

# Misoprostol for Early Pregnancy Failure

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**M**isoprostol (15-deoxy-16-hydroxy-16-methyl PGE1) is a stable, synthetic prostaglandin E1 analogue. It was originally developed in the 1970s for the prevention of peptic ulcers caused by non-steroidal anti-inflammatory drugs but has also come into wide use for various indications in obstetrics and gynecology. These indications include induced first- and second-trimester abortion, evacuation of the uterus in early pregnancy failure or missed abortion, induction of labor for both live fetuses and in cases of intrauterine fetal death, prevention and treatment of postpartum hemorrhage, and for cervical priming before various transcervical procedures [1].

First-trimester pregnancy failure is the most common complication of pregnancy, occurring in as many as 50% of conceptions, 12%–15% of clinical pregnancies and 2%–6% of pregnancies after detection of a fetal heart beat [2]. The standard treatment for pregnancy failure is surgical evacuation of the uterus. However, as early studies of misoprostol showed a relatively high success rate, misoprostol has gained popularity. A Pubmed search using the key words "early pregnancy failure and misoprostol" revealed 80 articles; changing the terms to "miscarriage and misoprostol" revealed over 190 publications. Many centers now offer misoprostol as the first line of treatment.

The early studies of misoprostol included a short follow-up period and absence of a gestational sac as the endpoint of treatment. Increased experience with medical management has shown many cases in which misoprostol fails to have the desired effect and the uterus has to be evacuated surgically by curettage. Hence, the study by Odeh and co-authors [3] in this issue of *IMAJ*, which attempts to determine whether various predictive factors can determine the efficacy of misoprostol are entirely laudable. The authors assessed gestational sac volume, parity and serum beta-human chorionic gonadotropin levels as predictive factors for success of treatment. They concluded that gestational sac volume is not a predictor of successful medical treatment for early pregnancy failure. Previous pregnancies and deliveries and higher  $\beta$ HCG concentration negatively affected the success rate of medical treatment.

However, the discussion regarding efficacy of treatment is hampered by a lack of standardization regarding various factors that impact the interpretation of efficacy and affect the quality of published studies [4]. The published studies use varying definitions of early pregnancy failure. This variation may account for some of the discrepancies in the results. Other variations include the dosing protocol, route of administration, follow-up regimens, and most importantly, the definition of success [2,4].

One of the most commonly used criteria for defining success in the early studies of medical management was sonographic measurement of anteroposterior endometrial thickness. A shadow of more than 15 mm was con-

sidered diagnostic of retained products of conception. This criterion was based on the thin endometrium found after curettage. The criterion of an endometrial thickness of 15 mm has been found to be invalid after mesoprostol therapy, leading to underestimation of treatment success. Odeh et al. [3] used 30 mm as their threshold. However, an endometrial thickness of 30 mm is also debatable. Others have concluded that ultrasonically determined absence of the gestational sac is the most relevant criterion for confirming treatment effect, and that endometrial thickness is not an indication for surgical intervention. The decision to intervene surgically should be based on a persistent gestational sac and clinical symptoms [4,5]. Failure of medical management may be said to occur when curettage is required. Failure of medical management ranges from 10 to 50% compared with 0 to 4% after surgical management [6]. Medical treatment for artificial termination of pregnancy has a failure rate as low as 5% [7]. This higher failure rate in missed abortion has led to a search for markers to predict success in order to improve patient selection. hCG levels, plasma progesterone and CA-125 have been investigated as possible predictors. In one of the author's series (D. Stockheim, personal communication), none of the above markers predicted success. Two other studies [8,9] failed to reveal an association between serum progesterone levels and the success rate of medical treatment for missed abortion. Gronlund et al. [8] used an hCG level of < 20,000 IU/L and gestational age < 75 days as a criterion for treatment. Using that definition, the success rate was significantly higher than in

$\beta$ HCG = beta-human chorionic gonadotropin

patients not fulfilling these criteria (90% and 65% respectively). Other favorable factors reported as predicting successful treatment is nulliparity, localized lower abdominal pain within the past 24 hours (suggesting that spontaneous contractions have commenced), vaginal bleeding in the last 24 hours (suggesting spontaneous placental separation), or a rhesus negative blood type [10].

It is also relevant that there are other side effects to medical treatment for early pregnancy failure. Patients report increased pain and other symptoms as compared to surgical evacuation [11]. Retained products of gestation may only be diagnosed later. The incidence has been reported to be 5% after the first menstrual period, following misoprostol treatment [2] (using hysteroscopy for diagnosis). There is also concern about the effect on future fertility, particularly if there are retained products of conception. However, a recent study has found that the method of treatment, whether medical or surgical, did not affect future fertility, and the live birth rate was similar – 80% within 5 years [12].

Despite the drawbacks noted above, medical treatment for early pregnancy

failure is a feasible option for the physician to offer. Although the efficacy is lower than that of surgical management, many women accept lower efficacy in order to avoid a surgical procedure. Medical treatment does take longer and is more painful, but patient satisfaction is high. Consequently, misoprostol is an efficacious and safe alternative for women preferring non-surgical treatment for early pregnancy failure.

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