

VACTERL ASSOCIATION: IMPACT OF HERBAL AND OTHER ABORTIFACIENTS¹*Azikiwe Cca and ²Ifezulike Cc¹Department of Pharmacology and Therapeutics, Chukwuemeka Odumegwu Ojukwu University, Awka. Nigeria.²Department of Paediatrics, Chukwuemeka Odumegwu Ojukwu University, Awka. Nigeria.

*Corresponding Author: Dr. Azikiwe Cca

Department of Pharmacology and Therapeutics, Chukwuemeka Odumegwu Ojukwu University, Awka. Nigeria.

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ABSTRACTS

Background: Misoprostol is a prostaglandin analogue used to ripen the cervix, an anti peptic ulcer disease, oxytocics and as an abortifacient. *Momordica foetida* is a tropical flowering plant used in folkore for treatment of stomach upsets and aid in labour during childbirth. **Case Report:** We report a case of a 17 year old social mother who worked as a food vendor. She took repeated doses of cytotec (Misoprostol) and aqueous extract of the freshly shoot and seeds of *Momordica foetida* in order to abort her unwanted pregnancy. All attempts up to 25 weeks of gestation however failed to terminate her pregnancy. She though experienced intermittent blood spotting and very occasional frank bleeding between 7 and 20 weeks of her gestation, there was no expulsion of the foetus. She came into spontaneous labour at 39 weeks 3 days but, had an obstruction necessitating her referral for a caesarean section at our facility. Anaesthesia was regional spinal and baby was delivered within a few minutes. The baby however gave a single shrill cry with the only present left eye wide open and passed on. Further examination revealed a hydroencephalous with an amorphous indentation, deformed ear lobes, club feet, absence of anal perforation, pigeon chest and polydactyl. **Conclusion:** We conclude that repeated doses of misoprostol and *Momordica foetida* by the young mother led to the VACTERL association of the child. There is a potential and dangerous teratogenic synergism between herbal and orthodox abortifacients. Timely public enlightenment is highly advised. We recommend further full researches on *Momordica foetida* and its synergism with misoprostol or other prostaglandin agonist or analogue.

KEYWORDS: Vacterl association, Abortion/miscarriage, Misoprostol, *Momordica foetida*, Multiple birth deformities, Teratogenic toxicity.

INTRODUCTION

Abortion is pregnancy loss within the first trimester while miscarriage is pregnancy loss after the first trimester but, before the standard age of viability. Abortion and miscarriage are in modern terms, used interchangeably as the word abortion tends to illicit lots of emotions, religious and legality issues. Abortion/miscarriage can be spontaneous or induced. Induction could be medical, surgical or illegal.

Misoprostol is a synthetic drug and a prostaglandin analogue. It has many medical uses including being used in the management of peptic ulcer diseases (PUD), especially when induced by non steroidal anti-inflammatory drugs (NSAIDs), as prophylaxis for PUD induced by NSAIDs, as an agent to ripen the cervix for labour induction, as an anti post partum haemorrhagic drug and as an abortion agent (Roston *et al.*, 2002).

For abortions it is used by itself or in combination with mifepristone or methotrexate. By itself, effectiveness for abortion is between 66% and 90% (Raymond *et al.*,

2019). Effectiveness is also affected by route of administration and the least effective route is the oral.

In Nigeria, the most popular and efficacious brand of misoprostol is *Cytotec* and it is readily sold as over the counter drug. The drug is however usually taken via the least effective route thus a high risk for failures in abortion.

Misoprostol is highly contraindicated in early and desired pregnancy as it could lead to an abortion or foetal abnormality. Among other unwanted effects of misoprostol are diarrhea, nausea, flatulence, vomiting, abdominal cramps, constipation, headache, dyspepsia, uterine hyper stimulation, uterine rupture and vaginal bleeding.

For mechanism of abortion, Misoprostol binds to myometrial cells to cause strong myometrial contractions leading to expulsion of the foetus. Misoprostol also causes cervical ripening with softening and dilation of the cervix. Misoprostol binds to and stimulates Prostaglandins EP₂, EP₃ and EP₄ but, seems to have no

effect on EP₁ receptor thus is expected to have a more restricted range of physiological and potentially toxic actions than prostaglandin E₂ or other analogs which activate all four prostaglandin receptors (Moreno, 2017; Wu *et al.*, 2017).

Misoprostol during the first trimester of pregnancy is associated with a specific malformative pattern (Moebius sequence and limb defects) whose incidence remains unknown (Vauzelle *et al.*, 2013).

Misoprostol, a synthetic analog of prostaglandin E₁, is currently used in Chile and other countries as an antiulcer medication, mainly for the prevention of non-steroidal anti-inflammatory-induced gastric ulcers. Due to its uterotonic properties, it is also indicated in obstetrics for induction of labor and termination of pregnancy. In this last case, misoprostol is either used alone or in combination with other oxytocic drugs such as methotrexate or mifepristone. The use of misoprostol as an abortifacient agent is considered to be safe since it rarely causes serious side effects. However up to 15 % of misoprostol-induced-abortions may not be successful, even under medical supervision, leading to in utero exposure to the drug and to the induction of a series of birth defects including limb and joints defects and Moebius syndrome (Cavieres, 2011).

Ineffective use of mifepristone and misoprostol in the first trimester of pregnancy may be associated with a risk of Möbius syndrome, primarily due to misoprostol activity. Women with ongoing pregnancy after failed abortion with misoprostol administration should be informed of this risk (Bos-Thompson *et al.*, 2008).

In a ten year retrospective review and meta-analysis to demonstrate the types and degree of malformations on infants whose mothers had misoprostol in the first trimester, the outcomes of interest included congenital anomalies, fetal death, low birth weight and prematurity (da Silva *et al.*, 2006).



Fig. 1: The freshly leaves and fruit of *Momordica foetida* on grassland.(Adapted from Wikipedia, on 25th February, 2020).

Momordica foetida is a perennial climbing vine native of tropical Africa, closely related to the bitter lemon (*M. charantia*) and balsam apple (*M. balsamina*). Its species name ("bad-smelling") refers to its unpleasant smell. It was previously named *M. morkorra* (A. Rich) and *M. cordata* (Cogn) (Jeffery, 1978; Burkill, 1985). It is called **akpana udene** in Anioma dialect of Nigeria (Fig 1). The plant grows in forest edges and similar habitats (including disturbed and cultivated land), woodland, and wooded grassland. Its leaves are wrinkled, heart-shaped with irregular edges, up to 18 cm wide. The flowers are yellow to yellow-orange. The fruit is a prolate spheroid, 3.5–7.5 cm long and 2.5–5 cm wide, bright orange and covered with soft spines. When fully ripe it splits from the bottom into three valves, exposing a cluster of black seeds, individually covered by a bright red, sticky, sweet pulp. The plant has perennial tuberous roots.



Fig 2: A cut through the fruit of *Momordica foetida* to reveal the seeds and pulp (Wikipedia, 2020).

The leaves, roots, seeds, pulp and stems are used differently in different parts of Africa for treatment of a wide range of ailments and disorders. It aids childbirth during labour (Kamatnesi-Mugisha *et al.*, 2007). It has in-vitro ascaricidal activity (Wasswa and Olila, 2006).

For abortions, the seeds and pulp (Fig 2) are ground into a paste and inserted deep into the vagina to induce cervical ripening and dilation. The uterus then contract and expel the foetus. A similar mechanism with misoprostol though not yet scientifically demonstrated and documented.

CASE REPORT

The case under review involved a young Nigerian girl of Igbo extraction. She was 17, unmarried and dropped out at secondary school level of education. She worked as a sales girl in a privately owned bar/restaurant. She was a primigravida and did all she could to terminate her pregnancy.

She bought misoprostol at the instance of a patent medicine dealer and took 400micrograms every fortnightly starting from about 6 or 7 weeks up to 24 or 26 weeks of her gestation. She also took several glasses

of the macerated freshly leaves and stems of *Momordica foetida*. Lastly, she inserted intra-vaginally the ground seeds and pulp of the plant to no avail. She though at several occasions experienced blood spotting and an episode of frank bleeding there was no expulsion of the foetus.

She did all she could to conceal her advancing pregnancy from friends, co-workers and employer. She eventually, came into spontaneous labour at 39 weeks 3days but, had an obstruction necessitating her referral for a caesarean section at our facility.

Anaesthesia was regional spinal and baby was delivered within a few minutes.

The baby however gave a single shrill cry with the only present left eye wide open and passed on.

Further examination revealed a hydroencephalous with an amorphous indentation, deformed ear lobes, club feet, absence of anal perforation, pigeon chest and polydactyl.



Fig 3: A photograph of the child with vacterl association.

DISCUSSION

Vacterl association is a disorder that affects many body systems. Vacterl stands for vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities. People diagnosed with vacterl association typically have at least three of these characteristic features (Gigante, 2006).

No specific genetic or chromosome problem has been identified with VACTERL association but, may be seen with some chromosomal defects such as Trisomy 18 and is more frequently seen in babies of diabetic mothers.

VACTERL association, however, is most likely caused by multiple factors (Hersh *et al.*, 2002).

VACTERL is an acronym for a nonrandom association of congenital anomalies for which the etiology is still poorly understood (Bernardi *et al.*, 2010). Vacterl association specifically refers to the abnormalities in structures derived from the embryonic mesoderm.

There is a wide range of manifestation of vacterl association so that the exact incidence within the population is not exactly known, but has been estimated to occur in one in 10,000 to 40,000 newborns.

Up to 75 percent of patients with vacterl association have been reported to have congenital heart disease.

Most cases of Vacterl associations are linked to insults or assault to the developing embryo and there seems to be a link to disruption in the vasculature thus leading to young organ death or malformation.

Thalidomide is a very potent teratogen capable of causing severe systemic malformations if the foetus is exposed during the sensitive period (Miller *et al.*, 2009).

Several malformations have been attributed to the process of vascular disruption. The central hypothesis for this etiology is that blood flow to a structure has been altered after that structure had formed normally. The decreased blood flow leads to hypoxia, endothelial cell damage, hemorrhage, tissue loss, and repair. After recovery, some structures are normal and others show either tissue loss or structural abnormalities, such as syndactyly and constriction rings (Holmes *et al.*, 2018).

Bernardi *et al.*, 2010 reported the case of a seven-month-old white girl whose mother had used misoprostol in the second month of pregnancy to induce abortion. On clinical evaluation, she was small for her age and presented hypotonia, anteverted nares, long philtrum and carp-like mouth. Her left hand had a reduction defect, with absence of the extremities of the second, third and fifth fingers and camptodactyly of the fourth finger. The ipsilateral lower limb presented significant shortening, especially rhizomelic shortening. Her left foot had a mirror configuration with seven toes and no identifiable hallux. The pelvis was hypoplastic. Esophageal atresia with tracheoesophageal fistula and imperforate anus were detected during the neonatal period.

Similar findings were reported earlier in 2008 where monozygote twins exhibited a variation in the degree and type of birth abnormalities (Camacho *et al.*, 2008). Perhaps as a mark of degree of exposure, type and source of the teratogenic substance.

From existing literature and our findings in the index case, it can be deduced that exposure of the developing

embryo or foetus to misoprostol by the young mother was responsible for the Vacterl association of the baby.

Momortica foetida has been scientifically documented as an oxytocic. A combination of this medicinal plant with misoprostol may have induced a synergistic effect on the foetus thus a marked multiple birth abnormalities.

The mechanism of action may stem from vascular disruption of blood supply to the young and developing organs to outright destruction of other cellular elements.

Abdulrahim, in 2010 however, reported a case of a 29 year old pregnant lady who took 10,800 micrograms of misoprostol orally and vaginally but, failed to terminate her pregnancy. Rarely at birth, however no foetal abnormality was detected.

CONCLUSION

We conclude that repeated doses of misoprostol and *Momortica foetida* by the young mother led to the VACTERL association of the child.

There is a potential and dangerous teratogenic synergism between herbal and orthodox abortifacients. Timely public enlightenment is highly advised.

We recommend further full researches on *Momordica foetida* and its synergism with misoprostol or other prostaglandin agonist or analogue.

REFERENCES

1. Abdulrahim AR: Abortion failure after illegal use of misoprostol---A case Report. *Eur J Contracept Reprod Health Care.*, 2010; 15(5): 376-378.
2. Bernardi P, Graziadio C, Rosa RF, Pfeil JN, Zen PR, Paskulin GA: Fibular dimelia and mirror polydactyl of the foot in a girl presenting additional features of the Vacterl association. *Sao Paulo Med J.*, 2010; 128(2): 99-101.
3. Bos-Thompson MA, Hillaire-Buys D, Roux C, Faillie JL, Amram D: Mobius syndrome in a neonate after mifepristone and misoprostol elective abortion failure. *Ann Pharmacother.*, 2008; 42(6): 888-892.
4. Burkill, H. M. (1985). *The Useful Plants of West Tropical Africa. I.* Kew Publishing. ISBN 094764301X.
5. Camacho AF, Schneider A, Dorsaninville D, Schutzman DL: Monozygotic twins discordant for VACTERL ASSOCIATION. *Prenat Diagn.*, 2008; 28(4): 366-368.
6. Cavieres MF: Developmental Toxicity of Misoprostol: An Update. *Rev Med Chil.*, 2011; 139(4): 516-523.
7. Da-Saliva Dal Pizzol T, Knop FP, Menque SS: Prenatal exposure to Misoprostol and congenital anomalies: Systematic review and met-analysis. *Reprod Toxicology*, 2006; 22(4): 666-671.
8. Gigante, Joseph *First Exposure to Pediatrics*. New York: McGraw-Hill, Medical Pub. Division, 2006; 351. ISBN 978-0071441704.
9. Wu HL, Marwah S, Wang P, Wang QM, Chen XW: Misoprostol for Medical Treatment of Missed Abortion: A Systematic Review and Network Meta-Analysis. *Sci Rep.*, 2017; 7(1): 1664. PMID: 28490770.
10. Hersh JH, Angle B, Fox TL, Barth RF, Bendon RW, Gowans G. "Developmental field defects: coming together of associations and sequences during blastogenesis". *Am J Med Genet*, 2002; 110(4): 320-323.
11. Holmes LB, Westgate Marie-Noel, Nasri H, Toufaily MH: Malformations attributed to the Process of Vascular Disruption. *Birth Defects Res.*, 2018; 110(2): 98-107.
12. Jeffrey, C. "*Cucurbitaceae*". *Flora Zambesiaca*, 1978; 4.
13. Kamatenesi-Mugisha M and Oryem-Origa H: Medicinal plants used to induce labour during childbirth in Western Uganda. *J. Ethnopharmacology*, 2007; 109(1): 1-9.
14. Miller MT, Ventura L, Stromland K: Thalidomide and Misoprostol: Ophthalmologic Manifestations and Associations Both Expected and Unexpected. *Birth defects Res. Clin Mol Tera.*, 2009; 85(8): 667-676.
15. Moreno JJ. "Eicosanoid receptors: Targets for the treatment of disrupted intestinal epithelial homeostasis". *European Journal of Pharmacology*, 2017; 796: 7-19. doi:10.1016/j.ejphar.2016.12.004. PMID 27940058.
16. Raymond, EG; Harrison, MS; Weaver, MA "*Efficacy of Misoprostol Alone for First-Trimester Medical Abortion: A Systematic Review*". *Obstetrics and Gynecology*, 2019; 133(1): 137-147. doi:10.1097/AOG.0000000000003017. PMC 6309472. PMID 30531568.
17. Rostom A, Dube C, Wells G, Tugwell P, Welch V, Jolicoeur E, McGowan J. "Prevention of NSAID-induced gastroduodenal ulcers". *Cochrane Database Syst Rev.*, 2002; 4: CD002296.
18. Vauzelle C, Beghin D, Cournot MP, Elefant E: Birth defects after exposure to misoprostol in the first trimester of pregnancy: Prospective Follow-Up study. *Repro Toxicol*, 2013; 36: 98-103.
19. Wasswa P and Olila D: The in-vitro ascaricidal activity of selected indigenous medicinal plants used in ethno veterinary practices in Uganda. *African Journal of Traditional, Complimentary and Alternative Medicine*, 2006; 3(2): 94-103.