

### Fever occurring after treatment administration for primary postpartum hemorrhage

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Gynuity Health Projects, in collaboration with investigators in Burkina Faso, Ecuador, Egypt, Turkey and Vietnam, is conducting a clinical trial to explore the effectiveness of misoprostol for the treatment of primary postpartum hemorrhage (PPH) in tertiary care facilities. The study is a double-blind, placebo-controlled, randomized trial of 800 mcg of sublingual misoprostol versus IV oxytocin, the standard first-line treatment in many hospital settings. In addition to our primary outcome measures – measured blood loss, change in hemoglobin, and use of additional uterotonics -- this study also assesses drug safety profiles, reported side effects, and acceptability. Preliminary results from data on reported side effects were presented recently at the XVIII Annual Meeting of the International Federation of Gynecologists and Obstetricians (FIGO) in Kuala Lumpur, Malaysia. Highlights from this presentation are discussed below.

#### A case review of high fevers in Quito, Ecuador

A higher than expected rate of high fever ( $\geq 40.0^{\circ}\text{C}$ ) has been reported among women receiving treatment for their diagnosed PPH at one hospital, in Quito, Ecuador. Since the PPH treatment administered is blinded for the purpose of conducting this clinical trial, the relationship between the occurrence of fever and the treatment received is unknown. Interestingly, a similar rate of high fever has not been observed at any of the eight other participating hospitals. Why then are high fevers clustered in only Quito, Ecuador? To answer this question, the study team in Ecuador has reviewed their clinical practices and patient characteristics possibly contributing to the rate of high fevers, and has contemplated environmental factors such as Quito's high elevation and genetic make-up of clientele. To date, no correlation has been confirmed between any of these factors and the occurrence of fever.

Elevated temperature, as well as transient shivering and diarrhea, are well-known, expected side effects of misoprostol. Scarce documentation exists on temperature trends in women experiencing high fever (over  $40.0^{\circ}\text{C}$ ) after postpartum administration. To capture the details related to the occurrence of this side effect in Ecuador, the study team has systematically documented the onset, duration, peak temperatures, and treatment of high fever among women with PPH. When fever is observed, the woman's body temperature is measured, and this continues hourly in the cases of high fever, using an oral mercury thermometer, until fever subsides. Tympanic and digital oral thermometers are being used to compare results with the mercury thermometer. Fever is treated with acetaminophen, aspirin, and cool compresses according to hospital protocol. Data collected thus far show that almost half the participants (87/186) receiving PPH treatment experienced an elevated body temperature ( $\geq 38.0^{\circ}\text{C}$ ). Twenty percent of all women (38/186) had high fevers  $\geq 40.0^{\circ}\text{C}$ . The overall trend for cases with high fever is a sharp increase in temperature within one hour of treatment with misoprostol, a peak 1-2 hours after treatment, and a gradual decline over a period of three hours. Temperatures remained above  $40.0^{\circ}\text{C}$  for less than two hours, measured below  $38.0^{\circ}\text{C}$  about six hours after treatment, and were commonly accompanied by moderate/severe shivering. Although the incidence of high fever was higher than expected at this site, this secondary effect was transient, non-life threatening, and did not lead to prolonged hospitalization.

Once the treatment arms are un-blinded and the relationship between the PPH treatments and side effects are known, additional research will be undertaken to explore the training implications for treating PPH and managing its side effects. Furthermore, a lower dose of misoprostol may possibly be investigated to determine its safety profile and effectiveness, if the currently studied dose of 800 mcg sublingual misoprostol proves efficacious in stopping hemorrhage.

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