INTRODUCTION

Misoprostol is a drug that belongs to synthetic prostaglandin E1 analog groups. This drug is approved by Food and Drug Administration, also in Indonesia, to be consumed orally as treatment and prevention of gastric ulcers associated with non-steroidal anti-inflammatory (NSAIDs) drugs because of the mucosal protective and antisecretory effect. Besides misoprostol for gastric ulcers, this drug can be used in obstetrics and gynecology cases for cervical ripening and uterotonics action.\(^1,2\)

The International Federation of Gynecology and Obstetrics (FIGO) has released a specific dosage of misoprostol for different purposes. The misoprostol dosage for pregnancy termination in >28 weeks is 25 mcg to 100 mcg per-vaginal or sublingual or buccal, every 6 hours.\(^3\) The maximum dose of misoprostol reported in the literature is 6 mg.

Manifestation of misoprostol toxicity, including hyperthermia, hypoxemia, rhabdomyolysis, fetal distress and death, metabolic acidosis and respiratory alkalosis. One article reported misoprostol toxicity, including tremors, fever, hypertension, tachycardia, abdominal cramp, and nausea.\(^4\) The toxic misoprostol dose in humans is unknown, and there is no antidote.\(^1\)

Acute toxicity of misoprostol can be manifested in several signs and symptoms. Misoprostol, the synthetic analog of prostaglandin E1, can cause increased cardiac output, vasodilation of most vascular beds, relaxation of bronchial smooth muscle, and a strong contraction of the uterine muscle. The effects of misoprostol on the intestinal smooth muscle are shortening transit time which leads to vomiting, diarrhea, and abdominal cramps. Prostaglandin E1 also mediates the febrile response in thermoregulation centers of the brain on exposure to pyrogens.\(^4\) Currently, the management of acute misoprostol toxicity is focused on supportive care. For oral ingestion, a one-time dose of activated charcoal with the dosage of 0.5-1.0 g/kg should be given. For intravaginal usage, the removal of misoprostol should be attempted. Patients with agitation should be given sedation with barbiturates, benzodiazepines, or intubation with neuropsychiatric therapy for severe cases. In case of hyperthermia and hypotension, cooling blanket therapies, crystalloids and vasopressors can be given if needed.\(^2\)

Acute misoprostol toxicity is rarely reported, including in the case of pregnant women. Up to this present time, there are only three articles that reported misoprostol overdose in pregnancy.\(^2,4,5\) The real incidence of misoprostol toxicity remains unclear. This article aims to discuss the effect of potentially acute

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**ABSTRACT**

**Background:** The International Federation of Gynecology and Obstetrics (FIGO) recommends the dosage of misoprostol for pregnancy termination in >28 weeks is 25 mcg to 100 mcg per-vaginal or sublingual or buccal, every 6 hours, and the maximum dose is 6 mg. Acute misoprostol toxicity is rarely reported, including in the case of pregnant women. This study aims to discuss the effect of potentially acute misoprostol toxicity in pregnant women and the fetus.

**Case Presentation:** A 17 years-old woman, G1, 32 weeks, presented with singleton intrauterine fetal death. The patient previously consumed 14 tabs of oral misoprostol and 4 tabs of misoprostol intravaginally. Her vital signs were within a normal level, his 4x/10'/40", and her fetal heart rhythm was negative. From vaginal touché found complete dilation. The patient led to bear down and born baby boy, demise fetal, 1965-gram, 43 cm, no maceration and placenta born completely. After delivery, the mother was in good condition. Misoprostol is a synthetic analog of prostaglandin E1, which can be used for uterotonics and cervical ripening. In pregnant women, misoprostol toxicity can induce hypertonic uterine contractions, leading to fetal distress and death, rhabdomyolysis, hyperthermia, respiratory alkalosis, hypoxemia, and metabolic acidosis. One article reported maternal death due to upper gastrointestinal bleeding and multiorgan failure. We analyze that intrauterine fetal death may happen because of excessive misoprostol that induces hypertonic uterine contraction, causing fetal distress and leading to fetal demise.

**Conclusion:** Excessive consumption of misoprostol or potentially acute misoprostol during the third-semester pregnancy can lead to harmful effects for both mother and fetus.

**Keywords:** Misoprostol Toxicity, Pregnancy, Stillbirth.
misoprostol toxicity in pregnant women and the fetus.

CASE REPORT

A 17 years-old woman, G1, 32 weeks of gestational age, presented in the Emergency Room with a chief complaint of frequent contraction for 6 hours before admission. At first, the patient had nausea and did not have menstruation, but she did not use a urinary pregnancy test before. The patient is unmarried, never had antenatal care and ultrasound exam before. The patient felt the first fetal movement since February 2021. The patient previously consumed 14 tabs of oral misoprostol and 4 tabs of misoprostol intravaginally. Vital signs and physical examination within a normal level, his 4x/10/40°, fetal heart rhythm negative. From vaginal touché found complete dilation. From vaginal touché found complete dilation, head on Hodge III-IV, amniotic membrane negative. Laboratory results showed anemia (10,9 g/dL) and leukocytosis (27.260 /uL). Other laboratory findings are within the normal level. The patient has been diagnosed with singleton intrauterine fetal death, head presentation, unmarried, unintended pregnancy, teenage pregnancy, underweight (IMT 17 kg/m²), and mother with misoprostol intoxication. The patient was led to bear down and born a baby boy, demise fetal, 1965-gram, 43 cm, no maceration, greenish amniotic fluid and placenta born completely. After delivery, the mother was in good condition, given bromocriptine 2 x 2.5 mg and stayed in the ward. Written informed consent was obtained from the patient.

DISCUSSION

Misoprostol is a synthetic analog of prostaglandin E1, which can be used for uterotonic and cervical ripening. In pregnant women, misoprostol toxicity can induce hypertonic uterine contractions, leading to fetal distress and death, rhabdomyolysis, hyperthermia, respiratory alkalosis, hypoxemia, and metabolic acidosis. Clinical manifestation of misoprostol toxicity shows few similarities in some case reports. An article reported the clinical manifestation of intravaginally misoprostol overdose 6000 mcg intravaginally and 600 mcg oral) including hyperthermia, hypotension, tachypnea, agitation, shaking chills, emesis, and intrauterine fetal death. This manifestation can be appeared because of the prostaglandin effects of misoprostol, specifically smooth muscle contraction that causes emesis, hyperthermia and abdominal cramp. Hyperthermia may be caused by shivering thermogenesis, altered thermoregulatory set point and increased catecholamine release.

One article reported a 19-year-old female pregnant at 31 weeks of gestational age ingested 6000 mcg of misoprostol and 2 mg of trifluoperazine. Clinical manifestations, including tachycardia, hyperthermia, agitation, hypoxemia, and tetanic uterus, developed in 2 hours, followed by intrauterine fetal death. These symptoms are mostly resolved with supportive care within 12 hours. Another article reported an older woman ingested 3000 mcg of misoprostol, then developed hyperthermia, nausea, tremor, abdominal cramp, hypertension and tachycardia. The majority of these symptoms resolved within 7 hours after hospital admission. One article reported maternal death due to upper gastrointestinal bleeding and multiorgan failure after ingesting 60 tablets of 12000 mcg of misoprostol.

We analyze that intrauterine fetal death in our patient may happen because of excessive misoprostol that induced hypertonic uterine contraction, causing fetal distress and leading to fetal demise. This case showed the relative safety of misoprostol. Although the patient consumed a large amount of misoprostol, this did not cause any toxicity symptoms and resolved after supportive care in a few hours. We assume the patient did not experience any toxicity symptoms because the total misoprostol dosage consumed had not reached the maximum dose. The patient consumed 2800 mcg of misoprostol, almost half the maximum dose of 6000 mcg. We did not perform any specific laboratory findings to investigate the level of misoprostol in this patient; we diagnosed this patient with misoprostol intoxication based on all the clinical findings.

All reported cases of misoprostol toxicity also showed the rapid onset of signs and symptoms and the complete resolution by 12 hours after consumption. This can be explained by the rapid onset of misoprostol, which peaks less than 15 minutes after ingestion, and the elimination half-life is 20-40 minutes. However, there is limited data about actual plasma misoprostol concentrations. Therefore, treatment of misoprostol toxicity should focus on supportive care. For oral ingestion, the patient can be given 0.5 – 1.0 g/kg activated charcoal in a one-time dose. If the misoprostol is inserted intravaginally, removal of the drugs from the vaginal should be attempted. Early fetal monitoring and delivery, as indicated, are important in pregnant patients.

This study has assessed the potentially acute misoprostol toxicity during the third semester of pregnancy. However, there is still a limitation regarding laboratory work to support the misoprostol toxicity diagnosis in our case. Further study is needed to assess the proper diagnosing tools and the best management for misoprostol toxicity in pregnant women to ensure the best maternal and fetal outcomes regarding this case in the future. To date, the risks of misoprostol toxicity are not completely known yet.

CONCLUSION

Excessive misoprostol or potentially acute misoprostol toxicity during the third semester of pregnancy can lead to harmful effects for the mother and fetus. We reported an intrauterine fetal death in a woman who ingested a large dose of oral and intravaginal misoprostol. The patient did not experience any toxicity symptoms and is in stable condition with supportive care. As clinically indicated, supportive care, fetal monitoring, and delivery should be performed in misoprostol toxicity cases, specifically in pregnant women.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

ETHICAL CONSIDERATION

This case report has received informed consent from the patient.

FUNDING

This study was not funded.
CASE REPORT

AUTHOR CONTRIBUTION
Riyan Hari Kurniawan was involved in concepting, designing, and as the guarantor of this article. Riyan Hari Kurniawan and Ni Putu Cahya were both involved in defining the intellectual content, forming a literature search, preparing the manuscript, editing the manuscript, and reviewing the manuscript.

REFERENCES