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Review

Xylazine Use in Pregnancy: The Effects of the Fentanyl Adulterant Xylazine on Pregnant Patients and the Developing Fetus

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ABSTRACT

Objective. A literature review was completed to outline the effects of xylazine on the pregnant patient while raising awareness of the increasing prevalence of opioid use disorder in pregnancy and the increase in adulterants in non-prescribed controlled substances.

Data Sources. PubMed and Google Scholar were searched using the key words "xylazine, adulterant," "xylazine, humans," "xylazine, pregnancy," and "xylazine, placenta" to identify the studies evaluating xylazine's effects on humans and the pregnant patient.

Study Selection. Studies were included if they provided information on symptoms of xylazine exposure, the prevalence of xylazine in pregnant humans and the hemodynamic effects of xylazine on both human and animal pregnant populations. Animal studies were included given the limited data on xylazine in pregnant humans. Four studies were utilized for background data and five studies were included in the final review of the effects of xylazine on pregnancy.

Results. Studies involving humans show that xylazine toxicity can cause respiratory depression, bradycardia, and central nervous system depression. There is evidence of xylazine in human umbilical cord tissue, showing that the fetus is exposed to xylazine. Animal studies show decreased uterine blood flow, increased uterine vascular resistance, and decreased fetal growth in response to xylazine.

Conclusions. Due to the limited studies on the effects of xylazine on pregnant populations, providers rely on animal studies for knowledge on xylazine's effects throughout pregnancy. Animal studies suggest an increased risk of adverse effects during pregnancy in response to xylazine. Future studies should focus on the pregnancy outcomes in patients exposed to xylazine to create more robust recommendations for treatment and pregnancy surveillance.

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INTRODUCTION

Opioid use disorder is one of the leading causes of pregnancy-associated morbidity and mortality in the Unites States.[1] Since 2010, opioid-related maternal deaths increased by 220%, with fentanyl being the most prevalent agent in related deaths.[1] While the treatment of opioid use disorder in pregnancy has been well described, there is little data regarding how adulterants within drugs impact the pregnant patient and the fetus. Adulterants are substances added to drugs that are intended to increase the value, increase the content, and modulate the activity of the drug while also increasing its desirability.[2] For non-prescription opioids, there is increased use of fentanyl and high potency synthetic opioids (HPSO).[3] Xylazine hydrochloride is an increasingly prevalent adulterant of fentanyl (Figure 1).[4] It is a potent alpha2-agonist that is used as a sedative and muscle relaxant in veterinary medicine and not approved for use in humans.[5]

Xylazine is not commonly included in routine immunoassay toxicology screenings. Therefore, identification of xylazine exposure in post-mortem patients is completed by medical examiners who utilize a gas chromatography–mass spectrometry exam on bodily fluids.[6] A recent development of a liquid chromatography-mass spectrometry in 2021 has been shown to accurately identify xylazine in fentanyl-screen positive urine samples.[7] This test found that 78% of fentanyl-screen positive urine samples were positive for xylazine.[7] This test could be utilized by hospital systems in the future to confirm and treat xylazine exposure. The cost-effectiveness of confirmatory testing must also be considered, especially if the prevalence of adulterants continues to increase and xylazine becomes ubiquitous in non-prescription medication.

The CDC analyzed unintentional and undetermined intent of overdose data from the State Unintentional Drug Overdose Reporting System (SUDORS) in 38 states and the District of Columbia (DC) in 2019.[6] They identified cases in which xylazine was listed as a contributing cause of death by the medical examiner or if xylazine was listed in the post-mortem toxicology report. In 45,676 overdose deaths in SUDORS in 2019, 1,357 were positive for xylazine. In those in which xylazine was detected, xylazine was listed as the cause of death in 64.3% of cases.[8] Additionally, a study across 10 states in the United States representing all four US Census Regions found that the presence of xylazine is increasingly prevalent in overdose deaths, increasing from 0.36% to 6.7% of deaths from 2015 to 2020, respectively.[6] This holds great importance, especially in evaluation of acute overdoses in both pregnant and nonpregnant populations. If standardized overdose or withdrawal protocols fail to stabilize patients, providers should consider the possibility that adulterants like xylazine are contributing to the clinical picture. While there are no standardized treatment algorithms for xylazine exposure, understanding how it impacts patients can assist providers when counseling about the risks of substance use disorder. Despite the increase in prevalence of both opioid use disorder in pregnancy and xylazine as an adulterant, there is limited data considering the in-utero effects of xylazine in humans. Hence, this paper aims to review the existing literature concerning the potential negative effects of xylazine on pregnancy. The objective is to review the pharmacological aspects of xylazine and how this impacts pregnancy while also increasing awareness regarding adulterant exposure.

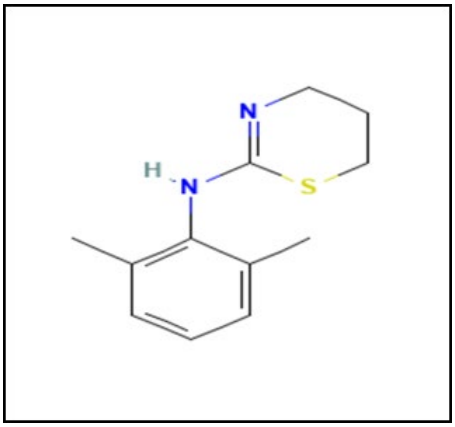

Figure 1. Molecular formula of xylazine.[9]

METHODS

A literature search was performed with PubMed and Google Scholar using the key words "xylazine, adulterant," "xylazine, humans," "xylazine, pregnancy," and "xylazine, placenta" to identify the studies considering xylazine's effects on humans and the pregnant patient. Only studies published in English and published between 2000 and 2023 were included. Studies were included if they provided novel information on hallmark symptoms of xylazine in humans, the prevalence of xylazine in pregnant humans, and the hemodynamic effects of xylazine on both human and animal pregnant populations. Animal studies were included given the limited data on xylazine in pregnant humans. Four studies were utilized for background data and five studies were included in the final review of the effects of xylazine on pregnancy, three being animal studies and two being human studies.

RESULTS

Xylazine use has been shown to cause a variety of symptoms. Xylazine is a potent central nervous system alpha-2 adrenergic agonist. It exerts autonomic effects by inhibiting the release of norepinephrine.[6] This then leads to bradycardia, decreased cardiac output, central nervous system depression, and hypotension.[6] Xylazine use is important to consider in patients with substance use disorder or in management of acute overdoses because it does not have a reversible antidote approved in humans and treatment often requires additional supportive care.[10]

The effects of xylazine on humans have been described, but there are few studies regarding its effects on pregnant people. Animal studies provide some insight into the potential consequences of xylazine during pregnancy. One of the first studies to identify uterine and placental effects of xylazine took place in 2002, where uterine blood flow measurements were assessed after the administration of xylazine in cows.[11] At 5 minutes and 45 minutes after the administration of 0.04 mg/kg of xylazine, the rate of uterine blood flow was measured. The study concluded that xylazine significantly reduces uterine blood flow and accessibility of oxygenated blood to the uterus compared to controls.[11] Specifically, xylazine reduced oxygen delivery to the uterus by 59% at 5 minutes and 32% at 45 minutes.[11] This may increase consequences of fetal hypoxemia, including fetal growth restriction, especially in the setting of chronic xylazine exposure.

Another study in 2014 identified changes in Doppler sonographic measures of uterine and placental blood vessels in cows during the last four weeks of pregnancy after receiving weekly injections of 2 mg/100 kg of Xylazine.[12] Doppler sonogram was used to measure the flow rates, pulse rates, and resistance indices of the uterine artery and umbilical artery throughout the study. Final measurements were compared to initial measurements for analysis. Xylazine exposure significantly increased the resistance index of the uterine arteries, but not the umbilical arteries.[12] Xylazine exposure also decreased the maternal pulse rate by 17% and the fetal pulse rate by 6%, and significantly decreased blood flow velocity in the uterine arteries.[12] Overall, the study found that xylazine decreased uterine blood flow by 10%.[12] This decreased blood flow in combination with increased vascular resistance and decreased maternal pulse rate can potentially lead to significant fetal hypoperfusion. While pulse rate was the only significant change in the umbilical artery in response to xylazine, the authors of the study conclude that xylazine has the potential to exacerbate hypoxia in a fetus.[12]

A study in 2013 analyzed the effects of a ketamine/xylazine combination, a common veterinary analgesic regimen, on fetal growth rate at different points in gestation in mice.[13] Pregnant mice were administered 100 mg/kg of ketamine and 10 mg/kg of xylazine at five different points in gestation. The ketamine/xylazine cohort showed significantly decreased fetal growth at various times throughout gestation including at the end of organogenesis and during the logarithmic growth phase.[13] The effects of xylazine and ketamine could not be separated in this study. However, in preliminary trials in this study, ketamine and xylazine were administered individually to pregnant mice during the logarithmic growth phase of gestation, and it was determined that xylazine was the cause of decreased fetal growth.[13] Notably, ketamine had no impact on fetal growth in these preliminary studies.[13]

Testing of human umbilical cord tissue as a mechanism to identify in utero exposure to a variety of adulterants was initially studied in 2023. This study collected umbilical cord tissue following delivery from drug-exposed mothers with the goal of better identifying the scope of in utero drug and adulterant exposure.[14] Findings from this study include the presence of xylazine in 3% of the study participants' umbilical cord tissue of all who were positive for opioid use.[14] While not a direct measure of in utero effects of xylazine, the presence of xylazine in umbilical cord tissue serves a marker for direct xylazine exposure to the human fetus.

Tables 1 and 2 provide an overview of both the animal and human studies that identified the potential impact of xylazine on pregnant patients, respectively.

Table 1. Animal studies included in final analysis.

Study	Objective	N	Results
Hodgson DS, et. al[11]	To determine effects of sedation achieved by xylazine on cardiopulmonary function and uterine blood flow in cows in late gestation	8	Xylazine reduces uterine blood flow and accessibility of oxygenated blood to the uterus.
Waldvogel D, et. al[12]	To determine changes in Doppler sonographic measures of uterine and placental blood vessels in cows during the last four weeks of pregnancy after receiving Xylazine	9	Xylazine decreased maternal and fetal pulse rate and decreased uterine blood flow while increasing the uterine artery resistance index.
Thaete LG, et. al[13]	To identify effects of a Ketamine/Xylazine combination on fetal growth rate at different points in gestation in mice	203	Ketamine/Xylazine cohort showed significantly decreased fetal growth at various times throughout gestation

Table 2. Human studies included in final analysis.

Study	Objective	N	Results
Spoerke DG, et. al[10]	Case series of Xylazine overdose	3	All patients developed bradycardia and respiratory depression in response to Xylazine
Midthun KM, et. al[14]	To use umbilical cord tissue from drug-exposed mothers to identify common drugs of abuse and adulterants as a marker of in utero exposure	300	Xylazine in 3% of the study participants' umbilical cord tissue of all who were positive for opioid use.

CONCLUSIONS

Healthcare providers need to be informed about the potential negative consequences of xylazine on both pregnant patients and the fetus, as data indicates a rise in maternal mortality resulting from opioid-related deaths and an accompanying rise in xylazine as an adulterant. Data suggest that other alpha-1-agonists like clonidine can increase risk for fetal growth restriction.[15] There are no specific guidelines for antenatal surveillance due to clonidine or other alpha-2-agonist exposure. However, we hypothesize that there may be benefit for additional screening growth ultrasounds or biophysical profile monitoring in this population that are normally utilized for those patients with increased risk of fetal growth restriction.[16] There is limited data on the effects of xylazine on the health of the human fetus during gestation due to the relatively new rise of xylazine and the ethical restraints of including pregnant patients in randomized control trials. Therefore, providers must turn to animal studies for knowledge on xylazine's effects throughout pregnancy. Additionally, the limited knowledge on how xylazine can impact pregnancy poses a challenge of building evidence-based guidelines for pregnant patients with xylazine exposure. The available evidence provides a basis for increased fetal surveillance in pregnancies complicated by opioid abuse disorders.

When assessing the consistency of evidence across the studies presented, most found similar results of xylazine having a negative impact on pregnancy, whether that be from decreased uterine perfusion or increased risk of fetal growth restriction. These consistent results should be utilized to build future guidelines regarding antenatal monitoring for pregnant patients exposed to xylazine. Future retrospective studies should focus on the exposure of xylazine in pregnant patients with substance use disorder and their pregnancy outcomes to create better recommendations for treatment.

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