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# Embryotoxicity of misoprostol: An expanded literature review and clinical case analysis

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**Abstract**

To review the teratogenic mechanisms of misoprostol, summarize clinical and experimental evidence, and present cases of congenital anomalies associated with prenatal exposure in Ecuador. A narrative review of indexed literature was conducted using PubMed, Scopus, and SciELO. Clinical and experimental studies on misoprostol teratogenicity were analyzed. Additionally, five cases of prenatal misoprostol exposure documented in public hospitals in Guayaquil were described, emphasizing phenotypic patterns and embryotoxicity mechanisms. The evidence consistently links first-trimester misoprostol exposure to congenital anomalies such as Moebius syndrome, encephalocele, craniofacial disruptions, and limb defects. The main proposed mechanism is vascular disruption secondary to uterine contractions, producing transient hypoxia and apoptosis in embryonic tissues. The Ecuadorian cases presented showed craniofacial asymmetry, facial paralysis, encephalocele, and limb malformations, aligning with this mechanism. Misoprostol use in early pregnancy, particularly when unsupervised, poses a serious risk to embryonic development. Literature and clinical cases underscore the need for preventive strategies and strengthened reproductive health services.

**Keywords:** Misoprostol, Embryotoxicity, Congenital anomalies, Moebius syndrome, Unsafe abortion, Vascular disruption.

## Introduction

Misoprostol, a synthetic analogue of prostaglandin E1, was originally developed for the prevention of Nonsteroidal Anti-Inflammatory Drug (NSAID)-induced gastric ulcers. Over time, its use has expanded widely in gynecology and obstetrics due to its ability to induce uterine contractions, ripen the cervix, and facilitate uterine evacuation [1].

Its effectiveness, low cost, and thermal stability have made misoprostol an accessible option in countries with limited resources and in contexts where access to safe medical services is restricted [8]. However, administration during the first trimester of pregnancy—particularly without medical supervision—has been associated with significant embryotoxic effects [2–4].

Several studies suggest that these effects are mediated by vascular disruption mechanisms triggered by uterine contractions that compromise fetal blood supply. This may lead to localized hypoxia and apoptosis in developing embryonic tissues, primarily affecting the central nervous system and craniofacial structures [3,6].

Multiple congenital defects have been reported in association with misoprostol exposure, including Moebius syndrome, facial paralysis, limb anomalies, micrognathia, encephalocele, and orofacial clefts [3–5]. The phenotypic expression of these effects varies depending on the timing of exposure, route of administration, dosage, and the presence of cofactors such as fever or concurrent drug use [6,7].

This review aims to describe the primary teratogenic mechanisms of misoprostol, summarize current clinical and experimental evidence, and present a case series observed in public hospitals in Ecuador, thereby contributing to a better understanding of the teratogenic risks associated with its inappropriate use (Figure 1).

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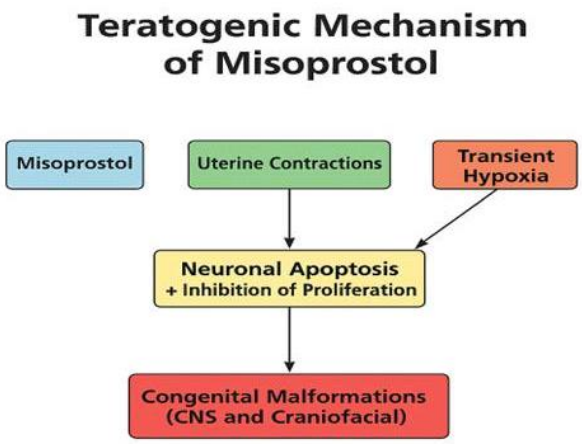



**Figure 1.** Proposed teratogenic mechanism of misoprostol

**Legend:** Uterine contractions induced by misoprostol may cause transient fetal hypoxia during critical stages of embryonic development, leading to neuronal apoptosis and impaired proliferation in the central nervous system and craniofacial structures, potentially resulting in congenital anomalies.

## Methods

### Study design

A narrative literature review was conducted to synthesize current clinical and experimental evidence on the teratogenic effects of misoprostol. The review was complemented by a descriptive analysis of five clinical cases of prenatal misoprostol exposure documented in public hospitals in Guayaquil, Ecuador.

## Literature Search Strategy

The literature search was performed in the PubMed, Scopus, Web of Science, and SciELO databases, covering publications from inception to May 2025. The search strategy combined the terms: "misoprostol", "embryotoxicity", "teratogenicity", "congenital anomalies", "Moebius syndrome", and "vascular disruption", using Boolean operators.

### Inclusion criteria were

- Original studies (case reports, case series, case-control, cohort, or experimental animal models) describing congenital anomalies following misoprostol exposure during pregnancy.
- Systematic or narrative reviews addressing teratogenic mechanisms of misoprostol.
- Articles available in English, Spanish, or Portuguese.

### Exclusion criteria were

- Studies evaluating misoprostol use after the second trimester.
- Reports lacking detailed information on exposure timing and outcomes.

Reference lists of the selected articles were also manually screened to identify additional relevant publications.

### Clinical case data collection

The five clinical cases were obtained from hospital medical records and pediatric follow-up evaluations. Data included maternal demographic characteristics, gestational age at exposure, misoprostol dosage and route of administration, co-exposures, and detailed neonatal clinical findings.

### Ethical considerations

This study followed the principles of the Declaration of Helsinki. Institutional authorization was obtained from the participating hospitals, and written informed consent was provided by the parents or legal guardians for the use of anonymized clinical information and photographs for scientific purposes. Artificial intelligence tools were used solely for the layout of the article.

## Results

### Experimental and clinical evidence of embryotoxic effects

The cumulative evidence on the teratogenicity of misoprostol derives from both clinical studies and experimental animal research. The primary proposed mechanism is vascular disruption: by inducing uterine contractions, misoprostol can cause transient episodes of hypoxia that compromise the development of specific embryonic regions,

particularly the central nervous system and craniofacial structures [2].

In humans, multiple observational studies have reported a strong association between prenatal exposure to misoprostol and congenital anomalies such as Moebius syndrome, characterized by congenital facial paralysis, ocular motility disorders, and oropharyngeal malformations [3]. Other recurrent anomalies include limb reduction defects, encephalocele, micrognathia, cleft palate, and neural tube defects [8].

A case-control study in Brazil identified misoprostol as the primary risk factor associated with disruptive malformations when used during the first trimester [9]. In murine experimental models, administration of misoprostol during the critical period of embryogenesis has been shown to induce neuronal apoptosis and inhibit cell proliferation in specific brain regions [10]. These findings support the hypothesis of selective susceptibility of the developing nervous system to early hypoxic and pharmacologic insults.

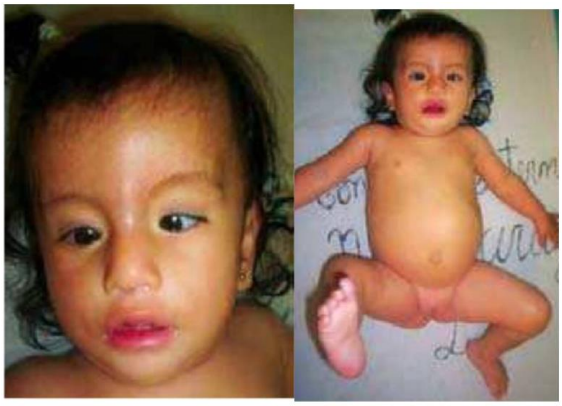
Phenotypic variability is notable, and not all cases of exposure result in malformations. Factors such as dosage, administration route (oral or vaginal), gestational age at exposure, and co-exposures (e.g., alcohol, fever, infections) are thought to modulate embryotoxic risk [11]. This variability underscores the need for broader studies integrating genetic, environmental, and pharmacokinetic factors.

## Case reports

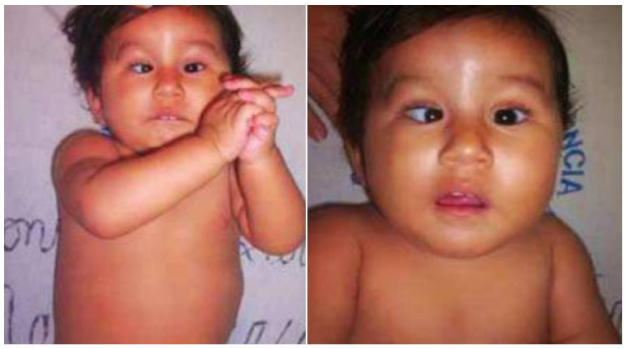
Five cases of first-trimester prenatal exposure to misoprostol were documented in public hospitals in Guayaquil, Ecuador. All presented anomalies consistent with fetal vascular disruption (see Table 1).

**Table 1.** Clinical characteristics of cases with prenatal exposure to misoprostol

| Case | Gestational age (weeks) | Dose (mcg) | Route | Main findings |
|---|---|---|---|---|
| 1 | 8 | 400 | Oral | Facial paralysis, micrognathia |
| 2 | 10 | 800 | Oral | Facial paralysis, micrognathia |
| 3 | 8 | 400 | Vaginal | Encephalocele, cleft lip and palate |
| 4 | 10 | — | Mixed | Hydranencephaly, clubfoot |
| 5 | 8 | 800 | Oral | Facial paralysis, clubfoot |

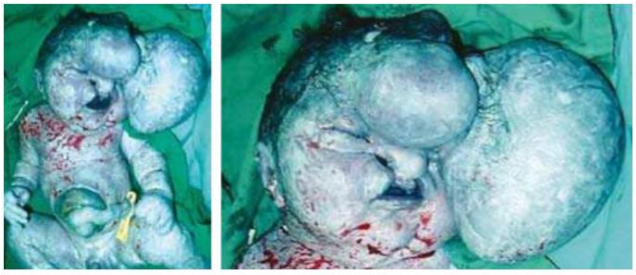


**Case 1:** A 4-year-old female with a history of maternal ingestion of 400 mcg of misoprostol during the first trimester. Physical examination revealed an expressionless facies, epicanthal folds, convergent strabismus of the left eye, broad nasal base, anteverted nares, tent-shaped mouth, thin lips, high-arched palate, microglossia, micrognathia, and large auricles. Congenital facial paralysis and developmental delay were diagnosed.

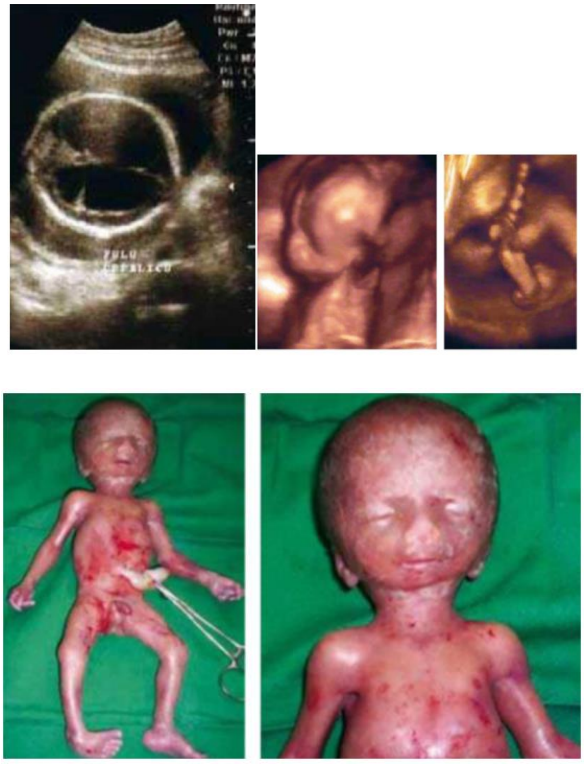


**Case 2:** Firstborn daughter of a non-consanguineous couple. Maternal history included ingestion of 800 mcg of misoprostol at 10 weeks' gestation. Findings included craniofacial asymmetry, right microphthalmia, orbital hypoplasia, low-set ears,

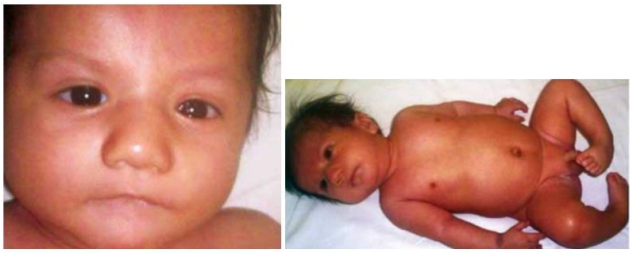
convergent strabismus, and right-sided facial paralysis.



**Case 3:** Product of the fourth pregnancy in a woman with two previous spontaneous abortions. Exposure consisted of 400 mcg of vaginal misoprostol at 8 weeks' gestation. Prenatal ultrasound revealed frontonasal encephalocele, ventriculomegaly, and mild polyhydramnios. Postnatal examination confirmed two protrusions (frontonasal and frontoparietal), bilateral exophthalmos, complete cleft lip and palate, micropenis, and encephalocele.



**Case 4:** First pregnancy in a non-consanguineous couple. Maternal exposures included alcohol intake (two beers) at 9 weeks, 30 tablets of primosiston at 7 weeks, and two misoprostol tablets (one oral, one vaginal) at 10 weeks' gestation. Diagnoses included hydrocephalus, bilateral clubfoot, micrognathia, frontal bossing, low-set and posteriorly rotated ears, high nasal bridge, and retrognathia. Neuroimaging revealed dilated ventricular cavities with reduced cerebral parenchyma, consistent with hydranencephaly.



**Case 5:** Male infant born to a non-consanguineous couple. Maternal history reported ingestion of 800 mcg of misoprostol at 8 weeks' gestation. The neonate presented with facial asymmetry, microphthalmia, convergent strabismus, left facial paralysis, and bilateral clubfoot.

These cases reinforce the suspected relationship between early misoprostol exposure and the occurrence of congenital anomalies, particularly those compatible with vascular disruption mechanisms in developing tissues.

## Discussion

The findings of this review are consistent with international literature describing the embryotoxic effects of misoprostol, particularly when administered during the first weeks of pregnancy [1–4]. The clinical patterns observed in our case series—including facial paralysis, micrognathia, orofacial clefts, and encephalocele—align with the vascular disruption mechanisms widely proposed in the pathophysiology of these anomalies [3,4].

Moebius syndrome, one of the most frequently reported defects associated with misoprostol exposure, involves impairment of cranial nerves VI and VII, resulting in congenital facial paralysis and ophthalmoparesis [5]. The literature suggests that these defects may arise from focal hypoxia occurring during critical stages of neuroembryonic development [3,4].

Importantly, not all cases of prenatal misoprostol

exposure result in malformations, indicating that teratogenicity is influenced by multiple factors. These include dosage, administration route, gestational age at exposure, and the presence of cofactors such as fever, viral infections, or concurrent substance use [6,7]. This variability highlights the complexity of predicting individual risk and underscores the need for further research integrating genetic predisposition, maternal comorbidities, and environmental exposures.

The use of misoprostol in unregulated contexts raises significant ethical and public health challenges. In many countries, women resort to this medication due to legal, economic, or structural barriers that limit access to safe abortion services [12]. Such scenarios increase the likelihood of unsupervised self-administration, which not only compromises maternal safety but also increases the risk of adverse embryonic outcomes.

Preventive strategies must therefore extend beyond the dissemination of clinical information to encompass comprehensive public health policies. These should include sexual and reproductive health education, improved availability of contraceptive methods, and the decriminalization and medical regulation of abortion in controlled clinical environments [13]. From a clinical perspective, health professionals must be trained to recognize early signs of congenital anomalies potentially related to misoprostol exposure, enabling timely intervention and appropriate counseling for affected families.

## Conclusions

Misoprostol, while effective and safe when used in regulated clinical settings, can act as a teratogenic agent when administered during the first trimester of pregnancy without appropriate medical supervision. Both experimental and clinical evidence support an association between this drug and severe congenital anomalies, particularly those linked to vascular disruption mechanisms [1–4].

The five clinical cases presented in this study reinforce this association, illustrating patterns of craniofacial and neurological malformations consistent with the proposed pathophysiology. These findings underscore the need for strengthened epidemiological surveillance, enhanced training for healthcare professionals to recognize and manage such anomalies, and the development of reproductive health programs that ensure safe, comprehensive, and rights-based care.

## Declarations

Ethics Statement This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The clinical cases presented were collected from public hospitals in Guayaquil, Ecuador. Written informed consent was obtained from the patients' parents or legal guardians for the inclusion of their anonymized clinical information. All identifying details have been omitted to protect patient confidentiality. The study protocol was reviewed and approved by the Ethics Committee of the Universidad de Guayaquil.

**Declarations of Interest:** None.

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**Disclosure statement:** The authors declare that they have no known financial or personal relationships that could have inappropriately influenced the work reported in this manuscript.

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