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Substance use in the perinatal period

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Abstract

Perinatal substance use remains a major public health problem and is associated with a number of deleterious maternal and fetal effects. Polysubstance use in pregnancy is common, and can potentiate adverse maternal and fetal outcomes. Tobacco is the most commonly used substance in pregnancy, followed by alcohol and illicit substances. The treatments for perinatal substance use are limited and consist mostly of behavioral and psychosocial interventions. Of these contingency management has shown the most efficacy. More recently, novel interventions such as progesterone for postpartum cocaine use have shown promise. The purpose of this review is to examine the recent literature on the use of tobacco, alcohol, cannabis, stimulants, and opioids in the perinatal period, their effects on maternal and fetal health and current treatments.

Keywords

pregnancy; drug; tobacco; smoking; alcohol; cannabis; marijuana; methamphetamine; cocaine; opiates; opioid; stimulant; perinatal; antenatal; postpartum

Introduction

Pregnant women use a range of licit and illicit substances with a common pattern of polysubstance use. According to the 2012 Survey on Drug Use and Health, 5.9% of pregnant women use illicit drugs, 8.5% drink alcohol and 15.9% smoke cigarettes [1], resulting in over 380,000 offspring exposed to illicit substances, over 550,000 exposed to alcohol and over 1 million exposed to tobacco in utero. National data show that in order of frequency of use, nicotine addiction is highest, followed by alcohol, marijuana and cocaine [2,3]. However, polysubstance use is as high as 50% in some studies [2,4].

Substance use in pregnancy can lead to a number of deleterious effects in the mother and her offspring (see Table 1). The impact of drug use in pregnancy varies depending upon the drug, point of exposure and extent of use. The most well established deleterious consequences are associated with alcohol use during pregnancy and the development of fetal alcohol syndrome and fetal alcohol effects [5]. Smoking during pregnancy exerts direct adverse effects on birth outcomes, including low birth weight, placental abruption, and increased infant mortality [6-8]. While illicit substances are associated with low birthweight, preterm delivery, placental abruption [9], and cognitive impairment [10,11]. The adverse

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effects of perinatal substance use are further complicated by the frequency of concurrent substance use, as noted above, and comorbid psychiatric illness [12,13]. In addition, women with substance use disorders frequently experience poor nutrition, inadequate prenatal care, poverty, chronic medical problems and domestic violence [14,15]. Substance use can also lead to disrupted parental care, and early dysfunctional maternal-infant interactions can compound the negative effects of prenatal drug exposure [16,17].

Concern for the impact of substances on their baby lead some women to moderate their use of drugs and alcohol during pregnancy [18]. In a recent prospective study on perinatal abstinence and relapse, we found that among women with substance use prior to pregnancy, 96% of women with heaving drinking, 78% of women with marijuana use, 73% of women with cocaine use, and 32% of cigarette smokers achieved abstinence in pregnancy [4]. Offsetting the decrease in pregnancy-related use is the precipitous increase in substance use during the 6 months to one year after delivery [4]. By three months postpartum, 58% of abstinent smokers, 51% of abstinent women who used alcohol, 41% of abstinent women who used marijuana and 27% of abstinent women who used cocaine relapsed [4]. Another study found that, even though the majority of women attained some level of abstinence from drug use during the third trimester of pregnancy, the net abstinence rate was only 24% because of the high likelihood of postpartum relapse [2]. This is unfortunate because maternal relapse occurs at a time when childcare needs are high and maternal bonding is critical to the development of the infant. These data show that perinatal substance use remains a major public health problem.

This review will examine the recent literature on the maternal and neonatal consequences of and available treatments for tobacco, alcohol, cannabis, stimulant, and opioid use in the perinatal period.

Tobacco

Tobacco use behavior among pregnant women includes cigarette and electronic cigarette smoking [19-21] and smokeless tobacco use [22,23]. These tobacco-related behaviors, as well as second hand smoke exposure [24] remain prevalent in the perinatal population, with 16% of pregnant women reporting smoking [1]. It is important to note that almost half of women who were smokers prior to conception quit smoking during pregnancy [25,26], particularly those with more education [27]; however, close to 80% relapse within a year following delivery [28]. In addition, women who smoked pre-pregnancy may cease breastfeeding early in order to restart smoking [29].

Interestingly, compared to other substance use in pregnancy, smokers have the lowest abstinence rates [4]. One potential reason for the lower rates of smoking abstinence might be that women with concurrent substance use substitute smoking for alcohol or illicit substance use while pregnant. Women may perceive illicit substances and alcohol as more harmful and less socially acceptable than cigarettes, and thus decide to give up use of the other substances but not cigarettes [30]. This is supported by the low smoking abstinence rates in women with concurrent substance use. In our prospective study, 77% of women with concurrent substance use were smokers and only 29% of them achieved abstinence [4]. This

is also in line with previous findings that smoking status is a predictor of illicit substance use in pregnancy [31,32]. Furthermore, while tobacco, alcohol, and illicit substances all lead to preterm delivery and low birthweight, tobacco has the greatest impact on both outcomes [33].

Tobacco-related fetal and pregnancy outcomes and the severity thereof can vary depending on the timing of exposure, and whether the exposure occurs during the first versus third trimester [34]. Research evaluating the timing of exposure demonstrates links with pregnancy or neonatal outcomes including low birth weight, which has been attributed with smoking throughout the gestational period, as compared quitting smoking by the fifth month of pregnancy, which is not associated with increased risk for low birth weight [35]. Additionally, mothers exhibiting persistent smoking patterns during the second and third trimesters had higher depressive symptomatology and stress relative to non-persistent smokers [36]. Recent research continues to demonstrate that tobacco and nicotine exposure are associated with adverse pregnancy outcomes, including damage to the umbilical cord structure [37], miscarriage [38], increased risk for ectopic pregnancy [39] and preterm delivery [23,40]. Smoking in pregnancy is also associated with increased infant morbidity and mortality [8,41-45], and second-hand smoke is associated deleterious health effects on newborns, which include increased risk for respiratory and ear infections, sudden infant death syndrome, behavioral dysfunction and cognitive impairment [46]. Further, prenatal exposure to cigarettes is associated with an increase in the probability of tobacco use [47] and experimentation with drugs among adolescents [48]. Smoking in pregnancy is also associated with antenatal depressive symptomatology in the mother [49] and altered maternal-fetal attachment [50].

Behavioral counseling is the mainstay of smoking cessation and relapse prevention in pregnancy; however, psychotherapeutic interventions are only modestly effective [51-54]. The efficacy and safety of pharmacologic treatments for smoking are not yet established in pregnant and postpartum women [51,55]. More recently, nicotine replacement therapy has been evaluated in several randomized clinical trials [56-59] and have shown limited efficacy in increasing the rates of abstinence. According to a 2013 Cochrane Review on interventions for smoking cessation in pregnant women, the most effective intervention for smoking cessation is contingency management (CM) with financial incentives [60]. CM for perinatal smoking has also been shown to improve birth outcomes [61]. The promise of CM as a smoking cessation intervention in pregnant women has recently been confirmed by an analytical review focusing specifically on CM [62], and a study that showed prolonged abstinence rates following the intervention, 20% at delivery and 10% six months postpartum [63].

More recent interventions for perinatal tobacco use and secondhand smoke exposure range from an indoor smoking ordinance [64], to nurse home visitation [65], a social marketing campaign [66], brief feedback regarding urinary cotinine results [67], and text messaging and smartphone interventions [68]. We are currently conducting a randomized control trial to examine the utility of oral micronized progesterone as an intervention to prevent smoking relapse in postpartum women (NCT01972464, ClinicalTrials.gov). Many of the current efforts appear to be promising for perinatal smoking cessation and relapse prevention.

However, ongoing challenges include the need for effectiveness trials and limited dissemination. Thus, researchers will be challenged to understand ways to minimize lost opportunities to reach larger and more diverse populations.

Alcohol

The majority of pregnant women are able to stop or cut down on drinking, with roughly 87% to 96% of women with heavy or at risk drinking achieving abstinence [4,69]. However, 6.4% of women in one study [69], and over 33% in another [70], did not reduce their alcohol consumption during pregnancy. The effects of alcohol consumption during pregnancy can range in severity depending on the timing of exposure, with the first trimester being most sensitive to alcohol-related birth outcomes [71]. Perinatal drinking is associated with many adverse fetal health effects [72-74], including fetal alcohol spectrum disorders [75,76], neurodevelopmental outcomes [77], and central nervous system deficits. Additionally, drinking while pregnant is associated with long-term effects such as speech and language outcomes [78], cognitive and behavioral challenges [79,80], and executive functioning deficits in children [81], and psychosocial consequences in adulthood [82].

Alcohol-related fetal and pregnancy outcomes and the severity thereof can vary depending on the timing of exposure; that is, effects linked with first trimester exposure [83] may be different from those associated with the second [84-86] or third trimester [87,88], and these in turn may differ from outcomes due to persistent use throughout the duration of pregnancy [89]. For example, alcohol consumption has been associated with oral clefts [83] during the first-trimester [83], adverse effects on rat brain weight during the second [84], and disruptions in rat neuroimmune systems [88]. Additional work is needed to further elucidate trimester- or month-specific maternal and fetal effects of perinatal alcohol use.

These effects, although potentially severe, are largely preventable by avoiding alcohol use in pregnancy. Brief interventions [90], particularly those that utilize motivational interviewing [91,92], can reduce perinatal alcohol use. Other recent interventions to reduce perinatal drinking have included counseling by midwives [93], screening via nonmedical community workers [94], and multimedia and educational efforts aimed to improve knowledge [95]. Additionally, recent work has highlighted the importance of social support in perinatal alcohol prevention, particularly for groups wherein social support has increased significance [96]. A randomized trial suggested that telephone-based brief intervention may have comparable success to in-person interventions in reducing perinatal drinking, and due to its relative cost-effectiveness, might be a viable avenue for additional work [97]. CM has not been well-studied for perinatal alcohol use.

Several recommendations have been put forward regarding possible ways to target perinatal alcohol use. One such suggestion is the screening of pregnant women in clinical settings, to provide clinicians with an opportunity to review health practices and encourage changes [98]. Surveillance, particularly of fetal alcohol syndrome, has also been suggested as an activity that may reduce alcohol-related consequences associated with perinatal drinking [99], as well as efforts to better identify groups at high risk of drinking during pregnancy earlier rather than later [100]. For example, one recommendation is to identify non-pregnant

women who intend to get pregnant but continue to drink, as these women may unknowingly expose a developing fetus to alcohol for weeks or months [101-103]. However, it is also important to understand how best to intervene against perinatal drinking among women who unintentionally became pregnant, as the relationship between unintended pregnancy and binge drinking has been documented [104]. One study examining college students' knowledge about fetal alcohol spectrum disorder found that undergraduates demonstrated adequate knowledge; however, additional investigation is needed to understand whether this corresponds to a lowered risk of problem drinking [105]. Thus, further research is needed to understand and identify specific mechanisms at play in perinatal alcohol use and best ways to intervene.

Cannabis

Cannabis is the most commonly used illicit substance during pregnancy and lactation [30,106]. Prevalence estimates of perinatal cannabis use range from 10% [107] or less to roughly 43% [108]. As with tobacco and alcohol use, while many women cease using cannabis during pregnancy [109], rates of past month cannabis use by the third trimester decrease to 1.4% [110].

Although many pregnant women may view their cannabis as harmless [111], it has been linked with adverse pregnancy outcomes and fetal effects. In a recent study confirmed prior findings and found cannabis use in pregnancy was associated with low birth weight (odds ratio (OR) = 1.7; 95% confidence interval (CI): 1.3–2.2), preterm labor (OR = 1.5; 95% CI: 1.1–1.9), small for gestational age (OR = 2.2; 95% CI: 1.8–2.7), and admission to the neonatal intensive care unit (OR = 2.0; 95% CI: 1.7–2.4) [112]. This retrospective cohort study used a large population health registry and controlled for known confounders, such as tobacco smoking, alcohol consumption, and use of other illicit drugs. Cannabis use in pregnancy is also associated with adverse effects on fetal and adolescent brain growth [111], poorer attention and executive functioning skills, lower academic achievement, increased behavioral problems [113]. Of note the effects of marijuana often seen in conjunction with other substances, and are most pronounced in heavy users. To our knowledge, no one has yet empirically evaluated whether differences exist with respect to perinatal cannabis outcomes or severity thereof, particularly regarding timing of exposure. Moreover, extant research on perinatal cannabis use is often confounded by multi-substance use [114]. As such, research is needed to examine specific maternal and fetal outcomes related to perinatal cannabis use as they differ by trimester or month.

Recent examinations of national demographic trends in perinatal cannabis use suggest that among pregnant cannabis users, criminal justice referrals, white non-Hispanic women, and those with a psychiatric comorbidity were common [108]. Additionally, recent work has shown that among pregnant treatment-seekers enrolled in a community substance abuse program, the prevalence of past psychiatric diagnosis, unemployment, disability, and single relationship status was high [115]. A retrospective cohort study on prenatal patients with positive cannabis screenings showed that cannabis was associated with level of education, employment, other substance use, depressive symptoms, and a history of abuse [107,109]. It is important to note that findings with respect to perinatal cannabis use have been somewhat

mixed [109], and additional work, particularly related to breastfeeding during the postpartum period [111] is needed. Recommendations for reducing perinatal cannabis use include screening pregnant women to promote early identification of cannabis use [111]. CBT [116-120], motivational interviewing [118,120], and CM therapies have been demonstrated to be effective for reducing marijuana use in women, but they have not been studied specifically with pregnant users. Thus, novel interventions specifically targeting cannabis use are needed, especially given the recent trends in marijuana legalization.

Stimulants

Cocaine

While the exact prevalence of cocaine use in pregnancy is not known, it is estimated to be 1.1% at any point in pregnancy [121]. Cocaine use in pregnancy received much attention in the media in the 1980s and 1990s, with exaggerated claims on the effects of cocaine on infants. While much of the scare of “crack babies” was unfounded, more recent large and rigorous studies have consistently identified several risk factors associated with cocaine use during pregnancy, including premature rupture of membranes, placental abruption, preterm birth, low birthweight, and small for gestational age infants [122]. This was confirmed in a recent meta-analysis that found prenatal cocaine exposure is significantly associated with preterm birth (OR = 3.38; 95% CI: 2.72–4.21), low birthweight (OR = 3.66; 95% CI: 2.90–4.63), and small for gestational age infants (OR = 3.23; 95% CI: 2.43–4.30) [123]. The long-term effects of prenatal cocaine exposure on cognitive, motor, and language development have been inconsistent, with some studies reporting positive findings [124,125] and some studies finding small or no effects [126]. This inconsistency is likely related to the confounding effects of the postnatal environment, including dysfunctional parenting [16,17] and unstable and chaotic home environments, and frequent polysubstance use in the mother [127].

Recent examinations of the timing of cocaine exposure with respect to maternal and fetal outcomes suggest that perinatal cocaine effects during the first trimester are associated with decreased head circumference and lower short-term memory among children [128], child and adolescent delinquent behavior [129,130], earlier age of sexual initiation [131], and adolescent initiation of other substance use [132]. Examinations of perinatal cocaine use during the second and third trimesters specifically are comparatively rare, possibly due to underreporting [133]. As such, further research in this area is needed.

The current evidence-based treatments for cocaine use in pregnancy are behavioral interventions, including cognitive-behavioral therapy (CBT), motivational interviewing and CM [134]. As with smoking, CM is the most promising intervention for cocaine-using pregnant women [127]. In a recent randomized trial comparing CM to community reinforcement approach and twelve-step facilitation, CM was associated with significantly greater duration of cocaine abstinence, higher proportion of cocaine-negative urine tests, and higher proportion of documented abstinence across the study period [135]. To date, there are no evidence-based pharmacological treatments for cocaine use in the perinatal period; however, a recent randomized, placebo-controlled trial conducted by our group found promise in the use of oral micronized progesterone for the postpartum cocaine use [136]. We

found more self-reported cocaine use during the 12 weeks of the trial in women randomized to placebo compared to women receiving micronized progesterone [136]. These findings are preliminary and need to be replicated in a larger clinical trial, but lend support to the use of progesterone for cocaine use in postpartum women.

Methamphetamine

Methamphetamine, a synthetic stimulant, remains the fastest growing illicit drug worldwide and tends to co-occur with the use of other substances and psychopathology in humans [137] and negative neurodevelopment effects in rats [138]. There are limited data on the prevalence of methamphetamine use in pregnancy, with national estimates varying from 0.7% to 5.2% [137]. Recent work shows that methamphetamine use is associated with shorter gestational ages, lower birthweight [139], fetal loss [140], developmental and behavioral deficits [141], gestational hypertension, preeclampsia, and intrauterine fetal death [142]. Fetal outcomes may vary based on exposure timing and duration[139]. Infants with a positive toxicology at delivery were smaller on average compared to infants with methamphetamine exposure during the first trimester only, who were in turn smaller than non-exposed infants [139].

A recent study combining reinforcement-based therapy (RBT) with a women-focused intervention among pregnant methamphetamine users showed that the intervention was appealing to participants and methamphetamine use decreased over the course of the study [143]. It is important to note, however, that there were no significant differences between the intervention and control conditions [143], similar to another study utilizing RBT for stimulant use in pregnancy [144]. While RBT appears to be promising intervention for methamphetamine use, further work is needed, particularly to ascertain whether pejorative attitudes towards methamphetamine might influence reporting rates. Interestingly a recent study showed that treatment with a monoclonal antibody therapy in pregnant rat dams offered maternal and fetal brain protection from adverse drug effects by reducing brain concentrations of methamphetamine [145]. Further work is needed to understand mechanisms underlying risks for methamphetamine use, and individuals for whom interventions might be more effective. Additionally, as pregnant women who use methamphetamine tend to exhibit low rates of antenatal care utilization, recommendations for future efforts may include encouragement of antenatal uptake and adherence [143].

Opiates

Opioid use has increased dramatically over the last decade, and the incidence of opioid use during pregnancy increased from 1.19 to 5.77 per 1000 hospital live births per year between 2000 and 2009 [146]. Opioid use in pregnancy includes both heroin and prescription opiates. With this increase in opioid use there was a corresponding increase in neonatal abstinence syndrome (NAS), the postnatal drug withdrawal syndrome caused by maternal opiate use, from 1.20 to 3.39 per 1000 hospital live births per year [146], the type of opioid exposure was not specified. NAS affects anywhere from 45% to 94% of infants exposed opioids in utero, this includes methadone and buprenorphine, and results in significant neonatal morbidity and high healthcare utilization [146,147]. NAS is characterized by numerous signs and symptoms, including increased irritability, hypertonia, tremors, feeding

difficulties, emesis, loose stools, seizures, and respiratory distress [148]. In addition to NAS, opioid use in pregnancy is associated with a significantly increased risk of low birthweight, respiratory complications, toxemia, third trimester bleeding and mortality [146,147], as well as postnatal growth deficiency, microcephaly, neurobehavioral problems, and sudden infant death syndrome [147]. Of note, cigarette smoking in pregnant women with opioid use disorder is highly prevalent, 77% to 95% [149,150], and can confound the impact of opioid use on adverse pregnancy outcomes. Empirical evidence evaluating exposure timing of opioids during the perinatal period exists [151]; however, to our knowledge, no one has yet evaluated differences in maternal and fetal outcomes or severity based on the timing of exposure.

Methadone maintenance is considered the standard of care for pregnant women with opiate use disorder [152]. Medically monitored conversion from illicit opioid use to opioid maintenance therapy decreases maternal and neonatal morbidity by providing superior relapse prevention with a stable opioid dosing regimen, reduced risk-taking behavior, enhanced compliance with prenatal care, and better neonatal outcomes rates [153]. In contrast, medication-assisted withdrawal is associated with a high opioid relapse rate, and some evidence suggests increased fetal morbidity and mortality rates [153]. More recently, buprenorphine has emerged as an effective treatment alternative for opioid use in pregnancy. In a randomized controlled trial that compared methadone and buprenorphine in pregnant opioid users, infants born to women treated with buprenorphine had a significantly shorter duration of treatment for NAS, required significantly lower doses of morphine for the treated of NAS symptoms, and had significantly shorter hospital stays than infants born to women treated with methadone [154]. However, methadone is superior to buprenorphine in retaining people in treatment. Compared to methadone, buprenorphine has lower retention rates with flexibly delivered doses and low fixed doses, but when fixed medium or high doses are used, buprenorphine and methadone are equally effective [155]. While medication-assisted treatment is the standard of care for opiate use disorder in pregnancy, CM has been shown to significantly increase full day treatment attendance and drug abstinence compared to controls [156]. Thus CM may serve as an important adjunct to methadone or buprenorphine pharmacotherapy in perinatal women. Breastfeeding is another important intervention as it is the only available intervention demonstrated to reduce NAS severity in opioid-exposed newborns is breastfeeding [157,158].

Conclusions

Summary

Perinatal substance use continues to be a significant problem in the United States. Effective treatments for substance use in pregnancy are limited; however, CM appears to have the most potential as an effective treatment across substances, and may improve compliance to prenatal care as well. Substance use in pregnancy can lead to a number of deleterious effects in mother and her offspring. The impact of drug use in pregnancy varies depending upon the drug, point of exposure and extent of use. Several variables are associated with adverse maternal and infant outcomes, in addition to the direct effects of drug exposure in utero. These include psychiatric comorbidity, polysubstance use, environmental stressors, limited

prenatal care and disrupted parental care. All of these factors contribute to adverse pregnancy outcomes and long-term effects. Furthermore, low birthweight, which is an adverse pregnancy outcome associated with all substance use in pregnancy, increases the risk of many neurodevelopmental and functional deficits [159]. Thus, it is difficult to discern the effect of a specific substance in isolation. All of these factors need to be considered in order to effectively address substance use in pregnancy and improve maternal and infant outcomes.

Future directions

Many health problems associated with the perinatal period can be prevented with adequate and timely medical care or intervention. Pregnancy is a time during which women tend to become more motivated to reduce substance use [25,26,69], but prevalence of continued substance use remains high [107,160,161]. There is a need to elucidate underlying mechanisms and develop empirically-driven interventions for postpartum health. Tailored, safe, and convenient treatments are needed to reduce substance-related morbidity and mortality by encouraging and capitalizing on pregnancy-related abstinence [162].

One promising avenue of research is the use of mobile devices as relapse prevention among postpartum women by targeting automatic cues for substance use. Automatic processes play an important role in addictive behaviors [163] and some novel approaches, termed cognitive bias modification, are currently being tested in their efficacy to target the automatic processes that sustain addiction. Initial, unpublished findings from this work suggest that this type of intervention can be administered on a mobile device and can reduce attentional bias to smoking cues in perinatal women (Foster D, Waters A, Forray A, 2015 College on Problems of Drug Dependence meeting, poster presentation). Future research should evaluate the longitudinal outcomes and efficacy of mobile interventions targeting perinatal substance use. Additional work and novel interventions are needed to capitalize on the naturally occurring abstinence and motivation to engage in healthy behaviors experienced by perinatal women.

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Table 1

Summary of Perinatal Substance Use Effects on Pregnancy and Infant Outcomes

	Tobacco	Alcohol	Cannabis	Stimulants	Opiates
Pregnancy outcomes					
Preterm birth	✓ [7,40]	✓ [72,164]	✓ [112]	✓ [122,123,165]	✓ [165,166]
Small for gestational age	✓ [7,8,165]	✓ [72,164]	✓ [112]	✓ [122,123,139]	✓ [167]
Low birthweight	✓ [7,8,165]	✓ [164]	✔ [112]	✓ [122,123,139]	✓ [168]
Miscarriage/Spontaneous abortion	✔ [38]	✓ [169,170]		✔ [140]	
Placental abruption	✔ [6-8]			✓ [122,123]	
Premature rupture of membranes	✔ [7]			✓ [122,123]	
Ectopic pregnancy	✔ [39]				
Infant effects					
Cognitive deficits	✔ [46]	✔ [171]	✓ [10,111]	✓ [11]	✓ [147]
Teratogenicity		✔ [171]			
Infant mortality/Sudden Infant Death Syndrome	✓ [7,8]				✓ [147]
Neonatal Withdrawal/Abstinence Syndrome		✔ [148]			✓ [146,147]
Behavioral Problems	✔ [46]	✔ [171]	✔ [113]	✔ [141]	✔ [172]