First published online: 23 June 2017

DOI: 10.1002/ijgo.12181

FIGO SPECIAL ARTICLE

WILEY International Journal of Gynecology & Obstetrics

FIGO's updated recommendations for misoprostol used alone in gynecology and obstetrics

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1 | BACKGROUND

In 2012, the International Federation of Obstetrics and Gynecology (FIGO) produced a chart detailing recommended dosages of misoprostol when used alone, for a variety of gynecologic and obstetric indications. In light of new evidence[1–13] and through expert deliberation, this chart has now been revised and expanded (Fig. 1). Some areas were particularly challenging to develop given the limited, low-quality, or inconsistent evidence. The present commentary is intended to explain some of the changes and decisions made.

2 | GENERAL CHANGES

The layout is now categorized vertically by gestation and horizontally by indication. Gestation is labelled and referred to as the number of weeks of gestation (<13 weeks, 13–26 weeks, and >26 weeks), with the final column being for postpartum use. However, in the case of incomplete abortion under 13 weeks, and inevitable abortion between 13–26 weeks, women should be treated on the basis of their uterine size rather than last menstrual period dating. Recommendations have been added for inevitable abortion and cervical preparation between 13 and 26 weeks, and for termination of pregnancy at more than 26 weeks.

3 | NUMBER OF DOSES

For less than 13 weeks' gestation, we decided to recommend a fixed number of doses without specifying a maximum. This is because many early pregnancy regimens will be used on an outpatient basis, so it is useful for healthcare providers to know in advance how many doses to give the client; there is also sufficient evidence to support a fixed number of doses for use in pregnancies of less than 13 weeks' gestation, as well as evidence that it is safe to give further doses if they are required.[1–4,14]

For 13–26 weeks' gestation, the notion of a maximum number of doses has been extrapolated from clinical research in which maximum doses are commonly noted not on the basis of patient safety issues or efficacy,[9] but rather as tangible endpoints. In clinical practice, however, they might not have great utility, and dosing should continue until expulsion, in the absence of rare complications. Suggesting that providers should discontinue dosing could actually increase risks, particularly when providers have few alternatives available if expulsion has not yet

occurred. Some unpublished studies and clinical experience have shown that complete expulsion can be safely achieved by continuing the regimen up to 72 hours, without compromising the woman's safety.[9]

4 | ROUTE OF ADMINISTRATION

Given recently published evidence,[2–9] we have added alternative routes for taking misoprostol; in most cases, this has meant the addition of the buccal route, in which the tablets are placed in the cheek for 30 minutes after which any remnants are swallowed. This route has a similar pharmacokinetic profile to the vaginal route. Further ongoing studies are indicating this to be a promising route for other indications on the chart, but these indications have not been included because data on efficacy have not been reported. Future studies will continue to provide evidence on what might be a variety of effective regimens and routes of administration. Although this could result in several available options for providers, it will also enable women's preferences to be taken into consideration. Women's preferences can vary, with some preferring the vaginal route (if inserting the pills themselves) and some preferring non-vaginal routes. However, the vaginal route should be avoided when there is bleeding and/or signs of infection. The chart does not include the rectal route. We recommend against using this route because the pharmacokinetic profile is not associated with the best efficacy.

5 | MISOPROSTOL USE IN PREGNANCIES WITH PREVIOUS CESAREAN OR TRANSMURAL UTERINE SCAR

The use of misoprostol at 13–26 weeks' gestation in women with previous cesarean or transmural uterine scar was debated because of concerns about an increased risk of uterine rupture. For fetal death, a Cochrane meta-analysis[15] reported mixed findings, concluding that the data were insufficient to assess the occurrence of uterine rupture. A few studies have reported no increased likelihood of rupture,[16] but often women with prior cesarean or uterine surgery are excluded from studies or reviews, or trials are insufficiently powered to detect a difference in safety outcomes as a result of the rarity of major adverse events. There is some evidence that, for terminations in this period, the risk of uterine rupture among women with a prior cesarean delivery using misoprostol is less than 0.3%[1,17]; other studies[9,18–20] concluded that there are no significant differences in outcomes for women with previous cesarean(s). We therefore concluded that misoprostol can be used for women with previous cesarean or other transmural uterine scar throughout 13–26 weeks.

There is insufficient evidence available to recommend a regimen of misoprostol for use at more than 26 weeks' gestation in women who have had a previous cesarean or transmural uterine scar. Therefore, without evidence to support a safe regimen, we do not provide one, other than to recommend following local protocol in these cases.

6 | MANAGEMENT OF PREGNANCY TERMINATION AND FETAL DEATH OVER 26 WEEKS' GESTATION

Although there is some evidence to support a decreasing dose with increasing gestational age, there is little evidence to support the advice given in some international and national clinical guidelines to use lower doses of misoprostol in cases of fetal death. Irrespective of the issue of recommendations for different doses, various reviews[15,20,21] have concluded that there is insufficient evidence overall of superiority of one dose or schedule of misoprostol over another for use in pregnancies at or over 13 weeks' gestation. In making recommendations, we acknowledged that providers might be keen to identify lowest possible doses because of reduced adverse effects,[21] but that it was also important to consider success rates and time to delivery: low doses have been shown to be associated with a longer induction-to-delivery interval and lower overall effectiveness,[15,21] and evidence has supported the safety of the "higher" doses for women.[7–9] Recommendations in the chart were compiled with this in mind, while also acknowledging that it is possible that a range of dosages could be effective and safe.

7 | RETAINED PLACENTA

There have been two studies of the use of misoprostol for the treatment of retained placenta following live birth, neither of which show any benefit over placebo.[22] We therefore do not recommend misoprostol for retained placenta in late pregnancy.

8 | SECONDARY PREVENTION OF POSTPARTUM HEMORRHAGE FOR COMMUNITY-BASED PROGRAMS

Secondary prevention is a community-based strategy that has been shown to be a comparable alternative to a universal prophylaxis approach in two large community trials (one in press).[12] Rather than medicating all women during the third stage of labor with a prophylactic dose, a regimen of 800 μg sublingual misoprostol (the same as for treatment) can be used to treat only women with higher-than-average bleeding (e.g. approximately 350 mL or more). Although there is limited published data, it was agreed that secondary prevention of PPH is a strong alternative approach to universal prophylaxis, because it involves medicating far fewer women (5%–10% vs 100%), thus causing fewer adverse effects and reducing costs.

9 | CONCLUSION

The FIGO *Misoprostol-only Recommended Regimens 2017* chart (Fig. 1) is the result of extensive collaboration among an international

MISOPROSTOL-ONLY RECOMMENDED REGIMENS 2017

<13 weeks' gestation	13–26 weeks' gestation	>26 weeks' gestation[8]	Postpartum use
Pregnancy termination[a,b,1] 800µg sl every 3 hours *or* pv*/bucc every 3–12 hours (2–3 doses)	**Pregnancy termination**[1,5,6] 13–24 weeks: 400µg pv*/sl/bucc every 3 hours[a,e] 25–26 weeks: 200µg pv*/sl/bucc every 4 hours[f]	**Pregnancy termination**[1,5,9] 27–28 weeks: 200µg pv*/sl/bucc every 4 hours[f,g] >28 weeks: 100µg pv*/sl/bucc every 6 hours	**Postpartum hemorrhage (PPH) prophylaxis**[i,2,10] 600µg po (x1) *or* **PPH secondary prevention**[j,11] (approx. ≥350ml blood loss) 800µg sl (x1)
Missed abortion[c,2] 800µg pv* every 3 hours (x2) *or* 600µg sl every 3 hours (x2)	**Fetal death**[f,g,1,5,6] 200µg pv*/sl/bucc every 4–6 hours	**Fetal death**[2,9] 27–28 weeks: 100µg pv*/sl/bucc every 4 hours[f] >28 weeks: 25µg pv* every 6 hours *or* 25µg po every 2 hours[h]	**PPH treatment**[k,2,10] 800µg sl (x1)
Incomplete abortion[a,2,3,4] 600µg po (x1) *or* 400µg sl (x1) *or* 400–800µg pv* (x1)	**Inevitable abortion**[g,2,3,5,6,7] 200µg pv*/sl/bucc every 6 hours	**Induction of labor**[h,2,9] 25µg pv* every 6 hours *or* 25µg po every 2 hours	
Cervical preparation for surgical abortion[d] 400µg sl 1 hour before procedure *or* pv* 3 hours before procedure	**Cervical preparation for surgical abortion**[a] 13–19 weeks: 400µg pv 3–4 hours before procedure >19 weeks: needs to be combined with other modalities		

References
- **a** WHO Clinical practice handbook for safe abortion, 2014
- **b** von Hertzen et al. Lancet, 2007; Sheldon et al. 2016 FIAPAC abstract
- **c** Gemzell-Danielsson et al. IJGO, 2007
- **d** Sääv et al. Human Reproduction, 2015; Kapp et al. Cochrane Database of Systematic Reviews, 2010
- **e** Dabash et al. IJGO, 2015
- **f** Perritt et al. Contraception, 2013
- **g** Mark et al. IJGO, 2015
- **h** WHO recommendations for induction of labour, 2011
- **i** FIGO Guidelines: Prevention of PPH with misoprostol, 2012
- **j** Raghavan et al. BJOG, 2015
- **k** FIGO Guidelines: Treatment of PPH with misoprostol, 2012

Notes
1. If mifepristone is available (preferable), follow the regimen prescribed for mifepristone + misoprostol[a]
2. Included in the WHO Model List of Essential Medicines
3. For incomplete/inevitable abortion women should be treated based on their uterine size rather than last menstrual period (LMP) dating
4. Leave to take effect over 1–2 weeks unless excessive bleeding or infection
5. An additional dose can be offered if the placenta has not been expelled 30 minutes after fetal expulsion
6. Several studies limited dosing to 5 times; most women have complete expulsion before use of 5 doses, but other studies continued beyond 5 and achieved a higher total success rate with no safety issues
7. Including ruptured membranes where delivery indicated
8. Follow local protocol if previous cesarean or transmural uterine scar
9. If only 200µg tablets are available, smaller doses can be made by dissolving in water (see www.misoprostol.org)
10. Where oxytocin is not available or storage conditions are inadequate
11. Option for community based programs

Route of Administration
pv – vaginal administration
sl – sublingual (under the tongue)
po – oral
bucc – buccal (in the cheek)

* Avoid pv (vaginal route) if bleeding and/or signs of infection

Rectal route is not included as a recommended route because the pharmacokinetic profile is not associated with the best efficacy

FIGURE 1 The FIGO misoprostol-only recommended regimens 2017 chart.

expert group. It has been endorsed by the FIGO Prevention of Unsafe Abortion Working Group and the FIGO Safe Motherhood and Newborn Health Committee, and approved by the FIGO Officers. Available in other languages and formats from http://figo.org, it is hoped that it will be as widely distributed and used as the previous version. Although these recommended dosages have been decided on the basis of current evidence available and expert opinion, new evidence is regularly emerging and thus there is a need to review and revise these recommendations in the future.

Misoprostol is an important medicine and, although it should not be used in preference over oxytocin for postpartum hemorrhage, or instead of mifepristone plus misoprostol for pregnancy termination, it could be the only medicine available in some circumstances, which is why FIGO believes this "misoprostol-only" chart is needed. Misoprostol must continue to be highlighted as an essential medicine and included in international documents, national guidelines, and essential medicines lists. Further, we must work to ensure the availability of high-quality misoprostol, and the establishment of policy and programs that support its availability and use.

The recent WHO guidelines on health worker roles in providing safe abortion care[23] outline a wide variety of healthcare providers who can manage medical abortion and postabortion care in the first trimester, with auxiliary nurses, nurses, and midwives listed, as well as lay health workers and doctors of complementary systems for some subtasks. Women can also fulfill some of the components of assessment and management themselves outside of a healthcare facility. It is anticipated that this misoprostol chart can be used by all healthcare providers identified in the WHO publication and that by implementing both, we will come closer to achieving optimal care for the women we aim to serve.

AUTHOR CONTRIBUTIONS

All authors contributed to the development of the chart and the writing of the commentary.

REFERENCES

1. WHO. *Clinical Practice Handbook for Safe Abortion*. Geneva: World Health Organization; 2014.
2. von Hertzen H, Piaggio G, Huong NT, et al. Efficacy of two intervals and two routes of administration of misoprostol for termination of early pregnancy: A randomised controlled equivalence trial. *Lancet*. 2007;369:1938–1946.
3. Sheldon W, Dzuba I, Sayette H, Durocher J, Winikoff B. Buccal versus sublingual misoprostol alone for early pregnancy termination in legally restricted Latin American settings: A randomized trial. Presented at FIAPAC; 2016, Lisbon, Portugal. FC25.
4. Gemzell-Danielsson K, Ho PC, Gómez Ponce de León R, Weeks A, Winikoff B. Misoprostol to treat missed abortion in the first trimester. *Int J Gynecol Obstet*. 2007;99(Suppl.2): S182–S185.
5. Sääv I, Kopp Kallner H, Fiala C, Gemzell-Danielsson K. Sublingual versus vaginal misoprostol for cervical dilatation 1 or 3 h prior to surgical abortion: A double-blinded RCT. *Hum Reprod*. 2015;30: 1314–1322.
6. Kapp N, Lohr PA, Ngo TD, Hayes JL. Cervical preparation for first trimester surgical abortion. *Cochrane Database Syst Rev*. 2010;2:CD007207.
7. Dabash R, Chelli H, Hajri S, Shochet T, Raghavan S, Winikoff B. A double-blind randomized controlled trial of mifepristone or placebo before buccal misoprostol for abortion at 14–21 weeks of pregnancy. *Int J Gynecol Obstet*. 2015;130:40–44.
8. Mark AG, Edelman A, Borgatta L. Second-trimester postabortion care for ruptured membranes, fetal demise, and incomplete abortion. *Int J Gynecol Obstet*. 2015;129:98–103.
9. Perritt JB, Burke A, Edelman AB. Interruption of nonviable pregnancies of 24-28 weeks' gestation using medical methods: Release date June 2013 SFP guideline #20133. *Contraception*. 2013;88: 341–349.
10. WHO. *WHO recommendations for induction of labour*. Geneva: World Health Organization; 2011.
11. International Federation of Gynecology and Obstetrics. Prevention of Post-Partum Haemorrhage with Misoprostol: FIGO Guideline in brief. Published 2012. http://www.figo.org/sites/default/files/uploads/project-publications/Miso/PPH%20prevention/Prevention%20of%20PPH%20with%20Misoprostol_In%20Brief_2012_English.pdf. Accessed October 17, 2016.
12. Raghavan S, Geller S, Miller S, et al. Misoprostol for primary versus secondary prevention of postpartum haemorrhage: A cluster-randomised non-inferiority community trial. *BJOG*. 2016;123:120–127.
13. International Federation of Gynecology and Obstetrics. Treatment of Post-Partum Haemorrhage with Misoprostol: FIGO Guideline in brief. Published 2012. http://www.figo.org/sites/default/files/uploads/project-publications/Miso/PPH%20treatment/Treatment%20of%20PPH%20with%20Misoprostol_In%20Brief_2012_English.pdf. Accessed October 17, 2016.
14. Gynuity Health Projects. Abortion Induction with Misoprostol Alone in Pregnancies Through 9 Weeks' LMP. Published 2013. http://gynuity.org/resources/read/misoprostol-for-early-abortion-en/. Accessed October 17, 2016.
15. Dodd JM, Crowther CA. Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death. *Cochrane Database Syst Rev*. 2010;4:CD004901.
16. Gómez PdLR, Wing D, Fiala C. Misoprostol for intrauterine fetal death. *Int J Gynecol Obstet*. 2007;99(Suppl.2):S190–S193.
17. Goyal V. Uterine rupture in second-trimester misoprostol-induced abortion after cesarean delivery: A systematic review. *Obstet Gynecol*. 2009;113:1117–1123.
18. Naguib AH, Morsi HM, Borg TF, Fayed ST, Hemeda HM. Vaginal misoprostol for second-trimester pregnancy termination after one previous cesarean delivery. *Int J Gynecol Obstet*. 2010;108:48–51.
19. Fawzy M, Abdel-Hady E-S. Midtrimester abortion using vaginal misoprostol for women with three or more prior cesarean deliveries. *Int J Gynecol Obstet*. 2010;110:50–52.
20. Allen R, O'Brien BM. Uses of misoprostol in obstetrics and gynecology. *Rev Obstet Gynecol*. 2009;2:159–168.
21. Wildschut H, Both MI, Medema S, Thomee E, Wildhagen MF, Kapp N. Medical methods for mid-trimester termination of pregnancy. *Cochrane Database Syst Rev*. 2011;1:CD005216.
22. Grillo-Ardila CF, Ruiz-Parra AI, Gaitán HG, Rodriguez-Malagon N. Prostaglandins for management of retained placenta. *Cochrane Database Syst Rev*. 2014;5:CD010312.
23. WHO. *Health worker roles in providing safe abortion care and post-abortion contraception*. Geneva: World Health Organization; 2015.