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CASE REPORT

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Unraveling the Effects – Mifepristone and Misoprostol Linked Congenital Anomalies

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ABSTRACT

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Introduction: Mifepristone and misoprostol are commonly used in medical abortion, known for their high efficacy. However, their potential association with congenital anomalies, particularly VACTERL anomaly, remains underexplored. This report presents a case of suspected adverse drug reaction leading to VACTERL anomaly.

Case Presentation: A 19-year-old primigravida at 36 weeks gestation presented with lower back and abdominal pain. She had a history of consuming abortion pills after confirming her pregnancy. She delivered a female infant with respiratory distress, diagnosed with multiple congenital anomalies including tracheoesophageal fistula, anal malformation, dextrocardia, and vertebral anomalies, consistent with VACTERL syndrome.

Discussion: This case discusses potential teratogenic effects, disruption of embryonic development, and possible genetic susceptibility as mechanisms for the observed anomalies. Although direct evidence is limited, this case highlights the need for further research and cautious use of these medications.

Conclusion: The case underscores the importance of informed clinical practice and vigilance in recognizing rare adverse drug reactions. Further studies are needed to establish a clear link between these medications and congenital anomalies.

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Introduction

Medical termination of pregnancy (MTP) is commonly achieved through the administration of mifepristone and misoprostol (Hayes JL et al., 2011). Mifepristone, a progesterone receptor antagonist, is typically administered first to block the hormone necessary for pregnancy maintenance, followed by misoprostol, a prostaglandin analog, to induce uterine contractions and expel the pregnancy tissue (Zhang J et al., 2022). This combination is highly effective, with a success rate of approximately 97% within the first 63 days of gestation (Li YT et al., 2011). However, in cases where MTP fails, the continued pregnancy may be at risk for various complications, including teratogenic effects due to exposure to these medications (Jingran G et al., 2024, Vauzelle C et al., 2013; Allen R et al., 2009; Beaman J et al., 2020).

The risk of congenital anomalies following failed MTP is a significant concern. Teratogenicity refers to the ability of a substance to cause birth defects or developmental malformations in the fetus (Kaleelullah RA et al., 2021; Genetic Alliance, 2010; DeSilva M et al., 2016). Drugs that are known teratogens, such as thalidomide, isotretinoin, and certain antiepileptic drugs, exert their effects by interfering with critical periods of fetal development, particularly during organogenesis (Tsamantioti ES et al., 2024). The mechanisms by which teratogens cause harm include disrupting cellular differentiation, causing DNA damage, altering blood supply, and affecting hormonal signaling pathways (van Gelder MM et al., 2010). Mifepristone and misoprostol, while not definitively established as teratogens, could potentially contribute to congenital anomalies if a pregnancy continues after attempted termination (Jingran G et al., 2024).

This case report presents a rare instance of a failed MTP leading to the development of VACTERL anomaly—a complex syndrome involving vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities (Solomon BD, 2011). The suspected link between the exposure to mifepristone and misoprostol and the subsequent congenital anomalies in this case underscores the importance of understanding the potential teratogenic risks associated with these drugs. This case is particularly interesting as it raises questions about the safety of medical abortion drugs when MTP fails, and highlights the need for increased vigilance and research in this area. The findings in this article are expected to contribute valuable insights into the safety profile of these widely used medications and their potential risks to fetal development.

Case Details

A 19-year-old primigravida, with an estimated gestational age of 36 weeks, presented to the emergency department at our tertiary care center on June 27, 2022, at 1:43 PM. She reported severe lower back pain and lower abdominal pain as her primary symptoms. This patient had not registered for prenatal care and had no history of antenatal checkups throughout her pregnancy.

Her medical history revealed that at approximately 6 weeks of gestation, following a missed menstrual period, she had confirmed her pregnancy. Due to familial issues, she opted to take abortion pills without medical supervision. Despite the consumption of these pills, she experienced no subsequent symptoms of abortion, such as vaginal bleeding, leaking, or abdominal pain, leading her to believe that the abortion attempt had failed. Consequently, she continued her pregnancy without seeking further medical consultation, forgoing any antenatal scans, supplements, or vaccinations.

Upon her presentation to the emergency department on June 27, 2022, a physical examination and additional investigations, including an ultrasound, confirmed that she was approximately 36 weeks pregnant. The assessments also revealed maternal anemia and polyhydramnios, a condition characterized by an excessive accumulation of amniotic fluid. Given her condition, the medical team decided to induce labor using intravenous oxytocin.

On June 28, 2022, at 12:45 AM, the patient delivered a female infant via normal vaginal delivery. The newborn initially cried immediately after birth, but shortly thereafter, exhibited signs of respiratory distress. Oxygen inhalation was promptly initiated, and the neonate was transferred to the Neonatal Intensive Care Unit (NICU) for further evaluation and management.

During the initial assessment in the NICU, the inability to pass a nasogastric (NG) tube prompted suspicion of a tracheoesophageal fistula, which was later confirmed by a chest X-ray that showed the coiling of the NG tube. As the respiratory distress worsened, the infant was intubated and placed on mechanical ventilation. Further physical examination and imaging studies revealed an anal malformation, dextrocardia, and vertebral anomalies. These findings collectively raised the suspicion of VACTERL association, a complex congenital syndrome characterized by Vertebral defects, Anal atresia, Cardiac defects, Tracheoesophageal fistula, Renal anomalies, and Limb abnormalities (Solomon BD, 2011).

Given the severity of the congenital anomalies, the infant was immediately referred to Indira Gandhi Hospital for specialized surgical and neonatal care. Prior to transfer, the neonate was administered a 1 mg intramuscular injection of Vitamin K. Routine vaccinations, including BCG, Hepatitis B, and OPV, were not administered at birth due to the infant's critical condition. All relevant medical records, including the discharge summary,

investigation results, and treatment details, were forwarded to the receiving hospital.

At Indira Gandhi Hospital, the infant underwent three surgical procedures in an attempt to correct the congenital anomalies. Postoperatively, the baby remained intubated and was fed via a nasogastric tube. Unfortunately, despite the intensive medical and surgical interventions, the infant succumbed to asphyxia two weeks following the surgeries.

Discussion

Medical Termination of Pregnancy and Teratogenic Risks

Medical abortion, a widely utilized non-surgical method for terminating pregnancies, predominantly involves the use of mifepristone and misoprostol (Zhang J et al., 2022). Mifepristone, a progesterone receptor antagonist, disrupts the uterine lining, leading to detachment of the embryo, while misoprostol, a prostaglandin E1 analog, induces uterine contractions to expel the embryo (Autry BM et al., 2024). This regimen is generally considered safe and effective, particularly when used during the early stages of pregnancy. However, like all pharmacological interventions, it is not without risks. In rare cases, the use of these drugs may result in adverse outcomes, including the failure of the intended abortion and subsequent teratogenic effects if the pregnancy continues (Allen R et al., 2009).

When medical abortion fails, as may occur in a small percentage of cases, the continued exposure of the developing fetus to these drugs can be problematic. The fetus, during critical stages of organogenesis, may be vulnerable to the teratogenic effects of mifepristone and misoprostol. Teratogens are agents that can disturb the development of an embryo or fetus, potentially leading to congenital malformations (Vauzelle C et al., 2013; Gheysen W et al., 2020; Haimov-Kochman R et al., 2007). The combination of these two drugs could interfere with normal embryonic development, leading to complex congenital anomalies such as VACTERL association (Su YT et al., 2023; van de Putte R et al., 2020).

VACTERL Anomaly and Potential Mechanisms

VACTERL association is a rare congenital condition involving anomalies across multiple organ systems. Each letter in the acronym represents a specific type of malformation that can occur independently or in combination with others (Solomon BD, 2011). The exact cause of VACTERL is not fully understood, but it is believed to arise from disruptions in embryonic development during the early stages of gestation (Stevenson RE et al., 2013).

Several potential mechanisms may explain how mifepristone and misoprostol could contribute to the development of such anomalies. Firstly, the teratogenic effects of these drugs could directly interfere with the normal development of various organ systems. Mifepristone disrupts progesterone signaling, which is crucial for maintaining pregnancy and supporting fetal development. Misoprostol, by inducing uterine contractions, may exacerbate these disruptions, potentially leading to incomplete or abnormal organogenesis (Vauzelle C et al., 2013; Autry BM et al., 2024; Su YT et al., 2021).

Secondly, the disruption of the hormonal environment by these drugs could impair the delicate balance required for proper fetal development. Progesterone plays a key role in preparing the uterine environment for implantation and maintaining pregnancy, and its inhibition by mifepristone could have far-reaching effects on the developing fetus. Misoprostol, by inducing uterine contractions, might also contribute to hypoxia or mechanical stress on the developing fetus, further increasing the risk of congenital anomalies (Cable JK et al., 2023; Bulletti C et al., 2022; Kerr RS et al., 2021; de Vaan MD et al., 2023).

Finally, genetic susceptibility could play a role in determining the fetus's vulnerability to these drugs. Some individuals may carry genetic variants that make them more prone to adverse developmental outcomes when exposed to teratogenic agents. In the presented case, it is possible that the infant had an underlying genetic predisposition that, when combined with the exposure to mifepristone and misoprostol, led to the development of VACTERL association (Gomes JDA et al., 2021; Genetic Alliance, 2010).

Causality Assessment Using the WHO Scale

Applying the WHO causality assessment criteria to this case involves evaluating the likelihood that the adverse event (VACTERL anomaly) was caused by the drugs in question (mifepristone and misoprostol). The WHO-UMC causality assessment system considers factors such as temporal relationship, existing knowledge of the drug's adverse effects, and alternative explanations for the observed event (WHO, 2024).

Temporal Relationship: The mother consumed the drugs during early pregnancy, a critical period for fetal organ development, making the temporal relationship plausible.

Existing Knowledge: While the teratogenic potential of mifepristone and misoprostol is documented, the specific association with VACTERL anomaly is not well established, suggesting the need for further investigation (Jingran G et al, 2024; Vauzelle C, 2013).

Alternative Explanations: Genetic predisposition or other environmental factors could also contribute to the

development of VACTERL anomaly (Reutter H et al., 2016; Reutter H et al., 2013)

Based on these criteria, the causality could be classified as "possible" under the WHO-UMC system, indicating that while a temporal association exists, the evidence is not definitive, and alternative causes have not been fully excluded.

Conclusion

This case of a 19-year-old pregnant woman who underwent a failed medical abortion with mifepristone and misoprostol, resulting in the birth of an infant with VACTERL anomaly, underscores the critical need for caution in the use of these drugs during pregnancy. While medical abortion is generally considered safe, this case highlights the potential for rare but serious adverse outcomes, particularly when the abortion fails and the pregnancy continues.

The potential teratogenic effects of mifepristone and misoprostol, their impact on embryonic development, and the role of genetic susceptibility warrant further research. Healthcare providers must ensure that patients are fully informed of the risks associated with medical abortion and consider alternative methods of pregnancy termination when feasible. This case also emphasizes the importance of vigilant monitoring and reporting of adverse drug reactions to enhance our understanding and improve the safety of reproductive healthcare practices.

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Conflict of Interest

Authors declered no conflict of interest.

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