Research Summary

HIGH FEVER INCIDENCE FOLLOWING TREATMENT WITH MISOPROSTOL FOR POSTPARTUM HEMORRHAGE

Misoprostol, an E1 prostaglandin, is a recognized treatment alternative to intravenous (IV) oxytocin, the gold standard uterotonic, for controlling postpartum hemorrhage (PPH) due to uterine atony (FIGO 2017). Two large double-blind, randomized, non-inferiority trials, conducted in five countries to evaluate the efficacy, safety and acceptability of IV oxytocin (40 IU) and sublingual misoprostol (800mcg), found both regimens stopped active bleeding within 20 minutes of administration in nine out of 10 women with PPH. While reports of fever and shivering were common among women treated with misoprostol, overall acceptability of the medicine was high.

Read more: Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin, Lancet 2010, Blum et al.; Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour, Lancet 2010, Winikoff et al.

An unexpected finding from these studies was the significant variability in the rates of shivering and fever across sites (see Table). Women from the site in Quito, Ecuador were especially prone to experiencing elevated temperature ≥40.0°C (≥104°F) after use of misoprostol. The findings prompted additional research to (1) explore whether a thermoregulatory response to misoprostol is based on genetic factors, and (2) characterize the occurrence of high fever in other settings.

Table: Rates of shivering, fever, and high fever (≥40.0°C) by site following sublingual treatment with misoprostol for PPH

	Shivering	Fever	High fever
Burkina Faso	65% (22/34)	29% (10/34)	0% (0/34)
Ecuador	90% (146/163)	93% (151/163)	36% (58/163)
Egypt	17% (72/434)	13% (57/434)	1% (3/434)
Turkey	76% (25/33)	42% (14/33)	3% (1/33)
Vietnam	50% (116/231)	32% (73/231)	4% (9/231)

Read more: High fever following postpartum administration of sublingual misoprostol, BJOG 2010, Durocher et al.

The role of genetic factors on misoprostol-induced fever

Genetic analyses were carried out by researchers from the University of Liverpool, using blood samples from 50 Ecuadorian women given PPH treatment with misoprostol in one hospital in Quito. The results showed a positive association between two prostaglandin transporter genes with misoprostol-induced fever and also that genetic variants slowed down misoprostol's transport across biological membranes when tested *in vitro*, leading to an increase in the drug level in the system. The researchers hypothesize that the high fever is likely to occur as a result of this mechanism.

Read more: Misoprostol-induced fever and genetic polymorphisms in drug transporters SLCO1B1 and ABCC4 in women of Latin American and European ancestry, Pharmacogenomics 2015, Alfirevic A et al.

Susceptibility to misoprostol-related high fever in Argentina

Additional research was completed in two hospitals in Corrientes, Argentina to document the rate of high fever following PPH treatment with misoprostol after vaginal birth. Shivering and fever were experienced by three-quarters (37/49) of women diagnosed and treated for PPH with misoprostol. Systematic temperature measurement after misoprostol administration confirmed a rate of high fever of 12.2% [95% confidence interval 4.6-24.8%]. Fever, irrespective of its severity, usually occurred between 60-90 minutes after receipt of the medicine and then gradually subsided. Overall, misoprostol's thermoregulatory effects were confirmed to be self-limiting, non-life threatening, and generally acceptable to women. Blood samples for these women will be analyzed to determine if there is any genetic predisposition to experiencing this effect (results forthcoming).

A clearer understanding of fever after misoprostol and the potential role of genetic factors will help providers know what to expect and avoid unnecessary interventions.

For guidance on use of misoprostol and management of side effects, see: Instructions for Use: Misoprostol for the Treatment of Postpartum Hemorrhage, Gynuity Health Projects 2017.

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