

Möbius Syndrome in a Neonate After Mifepristone and Misoprostol Elective Abortion Failure

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Administration of mifepristone plus misoprostol is the French protocol for medical elective abortion. This protocol involves the administration of mifepristone 600 mg, followed 36–48 hours later by an analog of prostaglandin E₁, oral misoprostol 400 µg (or vaginal geméprost 1 mg).¹ Mifepristone is a synthetic antiprogesterin used for abortion, and misoprostol induces uterine contractions. An ultrasonography is obligatory 14 days after mifepristone administration to verify termination of pregnancy, because vaginal bleeding, which may lead patients to conclude that abortion has been successful, can occur even if pregnancy continues. In France, medical abortion is allowed only for pregnancies less than 50 days of amenorrhea (equivalent to 36 days of gestation). The rate of complete abortion with this medical protocol is highest (91–97%) for women who are less than 49 days pregnant. The same protocol results in complete abortion for 88% of women who are less than 63 days pregnant.² In France, surgical abortion is authorized until the twelfth week of pregnancy (140 days of gestation) and can be used after chemical abortion failure.

The teratogenic risk of exposure to mifepristone and misoprostol for the fetus remains to be fully quantified. Indeed, it has not yet been documented that mifepristone alone is related to a teratogenic process. In contrast, when

OBJECTIVE: To report a case of a child born with Möbius syndrome following exposure in utero to mifepristone and misoprostol for elective abortion.

CASE SUMMARY: In the seventh week of pregnancy, a woman was administered mifepristone 600 mg and, 2 days later, misoprostol 400 µg for abortion. One month later, despite significant metrorrhagia, an ultrasound examination showed ongoing gestation. At 33 weeks and 3 days of gestation, the woman gave birth to a male with left facial palsy, microretrognathia, and axial hypotonia related to Möbius syndrome.

DISCUSSION: Möbius syndrome is characterized by unilateral or bilateral palsy of the abducens (VI) and facial (VII) cranial nerves. Other cranial nerves (eg, the hypoglossal [XII]), craniofacial or orofacial anomalies, and limb malformations are often associated. The etiology of the Möbius syndrome remains largely unknown and probably involves multiple factors. The most likely etiological hypothesis is disruption of the developing vascular system, with transient ischemia (particularly in the vertebral arteries) and fetal hypoxia. A teratogenic cause of Möbius syndrome has been suggested. The critical period for the development of Möbius syndrome following teratogen exposure appears to be 5–8 weeks of gestation. To date, mifepristone alone does not appear to have induced Möbius syndrome. In contrast, oral or vaginal misoprostol administration can lead to a significant increase in Doppler-measured uterine artery resistance and may induce uterine contractions. If these occur during the critical embryonic period, they may cause flexion in the areas of the sixth and seventh cranial nerves and decreased blood flow.

CONCLUSIONS: Ineffective use of mifepristone and misoprostol in the first trimester of pregnancy may be associated with a risk of Möbius syndrome, primarily due to misoprostol activity. Women with ongoing pregnancy after failed abortion with misoprostol administration should be informed of this risk.

KEY WORDS: fetal ischemia, mifepristone, misoprostol, Möbius syndrome, pregnancy.

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abortion fails, misoprostol has been suspected of causing teratogenic effects, including terminal limb defects and Möbius syndrome. Most reports have involved illegal use of the drug, such as cases reported in Brazil where elective abortion is not allowed.³⁻⁵ We report a case of Möbius syndrome following fetal exposure in utero to mifepristone and misoprostol for elective abortion.

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Case Report

A 28-year-old woman, with only moderate asthma treated occasionally by albuterol, became pregnant 3 years after a miscarriage and 1 year after a full-term pregnancy resulting in a healthy, normal child. No use of illicit drugs was reported. She decided to terminate this pregnancy and started the French protocol for chemical abortion at the beginning of the seventh week of gestation (day 43). She received oral mifepristone 600 mg and, 2 days later, misoprostol 400 µg. One month later, despite significant metrorrhagia, an ultrasound examination showed ongoing pregnancy, with no anomalies observed in the fetus. The patient requested genetic consultation during the fifteenth week of pregnancy; thus, pharmacovigilance advice was solicited to counsel the woman on teratogenic risks. A follow-up by a sonographer was started because the woman decided to continue her pregnancy.

The woman delivered a boy at 33 weeks and 3 days of pregnancy; his measurements were within normal parameters for his age of gestation: weight 2.28 kg, length 46 cm, and cranial perimeter 31 cm. The boy presented with transient respiratory distress, which was corrected rapidly. Diagnosis was immediate for left facial palsy, microretrognathia, and axial hypotonia related to Möbius syndrome (Figure 1). Eight weeks after birth, the left facial palsy and microretrognathia were still present. At month 4, the infant was able to suck without help, but he was still hypotonic and unable to lift his head completely or grasp objects.

The Naranjo probability scale indicated that the Möbius syndrome observed in this child was possibly related to misoprostol but doubtfully related to mifepristone.⁶ However, the Naranjo scale was not specifically developed to

determine the likelihood of fetal teratogenesis from prenatal exposure to a teratogen. This is exemplified in the fact that 5 of the 10 questions employed to construct this scale are not applicable to this case.

Discussion

Möbius syndrome is a rare disorder first described by Von Graefe in 1880 and identified and defined in 1888 by Paul Julius Möbius, a Leipzig neurologist, as an independent pathological entity.⁷ It consists of congenital unilateral or bilateral palsy of the abducens (VI) and facial (VII) cranial nerves. This sequence can be associated with palsy of other cranial nerves such as the trigeminal (V), the glossopharyngeal (IX), and the hypoglossal (XII). Other malformations, such as craniofacial and orofacial anomalies, face anomalies (eg, cleft palate, abnormalities of the tongue, the ear, micrognathia), and limb malformations (eg, club foot, syndactyly, arthrogyriposis) can occur concurrently with Möbius syndrome. Clinical examination at birth of a baby with Möbius syndrome shows unilateral or bilateral facial palsy, with suckling problems, significant salivation difficulties, and/or impaired facial expressions. Later in life, the observed abnormalities include a fixed smile, difficult ocular movements, hearing problems, dental anomalies, and speech defects.

Poland syndrome (hypoplasia of the pectoralis major muscle, syndactyly of the hand, hypoplasia of the forearm and/or the breast, agenesis of the nipple) and Pierre Robin syndrome (median posterior cleft palate, retrognathia, glossoptosis) may also occur with Möbius syndrome. Mental retardation and autism were also observed by some authors in one-third of a population of 25 patients with Möbius syndrome.⁸

The etiology of Möbius syndrome is largely unknown, but the vascular hypothesis appears to be the most plausible. The hypothesis is that transient ischemia, particularly in the vertebral arteries, is responsible for disruption of the developing vascular system and for fetal ischemia.^{4,7,9} Obstruction or premature regression of terminal arteries of the trigeminal (V) nerve and/or retarded formation of the basilar/vertebral system can lead to anomalies in cranial nerve development.¹⁰ In children with Möbius syndrome, focal brainstem necrosis with calcifications has been reported, as well as capillary telangiectasia in the mesencephalon and pons.¹¹ Dooley et al.¹² observed foci of brainstem calcification in 5 of 7 children studied and believed it was secondary to prenatal brainstem ischemia. Subclavian artery supply disruption sequence occurring around 6 weeks of gestation is related to several anomalies that occur in Poland and Möbius syn-



Figure 1. Left facial palsy in the 1-month-old baby described in case report (photo to D Amram).

dromes, the same phenomenon responsible for terminal limb defects and arthrogryposis^{9,13,14}

Two factors are important in understanding the pathophysiology of Möbius syndrome. First, cranial nerves VI and VII are primarily affected. Second, Möbius syndrome results when the disruption occurs in a precise period of embryonic development, between gestational weeks 5 and 8.^{4,15} Any pathological event that disturbs circulation during this critical period will cause brainstem alterations or widespread developmental defects.⁴ A few cases of Möbius syndrome appear to be of familial occurrence, sometimes associated with karyotypic changes.⁸ Why cranial nerve nuclei VI and VII are preferentially affected remains to be fully understood. Shepard¹⁶ postulated that the embryo is particularly vulnerable at this time of gestation because of the position of cranial nuclei for cranial nerves VI and VII. Both nerves are located in the ventral part of the rhombencephalon, near plication, in a thin, dilated portion of the brain with relative lack of tissue. If flexion occurs in this area, decreased blood flow will follow.

A teratogenic cause of Möbius syndrome has been suggested by many authors.^{4,8,16-22} Mifepristone, the first medicine given in the French medical abortion protocol, has not been found to be related to teratogenicity. In several case reports, pregnancies not successfully aborted with mifepristone continued to full term with no adverse effects on the newborn.²³ However, one case mentioned anomalies (complete lack of amniotic sac; no fetal stomach, gallbladder, or urinary tract; sirenomelia) possibly associated with mifepristone administration in early pregnancy (400 mg at 5 weeks' gestation).²⁴ In contrast, use of oral or vaginal misoprostol during the first trimester of pregnancy significantly reduces uterine arterial blood

flow. Doppler resistance indices are significantly increased 60–90 minutes after misoprostol administration (200 µg orally, or 200 µg intravaginally plus 200 µg orally) to pregnant women.^{25,26}

Based on these observations and those of our case report, we propose the following schema for misoprostol teratogenicity (Figure 2).^{2,4,7,9,14} Misoprostol induces intense uterine contractions and, thus, by a mechanical action, may be responsible for a flexion in the area of cranial nerves VI and VII. This flexion, along with the position of the embryo at the time of exposure (5–8 wk gestation), could likely result in marked vulnerability of the cranial nuclei to hemorrhage and cellular death. It may also lead to the death of other cranial nuclei; hence, the occurrence of other malformations as part of the Möbius syndrome. Uterine contractions also lead to hypoperfusion, which is responsible for fetal hypoxia and ischemia, resulting in endothelial cell injury and tissular lesions. Vascular disruption is also suspected in limb anomalies, especially terminal limb malformations.

Several associations between use of misoprostol and congenital malformations with fetal ischemia have been reported, especially in countries in which medical abortion is illegal.^{3-5,17-22} Table 1^{3-5,17,21,22} details case reports of Möbius syndrome secondary to the administration of misoprostol. These reports all concern illegal use of the medication for abortion (except 1 report of its use for peptic ulcer disease, a primary use of misoprostol, alone or in combination with nonsteroidal antiinflammatory drugs). In these reports, exposure to misoprostol varied from 400 to 16,000 µg, and no relation between dose and possible teratogenic effects is apparent. For Möbius syndrome, Pastuszack et al.¹⁷ and Da Silva et al.¹⁸ reported odds ratios of

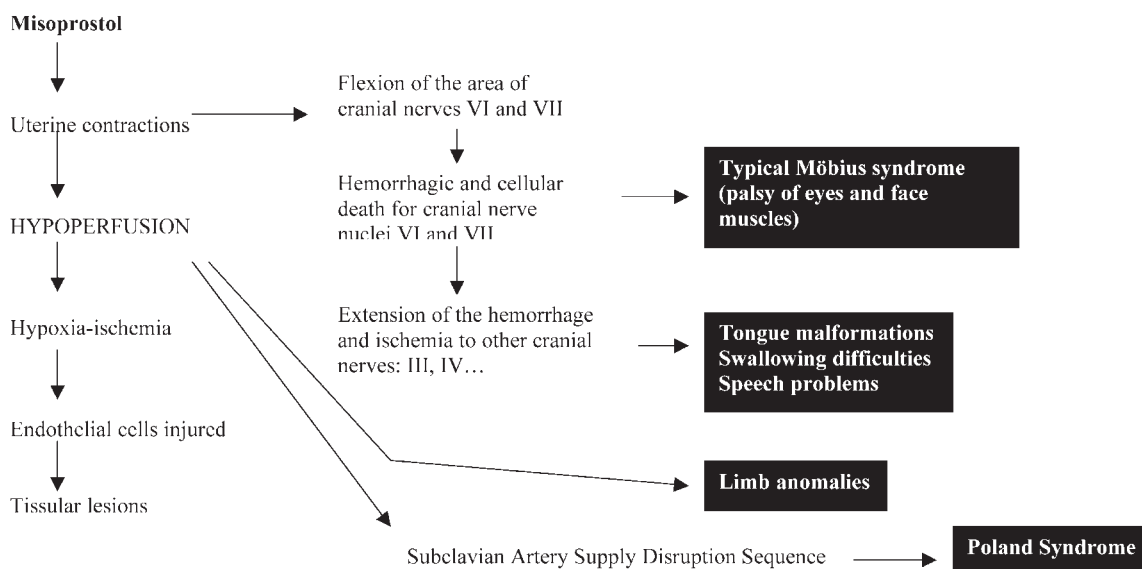


Figure 2. Proposed mechanism of misoprostol teratogenicity.^{2,4,7,9,14}

38.8 (95% CI 9.5 to 159.4) and 25.3 (95% CI 11.1 to 57.7), respectively. In support of the vascular hypothesis for Möbius syndrome, some cases have been described with other vasoconstrictor medications. Puvabanditsin et al.¹⁹ described a Poland/Möbius syndrome with brainstem calcifications that was related to multiple use of cocaine during the first trimester of pregnancy. In addition, the use of ergotamine 6 mg at 5 weeks and 4 days of gestation (day 39) was associated with uterine cramping within a few hours and bloody vaginal discharge the following day.²⁰ The baby girl who was exposed to ergotamine in utero was born at 37 weeks' gestation, with talipes deformities, facial paralysis, and tongue anomalies.

Conclusions

To our knowledge, this is the first published case report of Möbius syndrome following fetal exposure in utero to mifepristone and misoprostol according to the French protocol for elective medical abortion. To date, mifepristone does not appear to be related to an augmentation of teratogenic risk. In contrast, misoprostol can be involved in a teratogenic process. Extreme care should be given to pregnancies that continue despite misoprostol administration, especially when exposure occurs between weeks 5 and 8, a period of high embryo sensitivity to the teratogenic action of this drug. Precise ultrasonography should be performed to detect any malformations possibly related to misoprostol exposure (eg, limb defects), although it is almost impossible to detect Möbius syndrome before birth. Women considering medical abortion with the combination of mifepristone and misoprostol should be precisely counseled on the risks to their fetus if abortion failure occurs and surgical abortion is not desirable.

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Table 1. Cases of Möbius Syndrome after Misoprostol Use

Reference	Cases, N	Misoprostol Dose, µg	Use of Other Substances	Route of Administration, n	Gestational Time of Exposure, n	Associated Anomalies, n
Gonzalez (1998) ³	18	400–16,000 (mean 800)	not documented	oral, 7 oral and vaginal, 11	first mo, 4 second mo, 12 third mo, 2	hydrocephalus, 3 microcephaly, 1 brachydactyly, 1
Marques-Diaz (2003) ⁴	3	400–600	no	oral	second mo, 2 first trimester, 1	hand and foot abnormalities, 3 hydrocephalus, 1
Sanchez (2003) ⁵	1	600 + 900	not documented	oral and vaginal	first trimester	not documented
Pastuszek (1998) ¹⁷	47	842 ± 543	herbal preparations (15%) other drugs (6%)	oral, 20 vaginal, 3 oral and vaginal, 20 unknown, 4	first trimester	limb defects, 31 orofacial anomalies, 18
Gonzalez (1993) ²¹	4	600–1600 (mean 900)	no	oral, 1 oral and vaginal, 3	fourth wk, 1 second mo, 1 tenth–twelfth wk, 1 first trimester, 1	limb defects, 3
Vargas (2000) ²²	14	mean 800	herbal preparations (50%) other drugs	oral, 7 oral and vaginal, 7	majority, fifth–eighth wk of gestation	not documented

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Síndrome de Möbius en un Recién Nacido Después del Fallo de Mifepristona y Misoprostol Usados en un Aborto Electivo

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EXTRACTO

OBJETIVO: Reportar el caso de un niño que nació con el síndrome de Möbius después de ser expuesto en útero a mifepristona y misoprostol para un aborto electivo.

RESUMEN DEL CASO: Una mujer en su séptima semana de embarazo recibió 600 mg de mifepristona y, 2 días después, 400 µg de misoprostol para un aborto. Un mes después, a pesar de metrorragia importante, una examinación de ultrasonido demostró gestación continua. Después de 33 semanas y 3 días, la mujer dio a luz un niño que tenía parálisis facial del lado izquierdo, microrretrognatia, y hipotonía axial, los cuales estaban relacionados al síndrome de Möbius.

DISCUSIÓN: El síndrome de Möbius está caracterizado por parálisis de los nervios unilateral o bilateral del abducens (VI par) y (VII par) facial. Otros nervios, como por ejemplo el hipogloso (XII par), anomalías del

craneofaciales y orofaciales, y malformación de extremidades también están asociados con el síndrome de Möbius. La etiología del síndrome de Möbius permanece siendo en gran parte desconocida e implica probablemente factores múltiples. La hipótesis etiológica más probable es una interrupción en el desarrollo del sistema vascular, con isquemia transitoria, particularmente en las arterias vertebrales, e hipoxia fetal. Se ha sugerido una causa teratogénica del síndrome de Möbius. El período crítico para el desarrollo del síndrome de Möbius, después de exposición a un teratógeno, parece ser durante 5-8 semanas de gestación. Hasta la fecha, la administración solamente de mifepristona no parece inducir el síndrome de Möbius. En contraste, la administración oral o vaginal de misoprostol puede producir un aumento significativo en la resistencia de la arteria uterina medida por Doppler y puede inducir contracciones uterinas. Si estas ocurren durante el período embrionario crítico, esto puede causar flexión en el área de los nervios craneales de los pares VI y VII y una disminución en el flujo de sangre.

CONCLUSIONES: Este reporte demuestra que el uso infectivo de mifepristona y misoprostol durante el primer trimestre de embarazo esta asociado con el síndrome de Möbius y esta complicación esta principalmente asociado con la actividad de misoprostol. Mujeres con embarazos continuos después de un fallo de aborto con la administración de misoprostol deben ser informadas sobre este posible riesgo.

Traducido por Carlos da Camara

Un cas de Syndrome de Moebius chez un Nouveau-né Après Echec d'une Tentative d'IVG Médicamenteuse avec Administration de Mifépristone et de Misoprostol

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RÉSUMÉ

OBJECTIF: Il est rapporté ici un cas d'enfant né avec un syndrome de Moebius après exposition in utero à la mifepristone et au misoprostol dans le cadre de l'échec d'une interruption volontaire de grossesse.

RESUME DU CAS: Au cours de la septième semaine de grossesse, une femme a reçu 600 mg de mifepristone et, 2 jours plus tard, 400 µg de misoprostol, pour la réalisation d'une interruption volontaire de grossesse médicamenteuse. Une échographie réalisée un mois plus tard mettait en évidence une grossesse évolutive, malgré d'importantes métrorragies suite à la prise des médicaments. Après 33 semaines et 3 jours de grossesse, naissait un garçon présentant une paralysie faciale gauche, un microrétrognatisme et une hypotonie axiale, définissant un syndrome de Moebius.

DISCUSSION: Le syndrome de Moebius est caractérisé par une paralysie faciale uni-ou bilatérale, provoquée par une atteinte des nerfs crâniens abducens (VI) et facial (VII). D'autres nerfs crâniens, comme le nerf hypoglosse (XII), ainsi que des anomalies crano-et orofaciales, et des malformations au niveau des membres sont souvent associées. L'étiologie du syndrome de Moebius reste peu connue et inclue probablement de multiples facteurs. L'étiologie la plus probable est une interruption lors du développement du système vasculaire, responsable d'une ischémie temporaire, en particulier au niveau des artères vertébrales, et d'une hypoxie fœtale. Un mécanisme tératogénique a été suggéré et la période critique pour le développement d'un syndrome de Moebius se situerait entre la 5ème et la 8ème semaine de grossesse. A ce jour, la mifepristone seule n'est pas impliquée dans l'apparition d'un syndrome de Moebius. En revanche, l'utilisation par voie orale ou vaginale du misoprostol peut conduire à une augmentation significative de l'index de résistance des artères utérines mesuré par Doppler et induit des contractions utérines. Si ces phénomènes se produisent au cours de la période embryonnaire critique, ils peuvent être responsables d'une flexion dans la zone des nerfs crâniens VI et VII et d'une diminution du flux sanguin.

CONCLUSIONS: Le cas de cet enfant montre que l'utilisation de la mifepristone et du misoprostol au cours du premier trimestre de la grossesse est associée à un risque de survenue de syndrome de Moebius, principalement du à l'action du misoprostol. Les femmes dont la grossesse se poursuit après l'échec d'un avortement avec administration de misoprostol doivent être informées de ce risque.

Traduit par Marie-Andrée Bos-Thompson