Investigating Mechanisms of Stillbirth in the Setting of Prenatal Substance Use

Corrie B. Miller, Tricia Wright

ABSTRACT

Introduction: Intrauterine fetal demise affects between 0.4-0.8% of pregnancies worldwide. This significant adverse pregnancy outcome continues to be poorly understood. *In utero* exposure to substances increases the risk of stillbirth to varying degrees according to the type of substance and degree of exposure. The aim of this qualitative narrative review is to investigate common biologic relationships between stillbirth and maternal substance use.

Methods: A PubMed literature search was conducted to query the most commonly used substances and biologic mechanisms of stillbirth. Search terms included "stillbirth," "intrauterine fetal demise," "placenta," "cocaine," "tobacco," "alcohol," "methamphetamines," "opioids/opiates," and "cannabis."

Results: There are very few studies identifying a direct link between substance use and stillbirth. Several studies demonstrate associations with placental lesions of insufficiency including poor invasion, vasoconstriction, and sequestration of toxic substances that inhibit nutrient transport. Restricted fetal growth is the most common finding in pregnancies complicated by all types of substance use.

Discussion: More research is needed to understand the biologic mechanisms of stillbirth. Such knowledge will be foundational to understanding how to prevent and treat the adverse effects of substances during pregnancy. *Acad Forensic Pathol. 2018 8(4): 865-873*

AUTHORS

Corrie B. Miller DO, University of Hawaii System - Obstetrics, Gynecology and Women's Health

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

Tricia Wright MD MS FACOG FASAM, University of Hawaii System - Obstetrics, Gynecology and Women's Health

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, general supervision, general administrative support, writing assistance and/or technical editing.

CORRESPONDENCE

Tricia Wright MD MS FACOG FASAM, 1319 Punahou St. Ste 824, Honolulu HI 96826, tewright@hawaii.edu

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Substance use, Pregnancy, Intrauterine fetal demise

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

 • (ISSN: 1925-3621) • https://doi.org/10.1177/1925362118821471
Submitted for consideration on 2 Sep 2018. Accepted for publication on 22 Oct 2018

INTRODUCTION

Stillbirth is defined as intrauterine fetal demise after 20 weeks gestation or greater than 350 g fetal weight (1). Approximately 2.65 million pregnancies worldwide are affected annually (2). Rates of stillbirth vary between countries ranging from 4-6 per 1000 births in developed nations to 8-10 per 1000 births in low-income countries (3, 4). This devastating problem stems from a variety of etiologies and our understanding of mechanisms behind stillbirth continues to evolve.

Similarly, varying rates of women report substance use in their reproductive years worldwide. Within the United States, 10% report alcohol consumption, 17% smoke tobacco, and an estimated 4.4% of pregnant women report illicit drug use during pregnancy (5, 6). These rates are higher across Europe and Australia, with a third to half of women reporting using alcohol, 25% tobacco, and upwards of 8% illicit substances (7, 8). This makes substance use disorder (SUD) as common as other medical conditions during pregnancy that are risk factors for stillbirth such as hypertension or diabetes (9). With regards to the type of illicit substances, the data is less well defined and varies among regions. Trends in popularity among various substances confounds some studies collecting data across multiple decades. The opioid crisis has taken center stage in recent years, but psychostimulants and cannabinoids are also reported with increasing frequency among pregnant women.

The association between stillbirth and maternal consumption of toxic or stimulant substances is well documented. Consistently, large, population-based studies reveal an increased risk of stillbirth for women consuming alcohol (Odds Ratio [OR] 1.36; 95% Confidence Interval [CI] 1.05–1.76) (10), tobacco (OR 1.36; 95% CI 1.27–1.46) (11), opioids (OR 1.5; 95% CI 1.3 - 1.8) (12), or methamphetamine (OR 5.1; 95% CI 3.7-7.2) (13), while adjusting for confounding factors. Maternal medical conditions such as hypertension, diabetes, or drug use are reported to contribute to approximately 20% of stillbirths that have an identifiable cause. Such conditions are modifiable risk factors and adequate management can prevent adverse pregnancy outcomes (14). Patel and colleagues used the Nationwide Inpatient Sample (NIS) database to investigate the association between maternal medical conditions and stillbirth (15). In this study, ICD-9 codes were used to analyze the risk of stillbirth in women with chronic conditions versus those without. Accounting for many other covariates in a multivariable logistic regression, the study still noted increased odds of stillbirth in women using alcohol (OR 1.62; 95% CI 1.37-1.93) and illicit drugs (OR 1.7; 95% CI 1.62-1.82). There was a weak effect from tobacco (OR 1.06; 95% CI 1.03-1.11) (15).

Beyond database derived correlations, prospective data helps to identify risk factors for stillbirth. The Stillbirth Collaborative Research Network (SCRN) performed a multisite case-control study, enrolling patients in order to prospectively collect important parameters. Controlling for multiple confounders, they noted an association with stillbirth and history of drug addiction prior to pregnancy (4.5% stillbirths, 2.1% live births) (vs. never use; Adjusted OR [AOR], 2.08; 95% CI, 1.12–3.88); smoking during the three months prior to pregnancy (<10 cigarettes/day, 10.0% stillbirths, 6.5% live births) (vs. none; AOR, 1.55 [95% CI, 1.02–2.35]) and tobacco use during pregnancy (OR 1.94, 95% CI 1.04-3.55). Interestingly, in this analysis, alcohol and drug use were not statistically significantly associated with stillbirth but the numbers were low (14, 16).

The SCRN also demonstrated a direct biologic correlation in this cohort. Toxicology analysis was performed on maternal serum and umbilical cord blood, according to maternal selection. Mothers could opt out of specific testing, if desired, at the time of consent. About half of enrollees did not have these tests performed, generating a self-selection bias, yet in this population twice as many patients with stillbirth tested positive for any substance versus mothers with a livebirth (7% vs. 3.5%; OR 1.94; 95% CI 1.16–3.27).

The effects of substance use result in increased neonatal deaths as well. Viteri looked at any type of maternally reported substance use and risk of prematurity

and neonatal death. There was an increased risk of a composite outcome of stillbirth, neonatal death within one year of life, or moderate-to-severe cerebral palsy by the age of two. This risk was magnified in patients with preterm delivery (17). In a cohort of patients that delivered preterm, those that delivered between 32-36 $^{6}/_{7}$ weeks gestation had an adjusted odds ratio of 6.5 (95% CI 1.14-36.99). Other studies have noted an increased risk of sudden infant death syndrome (SIDS) and neonatal death from exposures to substances outside of the setting of prematurity (18).

There are several challenges to interpreting the exact contribution of substance use to the problem of stillbirth. First, many studies in the current literature define consumption rates by self-reported data without biologically testing to confirm quantity of substance. The quantity and frequency of use is difficult to measure, and consumption may vary throughout gestation. Furthermore, patients using one illicit substance are more likely to use multiple substances (7). Aliyu looked at birth record data for women in Missouri and noted that more than half of women who admitted to consuming alcohol during pregnancy also smoked tobacco (19). Those who use cocaine are four times more likely to use tobacco than those who do not (20). Many substances, especially stimulants, work synergistically to increase the risk of poor pregnancy outcomes (21). Finally, socioeconomic confounders are also vast, as those who consume substances are more likely to not seek adequate prenatal care, suffer from mental illness (22), have a lower socioeconomic status, experience intimate partner violence and trauma, or inflict maternal self-harm (23).

While many studies demonstrate the correlation between maternal substance use in pregnancy and the risk of fetal death, the causation is more difficult to define. Understanding the exact pathophysiology behind various substances remains a challenge. Yet, by expanding research in this area we may find new ways to decrease the adverse effects of substance use in pregnancy, as well as modulate the synergistic additive effects of an adverse social environment.

METHODS

This narrative literature review sought to identify common themes in the scientific literature that contribute to understanding of biologic mechanisms behind stillbirth. A PubMed literature search was conducted using MESH terms. Search strategy included "stillbirth" and the following terms individually using the "AND" function: "substance use," "substance abuse," "cocaine," "tobacco," "alcohol," "methamphetamines," "opioids OR opiates," and "cannabis." The same individual MESH terms (substance types aforementioned) were also applied to "intrauterine fetal demise," "placenta," and "pathology." Hand searches of the references of retrieved articles were also performed. Human and animal studies published in English between January 1970 and July 2018 were reviewed by the authors and referenced if biologic findings related to the placenta or fetus were included in the study. Original research articles were used to synthesize biologic findings associated with stillbirth. Review articles were only included if some clinical or biologic finding was analyzed in a meta-analysis format. The information was summarized according to substance type.

RESULTS

The search strategy yielded 1313 unique articles. Of these articles, 24 specifically studied biologic or histologic effects of substance use on the placenta, fetus, or neonate. **Table 1** demonstrates the number of studies according to substance type.

DISCUSSION

Mechanisms For Stillbirth – What Do We Know?

Substances used as stimulants likely have similar physiologic effects on the feto-placental unit. Cocaine, methamphetamines, and especially tobacco, are associated with intrauterine fetal growth restriction (IUGR), placental vasoconstriction, and fetal hypertension (24). If used later in gestation, more subtle effects occur, affecting early childhood development. Changes in neurotransmitters, neurotransmitter recep-

tors, and brain organization are all seen with the stimulant-like substances in neonates (25). The risk for placental abruption is increased three-fold in women who use substances such as these and is a large contributor to fetal demise (26).

Tobacco

Tobacco is the most common substance used in pregnancy and also one of the most studied. The metabolites of tobacco have low molecular weight, easily cross the placenta, and have been found in umbilical cord blood, fetal blood, urine, and meconium (6). As nicotine and its byproduct, cotinine, cross the placenta, the fetus is left with higher concentrations than the mother due to slower metabolism and excretion. The composition of cigarettes includes several other harmful toxins including cyanide, sulphides, cadmium, and carcinogenic hydrocarbons (27).

Several studies have investigated how components of tobacco exert direct effects on placental development, growth, and function. Abnormal cytotrophoblastic invasion is seen during the first trimester. Later, placental histology demonstrates thickening of the trophoblastic basement membrane, increased collagen in the villous mesenchyme, less neovascularization, and significant villous arteriole swelling (28). These findings are not reversed with smoking cessation (6). As the placenta develops, tobacco also decreases cytotrophoblast proliferation and differentiation (29). Poor placentation results in insufficient oxygen and nutritional support for the fetus in later gestation. Tobacco also exerts effects on various enzymatic activities within the placenta. A 30% reduction in the mitochondrial enzymatic activity of Complex III has been demonstrated in placental mitochondria from smokers compared with nonsmokers (30). Less respiratory function can lead to oxidative stress and, theoretically, contribute to intrauterine fetal demise.

At term, cadmium and nicotine concentrations are equivalent in umbilical cord and maternal serum. Cadmium first accumulates in villous tissue where it is sequestered until concentrations are saturated and the villi can no longer isolate it away from the fetus. This delayed toxic effect is additive on top of abnormal placentation. High cadmium levels produce necrosis within villi in rat models, demonstrating that the toxic chemical creates hypoxia (31). Through decreased placental mass, vasoconstriction, and decreased respiratory function, maternal smoking leads to restricted fetal growth as there is limited energy availability within cells and decreased nutrient transport. Vasoconstriction in early gestation leads to IUGR in the third trimester. Without recognizing this and performing antepartum fetal surveillance, the fetus may succumb to hypoxia. Gardosi and colleagues noted that the main association with tobacco use and stillbirth was related to growth restriction. They noted that women who were smokers but did not have fetal growth restriction had a similar rate of stillbirth as nonsmokers (32).

Cocaine

Cocaine is similarly associated with adverse pregnancy outcomes like fetal growth restriction, placental

Table 1: Number of Studies According to Substance Type

Substance Type	Biologic Unit Investigated	Number of studies identified [References]
Tobacco	Neonatal biometry, placenta morphology, placenta oxidation	6 [27-31, 43]
Alcohol	Placenta, fetus, neonate, myometrium	4 [47-49, 51]
Stimulants (Cocaine and Amphetamines)	Fetal growth, placenta, neonatal neurologic development, autopsy	9 [20, 24-25, 33-36, 39, 41]
Opioids	Fetal, placental pathology	2 [52, 54]
Cannabis	Placental gene regulation	1 [58]
Multiple Substances	Placental abruption	2 [26, 53]

abruption, and stillbirth (33). Cocaine blocks reuptake of dopamine within the nervous system. The drug also readily crosses the placenta and is found in increased concentrations in amniotic fluid compared to maternal serum (23). Some of the consequences of cocaine use to the feto-placental unit include increased uterine tone, vasoconstriction, hypertension (6), and decreased steroid production leading to less endogenous progesterone (34).

The strong association with fetal growth restriction is generally seen in later gestation. The Maternal Lifestyle Study looked at maternal and neonatal outcomes among 1072 infants exposed to cocaine and 7565 cocaine negative dyads. After controlling for other confounders, they noted smaller percentile estimates for birth weight, length, and head circumference in the exposed group, and described a significant growth deceleration, especially after 32 weeks gestation (20).

The mechanisms that lead to decreased fetal growth may contribute to stillbirth, although this has yet to be demonstrated. Several theories about fetal growth restriction exist, the most prevailing being decreased uterine blood flow secondary to decreased uptake of the sympathomimetic neurotransmitters. This leads to hypertension, tachycardia, and extreme vasoconstrictive effects. Placental infarcts and abruption can occur at any time during pregnancy, leading to fetal hypoxia (35). Other possible, and perhaps simultaneous, effects include detrimentally impacting global brain development (36), decreased maternal nutrition, impaired placental amino acid transport (37), and endocrine disruption (20). Campillo studied cocaine exposure in pregnant rats and noticed an increase in stillbirths, decreased birth weight, decreased central nervous system weight, and symmetrical growth restriction (33).

Amphetamines

According to the US National Survey on Drug Use and Health 2012, 7.2% of women aged 12-44 years old reported using methamphetamines (13). In high-use regions of the US, 5.7% admitted to use during pregnancy (13, 38). Methamphetamine prevents the reuptake of serotonin, norepinephrine, and dopamine, exerting stimulant effects primarily on the central nervous system, but also peripheral tissues including the cardiovascular and pulmonary systems. The feto-placental unit is also vulnerable to these effects and experiences decreased uterine blood flow, increased vascular resistance, and elevations in fetal blood pressure (39). This occurs in a dose-dependent manner in animal models (24, 40). After administration of methamphetamine to pregnant sheep, Stek et al. observed increases in maternal and fetal blood pressure and uterine vascular resistance and a decrease in uterine blood flow in a dose-related fashion. Burchfield et al. also noticed these changes and demonstrated quick placental transfer within 30 seconds of administration. Fetuses were exposed for a longer period of time due to a longer elimination half-life (41). Both studies showed the vascular changes led to hypoxemia and acidemia in the fetus.

In addition to long-term hypoxia, fetuses and neonates may not be able to mount an adequate sympathomimetic response due to the decrease in catecholamines caused by the drug. Catecholamines are depleted through several pathways including impaired epinephrine release, less conversion to norepinephrine, and inhibition of norepinephrine uptake by transporters in reproductive tissues. This is exhibited in the decreased levels of norepinephrine in term umbilical cord blood samples from women using methamphetamines during pregnancy (42). Similar to tobacco exposure, fetuses and neonates have a deficient autonomic response in the setting of hypoxia, and are thus more vulnerable to *in utero* and postnatal hypoxic events (43). In addition, pregnancies with methamphetamine use are often complicated by fetal growth restriction, which can make the fetus even more vulnerable with less nutrient and oxygen reserve (44). While not directly demonstrated in animal models, such mechanisms could lead to a fetal demise.

Alcohol

Overall, alcohol consumption during pregnancy is very common worldwide. In the US, one in ten women report any alcohol use, and one in 33 report

binge-drinking within 30 days of initiating prenatal care (45). Consumption is much higher in Europe. The rates of fetal alcohol syndrome (FAS) range from 0.2-1.5 per 1000 live births in some regions (46), while childhood studies in high-prevalence regions estimate closer to 6-9 per 1000 children may be affected (47). Intrauterine alcohol exposure is a risk factor for fetal mortality as well as infant and child mortality. After maternal consumption, fetal blood alcohol levels reach the same as the mother shortly after. The metabolites continue to be consumed as they are excreted into the amniotic fluid, prolonging exposure time to the fetus (48).

The mechanisms leading to stillbirth are hypothesized to also involve placental dysfunction. Animal models have demonstrated decreased blood flow and increased intravascular coagulation within the placenta (49). Kesmodel reported an increased risk of stillbirth due to complications arising from fetoplacental insufficiency (50). Older studies have noticed an association with placental abruption with maternal alcohol consumption, although newer results are less consistent (51). Other hypothesized pathways include changes in hypoglycemia (47), and increased prostaglandins release that decreases cell division and ultimately resulting in early fetal demise (19, 52).

Opioids

Opioids exert less risk on exposed fetuses and infants than other stimulant-like substances with regards to overall mortality. Maeda et al. performed an analysis of opioid dependent mothers in the United States, using the NIS database with ICD-10 codes. Obstetric outcomes of patients with opioid use/dependence were compared to controls without substance use disorder and also to another cohort of patients who used of illicit drugs, alcohol, or tobacco but not opioids. In their analysis, opioid use in pregnancy was moderately associated with stillbirth (OR 1.5; 95% CI 1.3-1.8), but when comparing this rate to patients who used other substances, the effect disappeared (OR 0.9, 95% CI 0.7-1.1) (12). This demonstrates that while there may be an increased risk over baseline, this effect is weaker than seen with other substances.

More research is needed on direct mechanisms that could lead to this risk. In looking at placentas of women treated for opioid use disorder, histology demonstrated that delayed villous maturation was present significantly more in women using opioids versus those who were not (38.82 vs. 16.47%; $p < 0.002$) (53). This lesion has been correlated with stillbirths in other settings (54). Delayed villous maturation is associated with findings of uteroplacental insufficiency and abnormal uterine artery doppler findings due to poor perfusion at the terminal villus. The finding can be nonspecific as it is also seen in pregnancies affected by gestational diabetes, anemia, smoking, air pollution, and genetic abnormalities. However, the two-fold increase in those exposed to opioids may point to an underlying mechanism of placental insufficiency increasing the risk of intrauterine fetal demise.

Other studies demonstrate the fetal and neonatal risks associated with repeated maternal opioid withdrawal. As a mother experiences withdrawal or complete detoxification, an increase in catecholamine release leads to subsequent systemic vasoconstriction, uterine contractility, and decreased placental blood flow (12). Likewise, the fetus also experiences withdrawal and increased oxygen requirements from hyperactivity. Circulating levels of catecholamines are noted in the amniotic fluid (55). Alleviating repeated cycles of withdrawal through medication assisted treatment with methadone or buprenorphine reduces this stress created from hypoxia and is associated with less adverse pregnancy outcomes (56, 57).

Cannabis

The SCRN looked at cord homogenate and maternal cotinine levels in 663 stillbirth deliveries and 1932 live birth deliveries. The most common individual drug seen in these specimens was cannabis. Cannabis was associated with a two-fold risk of stillbirth (OR 2.34, 95% CI 1.13–4.81), but this was somewhat confounded by tobacco use. Yet, even after adjusting for tobacco use, that two-fold stillbirth risk was only lessened by 10%. Furthermore, the stillbirth risk associated with smoking was not lessened by adjusting for tetrahydrocannabinolic acid. The authors concluded

that there is a possible association between cannabis and stillbirth that is not attributable to concomitant tobacco use. None of the fetuses exposed to cannabis had birthweights that were small for gestational age, highlighting possibly another mechanism by which this might occur (58).

Tetrahydrocannabinol is the active ingredient in marijuana and readily crosses the placenta. This metabolite is fat soluble and has a prolonged tissue half-life of approximately six days, though it may be longer in the fetus. Smoking marijuana yields higher blood carboxyhemoglobin than smoking cigarettes and may decrease fetal oxygenation by this pathway (6). Furthermore, *in vitro* studies demonstrate that trophoblastic cells exposed to delta-9-tetrahydrocannabinol (D9-THC) have decreased proliferation and a gene expression profile affecting genes modulating growth, apoptosis, cell morphology, and ion exchange pathways (59). This highlights a mechanism that may be more related to decreased proliferation rather than vasoconstriction.

CONCLUSION

Several themes in the literature demonstrate adverse effects of substance use on pregnancy outcomes. Specifically, poor placental perfusion, inadequate nutrient transport, and fetal growth restriction are more common in pregnancies affected by substance use. Because these insults are also seen more frequently in stillbirths, inferences can be made that link these insults to a mechanism of stillbirth. Direct evidence of a causal mechanism is still lacking. There is a need to investigate not only exact pathways, but also prevention and treatment strategies. As there are many etiologies of stillbirth, there are likely various contributing mechanisms that increase the risk of this adverse outcome. *In vitro* and *in vivo* pathway analyses may shed light on this question. Such models eliminate confounding social and environmental factors. Yet, an adverse social environment is an important component to study as well, as modifying the adverse environment appears to produce improved biological outcomes.

Strong social support and enrollment in prenatal care modulate the detrimental effects associated with substance use. Women who actively engage in prenatal care even without abstaining from substances have improved outcomes, highlighting the strong biopsychosocial influences on fetal development. For instance, patients randomized to enhanced prenatal care with illicit drug treatment programs demonstrated improvements in birth outcomes even if they were not successful in making behavioral changes towards decreased use or abstinence (60, 61). El-Mohandes et al. also noted in a cohort of pregnant women in Washington D.C., that those who continued to use substances throughout pregnancy but had four or more prenatal visits had better pregnancy outcomes with larger birthweights and less preterm delivery (62). This may be due to earlier detection of growth restriction or fetal hypoxemia and increased antenatal surveillance. Investigating these mechanisms on the biologic effect of substance use will be very clinically useful.

Overall, our understanding of direct mechanisms behind substance use and stillbirth remains limited. More studies are warranted to not only understand the physiologic basis but also the environmental modulators of this relationship.

REFERENCES

1) Page JM, Silver RM. Evaluation of stillbirth. *Curr Opin Obstet Gynecol*. 2018 Apr; 30(2):130-5. PMID: 29489503. https://doi.org/10.1097/GCO.0000000000000441.

2) Cousens S, Blencowe H, Stanton C, et al. National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis. *Lancet*. 2011 Apr 16; 377(9774):1319-30. PMID: 21496917. https://doi.org/10.1016/S0140-6736(10)62310-0.

3) MacDorman MF, Kirmeyer SE, Wilson EC. Fetal and perinatal mortality, United States, 2006. *Natl Vital Stat Rep*. 2012 Aug 28; 60(8):1-22. PMID: 24979970.

4) McClure EM, Saleem S, Pasha O, Goldenberg RL. Stillbirth in developing countries: a review of causes, risk factors and prevention strategies. *J Matern Fetal Neonatal Med*. 2009 Mar; 22(3):183-90. PMID: 19089779. PMCID: PMC3893926. https://doi.org/10.1080/14767050802559129.

5) Płotka J, Narkowicz S, Polkowska Z, et al. Effects of addictive substances during pregnancy and infancy and their analysis in biological materials. *Rev Environ Contam Toxicol*. 2014; 227:55-77. PMID: 24158579. https://doi.org/10.1007/978-3-319-01327-5_2.

6) Soto E, Bahado-Singh R. Fetal abnormal growth associated with substance abuse. *Clin Obstet Gynecol*. 2013 Mar; 56(1):142-53. PMID: 23314718. https://doi.org/10.1097/GRF.0b013e31827e6b60.

7) Kennare R, Heard A, Chan A. Substance use during pregnancy: risk factors and obstetric and perinatal outcomes in South Australia. *Aust N Z J Obstet Gynaecol*. 2005 Jun; 45(3):220-5. PMID: 15904448. https://doi.org/10.1111/j.1479-828X.2005.00379.x.

8) Tsakiridis I, Mamopoulos A, Papazisis G, et al. Prevalence of smoking during pregnancy and associated risk factors: a cross-sectional study in Northern Greece. *Eur J Public Health*. 2018 Apr 1; 28(2): 321-25. PMID: 29342261. https://doi.org/10.1093/eurpub/cky004.

9) Wright TE. Screening, brief intervention, and referral to treatment for opioid and other substance use during infertility treatment. *Fertil Steril*. 2017 Aug; 108(2):214-221. PMID: 28697912. https://doi.org/10.1016/j.fertnstert.2017.06.012.

10) O'Leary C, Jacoby P, D'Antoine H, et al. Heavy prenatal alcohol exposure and increased risk of stillbirth. *BJOG*. 2012 Jul; 119(8): 945-52. PMID: 22568788. https://doi.org/10.1111/j.1471-0528.2012.03333.x.

11) Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet*. 2011 Apr 16; 377(9774):1331-40. PMID: 21496916. https://doi.org/10.1016/S0140-6736(10)62233-7.

12) Maeda A1, Bateman BT, Clancy CR, et al. Opioid abuse and dependence during pregnancy: temporal trends and obstetrical outcomes. *Anesthesiology*. 2014 Dec; 121(6):1158-65. PMID: 25405293. https://doi.org/10.1097/ALN.0000000000000472.

13) Gorman MC, Orme KS, Nguyen NT, et al. Outcomes in pregnancies complicated by methamphetamine use. *Am J Obstet Gynecol*. 2014 Oct; 211(4):429.e1-7. PMID: 24905417. https://doi.org/10.1016/j.ajog.2014.06.005.

14) Stillbirth Collaborative Research Network Writing Group. Association between stillbirth and risk factors known at pregnancy confirmation. *JAMA*. 2011 Dec 14; 306(22):2469-79. PMID: 22166606. PMCID: PMC3807602. https://doi.org/10.1001/jama.2011.1798.

15) Patel EM, Goodnight WH, James AH, Grotegut CA. Temporal trends in maternal medical conditions and stillbirth. *Am J Obstet Gynecol*. 2015 May; 212(5):673.e1-11. PMID: 25530599. https://doi.org/10.1016/j.ajog.2014.12.021.

16) Page JM, Thorsten V, Reddy UM, et al. Potentially preventable stillbirth in a diverse U.S. cohort. *Obstet Gynecol*. 2018 Feb; 131(2):336-43. PMID: 29324601. PMCID: 5785410. https://doi.org/10.1097/AOG.0000000000002421.

17) Viteri OA, Mendez-Figueroa H, Pedroza C, et al. Relationship between self-reported maternal substance abuse and adverse outcomes in the premature newborn. *Am J Perinatol*. 2016 Jan; 33(2):165-71. PMID: 26344011. https://doi.org/10.1055/s-0035-1563549.

18) Bailey BA, Sokol RJ. Prenatal alcohol exposure and miscarriage, stillbirth, preterm delivery, and sudden infant death syndrome. *Alcohol Res Health*. 2011; 34(1):86-91. PMID: 23580045. PMCID: PMC3860553.

19) Aliyu MH, Wilson RE, Zoorob R, et al. Alcohol consumption during pregnancy and the risk of early stillbirth among singletons. *Alcohol*. 2008 Aug; 42(5):369-74. PMID: 18562153. https://doi.org/10.1016/j.alcohol.2008.04.003.

20) Bada HS, Das A, Bauer CR, et al. Gestational cocaine exposure and intrauterine growth: maternal lifestyle study. *Obstet Gynecol*. 2002 Nov; 100(5 Pt 1):916-24. PMID: 12423853. https://doi.org/10.1016/s0029-7844(02)02199-3.

21) Odendaal HJ, Steyn DW, Elliott A, Burd L. Combined effects of cigarette smoking and alcohol consumption on perinatal outcome. *Gynecol Obstet Invest*. 2009; 67(1):1-8. PMID: 18685256. https://doi.org/10.1159/000150597.

22) Zhao L, McCauley K, Sheeran L. The interaction of pregnancy, substance use and mental illness on birthing outcomes in Australia. *Midwifery*. 2017 Nov; 54:81-88. PMID: 28886465. https://doi.org/10.1016/j.midw.2017.08.007.

23) Izquierdo LA, Yonke N. Fetal surveillance in late pregnancy and during labor. *Obstet Gynecol Clin North Am*. 2014 Jun; 41(2):307-15. PMID: 24845492. https://doi.org/10.1016/j.ogc.2014.02.009.

24) Stek AM Baker RS, Fisher BK, et al. Fetal responses to maternal and fetal methamphetamine administration in sheep. *Am J Obstet Gynecol*. 1995 Nov; 173(5):1592-8. PMID: 7503206. https://doi.org/10.1016/0002-9378(95)90654-1.

25) Chang L, Oishi K, Skranes J, et al. Sex-specific alterations of white matter developmental trajectories in infants with prenatal exposure to methamphetamine and tobacco. *JAMA Psychiatry*. 2016 Dec 1; 73(12):1217-27. PMID: 27829078. https://doi.org/10.1001/jamapsychiatry.2016.2794.

26) McDonald SD, Vermeulen MJ, Ray JG. Risk of fetal death associated with maternal drug dependence and placental abruption: a population-based study. *J Obstet Gynaecol Can*. 2007 Jul; 29(7):556-9. PMID: 17623568. https://doi.org/10.1016/S1701-2163(16)32511-7.

27) Zhang J, Ratcliffe JM. Paternal smoking and birthweight in Shanghai. *Am J Public Health*. 1993 Feb; 83(2):207-10. PMID: 8427324. PMCID: 1694594. https://doi.org/10.2105/ajph.83.2.207.

28) Asmussen I. Ultrastructure of the human placenta at term. Observations on placentas from newborn children of smoking and non-smoking mothers. *Acta Obstet Gynecol Scand*. 1977; 56(2):119-26. PMID: 857592. https://doi.org/10.3109/00016347709158353.

29) Jauniaux E, Burton GJ. The effect of smoking in pregnancy on early placental morphology. *Obstet Gynecol*. 1992 May; 79(5 (Pt 1)):645-8. PMID: 1565343.

30) Bouhours-Nouet N, May-Panloup P, Coutant R, et al. Maternal smoking is associated with mitochondrial DNA depletion and respiratory chain complex III deficiency in placenta. *Am J Physiol Endocrinol Metab*. 2005 Jan; 288(1):E171-7. PMID: 15585597. https://doi.org/10.1152/ajpendo.00260.2003.

31) Jauniaux E, Burton GJ. Morphological and biological effects of maternal exposure to tobacco smoke on the feto-placental unit. *Early Hum Dev*. 2007 Nov; 83(11):699-706. PMID: 17900829. https://doi.org/10.1016/j.earlhumdev.2007.07.016.

32) Gardosi J, Madurasinghe V, Williams M, et al. Maternal and fetal risk factors for stillbirth: population based study. *BMJ*. 2013 Jan 24; 346: f108. PMID: 23349424. PMCID: PMC3554866. https://doi.org/10.1136/bmj.f108.

33) Morild I, Stajic M. Cocaine and fetal death. *Forensic Sci Int*. 1990 Sep; 47(2):181-9. PMID: 2227733. https://doi.org/10.1016/0379-0738(90)90212-h.

34) Wu L, Yan J, Qu SC, et al. Abnormal regulation for progesterone production in placenta with prenatal cocaine exposure in rats. *Placenta*. 2012 Dec; 33(12):977-81. PMID: 23103204. https://doi.org/10.1016/j.placenta.2012.10.001.

35) Sims MA, Collins KA. Fetal death. A 10-year retrospective study. *Am J Forensic Med Pathol*. 2001 Sep; 22(3):261-5. PMID: 11563736. https://doi.org/10.1097/00000433-200109000-00012.

36) Campillo F, Remezal M, Vez MD, et al. Symmetrical fetal growth retardation after gestational cocaine exposure in the rat. *Eur J Obstet Gynecol Reprod Biol*. 2004 Dec 1; 117(2):148-53. PMID: 15541849. https://doi.org/10.1016/j.ejogrb.2004.03.004.

37) Narkowicz S, Płotka J, Polkowska Ż, et al. Prenatal exposure to substance of abuse: a worldwide problem. *Environ Int*. 2013 Apr; 54: 141-63. PMID: 23454110. https://doi.org/10.1016/j.envint.2013.01.011.

38) Arria AM, Derauf C, Lagasse LL, et al. . Methamphetamine and other substance use during pregnancy: preliminary estimates from the Infant Development, Environment, and Lifestyle (IDEAL) study. *Matern Child Health J*. 2006 May; 10(3):293-302. PMID: 16395620. https://doi.org/10.1007/s10995-005-0052-0.

39) Ladhani NN, Shah PS, Murphy KE, Knowledge Synthesis Group on Determinants of Preterm/LBW Births. Prenatal amphetamine exposure and birth outcomes: a systematic review and metaanalysis. *Am J Obstet Gynecol*. 2011 Sep; 205(3):219.e1-7. PMID: 21658669. https://doi.org/10.1016/j.ajog.2011.04.016.

40) Otero C, Boles S, Young NK, Dennis K. Methamphetamine: addiction, treatment, outcomes and implications. Rockville (MD): U.S. Department of Health and Human Services, SAMHSA; 2004. 29 p.

41) Burchfield DJ, Lucas VW, Abrams RM, et al. Disposition and pharmacodynamics of methamphetamine in pregnant sheep. *JAMA*. 1991 Apr 17; 265(15):1968-73. PMID: 2008026. https://doi.org/10.1001/jama.1991.03460150072026.

42) Collier AC, Sato BL, Milam KA, Wright TE. Methamphetamine, smoking, and gestational hypertension affect norepinephrine levels in umbilical cord tissues. *Clin Exp Obstet Gynecol*. 2015; 42(5):580-5. PMID: 26524802.

43) Oncken CA, Henry KM, Campbell WA, et al. Effect of maternal smoking on fetal catecholamine concentrations at birth. *Pediatr Res*. 2003 Jan; 53(1):119-24. PMID: 12508090. https://doi.org/10.1203/00006450-200301000-00020.

44) Kalaitzopoulos DR, Chatzistergiou K, Amylidi AL, et al. Effect of methamphetamine hydrochloride on pregnancy outcome: a systematic review and meta-analysis. *J Addict Med*. 2018 May/Jun; 12(3): 220-226. PMID: 29509557. https://doi.org/10.1097/ADM.0000000000000391.

45) Centers for Disease Control and Prevention [Internet]. Atlanta: US Department of Health and Human Services; c2018. Fetal alcohol spectrum disorders (FASDs); [updated 2018 Jun 4; cited 2018 Sep 2]. Available from: https://www.cdc.gov/ncbddd/fasd/data.html#ref.

46) Centers for Disease Control and Prevention (CDC). Fetal alcohol syndrome--Alaska, Arizona, Colorado, and New York, 1995-1997. *MMWR Morb Mortal Wkly Rep*. 2002 May 24; 51(20):433-5. PMID: 12056499.

47) May PA, Baete A, Russo J, et al. Prevalence and characteristics of fetal alcohol spectrum disorders. *Pediatrics*. 2014 Nov; 134(5):855-66. PMID: 25349310. PMCID: PMC4210790. https://doi.org/10.1542/peds.2013-3319.

48) Burd L, Blair J, Dropps K. Prenatal alcohol exposure, blood alcohol concentrations and alcohol elimination rates for the mother, fetus and newborn. *J Perinatol*. 2012 Sep; 32(9):652-9. PMID: 22595965. https://doi.org/10.1038/jp.2012.57.

49) Jones PJ, Leichter J, Lee M. Placental blood flow in rats fed alcohol before and during gestation. *Life Sci*. 1981 Sep 14; 29(11):1153-9. PMID: 7289779. https://doi.org/10.1016/0024-3205(81)90204-6.

50) Kesmodel U, Wisborg K, Olsen SF, et al. Moderate alcohol intake during pregnancy and the risk of stillbirth and death in the first year of life. *Am J Epidemiol*. 2002 Feb 15; 155(4):305-12. PMID: 11836194. https://doi.org/10.1093/aje/155.4.305.

51) Conner CS. Marijuana and alcohol use in pregnancy. *Drug Intell Clin Pharm*. 1984 Mar; 18(3):233-4. PMID: 6365495. https://doi.org/10.1177/106002808401800308.

52) Anton RF, Becker HC, Randall CL. Ethanol increases PGE and thromboxane production in mouse pregnant uterine tissue. *Life Sci*. 1990; 46(16):1145-53. PMID: 2342401. https://doi.org/10.1016/0024-3205(90)90451-v.

53) Serra AE, Lemon LS, Mokhtari NB, et al. Delayed villous maturation in term placentas exposed to opioid maintenance therapy: a retrospective cohort study. *Am J Obstet Gynecol*. 2017 Apr; 216(4):418.e1-418.e5. PMID: 28024988. https://doi.org/10.1016/j.ajog.2016.12.016.

54) Ananthan A, Nanavati R, Sathe P, Balasubramanian H. Placental findings in singleton stillbirths: A Case-control Study. *J Trop Pediatr*. 2018 Feb 6. PMID: 29420825. https://doi.org/10.1093/tropej/fmy006.

55) Zuspan FP, Gumpel JA, Mejia-Zelaya A, et al. Fetal stress from methadone withdrawal. *Am J Obstet Gynecol*. 1975 May 1; 122(1):43-6. PMID: 1130446. https://doi.org/10.1016/0002-9378(75)90613-4.

56) Jones HE, Martin PR, Heil SH, et al. Treatment of opioid-dependent pregnant women: clinical and research issues. *J Subst Abuse Treat*. 2008 Oct; 35(3):245-59. PMID: 18248941. PMCID: PMC2633026. https://doi.org/10.1016/j.jsat.2007.10.007.

57) Terplan M, Laird HJ, Hand DJ, et al. Opioid detoxification during pregnancy: a systematic review. *Obstet Gynecol*. 2018 May; 131(5): 803-14. PMID: 29630016. PMCID: PMC6034119. https://doi.org/10.1097/AOG.0000000000002562.

58) Varner MW, Silver RM, Rowland Hogue CJ, et al. Association between stillbirth and illicit drug use and smoking during pregnancy. *Obstet Gynecol*. 2014 Jan; 123(1):113-25. PMID: 24463671. PMCID: PMC3931517. https://doi.org/10.1097/AOG.0000000000000052.

59) Khare M, Taylor AH, Konje JC, Bell SC. Delta9-tetrahydrocannabinol inhibits cytotrophoblast cell proliferation and modulates gene transcription. *Mol Hum Reprod*. 2006 May; 12(5):321-33. PMID: 16597638. https://doi.org/10.1093/molehr/gal036.

60) Elk R, Mangus L, Rhoades H, et al. Cessation of cocaine use during pregnancy: effects of contingency management interventions on maintaining abstinence and complying with prenatal care. *Addict Behav*. 1998 Jan-Feb; 23(1):57-64. PMID: 9468743. https://doi.org/10.1016/s0306-4603(97)00020-8.

61) Carroll KM Chang G, Behr H, et al. Improving treatment outcome in pregnant, methadone-maintained women: results from a randomized clinical trial. *Am J Addict*. 1994; 4(1):56-9. https://doi.org/10.1111/j.1521-0391.1995.tb00259.x.

62) El-Mohandes A, Herman AA, Nabil El-Khorazaty M, et al. Prenatal care reduces the impact of illicit drug use on perinatal outcomes. *J Perinatol*. 2003 Jul-Aug; 23(5):354-60. PMID: 12847528. https://doi.org/10.1038/sj.jp.7210933.