RESEARCH ARTICLE

Comparison of Pregnancy Outcomes between Ongoing Pregnancies after Accidental Misoprostol Use and Normal Pregnancies: A Case-control Study

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Abstract

Aim: Literature reports are conflicting regarding the association of anomalies with misoprostol use. We conducted this study to assess the association of misoprostol with congenital abnormalities.

Materials and methods: In this prospective case–control study, women with early pregnancy were recruited from the antenatal clinic and divided into cases and controls on the basis of exposure to misoprostol. They attended antenatal visits, delivered at the hospital, and their babies were examined for abnormalities before discharge.

Results: There were 22 (9.2%) babies with abnormalities in the misoprostol group and 16 (6.2%) abnormalities in controls ($p = 0.208$). When stratified according to the type of exposure to misoprostol, abnormalities were significantly higher in those with intended exposure than in accidental exposure (12.3 vs 3.5%, $p = 0.023$). Misoprostol exposure was not significantly associated with abnormalities. Controls were less likely to have abnormalities than those with misoprostol exposure, but this did not remain significant after all cofounders were added to the model.

Conclusion: Exposure to misoprostol leads to more congenital abnormalities. However, chances of having a baby with an abnormality are not significantly increased with misoprostol exposure when all other risk factors are controlled for. These findings may aid clinicians in reassuring low-risk women with accidental exposure in early pregnancy.

Clinical significance: Women with accidental exposure to misoprostol are less likely to have congenital abnormalities than those with voluntary exposure because they were found to ingest a lesser amount of the drug.

Keywords: Abortifacient, Congenital abnormalities, Misoprostol, Unwanted pregnancies.

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Introduction

Misoprostol (a synthetic analog of natural prostaglandin E1; Cytotec, Pfizer, Connecticut, United States of America) is available as an over-the-counter medication in Pakistan. It is commonly used to prevent and treat gastritis associated with nonsteroidal anti-inflammatory drug use and is abused to get rid of unwanted pregnancies.[1] Because abortion is illegal, women may or may not use the recommended abortion regimen and this leads to ongoing pregnancies despite abortifacient use.[2] Women who self-medicate in such cases later visit the outpatient departments with ongoing pregnancies and are concerned about the adverse effects of the medication on their unborn baby.[3] In case of anomalies, women are more likely to accept the use of misoprostol than on the initial visit. Literature reports are conflicting regarding the association of anomalies with misoprostol use. Preliminary data suggested an association of misoprostol with vascular disruption type defects.[4] Association with Mobius syndrome has received the most attention. But Mobius is a rare disorder (one in 10,000 to one in 50,000), and the severity of the syndrome is similar in cases where misoprostol was consumed and in cases where it was not used.[5] Evidence is accumulating that defects may not be directly associated with misoprostol use.[6] Indication of use was also associated with defects, with women who planned to induce abortion having more defects than those with accidental exposure.[7] Moreover, a recent study showed that the spectrum of abnormalities associated with mifepristone exposure is different, but rates of malformation are not significantly higher than the general population.[8] The data collected in this regard suffers many biases due to study designs and recruitment. We undertook this study to assess the association of misoprostol with congenital abnormalities. In our study, women with accidental exposure to misoprostol or those who attempted induced abortion were followed throughout the pregnancy and postpartum; the

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congenital defects are compared to controls that did not have any exposure to misoprostol specifically.

Materials and Methods

The present study was a prospective case–control study conducted at Aziz Medical Center from January 2017 to December 2019. Women aged 20–35 years, with early pregnancy, were approached for the study. Women were included if an early scan showed a single alive fetus of no more than 12 weeks and 6 days, with no gross abnormality, and they were willing to be compliant with follow-up and planned to deliver at the same hospital. Excluded from the study were women with no fetal hearts on the initial scan, gestation >13 weeks, active bleeding at the time of presentation, life-threatening emergency that needed emergency measures, and women who conceived on teratogenic drugs as outlined by the Food and Drug Administration category. Also excluded were women who planned to have induced abortions. Such termination was, however, not available at the hospital because of legal concerns. We also excluded women with known diabetes, smokers, and those who admitted to substance use.

Sample Size Estimation

Literature reports that with misoprostol exposure, anomalies are seen in 4% of pregnancies as compared to 1.8 % in the unexposed population [4 vs 1.8%, respectively; odds ratio (OR) of 2.2]. The background congenital abnormality rate of the Pakistani population is 7 %. Now assuming that the misoprostol exposure would lead to abnormalities, with a power of 80% (1-β) and a one-sided 0.05 risk of type I error (α), we needed 286 patients with misoprostol exposure and 286 in the control group to demonstrate an increase in anomalies with misoprostol use (Sample Size Determination in Health Studies, Version 2.00, Copyright (c) 1996–1998, World Health Organization).

Brief history and informed consent was taken prior to the study from all participants. Women were divided into cases and controls on the basis of exposure to misoprostol.

Cases

Women who admitted to misoprostol use accidentally (accidental use) or for induced abortion (intended use) were included as cases.

Accidental Use

It was identified on detailed drug history. In case any drug containing misoprostol was identified, women were asked about the dosage they had been taking, and the total exposure for the pregnancy was calculated from the last menstrual period (LMP).

Intended Use

Women who presented with a failed attempt at abortion were also included as cases. A detailed history was taken to ascertain the route and dosage of misoprostol. They were asked about the formulation they used and the number of pills they consumed to calculate the dosage ingested/used. Women in the study used the oral route only.

Controls

These were women from the same population but no reported exposure to misoprostol.

Both groups attended for antenatal visits.

Evaluation of High-risk Factors

The women were specifically asked about risk factors for anomalies, that is, family history of congenital abnormalities, fever in the first trimester, folic acid intake, cousin marriage, and pregnancy exposure (unintended or accidental). The responses were entered into the performa.

Anomaly Scan and Pediatricians Opinion

All women had an anomaly scan between 18 and 21 weeks. In case of an anomaly, pediatrician's opinion was taken. Parents were explained in detail about compatibility with life, corrective procedures if available, and follow-up in the prenatal and early neonatal period. They were then asked to make an informed choice about the continuation of pregnancy. Those who chose to terminate were offered a termination. Those with anomalies where correction was possible were asked to deliver at a center where expertise was available. The pediatrician in charge later reviewed these babies.

The primary outcome measure was the rate of malformations. All abnormalities were assessed by the same pediatrician at birth and were later confirmed by a birth defect specialist. Secondary outcome measures were the miscarriage rate, which were calculated for the total number of women included. Women who were excluded due to asking for termination and who were lost to follow-up were therefore excluded. Preterm deliveries are defined as births that took place before 37 weeks of gestation. Gestational age was calculated from the date of the LMP or using an early trimester scan. Premature births, defined as birth occurring before 37 weeks after LMP, and birth weight. Birth weight was categorized into three categories, low birth weight (<2.5 kg), appropriate birth weight (2.5–4 kg), and birth weight >4 kg (macrosomia).

A performa was used to collect data. All responses were coded and confidentiality maintained. Approval from the Institutional Review Board was taken IRB 113-2016.

Statistical Analysis

Data was entered and analyzed using Statistical Package for the Social Sciences version 15. Quantitative variables were presented by mean and standard deviation (SD). The *t*-test for two independent samples was used to compare means for both groups; cases and controls. Frequencies and percentages were calculated for qualitative variables, and chi-squared test and Fisher's exact test were used to compare the groups at $p < 0.05$ level of significance.

Another comparison was done to assess the association of type of exposure (intended vs accidental) in women exposed to misoprostol. A further analysis was done for abnormalities and associated risk factors to assess the association between variables. The strength of the association was confirmed by a logistic regression model.

The type of anomalies was also stratified according to groups (controls and cases).

Results

Sample

During the study period, 606 women satisfied the inclusion criteria and were approached for the study. Out of these 606, 12 refused to participate. The remaining 594 were included. In the misoprostol group, 299 women were initially included, 15 had to be excluded because of the decision to terminate the pregnancy after the initial visit ($n = 9$), or because they were lost to follow-up ($n = 6$),

284 women with misoprostol exposure were thus included in the final analysis.

In the control group, 295 women were included but eight had to be excluded because they were lost to follow-up ($n = 2$) or delivered at some other clinic ($n = 6$). The control group therefore comprised 287 women.

The basic characteristics of the study population are summarized in Table 1. The mean age of women was 29.18 ± 5.27 years.

Congenital Abnormalities in Misoprostol Group vs Controls

There were 22 (9.2%) babies with abnormalities in the misoprostol group and 16 (6.2%) abnormalities in controls. This difference, however, failed to reach statistical significance $p = 0.208$. Miscarriages were significantly more common in the cases as compared to the control group (15.4 vs 9.1%, p-value = 0.019) (Table 2).

Table 1: Characteristics of study population ($N = 571$)

Characteristics		*Mean ± SD OR count (N%)*
Age in years		29.18 ± 2.27
Fever in early pregnancy	Yes	69 (12.0%)
	No	502 (88.0%)
Family history of abnormality	Yes	80 (14.0%)
	No	491 (86.0%)
Cousin marriage	Yes	100 (17.6%)
	No	471 (82.4%)
Folate intake periconception	Yes	413 (72.3%)
	No	158 (27.7%)
History of previous miscarriage	Yes	86 (15.0%)
	No	485 (85.0%)
Parity	0	142 (24.86%)
	1–2	284 (49.7%)
	3 or more	145 (25.4%)
Groups	Misoprostol	284 (49.3%)
	Control	287 (50.6%)
Outcome of pregnancy	Live births	499 (87.3%)
	Ectopic	2 (0.3%)
	Miscarriages	70 (12.3%)
Abnormality ($n = 499$)	No	461 (92.4%)
	Yes	38 (7.6%)
Gender of baby ($n = 499$)	Male	239 (47.9%)
	Female	260 (52.1%)
Gestational age at delivery ($n = 499$)	<34 weeks	19 (3.8%)
	34–36 + 6 weeks	69 (13.8%)
	37 weeks or more	411 (82.4%)
Mode of delivery ($n = 499$)	cesarean	172 (34.5%)
	Normal delivery	327 (65.5%)
Weight of baby ($n = 499$)	<2.5 kg	118 (23.6%)
	2.5–4 kg	260 (52.1%)
	>4 kg	121 (24.2%)

Congenital Abnormalities in intended Use Group vs Accidental Group

Abnormalities were significantly more common in those with intended exposure (12.3 vs 3.5%, $p = 0.023$). These women were of older age (29.1 ± 5.26 years vs 27.70 ± 5.65 years, $p = 0.027$), took a lower dose of misoprostol (855.84 ± 436.56 µg vs 2648.84 ± 298.92 µg, $p < 0.001$), and had a later exposure to the teratogen (7.29 ± 1.62 weeks vs 5.03 ± 1.48 weeks, $p = 0.001$) (Table 3).

Association of Abnormalities with Risk Factors, Confounders and Exposure to Misoprostol

There was a significant association of abnormalities with age, fever in the first trimester, cousin marriage, previous history of miscarriage, folate consumption periconception, mode of delivery, and weight of baby Table 4. However, misoprostol exposure was not significantly associated with abnormalities. Controls were less likely to have abnormalities than misoprostol exposure, but this did not remain significant after all cofounders were added to the model (Table 5).

Discussion

Main Findings

Our study showed that the abnormality rate was higher (9.2%) after exposure to misoprostol in the first trimester than controls (6.2%). This rate did not reach statistical significance. Miscarriages were significantly more common in the cases as compared to the control group.

Abnormalities were significantly higher in those with intended exposure as compared to accidental use. But women who had voluntary exposure to misoprostol were older, more likely to use a higher dose, and used the medication later in gestation.

The spectrum of abnormalities in our study varied between the groups; women with misoprostol were more likely to have vascular disruption and cranial nerve defects than controls with no such exposure.

Interpretation

The rate of congenital malformations in our study was 5.5% for controls. Worldwide reported figures range from 3 to 7%.[9] But considering the fact that these abnormalities depend on a variety of factors, no two studies are actually comparable in this regard. The rate for France is 3.5%, while that from Taiwan is 4.3%, and Oman is 2.46%.[8,10] These figures further confirm that a comparison group of controls is extremely necessary in such studies. Data on the continuation of pregnancy after exposure to misoprostol remains scarce. The data available is mostly in the form of retrospective studies or case reports that are hugely biased due to maternal recall.[11] Another problem is the fact that the majority of such studies are focused on abnormalities and do not report sufficiently on pregnancy outcomes and risk factors.[7] Our study has a prospective case–control design, and we also collected data on risk factors to ensure a better comparison between cases and controls. We excluded women with diabetes, age >40 years, and substance abuse to minimize the effect of these confounders on data. Our study still showed a higher number of miscarriages in cases than

Table 2: Comparison of controls and those exposed to misoprostol

		Group		
		Misoprostol n = 284	*Controls n = 287*	
Characteristics		*Mean ± SD or count*	*Mean ± SD or count mean*	*p-value*
Age in years		29.21 ± 5.20	29.15 ± 5.35	0.889
Fever in early pregnancy	Yes	30 (10.6%)	37 (13.2%)	0.431
	No	254 (89.3%)	250 (86.9%)	
Family history of abnormality	Yes	39 (13.8%)	41 (14.3%)	0.863
	No	245 (86.2%)	246 (85.7%)	
Cousin marriage	Yes	52 (18.3%)	49 (17.0%)	0.694
	No	232 (81.7%)	238 (83.0%)	
Folate during periconception	Yes	195 (68.8%)	217 (75.7%)	0.084
	No	89 (31.3%)	70 (24.3%)	
History of previous miscarriage	Yes	45 (15.8%)	41 (14.3%)	0.629
	No	239 (84.2%)	246 (85.7%)	
Parity	0	55 (19.3%)	87 (30.3%)	0.071
	1–2	161 (56.6%)	123 (42.8%)	
	3 or more	68 (23.9%)	77 (26.8%)	
Outcome	Live births	240 (84.5%)	259 (90.3)	0.014*
	Ectopic	0	2 (0.6%)	
	Miscarriages	44 (15.49%)	26 (9.1%)	
Abnormality (*n* = 499)	No	218 (90.8%)	243 (93.8%)	0.208
	Yes	22 (9.2%)	16 (6.2%)	
Gender of baby (*n* = 499)	Male	112 (46.7%)	127 (49.0%)	0.597
	Female	128 (53.3%)	132 (51.0%)	
Gestational age at delivery (*n* = 499)	Less than 34 weeks	8 (3.3%)	12 (4.6%)	0.506
	34–36 + 6 weeks	36 (15%)	46 (17.8%)	
	37 weeks or more	196 (81.7%)	201 (77.6%)	
Mode of delivery (*n* = 499)	Cesarean	88 (36.7%)	83 (32.0%)	0.277
	Normal delivery	152 (63.3%)	176 (68.0%)	
Weight of baby (*n* = 499)	<2.5 kg	47 (19.6%)	71 (27.4%)	0.061
	2.5–4 kg	137 (57.1%)	123 (47.5%)	
	>4 kg	56 (23.3%)	65 (25.1%)	

**p*-value is significant at <0.05

in controls. The rate seems even higher if we take into account the fact that the participants were included after having evidence of fetal hearts on the scan. This finding was also reported from a Danish study where accidental exposure to misoprostol increased the odds of miscarriage 3.6 times.[12]

However, misoprostol exposure was not significantly associated with abnormalities. While the OR is not statistically significant, the confidence interval (CI) suggests that the magnitude of the effect could be anywhere from a 0.8-fold increase to a 5.88-fold increase. A larger study is needed to generate a more precise estimate of the effect. A positive OR does not necessarily indicate an association that is significant statistically. The particular size and composition of that sample are also very important; in the presence of cofounders, the association may not remain significant.

Personal and family history of congenital abnormalities, cousin marriages, and increased age of mother and folate intake are common risk factors for congenital abnormalities.[13] In our study, the cases and controls were not significantly different from each other in these risk factors. This may also be a reason for nonsignificant differences in the number of abnormalities. These risk factors may be a reason for the perceived increase in previous studies where a control group was either missing[7] or was significantly different from the cases. Our results should, however, be interpreted with extreme caution. Statistically, we did not find a significant difference, but the difference in rate was apparent. We would further comment that the rate of anomalies in women with accidental exposure (3.9%) is slightly lower than the women who used misoprostol on purpose (6.2%). But those women were of lower age and used misoprostol

Table 3: Stratification according to the type of exposure in the misoprostol group

		Type of exposure		
		Intended (n = 186)	*Accidental (n = 98)*	
Characteristics		*Mean ± SD Count (n%)*	*Mean ± SD Count (n%)*	*p-value*
Age in years		29.31 ± 5.26	27.70 ± 5.65	0.027*
Dose in Microgram		855.84 ± 436.56	2648.84 ± 298.92	0.001*
Gestational age in weeks at exposure		7.29 ± 1.62	5.03 ± 1.48	0.001*
Fever in early pregnancy	Yes	19 (10.3%)	11 (11.2%)	0.815
	No	167 (89.7%)	87 (88.8%)	
Family history of abnormality	Yes	27 (14.5%)	12 (12.2%)	0.592
	No	159 (85.7%)	86 (87.8%)	
Cousin marriage	Yes	38 (20.4%)	15 (15.3%)	0.294
	No	148 (79.5%)	83 (84.9%)	
Folate intake	Yes	124 (66.9%)	72 (73.4%)	0.260
	No	62 (33.1%)	26 (26.7%)	
History of previous miscarriage	Yes	29 (15.6%)	16 (16.3%)	0.878
	No	157 (84.4%)	82 (83.7%)	
Parity	0	31 (17.2%)	24 (24.2%)	0.464
	1–2	111 (59.6%)	50 (51.6%)	
	3 or more	44 (23.6%)	24 (24.2%)	
Outcomes	Livebirths	154 (82.7%)	86 (87.7)	0.303
	Miscarriages	32 (17.3%)	12 (12.2)	
	Ectopic	0	0	
Abnormality (*n* = 240)	No	135 (87.7%)	83 (96.5%)	0.023*
	Yes	19 (12.3%)	3 (3.5%)	
Gestational age at delivery	<34 weeks	2 (1.3%)	6 (7.0%)	0.56
	34–36 + 6 weeks	26 (16.9%)	10 (11.6%)	
	37 weeks or more	126 (81.8%)	70 (81.4%)	
Weight	<2.5 kg	27 (17.5%)	20 (23.3%)	0.467
	2.5–4 kg	92 (59.7%)	45 (52.3%)	
	>4 kg	35 (22.7%)	21 (24.4%)	
Gender of baby	Male	75 (48.7%)	37 (43.0%)	0.398
	Female	79 (51.3%)	49 (57.0%)	
Mode of delivery	Cesarean	55 (35.7%)	31 (36.0%)	0.959
	Normal delivery	99 (64.3%)	55 (64.0%)	

*p-value is significant at <0.05

earlier than the intended use. Age is a confounding variable, and therefore data should be interpreted in light of the confounders.

Therefore, stratification according to the type of exposure reveals much more relevant information. Women who used misoprostol voluntarily were more likely to use a larger dose and used it later in the pregnancy and had a greater risk of abnormalities. This observation may imply a dose-response relationship with abnormalities. The dose used by these women is a confounding variable, and these women were older. We would therefore suggest a complete history gives a complete picture in these cases.

Women with misoprostol exposure were significantly more likely to have a miscarriage. The abnormalities encountered in cases with misoprostol exposure were of vascular disruption type and were, therefore, similar to that reported previously in the literature.[14] Due to the relatively small number of cases and controls included, a statistical test was not used. This would continue to remain a ground for criticism because abnormalities vary in populations, and pregnancies with exposure to misoprostol are not frequently reported. The historical analysis from Brazil, where 86 cases were matched to controls, also showed the same results, but the authors concluded that the study might be limited by the smaller numbers included.[14] However, there was a stark contrast in the type of abnormalities. In our study, misoprostol was associated with cranial defects (n = 3) and vascular disruption type abnormalities. This is in agreement with the data reported previously.

Table 4: Association of abnormalities with risk factors, confounders, and exposure to misoprostol

		Abnormality		
		Yes	*No*	
		Mean ± SD	*Mean ± SD*	*p-value*
Age		32.32 ± 4.65	28.92 ± 5.24	<0.001
Fever in first trimester	Yes	18 (47.4%)	42 (9.1%)	<0.001
	No	20 (52.6%)	419 (90.9%)	
Family history of congenital abnormality	Yes	16 (42.1%)	54 (11.7%)	<0.001
	No	22 (57.9%)	407 (88.3%)	
Cousin marriage	Yes	18 (47.4%)	70 (15.2%)	<0.001
	No	20 (52.6%)	391 (84.8%)	
Previous history of miscarriage	Yes	17 (44.7%)	58 (12.6%)	<0.001
	No	21 (55.3%)	403 (87.4%)	
Folate periconception	Yes	6 (15.8%)	355 (77.0%)	<0.001
	No	32 (84.2%)	106 (23.0%)	
Group	Misoprostol	22 (57.9%)	218 (47.3%)	0.208
	Control	16 (42.1%)	243 (52.7%)	
Gender of Baby	Male	22 (57.9%)	217 (47.1%)	0.199
	Female	16 (42.1%)	244 (52.9%)	
Gestational age at delivery	<34 weeks	3 (7.9%)	16 (3.5%)	0.350
	34–36 + 6 weeks	6 (15.8%)	63 (13.7%)	
	37 weeks or more	29 (76.3%)	382 (82.9%)	
Mode of delivery	Cesarean	22 (57.9%)	150 (32.5%)	0.002
	Normal delivery	16 (42.1%)	311 (67.5%)	
Weight of baby	<2 kg	13 (34.2%)	105 (22.8%)	0.034
	2–3 kg	22 (57.9%)	238 (51.6%)	
	>3 kg	3 (7.9%)	118 (25.6%)	

Table 5: Association of abnormalities with risk factors, confounders, and exposure to misoprostol

	B	*OR*	*95% CI*	*p-value*
Age in years	0.135	1.144	1.040–1.260	0.006
Fever in the first trimester	1.911	6.757	2.512–18.174	0.001
Family history of congenital abnormality	1.220	3.388	1.235–9.292	0.014
Cousin marriage	1.501	4.487	1.716–11.729	0.002
Previous history of miscarriages	1.159	3.187	1.192–8.518	0.021
Folate periconception	–2.789	0.061	0.020–0.188	0.001
Mode of delivery (normal delivery)	–0.327	1.100	0.382–3.169	0.860
Weight of baby in kg	–0.748	0.473	0.214–1.046	0.064
Female gender	–0.590	0.555	0.220–1.396	0.211
Gestational age at delivery	–0.548	0.578	0.214–1.046	0.278
Misoprostol exposure	0.809	2.2	0.850–5.88	0.100

B = unstandardized beta coefficient

We therefore maintain that abnormalities are not significantly greater but significantly differ in the spectrum. Women with accidental exposure can be counselled in light of these findings.

Strengths and Limitations

Our study is unique because misoprostol is available as an over-the-counter medication in the country. We used a control group from the same population to ensure the comparability of groups. We excluded women with diabetes and age >35 years as they may have more abnormalities and miscarriages than other groups.

A major limitation is the fact that the dose used by these women is not the standard recommended dose used for inducing abortion. Women ingested misoprostol in varying doses. Another limitation is the fact that mifepristone is not commonly available, and therefore the effect of the combination of both would not be answered by our study.

Conclusion

The chances of having a baby with an abnormality are not significantly increased in women with misoprostol exposure, but caution is advised in interpreting these findings. However, these findings may aid clinicians in reassuring younger women with accidental exposure in early pregnancy.

Clinical Significance

Women with accidental exposure to misoprostol are less likely to have congenital abnormalities than those with voluntary exposure because they were found to ingest a lesser amount of the drug.

Details of Ethical Approval

The hospital administrator gave permission for conducting the study. The principles of Helsinki's Declaration were followed. Data was coded and confidentiality was ensured. Approval from the Institutional Review Board was taken IRB 113-2016.

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