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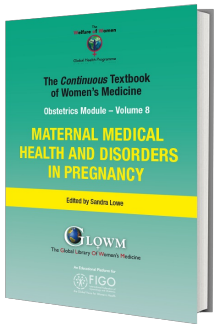

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MATERNAL MEDICAL HEALTH AND DISORDERS IN PREGNANCY

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Chapter

Drug Addiction

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INTRODUCTION

In the United States, women comprise 40% of those with a lifetime substance use disorder (SUD), with 12% having a substance use disorder in the past 12 months.[1] We know that women are at highest risk for developing SUD during reproductive years, especially between the ages 18 and 29. Meaning, that women who are pregnant or soon to become pregnant are at an increased risk for substance abuse.[2] According to a national survey conducted in the US in 2012, 5.9% of pregnant women use illicit drugs, 8.5% drink alcohol and 15.9% smoke cigarettes. This results in over 380,000 offspring exposed to an illicit substance, over 550,000 exposed to alcohol and over 1 million exposed to tobacco. The most commonly used substance in pregnancy is nicotine, followed by alcohol, cannabis and cocaine. In middle- and low-income countries cannabis and amphetamines are the most commonly used illicit substances by women of reproductive age. Polysubstance use is as high as 50% in some studies, therefore many women and their offspring are exposed to multiple substances during pregnancy.[3] Exacerbating the problem of SUD is the rise in the number of prescriptions for controlled substances being written. Women may be more vulnerable to prescription drug misuse due to higher rates of prescriptions for tranquilizers and sedative medications, as well as being more likely to obtain controlled drugs.

Substance use disorders can lead to serious long-lasting consequences for women and infants including miscarriage, stillbirth, intoxication and withdrawal at delivery, as well as lasting cognitive and behavioral abnormalities in children. Studying these effects is difficult for several reasons. Most studies are performed retrospectively and even when done longitudinally and the offspring followed, the prenatal exposure is typically assessed after birth, increasing likelihood of recall bias. Women may under report the amount of use if asked during pregnancy because of stigma and legal consequences. If pregnancy has passed without major consequence, the mother's reporting may be more accurate. Additionally, there is not experimental control over the dose, the frequency, the pattern or the gestational timing of use. Therefore, it is nearly impossible to obtain a reliable or valid measure of prenatal abuse and its specific consequences.

Other factors, such as maternal and fetal malnutrition, lack of adequate prenatal medical care, exposure to sexually transmitted and other infectious diseases, polysubstance use, impoverished housing or postnatal parental drug abuse all impact perinatal findings.

Early dysfunctional maternal-infant relationship can potentiate the negative effects of prenatal drug exposure. The first year of attachment plays an integral role in the psychological development of the child and the overall stability of the mother-baby dyad in the long term.

One way to conceptualize addiction is as an attachment disorder. If one has an insecure pattern of attachments, they are likely to self-regulate using substances. As attachment to the substance increases, the person withdraws or detaches from their social environment.[4] When a person stops using their drug of choice, understandably, their distress increases as they are unable to regulate affect effectively, which in turn, predisposes them to relapse. Attachment based principles when applied to this subset of population could be valuable. These principles can be used in group settings in perinatal mental health programs or substance use treatment programs, along with helping patients to develop more adaptive coping skills and safer behaviors.

This chapter reviews the available data regarding specific substances and their impact in the perinatal period, with understanding of the multiple confounders related to these findings as discussed above. Our hope is that this information can help to better counsel and care for women with a substance use disorder during the perinatal period.

OPIOID USE DISORDER IN THE PERINATAL PERIOD

Opioid use disorder (OUD) has been increasing at alarmingly high rates for both men and woman in the US, with more than 130 people dying of an overdose from opioids everyday.[5] In 2017, more than 47,000 Americans died because of an opioid overdose, including prescription opioids, heroin, and illicitly manufactured fentanyl, a powerful synthetic opioid.[5] Women have higher rates of prescription opioid use in the past 30 days compared to men.[6] It is estimated that approximately 19 females die every day in the US of an overdose involving prescription opioids.[7,8] Research shows gender specific risk factors that predispose women to a higher risk of developing OUD. These include:

1. Women report lower pain sensitivity, more likely to present with conditions causing chronic pain,[9,10] hence they are more likely to be prescribed prescription opioid pain medications for longer periods and in higher doses;
2. Women are more likely to obtain prescriptions for controlled drugs;[11]
3. Women show higher rates of doctor shopping;[12]
4. Telescoping effect – women progress to dependence quicker;[13]
5. Women tend to experience more cravings;[14]
6. Emotional distress is identified as a risk factor for hazardous prescription opioid use among women but not among men.[15]

According to the American College of Obstetrics and Gynecology, 1% of pregnant women report nonmedical use of opioid pain medications.[16] As per the CDC, the number of pregnant women with OUD at labor and delivery has more than quadrupled from 1999 to 2014.[7,8] Medical and obstetrical care of this subset of women presents with multiple challenges, as they display more high risk behaviors such as impaired decision making, interpersonal violence (IPV), higher rates of trauma exposure and post-traumatic stress disorder (PTSD), inadequate housing, less frequent and inconsistent prenatal care, and are more likely to become involved with legal or child welfare agencies.[17] These women are at a higher risk for infectious diseases such as hepatitis, sexually transmitted diseases and their related complications.

Pregnant women with an opioid use disorder are at increased risk for adverse pregnancy outcomes including preterm labor, fetal death, growth restriction, and neonatal abstinence syndrome.[18] Neonatal abstinence syndrome (NAS) encompasses signs and symptoms experienced by the newborn after abrupt discontinuation of gestational exposure to substances. It is not limited to opioids, and polysubstance use can present with higher severity.[19] According to studies, an interplay of genetic, epigenetic and environmental factors leads to significant variability in clinical presentation of this

syndrome. A recent study highlighted the importance of postnatal experiences shaping clinical presentation. According to this study, infants placed with mothers postnatally required less pharmacotherapy and had shorter lengths of stay, hence underlining the significance of bonding within the mother-baby dyad.[20]

Untreated OUD can pose a high risk of relapse in the postpartum period[21] that can lead to adverse complications for the mother's mood and psychiatric stability, which in turn could affect the bonding in the mother-baby dyad.[22] Insecure attachments can have long lasting consequences on both the mother's and the child's emotional well-being.[23] Of note, according to latest neuroscientific research, there exists a link between social attachments and opioids. It is known now, that the reinforcing positive affect of social bonds is mediated in part by the opioid circuitry in the brain along with effects of oxytocin.[24] Maintaining sobriety during pregnancy and in the postpartum period is of utmost importance to optimize maternal and infant outcomes both in the short and long term.

Opioids are one of the most addictive substances present today; one of the reasons being strong behavioral and affective conditioning developing with chronic use.[25] Conditioning predisposes to cravings, which in turn is a risk factor for relapse.[25,26] Medication assisted treatment (MAT) with methadone or buprenorphine is integral in treatment of these cravings and cycles of withdrawal to prevent relapse.[26] Stability and sobriety maintained on MAT is associated with favorable outcomes such as longer durations of maternal drug abstinence and obstetric care compliance, avoidance of associated risk behaviors, reductions in fetal illicit drug exposure, avoidance of repeated cycles of intoxication and withdrawal associated with continued opioid abuse.[27] Neonatal outcomes have shown improvement as well.[27] Historically, methadone maintenance has been the recommended standard of care over no treatment or medication-assisted withdrawal for OUD during the perinatal period,[27,28] In the past decade or so, buprenorphine has been studied and increasingly utilized to treat opioid dependence in pregnant women. Findings, from the MOTHER study, report that buprenorphine may reduce the incidence and severity of the neonatal abstinence syndrome, thus reducing lengths of stay in the hospital for the infant.[27,28]

There is a paucity of research data for naltrexone use during pregnancy with most studies being retrospective cohort studies and case series.[29] One study comparing 17 pregnant women managed with extended-release naltrexone with 90 patients on methadone, showed no difference in mean gestational age or birth weight at delivery, but a higher 1-minute Apgar score with naltrexone use.[30] In another study that compared women treated with MAT vs. naltrexone, showed increased rates of overall early pregnancy loss in the naltrexone group, but did not have significantly different rates of obstetric complications or increased use of anesthetics or analgesics. Neonates exposed to naltrexone *in utero* had a shorter hospital length of stay and lower rates of NAS. There was no evidence of increased rates of still births or mortality as compared with nonopioid-exposed neonates. An elevated rate of urogenital anomalies was noted, however, the overall rate of birth anomalies was not statistically different in the opioid vs. nonopioid exposed women.[30,31] Currently there are no protocols or guidelines to manage detoxification during pregnancy.[32] Thus, use of naltrexone during pregnancy is not recommended as first line, and a transition to treatment with methadone or buprenorphine should be discussed with these women.

Over the years, studies have been conducted for use of MAT in breastfeeding. Methadone, findings suggest, the relative infant dose (RID) averages less than 2.8%. This is significantly less than the conventional cut-off value of 10%. This small amount in the breastmilk can reduce the incidence of neonatal abstinence syndrome when infants are breastfed.[33] With regards to buprenorphine use in breastfeeding, no evidence has been found of major adverse effects in the breastfed infants,[34] and the RID is well below 10% (0.09–2.52%).[35,36] Mothers on MAT should be encouraged to breastfeed unless there is an absolute contraindication such as comorbid drug use, infectious diseases, etc. With use of MAT, infants should be monitored for sedation, not waking up to feed, slowed breathing rate/apnea and constipation.

Psychosocial treatment in conjunction with MAT yields the best outcomes in treatment of opioid use disorder.[37] These therapeutic interventions should ideally include at least psychosocial needs assessment, supportive counseling, links to existing family supports, and referrals to community services[38] in every patient.

TOBACCO USE DISORDER IN THE PERINATAL PERIOD

In the US, approximately 12–25% of women smoke during their pregnancies.[39] In the UK, over one-quarter of women who smoke continue to do so during pregnancy.[37] Many of these women who continue to smoke, tend to be young, unmarried and from low socioeconomic communities.[40] We know that in humans, nicotine passes rapidly and completely across the placenta, with fetal concentrations generally being 15% above maternal levels.[41] This knowledge in combination with the well documented serious health complications of smoking are concerns for the effects smoking can have on a pregnancy, the fetus and the developing infant.

Cigarette smoke decreases uterine blood flow and therefore interferes with normal placental functioning. Consequently, the fetus is deprived of nutrients and oxygen, resulting in episodic fetal hypoxia and malnutrition, likely leading to intrauterine growth retardation.[42] Repeated studies have shown a dose–response relationship between maternal smoking and low birth weight as well as spontaneous abortion.[43] The birth weight deficit associated with smoking is 100–300 g and is directly associated with the number of cigarettes smoked. Low birth weight (<2500 g) is the best studied complication of cigarette exposure. An estimated 5–8% of preterm deliveries, 13–19% of term deliveries of infants with low birth weight, 23–34% cases of sudden infant death syndrome and 5–7% of preterm related infant deaths are attributed to prenatal smoking.[44] In addition to these serious consequences of smoking, neonates have been reported to have abnormal behaviors at the time of delivery, including hypertonicity, tremors and increased startle responses.[45]

Congenital malformations due to cigarette smoking have not been reported, although nicotine has effects on the developing fetus. Nicotine acts as a neuroteratogen and interferes with the developing nervous system[46] with direct effects on the nicotinic acetylcholine receptors.[47] The products of cigarette smoke, including carbon monoxide and tobacco tar have been shown to directly affect the fetal brain.[43] Reports following children postnatally have established that maternal smoking during pregnancy can also adversely affect cognitive development and behavior of children and adolescents. Numerous studies have reported an association between smoking during pregnancy and attention deficit hyperactivity disorder (ADHD) or ADHD symptoms.[48] Increased rates of externalizing behavior and aggression[49] have also been reported, including increased rates of oppositional behavior, conduct disorder and criminality in adulthood.[43] A recent large cohort study found a dose–response relationship between maternal self-reported daily smoking and both criminal arrest, psychiatric hospitalization and substance use disorder.[50] There is also evidence that maternal smoking may increase children's risk for early onset tobacco smoking.[39] It is important to remember that not all studies have found a negative relationship between prenatal maternal smoking and cognitive outcomes in children.[51] It is difficult to separate these adverse outcomes from other confounding environmental and genetic factors, including parental characteristics (ethnicity, IQ, psychiatric history and parenting style), maternal characteristics (health, exposure to other substances, age), smoking characteristics (intensity, gestational age of consumption), and offspring characteristics (parity, birth order and sex).[43]

Most women who can quit smoking by themselves during pregnancy are able to stop prior to their first prenatal visit. Those who are not able to stop by this visit, are likely to continue smoking during pregnancy.[52] Therefore, if a women presents to prenatal visits with ongoing cigarette use, they would benefit from intensive smoking cessation counseling. Clearly abstinence in early pregnancy will produce the greatest benefits to both mother and child, but it is important to remind patients that quitting any time during pregnancy can yield benefits. Additionally, reduction in the number of cigarettes has not produced consistent improvements in perinatal outcomes and therefore complete cessation should be recommended.[53,54] Pregnant smokers should be given rigorous psychosocial interventions throughout pregnancy, not only for cessation, but also to ensure abstinence. If these interventions are not successful, a risks benefit discussion with patient regarding pharmacotherapy for smoking cessation should be initiated.[55] A number of organizations uniformly recommend that nicotine replacement therapy should be considered if non-pharmacological therapies have been unsuccessful. Bupropion is recommended if patients have failed a trial of nicotine replacement and the benefits appears to outweigh the risks.[55] Varenicline is a smoking cessation aid for which limited data exist concerning safety during human pregnancy. Given the lack of information and the availability of alternative treatment options, it is recommended to avoid using varenicline for smoking cessation in pregnant women.[56]

The frequency of postpartum return to smoking is a significant problem, with nearly 50% of mothers who were able to

abstain from smoking in pregnancy return to smoking within 6 months postpartum.[57] In a large cohort study of more than 13,000 children, it was found that the highest risk for childhood-onset conduct problems were for children whose mother not only smoked in her pregnancy, but who also continued to smoke after birth.[58] It is therefore important to continue to monitor mothers in the postpartum period regarding nicotine use and continue to offer smoking cessation interventions.

CANNABIS USE DISORDER IN PREGNANCY

Cannabis is the most widely used illicit drug in the world[59] and in the US, cannabis is the most pervasively used illicit substance among individuals who are 12 years of age or older. According to data from the US National Survey on Drug Use and Health, 32% of individuals aged 18–25 have used cannabis within the past year and 19% have used in the past month.[60] With the known prevalence of cannabis use among individuals of childbearing age, the changes in legislation in many countries allowing for increased availability of both medicinal as well as recreational use, as well as the perception that cannabis is a “safe drug”, it is not surprising that many women are choosing to use marijuana during pregnancy. The American College of Obstetricians and Gynecologists reports that 2–5% of women use cannabis during pregnancy. This number increases among socioeconomically disadvantaged women in urban areas where the frequency of use during pregnancy is estimated to be between 15% and 28%.[61] Knowledge that cannabis is highly lipid soluble and readily crosses the placenta and the blood brain barrier with products and metabolites that accumulate in the fetus, including in the brain and adipose tissue, raises concerns for possible adverse effects on the developing fetus and neonate.[62] Most published studies on the use of cannabis during pregnancy report inconsistent results in many of the fetal and neonatal outcomes. This remains a difficult population to study, due to the varying potency of the drug, frequency of use, as well as routes of administration (edibles, smoking, etc.). In addition, women who use cannabis often have multiple confounding factors that may contribute to adverse outcomes, such as other drug exposures as well as sociodemographic factors.[63]

Cannabis has not been associated with specific congenital anomalies, although it is important to note that there have been reports of malformations in this population. One study found that maternal and paternal cannabis use increased risk for ventricle septal defects,[64] other studies have documented an increased risk of Ebstein’s anomaly and gastroschisis.[65,66,67] There are studies looking at the effects of prenatal cannabis use on fetal growth, rates of stillbirth and preterm delivery; however, published data for these outcomes are inconsistent.[63]

Based on knowledge that the use of cannabis during pregnancy can alter the fetal endogenous cannabinoid signaling system, which is present in almost every brain structure even at early embryonic stages, concern for infant neurodevelopment as a result of prenatal cannabis exposure is growing.[68] Findings have included impaired executive function with difficulty organizing, integrating specific cognitive and output processes and abnormalities in cognition and emotionality.[69] The Ottowa Prenatal Prospective Study is a prospective study of approximately 300 white, middle class, low risk women who self-reported using at least 6 joints per week during pregnancy. Infants were followed throughout childhood and presented with a range of developmental issues at various ages. When the offspring reached the age of 4 years old they were found to have significantly lower scores on several verbal and memory subscales.[70]

Due to the lipophilic properties of cannabis, it should readily transfer into breastmilk[71] and THC and its metabolites have been detected in the organs of offspring after transfer into mother’s milk.[72] However, it has been estimated that a rather low maternal weight-adjusted dose (or relative infant dose) of 0.8% is transferred to infant.[73] Additionally, the oral bioavailability of THC is only 2–14% (in adult studies)[74] and therefore the amount actually transferred to the infant is likely very low. In addition to exposure via breastmilk, infants have additional exposure when mothers choose to smoke marijuana in the postpartum period, primarily through passive inhalation. Concerns for effects of both smoke and THC exposure through inhalation would likely have a negative impact on infants, although there are few data into the amount or impact passive smoke inhalation of cannabis may have on newborns.

There is are a lot of conflicting data and beliefs regarding the effects (both negative and positive) of cannabis use. Reported benefits of cannabis have included treatment of anxiety, pain, insomnia, nausea and even cancer.[75] It is

important to remember that cannabis has not been shown to be harmless during pregnancy. Given this and the potential for marijuana to negatively impact the developing brain, the American College of Obstetricians and Gynecologists recommends not using cannabis while trying to get pregnant or during pregnancy.[63] In addition, there are no data showing that cannabis use would be beneficial to a breastfeeding infant and current evidence is insufficient to know if it could cause significant harm. Therefore, it is also recommended that mothers abstain from cannabis use if they choose to breastfeed.

ALCOHOL USE IN THE PERINATAL PERIOD

Active alcohol use disorder during pregnancy can have several adverse effects on the mother-baby dyad, both physiologically and psychologically. Older estimates reported about 15–20% of pregnant women worldwide continue alcohol use during pregnancy.[76,77] According to latest data from the CDC, 10% of pregnant women in the US report drinking alcohol, and about a third of those who drink alcohol say they binge drink. Considering the high rates of unplanned pregnancies, these figures may be much higher in the first trimester before pregnancy has been diagnosed. Estimating the amount of alcohol women drink can be complicated and inexact, given variations in research studies defining what constitutes heavy, moderate or light alcohol consumption, numerous units of measurements, and varied strengths of different types of alcohol.[78] These variations pose a significant limitation when assessing prevalence rates and outcomes related to alcohol use during pregnancy. Due to these complications, there is no quantity of alcohol that is currently considered “safe” during pregnancy.

The effects of alcohol on the fetus are influenced not just by the absolute amount of alcohol consumed, but also by the pattern of alcohol consumption, exposure-threshold amounts of alcohol in the blood, as well as the timing of exposure during pregnancy.[78] Other factors such as maternal age and her nutritional status, fetal susceptibility and concurrent use of other psychoactive substances may also influence fetal outcomes.[76,79,80] There is ample evidence documenting the toxic and teratogenic effects of alcohol on the fetus as well as maternal health. Alcohol can cross the placental barrier and can directly affect important developmental processes in the fetus, as well as cause damage to the maternal tissues and the placenta itself, thus adversely affecting perinatal outcomes.[78]

In 1973, the term Fetal Alcohol Syndrome (FAS) was coined to describe the pattern of “craniofacial, limb, and cardiovascular defects associated with prenatal-onset growth deficiency and developmental delay.”[81] Other clinical manifestations of FAS may include cardiac anomalies, urogenital defects, skeletal abnormalities, and visual and hearing problems.[78] Fetal alcohol spectrum disorders (FASD) cover a broader range of adverse effects in children who do not present with the full spectrum of abnormalities seen in FAS. These include low birth weight, preterm birth, small for gestational age,[82] spontaneous abortions[83] behavioral problems,[84] developmental delays[85] and cognitive deficits.[86] Children with fetal alcohol spectrum disorders often demonstrate poor impulse control, problems in social perception, deficits in higher level receptive and expressive language, poor capacity for abstraction, and problems in memory, attention and judgement.[85,87,88,89] These children then grow up into adults struggling with the long-term effects such as higher incidence of mental health problems, disruptive school experience, trouble with the law, substance abuse problems and an increased need for dependent living.

FASD places an immense financial burden on the society,[90] considering the life-long implications of the above stated deficits and abnormalities. However, it is largely preventable by complete abstinence from alcohol during pregnancy. Latest epidemiological data reports that one of every 13 pregnant women who consumed alcohol during pregnancy is estimated to have had a child with FASD, leading to an estimate of more than 1700 infants with FASD being born every day (630 000 every year) globally.[91] FASD is notably more frequent among special populations (e.g. aboriginal populations, children in care, incarcerated populations, and those in psychiatric care). The higher prevalence emphasizes that these high-risk populations deserve special attention for the planning and organization of targeted screening strategies, improved access to diagnostic services, and prevention of maternal alcohol consumption.[91] Clinicians from multiple specialties including primary care, OBGYNs and behavioral health, frequently encounter alcohol use disorder in women of reproductive age and can have a large impact on preventing FASD by providing psychoeducation and screening for risky drinking in these patient populations. Scales such as T-ACE/T-ACER-3[26] (Tolerance, Annoyance, Cut

down attempts, Eye opener), TWEAK[27] (Tolerance, Worried, Eye-opener, Amnesia, K/Cut down attempts), and SURP-P[28,29,30] (Substance Use Risk Pro file-Pregnancy) have been empirically validated specifically for use in pregnant women.

It is also important to note that maternal drinking can negatively impact families in a variety of ways, starting from effects on the attachment in the mother-baby dyad. Frequent, heavy maternal drinking is associated with poorer family functioning, poorer intellectual stimulation, and increased domestic violence.[92] One study showed that mothers with alcohol dependence are more likely to report punitive behaviors toward their children.[93]

Multiple studies have shown that pregnancy can be a time of increased motivation to decrease or stop drinking, and relatively higher rates of success in doing so.[94] Relative to their non-pregnant peers, pregnant women consume overall less alcohol.[95] In 2006, a Norwegian population-based study of 1500 women, demonstrated that 85% altered their alcohol consumption upon learning of their pregnancy, with fetal well-being cited as the primary reason for the change.[96] Data from the US Substance Abuse and Mental Health Services Administration (SAMHSA) cites decreasing alcohol consumption as pregnancy progresses, with 2013 rates of consumption in the first, second, and third trimesters falling from 17.9% to 4.2% to 3.7%, respectively.[97] These women who continue to drink during pregnancy face a lot of psychosocial and physiological challenges, and require tactful clinical discussions using motivational interviewing to address ambivalence and evoke change.

Acute alcohol withdrawal is a complex, potentially fatal medical condition arising from an imbalance between GABA-ergic inhibitions and glutamatergic hyperactivity. It can clinically present with an array of symptoms such as restlessness, tremors, hypertension, tachycardia, seizures, hyperthermia, hallucinations and death in severe cases. It can quickly escalate needing inpatient treatment and stabilization. During pregnancy, acute withdrawal could predispose the patient and fetus to obstetrical complications, leading to possible adverse outcomes for the mother-baby dyad. Therefore, acute withdrawal during pregnancy needs close observation and prompt treatment interventions. In general, there is lack of standard guidelines targeting alcohol withdrawal treatment for pregnant women. However, principles for treatment of withdrawal used in non-pregnant adults would apply to the pregnant population. Since alcohol withdrawal is a hypoGABA-ergic state, medications modulating the GABA receptor system such as benzodiazepines have been first line in treatment. To make treatment decisions, careful consideration would have to be given to the risks related to untreated withdrawal at that particular stage in pregnancy versus known associated risks of benzodiazepines.

Protracted withdrawal from alcohol can last up to 12–18 months; presenting as cravings, dysphoric mood, restlessness, anxiety, insomnia, anhedonia and negative affect.[98] These symptoms if untreated predispose the patient to relapse. Naltrexone, disulfiram and acamprosate have been FDA approved for treatment of alcohol use disorder. More recently, studies have shown evidence of gabapentin in doses of 900–1800 mg/day to reduce alcohol cravings.[99] Gabapentin can also be helpful in managing the restlessness, insomnia and anxiety often seen in protracted withdrawal. Safety data for use during pregnancy are limited for all the above stated medications. Although available data on naltrexone does not show an association with birth defects,[100] there is a significant lack of documentation on the subject for it to be used with clinical comfort. There are some studies suggesting that disulfiram in the first trimester may increase the risk of fetal malformations.[101] Also, in the case of relapse, the severity of the disulfiram-alcohol reaction could lead to significant obstetrical and medical risk. Animal data suggest possible teratogenic effects of acamprosate,[102] but there are no human trials currently. Most data on use of gabapentin during pregnancy have been in the context of seizures, chronic pelvic pain,[103] and hyperemesis gravidarum.[104] Findings have been inconsistent, some studies showing an increased risk of birth defects,[105] but others unable to support this evidence.[106] Thus, for it to be used during pregnancy, especially in the first trimester, risks related to relapse despite using all other psychosocial interventions would have to outweigh known associated risks of gabapentin use. Wide-ranging interventions such as motivational enhancement therapy, brief intervention and cognitive behavioral therapies, contingency management, modified DBT have been used for alcohol use disorders in the non-pregnant population. These would have similar benefits for use during pregnancy as well.

Although pregnancy can be a motivator to achieve abstinence, unfortunately, the postpartum period is riddled with many risk factors predisposing these women to relapse. These risk factors include physiological stressors in the postpartum period such as rapid hormonal changes, sleep deprivation, struggles with breastfeeding, and psychosocial factors such as role transition, changes in the parental relationship and family systems interfering with effective

interpersonal communication and increasing chances of conflict, activation of prior traumas and anxieties, and attachment issues. One study found that at 6–12 weeks postpartum 37.8% of women who were frequent drinkers before pregnancy reported postpartum risky drinking.[107] A similar pattern of reduced drinking during pregnancy, followed by a steady increase after the birth of a child, has been noted among unmarried adolescents.[108] The steady rise in alcohol use was most notable during the first 6 months postpartum. A Canadian study including 300 women, demonstrated a significant reduction in alcohol intake and heavy episodic drinking during pregnancy. By 12 months postpartum, however, heavy episodic drinking had returned to baseline levels, and most women had returned to their pre-pregnancy drinking behavior.[109] Hence, in the postpartum period, close monitoring and follow up, psychosocial support and treatment of psychiatric comorbidities is integral to the maintenance of sobriety.

STIMULANTS USE DISORDER IN THE PERINATAL PERIOD

In the past decade, the frequency of ADHD diagnosis and treatment has been rising in adults[110] and therefore increasing prescriptions for stimulant medications has also risen in this population. In the US, ~1% of pregnant women use drugs for treatment of ADHD, which ranks these medications among the most commonly used prescription drugs during pregnancy.[111] Considering the high rate of unplanned pregnancies among young women, the potential for exposure to stimulants in early pregnancy is also high.[112] Prescription stimulants are designated as a schedule II controlled drug because of their highly addictive nature.

Estimates on the prevalence of prescription stimulant abuse during pregnancy are lacking in the current literature. It has been estimated that the prevalence rates of crack cocaine use among pregnant women, ranges from 1.8% to 18%.[113] Women at elevated risks for abuse of stimulants (including prescription drugs and cocaine) include those who are young, unmarried, less educated and from lower socioeconomic communities.[114,115,116]

Data regarding the safety of stimulant use in pregnancy are limited. Animal studies suggest that amphetamines at high doses may increase the risk of cardiac and other malformations.[117] One study showed that use of stimulants during pregnancy was associated with a higher risk for neonatal morbidity, especially central nervous system–related disorders such as seizures.[118] According to a study by the CDC on the relationship between early pregnancy stimulant use and risk for specific birth defects, stimulant use is associated with an increased risk for gastroschisis, omphalocele, and transverse limb deficiency.[119] Outcomes specifically comparing use of methylphenidate and mixed amphetamine salts, have suggested a small increased risk of cardiac malformations associated with intrauterine exposure to methylphenidate but not amphetamines.[116] Findings do suggest active stimulant abuse in pregnancy is associated with maternal hypertension, postpartum hemorrhage, preterm labor, placental abruption, intrauterine growth restriction, low birth weight, and neonatal death.[120] Maternal appetite can be significantly lowered by stimulants thus leading to poor maternal nutrition.[121] A significant limitation has been the inability to rule out the effect of confounding factors such as higher rates of poor prenatal care in this population, trauma, interpersonal violence and comorbid substance use such as cigarette smoking. Furthermore, abuse of stimulants can destabilize mood and worsen psychotic symptoms in people at risk or suffering from comorbid psychiatric illness.

Studies to assess safety of stimulants in breastfeeding, as well as the longer-term effects on the neurological development of the infant, are limited. However, there is some evidence that at dosages prescribed for medical indications, amphetamines[122,123] and methylphenidate[124] do not have any adverse effects in infants. Large dosages of stimulants (as in the case of abuse) might interfere with milk production, especially in women whose lactation is not well established.[122] In these studies, the sample size was very small; hence, data are to be interpreted with caution. In mothers who are actively abusing higher doses, breastfeeding is discouraged.

BENZODIAZEPINE USE DISORDER IN THE PERINATAL PERIOD

Benzodiazepines are commonly prescribed for anxiety, insomnia, mood disorders and epilepsy. In a 2015–2016 survey by the National Surveys on Drug Use and Health, it was found that 12.5% of adults in the US used benzodiazepines,

which is approximately 30.5 million people. That study also reported that only 2.1% of US adults misused them and only 0.2% met the criteria for benzodiazepine use disorder.[125] Benzodiazepines are among the most widely prescribed drugs in pregnancy, with some studies showing up to 40% of women being given this class of medication at some stage of pregnancy.[126]

There have been reports of a 60% increased risk of spontaneous abortion observed in early pregnancy with concurrent benzodiazepine exposure compared to women with depression and anxiety not using benzodiazepines in the first trimester.[127] A recent study has shown that exposure to benzodiazepines in early pregnancy is associated with an increased risk of spontaneous abortion, with that risk increasing with increasing daily doses of benzodiazepines (suggesting a dose-response effect). Adverse effects specifically related to diazepam have been reported during all stages of pregnancy, with concerns regarding increased risk of facial clefts.[126] One study of 278 children with cleft lip and/or palate found that diazepam ingestion was four times more common during pregnancy.[128,129] Another study found that in mothers using anxiolytic drugs in the first trimester (mostly diazepam) had a threefold relative risk for cleft lip with or without cleft palate. This study did not find associations with any other malformations.[130,131] Not all studies have found an association between benzodiazepines and cleft palate (or other malformations). Many of the women included in these studies had multiple comorbidities, including epilepsy, diabetes and psychiatric illnesses that carry their own risks for pregnancy and neonatal outcomes. Additionally, medical, obstetrical and family histories of malformations were not always evaluated and, therefore, understanding the risk associated with benzodiazepines is difficult.[126] In most studies involving first trimester use of benzodiazepines, the majority of infants were normal at birth.[126]

Adverse events have been seen after delivery in infants exposed to benzodiazepines in the third trimester of pregnancy. Studies have shown diazepam and its metabolites are detectable in babies for up to 8 days after delivery.[132] Effects to infants after delivery include “floppy infant syndrome,” low Apgar scores, apneic spells, hypotonia, reluctance to feed and impaired metabolic responses to cold stress.[132] In mothers who chronically use benzodiazepines during pregnancy, there is increased risk of infant withdrawal symptoms including tremor, irritability, diarrhea, vomiting, vigorous sucking and hypertonicity.[133] There have been reports of longer term complications with maternal benzodiazepine use, including reports of motor and developmental delays. In a study of 550 children with perinatal exposure to benzodiazepines they did not see changes to neurobehavioral development or IQ. However, some data showed that there was a small number of children that were slower to develop during the first year, but they did exhibit catch up growth with normal development by age of 4 years old.[126] In the studies in which developmental deficits did persist, it was not possible to prove a cause-effect relationship with benzodiazepine exposure. As these children were often from families where there was maternal illness requiring prolonged drug therapy or other social and economic stressors.[126]

In mothers using benzodiazepines during breastfeeding, there have been reports of neonatal sedation associated with valium, these complications have not been reported with other benzodiazepines.[134] Caution regarding maternal sedation during care of infant is important to review with patients.

PRACTICE RECOMMENDATIONS

- **In the US, 12% of women have been diagnosed with a substance use disorder in the past 12 months with the highest risk time for developing a substance use disorder being during a woman’s reproductive years.**
- **Substance use in pregnancy can lead to pregnancy complications such as miscarriage, stillbirth, intoxication and withdrawal at time of delivery, as well as fetal malformations and long lasting cognitive and behavioral abnormalities in children.**
- **The effects of substance use on pregnancy is difficult to study due to recall bias, under reporting (due to stigma and legal consequences), lack of control of the dose, potency and gestational timing of exposure as well as multiple other confounders often experienced by this population such as poor prenatal care, infectious disease and poverty.**
- **Many women are motivated for sobriety in pregnancy and decreased rates of substance use are seen in the**

perinatal period. However, high rates of relapse are seen in the postpartum period.

- **Opioids are one of the most addictive substances available today and the number of pregnant women presenting to labor and delivery with an opioid use disorder has more than quadrupled in the past decade. The recommended treatment for pregnant women with opioid use disorder (OUD) is medication assisted treatment (MAT) with either methadone or buprenorphine.**
- **Tobacco use disorder in pregnancy decreases uterine blood flow, leading to fetal malnutrition, hypoxia and IUGR. Additional complications seen in this population include low birth weight and spontaneous abortion. First line treatment includes psychosocial interventions, with discussion of nicotine replacement if nonpharmacologic strategies are unsuccessful.**
- **Cannabis is the most widely used illicit drug in the world, with increasing rates of use seen in the perinatal population. Data regarding effects in pregnancy have been inconsistent, although there has not been consistent data showing that it is safe in pregnancy. The American College of Obstetricians recommends abstinence from cannabis in women trying to get pregnant, pregnant women, and women who are breastfeeding.**
- **There is no amount of alcohol that is currently considered safe during pregnancy. It is estimated that 1 of every 13 pregnant women who consume alcohol during pregnancy have a child with fetal alcohol syndrome disorder. The only known way to prevent this is by complete abstinence during pregnancy.**
- **Active abuse of stimulants during pregnancy has been associated with maternal hypertension, postpartum hemorrhage, preterm labor, placental abruption, intrauterine growth restriction, low birth weight and neonatal death.**
- **Use of benzodiazepines during pregnancy has been associated with increased rates of spontaneous abortion, cleft palate, intoxication and withdrawal including “floppy baby syndrome.”**

CONFLICTS OF INTEREST

The authors of this chapter declare that they have no interests that conflict with the contents of the chapter.

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