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Short Commentary

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Fever with Misoprostol; A Clinical Confounder in Times of COVID19

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Abstract

Medical abortion is now a standard method of providing abortion care.Due to lockdown during the current COVID 19 pandemic, there has been a 400 percent increase in the requests for medical abortions. Fever is a well described side effect of misoprostol and usually related to the dose and route of administration. Febrile responses can be a confounding symptom with possibility of maternal infections that have serious consequences.

Keywords: Fever; Misoprostol; Medical abortion

Introduction

Over the past three decades, medical methods of abortion have been developed throughout the world and are now a standard method of providing abortion care.Due to lockdown during the current COVID 19 pandemic, there has been a 400 percent increase in the requests for medical abortions. This procedure is performed from the time a woman confirms pregnancy and up to 63 days of gestation (calculated from the first day of the last menstrual period). Medical abortion provides a safe, effective, non invasive and acceptable termination of pregnancy in both high and low-resource settings on an outpatient basis without need for skilled surgical abortion providers with a 95 percent to 98 percent success rate [1,2].

Following a physical exam to determine eligibility for a medical abortion procedure, and exclusion of ectopic pregnancy, ovarian mass, IUD, corticosteroid use, adrenal failure, anemia, bleeding disorders or use of blood thinners, asthma, liver or kidney problems, heart disease and hypertension, a combination regimen of mifepristone and misoprostol regimen is initiated to terminate the pregnancy [3,4].

Pharmacology of Drugs used in Medical Abortion

Mifepristone: Mifepristone (RU-486) is a derivative of norethindrone that binds to the progesterone receptor and acts as an antagonist. When administered orally, mifepristone is well absorbed and reaches peak plasma levels within 2 hours. The drug acts on the pregnant and induces decidual necrosis, cervical softening, increased uterine contractility 24-36 hours after administration and enhances uterine sensitivity to prostaglandins fivefold. The drug has a half life of 24 to 29 hours and, due to non linear pharmacokinetics, a dose of 100 mg is as effective as that of 600 mg.

Misoprostol: Misoprostol is a synthetic prostaglandin E_1 analogue developed in 1973 for the treatment of gastric ulcers. The drug is well absorbed and undergoes rapid first pass metabolism by a process of de-esterification to form misoprostol acid which is responsible for its clinical activity. Administered orally, peak plasma levels of the drug are achieved by 30 minutes and levels decline rapidly within 120 minutes. By vaginal route, absorption is slower and peaks by 70 to 80 minutes and levels slowly decline over 6 hours. Tablets are available in two strengths 100 and 200 mcg and suppository of 200 mcg strength for inducing medical abortion and stable at room temperatures [5].

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Misoprostol has uterotonic and cervical priming actions. Buccal and sublingual routes have high efficacy as drug absorption is rapid but the greater maximum concentration results in more adverse effects when compared to the vaginal route. The latter is preferred by women to complete the medical abortion process sooner because of the ability to use the misoprostol 6 hours or less from the time of mifepristone administration Misoprostol-only medical abortion regimens are significantly less effective than those that use a combination of mifepristone and misoprostol [6].

Standard dose schedule for medical abortions is mifepristone 200 mg orally, followed approximately 48 hours later by misoprostol 800 micrograms orally (preferable). Expulsion of the fetus takes a few hours or, sometimes, even days. A physical exam is given one to two weeks later to ensure complete expulsion of products of conception and also for contraceptive advice.

Discussion

Fever is a well described side effect of misoprostol and usually related to the dose and route of administration. Racial differences in response has reported with hyperthermia reactions amongst Ecuadorian women[7]. Higher rates elevated body temperature are associated with oral and sublingual routes of administration, which achieve a higher and quicker maximum plasma concentration than vaginal or rectal administration. Incidence of fever being 76 versus 54% with oral and sublingual routes, and 9 versus 1 % respectively for vaginal and rectal administration. Fever is usually transient, with onset 15-45 minutes after dose administration and resolving within 6 to12 hours.

The mechanism of endogenous fever production is through the prostaglandins E-series that are primary mediators of fever induction through EP3 receptors. They interfere with the thermoregulation centre in the hypothalamus causing an upward shift in the hypothalamic set point. This triggers the body to conserve and produce heat to attain the new set point, manifesting clinically as fever. The 30–60-minute lag between the peaks in plasma concentration and temperature is probably due to the time it takes for the febrile signal to be received and processed in the hypothalamus, as well as for the physiological processes associated with fever to elevate the body temperature [8].

A majority of fevers develop within 10 h after the administration of misoprostol and regress to normal limits after expulsion of products of conception. Compared to those who do not develop fever, women with fever are more often of advanced gestational age, nulliparous and having a longer induction-expulsion time. Hyperthermic response i.e. fever >40°C are rare among Indian population and not reported.A 3% drop in hCG level and/or endometrial thickness of <10 mm in ultrasound examination are taken as indices of termination of pregnancy with an overall success rate of 98.2%.

Fever can also be associated with infection. Maternal infections are associated with 15% mortality rate and further confounding diagnosis during times of COVID 19. It important, therefore, to determine the exact etiology of fever. Laboratory tests like leucocyte counts, urine routine and microscopic examination CRP, procalcitonin, urine, blood and vaginal swab for culture as well as serological tests for COVID infection are advisable when fever persists beyond 24 hours.

Misoprostol associated fever does not respond to aspirin. General management practices for reducing fever like removing blankets from the patient, applying cool compresses, administering oral acetaminophen, and ensuring adequate hydration by mouth or IV are adequate. Antibiotics and/or antiviral drugs may be exhibited based on results of investigations.

Conclusion

Misoprostol induced fever can be a confounder in times of COVID 19 and identified by the absence of respiratory symptoms and transient nature of the febrile reaction.

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