Misoprostol Teratogenicity in Six Filipino Children: a Case Series

Mary Anne D. Chiong[1,2], Eva Maria Cutiongco-de la Paz[1,2]

[1]*Department of Pediatrics, College of Medicine and Philippine General Hospital, University of the Philippines Manila;*
[2] *Institute of Human Genetics, National Institutes of Health, University of the Philippines Manila*

ABSTRACT

Misoprostol is a prostaglandin analogue that has been misused as an abortifacient. We report on six Filipino children who were exposed to the drug in utero with consequent craniofacial and limb abnormalities. Moebius sequence was seen in three of them, two presented with hydrocephalus and limb reduction defects, and one had the oromandibular limb hypogenesis spectrum of defects.

Key Words: misoprostol, Moebius sequence, oromandibular limb hypogenesis spectrum, hydrocephalus, limb reduction defects

Introduction

Induced abortion is legally and morally prohibited in the Philippines, but an unknown number of women in their reproductive age are faced with unwanted pregnancies and some resort to abortion to terminate the pregnancy. The overall rate of induced abortion was 9.6% in a study done by Festin et al. Various methods used for induction were catheter insertion, uterine manipulation and administration of drugs. One of the most commonly used drugs was misoprostol, which showed an increasing trend of consumption and had an overall rate of use of 20.1%.[1]

Misoprostol is a synthetic 15-deoxy-16-hydroxy-16-methylanalog of prostaglandin E1 and was the first prostaglandin to be registered for the treatment of peptic ulcer disease. However, its gastrointestinal effects were overshadowed by the abortifacient effect of the drug and the potential inadvertent or deliberate misuse by pregnant women. It induces abortion in early pregnancy by its significant uterotonic effects.[2] It is being used during the third stage of labor after vaginal delivery to prevent post partum hemorrhage.[3] But, some studies have shown that misoprostol is not very effective in inducing abortions, and exposure to the drug in utero can cause abnormalities in the fetus.[4-7]

We report on six Filipino patients presenting primarily with craniofacial and limb defects after prenatal misoprostol exposure.

Corresponding author: Mary Anne D. Chiong, MD
Institute of Human Genetics, National Institutes of Health,
University of the Philippines Manila
625 Pedro Gil Street, Ermita Manila 1000, Philippines
Telephone: +632 536 7002
E-mail: madchiong@post.upm.edu.ph

Clinical Reports

Patient 1

This newborn male patient was born to a 22 year old primigravid mother who took 4 tablets (200 mcg tablet) of misoprostol (Cytotec) orally at 3 months age of gestation followed by vaginal bleeding. There was no intravaginal use of misoprostol or intake of other abortifacients. The pregnancy continued with no other complications except for a finding of ventriculomegaly on prenatal ultrasound at 5 months age of gestation and oligohydramnios at 8 months age of gestation.

He was delivered prematurely after a cesarean section with Apgar scores of 6 and 9 at 1 and 5 minutes, respectively. Birth weight was 1.5 kg (3rd-50th percentile), length was 48 cm (>97th percentile) and head circumference was 33 cm (> 97th percentile). Physical findings included a large anterior fontanelle with gaping cranial sutures, low set ears with hypoplastic helices, flat nasal bridge, hypoplastic nipples and undescended testes with minimal scrotal rugae. Limb findings showed amputated 1st, 2nd, 3rd and 4th digits on the right hand, and 2nd-3rd toe syndactyly on both feet with hypoplastic nailbeds. The rest of the physical and neurologic examinations were normal. She succumbed to sepsis on the second week of life (Figure 1).

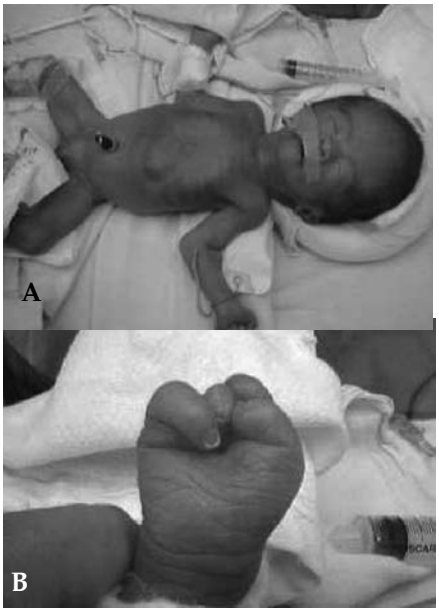

Figure 1. A) Hydrocephalus. B) Limb reduction defects (with permission).

Patient 2

This 3 week old male was the first child of a 22 year old mother and a 32 year old father. On the 8th week of gestation, the mother took 2 tablets of 200 mcg misoprostol (Cytotec) in a single oral dose, after which, she had vaginal bleeding. There was no intravaginal use of misoprostol or intake of other abortifacients. The pregnancy continued uneventfully and the child was born at term. Delivery was normal and the patient had good Apgar scores. His birth weight was 2 kg (<5th percentile) and the following were noted at birth: microphthalmia, micrognathia, finger and nail anomalies.

At the time of examination, his weight was 2.05 kg and length was 47 cm, both below the 5th percentile for age, and his head circumference was 29.5 cm (<2SD). Pertinent physical findings showed biparietal bossing with open flat anterior fontanelle, microphthalmia with fusion of the eyelids, prominent high nasal bridge and tip, low set posteriorly rotated ears with hypoplastic helices, mandibular hypoplasia with micrognathia, and a tongue that was fused to the palate making him unable to fully open his mouth. The child was fed by a nasogastric tube since birth. Limb anomalies included agenesis of the distal phalanges and nails of fingers 2, 3, 4 and 5 on the left limb, hypoplastic nailbed on the 3rd digit of the right limb, transverse palmar creases on both hands and 2nd-3rd toe syndactyly. Neurologic examination showed bilateral palsy of the cranial nerves VI and VII. Oromandibular limb hypogenesis spectrum was the primary diagnosis given (Figure 2).

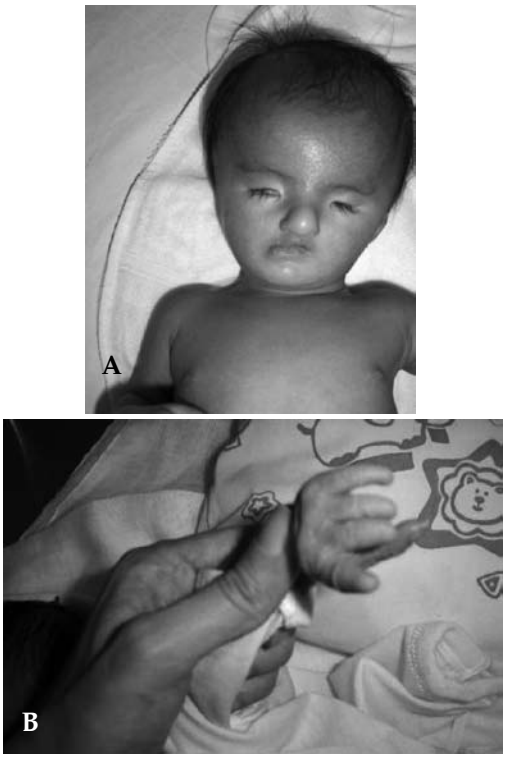

Figure 2. A) Microphthalmia, mandibular hypoplasia and micrognathia. B) Limb reduction defects (with permission).

Cranial CT scan showed corpus callosum dysgenesis with heterorotopia on both lateral ventricles. Ophthalmologic examination revealed sclerocornea on the right and cryptophthalmos on the left. On CT scan, the left eye globe was small while that of the right showed enhancement of the cornea with calcification of the lens. Both optic nerves were normal. 2D echocardiography was normal. Chromosomal analysis revealed a normal male karyotype.

Patient 3

This female infant was born to a non-consanguineous 19 year old father and a 22 year old primigravid mother who took 1 tablet (200 mcg) of misoprostol (Cytotec) orally at 2 months age of gestation. She did not have vaginal bleeding or uterine contractions and the pregnancy went on uneventfully to term. There was no intravaginal use of misoprostol or intake of other abortifacients.

She was delivered by cesarean section with good Apgar scores and birth weight was 3.3 kg (50th percentile). There was bilateral facial paralysis and a diagnosis of Moebius sequence was made.

She had recurrent bouts of aspiration pneumonia, and bronchoscopy done at 2 ½ months old revealed laryngomalacia and she underwent tracheostomy. She also had gastroesophageal reflux disease and underwent gastrostomy with fundoplication at the same age. Cranial MRI was normal. Electromyography-Nerve Conduction Velocity studies showed severe denervation of the face, left more than the right.

She was examined at 4 months old while admitted for nosocomial pneumonia. During this time, her head circumference was 38.5 cm (<2 SD), her length which was 55 cm and weight which was 4 kg were both below the 5th percentile. Physical findings included prominent parietal and occipital bones, downslanting palpebral fissures, flat nasal bridge with anteverted nares, shallow philtrum, high arched palate, tented upper lip and micrognathia. There were no limb abnormalities and the rest of the physical examination was normal. Neurologic examination revealed bilateral lateral rectus and seventh cranial nerve palsies.

She died at home 2 weeks after discharge from severe dehydration secondary to acute gastroenteritis. No autopsy was done.

Patient 4

This female patient was the first child of a healthy and non-consanguineous couple, both 19 years of age. The mother took 5 tablets (200 mcg tablet) of misoprostol (Cytotec) orally during the 1st trimester of pregnancy followed by vaginal spotting but the pregnancy continued uneventfully to term. There was no intravaginal use of misoprostol or intake of other abortifacients.

She was born spontaneously with note of a weak cry at birth. Her birth weight was 2.3 kg (<5th percentile). Facial palsy, cleft palate and a right clubfoot were noted. She stayed in the nursery for 40 days due to feeding difficulties.

A diagnosis of Moebius sequence was given.

Chromosomal analysis showed a normal female karyotype. Cranial ultrasound was normal. The auditory brainstem response revealed severe sensorineural hearing loss on the right and moderate hearing loss on the left. Delayed visual maturity and lateral rectus palsy were seen on ophthalmologic evaluation. Serial casting was done on the right foot. Psychomotor development showed global developmental delay.

She was lost to follow up and on re-evaluation at 5 years old, her head circumference was 49.5 cm (50th percentile), weight was 15.5 kg (5th percentile) and length was 107 cm (50th percentile). Pertinent physical findings showed myopathic facies with bilateral ptosis and bilateral epicanthal folds, flat nasal bridge with anteverted nares, cupped ears and an unrepaired cleft palate. Limb anomalies showed bilateral simian crease and clinodactyly of the 5th digits and talipes equinovarus deformity of the right foot. Neurologic examination showed bilateral palsy of the 6th and 7th cranial nerves. The tongue was also deviated to the left (Figure 3).

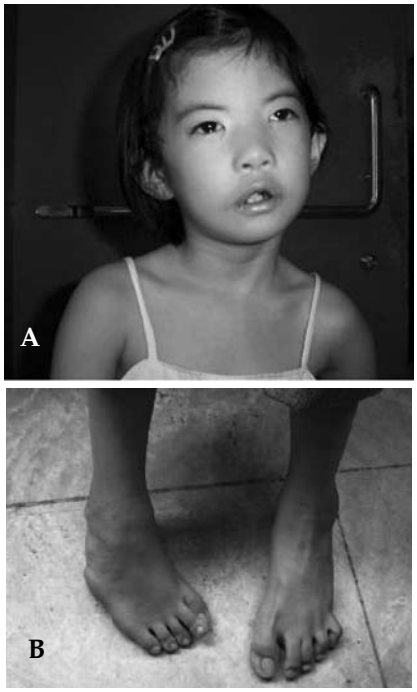

Figure 3. A) Myopathic facies (with permission). B) Talipes equinovarus.

Patient 5

This female child was born to a non-consanguineous 38 year old father and a 36 year old primigravid mother who took 5 tablets of misoprostol (Cytotec) orally twice on separate occasions at 3 months age of gestation. There was no intravaginal use of misoprostol or intake of other abortifacients. There were no uterine contractions or vaginal bleeding after intake and the pregnancy went on. A prenatal ultrasound done at 8 months age of gestation showed symmetrical obstructive hydrocephalus.

The baby was delivered full term via spontaneous vaginal delivery with good Apgar scores. She had a birth weight of 2.7 kg. Limb reduction defects were noted. CT scan of the head revealed corpus callosum dysgenesis with absent septum pellucidum, cerebral atrophy on the right hemisphere and dilated lateral ventricles.

She never had seizures. Gross motor milestones were achieved at par with age. There were delays however, on fine motor, language and personal/social skills.

At the time of examination at 29 months old, she was observed to be hyperactive. Head circumference was 43.5 cm (< 2SD), and weight of 10.3 kg and length of 78 cm were both below the 5th percentile for age. Pertinent physical findings showed dolicocephaly with frontal bossing, bilateral epicanthal folds, flat nasal bridge and cupped ears. Limb reduction of the right 5th digit and the left 3rd digit were noted. A constriction band was noted on the left lower leg. Except for esotropia on the right eye, neurologic examination was normal for age (Figure 4).

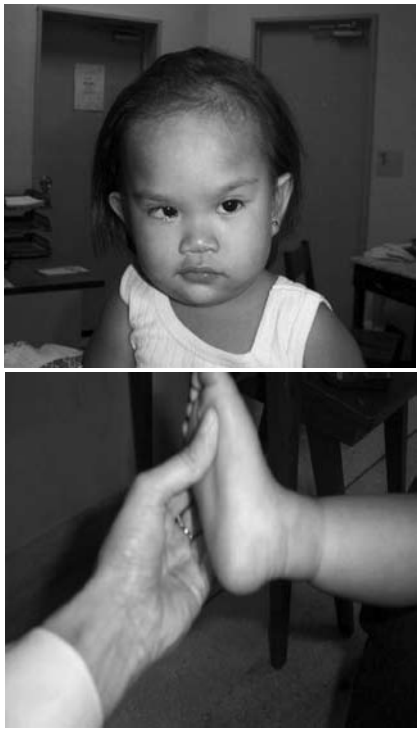

Figure 4. A) Frontal bossing and esotropia (with permission). B) Constriction band on the leg.

Patient 6

This newborn male was the product of a non-consanguineous 25 year old father and a 24 year old G3 P2 mother who took 1 tablet (200 mcg) of misoprostol (Cytotec) in a single oral dose during the 1st trimester of her pregnancy. She did not have vaginal bleeding or uterine contractions and the pregnancy was carried on to term uneventfully. There was no intravaginal use of misoprostol or intake of other abortifacients.

He was born by spontaneous vaginal delivery with no perinatal complications. His birth weight was 3.5 kg (50th – 97th percentile), length was 50 cm (50th percentile) and head circumference was 32 cm (3rd percentile). Unusual facies and bilateral clubfoot were noted at birth.

Pertinent physical findings showed a sloping forehead, bilateral epicanthal folds, flat broad nasal bridge, flat philtrum, thin upper lip and micrognathia, right firm scrotal mass and bilateral equinovarus foot deformity. Neurologic examination revealed bilateral facial nerve palsy. A diagnosis of Moebius sequence and neonatal sepsis were made (Figure 5).

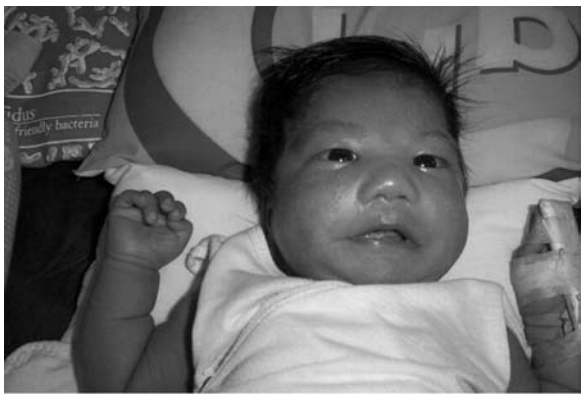

Figure 5. Facial palsy (with permission).

Cranial ultrasound and 2D echocardiography were normal. Abdominal ultrasound showed a complex mass on the right lower lobe which was confirmed by CT scan to be an adrenal hematoma. Bleeding parameters were deranged. The scrotal mass ruptured into an abscess. He remained hospitalized for septicemia and was discharged improved at 5 weeks of life.

Discussion

The first report of fetal damage from unsuccessful use of misoprostol to induce abortion, described unusually large lateral defects of the scalp and cranium in five subjects.[4] Gonzales et al on the other hand, initially reported on various limb deformities with or without cranial nerve palsies associated with prenatal exposure to misoprostol.[5] This was followed by a bigger study which further defined the common phenotypical effects of exposure to the drug. Indeed, the most distinctive phenotype observed were arthrogryposis confined to the legs and terminal transverse limb defects with or without Moebius sequence.[6]

Meanwhile, Orioli and Castilla recently reviewed the congenital defects described previously with misoprostol prenatal exposure. Out of 53 patients reported in literature, cranial nerve palsy was the most frequently observed abnormality occurring in 25 out of 53 patients, followed by equinovarus feet (24/53), hydrocephalus (14/53), transverse limb defects (13/53) and arthrogryposis (10/53) among others (Table 1).[7]

Table 1. Summary of congenital defects described previously with Misoprostol prenatal exposure and the defects seen in our 6 patients

Defects	Frequency of Occurrence	Our patients
1. Cranial nerve palsy	25/53	4/6
2. Equinovarus feet	24/53	2/6
3. Hydrocephalus	14/53	2/6
4. Terminal transverse limb defect	13/53	3/6
5. Arthrogryposis	10/53	0/6
6. Syndactyly	7/53	2/6
7. Limb constriction ring	5/53	1/6
8. Microcephaly	4/53	3/6
9. Brachydactyly	3/53	0/6
10. Hypospadias	2/53	0/6
11. Cleft palate/Bifid uvula	2/53	1/6
12. Nail hypoplasia	2/53	2/6
13. Omphalocoele	2/53	0/6
14. Intrauterine growth retardation	1/53	0/6
15. Scalp and skull defect	1/53	0/6
16. Dextrocardia	1/53	0/6
17. Agenesis of abdominal muscles	1/53	0/6
18. Congenital brain malformation	0/53	2/6
19.Congenital eye anomalies	0/53	1/6

Since case reports cannot prove a causal link between in utero exposure to misoprostol and birth defects, the association between misoprostol teratogenicity and specific congenital defects was verified through an epidemiologic assessment of all malformed and non-malformed newborn infants across ten Latin-American countries in South America. Four of the five more commonly observed congenital defects in newborns exposed to misoprostol were found to be in excess i.e. constriction ring, terminal transverse limb defects, hydrocephalus and arthrogryposis. Cranial nerve palsies were not frequently reported as these were not expected to be obvious at birth. Thus, the high association between the four congenital defects and misoprostol exposure seemed indicative of a real teratogenic effect. Furthermore, 13 different defects (extra nipple, cleft lip+/- cleft palate, post axial polydactyly, holoprosencephaly, hydronephrosis, preauricular tag, pigmented nevus, interatrial septal defect, ear defect, cephalocoele, bladder exstrophy, gastroschisis and malpositioned toes) not described in literature were seen in the misoprostol exposed cases, but only holoprosencephaly and bladder exstrophy significantly exceeded the expected number. Only two of their malformed cases, presented with multiple anomalies which probably belonged to the oromandibular limb hypogenesis spectrum.[7]

Our patients presented with features of misoprostol teratogenicity not generally different from those of the previously reported cases. Four of them presented with Moebius sequence, one as part of the oromandibular limb hypogenesis spectrum and the three as isolated cases. Out

of the three, two had talipes equinovarus deformity and one with cranial nerve palsy alone. The other two patients both presented with hydrocephalus and limb reduction defects.

The most severe phenotype observed among our patients was the oromandibular limb hypogenesis spectrum of defects in Patient 2. The etiology is unknown but a disruptive vascular mechanism has been suggested. This most likely occurs in the distal regions of the body such as the distal limbs, tongue and parts of the brain. Features include small mouth, micrognathia, hypoglossia / aglossia, glossopalatine ankylosis, cleft palate, cranial nerve palsies, hypodactyly / adactyly and brain defects.[8] He also had significant eye abnormalities such as sclerocornea and cryptophthalmos that have neither been reported in oromandibular limb hypogenesis spectrum nor in previously reported cases of misoprostol exposure.

The laryngomalacia and gastroesophageal reflux noted in patient 3 are common congenital anomalies resulting from the weakness of the supporting structures of the larynx and hypotonia of the lower esophageal sphincter, respectively. These conditions resolve spontaneously around 2 years of age when the muscular support improves and may not be part of Moebius sequence per se.

The severe hearing loss in Patient 4 together with her facial paralysis with tongue deviation to the left and feeding difficulties may all be due to the multiple cranial nerve nuclei abnormalities that primarily underlie the pathogenic mechanism in Moebius sequence. Cranial and radiopathologic findings in Moebius sequence such as brainstem hypoplasia, focal brainstem necrosis and symmetric calcifications at the junction of the midbrain and the pons highly support the embryopathogenesis.[9]

The brain malformations in Patients 2 and 5 consisting of corpus callosum dysgenesis, absent septum pellucidum, brain heterotopias and cerebral atrophy, to our knowledge, have not yet been reported as among the cranial malformations seen in misoprostol prenatal exposure. These are highly suggestive of the further teratogenic effects of the drug in the developing fetal brain.

The abnormalities observed in children exposed to misoprostol in utero have been attributed to vascular disruption. Shepard has postulated that uterine contractions produced by misoprostol in the second month of pregnancy, when the amount of amniotic fluid is small, lead to anterior-posterior embryonic compression at the level of the 6th and 7th cranial nerves and subsequent vascular interruption, explaining the preferential lesions of cranial nerve nuclei in Moebius sequence.[10] Likewise, the intense vasoconstriction and uterine contractions produced by prostaglandin were also proposed to result in distal ischemia in the fetus, leading to the digital anomalies observed. The mechanism of formation of hydrocephalus was also through vasoconstriction and hypoxia, with or without associated hemorrhage, leading to stenosis of the foramina of Munro.[11] Sodre et al, found by angiography and Doppler flow analysis of 30 children, that equinovarus deformity was associated with hypoplasia or premature termination of the anterior tibial artery and the middle plantar arteries.[12]

In conclusion, the cases we described contributed to the previous reports in the literature about the association of prenatal use of misoprostol as abortifacient and congenital defects of vascular disruption type. In the Philippines, financial difficulty and spacing of children outweigh the legal and religious sanctions abortion bears. With the dangers posed by misoprostol as an abortifacient, massive efforts should be exerted to inform women about its harmful effects on the fetus. The Bureau of Food and Drug in 2002 has warned pharmacists, drugstore owners and consumers against using, selling and dispensing of misoprostol (Cytotec).[13] However, at the present time, the drug can still be bought in the black market. The respective authorities should therefore take appropriate measures to apprehend the people dealing with the dispensing and selling of this drug.

References

1. Festin M, Habana MA, Galvez-Millan P. Patterns of induced abortion seen at the Department of Obstetrics and Gynecology, Philippine General Hospital. Phil J of Obs Gyn. 1997;21:65-73.
2. Norman JE, Thong K, Baird DT . Uterine contractility and induction of abortion in early pregnancy by Misoprostol and Mifepristone. Lancet. 1991;338:1233-1236.
3. Cochrane Database of Systematic Reviews. Prostaglandins for preventing postpartum haemorrhage. 2007; 18 (3):CD000494.
4. Fonseca W, Alencar AJ, Mota FS. Misoprostol and congenital malformations. Lancet. 1991; 338:56.
5. Gonzalez CH, Vargas FR, Perez AB, et al. Limb deficiency with or without Mobius sequence in seven Brazilian children associated with Misoprostol use in the first trimester of pregnancy. Am J Med Genet. 1993; 47: 59-64.
6. Gonzalez CH, Marques-Dias MJ, Kim CA, et al. Congenital abnormalities in Brazilian children associated with Misoprostol misuse in first trimester of pregnancy. Lancet. 1998; 351: 1624-1627.
7. Orioli I, Castilla E. Epidemiological assessment of Misoprostol teratogenicity. British J of Obst Gyn. 2000;107: 519-523.
8. Jones KL Smith's recognizable pattern of human malformations, 5th edition. W.B. Saunders Company, 1997:646-647.
9. D'Cruz OF, Swisher CN, Jaradeh S, Tang T, Konkol RJ. Mobius syndrome: evidence for a vascular etiology. J Child Neurol. 1993 Jul; 8 : 260-5.
10. Shepard TH. Mobius syndrome after Misoprostol: a possible teratogenic mechanism. Lancet. 1995; 346:780.
11. Collins FS, Mahoney M. Hydrocephalus and abnormal digits after failed first trimester prostaglandin abortion attempt. J Pediatr. 1983;102: 620-621.
12. Sodre H, Brushcini S,Mestriner LA, et al. Arterial abnormalities in talipes equinovarus as assessed by angiography and Doppler. J Pediatr Orthop. 1990; 10: 101-104.
13. Misoprostol Unregistered Drug Product. BFAD Advisory 2002-02. Available at http://www.bfad.gov.ph/. Accessed September 3, 2004.