urine screening “…should be ordered when a SUD is possible”. A combination of repeated self-reporting and maternal urine analyses has been suggested to provide the best information of SUD throughout pregnancy (60). Biological specimens obtained at birth can be helpful in the absence of any other information.

4. DISCUSSION

If OUD is identified during pregnancy, the pregnant woman should not be advised to continue use or undergo detoxification. Due to missing data, detoxification should only by recommended in selected patients under careful medication-assisted maintenance, hospitalization, support and monitoring (19, 21). With respect to the choice between methadone and buprenorphine, our review of the literature demonstrates that buprenorphine is safe and may be better than methadone with respect to NAS variables. In addition, buprenorphine has practical advantages, since methadone typically requires daily clinic visits (depending on local opportunities), whereas buprenorphine can be dispensed weekly (11). Pregnant women should continue with buprenorphine or methadone prior to conception if they are stable on this regimen, since changing regimens is associated with fetomaternal risks of destabilization (17). There does not appear to be a dose-response relationship, influence of timing of initiation or duration of treatment. Accordingly, it may be counterproductive to reduce the dose. Appropriate dosing adjustments throughout pregnancy should be by slow, gradual increase of dose to prevent withdrawal and relapse into SUD. In addition, split dosing may be the solution to maintain steady-state levels. In some cases, methadone may be preferred in pregnant women with a

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dependency on opioids. We do not understand why, but it could be due to the ceiling effect of buprenorphine at maximal doses (26).

Guidelines with respect to the management of pregnant women with SUD provide strong recommendations albeit based on limited evidence (8, 11). There is a lack of well-controlled studies, mainly because randomized clinical trials are rarely conducted in this population group (2, 11). While most of the literature compares methadone with buprenorphine, more research is necessary with respect to alternatives, since in some areas, clinicians do not have ready access to these medications, and the use of other opioid products such as long acting morphine may be necessary. The focus of the existing literature relates mainly to NAS and ignores other obstetric, fetal or neonatal outcomes. Accordingly, by focusing on the reduction of NAS, we might overlook abstinence during pregnancy, which might lead to erroneous recommendations. While buprenorphine may improve neonatal outcomes compared to methadone, guidelines do not recommend buprenorphine over methadone, and methadone remains the standard solution. We suggest that buprenorphine should be first line treatment over methadone.

Studies vary in their design, inclusion of women with different indications for use/treatment, opioid type, control groups, concomitant substances, length and dose of exposure, frequency of use, exposure by gestation, route of administration, inclusion of preterm infants and sample sizes. Some studies report on the same sample or a subsample of participants. Pooling data from studies with different designs and from studies on the same sample provides a challenge. It may result in biased correlations and must be considered with caution. The vast majority of results may also be affected by other contributing factors such as maternal health, psychological and socioeconomic issues. Furthermore, the majority of studies applied maternal retrospective self-reporting of substance use during pregnancy with the additional risk of recall bias. This implies a risk of both over- and underestimation of associations between prenatal substance exposure and negative outcomes.

Pregnant women with SUD have lower participation in antenatal care and may conceal their use for a number of reasons such as i) illegality; ii) criminal charges; iii) loss of custody of the neonate or iv) associated stigma (by the pregnant woman or her family) (11). It has been suggested, that fetal withdrawal is linked to maternal withdrawal symptoms. However, changes in fetal neurobehavior can be present without concurrent maternal physiological withdrawal symptoms (44). We propose a model of repeated self-reporting and maternal urine analyses during antenatal care. By universal screening, early detection of SUD in pregnancy is possible. Pregnant women with SUD are more likely to attend for ultrasound scanning and we suggest screening at this time, around 12 weeks gestation in most high-income countries.
Universal screening is associated with ethical concerns and perceptions, such as a challenge to maternal autonomy, prioritizing the fetus before the mother, and risk of decreased participation in antenatal care (61). As the ACOG highlights, urine screening contains additional concerns, since negative tests do not exclude intermittent SUD and may not detect all possible substances (4). Screening also requires a precise and validated test with a high sensitivity, suitable cut-off points and an “agreed policy on the further diagnostic investigation of individuals with a positive test result” (61). In addition, urine screening should be confirmed by mass spectrometry (4). We recommend routine guidelines for follow-up, and a risk: benefit analysis of the screening procedures. We also recommend future research into newer urine test kits that include detection of current, relevant substances with increased windows of detection.

5 CONCLUSION

Continued use of opioids or detoxification should not be recommended, and buprenorphine should be the choice of Opioid Agonist Pharmacotherapy. Furthermore, a combination of sequential self-reporting and maternal urine analyses is a reasonable compromise to identify fetal exposure in pregnancy. We suggest universal screening in early antenatal care and recommend future studies on screening methods. Postnatally, biological specimens obtained at birth from mother and/or baby can identify intrauterine fetal exposure.

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2. SAMHSA. A Collaborative Approach to the Treatment of Pregnant Women with Opioid Use Disorders. Substance Abuse and Mental Health Services Administration (SAMHSA); 2016.

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Supporting Information legends

Table S1a. Detoxification (Section 3.1.1).

Table S1b. Methadone vs Buprenorphine (Section 3.1.4). The reference list was restricted to 60 references according to journal instructions. A full reference list can be provided by main author.

Table S1c. Reducing buprenorphine or methadone dose (Section 3.1.5).

Table S1d. Dose-response relationship between opioids and neonatal abstinence syndrome (NAS) (Section 3.1.5). The reference list was restricted to 60 references according to journal instructions. A full reference list can be provided by main author.

Table S1e. Duration of treatment and timing of initiation of opioid agonist pharmacotherapy and neonatal abstinence syndrome (NAS) variables (Section 3.1.6).
Table S1f. Ceiling effect of substitution treatment (Section 3.1.6). NAS, neonatal abstinence syndrome.

Table S1g. Metabolic changes during pregnancy (Section 3.1.6). The reference list was restricted to 60 references according to journal instructions. A full reference list can be provided by main author.

Table S1h. Split-dosing of methadone (Section 3.1.6).

Table S1i. Fetal withdrawal monitoring (Section 3.2.1).

Table S1j. Monitoring of substance exposure (Section 3.2.2). The reference list was restricted to 60 references according to journal instructions. A full reference list can be provided by main author.

Figures

Figure 1: Flowchart, inclusion of articles. Details of search strategy are available on request, including hand search through references in articles *.
Inclusion filter:
Studies focusing on:
1: Management of pregnant women with opioid use
2: Perinatal outcomes among infants exposed to opioid use in pregnancy
Publication date: from 2007/01/01 to 2017/01/01
Study design: clinical trials, randomized controlled trials, controlled clinical trials, meta-analyses, systematic reviews, and reviews.
Language: Danish, English, German, Norwegian, and Swedish
Included in all: 3688 articles.

Exclusion of studies focusing on:
cocaine, amphetamines, MDMA, benzodiazepines, and cannabis.
Excluded in all: 115 articles.

Exclusion of studies focusing on:
animal studies, volumetry, structural brain abnormalities, maternal outcomes beyond obstetric relevant, motivational therapy, studies with monetary reinforcement for attendance, motivational enhancement therapy, studies not distinguishing between individual effects of different substances, studies focusing on peripartum pain, lactation, and treatment of neonatal abstinence syndrome, and finally studies on longterm effects on the child.
Studies about the above were excluded unless they contained data with wanted focus.
Excluded in all: 155 articles.

Exclusion based on title, abstract, or repetition:
Excluded in all: 3219 articles.

Inclusion results:
Included in all: 469 articles.

Inclusion of studies focusing on:
cocaine, amphetamines, MDMA, benzodiazepines, and cannabis.
Excluded in all: 115 articles.

Included in all*: 323 articles.

Final inclusion:
208 articles.

Figure 2: Alternatives to continued use of opioids and their advantages and disadvantages. Based on the references 2-5, 9, 11, 13, 14, 17. NAS, neonatal abstinence syndrome.
For details on maternal, obstetrical, fetal, and neonatal complications, see our associated manuscript.
<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th>Final inclusion</th>
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<tr>
<td>Studies focusing on:</td>
<td>208 articles</td>
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<tr>
<td>Management of pregnant woman with opioid use.</td>
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<td>Exclusion results: 215 excluded, 6 included.</td>
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Opioid use during pregnancy

Continued opioid use
- Advantages: none medical.
- Disadvantages: risk of maternal, obstetrical, fetal, and neonatal complications.

Alternative 1: detoxification
- Advantages: prevents NAS
- Disadvantages: cycle between abstinences, relapse and intoxication causing fluctuating concentrations of opioid, which again increases the risk of maternal, obstetrical, fetal, and neonatal complications.

Alternative 2: methadone
- Disadvantages: NAS may be worse than after exposure to continued use of other opioids.

Alternative 3: buprenorphine
- Advantages: akin methadone, but also advantages over methadone with milder withdrawal symptoms, better NAS variables, and even lower risk of maternal, obstetrical, fetal, and neonatal complications.
- Disadvantages: NAS and an even lower ceiling of effect compared to methadone.