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Misoprostol and teratogenicity: Reviewing the evidence

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Report of a Meeting

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Background

Misoprostol, a prostaglandin E1 analog, is currently marketed by Pharmacia Corporation as Cytotec® for the prevention and treatment of gastric ulcers. The drug is inexpensive and is registered for use in over 80 countries. Many scientific articles have been published that show the preparation to be safe and effective for various reproductive health indications, including cervical softening and early pregnancy termination. Owing to the extensive body of published literature on these indications, misoprostol is now widely used for several reproductive health indications and has the potential to improve the lives of women worldwide.

The abortifacient properties of misoprostol are well known to medical professionals and frequently to the public. Because the drug is available at low cost, many women have opted for self-administration of the method to terminate their pregnancies. The pharmaceutical industry, feminist groups, and the public health community have raised the concern that if such an abortion attempt fails and the pregnancy results in a live birth, exposure of the fetus to misoprostol *in utero* could increase the risk of birth anomalies. The most extensively documented accounts of self-medication with misoprostol for induced abortion have come from Brazil. The case of Brazil therefore provides a unique opportunity for studying the potential teratogenicity of misoprostol.

The case of Brazil

Abortion is permitted in Brazil only under limited circumstances (to save a woman's life or in the case of rape), and, consequently, clandestine abortion is common. In 1991 an estimated 1,433,350 abortions occurred, equaling a rate of 36.5 abortions per 1,000 women of reproductive age (15–49 years).[1] Despite legal restrictions, Brazilian women average 1.3 abortions by the age of 50.[1] In 1986 Cytotec® was approved in Brazil for the treatment of gastric ulcers and was frequently available without prescription directly from pharmacies. Use of the drug became widespread not only for its gastrointestinal indications but also for pregnancy termination. According to a survey conducted in seven hospitals in Rio de Janeiro in 1991, approximately 57% of women admitted to hospitals with incomplete abortion reported having used misoprostol.[2] In Recife, use of the drug for pregnancy termination was associated with reductions in abortion morbidity.[3] Yet two years after misoprostol's approval, countrywide campaigns arose to urge the federal government to withdraw Cytotec® from pharmacies or to restrict its sales to medical prescription only. In response, several state governments began to limit its availability. In May 1991 authorities in Rio de Janeiro restricted the use of misoprostol to hospitals only. In July the state of Ceara imposed a total ban that currently remains in effect. That same month, the federal Ministry of Health instituted new regulations that misoprostol could only be obtained by medical prescription and must be dispensed at official drugstores.[4]

Simultaneously, concerns about the medical safety of misoprostol emerged in early 1991 when the first cases of fetal anomalies associated with misoprostol use were reported in Ceara.[5,6] Because estimates suggested that 5–10% of women exposed to misoprostol carried their pregnancies to term, the risks of teratogenicity after failed abortion and continuing pregnancy were perceived to be high. As a result, ongoing surveillance efforts (i.e., the Latin American

Collaborative Study of Congenital Malformations and the Teratogen Information Service) focused on fetal defects associated with misoprostol use. In addition, anecdotal reports of anomalies among infants exposed *in utero* began to appear in the literature[7–11] and, subsequently, more formal epidemiological studies were conducted.[12–15]

Product labeling for teratogenicity

In 1979 the U.S. Food and Drug Administration (FDA) developed a therapeutic guideline on the use of agents during pregnancy. The purpose of the guideline is to provide physicians with a means of assessing the risk to a fetus from use of a particular agent by a pregnant woman. The guideline consists of five ratings:

A: Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.

B: No evidence of risk in humans. Animal findings show risk, but human findings do not show risk; or, if no adequate human studies have been completed, animal findings are negative.

C: Risk cannot be ruled out. Human studies have not been conducted, and animal studies are either positive for fetal risk or are absent as well; however, potential benefits may justify the potential risk.

D: Positive evidence of risk. Investigational or postmarketing data show risk to the fetus; nevertheless, potential benefits may outweigh potential risks.

X: Contraindicated in pregnancy. Animal or human studies or investigational or postmarketing reports show risk to the fetus, which clearly outweighs any possible benefit.

Risk to the fetus in this schema entails *any* type of harm, not solely the specific risk of congenital anomalies. The rating of misoprostol is X, and therefore its listing as contraindicated in pregnancy is based on misoprostol's known abortifacient properties. Teratogenicity was not a determinant of the rating in the original registration in the United States. In 1994 the Teratology Society concluded that the 1979 ratings were not useful for therapeutic guidance and should be eliminated from drug labels. Instead, the society recommended including wording on drug labels that interpreted the available data on the developmental toxicity of the drug and provided estimates of the drug's teratogenic risk.[16]

In April 2002 the label for misoprostol was changed to highlight the distinction between risks to the well-being of the fetus generally and teratogenicity specifically. While the label clearly warns that women should be advised of the abortifacient property of misoprostol and cautioned not to give the drug to others, it also states that although congenital anomalies have been associated with fetal exposure to the drug, a teratogenic mechanism has not been demonstrated. It notes that there have been reports of anomalies (including skull defects, cranial nerve palsies, facial malformations, and limb defects) after exposure *in utero* to misoprostol but also states that the drug "is not fetotoxic or teratogenic in rats and rabbits at doses 625 and 63 times the human dose, respectively."[17]

Evaluating the Teratogenicity of Misoprostol

On 22 May 2002, the Population Council convened a small group of experts from the fields of embryology, obstetrics and gynecology, epidemiology, teratology, physiology, and drug development to discuss the possible teratogenic effects of misoprostol. In a daylong meeting, participants reviewed current embryologic and epidemiological evidence and identified relevant policy implications and future research needs.

To formulate a paradigm for evaluating misoprostol as a teratogenic agent, criteria for establishing human teratogenicity of an agent were reviewed[18,19] and integrated into the following list for discussion:*

1. Teratogenicity in animals
2. Careful delineation of clinical case reports
3. Recognizable pattern of anomalies
4. Proven exposure to agent at critical time(s) in development
5. Biological plausibility
6. Substantially and statistically higher prevalence of anomalies in exposed versus nonexposed fetuses
7. Consistency between epidemiological studies
8. Increased incidence of anomalies in a population after introduction of the agent

Participants applied the above eight criteria to the available evidence on misoprostol in order to assess the likelihood that the drug could be teratogenic.

Criterion 1: Teratogenicity in animals

The manufacturer of misoprostol has stated, after considerable testing in rat and rabbit models, that there has been no association of misoprostol with birth anomalies.[20] A review of the scientific literature identified only one study that assessed the embryotoxicity of misoprostol in animal models. It found a statistical association between misoprostol and malformations.[21] Nonetheless, such an association does not establish that fetal defects will occur in humans following exposure to misoprostol *in utero*, as animal models of teratogenicity have limited value in predicting human teratogenicity. Case reports and epidemiological studies documenting human exposure provide stronger evidence than animal models and speak to the need for epidemiological studies, if none exist.

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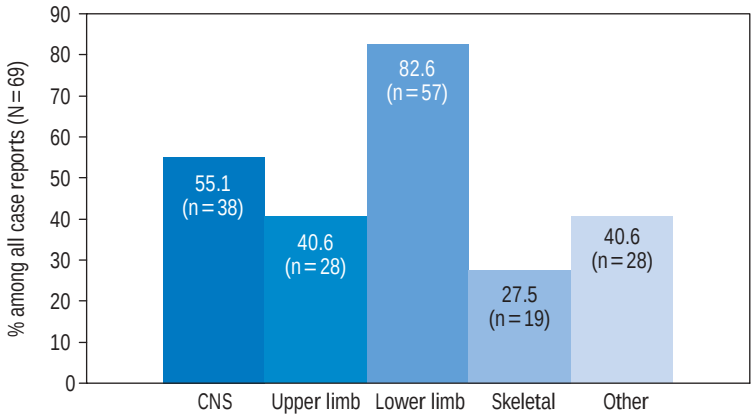
* Criteria 2, 4, and 7 are essential; other criteria are helpful but not essential.

Criterion 2: Careful delineation of clinical case reports

An electronic search using PubMed and the search terms “misoprostol,” “prostaglandin,” “birth defects,” “birth anomalies,” “congenital anomalies,” and “teratogenicity” produced six articles summarizing 69 case reports of congenital defects associated with misoprostol use during gestation.[7–11,22] Nearly all of the reports (97.1%, n=67) were from Brazil. One case (from the United States) documented congenital defects in a stillbirth. In only one case (from South Africa) was the use of misoprostol medically supervised and recorded. All other cases appear to be reports by patients of self-prescribed, self-administered, and nonvalidated use.

Over 35 different anomalies were reported and can be categorized by organ group (Figure 1). Lower limb defects, the most commonly described type, were reported in four-fifths (82.6%, n=57) of the total cases. Over half of the cases (55.1%, n=38) exhibited anomalies of the central nervous system, while two-fifths (40.6%, n=28) and one-quarter (27.5%, n=19) presented with upper limb and skeletal anomalies, respectively. Two-fifths (40.6%, n=28) of the cases reported other anomalies, such as defects of the genitalia, eyes, or palate. Additionally, there were 17 reports of limb anomalies without specification of the limb. These defects, therefore, could not be included in the above frequency descriptions.

Figure 1. Types of anomalies



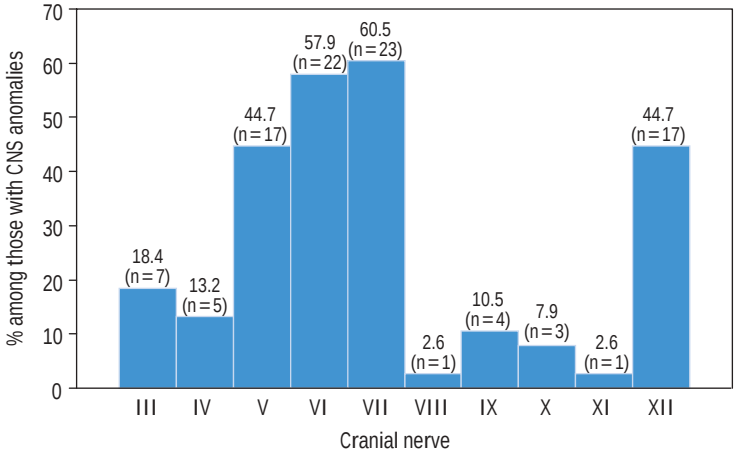
Lower limb anomalies. Among cases with lower limb anomalies (n=57), the most common anomaly reported was equinovarus (clubfoot) (80.7%, n=46) (Table 1). One-sixth of cases (15.8%, n=9) had meromelia (partial absence of a limb), and one-seventh had arthrogryposis (constriction of the joints) (14.0%, n=8). There were no cases of amelia (total absence of a limb).

Central nervous system anomalies. The most common defects among cases with central nervous system defects (n=38) involved the cranial nerves (Figure 2). Anomalies were reported in cranial nerves III–XII with the majority relating to cranial nerves VI (57.9%, n=22) and VII (60.5%, n=23). Cranial nerves V and XII were next most commonly affected, in less than half of cases (44.7%, n=17).

Table 1. Lower limb anomalies (n=57)

	%	n
Equinovarus	80.7	46
Meromelia	15.8	9
Arthrogryposis	14.0	8
Hip dislocation	10.5	6
Amniotic band/constriction ring	8.8	5
Syndactyly	8.8	5
Nail hypoplasia/agenesis	7.0	4
Brachydactyly	1.8	1

Figure 2. Cranial nerve anomalies (n=38)



Many of the cases with central nervous system anomalies were noted to have some or all of the features of Möbius syndrome. Möbius syndrome is a rare condition characterized by the loss of function of the motor cranial nerves and is said to be associated with fetal misoprostol exposure. Approximately 300 cases of Möbius syndrome have been identified in the medical literature, but its prevalence and incidence are unknown. An estimated 2% of cases are believed to have genetic causes.* Precise definition and diagnostic criteria vary in the medical literature; however, the syndrome is commonly associated with congenital facial diplegia (paralysis on both sides of the face). Quite often, it is accompanied by congenital limb abnormalities.[23]

In general, cranial nerves VI–XII (with the exception of cranial nerve VIII) are believed to be involved in Möbius syndrome. Cranial nerve VII is involved in all reported cases, while cranial nerve VI appears to be involved in about three-quarters. Cranial nerve XII is involved in a smaller proportion of cases and, even more rarely, cranial nerves III and IV are involved.[23]

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* The pathophysiology of Möbius syndrome remains unclear. Theories of vascular etiology have received substantial attention. One theory states that the disruption of blood flow in the basilar artery or the premature regression of the primitive trigeminal arteries is involved. A second theory postulates that the disruption of the subclavian artery is the cause. The frequent association of limb abnormalities with Möbius syndrome suggests that normal morphogenesis is somehow disrupted. This disruption most likely occurs during the fourth through the eighth weeks of gestation, the critical development period for the limbs.[23]

Table 2. Upper limb anomalies (n=28)

	%	n
Meromelia	46.4	13
Syndactyly	21.4	6
Amniotic band/constriction ring	17.9	5
Arthrogryposis	17.9	5
Nail hypoplasia/agenesis	14.3	4
Brachydactyly	7.1	2
Polydactyly	3.6	1

Of the 38 cases of central nervous system anomalies, only three (7.9%) were diagnosed as Möbius syndrome; however, among the 23 case reports of a cranial nerve VII anomaly, the vast majority also had an anomaly of cranial nerve VI (91.3%, n=21) and cranial nerve XII (69.6%, n=16). Of the 24 case reports with an anomaly of cranial nerve VI, VII, or XII, 70.8% (n=17) demonstrated defects of all three nerves. Additionally, the concurrent anomalies of cranial nerves VI and VII were positively associated with upper limb anomalies ($p<0.004$, N=69) but not with lower limb anomalies ($p<0.352$, N=69).

Upper limb anomalies. Close to half of cases with upper limb anomalies (n=28) presented with meromelia (46.4%, n=13) (Table 2). Twelve of the thirteen reports of meromelia consisted of agenesis or absence of the phalanges. One-fifth of cases (21.4%, n=6) exhibited syndactyly (webbing of fingers), and a similar number of reports indicated amniotic band/constriction ring and arthrogryposis (constriction of the joints) (each 17.9%, n=5). There were no cases of amelia.

Criterion 3: Recognizable pattern of anomalies

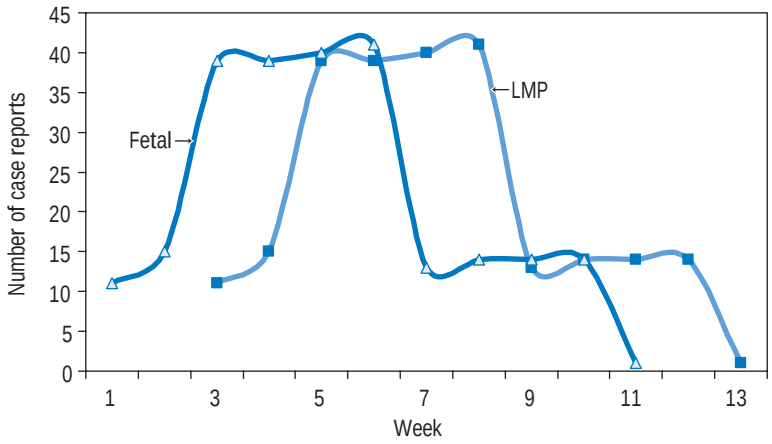
Almost all of the reported anomalies appear to fall into one of a few groupings: lower limb anomalies, central nervous system anomalies, and upper limb anomalies. Equinovarus (clubfoot) is the most common among all cases (66.7%, n=46). The next most frequent among all cases are anomalies of the central nervous system, primarily of cranial nerves VII (33.3%, n=23), VI (31.9%, n=22), V (24.6%, n=17), and XII (24.6%, n=17). Agenesis or absence of the fingers (18.8%, n=13) is the next most prevalent. Although a variety of anomalies have been documented after exposure to misoprostol *in utero*, these do not seem to constitute a specific syndrome. A specific defect or syndrome could be helpful in making the case for the teratogenicity of misoprostol.

Criterion 4: Proven exposure to agent at critical time(s) in development

Misoprostol exposure among the 69 case reports can be described by gestational age at exposure, number of days of exposure, total dosage, and route of administration.

Gestational age at exposure. All reports of gestational age at exposure were subject to recall bias, as the exposure was ascertained several months after birth. In addition, because almost all women self-medicated, clinical dating (i.e., bimanual exam or ultrasound) was not available for

Figure 3. Gestational age at exposure



the day(s) of exposure. Finally, gestational age was not consistently assessed in the case reports and at times required interpretation. When it was not explicit in a case report, stated gestational age at exposure was assumed to be based on the date of last menstrual period (LMP), and embryonic/fetal age was calculated based on the reported gestational age (Figure 3).

The majority of exposures occurred between the third and sixth week of development (5–8 weeks LMP). Few exposures occurred during the first two weeks of development (3–4 weeks LMP, which would generally fall before the first missed menses) followed by a substantial increase in exposures at week three of development (5 weeks LMP, or the first week after missed menses). A noticeable decrease in reported exposures occurred after week six of development (8 weeks LMP). There were no reported exposures beyond the eleventh week of development (13 weeks LMP).

Using this information, the reported gestational age of exposure can be compared to the sensitivity period of development of the three affected systems. For limbs, the highly sensitive period extends from 24 to 36 days after fertilization (about 5.5–7.5 weeks LMP or 3.5–5 weeks embryonic/fetal age). The less-sensitive period extends from 36 days to 56 days after fertilization (7–10 weeks LMP or 5–8 weeks embryonic/fetal age). During the highly sensitive period, particularly before day 33, more severe anomalies (e.g., absence of the limbs and hands) are produced. Toxic exposures on days 34–36 after fertilization can result in less-severe anomalies, such as absence of the thumbs. Among the cases of limb abnormalities associated with misoprostol use, a large proportion of reported exposures occurred during the sensitivity period. Many occurred during the highly sensitive period (Figure 4).

For the central nervous system, the highly sensitive period extends from week three through sixteen of development (5–18 weeks LMP). Thus, the majority of cases with central nervous system defects were reportedly exposed to misoprostol during the highly sensitive period (Figure 5).

It appears that the exposure period of the majority of case reports is consistent with the sensitive periods of development for the relevant anomaly. This consistency is evident for anomalies of the upper and lower limbs and the central nervous system.

Figure 4. Sensitivity period: Limbs

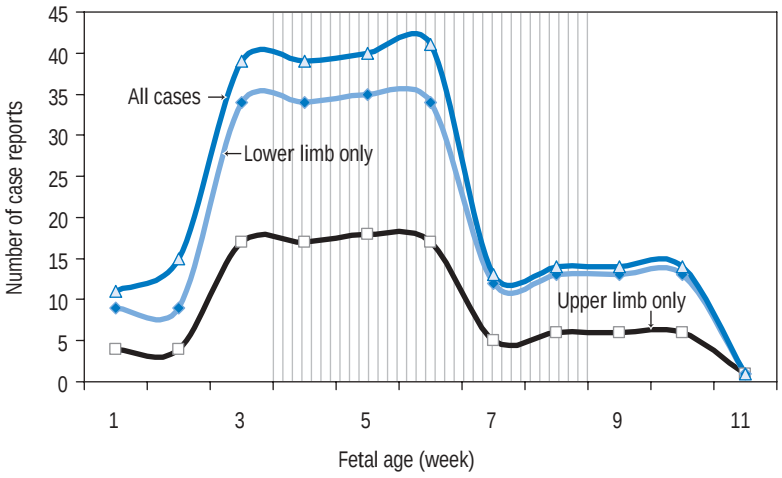
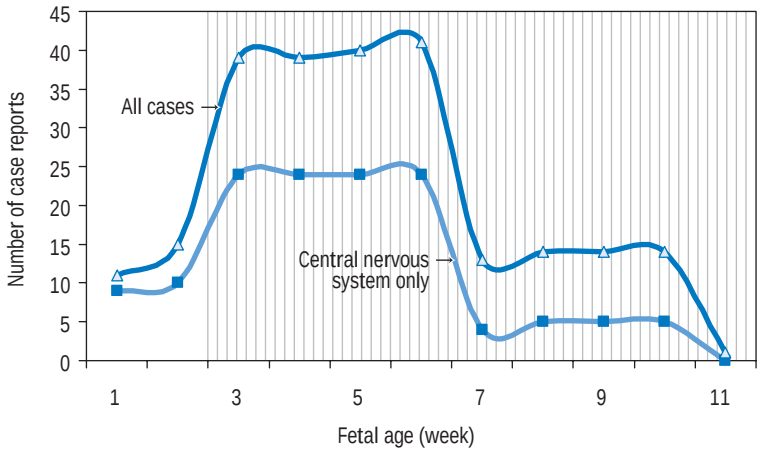
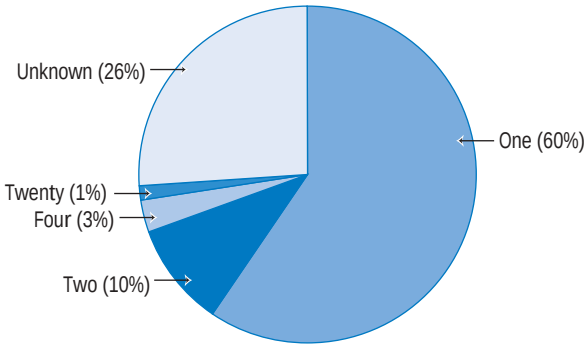


Figure 5. Sensitivity period: Central nervous system



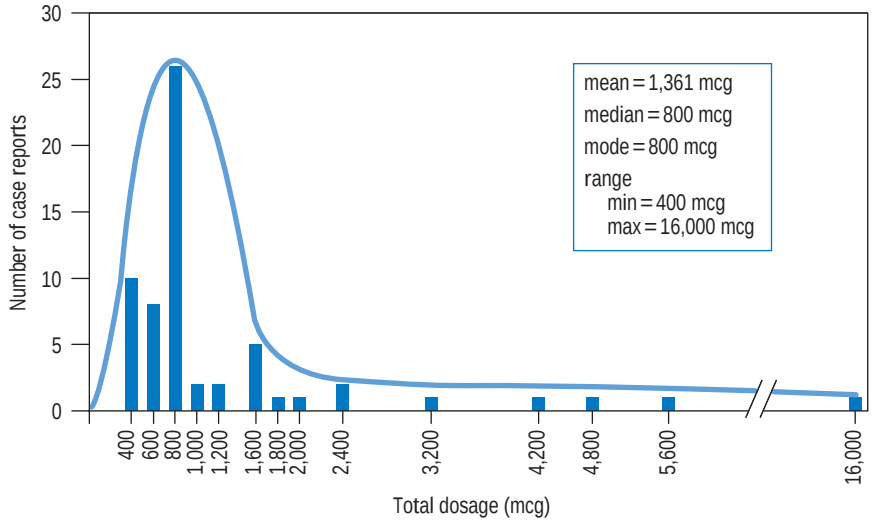
Number of days of exposure. Well over half (59.4%, n=41) of the women self-administered misoprostol on one day only, and another tenth (10.1%, n=7) administered the drug on two days (Figure 6). Two women self-administered misoprostol on four days, and one woman did so for 20 days. Data for 18 women (26.1%) were not available. The most common regimen of drug administration was an 800 mcg dose on one day (27.5% of the 69 women). The next most common regimens were a 600 mcg dose on one day and a 400 mcg dose on one day, each occurring in seven women (10.1%).

Figure 6. Days of exposure (N=69)



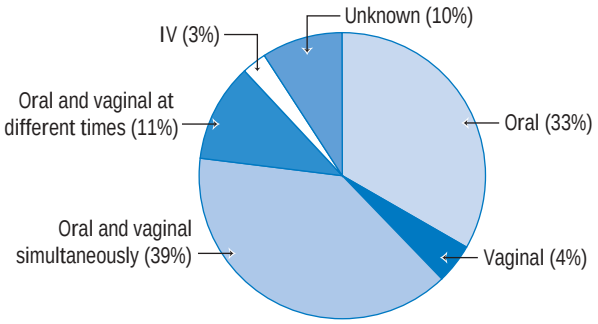
Total dosage. Of the 69 case reports, 62 provided data on total dosage of misoprostol, which ranged from 400 mcg to 16,000 mcg. The mean dosage was 1,361 mcg. Both the median and mode dosage were 800 mcg (Figure 7). There is no difference in total dosage among the three groups of anomalies.

Figure 7. Total dosage (n=62)



Route of administration. Administration of misoprostol occurred in one of six ways: oral only, vaginal only, oral and vaginal simultaneously, oral and vaginal at different times, intravenous, and unknown (Figure 8). Two-fifths of women (39.1%, n=27) self-administered misoprostol simultaneously by oral and vaginal routes. One-third (33.3%, n=23) administered it orally only. Data were missing for a tenth of the women (10.1%, n=7). Two women reported taking misoprostol intravenously. This is highly unlikely, however, as misoprostol is formulated in tablets only. There was no difference in reported route of administration among the three major anomaly types.

Figure 8. Route of administration (N=69)



Criterion 5: Biological plausibility

One theory of teratogenic mechanism focuses on uterine contractions stimulated by misoprostol. The theory proposes that misoprostol-induced contractions may bend the embryo in the area of cranial nuclei VI and VII, thereby decreasing blood flow in the area, which results in hemorrhage and/or cell death in the cranial nuclei.[24]

A more commonly proposed mechanism of teratology involves vascular disruption caused by strong uterine contractions. The contractions may create physical compression on the placental–fetal unit, leading to hypoperfusion (decreased blood flow), hypoxia (reduced oxygen supply), or vascular obstruction in the fetus—depending on the length of the contractions and the period of exposure. In the case of limb abnormalities, reduction anomalies could result from contractions that affect the capillary plexus of the fetus, which is very sensitive during the early stages of development. During the "watershed" period of development (the time period during which the primitive vessels of the capillary plexus develop), the capillary plexus is subject to rupture with changes in pressure, resulting in defects. For example, disruption of the marginal vein of the plexus is related to terminal limb defects. Such insults can lead to failure of apoptosis (tissue necrosis) and subsequent syndactyly (webbing of fingers). Yet, it remains unclear how severe an insult is necessary to create specific developmental defects.

The vascular disruption process is complex, and attendant consequences for the fetus are multiple, depending on mechanism, severity, and timing. For example, exposure to misoprostol

could occur during the embryonic stage, yet a defect may result from vascular placental insufficiency affecting development at some point later in gestation. Consequently, such a "delayed" effect could result in limb reduction anomalies not normally associated with the actual period of drug exposure.

The effects of misoprostol may also occur on the molecular level. Owing to genetic differences, some fetuses may be more susceptible than others to certain teratogenic effects, with resulting defects in some organ systems and not others. Most experts do not believe that misoprostol acts on a molecular or cellular level to cause defects, however, detailed study of molecular teratology in the near future may provide a better understanding of this aspect of teratogenicity.

Because other prostaglandins have been linked to the occurrence of fetal defects by inducing uterine contractions that contribute to the disruption of the fetal–placental unit, it is tempting to use these examples as a reference for understanding the teratogenic potential of misoprostol. One caveat, however, is that contractions induced by different prostaglandins are not necessarily equivalent. Individual prostaglandins affect different receptors in the uterus and therefore could result in varying strengths of contractions and different teratologic outcomes.

At this point, there appears to be a biologically plausible mechanism for misoprostol teratogenicity. It seems reasonable to hypothesize that misoprostol-induced contractions could result in a range of defects that are initiated by vascular disruption of the fetal–placental unit.

Criterion 6: Substantially and statistically higher prevalence of anomalies in exposed versus nonexposed fetuses

Case reports are useful for indicating the potential teratogenicity of misoprostol but should not be mistaken for proof of a true teratogenic effect. To determine an association between misoprostol and birth defects, studies comparing case and control groups are necessary.

Because the incidence of the anomalies in question is very low, it is difficult to measure their prevalence precisely in population-based studies. While prospective human studies would provide the strongest evidence, they require large samples and become prohibitively expensive when searching for a rare exposure and an even rarer outcome. Indeed, Schuler et al.[13] found that among 67 infants exposed to misoprostol *in utero* and 81 who were unexposed, the incidence of birth defects—including constriction rings of the arms, hepatosplenomegaly (enlargement of the spleen and liver), pulmonary hypertension, persistent fetal circulation, eye cataract, cryptorchidism (undescended testis), and cavernous hemangioma (vascular tumor)—was 3% and 2.5%, respectively (RR=1.21; 95% CI, 0.17, 8.35), a nonsignificant difference. Because of the small sample size, the study had a statistical power (i.e., the probability that a finding of no difference between study groups will be rejected, even if a difference between groups truly exists) of only 5% to detect a relative risk of 1.21 at the 5% significance level. To detect a statistically significant relative risk of 2 (at the level of 5% defects in exposed vs. 2.5% or less in unexposed infants), a study of 880 exposed and 880 unexposed live births would have been necessary. Because of the rarity of the exposure in the population (Orioli and Castilla[14] estimate a 0.6% exposure rate), a longitudinal study such as this one would have required screening

146,667 infants to find 880 who were exposed to misoprostol. Case-control studies, on the other hand, can efficiently provide causal evidence for determining teratogenic potential.

To determine a higher prevalence of anomalies among infants exposed to misoprostol than infants not exposed, the following three criteria are important for any reliable study:

- *Temporality of the association.* Exposure to misoprostol must have occurred prior to the occurrence of the anomaly.
- *Strength of the association.* In a prospective study, the magnitude of the association must indicate that the incidence of defects is substantially greater in those exposed than in those unexposed to misoprostol; in a retrospective (case-control) study, the incidence of misoprostol exposure *in utero* must be substantially greater in cases (those with defects) than in controls (those without defects).
- *Dose-response relationship.* The odds ratio should increase with the amount of exposure to misoprostol. A threshold effect can also increase confidence in a causal relationship between misoprostol exposure *in utero* and incidence of defects.

Three human studies (Pastuszak et al.,[12] Orioli and Castilla,[14] and Vargas et al.[15]), all of which were conducted in Brazil, have adequate methodological design (including statistical power) to determine a higher prevalence of anomalies among infants exposed to misoprostol compared to those not exposed. In all three studies, administration of misoprostol was reported to have occurred early in the gestational period, most often during the first trimester. It is difficult to determine in these studies a true temporality of association between misoprostol exposure and occurrence of a birth defect as the reported anomalies could not be identified until after birth and theoretically could have been caused before misoprostol exposure.

In all three studies, there is a strong, measured association between misoprostol exposure and birth defects. Pastuszak et al. conducted a case-control study to compare the frequency of misoprostol use during the first trimester by mothers of infants diagnosed with Möbius syndrome and mothers of infants diagnosed with neural-tube defects. The authors found that infants with Möbius syndrome were 29.7 times more likely (95% CI, 11.6, 76.0) to have been reported as exposed to misoprostol *in utero* than infants with neural-tube defects.[12]

Orioli and Castilla conducted a case-control study to examine whether congenital anomalies were associated with misoprostol exposure. Cases were identified from a registry of birth defects, and controls were defined as the next nonmalformed infant of the same sex born in the same hospital as the malformed infant. There was no overall difference in misoprostol exposure between malformed and nonmalformed infants. However, after reanalyzing the researchers' published data, certain anomalies appeared to be associated with misoprostol exposure. Cases for this reanalysis were defined as infants with one of 15 types of congenital anomalies previously described in the literature as being associated with misoprostol exposure or one of another 13 anomalies identified in the registry among misoprostol-exposed infants. The frequency of misoprostol exposure among cases of each of the 28 specified birth defects was compared with the frequency of exposure within the study's entire control group. Out of the 28 comparisons of various anomalies between cases (malformed) and controls (nonmalformed), 11 comparisons

were statistically significant. Approximately only 1.5 such comparisons would be expected to be significant by chance alone.[14]

Vargas et al. conducted a case-control study to compare the frequency of misoprostol exposure *in utero* among infants diagnosed with a vascular disruption defect and infants diagnosed with other defects. The authors found that infants with a vascular disruption defect were 22.0 times more likely (95% CI, 7.3, 81.3) to have been reported as exposed to misoprostol than infants with other defects. Additionally, infants with Möbius syndrome were 7.0 times more likely to have been reported as exposed to misoprostol, and infants with a terminal transverse limb reduction anomaly were 3.0 times more likely to have been reported as exposed to misoprostol than infants with other defects. After excluding those infants with Möbius syndrome and with terminal transverse limb reduction anomalies, the frequency of misoprostol exposure was 7.5 times higher (95% CI, 1.23, 78.7) among infants with a vascular disruption defect compared to infants with other defects. All of these comparisons were statistically significant.[15]

Vargas et al. are the only researchers who examined dose response. Infants exposed to 5 tablets (1 mg) were 3.51 times more likely (p=0.04) to have a vascular disruption defect than infants exposed to less than 5 tablets (<1 mg).[15]

With the exception of the research by Orioli and Castilla (overall OR=1.54 for exposed vs. nonexposed, 95% CI, 0.09, 2.77, p=0.09), the strength of the observed associations in these studies was high. Many odds ratios were greater than 2.5. In fact, a nonsignificant overall OR is not inconsistent with such a conclusion. For example, it is biologically reasonable that the overall OR (comparing the odds of exposure to misoprostol of infants with and without any one of the 28 identified defects) was not significant, while the comparisons based on specific defects (limb and cranial anomalies) did yield significant differences. Overall, however, the data from all three studies suggest that the absolute risk of teratogenicity with misoprostol exposure (i.e., the number of cases attributable to exposure) appears to be low.

Criterion 7: Consistency between epidemiological studies

The three case-control studies conducted in human populations demonstrated a higher prevalence of anomalies among misoprostol-exposed infants. Pastuszak et al., Orioli and Castilla, and Vargas et al. demonstrate a consistent association between misoprostol exposure and birth anomalies. At the same time, it is important to view the study results within the context of their limitations.

Systematic ascertainment bias could have affected the results in the studies by Pastuszak et al. and Vargas et al. Study physicians may have been aware of the alleged relationship between Möbius syndrome and misoprostol and could consequently have assessed misoprostol exposure more closely in infants with Möbius syndrome than in infants with other types of defects.

Systematic reporting bias may also have skewed results in two of the studies. In Orioli and Castilla's study, mothers of malformed infants may have been more likely than mothers of healthy infants to remember their exposure to misoprostol. In order to discern a reason for their child's

condition, women with malformed infants may have more thoroughly considered possible gestational exposures. In contrast, women with healthy infants may not have remembered, or even thought about, their misoprostol exposure because of lack of a similar motivating factor. In the study by Pastuszak et al., mothers of infants with neural-tube defects were interviewed shortly after delivery, but mothers of infants with Möbius syndrome were interviewed years later. Because abortion is illegal in Brazil, women who reported their misoprostol exposure years after the exposure might have been less fearful of legal repercussions because of the lag between exposure and reporting. Vargas et al. recognized this potential bias and controlled for the possible effect on study results. Study investigators used structured questionnaires that were applied identically to all mothers interviewed. The findings were similar to those of Pastuszak et al. and Orioli and Castilla, supporting the likelihood of a relationship between misoprostol use and birth anomalies.

In addition, other unascertained exposures could theoretically account for the statistical associations between misoprostol use and fetal defects. All studies found sociological or reproductive differences between the case and control groups but did not statistically adjust for them.

Two more factors could lead to inadequate conclusions from the available data. First, the distribution of the timing of exposure in the published studies may differ from the true population distribution of exposures. With self-administration of a drug for a legally restricted indication, observational data are not likely to provide an accurate assessment of the true population exposure, and any estimated effect, therefore, is likely not to be representative of the situation in the real world. Second, and conversely, women who are pregnant with “defective” fetuses may be more likely to successfully abort with misoprostol because of the physical problems of those fetuses (i.e., misoprostol may work differentially if a women has a defective fetus). Such a mechanism would make it less likely that one would find an effect (e.g., the teratogenicity of misoprostol).

Criterion 8: Increased incidence of anomalies in a population after introduction of the agent

Although gestational misoprostol exposure appears relatively common in Brazil, the observed incidence of these anomalies in the general population does not appear to be high nor to be rising and falling with prevalence of misoprostol use. The lack of documentation of increases and decreases in the number of reported anomalies after introduction and restriction of misoprostol in Brazil does not lend additional support to the hypothesis that misoprostol use in pregnancy is associated with birth defects. In addition, the anomalies that seem to be associated with misoprostol exposure account for a relatively small proportion of all birth defects.

Summary of Criteria for Evaluating Teratogenicity

According to the animal model evidence reported by the drug manufacturer and the scientific literature, only one study involving rats has demonstrated a teratogenic effect of misoprostol. Because animal studies are a weak gauge of teratogenicity in humans, this evidence provides little evidence about misoprostol’s teratogenic potential. It does, however, provide cause to examine the case report evidence.

A diligent review of the 69 case reports identified in the scientific literature reveals that the majority of the reported anomalies can be classified as pertaining to the central nervous system and the upper and lower limbs. The most frequent anomalies identified among all cases are equinovarus (clubfoot) (66.7%, n=46), followed by anomalies of cranial nerves VII (33.3%, n=23), VI (31.9%, n=22), V (24.6%, n=17), and XII (24.6%, n=17). Agenesis or absence of the fingers (18.8%, n=13) is next most common. The exposure period to misoprostol of the majority of case reports is consistent with the sensitive periods of development of the related anomalies (i.e., those affecting the upper and lower limbs and the central nervous system).

A plausible teratogenic mechanism involves uterine contractions induced by misoprostol. Such contractions could potentially create a vascular disruption of the fetal–placental unit, resulting in a range of defects. The specific etiology of vascular disruption defects remains unclear, but the case report evidence is consistent with current knowledge.

Overall, the reviewed studies demonstrate a coherent association between misoprostol exposure and the incidence of birth anomalies. Three case-control studies conducted in human populations consistently demonstrated a higher prevalence of anomalies among misoprostol-exposed infants. Even with this strong association, however, the absolute risk of teratogenicity with misoprostol exposure appears low. Evidence gathered from population-based registries in Brazil indicates the observed incidence of these anomalies does not appear to be high, even though gestational misoprostol exposure seems relatively frequent in the country.

Policy Implications

Building public health policy on this subject must take into account cause and effect, risk and benefit. For example, is it possible that the physiological process of abortion failure, and not misoprostol itself, is teratogenic? Other prostaglandins used for pregnancy termination have been linked with the occurrence of similar birth anomalies,[25,26] but even more suggestive of a general effect is the fact that dilation and curettage has also been associated with vascular disruption defects, specifically amniotic band syndrome, limb defects,[27] and arthrogryposis.[28] Examining the embryos of women whose misoprostol abortions failed and who subsequently underwent surgical terminations could clarify the pathogenesis of the birth defects. However, identifying structural abnormalities in very early embryos presents difficult challenges. One previous attempt to examine embryonic abnormalities in very early embryos after medical abortion produced no scientifically tenable results.[29]

The public health implications of informal, self-administered misoprostol use should be carefully considered and best practices defined, with attention to both public and provider education. One educational component involves the counseling of women with failed misoprostol abortions and the relevant discussion of the risk of malformations. Although the increased (relative) risk of defects due to misoprostol use appears real, the attributable (absolute) risk appears small. While an exact rate is unknown and is likely difficult to determine, using available evidence misoprostol could be construed as a “mini-teratogen” (defined as an agent that causes less than 10 defects per 1,000 exposures).[30] This should be

somewhat reassuring, although women need to be strongly cautioned that there appears to be a real (if small) risk of malformations of pregnancies carried to term after *in utero* exposure to misoprostol. In fact, exposure of a fetus to misoprostol might therefore be one reason to provide abortion services in cases of ongoing pregnancies in otherwise restrictive environments.

In order to provide accurate information to both women and providers, a stronger evaluation of the attributable teratogenic risk is important. Two types of registries in Brazil (i.e., the Latin-American Collaborative Study of Congenital Malformations and the Teratogen Information Service) collect population data on congenital anomalies and could be useful for conducting population-level research leading to better estimates of this phenomenon.

Foremost, it is imperative that policies focus not on the misuse of the drug but on good clinical practice. Although the Brazilian case is informative, legislation created merely in reaction to improper use does not adequately address the problem of women's unmet reproductive health needs. In low-resource areas and in countries where abortion is illegal, a woman's choices for pregnancy termination frequently are not between misoprostol or a safe abortion but rather between misoprostol and methods that are far less safe for the woman's health. It is now widely accepted that women who succeed in terminating their pregnancies with misoprostol potentially avoid the negative consequences of other methods that are typically less safe but common where abortion services are unavailable or restricted.[31] The paramount consideration is that the likelihood of anomalies in an infant exposed to misoprostol *in utero* is substantially less than the likelihood of disability or death of the mother following use of unsafe methods of abortion—which in turn has serious repercussions on the health and survival of her other children. The availability and self-use of misoprostol may, in fact, improve a population's health by decreasing morbidity and mortality among women of reproductive age with less detriment to the health of children overall. Such appears to have been the case in Brazil.[32]

The danger in places like Brazil may arise not so much from women taking misoprostol but from the fact that when use of misoprostol does not result in successful pregnancy termination, women may have no access to appropriate care for fear of legal or social repercussions. In such situations, education is key. Information should be available about the risks of misoprostol use and actions to take if pregnancy is ongoing after its use. Prevention messages that enhance providers' (including physicians, nurses, and pharmacists) knowledge about misoprostol would be helpful. Where such information does not yet exist, studies must be undertaken to derive the essential facts.

Conclusion

In this meeting, current embryologic and epidemiological evidence associating misoprostol use with birth anomalies was evaluated. The analysis consisted of a review of case reports identified in the literature, of possible biological bases for teratogenesis, and of other relevant human and animal studies. There is an association between birth defects and *in utero* exposure to misoprostol. It appears that the abortion process induced by misoprostol (e.g., uterine contraction

and bleeding) could be causative, leading to temporary vascular disruption in the placental–fetal unit. This disruption could reduce the blood supply to the placenta and result in hypoperfusion, hypoxia, or vascular obstruction in the fetus. A wide range of defects is possible, but the most commonly cited following *in utero* exposure to misoprostol are equinovarus (clubfoot), cranial nerve anomalies (affecting nerves V, VI, VII, and XII), and absence of the fingers.

Further research is necessary to clarify the biological effect of misoprostol on the placenta and embryo. More subtle anomalies, particularly of the central nervous system, resulting from misoprostol exposure *in utero* may still remain unidentified. In addition, ecologic analysis, comparing malformation rates before and after the introduction of widespread misoprostol self-use, would help to identify secular trends. Meanwhile, efforts to inform providers and women about the risks of misoprostol use can reduce the potential for birth defects following exposure to the drug.

While the relative risk of malformations appears real, epidemiological studies indicate that the absolute risk (i.e., the number of cases) is low (less than 10 malformations per 1,000 births exposed to misoprostol *in utero*). This risk estimate ought to be clearly communicated when educating women on the risk of fetal defects following *in utero* exposure to misoprostol. Only with such information can women make fully informed reproductive health decisions. Similarly, this risk, like all risks, must be placed in context. For example, in low-resource settings and in countries where access to safe, legal abortion is limited, misoprostol is generally a rather safe, low-cost abortion option for women seeking to terminate a pregnancy, with fewer repercussions than unsafe abortion. In fact, the availability of misoprostol was shown to reduce morbidity associated with unsafe abortion. The potential public health benefits of this drug for women must also be weighed in the overall discussion and decisionmaking on policy alternatives.

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