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ORIGINAL ARTICLE

Home-Based Extended Low-Dose Oral Misoprostol in Management of First-Trimester Pregnancy Loss in Low-Resource Communities: A Randomized Trial

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Abstract

Objective To investigate the efficacy, safety and tolerability of a home-based extended low-dose oral misoprostol for management of first-trimester pregnancy loss.

Materials and Methods A randomized trial that was conducted in the Woman's Health University Hospital and El-eman Maternity Hospital, Assiut, Egypt. One hundred and sixty patients were included. They were randomly assigned to receive four tablets of 200 µg misoprostol vaginally (max. 800 µg-hospital group) or 12 tablets orally, one every 3 h, over 2 consecutive days (max. 2400 µg-extended low-dose home group). For failed first dose, another similar second dose was given. Primary outcome measure was the percentage of patients with 'medically completed miscarriages' in each group (including complete miscarriages + incomplete miscarriages with successful post-miscarriage misoprostol).

Results The total number of patients with 'medically completed miscarriages' in home group was 65/79 (82.3%), which was comparable to the hospital group (52/71 or 73.2%) ($P = 0.182$). However, the majority of patients in home group had significantly successful miscarriages after a single course of low-dose oral misoprostol, experienced much less heavy bleeding attacks and had less systemic side effects.

Conclusion In low-resource communities, the home-based extended low-dose oral misoprostol protocol proved high efficacy, safety and tolerability in management of first-trimester pregnancy loss.

Keywords Oral misoprostol · Low dose · First trimester · Pregnancy loss

Introduction

The latest NICE guideline recommends that: For women with missed miscarriage, a single dose of 800 µg (oral or vaginal) of misoprostol was the most effective overall. When used at the same dose, both vaginal and oral routes of administration had similar effectiveness, and that both were more effective than sublingual administration. The majority of side effects did not show a difference by route [1].

Actually, most women favor oral route to avoid the unpleasant vaginal examination, and furthermore, there is a wide variation in the absorption of misoprostol through the vaginal epithelium among different women. Moreover, when studying pharmacokinetics of repeated doses of misoprostol, onset of vaginal bleeding could adversely affect its absorption [2]. The FIGO's updated recommendations restricted vaginal route of misoprostol when there is bleeding and/or signs of infection [3]. However, using high-dose

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oral misoprostol may be associated with significant GIT and systemic side effects [2, 3].

Women's preferences depend upon their cultural background and traditions. In Upper Egypt, women reside in low socioeconomic standards, they desire for privacy, reluctant to be inpatients, and they are not willing to experience repeated vaginal examinations/medications. Even, these women did not accept either sublingual or buccal misoprostol, due to the long latent period (> 30 min) needed to allow absorption of each dose. Thus, a home-based low-dose oral treatment for early pregnancy loss can be highly acceptable and cost-effective.

Objectives

To investigate the efficacy, safety and tolerability of a suggested home-based extended low-dose oral misoprostol compared to the hospital-based standard vaginal dose (800 µg) in management of first-trimester pregnancy loss.

Patients and Methods

Trial Design and Setting

The current study was a registered, randomized clinical trial (ClinicalTrials.gov ID: NCT03148314). The study participants were recruited from the Obstetric Outpatient Clinics of the Woman's Health University Hospital, Assiut University (this is the biggest tertiary hospital in Upper Egypt, with 400 beds and average of 9000 deliveries per year) and El-eman Old Hospital (a central MOH maternity hospital with 150 beds and average of 3000 deliveries per year) Assiut city, Egypt (from July 1, 2017 to June 30, 2018).

Eligible Participants

According to the current NICE guideline, patients with final diagnosis of first-trimester pregnancy loss were admitted into the study [1]. The 'first-trimester pregnancy loss' was further classified as a 'missed miscarriage,' if an embryo or fetus was present but was dead, or 'anembryonic pregnancy,' if no embryo had developed within the gestation sac.

Inclusion criteria:

1. Single dead embryo/fetus or anembryonic pregnancy
2. Up to 12th weeks' gestation (by dates/ultrasonography)
3. No scarred uterus or just one lower segment cesarean scar (LSCS)
4. No or minimal bleeding
5. No evidence of infection
6. Accepting to participate in the study

Exclusion Criteria:

1. Suspected molar pregnancy.
2. Significant anemia (Hb < 9 gm/dl).
3. Known severe cardiovascular diseases.
4. Current breast-feeding.
5. Hemoglobinopathies.
6. Hemorrhagic disorders and anti-coagulation therapy (aspirin accepted).
7. No contraindication to use of misoprostol as inflammatory bowel disease, asthma and liver disease.
8. Patient living in remote areas (> 20 km).

Sample Size and Randomization

We assumed an average success rate of 80%, for the standard 800 µg vaginal misoprostol dose and 50% for our suggested extended low-dose oral protocol. To detect a significant difference of 90% efficacy among the two groups, with a power of 80%, and incidence of first-trimester missed miscarriage being 10–20%, two-tailed of 5% required a minimum of 70 patients in each group, thus achieving a sample size of 140 patients was required (as calculated through 'Epi info package' software). To compensate for loss to follow-up, we planned for 80 subjects in each group. Out of 189 patients counseled for participation in the study, 160 responded. Subjects were randomly assigned to either the home-based or hospital-based protocol in a 1:1 ratio. Randomization was conducted using a computer-generated table of random numbers with allocation concealment.

Intervention and Follow Up Schedule

A standardized dose of misoprostol was given for each patient in both groups of the study, which was 800 µg vaginally or 2400 µg by oral route. Misoprostol is available in Egypt as white tablets of 200 µg (Misotac®, Sigma, Egypt). It is only licensed for hospital use. If needed (i.e., failed first dose), another similar second dose was given. Patients, who refused to repeat the dose, were referred for surgical evacuation and were discontinued from the study.

For the hospital-based protocol, we followed the FIGO guidelines; the patients were administered 800 µg of misoprostol vaginally [4]. The attending physician placed four tablets of 200 µg each in the posterior fornix of the vagina. If no response, the dose was repeated after 8 h (max. dose: 800 µg × 2 = 1600 µg). If no response was achieved, within 24 h after last misoprostol dose, patients underwent dilation and evacuation. According to NICE guidelines, complete miscarriage was defined as no gestational sac and endometrial thickness ≤ 15 mm on TVUS [1]. Patients were monitored for 12 h following complete miscarriage or surgical

evacuation and then discharged with analgesics and prophylactic antibiotics for 5 days.

Patients allocated to the suggested home-based extended low-dose protocol were dispensed 12 tablets misoprostol, each 200 μg, one tablet repeated every 3 h for a maximum of six doses over 18 h (200 μg × 6 = 1200 μg); then rest for 6 h then, the same dose was continued next day (max. dose: 1200 μg × 2 days = 2400 μg). They were followed by phone calls, and they were instructed to return to the hospital if they experience serious bleeding or 5 days after the last dose. According to the findings on TVUS, the full dose was repeated again for those failed to response for the first course or dilatation and evacuation was offered for those who refused repeating treatment and were discontinued from the study. Finally, surgical evacuation was offered for failures of the second week repeated dose. Anti-D rhesus prophylaxis was given when indicated. Prophylactic antibiotics were prescribed.

For safety of patients in the home-based regimen, they were instructed regarding possible emergency transportation including: national ambulance service, our university hospital ambulance service, private car, etc. In addition, a mobile telephone contact number was a criterion to allow urgent contact, and the maximum distance of residency was 20 km., which means 15–20 min trip by ambulance.

Every woman was evaluated 14 days post-miscarriage (either medical or surgical) when they underwent bimanual pelvic examination, TVUS and an interview to assess quantity of post-miscarriage bleeding days and amount, as heavy (> periods), moderate (= periods) or mild (< periods), and to determine each woman's experience with side effects.

Selection of Misoprostol Oral Dose Timing

This was based on the pharmacokinetics of oral misoprostol, the serum levels decline sharply after 2 h before they become critically low by 3 h after oral ingestion [5]; thus with 3-h intervals, sufficient serum levels could be maintained.

Management of Incomplete Miscarriage

Incomplete miscarriage was defined as persistence of heavy bleeding or significant residual intrauterine echogenic contents ≥ 15 mm in diameter [1]. These patients were offered single doses of oral misoprostol 600 μg [4]. Lastly, persistent heavy bleeding or significant intrauterine echogenic contents were managed surgically by evacuation of retained products of conception (ERPC).

Study Outcomes

- *Primary outcome measure* Percentage of patients with 'medically completed miscarriages' in each group. This included both patients passed into complete miscarriage plus those with incomplete miscarriage and responded to post-miscarriage oral misoprostol.
- *Secondary outcome measures* Number of misoprostol doses/tablets, induction-to-miscarriage time, need for post-miscarriage medical or surgical intervention and maternal morbidities (as bleeding–infection–misoprostol side effects—complications of treatment or surgery).

Statistical analysis

The data were collected and entered onto a Microsoft Access Database and were analyzed using the Statistical Package for Social Science (SPSS Inc., Chicago, version 19). Enumeration data were expressed as numbers and percentages (*n* and %) and compared using the Chi-square test. Quantitative data were expressed as mean ± SD and compared using the Student's *t* test for normally distributed data. A $p < 0.05$ was interpreted as statistically significant.

Ethical Considerations

Reviewing and revising of the proposal was carried out via the Ethical Review Committees of The Department of Obstetrics and Gynecology and Assiut College of Medicine. Informed consents (written or verbal) were obtained from those who accepted to participate in the study. Patients were also allowed to request a surgical termination at any time; however, they were excluded from the study.

Results

Study Flow Chart (Fig. 1)

Out of the 1111 examined pregnant women, 189 women (~ 17%) were diagnosed as first-trimester pregnancy loss and were eligible to be included in the study. Twenty-nine patients refused participation, and 160 women were included. During the study period, 150 out of 160 women completed the study (i.e., ~ 93.75% continuation rate).

Demographic and Obstetric Characteristics (Table 1)

All demonstrated admission characteristics were homogenous between the two groups, with no statistically significant differences.

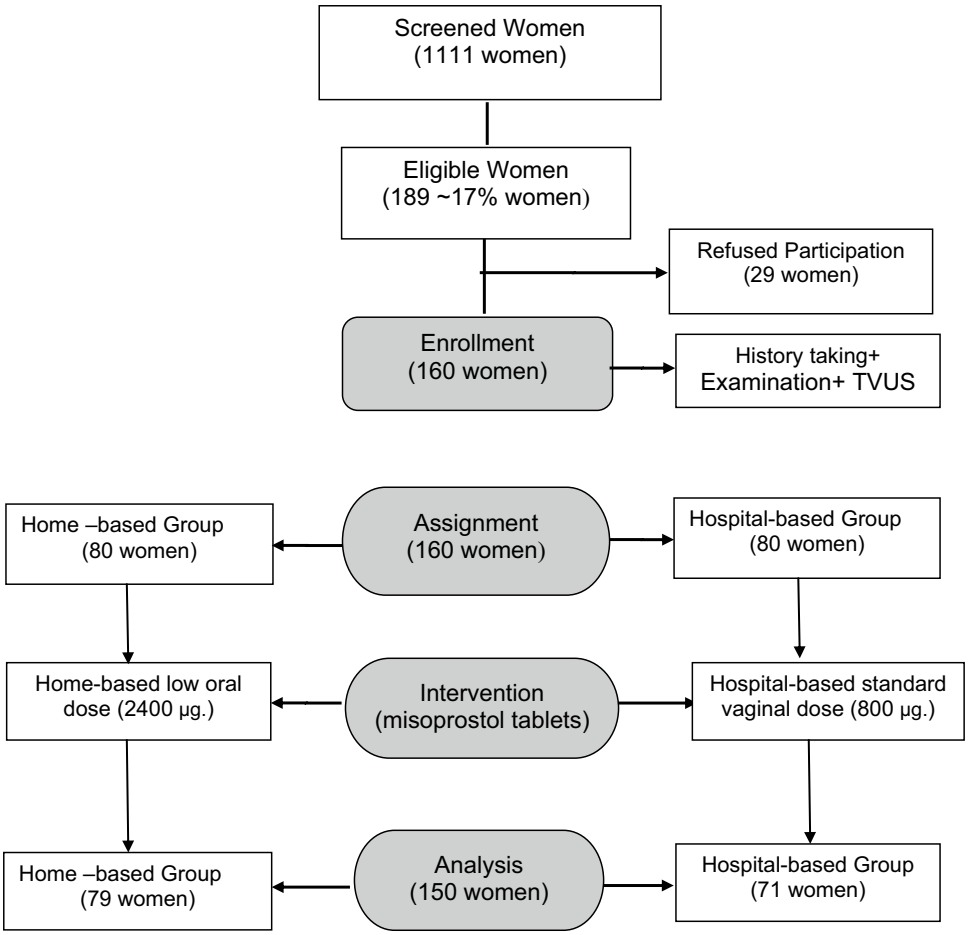

Fig. 1 Depicts the study flow chart

Findings on Digital Pelvic Examination and Transvaginal Ultrasonographic Scanning (Table 2)

On admission, the majority of patients had closed, non-effaced cervices, and they had no vaginal bleeding/spotting. In home group, 41.8% had anembryonic pregnancy versus 35.2% in hospital group. No statistically significant differences were detected regarding all these variables.

Miscarriage Data (Table 3)

The majority of patients in home group (compared to hospital group) had significantly successful miscarriages after a single 2-day treatment course of extended low-dose oral misoprostol (~80% vs. ~45%; respectively, $P=0.000$), experienced much less heavy bleeding attacks (31.6% vs. 66.2%; respectively, $P=0.000$) and had less systemic side effects (11.4% vs. 29.6%; respectively ($P=0.005$). As expected, patients in home group had significantly higher number of misoprostol tablets (12.8 ± 6.5 vs. 7.55.3.4 in hospital group, $P=0.000$) and significantly longer induction-to-miscarriage time (43.8 ± 23.51 vs. 13.5 ± 9.9 h in hospital group, $P=0.000$).

Post-Miscarriage Data (Table 4)

The success rates (i.e., complete miscarriages) were comparable between groups, with a difference of no statistical significance (~71% for home group vs. 60.6% in hospital group; $P=0.412$), and similarly, the number of patients who received post-miscarriage misoprostol, the number of patients who went into post-miscarriage ERPC and the number of post-miscarriage bleeding/spotting days. Regarding the duration of hospital stay, as expected, it was significantly longer for the hospital group because all patients were managed as inpatients.

Summary of Study Primary Outcome (Table 5)

The total number of patients with medically completed miscarriages (including complete miscarriages + incomplete miscarriages with successful post-miscarriage misoprostol) in home group was 65/79 (82.3%). This was in comparison with the hospital group (52/71 or 73.2%), with a difference

Table 1 Demographic and obstetric characteristics of patients

	Home group ($n=79$)	Hospital group ($n=71$)	P value
Age (years) (mean ± SD)	28.76 ± 5.81	27.37 ± 6.43	0.102
BMI (kg/m^2) (mean ± SD)	22.13 ± 3.47	21.25 ± 4.48	0.815
Occupation (*n* and %)			0.622
Housewife	76 (96.2%)	70 (98.6%)	
Employee	3 (3.8%)	1 (1.4%)	
Residence (*n* and %)			0.05*
Slums/rural	43 (54.4%)	32 (45.1%)	
Urban	18 (22.8%)	30 (42.3%)	
Semi-urban	18 (22.8%)	9 (12.7%)	
Gravidity (mean ± SD)	4.08 ± 2.21	3.52 ± 1.71	0.149
Parity (mean ± SD)	2.52 ± 1.71	2.23 ± 1.49	0.290
Miscarriage (mean ± SD)	0.59 ± 0.90	0.35 ± 0.61	0.112
Previous one LSCS (*n* and %)			0.879
Yes	31 (39.2%)	27 (38.0%)	
No	48 (60.8%)	44 (62.0%)	
Previous medical miscarriage (*n* and %)			0.166
Yes	14 (17.7%)	7 (9.9%)	
No	65 (82.3%)	64 (90.1%)	
Gestational age by LMP (weeks) (mean ± SD)	9.7 ± 1.8	9.8 ± 1.3	0.115
Presenting symptom (*n* and %)			0.415
Asymptomatic	31 (39.2%)	23 (32.4%)	
Spotting	20 (25.3%)	20 (28.2%)	
Colic	19 (24.1%)	16 (22.5%)	
Minimal bleeding	9 (11.4%)	12 (16.9%)	

LSCS lower segment cesarean section, *LMP* last menstrual period

*Statistical significance if p value < 0.05

Table 2 Findings on digital pelvic examination and transvaginal ultrasonographic scanning (TVUS)

	Home group ($n=79$)	Hospital group (n = 71)	P value
Cervical dilatation (*n* and %)			0.190
Closed	57 (72.2%)	49 (60.0%)	
Tip of finger	17 (21.5%)	15 (21.1%)	
One finger	5 (6.3%)	7 (9.9%)	
Partial effacement (*n* and %)			0.094
Yes	4 (5.1%)	11 (15.5%)	
No	75 (94.9%)	60 (84.5%)	
Minimal vaginal bleeding/spotting (*n* and %)			0.229
Yes	28 (35.4%)	32 (45.1%)	
No	51 (64.6%)	39 (54.9%)	
TVUS findings (*n* and %)			
Blighted ovum	33 (41.8%)	25 (35.2%)	
Embryo (< 10 weeks)	23 (29.1%)	22 (31.0%)	0.162
Fetus (≥ 10–12 weeks)	23 (29.1%)	24 (33.8%)	
Mean of GSD (mm) (mean ± SD)	27.38 ± 5.4	28.67 ± 4.8	0.435
Mean of GSD (weeks) (mean ± SD)	8.7 ± 1.1	8.9 ± 1.3	0.321
Mean of CRL (mm) (mean ± SD)	23.67 ± 11.2	24.56 ± 12.2	0.221
Mean of CRL (weeks) (mean ± SD)	9.7 ± 2.3	9.9 ± 2.4	0.343

TVUS transvaginal ultrasonographic scanning, *GSD* gestational sac diameter, *CRL* crown–rump length

Table 3 Miscarriage data

	Home group ($n=79$)	Hospital group ($n=71$)	P value
Number of courses (n and %)			0.000*
Single course	63 (79.7%)	32 (45.1%)	
Double courses	16 (20.3%)	39 (54.9%)	
Number of tablets (mean ± SD)	12.8 ± 6.5	7.55 ± 3.4	0.000*
Induction-to-miscarriage time (h) (mean ± SD)	43.8 ± 23.51	13.5 ± 9.9	0.000*
Amount of bleeding (n and %)			0.000*
No bleeding (*failures*)	9 (11.4%)	11 (15.5%)	
Menstrual like	45 (57%)	13 (18.3%)	
Heavy bleeding	25 (31.6%)	47 (66.2%)	
Side effects (n and %)			0.005*
Yes	9 (11.4%)	21 (29.6%)	
No	70 (88.6%)	50 (70.4%)	
Pattern of side effects (n and %)	***n* = 9/79**	***n* = 21/71**	
Fever	3 (3.3%)	5 (7%)	0.666
Diarrhea	2 (2.1%)	0 (0.0%)	0.083
Nausea	2 (2.1%)	1 (1.5%)	0.207
Severe colic	2 (2.1%)	15 (21.1%)	0.020*

*Statistical significance if p value < 0.05

Table 4 Post-miscarriage data

	Home group ($n=79$)	Hospital group ($n=71$)	P value
Primary outcome (n and %)			0.412
Complete miscarriage	56 (70.9%)	43 (60.6%)	
Incomplete miscarriage	14 (17.7%)	17 (23.9%)	
Failed miscarriage	9 (11.4%)	11 (15.5%)	
Post-miscarriage misoprostol (n and %)			0.321
Yes	14 (17.7%)	17 (23.9%)	
No	65 (82.3%)	54 (76.1%)	
Post-miscarriage ERPC (n and %)			0.283
Yes	5 (6.3%)	8 (11.3%)	
No	74 (93.7%)	63 (88.7%)	
Post-miscarriage bleeding/spotting (days) (mean ± SD)	7.5 ± 6.4	6.7 ± 5.5	0.139
Hospital in-patient admission (n and %)			0.000*
Yes	5 (6.3%)	71 (100.0%)	
No	74 (93.7%)	0 (0.0%)	
Duration of hospital admission (h) (mean ± SD)	9.82 ± 8.58	27.8 ± 10.1	0.000*

ERPC evacuation of retained products of conception

*Statistical significance if p value < 0.05

of no statistical significance ($P=0.182$). No maternal morbidities were recorded in both groups (no blood transfusion, infection or surgical complications).

Discussion

In the current study, we investigated the efficacy and safety of a new home-based extended low-dose oral misoprostol (200 µg/3 h × 12 tablets = 2400 µg/over 48 h) in management of first-trimester early pregnancy loss. This new protocol

Table 5 Summary of study primary outcome

	Home group ($n=79$)	Hospital group ($n=71$)	P value
Medically completed miscarriages (n and %)	**65 (82.3%)**	**52 (73.2%)**	0.182*
Complete miscarriage	56 (70.9%)	43 (60.6%)	
Post-miscarriage misoprostol	9 (11.4%)	9 (12.7%)	
Surgically completed miscarriages (n and %)	**14 (17.7%)**	**19 (26.8%)**	
Failed miscarriage	9 (11.4%)	11 (15.5%)	
Post-miscarriage ERPC	5 (6.3%)	8 (11.3%)	

ERPC evacuation of retained products of conception

*P value is calculated for total numbers in bold

showed a comparable efficacy to the hospital-based standard vaginal 800 µg misoprostol protocol (82.3% vs. 73.2%; respectively, $P=0.182$).

Our hospital-based standard protocol of vaginal 800 µg misoprostol is that recommended by FIGO for medical treatment of first-trimester early pregnancy loss [6]. This protocol was effective in 73.2% of our patients. The success rate is favorably comparable to a considerable number of similar studies. Indeed, such a simple comparison with other studies is not practical because of the wide variations of success rates (ranging from ~ 39% to ~ 88.5%) and marked heterogeneity of the studies [7].

Far to our knowledge, no similar studies are available including such an extended low-dose oral misoprostol protocol. However, our results are generally comparable to few studies that included a wide range of oral misoprostol maximum doses, ranging from 600 µg to 2400 µg/24 h, with different follow up protocols. In spite of the marked heterogenecity and even poor methodology of some of these studies, they pointed to the efficacy and safety of oral misoprostol in management of early pregnancy loss (success rates: ~ 60% to ~ 90%) [8–12].

A previous prospective cohort study done by my colleagues Metwaly et al. [8] proved that the use of oral misoprostol in single dose of 600 µg at home as a method for termination of first-trimester missed miscarriage was effective (75%, success rate), tolerable and acceptable. In a study done by Benchamanon and Phupong [9], the overall rate of complete termination with misoprostol was 61.38% within the first 48 h of receiving a single dose of oral misoprostol 600 µg. Gupta et al. [10] included 250 patients who were given 200 µg of misoprostol orally at 12-h interval for two successive days, with a maximum of four doses (max dose = 200 µg × 4 = 800 µg). The success rate was observed in 225 (90%) of patients. The most common side effects observed were cramping/abdominal pain (36%).

A recent small observational study included that 81 pregnant women with early pregnancy failure were given misoprostol at a high dose of 800 µg orally and repeated every 3 h for a maximum of three doses, if required (max. dose 800 × 3 = 2400 µg). Misoprostol was effective in 60 (74.07%) patients with a very low incidence of side effects as nausea (4.94%), vaginal bleeding (3.70%), abdominal cramps (3.70%) and diarrhea (2.47%) [11]. These results are comparable to those obtained by Marwah et al. [12]; however, they only used a half dose of oral misoprostol that included 400 µg every 6 h for three successive doses. (max. dose 400 × 3 doses = 1200 µg). In spite of the differences in oral misoprostol doses in these studies, the recorded efficacy and side effects are in parallel to our results.

Besides the satisfactory success rate (82.3%) of the home-based extended low-dose oral misoprostol protocol, our results showed interesting findings to be highlighted. Compared to the hospital-based group, most of patients of the home-based group received just a single 2-day oral course, experienced much less heavy bleeding and had significantly less systemic side effects, which were easily tolerable (Table 3). None of the patients stopped their low-dose oral misoprostol treatment. These findings reflect the high efficacy, safety and tolerability of this protocol.

Such advantages of this extended low-dose oral misoprostol protocol can be explained by the expected gradual and sustained effective serum concentrations of misoprostol. This may create a miscarriage scenario that mimics the course of spontaneous miscarriage. Tang et al. [13] reported that various studies on uterine contractility have demonstrated that a sustained level, rather than a high serum level, is required for the development of regular effective uterine contractions.

There were no recorded emergency visits among patients of home group and no women suffered from serious bleeding that indicated anti-shock measures or blood transfusion. On the contrary, a recent large prospective study (included 480 subjects) on the use of high-dose oral misoprostol, 600 µg every 6 h and up to four doses (max. dose 2400 µg/24 h), warned that women where failure was documented, excessive bleeding (61%) was most prevalent followed by incomplete miscarriage (36%). They concluded that such a high-dose oral misoprostol protocol for missed miscarriage should only be considered to patients in hospital settings [14]. Zhang et al. [15] reported visits to the emergency units

by 3% of women within 24 h after treatment with 800 μg vaginal misoprostol due to heavy bleeding.

Up to 39% (58/150) of patients included in the current study had previous one LSCS and were homogenously distributed in both groups. None of them had any complications due to the use of misoprostol with previous cesarean section scars. The recent FIGO's recommendations concluded that misoprostol could be used for women with previous cesarean or other transmural uterine scar up to 26 weeks [3].

Nevertheless, the suggested home-based extended low-dose oral misoprostol protocol has a few inherent disadvantages, including the increased number of misoprostol tablets per course and the prolonged latent period before expulsion. These features were generally reported in previously mentioned studies [8–12]. Interestingly, these features were completely acceptable on counseling of home group patients.

In conclusion, the suggested home-based extended low-dose misoprostol protocol proved high efficacy, safety and tolerability in management of first-trimester pregnancy loss. In low-resource communities, it can be an ideal alternative to other routes to decrease the burden/coast on tertiary healthcare centers.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval Obtained approval of the ethical review committees of the department of Obstetrics and Gynecology and Assiut College of Medicine.

Informed Consent Informed consent was obtained.

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