

USE OF MISOPROSTOL DURING PREGNANCY AND MÖBIUS' SYNDROME
IN INFANTS

ANNE L. PASTUSZAK, M.Sc., LAVINIA SCHÜLER, M.D., Ph.D., CARLOS E. SPECK-MARTINS, M.D.,
KATIA-EDNI F.A. COELHO, M.D., SYNTHIA M. CORDELLO, M.D., FERNANDO VARGAS, M.D., DECIO BRUNONI, M.D., Ph.D.,
IDA V.D. SCHWARZ, M.D., MARIELA LARRANDABURU, M.D., HELOISA SAFATTE, M.D., VERA F.A. MELONI, M.D.,
AND GIDEON KOREN, M.D.

ABSTRACT

Background Patients with upper gastrointestinal ulceration may be treated with misoprostol, but it is not recommended for pregnant women because it may stimulate uterine contractions and cause vaginal bleeding and miscarriage. Recent data from Brazil, where misoprostol is used orally and vaginally as an abortifacient, have suggested a relation between the use of misoprostol by women in an unsuccessful attempt to terminate pregnancy and Möbius' syndrome (congenital facial paralysis) in their infants.

Methods We compared the frequency of misoprostol use during the first trimester by mothers of infants in whom Möbius' syndrome was diagnosed and mothers of infants with neural-tube defects in Brazil. All diagnoses in infants were made between January 16, 1990, and May 31, 1996, by clinical geneticists at seven hospitals who also interviewed the mothers and recorded information about the administration of misoprostol, among other data.

Results We identified 96 infants with Möbius' syndrome and matched them with 96 infants with neural-tube defects. The mean age at the time of the diagnosis of Möbius' syndrome was 16 months (range, 0.5 to 78), and the diagnosis of neural-tube defects was made within 1 week of birth in most cases. Among the mothers of the 96 infants with Möbius' syndrome, 47 (49 percent) had used misoprostol in the first trimester of pregnancy, as compared with 3 (3 percent) of the mothers of the 96 infants with neural-tube defects (odds ratio, 29.7; 95 percent confidence interval, 11.6 to 76.0). Twenty of the mothers of the infants with Möbius' syndrome had taken misoprostol only orally (odds ratio, 38.8; 95 percent confidence interval, 9.5 to 159.4), 20 had taken misoprostol both orally and vaginally, 3 had taken the drug vaginally, and 4 did not report how they took the drug.

Conclusions Attempted abortion with misoprostol is associated with an increased risk of Möbius' syndrome in infants. (N Engl J Med 1998;338:1881-5.)

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MISOPROSTOL is a synthetic prostaglandin E₁ analogue with greater anti-secretory and mucosal-protective activity than natural prostaglandins. It is used to prevent and treat gastrointestinal lesions induced by nonsteroidal antiinflammatory drugs and upper gastrointestinal ulceration. It is not recom-

mended for use during pregnancy, because it may stimulate uterine contractions and cause vaginal bleeding, which may endanger fetal survival. The combination of misoprostol and mifepristone or methotrexate has been used for the elective induction of abortion.^{1,2} In Brazil, where elective abortions are prohibited, 57 to 75 percent of women who attempt abortion use misoprostol, which can be obtained over the counter.³⁻⁵ However, misoprostol often fails to induce abortion during the first trimester,⁶ and up to 80 percent of the pregnancies in women who use this agent continue to term.

Although misoprostol has no teratogenic actions in pregnant rats⁷⁻⁹ and mice,¹⁰ there are reports of Möbius' syndrome (congenital facial paralysis, with or without limb defects) in infants whose mothers took misoprostol in an unsuccessful attempt at abortion.¹¹⁻¹⁴ In one study, in a small cohort of 20 women who used misoprostol unsuccessfully as an abortifacient during the first trimester, 3 had a second-trimester abortion, and 17 gave birth to infants without malformations.¹⁵ The purpose of our study was to compare the frequency of misoprostol use during the first trimester of pregnancy between mothers of infants with Möbius' syndrome and mothers of infants with neural-tube defects.

METHODS**Subjects**

Between January 16, 1990, and May 31, 1996, 96 infants 0.5 to 78 months of age were given a diagnosis of Möbius' syndrome by geneticists at seven hospitals in Brazil. Möbius' syndrome was defined as bilateral or unilateral facial-nerve paralysis (paralysis of

From the Motherisk Program, Hospital for Sick Children, and the Fetal Diagnosis and Treatment Centre, University of Toronto, Toronto (A.L.P., G.K.); Departamento de Genetica, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil (L.S.); Unidade de Genetica, Hospital de Clinicas de Porto Alegre, Brazil (L.S., I.V.D.S., M.L.); Setor de Genetica, Rede de Hospitais Sarah, Brasilia, Brazil (C.E.S.-M., H.S.); Setor de Genetica, Rede de Hospitais Sarah, Salvador, Brazil (K.-E.F.A.C., S.M.C.); Setor de Genetica, Hospital Universitario Gaffre-Guinle, Rio de Janeiro, Brazil (F.V.); and Disciplina de Genetica, Escola Paulista de Medicina, Universidade Federal de São Paulo, and Unidade de Citogenetica, Hospital dos Servidores Publicos do Estado de São Paulo, São Paulo, Brazil (D.B., V.F.A.M.). Address reprint requests to Dr. Pastuszak at the Fetal Diagnosis and Treatment Centre, University of Toronto, Hospital for Sick Children, 555 University Ave., Toronto, ON M5G 1X8, Canada.

Jordão C. Neto, M.D. (Disciplina de Genetica, Escola Paulista de Medicina, Universidade Federal de São Paulo, and Unidade de Citogenetica, Hospital dos Servidores Publicos do Estado de São Paulo, São Paulo, Brazil) was also an author.

cranial nerve VII), with or without other neurologic signs or malformations.¹⁶ Infants were excluded if they had muscular dystrophy, myopathy, or generalized neuropathy, Möbius' syndrome due to dominant inheritance (in a child with an affected parent), or a birth date before January 1, 1990. None of these infants were included in the report by Gonzalez et al.¹² or described in a case report. At the time of clinical diagnosis, the geneticists interviewed the mothers about their pregnancies and recorded the information in the mothers' records. Subsequently, information on maternal demographic characteristics (age and highest level of education), obstetrical and medical history, prenatal exposures (to alcohol, cigarettes, and hyperthermia), misoprostol treatment (indication, route, dose, duration, and complications), outcome of pregnancy (the infant's sex, type of delivery, gestational age at delivery, and birth weight), and the diagnosis in the infant was extracted from the records by personnel using a standardized form and sent to Toronto, where the forms were translated from Portuguese to English for data entry and analysis.

As controls, we studied 96 randomly chosen infants born during the same period who were given a diagnosis of a neural-tube defect (meningocele, meningomyelocele, anencephaly, or encephalocele) by the same clinical geneticists at the same hospitals within the first week of life. Infants with neural-tube defects due to amniotic-band sequence (disruption anomalies due to early amniotic rupture, such as syndactyly, ring constrictions, digit or limb amputations, facial clefting, encephalocele, or chest- or abdominal-wall defects) were excluded.

Statistical Analysis

The data were used to calculate a point estimate of the odds ratio and 95 percent confidence interval for Möbius' syndrome associated with misoprostol use during the first trimester of pregnancy by the test-based approach of Miettinen,¹⁷ which yields intervals slightly narrower than those calculated by Woolf's method.¹⁸ We also calculated the odds ratio and 95 percent confidence interval for misoprostol use with stratification according to the route of administration and the date of clinical diagnosis, because the Brazilian geneticists might have been biased in favor of a possible association between misoprostol and Möbius' syndrome after the publication of the article of Gonzalez et al. in 1993, which

postulated such an association.¹² Continuous data, expressed as means \pm SD, were compared with use of unpaired Student's t-tests, and categorical data were compared with use of chi-square analysis or Fisher's exact test, as appropriate.

RESULTS

The characteristics of the 96 infants with Möbius' syndrome and the 96 infants with neural-tube defects who were born at the same hospitals during the same period are shown in Table 1. The neural-tube defects included encephalocele, meningocele and meningomyelocele (each with or without hydrocephalus), and anencephaly. The mothers of the infants with neural-tube defects were older than the mothers of the infants with Möbius' syndrome. There were no differences between the two groups of mothers in educational level, gravidity, parity, number of previous miscarriages, number of previous induced abortions, rate of consanguinity with the infant's father, cigarette-smoking status, alcohol consumption, or presence or absence of hyperthermia (temperature, $\geq 38^\circ\text{C}$) in the first trimester of pregnancy (data not shown).

The numbers of male and female infants in the two groups were similar, as were their gestational ages (Table 1). More infants with neural-tube defects than with Möbius' syndrome had low birth weights (<2500 g), and they were more likely to have been delivered by cesarean section. The clinical manifestations of Möbius' syndrome, according to whether or not the infants were exposed to misoprostol in utero, are shown in Table 2. There were no significant differences in the pattern of anomalies between the exposed and nonexposed infants.

TABLE 1. CHARACTERISTICS OF INFANTS WITH MÖBIUS' SYNDROME OR NEURAL-TUBE DEFECTS.*

CHARACTERISTIC	MÖBIUS' SYNDROME (N=96)		NEURAL-TUBE DEFECTS (N=96)		P VALUE
	NO. WITH DATA	VALUE	NO. WITH DATA	VALUE	
Maternal age — yr	96	24 \pm 6	96	26 \pm 6	0.02
Maternal history of stillbirth — no. (%)	91	1 (1)	93	11 (12)	0.008
Sex — no. (%)	95		93		0.90
Male		56 (59)		53 (57)	
Female		39 (41)		40 (43)	
Type of delivery — no. (%)	63		62		0.06
Vaginal		42 (67)		30 (48)	
Cesarean		21 (33)		32 (52)	
Gestational age at delivery — wk	10	37 \pm 5	35	35 \pm 6	0.52
Timing of delivery — no. (%)	96		96		
Term (≥ 37 wk)		92 (96)		79 (82)	
Preterm (<37 wk)		4 (4)		17 (18)	
Birth weight — g	40	2945 \pm 513	40	2672 \pm 810	0.08
Low birth weight (<2500 g) — no. (%)	40	4 (10)	40	13 (32)	0.03

*The respective numbers of infants with Möbius' syndrome and infants with neural-tube defects from the different centers were as follows: 29 and 25 from Brasilia, 26 and 26 from Salvador, 18 and 22 from Rio de Janeiro, 17 and 19 from São Paulo, and 6 and 4 from Porto Alegre. Plus-minus values are means \pm SD.

TABLE 2. CLINICAL MANIFESTATIONS IN INFANTS WITH MÖBIUS' SYNDROME WHO WERE EXPOSED TO MISOPROSTOL AND THOSE WHO WERE NOT EXPOSED.

MANIFESTATION	EXPOSED	NOT	P
	(N=47)	EXPOSED (N=49)	
	no. (%)		
Bilateral facial-nerve (cranial nerve VII) paralysis	34 (72)	36 (73)	0.92
Abducens-nerve (cranial nerve VI) paralysis	39 (83)	37 (76)	0.52
Other cranial-nerve palsy	10 (21)	8 (16)	0.72
Limb defects			
All types combined	31 (66)	28 (57)	0.50
Club feet only	25 (53)	18 (37)	0.21
Limb reduction*	6 (13)	10 (20)	0.64
Orofacial anomalies	18 (38)	11 (22)	0.16
Mental retardation	26 (55)	26 (53)	0.99
Other defects	15 (32)	14 (29)	0.89

*Limb reduction was present with or without other manifestations.

Among the mothers of the 96 infants with Möbius' syndrome, 47 (49 percent) had used misoprostol in the first trimester of pregnancy, as compared with 3 (3 percent) of the mothers of the 96 infants with neural-tube defects (odds ratio, 29.7; 95 percent confidence interval, 11.6 to 76.0). When misoprostol was taken only orally (as was the case for 20 women whose infants had Möbius' syndrome), the odds ratio was 38.8 (95 percent confidence interval, 9.5 to 159.4). The values were similar for the 20 women who used misoprostol both orally and vaginally. Three women took the drug vaginally, and the route of administration was unknown in four.

Mothers of Infants with Möbius' Syndrome

Of the 47 mothers who reported misoprostol use, 46 administered it to themselves as an abortifacient and 1 used it as treatment for peptic ulcer disease. Data about the duration of use were available for 40 women. Thirty-seven of them used misoprostol for only 1 day, but one used it for 4 days, one for 6 days, and one for 10 days. In Brazil each capsule contains 200 µg of misoprostol. Information on the number of capsules taken was available for 43 women; 15 took 1 to 3 capsules, 20 took 4, 4 took 8, 1 took 5, 1 took 6, 1 took 10, and 1 took 18. The mean dose for these 47 mothers was 842±543 µg. Forty-seven percent (20 of 43) took misoprostol orally only, 20 (47 percent) used misoprostol both orally and vaginally, and 3 (7 percent) administered misoprostol vaginally only.

Thirty-three of the 49 women for whom informa-

tion was available reported vaginal bleeding after taking misoprostol (10 reported bleeding on the same day and 2 on the next day). Seven women reported abdominal cramps, seven reported no side effects, one reported loss of amniotic fluid, and one reported abdominal cramps and vaginal bleeding. Of 46 women who used misoprostol and for whom such data were available, 6 used misoprostol a second time (5 during the first trimester and 1 during the third trimester). Information about the women's use of other products intended as abortifacients during the pregnancy was available for 87 women; 13 (15 percent) had used herbal preparations, and 5 (6 percent) had used other pharmacologic means, such as acetaminophen or antibiotics.

The exact timing of prenatal exposure to misoprostol was difficult to determine in many cases, because the pregnancy history was obtained after the child's birth (sometimes two or three years later), and many women could not recall the precise dates. In 35 cases, we could assign misoprostol exposure to the first two calendar months of pregnancy. In eight cases (23 percent), exposure was determined to have occurred in the third month, and in one case in the second trimester; in the case of these women, we cannot rule out the possibility that a mistake was made in pregnancy dating or that the association between exposure and Möbius' syndrome was only casual.

Mothers of Infants with Neural-Tube Defects

Only three of the mothers of infants with neural-tube defects had used misoprostol in the first trimester with the intention of causing abortion. For one woman, no further details of misoprostol use were available; the other two had used it for one day. One woman took 800 µg orally and the second, who could not recall the dose, used it both orally and vaginally. Five of 49 mothers for whom information was recorded reported vaginal bleeding during pregnancy.

DISCUSSION

In this study of Brazilian infants, we found a strong association between Möbius' syndrome and prenatal use of misoprostol by their mothers. Because Möbius' syndrome is not recorded in current registries of birth defects in Brazil, we do not know whether its incidence has increased during the past few years. In addition, although we interviewed the mothers of 96 infants with Möbius' syndrome, we do not know how many such infants have not been seen by the geneticists in these centers.

It is biologically plausible that exposure to misoprostol might cause Möbius' syndrome. The syndrome may be due to vascular disruption of the subclavian artery during the fourth to sixth weeks of embryonic development. Environmental insults, in-

cluding failed abortion, prolonged rupture of membranes, and chorionic-villus sampling, have been implicated in its pathogenesis.^{19,20} Misoprostol exposure during the first two months of pregnancy could cause an ischemic event in the embryonic brain stem that might result in Möbius' syndrome.²¹ Two cases of maternal antenatal splenic rupture and hypotension followed by the birth of an infant with Möbius' syndrome have been reported.²² In these cases, the mothers were 8 and 14 weeks pregnant at the time of the accident. Both infants had hypoxic-ischemic brain-stem damage. Whatever the pathophysiology, our results suggest that the window of susceptibility for fetal development of Möbius' syndrome is wider than previously thought.

To avoid the problem of differential maternal recall of exposure and to reduce the variation in the quality and depth of interviews, we studied infants with neural-tube defects, which have numerous different causes, as controls. However, there are possible sources of bias in our study. Mothers in both groups might have been reluctant to report the use of misoprostol because of the legal and moral implications of using an abortifacient in Brazil. Conversely, overreporting is unlikely because there is no reason to expect that a woman would falsely state that she had used a medicine for the illegal purpose of aborting a pregnancy.

The possibility of underascertainment of misoprostol use by the mothers of the infants with neural-tube defects in relation to the mothers of infants with Möbius' syndrome should be considered. In the former group, the rate of exposure was 3 percent. This rate is similar to an estimate of the rate of misoprostol use by women delivering normal infants at term in seven public hospitals in Rio de Janeiro, Brazil.³ In that case-control study, which assessed the determinants of abortion, 6 percent of women who had wanted to terminate their pregnancies reported using misoprostol. Another 5 percent reported using a drug to produce abortion but could not recall its name. If 11 percent (instead of 3 percent) of the mothers of infants with neural-tube defects had used misoprostol, the odds ratio for the association of misoprostol use and Möbius' syndrome would have been 8.2 (95 percent confidence interval, 4.1 to 16.8), still a significant association. However, there is no reason to believe that mothers giving birth to children with neural-tube defects were more likely to deny using misoprostol than mothers of infants with Möbius' syndrome.

Our ascertainment of misoprostol exposure may also have been affected by the length of time between exposure and diagnosis. The mothers of infants with Möbius' syndrome were interviewed up to six years after the birth of their children, whereas the mothers of infants with neural-tube defects were interviewed soon after delivery. If this were a source

of bias, then the mothers of infants with neural-tube defects should have reported higher rates of misoprostol exposure than the mothers of infants with Möbius' syndrome.

Finally, the report by Gonzalez et al.¹² in 1993 of four cases of Möbius' syndrome after maternal misoprostol use may have prompted some physicians to question mothers of children with facial paralysis more thoroughly than they might have questioned mothers of children with other malformations. To correct for this potential bias, we calculated the odds ratios for cases diagnosed before 1993 and in 1993 or later. The respective odds ratios were 46.5 (95 percent confidence interval, 5.7 to 377.8) and 66.4 (95 percent confidence interval, 15.4 to 239.8), with similar rates of exposure during the two periods — 5 of 11 mothers (45 percent) and 42 of 85 mothers (49 percent). The absolute number of infants with Möbius' syndrome identified from 1990 through 1992 was small, because the two centers that contributed the majority of cases were established after 1992.

Our study strongly suggests an association between the use of misoprostol for attempted abortion and subsequent Möbius' syndrome in live-born infants, although the absolute teratogenic risk of misoprostol use is probably low.²³ Women taking misoprostol for upper gastrointestinal ulceration should be informed about the teratogenic potential of the drug and counseled to use a birth-control method that suits their lifestyle and will afford the greatest contraceptive protection. Administration of misoprostol during pregnancy should be strongly discouraged, given the drug's low efficacy and its likelihood of causing fetal malformations.

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