Anencephaly and other multiple fetal anomalies in multi-addictive drug pregnant woman (A case report)

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Anencephaly and other multiple fetal anomalies in multi-drug addictive pregnant woman (A case report).

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Abstract

A 17-year-old pregnant woman, with a history of Tramadol, Methamphetamine, Pregabalin and Chloral hydrate use before and during pregnancy, admitted with severe vaginal bleeding and uterine contraction. An emergent cesarean delivery was performed. Multiple fetal anomalies involving all the body systems were observed, and the fetus passed away seven minutes later. The woman was addicted to four psychological drugs which were Pregabalin, Chloral hydrate, Methamphetamine, and Tramadol before and during pregnancy. Pregabalin is considered the last treatment option for various neurological diseases in pregnant women and more research is required to assess its safety for pregnant women. For Chloral hydrate (CH) the literature
hasn’t mentioned any previous study about the teratogenic effect of CH on fetus due to mother intake. With addiction to Methamphetamine, cleft palate and other cognitive, neurological, and behavioral outcomes were observed in many studies. Cardiovascular, gastrointestinal, musculoskeletal and many congenital deformities have been detected among women with tramadol use. To our knowledge, this is the first case that deals with multi-drug use during pregnancy since previous cases were only about one drug.

More research on addiction to more than one of these drugs is desirable to extend our knowledge about their common impact on both the pregnant woman and her fetus.

**Keywords:**
Pregnant, addiction, methamphetamine, tramadol, opioid, chloral hydrate, pregabalin, fetal anomalies, anencephaly, ectopia cordis.

**Introduction:**
Since the beginning of recorded human history, addiction to addictive substances has been a medical and social issue. [1]

Nucleus accumbens dopamine levels control drug self-administration, which is carried out in order to sustain a desirable hedonistic level by keeping nucleus accumbens dopamine within a particular raised range. Chronic use of some classes of addictive medicines leads to the development of tolerance to the sensation of euphoria. [1]

Drug consumption during pregnancy carries a number of possible risks for the developing fetus, and in order to improve the health of both mother and fetus, it is essential to recognize and address the issue by understanding the effects of substance misuse during pregnancy on both parties. [2]

The effects of drug usage during pregnancy differ according to the drug, the dosage, and the duration of exposure period. Using illegal drugs increases the risk of low birthweight, premature delivery, abruption of the placenta, and cognitive decline. [3]

The unique case that we discuss in this study involves a young pregnant lady who used drugs both before and during her pregnancy, including (Tramadol, Methamphetamine, Pregabalin and Chloral hydrate) which resulted many complications that led to fetal malformations and fetal death after delivery.

**Case presentation:**
A 17-year-old G6P0A5 woman, with a history of Tramadol, Methamphetamine, Pregabalin and Chloral hydrate use before and during pregnancy, admitted to the emergency department at 36 weeks and 5 days of gestation with severe vaginal bleeding and uterine contraction. The woman was suffering from poor living conditions. She was transferred by police to reform institute on charges of drugs and abnormal behavior several times, the last of which was during her late pregnancy. Therefore, she did not receive any health care, and the health status of the fetus was not determined, whether through an ultrasound or other tests.

**Methods:** The woman’s psychological condition was not determined because she was not presented to a psychiatrist. Upon clinical examination, heart rate was 84, and blood pressure was 110/70. Laboratory tests were unremarkable except for decreased hemoglobin due to blood loss. An ultrasound was performed, which revealed an anencephalic single fetus with gastroschisis, ectopia cordis, femur length (FL) was estimated with 28 gestational weeks). The results of the ultrasound and the physical examination indicated the presence of placental abruption. The fetal heart rate tracing demonstrated a deceleration down to a nadir of 50 beats per minute.

An emergent cesarean delivery was performed.

**Conclusion and Results:** A male neonate was born in a severely poor general condition, weighing 600 grams, and passed away seven minutes later. Multiple fetal anomalies involving all body systems were observed including anencephaly, exophthalmos of both eyes, cleft palate, absence of the nose (Fig.1). Gastroschisis (Fig.2), Ectopia cordis (Fig.3). Absence of the testes and a small penis, absence of the spinal
cord, imperforate anus, and clubfoot (Fig.4). These anomalies were detected upon further examination of the newborn’s body systems,

There exists no familial history indicative of embryos displaying congenital deformities.

**Discussion:**

Substance abuse during pregnancy is still an important health concern and has several harmful impacts on both the mother and the fetus. Pregnant women are frequently abusing polysubstance, which may aggravate harmful effects on both the mother and the fetus.[3] Pregnancy is a state where there are pharmacokinetic alterations affecting absorption, distribution, metabolism and elimination. The type of the substance, its dosage, period of pregnancy, and most importantly, the individual in consideration all influence these effects.[4] This woman was addicted to four psychological drugs which were Pregabalin, Chloral hydrate, Methamphetamine, and Tramadol before pregnancy and continued taking them during pregnancy. Psychological drugs have the potential to be teratogenic, meaning they raise the possibility of birth defects and poor cognitive outcomes.[4] Pregabalin is an alkylated derivative of gamma aminobutyric acid (GABA) that is legally permitted by many countries for the treatment of neuropathic syndromes, fibromyalgia, partial onset seizures, and generalized anxiety disorder.

It works by binding to calcium channels, regulating calcium influx, and affecting GABAergic neurotransmission; therefore, its analgesic, anxiolytic, and antiepileptic properties are conferred by this method of action.[5] Furthermore, Pregabalin has also been shown to cross the placenta in mice, rats, and monkeys.[6] Its exposure was associated with a higher incidence of significant abnormalities when compared to nonexposed pregnancies with a rate of 5.9 per 100 live births, compared to 3.3 per 100 for unexposed pregnancies.[7] Moreover, some animal studies with antiepileptic drugs like pregabalin have reported skeletal malformations, orofacial clefts, neural tube defects such as spina bifida, increased rates of spontaneous abortions, growth retardation, and behavioral anomalies.[8, 9]

Due to a lack of safety studies in pregnancy, pregabalin is considered the last treatment option for various neurological diseases for pregnant women and more research is required to assess its safety for pregnant women as well as its potential effects on the health of the fetus.[6]

On the other hand, Chloral hydrate (CH) was one of the most commonly used sedatives for non-invasive diagnostic procedures in clinics, like performing transthoracic echocardiography (TTE) and objective hearing tests for children. However, it’s no longer in use except in China.[10] It works by ameliorating GABAa receptor function; thus, decelerating central nervous system performance.[11] Because it is no longer used, the literature hasn’t mentioned any previous study about the teratogenic effect of CH on fetus due to mother intake. The third drug, which is Methamphetamine (MA), is a central nervous system stimulant that causes high dopamine, serotonin, and norepinephrine presynaptic concentrations. The use of this substance is linked with high levels of energy and exhilaration. It is the only illegal drug that can be made from everyday products like decongestants and cough syrups sold over-the-counter. With a high bioavailability, it may be smoked, snorted, injected, and used rectally. MA raises the risk of myocardial infarction, hypertension, cardiomyopathy, and stroke due to its alpha and beta adrenergic effects.[12] It’s one of the most widely utilized illicit substances during pregnancy is MA.[13] In addition, a study published in 2019 showed that the studies that have been released before couldn’t prove that there is relevance between Mmethamphetamine and the congenital malformations except cleft palate.[12] Nevertheless, an environmental scan was published in 2021 to show the impact of MA use during pregnancy on the pregnant women and on their fetuses, the study extracted data from 80 articles and identified 463 results related to 210 outcomes and seven interventions. The outcomes were distributed in 6 categories: 41% for general neonatal/infant outcomes,16% for cognitive outcomes, 15% for neurological outcomes, 14% for behavioral outcomes, 11% for maternal outcomes, and 3% for interventions (maternal/neonatal).[14] In this case, multiple outcomes from previous categories were found in the same fetus, compared to other cases where the fetus suffered from few manifestations, except the behavioral outcomes which we couldn’t indicate because of the fetus’s death.

Ultimately, tramadol is a common centrally acting atypical opioid analgesic prescription. Even though this
medication is used extensively, not much is known about its potential teratogenicity.[15] Prescribed opioid painkiller usage during pregnancy is a public health issue, since it affects 2%–4% of pregnancies. Opioid analgesics have the potential to damage fetuses since they can cross the placenta. There is conflicting and incomplete data about the safety of opioid analgesics for pain management during pregnancy.[16] A cohort study in Ontario published in 2022 included a 599,579 pregnancies to study the relationship between prescribed opioid analgesics in early pregnancy and the risk of congenital anomalies, 11,903 were exposed to opioid analgesics, 781 pregnant women were in contact with tramadol, 38 was the number of fetuses with a congenital anomalies classified by organ system: 11 for cardiovascular, 10 for gastrointestinal, 16 for musculoskeletal. Urinary, neoplasms, and oral clefts share the same number of anomalies from 5 to 6. The previous study indicates that although the absolute incidence of anomalies is minimal, there may be a little increased risk of congenital abnormalities with exposure to opioid analgesics.[16] Another cohort study documented all pregnancies in Denmark between 1997 and 2016 and was also published in 2022 to study the risk of spontaneous abortion or major congenital malformations due to tramadol exposure during early pregnancy, the result of this study presents that 4% of pregnancies with maternal exposure to the drug experienced a significant congenital deformity compared to pregnancies without maternal exposure at a rate of 3.8%, according to this result the study suggested that taking tramadol does not seem to be linked to severe congenital abnormalities.[17]

The fetus in our study presented with multiple anomalies including anencephaly, exophthalmos of both eyes, cleft palate, absence of the nose, gastroschisis, ectopia cordis, absence of the testes, a small penis, absence of the spinal cord, imperforate anus, and clubfoot. We attribute these multi-system anomalies to the multiple illicit drugs use of the mother during pregnancy. To our knowledge, this is the first case that deals with multi-drug use during pregnancy since previous cases were only about one drug.

**Conclusion:**

There are only a few studies in the medical literature about the teratogenic effects of the addiction to each previously mentioned drug individually; however, there isn’t any study about the combined effect of two or more of them. Furthermore, the anomalies in the previous studies weren’t similar to the anomalies in our case, which involved many fetal body systems, so we attribute these multi-system developmental abnormalities in the fetus to multiple drug use by the mother. Therefore, further research on addiction to more than one of these drugs is desirable to extend our knowledge about their common impact on both the pregnant woman and her fetus including its growth and possible anomalies.

**Author contribution**

MD contributed to drafting, reviewing, editing and approved the final manuscript.

KK contributed to drafting, reviewing, editing and approved the final manuscript.

MZ contributed to drafting, reviewing, editing and approved the final manuscript. NF contributed to drafting, editing and approved the final manuscript.

SH contributed to drafting, reviewing, editing, corresponding, and approved the final manuscript. RO contributed to reviewing, supervising and approved the final manuscript.

HK contributed to drafting, editing and approved the final manuscript.

**Ethics approval:**

Our institution does not require ethical approval for reporting individual cases or case series.

**Informed consent**

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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**Figure legends:**

Fig. 1: Anencephaly, exophthalmos of both eyes, cleft palate, absence of the nose.

Fig. 2: Gastroschisis

Fig. 3: Ectopia cordis

Fig. 4: Absence of the testes and a small penis, absence of the spinal cord, imperforate anus, and clubfoot

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