Journal of Pediatrics & Child Health Care

Open Access

Austin Publishing Group

Special Article – Neonatology

Polydrug Abuse and Fetal Exposure: A Review

Andrews L[1], Davies TH[1]*, Linz M[2] and Payne M[3]

[1]Department of Clinical and Translational Sciences, Joan C Edwards School of Medicine, Marshall University, USA

[2]Department of Psychology, Marshall University, USA

[3]Department of Neuroscience, Joan C Edwards School of Medicine, Marshall University, USA

***Corresponding author:** Davies TH, Department of Clinical and Translational Science, Joan C Edwards School of Medicine, Marshall University, 1600 Medical Center Drive, Huntington, WV 25701, USA

Received: January 01, 2018; **Accepted:** February 09, 2018; **Published:** February 16, 2018

Abstract

Recently the United States has seen an increase in the opioid drug use with a consequential rise neonatal abstinence syndrome. Although the increase of incidence is a complex public health crisis, it is important to discuss that opioid abuse and neonatal abstinence syndrome is not a completely unique public health issue. This is not the first time in which there have been public health concerns regarding the long-term impacts of substance use during pregnancy. The increase of opioid abuse denotes a time period that is comparable to that of nicotine, alcohol, cocaine, methamphetamine, and marijuana abuse. The focus of researchers and clinicians has been to isolate each substance and determine the individual effects of that substance on the neonate. While the individual effects of each substance are exceedingly important, it is imperative to understand substance abuse and its impact in pregnancy at a holistic, systemic level as well as an individual chemical level. Throughout public health history each substance use epidemic has been handled as a separate disease process. Few studies have utilized the information gleaned from previous public health crises involving substances to create an ecologically valid model for the general impacts of substance use in utero. In other words, the information known about substance abuse as a whole should be applied when studying individual substances. The purpose of this article is to discuss the usefulness of such an approach and to highlight the data gaps in the neonatal impact of substance abuse.

Keywords: NAS; NOWS; Fetal drug exposure; FAS; Opioids; Nicotine; Marijuana; Cocaine; Methamphetamine

Abbreviations

NAS: Neonatal Abstinence Syndrome; NOWS: Neonatal Opioid Withdrawal Syndrome; FAS: Fetal Alcohol Syndrome

Introduction

Recently the United States has experienced an increase in the use of opioid drugs. In 2012, the number of opioid prescriptions climbed to 259 million, a number sufficient enough for every American adult to have one bottle [1]. While numerous reports illuminate an astonishing epidemic, [2-4] many researchers agree that the data available may underestimate the problem as these increases are overwhelming the capacity of traditional resources [5,6]. Since the incidence has grown nearly five-fold since 2000, an estimated $1.5 billion in annual hospital expenditures has been reported across the United States [5].

Whether prescribed by a physician or obtained illegally opioid addiction is a cumbersome public health issue, one of which affects pregnant women and their infants by proxy [7]. Opioids cross the placenta very rapidly, creating a drug equilibrium between fetus and mother and this equilibrium has the potential to affect the developing fetus in many ways [8]. One of the most common effects of intrauterine exposure to opioids is Neonatal Abstinence Syndrome (NAS), a withdrawal syndrome that occurs shortly after birth due to the abrupt cessation of opioid delivery to the infant. In the U.S. it is estimated that one infant is born every 25 minutes with NAS representing $1.5 billion in additional hospital charges [9,10].This is not the first time in which substance abuse during pregnancy has led to a neonatal disorder or disease. These substances are the most common drugs of prenatal exposure according to Behnke *et al.*, [8]. The focus of researchers and clinicians has been to isolate each substance and determine the individual effects that substance has on the neonate. While the individual effects of each substance are exceedingly important, it is also important understand substance abuse disorder as a whole. Throughout public health history each substance has been treated as if it's a new separate disease and few studies have implemented the information known about one substance in the study of a different substance largely due to the difficulty of studying this population and small sample sizes. Thus, data substance abuse as a whole may or may not be applied when studying individual substances creating important gaps. The purpose of this article is to highlight these data gaps.

Methods

A systematic literature search of published research in PubMed and Medline using the key words "long-term outcomes", "neonatal abstinence syndrome", "intrauterine exposure", "cocaine exposure", "nicotine and alcohol exposure", "marijuana exposure", and "fetal effects of psychoactive drugs" resulted in 41 journal articles related to the subject, 32 of which were used to write the first draft. The search was not limited based on date, or study design although almost all the studies were case-control studies. Areas of concern were methodological approaches to studying fetal effects of nicotine, alcohol, cocaine, marijuana, and opioids.

Literature Review

The most commonly abused substances during pregnancy are

Citation: Andrews L, Davies TH, Linz M and Payne M. Polydrug Abuse and Fetal Exposure: A Review. J Pediatr & Child Health Care. 2018; 3(1): 1019.

Table 1: Published short and long term outcomes in children prenatally exposed to neuroactive substances and the research methods used to elucidate the data.

Substance	Research Procedures	Short-term Outcomes	Long-term Outcomes
Nicotine	Dosage Gestational timing	Oral facial clefts Low birth weight Intrauterine growth restrictions Alteration in brain metabolism Alteration in neurotransmitter systems Poor self-regulation	Impulsivity Attention problems Hyperactivity Negative externalizing behaviors Aggression Oppositional defiance Huger rate of delinquency Abnormalities in learning and memory Slightly lower IG scores Poor language development, comprehension, and reading abilities Higher rates of criminal behavior Substance abuse
Alcohol	Dosage Frequency of exposure Pattern of exposure	Fetal Alcohol Syndrome characterized by: Prenatal growth retardation Postnatal growth retardation Central nervous system dysfunction Small head circumference Short palpebral fissure Thin upper lip Hypoplastic philtrum	Attention problems Adaptive behavioral problems Disrupted school experiences Delinquent behavior Criminal behavior Higher rate of substance abuse
Cocaine	Dosage Gestational timing Duration of exposure Postnatal care	Decreased birth weight Growth retardation	Poor cognitive performance Poor language skills Poor behavioral and executive functioning Disrupted attention Poor working memory Deficits in information processing Deficits in problem solving
Methamphetamine	Dosage Gestational timing	Decreased birth weight Decreased length Decreased head circumference Growth restrictions Cardiac abnormalities Abnormal brain development	Attention problems Verbal memory deficits Nonverbal intelligence deficiency Fine motor skills deficiency Externalizing behavioral problems
Marijuana	Presence or absence of exposure	Decreased birth weight Shorter gestational lengths Restricted growth	Higher order function problems Executive function problems Verbal deficits Memory issues Altered emotional regulation Attention deficits Elevated impulsivity Hyperactivity
Opioids	Presence or absence of exposure	Neonatal Abstinence Syndrome characterized by: Tremors Irritability Sleep problems High-pitched crying Tight muscle tone Hyperactive reflexes Seizures Excessive yawning, sneezing Poor feeding Diarrhea Vomiting Dehydration Sweating Unstable temperature	Hyperactivity Short attention span Memory issues Perceptual problems Impulsivity Attention problems Vision deficits Cognitive and behavioral issues

nicotine, alcohol, cocaine, marijuana, and opioids. These drugs seem to spike in sensitive periods of time creating a pattern in which the methods of research on substance abuse can be observed. For example, research on fetal nicotine effects became prevalent after a spike in smoking during pregnancy shortly after that spike public health saw a spike in awareness of alcohol use during pregnancy. Although the history of substance abuse can be followed fairly well, the methodological approaches to studying these substances can to differ from substance to substance.

Nicotine

The association of prenatal nicotine exposure and the negative effects on the fetus has been studied since the late 1950s [11]. Since then nicotine remains one of the most popular legal drugs used during pregnancy, second to alcohol [12]. The effects of nicotine on the neonate has been shown to be dose dependent [12-15]. When pregnant women stop smoking during pregnancy research shows that the effects or risk of effects decreases [15]. Thus, number of cigarettes smoked a day can is used to predict the effect on the fetus.

A large amount of data outlining and explaining the effects of prenatal nicotine exposure aimed to advocate for smoking cessation before pregnancy exists. In that wealth of research, nicotine has been described as an agonist of the nicotinic acetylcholine receptor which is expressed in the first trimester in humans and therefore an emphasis is largely placed on smoking cessation before pregnancy occurs [16]. However, studies aimed to evaluate the gestational period of time in which exposure occurs have produced conflicting results. One study indicated that there was not a significant difference between infants exposed to nicotine throughout pregnancy when compared to those only exposed in the first trimester [17]. Cornelius *et al*., indicated that exposure during second and third trimester has been linked to attention problems [18]. Another study indicated that third trimester exposure was linked to oppositional behavior [19]. Therefore, while it is clear that a dose-response relationship exists it is not clear if that response is sensitive to the gestational age in which prenatal exposure occurs.

The short-term effects of prenatal nicotine exposure have been known for decades. Prenatal nicotine exposure has been associated with oral facial clefts, low birth weight and intrauterine growth restrictions [20,21]. Nicotine has been shown to have a significant effect on brain development including alterations in brain metabolism and neurotransmitter systems [20]. Infants with prenatal nicotine exposure have shown signs of poor self-regulation and require more therapeutic handling [22]. While the short-term effects have been known for decades, [23-25] the long-term effects have more recently been the focus of research. Long-term effect of prenatal nicotine exposure include impulsivity, attention problems, hyperactivity, negative externalizing behaviors, aggression, oppositional defiance, and higher rates of delinquency [26,27]. Prenatal Nicotine exposure is also associated with abnormalities in learning and memory which encompasses slightly lower IQ scores, poor language development and comprehension, and poor reading abilities [26,28,29]. These complications with behavior and cognition extend from early childhood into adulthood and have been shown to lead to higher rates of criminal behavior and substance abuse [30]. Children exposed prenatally are more likely to exhibit these behaviors than children only exposed during the postnatal period [31].

Alcohol

Almost 20 years later studies began to focus on prenatal alcohol exposure. Following a rise in alcohol use during pregnancy, Jones *et al*., first termed fetal alcohol syndrome to describe the effects of prenatal alcohol exposure [32]. While fetal alcohol exposure is the obvious direct cause of Fetal Alcohol Syndrome (FAS), not all infants exposed to alcohol prenatally develop FAS. Quantity, frequency, and the pattern of alcohol consumption is an important factor when predicting and studying the effects of prenatal alcohol exposure. In 1999, Jacobson and Jacobson indicated that patterns of alcohol drinking can modulate the severity of resultant deficits [33]. Several studies have shown that "moderate" drinking has much more of an impact on child development when a mother consumes a specific number of drinks in a single day than when she consumes the same number of drinks across several days drinking one or two drinks per day. For example, consuming three drinks in one day could be more harmful than drinking one drink a day for three days [8,33,34]. This indicates that even low level of consumption which has been noted to have less severe effects can be more harmful depending on the pattern in which the alcohol is consumed, clear demonstrating dose dependency.

Table 2: Common Signs and Symptoms of Children Prenatally Exposed to Substances.

Long-term Outcomes
Attention Deficits
Executive Functioning Problems
Altered Emotional Regulation
Disruptive Behavior

FAS is the most common short-term effect of prenatal alcohol exposure and is characterized by prenatal and/or postnatal growth retardation, Central Nervous System (CNS) dysfunction, and the fulfillment of at least two of the following: small head circumference, short palpebral fissure, thin upper lip, and hypoplastic philtrum [35]. Full FAS phenotype as described previously, is only observed in infants whose mothers' alcohol consumption history either consists of chronic, daily, and heavy consumption or frequent, heavy, intermittent alcohol consumption [35--38]. For example research has shown that full FAS phenotype requires consuming five to six drinks per occasion with a monthly consumption of at least 45 drinks. While partial FAS phenotype is more difficult to determine than full FAS phenotype [39]. It is well known that dose and frequency is pertinent to phenotype as well. Partial FAS phenotype is defined as fulfillment of two of the FAS criteria previously discussed [8,35].

The short-term outcomes of prenatal alcohol exposure particularly FAS are well understood. The long-term effects however are more difficult to determine. The long-term effect of FAS extend into adulthood and include attention problems, adaptive behavioral problems, disrupted school experiences, delinquent and/or criminal behavior [8,35,40,41]. Prenatal alcohol exposures has also been associated with a higher rate of substance abuse in adulthood for this population [8]. These long-term effects are believed to stem from the CNS dysfunction associated with FAS diagnosis.

Cocaine

In the 1980's shortly following a spike in alcohol use, cocaine became one of the most frequently abused illicit substances during pregnancy [42]. As a result, cocaine quickly became one of the most researched substance in regards to the potential teratogenic effects on the fetus [42]. Early research and predictions were poorly controlled and the outcomes were exaggerated creating a negative media hysteria and overall stigma around this population [42, 43]. Better controlled, more recent studies have shown however, that the effects of prenatal cocaine exposure may be more subtle than originally reported [42]. Many studies vary on the impact of prenatal cocaine exposure some have reported severe physical deformities, while other studies report much more subtle effects or even no effects at all [43,44]. Even though the studies vary on the impact of prenatal cocaine exposure, the studies largely agree that the magnitude of these effects is dependent on dosage, gestational timing, duration of exposure and postnatal care [12,42,45]. Interestingly a few studies in regards to prenatal cocaine exposure have acknowledged that cocaine is rarely used in isolation and proposed that polysubstance use a major concern [12,45].

Prenatal cocaine exposure has negative physical effects on the fetus including decreased birth weight and growth restrictions

[42,43,44]. These growth restrictions have been shown to extend beyond infancy with restrictions observed in children who are as old as ten years of age [44]. The long-term effects of prenatal cocaine exposure also include poor cognitive performance in language skills, behavioral and executive functioning all of which extend into adulthood [8,44,46]. Executive function was further defined for this population as disruption in attention, behavior, cognition, working memory, information processing, and problem solving [8,44].

Methamphetamine

The number of people 12 years old and over who have tried methamphetamine (meth) once in their life time has increased from 2.5% in 1997 to 5.3% in 2007 [42]. This concerning increase has led to the thought that meth may be growing to become the drug of choice for adults in the United States including pregnant women [42]. Despite the increase in use and the use during pregnancy, little is known about the use of meth in pregnant woman or the short-term effects [47]. Even less information is available long-term effect on the fetus who is exposed to meth prenatally [42,44,47]. The most common effects associated with prenatal meth exposure are growth restrictions that have been shown to extend past infancy, decreased birth weight, decreased length, and decreased head circumference [8,44,48]. Prenatal exposure has also been associated with cardiac abnormalities and abnormal brain development [8,44,49]. The associated long-term effect of prenatal exposure includes vision disturbances, defects with attention, verbal memory, nonverbal intelligence, fine motor skills and externalizing behavioral problems [8,42,44].

The presence and severity of the effects listed above are believed to be dependent upon the amount of meth exposure. Therefore, a dose-relationship has been observed with prenatal meth exposure [42,44]. Animal models support the dose-relationship of prenatal exposure and in addition, animal models have indicated that gestational timing of exposure, particularly in the third trimester are associated with more sever effects [42]. Animal models have also indicated that there is a long-lasting toxicity to the developing central nervous system of the exposed fetus [42].

Marijuana

Recently cannabis, commonly referred to as marijuana, has been legalized in Colorado and Washington and has since been decriminalized in many other states with an expectation for additional states to follow suit. Medical marijuana is also legal in many states and is even used in pregnancy to combat nausea. Therefore, prenatal exposure to marijuana is a growing concern. While prenatal exposure to marijuana has been an occurrence before legalization and decriminalization, one can imagine that marijuana could follow the trend of other legal but teratogenic substances such as nicotine and alcohol. While legality and safety are not interchangeable in regards to marijuana use, it is important to note that as marijuana use has increased the belief that marijuana is harmful has decreased despite having few studies to determine outcomes [50].

In prenatal marijuana exposure, fetal delta-9-tetrahydrocannacional (THC) level concentrations have been found to be lower than the concentration of THC in the mother in animal models indicating that the placenta may limit fetal exposure [8]. However even though the placenta may limit the exposure, the fetus is still exposed and this may lead to negative outcomes. Furthermore, the concentration of THC in marijuana has greatly increased over the years indicating a chance of greater fetal exposure to THC [51]. Relatively few studies have been conducted in regards to the effects of prenatal marijuana exposure despite the growing use among pregnant women and evidence that marijuana crosses the placenta. Some studies have indicated that gestational timing of exposure can predict specific long-term effects [52,53]. The majority of the studies however do not indicate gestational timing or a dose response for marijuana [44],50,54]. These studies instead focus on the presence or absence of exposure. One study in particular indicated that additional substances such as nicotine and alcohol can make the effects of marijuana difficult to determine [54]. However, this study only indicated co-substance abuse with no reference to polysubstance abuse or illicit drug use in combination with marijuana.

Prenatal marijuana exposure is associated with shorter gestational lengths, decreased birth weight, and restricted growth [8,44]. The long-term effects of prenatal marijuana exposure are not generalized to overall cognitions but are specific to higher order function, especially executive function [8,44]. The executive function deficits include verbal deficits, memory issues, altered emotional regulation, attention deficits, elevated impulsivity, and hyperactivity [8,44].

Opioids

The literature review thus far has discussed substances commonly used in pregnant women in the past decades. Recently, opioid abuse has been the focus of researchers and clinicians as a spike in opioid abuse has occurred. While the opioid epidemic is not entirely unique to the epidemiology of substance abuse, it is unique in that opioid cessation is not recommended for pregnancy [55]. The American Academy of Pediatrics and American College of Obstetricians and Gynecologists recommends opioid maintenance therapy instead of detoxification of pregnant women using opioids [55]. Buprenorphine has become the gold standard of opioid maintenance therapy however it is important to note that although recommended these maintenance strategies are not void of substantial risk to the fetus [56]. Buprenorphine, or any other substance used in maintenance therapies can cross the placenta and cause negative fetal outcomes. These maintenance therapy options do however aim to provide stability to the situation as a whole. Detoxification is not recommended for several reasons one of which being maternal risk of relapse [55]. By providing Buprenorphine, the therapy is aimed at stabilizing the mother in such a way that risk of relapse, binging, and using more potent or different substance is at a minimum. Maintenance therapies also aim to stabilize the mother psychologically. In turn, these maintenance therapies have a stabilizing effect for the fetus. Incidence, peak severity score, duration, and length of required hospital stay due to Neonatal Abstinence Syndrome (NAS) appear to be less severe in infants born to mothers following a buprenorphine maintenance therapy when compared to mothers not enrolled in maintenance therapies who continue to use illicit opioids [57]. This recommended maintenance therapy aims to create an environment for the infant in which the predictable outcomes of using methadone become a reality instead of the unpredictable outcomes of illicit opioid abuse.

Once the infant is born onset of NAS symptoms can manifest anywhere from 24 to 72 hours after birth, although one study found

that symptoms can manifest much earlier [5]. The severity of these symptoms is estimated by an approved scoring system, the most common being the Finnegan Neonatal Abstinence Severity Score [5]. Scores are calculated at the onset of symptoms and again periodically at specific time periods throughout the length of hospitalization. Treatment decisions are based upon these scores and can range from nonpharmacological to pharmacological treatment options. Nonpharmacological treatment includes tight swaddling in a dark, quiet environment, parental involvement and other interventions designed to reduce external stimuli [6]. Newborns that fail to respond to nonpharmacological treatment or score within a specific range, are treated with opioid replacement therapy with either buprenorphine, being the gold standard, or methadone according to the American Academy of Pediatrics Policy Statement on Infant Withdrawal [56]. Opioid dependence is weaned in accordance to ongoing Finnegan scores until pharmacological treatment is no longer needed and discharge from the hospital facility is possible. Typically, nonpharmacological and pharmacological treatments are implemented simultaneously.

The opioid maintenance therapy and the treatment of NAS with recommended opioids creates a unique situation in which the infant is exposed to a potential teratogenic substance both prenatally and postnatal. Both the prenatal maintenance therapy and the postnatal treatment of NAS allow for an appropriately tittered dosing regimen that is highly and tightly regulated. However, no articles providing information on dosage, frequency, gestational timing regarding to how these factors effect outcomes could be found in this systematic review.

NAS, encompassing the short-term effects of prenatal opioid exposure is well defined however; the research studies focused on long-term outcomes have provided conflicting results. Very little information is available of the long-term outcomes on behavior and cognitive issues related to opioid exposure. In one study Behnke *et al*., indicated that hyperactivity and short attention span has been observed in toddlers with NAS [8]. The same study also indicated that memory and perceptual issues have been observed in older children with NAS diagnosis. In a different study Maguire *et al*., showed that five to six-year-old children exposed prenatally to Buprenorphine demonstrated hyperactivity, impulsivity, and attention problems [58]. In addition to cognitive and behavioral issues there is growing evidence that suggests vision is affected by intrauterine opioid exposure.

Polysubstance Abuse

While opioid abuse is growing and concerning, opioids are rarely abused in isolation. The same can be said for all of the substances previously discussed in this article. Polysubstance abuse is the reality in this population and this makes studying any one substance difficult. It is possible however, to take the information that is known about commonly abused substances and apply that knowledge to recent studies to try to tease out the specific effects of an individual substance. On the other hand that same information can also be compared and used simultaneously to create an improved methodological approach in studying substance abuse as a whole. The methodological approach for each individual substance seems to differ creating a system in which each substance is treated as an individual disease. All of the drugs discussed are believed to readily cross the placenta and to have some effect on the fetus. While it is important to note that not all of these drugs will induce a withdrawal syndrome, polysubstance abuse can cause differing signs and symptoms as well as a possibility of altering the severity of withdrawal and/or both short and long-term outcomes.

Discussion

Illicit drug use in women has not decreased in spite of educational programs, prevention methods, and rehabilitation efforts [56]. The pattern of illicit drug use in women especially in young adolescent females has developed in such a way that women are more likely to use illicit drugs than men in the same age group [56]. The use of legal substances such as nicotine and alcohol, during pregnancy also represents an environment in which infants are at risk for negative outcomes. While the instances of substance abuse have grown in the past decade's researchers agree that many of the reported substances abused are underestimated. This underestimation can be due to many different factors such as negative stigma associated with substance abuse disorder, fear of prosecution, fear of potentially losing the child, or fear of any negative outcome directly associated with the substance abuse disorder [44]. This can lead to a decrease in women who seek treatment or prenatal care and a decrease in the full disclosure of the substance abuse disorder. Lack of treatment, prenatal care, and honesty of substance abuse can lead to poor infant outcomes. Improved public education on the complex issues surrounding substance abuse seem warranted.

Research in any substance abuse population is difficult due to many confounding factors in addition to the issues that encompass underestimation. This population can be unstable and unreliable due to social and economic status making long-term follow up studies problematic to complete. Other confounding factors such as social and economic status, high risk environments and polysubstance abuse can make the research more difficult. Many researchers agree that environmental risks will magnify any weakness caused by the opioid exposure or any substance abuse exposure [59]. Therefore, it is difficult and may even be impossible to fully tease out the confounding factors from the research objective. Almost all study designs control for these confounding factors, however there seems to be no consistent method to which those factors are controlled (Table 1).

Researchers agree that the dosage, gestational timing of exposure, frequency of exposure, and pattern of exposure can be predictive of outcomes or severity of outcomes. However, few studies include all of these factors. Nicotine studies for instance focus on dosage as determined by cigarettes smoked per day or packs per day however the other factors either have conflicting results or have not been studied. Alcohol studies focused on dosage, frequency, and pattern of exposure however, polysubstance abuse is omitted from the research. Cocaine exposure research focused on dosage, gestational timing, and frequency. While pattern of exposure was omitted some studies acknowledged that polysubstance abuse was a main contributing factor to fetal outcomes. Methamphetamine exposure focuses on dosage and animal models focused on methamphetamine exposure focuses on gestational timing. However, pattern and frequency are not mentioned. More studies have focused on marijuana exposure

however; conflicting results have made the effects unclear. The majority of the research studies on marijuana focus on the gestational timing of exposure largely omitting dosage, frequency and pattern of exposure. These studies seem to focus solely on whether or not prenatal marijuana exposure did or did not occur. Some marijuana studies did include co-substance abuse but in regards to legal substances such as nicotine and alcohol, refraining from discussing polysubstance abuse with illicit substances.

As a spike in opioid abuse has occurred the effects of prenatal opioid exposure have been a major public health concern. Research with opioid exposure to the best of our knowledge does not focus on dosage, gestational timing, frequency of exposure, or pattern of exposure. These studies, much like studies on marijuana exposure, seem to solely focus on whether or not exposure did or did not occur. In situations in which the mother is enrolled in a maintenance therapy program the opioid dosage is known as well as the gestational timing, frequency, and exposure pattern by way of therapy design. Although polysubstance abuse is likely and the dosage, timing, frequency, and pattern of any additional substances used may not be known the buprenorphine levels can be mostly accounted for. In addition, once the infant is born and pharmacological treatment is initiated, the dosage, timing, frequency, and exposure pattern is known, appropriately tapered, and tightly regulated. This information could perhaps be used in evaluating outcomes.

It is important to note that when discussing the methods dosage, or concentration of the drug is extremely important to the outcome. Drug concentration can be quantified through different methods and that quantification can lead to important implications of fetal outcomes. For example, it is believed that the placenta limits THC exposure however THC concentration in marijuana is increasing [51]. This uncontrolled increase becomes an issue when discussing fetal exposure. Even though the exposure might be limited, due to an increase in the concentration the exposure may be worse than originally thought. Furthermore, when discussing illicit street drugs the concentrations of the differing substances that are sold as meth or cocaine for instance can differ greatly from concentrations of prescribed substances that are abused. It is known that increasing the concentration of any drug will increase the effects therefore knowing the concentration of these substances in regards to prenatal exposure is detrimental to the research. However, few studies indicated the concentration of the substances abused during pregnancy and it is challenging to control for environmental and other factors (Table 2).

Conclusion

With the consistently growing number of individuals affected by substance abuse there is a constant need for furthering research so outcomes can be clearly defined. Not only is furthering research needed to determine outcomes of substance abuse but also mental health and educational services need to be improved upon for this population [60]. Models for prenatal polysubstance exposure are warranted for this vulnerable population [44,60]. While opioid abuse has spiked in recent years it can be predicted that a different substance will emerge and spike in the future and improved consistent research methods could positively impact that population.

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