

# Teratogen exposure and congenital ocular abnormalities in Brazilian patients with Möbius sequence

## *Exposição à teratogênicos e anormalidades oculares congênitas em pacientes brasileiros portadores da seqüência de Möbius*

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### ABSTRACT

**Purpose:** To assess the sociodemographic profiles, teratogen exposures, and ocular congenital abnormalities in Brazilian patients with Möbius sequence.

**Method:** Forty-four patients were recruited from the Brazilian Möbius Sequence Society. This cross-section comprised 41 patients (age, mean  $\pm$  standard deviation,  $9.0 \pm 5.5$  years) who fulfilled the inclusion criteria. The parent or caregiver answered a questionnaire regarding sociodemographic data and pregnancy history. Patients underwent ophthalmological assessments. They were subdivided into groups according to misoprostol exposure during pregnancy, and the two groups were compared.

**Results:** Mothers/caregivers reported unplanned pregnancies in 36 (88%) cases. Of these, 19 (53%) used misoprostol during their first trimesters. A stable marital status tended to be more frequent in the unexposed group ( $P=0.051$ ). Incomplete elementary school education was reported by two (11%) mothers in the exposed group and by three (14%) mothers in the unexposed group ( $P=0.538$ ). The mothers' gestational exposures to cocaine, marijuana, alcohol, and cigarettes were similar in both groups ( $P=0.297$ ,  $P=0.297$ ,  $P=0.428$ , and  $P=0.444$ , respectively). One (5%) case of Rubella infection during pregnancy was found in the unexposed group. The main malformations in the exposed and unexposed groups were the following: strabismus (72% and 77%, respectively), lack of emotional tearing (47% and 36%, respectively), and lagophthalmos (32% and 41%, respectively).

**Conclusions:** Stable marital statuses tended to be more frequent among mothers that did not take misoprostol during pregnancy. Exposures to other teratogens and the main ocular abnormalities were similar in both groups.

**Keywords:** Möbius syndrome/physiopathology; Teratogens; Congenital abnormalities/etiology; Misoprostol/adverse effects; Pregnancy complications

### RESUMO

**Objetivo:** Descrever o perfil sócio demográfico, exposição à teratogênicos e anormalidades oculares congênitas em pacientes brasileiros portadores da seqüência de Möbius.

**Método:** Quarenta e quatro pacientes recrutados da Sociedade Brasileira de Seqüência de Möbius foram examinados. Este estudo transversal incluiu 41 pacientes que preencheram os critérios de inclusão do estudo (média das idades:  $9,0 \pm 5,5$  anos). Mãe/responsável dos pacientes responderam a um questionário sobre perfil sócio demográfico e história gestacional. Foi realizado exame oftalmológico de todos os pacientes. Eles foram agrupados em dois grupos de acordo com a exposição ao misoprostol durante a gestação e seus dados foram comparados.

**Resultados:** Mães/responsáveis referiram gravidez indesejada em 36 (88%) dos casos. Destas, 19 (53%) fizeram uso de misoprostol no primeiro trimestre de gestação. Houve uma tendência do grupo de mães não expostas ao misoprostol de terem um estado civil estável ( $P=0,051$ ). Duas (11%) mães do grupo de expostas ao misoprostol relataram primeiro grau incompleto e três (14%) do grupo de não expostas ( $P=0,538$ ). A exposição das mães à cocaína, maconha, álcool e cigarro foi similar em ambos os grupos ( $P=0,297$ ,  $P=0,297$ ,  $P=0,428$ ,  $P=0,444$ , respectivamente). Houve um caso (5%) de Rubéola no grupo de mães não expostas. As principais malformações associadas nos pacientes expostos e não expostos foram, respectivamente: estrabismo (72% e 77%), e diminuição da lágrima emocional (47% e 36%) e lagofthalmia (32% and 41%).

**Conclusão:** Estado civil estável foi mais frequente em mães que não fizeram uso de misoprostol durante a gestação. Exposição à outros teratogênicos e malformações oculares tiveram distribuição semelhante em ambos os grupos.

**Descritores:** Síndrome de Möbius/fisiopatologia; Teratogênicos; Anormalidades congênicas/etiologia; Misoprostol/efeitos adversos; Complicações na gravidez

### INTRODUCTION

Congenital anomalies are considered increasingly important in public health due to the associated high morbidity and mortality rates<sup>(1)</sup>. In most cases, the cause is presumably multifactorial<sup>(2-4)</sup>. Teratogens are associated with 2% to 10% of cases<sup>(2,3)</sup>. Sociocultural factors in developing countries favor increased exposures to teratogens<sup>(5,6)</sup>.

The use of abortive medications, such as misoprostol and certain herbal teas, are common in these countries<sup>(7,8)</sup> and are associated with congenital anomalies<sup>(7,9-11)</sup>.

Möbius sequence is a rare congenital disorder with an estimated prevalence in the general population of 1:500 to 1:5,000 newborns<sup>(7,12)</sup>. Although most cases are sporadic and some have been re-

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lated to genetic mutations<sup>(13-15)</sup>, intrauterine exposure to misoprostol and other teratogens has been associated with its occurrence<sup>(16-21)</sup>. The aim of the present study was to report the sociodemographic profiles, teratogen exposures, and congenital abnormalities in patients with Möbius sequence.

## METHODS

This cross-sectional study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee on Human Research of the Santa Casa de Misericórdia of São Paulo. Each patient and/or caregiver gave written informed consent before being included in the study. The data used in this study were collected by a multidisciplinary team from several institutions from North America (University of Illinois, Chicago) and Brazil [Altino Ventura Foundation and Hospital de Olhos de Pernambuco in Recife; as well as College of Medical Sciences of Santa Casa of São Paulo; Federal University of São Paulo (UNIFESP); University of São Paulo (USP); Disabled Children Assistance Association (AACD); Epileptic Children Psychiatry Assistance Group; and Cema Institute, in São Paulo.

The Brazilian Möbius Syndrome Society is an association in southeastern Brazil for patients with Möbius sequence. The patients were recruited by telephone, email, or fax, and 44 patients were assessed in two consecutive days at the Department of Ophthalmology of the College of Medical Science of Santa Casa of São Paulo. A standardized questionnaire was used to collect the sociodemographic data and the pregnancy histories from the parents or caregivers. The following main variables were assessed: expected/unexpected pregnancy, mother's marital status at the time of the pregnancy, education (maximum education achieved by the mother at the time of pregnancy), symptoms during pregnancy, and exposure to medications, such as misoprostol and/or other teratogens.

The inclusion criteria were uni-orbi-lateral congenital sixth and seventh nerve paralysis<sup>(7)</sup>. Poland-Möbius sequence was defined as the association of Möbius sequence with unilateral aplasia of the pectoralis major muscle and an ipsilateral hand anomaly<sup>(18)</sup>.

The patients<sup>(13)</sup> underwent a multidisciplinary assessment that consisted of clinical, ophthalmological, neurological, genetic, psychiatric, psychological, and dental examinations. In the present study, we describe the mothers' sociodemographic data and the patients' congenital ocular malformations (strabismus, lagophthalmos, aberrant tearing, and lack of emotional tearing).

The ophthalmological assessment included evaluations of eye alignment, movement limitations, eyelid positions, and lacrimal alterations. The strabismus was classified as convergent (esotropia), divergent (exotropia), or vertical (hyper- or hypo-tropia). Congenital aberrant tearing was considered in cases presenting paradoxical gustolacrimal tearing (tearing when eating or crocodile tears), lack of emotional (psychic) lacrimation, or unusual late onset of tearing<sup>(22)</sup>. Late onset of tearing was defined in this study as tearing that started after the patient was 1 year old<sup>(23-25)</sup>.

For comparison, patients were divided into two groups according to misoprostol exposure during pregnancy. Statistical analyses were performed with SPSS for Windows (version 12.0, IBM Corporation, Armonk, NY, USA). Continuous data were expressed by mean  $\pm$  standard deviation (SD), and categorical data were expressed as percentages. Chi-square and Student's *t*-tests were used to compare the groups that were exposed or not exposed to misoprostol or to other teratogens. *P* values less than 0.05 were considered statistically significant.

## RESULTS

Forty-one patients met the inclusion criteria and were enrolled in the study. Their mean  $\pm$  standard deviation (SD) age was  $9.0 \pm 5.5$  years (range, 2 to 22 years), and 24 (59%) were male. Nineteen (46%) patients had a history of intrauterine misoprostol exposure. Of these,

13 (68.4%) patients were male, and the mean  $\pm$  SD age of the group was  $9.1 \pm 4.8$  (range, 3 to 22 years). Similarly, 11 (50%) of the 22 patients with no history of misoprostol exposure during pregnancy were male ( $P=0.381$ ), and the mean  $\pm$  SD age of the group was  $8.9 \pm 6.1$  (range, 2 to 21 years).

Thirty-five (85%) mothers denied previous abortions, three (7%) reported a previous induced abortion, and three (7%) had a previous miscarriage. Thirty-six (88%) mothers reported that the pregnancy with their son/daughter who was included in the study was not planned. Of these, 20 (56%) admitted to thinking about abortion, and 19 (53%) used misoprostol as an abortifacient during the first trimester. Eleven (84%) of these 19 women used oral and vaginal pills, and two (15%) only took oral pills. Six (32%) caregivers did not know which misoprostol route of administration was used by the mother nor the number of pills taken. The average  $\pm$  SD amount of pills administered orally was  $2.2 \pm 0.5$  pills (range, 1-8 pills), and the average  $\pm$  SD administered vaginally was  $2.1 \pm 0.3$  pills (range, 1-4 pills). The average  $\pm$  SD time of administration after fertilization was  $7.0 \pm 1.2$  weeks (range, 2-14 weeks). After misoprostol administration, five (39%) mothers had cramps, and four (31%) presented bleeding, although none were hospitalized.

The mothers' mean  $\pm$  SD age at the time of pregnancy was  $24.3 \pm 4.9$  years (range, 16 to 35 years). The mean  $\pm$  SD age of the mothers who used misoprostol was  $23.5 \pm 4.7$  years (range, 17 to 33 years), and that of the mothers that did not use the drug was  $25.0 \pm 5.2$  years (range, 16 to 35;  $P=0.351$ ). A stable marital status was reported by four (25%) of the mothers that used misoprostol and by 13 (62%) of the mothers that did not use misoprostol ( $P=0.051$ ) (Table 1).

The mothers' highest educational levels at the time of pregnancy in both groups were not significantly different ( $P=0.538$ ) (Table 2).

Thirty-four (87%) mothers reported specific symptoms during their pregnancy. The main symptoms were nausea (56%), heartburn (59%), and vomiting (46%) (Table 3).

Twenty-three (56%) of the 41 mothers in the study were exposed to a teratogen during pregnancy; four (10%) were from the unexposed to misoprostol group, and 19 (46%) were from the exposed group. In the exposed group, four (21%) were associated with other teratogen(s) during pregnancy. In two (5%) cases, the mothers used misoprostol, cocaine, cigarettes, and marijuana. Nevertheless, the distributions of teratogens (rubella, cocaine, marijuana, cigarettes, and alcohol) were similar in both groups ( $P=0.537$ ,  $P=0.209$ ,  $P=0.209$ ,  $P=0.444$ , and  $P=0.428$ , respectively) (Table 4).

In all 41 patients, the main congenital malformations that were found were strabismus, lack of emotional tearing, and lagophthalmos, with similar distributions between the two groups ( $P=0.387$ ,  $P=0.693$ , and  $P=0.769$ , respectively) (Table 4). Of the patients with strabismus, 24 (80%) had esotropia. One (5%) patient in the exposed group presented Duane syndrome, and another case (5%) presented esotropia that was associated with Poland-Möbius sequence. This last patient had been previously treated for a corneal ulcer. Two (9%) of the unexposed patients presented concomitant third nerve palsy and exotropia.

There was aberrant tearing when eating (crocodile tears) in 12 (29%) patients from both groups, with five (42%) unilateral and seven (58%) bilateral. The absence of emotional tears was seen in 17 (42%) patients, and late-onset tearing was seen in 13 (33%). An increased pattern of spontaneous tearing was reported in seven (17%) patients from both groups.

## DISCUSSION

Teratogens are factors that are external to the fetal genome that induce structural and functional disturbances during prenatal development. External factors, including medications, are responsible for 5% of congenital malformations<sup>(1,6,26)</sup>. In unexpected pregnancies, the risk of exposure to teratogens is higher<sup>(2,4)</sup>. In North America, 50% of all

**Table 1. Sociodemographic profiles of the mothers of patients with Möbius sequence**

	Misoprostol exposure		Total (n=41)	p value
	Yes (n=19)	No (n=22)		
	n (%)	n (%)	n (%)	
Age at pregnancy (years)	18 (100)*	21 (100)*	39 (100)	0.351
16-20	4 ( 22)	5 ( 24)	9 ( 23)	
21-25	9 ( 50)	6 ( 29)	15 ( 38)	
26-30	4 ( 22)	7 ( 33)	11 ( 28)	
31-35	1 ( 6)	3 ( 14)	4 ( 10)	
Marital status	17 (100)†	21 (100)*	38 (100)	0.051
Single/divorced	13 ( 76)	8 ( 38)	21 ( 55)	
Married	3 ( 18)	11 ( 52)	14 ( 37)	
Stable union	1 ( 6)	2 ( 10)	3 ( 8)	
Education*	18 (100)*	21 (100)	39 (100)	0.538
Illiterate	0 ( 0)	0 ( 0)	0 ( 0)	
Incomplete elementary	2 ( 11)	3 ( 14)	5 ( 13)	
Complete elementary	3 ( 17)	2 ( 9)	5 ( 13)	
Complete secondary	8 ( 44)	10 ( 48)	18 ( 46)	
Complete university	5 ( 28)	6 ( 29)	11 ( 28)	

\*= data were not known for one mother; †= data were not known for two mothers.

**Table 2. Gestational signs and symptoms reported by the mothers of patients with Möbius sequence**

Symptoms	Misoprostol exposure		p value
	Yes (n=19)	No (n=22)	
	n (%)	n (%)	
Bleeding	9 (56)	7 ( 44)	0.233
Contractions/pain	8 (62)	5 ( 39)	0.368
Nausea	9 (41)	13 ( 59)	0.336
Heartburn	10 (44)	13 ( 57)	0.469
Vomiting	9 (50)	9 ( 50)	0.451
Headache	6 (38)	10 ( 63)	0.283
Fever	4 (80)	1 ( 20)	-
Cutaneous rash	0 ( 0)	1 (100)	-

pregnancies are unexpected or unplanned, and, in Brazil, a previous study reported that 48% of pregnant women between the ages of 18 and 39 use abortifacient drugs<sup>(3,27)</sup>. Misoprostol is the main method (94%) used to induce illegal abortions among adolescents in the State of Piauí (northeastern Brazil), and this drug was associated with herbal tea in one case<sup>(11)</sup>. In the current study, the majority of mothers (90.2%) of patients with Möbius sequence reported an unplanned pregnancy. Of these, 48.8% considered terminating the pregnancy, and 46.3% used misoprostol as an abortifacient drug. Two patients used misoprostol with herbal tea to induce abortion. Herbal tea was used by one mother in the unexposed group.

Misoprostol is a synthetic analog of prostaglandin E<sub>1</sub> and is used in 72 countries<sup>(7,10,28)</sup>. It is approved by the Food and Drug Administration for use to prevent and treat gastroduodenal ulcers that are induced by nonsteroidal anti-inflammatories<sup>(3,13)</sup>. The use of misoprostol as an abortifacient in countries where abortion is illegal is common because of its low cost, easy administration, quick absorption, and few side effects<sup>(7,10,28)</sup>. Fonseca et al.<sup>(8)</sup> reported the use of misoprostol in 66% of 2,084 women that attempted to induce an abortion. In Brazil, as in other Latin American countries, misoprostol is the main drug

used for abortions obtained through the black market<sup>(7,8,19,29)</sup>. The illegal commerce of misoprostol favors drug adulteration and increases the risk of subdosage, thus compromising the drug's efficacy<sup>(11,29)</sup>.

It is very challenging to identify the specific teratogen that is responsible for a congenital abnormality, and women are frequently exposed to more than one teratogen during pregnancy<sup>(3,5)</sup>. In addition, in more than 50% of cases, the environmental agent that caused a fetal anomaly is not identified<sup>(3)</sup>. Misoprostol, alcohol, cigarettes, marijuana, cocaine, and rubella have been associated with Möbius sequence<sup>(7,10,13,16-18,20,21,29,30)</sup>. In the present study, teratogens could be identified in most cases (56%), and 9.8% of the mothers were exposed to more than one teratogen. Furthermore, an isolated rubella infection during pregnancy was reported by one of the mothers.

A previous study of patients with Möbius sequence reported a male: female ratio of 1.3:1, which was similar to the results of our study<sup>(31)</sup>. In the northeastern region of Brazil, the mothers of children with Möbius sequence took 600 to 2,800 µg of misoprostol between the fourth and sixth postfertilization week<sup>(7)</sup>. In the present study, the mothers of children with Möbius sequence in the southeastern region of Brazil reported that they took 400 µg to 2,400 µg of misoprostol between the second and fourteenth postfertilization week.

In previous studies, the profiles of mothers of children with Möbius sequence that used misoprostol included the following characteristics: young age, low income, lower level of education, unstable marital status, and precarious access to the public health system<sup>(7,10,31)</sup>. The results of the present study agreed with these previous findings; the mothers that used misoprostol were generally younger and single or divorced. Conversely, the percentages of mothers with low education were similar in both groups.

The main symptoms that were reported by the mothers that used misoprostol during pregnancy were cramps and bleeding, which are related to the increased uterine muscle contractions induced by misoprostol<sup>(20)</sup>. The main recreational drugs used by these mothers were cigarettes and alcohol, although there were cases of marijuana and cocaine use. In contrast, another study of patients with Möbius sequence in northeastern Brazil reported that no cases were exposed to recreational drugs, cigarettes, alcohol, or rubella<sup>(7,31)</sup>. Brazil is a continental country with sociodemographic and regional differences that possibly justify this discrepancy. Even in developed countries

**Table 3. Exposure to other teratogens during pregnancy as reported by the mothers of patients with Möbius sequence**

Other teratogens	Misoprostol exposure		Total (n=41)	p value
	Yes (n=19) n (%)	No (n=22) n (%)		
Rubella	0 ( 0)	1 (5)	1 ( 4)	0.537
Cocaine	2 (11)	0 (0)	2 ( 5)	0.209
Marijuana	2 (11)	0 (0)	2 ( 5)	0.209
Cigarettes*	2 (11)	1 (5)	3 ( 7)	0.444
Alcohol	3 (16)	2 (9)	5 (12)	0.428

\*= one or more pack of cigarettes during pregnancy.

**Table 4. Congenital ocular malformation distribution according to misoprostol exposure during pregnancy**

Variables	Misoprostol exposure		Total	p value
	Yes (n=19) n (%)	No (n=22) n (%)	(n=41) n (%)	
Strabismus	13 (72)*	17 (77)	30 (75)	0.387
XT	2 (15)	3 (18)	5 (17)	
ET	11 (85)	13 (76)	24 (80)	
HT	0 ( 0)	1 ( 6)	1 ( 3)	
Lagophthalmos	6 (32)	9 (41)	15 (37)	0.769
Late-onset tearing	7 (37)	6 (29)*	13 (33)	0.374
Aberrant tears (crocodile tears)	7 (37)	5 (23)	12 (29)	0.518
OU	4 (57)	3 (60)	7 (58)	
OD	1 (14)	1 (20)	2 (17)	
OS	2 (29)	1 (20)	3 (25)	
Lack of emotional tearing	9 (47)	8 (36)	17 (42)	0.693
OU	4 (44)	6 (75)	10 (59)	
OD	3 (33)	0 ( 0)	3 (18)	
OS	2 (22)	2 (25)	4 (23)	

\*= data is not known for one Möbius patient.

XT= exotropia; ET= esotropia; HT= hypertropia; OD= right eye; OS, left eye; OU= both eyes.

with better prenatal care, the lack of knowledge about drugs' effects (therapeutic and recreational) is still responsible for several fetal malformations<sup>(3,5)</sup>.

Maternal exposure to misoprostol during organogenesis (first trimester) does not induce abortion in most cases, but it is frequently associated with the appearance of congenital anomalies, such as skullcap, cranial nerve and limb defects, arthrogryposis, facial anomalies, and Möbius sequence<sup>(6,7,10)</sup>. The findings of the present study corroborated with previous studies that reported ocular motility defects, palpebral ptosis, aberrant tearing, corneal opacification, refractive errors, and amblyopia as the main ocular findings in misoprostol-exposed patients during pregnancy<sup>(7,27,32,33)</sup>.

The most common eye motility pattern in patients with Möbius sequence is horizontal gaze paresis that is usually associated with marked abduction limitations and variable adduction deficits<sup>(32,33)</sup>. In the present series, strabismus was observed in 73.2%, and the most frequent form was esotropia (80%). This finding corroborated those of another study that found strabismus in 71.7% and 60.0% and esotropia in 39.1% and 40.0% of Brazilian and Italian cases, respectively<sup>(31)</sup>.

The presence of anomalous tearing is in accordance with the theory of focal (nuclear) damage in the lower brainstem during early embryogenesis. In our study, the incidence of aberrant tearing was

29%<sup>(22)</sup>. Prior investigations have reported this same symptom in patients with Möbius sequence in Northeastern Brazil and Italy in 45% and 17.9% of children, respectively<sup>(13,22)</sup>. Lagophthalmos was also found in more than one-third of the individuals with Möbius sequence who were assessed in the present study, and this was a higher percentage than the percentage described in a previous study (14.3%)<sup>(32)</sup>.

The main limitations of the current study were the sample size and the low prevalence of target outcomes due to Möbius sequence being a rare disorder. However, investigations of these children are highly relevant for a better understanding of specific risk factors because there is still much unknown concerning its complex etiology. This kind of study may provide insights to better plan preventive policies that have been shown to be effective in other contexts.

In summary, although there were no statistically significant differences in the studied variables between the groups, stable marital status tended to be more frequent among mothers that did not take misoprostol during pregnancy. The exposure to teratogens during pregnancy and associated ocular malformations were found in the majority of cases, and there were similar distributions of these variables in both groups. This study highlighted the importance of prenatal care as a preventive factor for Möbius sequence, which has significant implications for both public health and the patients' families.

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