





REVIEW



Outcome of first trimester medical termination of pregnancy: definitions and management

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ABSTRACT

Objective: Medical termination of pregnancy (MToP, or medical abortion) is a highly effective method with a reported efficacy of 95–98%. However, different criteria are currently used to define success, and there are different recommendations for the treatment of what is considered a failure of MToP. This work was undertaken to develop a consensus around a set of well-defined MToP outcomes, as recommended by the Core Outcomes in Women's and Newborn Health initiative.

Methods: A literature search was made of national and international guidelines and of recommendations of expert groups for various outcomes of MToP and subsequent management. Based on a review of the findings, a group of European experts in MToP undertook a consensus process to agree on a set of core MToP outcomes.

Results: The following core MToP outcomes were defined: success, failure (ongoing pregnancy), need for additional treatment (medical or surgical) to complete MToP (missed abortion, incomplete abortion), complications and the woman's request for additional treatment (medical or surgical). Recommendations for the management of unsuccessful outcomes were also formulated.

Conclusion: New definitions of MToP outcomes that are more focused on objective criteria and consequently less dependent on provider interpretation are proposed. This should allow better comparison of the efficacy of different regimens and improve the management of failed or incomplete abortion.

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Introduction

Medical termination of pregnancy (MToP, or medical abortion) is a highly effective method with a reported efficacy of 95–98% [1]. However, different definitions of treatment success are used in various publications and clinical guidelines [2]. Most include provider-dependent criteria. The absence of a standard, clear and consistent definition makes it difficult to compare the outcome of different studies or different regimens of mifepristone and misoprostol for MToP. Also, an unambiguous definition of failed or incomplete abortion is needed to give clear guidelines for managing these outcomes.

Most international guidelines, expert groups and clinical trials define the success of MToP as complete termination of pregnancy without recourse to a surgical procedure. This is also true for the recent Medical Abortion Reporting of Efficacy (MARE) guidelines [3]. However, other definitions of MToP outcome may be found in clinical guidelines, as well as different recommendations for managing incomplete or failed MToP: surgery, additional medical treatment or expectant management.

The frequency of surgical intervention following MToP is provider-dependent, especially for incomplete abortion diagnosed via ultrasound, which carries the risk of misinterpreting a thick and heterogeneous appearance of the

endometrium as an incomplete abortion [4]. Using the rate of surgical intervention as an indicator for success is misleading for another reason: some providers treat unsuccessful outcomes medically instead of surgically, by repeating the combined treatment or giving an extra dose of misoprostol [5]. Ongoing pregnancy after MToP can also be treated by repeating the treatment regimen and thus avoiding surgical intervention.

Guidelines and clinical practice differ in the number of additional misoprostol doses and the indications for which they are given. Providers also vary considerably in their threshold for administering additional medical treatment to complete the expulsion of the uterine cavity contents (gestational sac, blood clots or residua, of various diameters), especially when retained products of conception are diagnosed by ultrasound [1]. Another difficulty is that the rate of surgical intervention may be biased, since some clinical trials classify surgical evacuation at the woman's request as a failure, while others only do so if it has been carried out for medical reasons [2].

All these factors make the rate of surgical intervention highly variable, provider-dependent and open to bias, and therefore unsuitable to define success of MToP.

An evidence-based and objective definition of MToP outcome is urgently needed, especially as MToP is used

Table 1. MToP outcome definitions.

Outcome	Gynuity Health Projects [13]	HAS [15]	WHO [8]
Success	Complete termination of pregnancy without the need for a surgical procedure	Complete termination of pregnancy without the need for a surgical procedure	
Failure	Recourse to a surgical procedure: may be the result of ongoing pregnancy, incomplete expulsion, heavy bleeding, judgement of the provider that procedure should be terminated surgically, or request of the woman	Surgery for any of the following: ongoing pregnancy, incomplete expulsion, heavy bleeding requiring surgical haemostasis, surgery requested by the woman Better assessment: rate of ongoing pregnancies	
Complete abortion			All products of conception (embryo/fetus, placenta and membranes) are expelled
Incomplete abortion			Although the fetus is expelled, part or all the placenta is retained
Missed abortion			Pregnancy where the fetus has died but fetal tissue and placenta are retained in the uterus

Empty boxes correspond to no guideline definitions.

increasingly around the world. Therefore, this study endeavours to develop a consensus around a set of relevant and well-defined first trimester MToP outcomes, as recommended by the Core Outcomes in Women's and Newborn Health initiative [6]. It may be considered a first step for the Standardizing Abortion Research Outcomes project, dedicated to producing, disseminating and implementing a core outcome dataset for medical and surgical abortion research [7].

Methods

Literature review

We conducted a literature review of international guidelines published from 2007 to 2017 for success and failure definitions, as well as for failure management. The following international guidelines on MToP, including national guidelines from European countries, were searched: World Health Organization (WHO) 2008 [8], 2012 [9] and 2014 [10]; International Planned Parenthood Federation (IPPF) 2008 [11]; International Federation of Gynecology and Obstetrics (FIGO) 2011 [12]; Gynuity Health Projects 2009 [13] and European guidelines: France (Haute Autorité de Santé [HAS] 2010 [14,15]); UK (Royal College of Obstetricians and Gynaecologists [RCOG] 2011 [16] and 2015 [17]); and Swedish Society of Obstetrics and Gynaecology (SFOG) guidelines 2018 [18]. Recent MARE guidelines aiming to improve the reporting of MToP efficacy were also included [3].

These national and international guidelines were also searched to find information on managing different types of MToP outcome [2–4].

Role of the expert group

The expert group included clinicians, researchers and members of the pharmaceutical industry involved in MToP. Drawing on the literature search, the group established consensus definitions of MToP outcome, as well as consensus proposals based on the evidence for management of non-successful outcomes. Any disagreement between members of the expert group was discussed in depth

during face-to-face meetings involving all experts. They agreed on the final definitions proposed below.

Results

Below is a summary of the available guidelines pertaining to MToP definitions and outcome management.

Definitions of success and failure

No clearly specified definition of success or failure was found in WHO [8–10], FIGO [12] or RCOG [16,17] sources. Definitions were available from IPPF [11], Gynuity Health Projects [13] and HAS [14,15], but they varied considerably (Table 1).

Management of abortion outcome

WHO guidelines suggest offering vacuum aspiration or repeat administration of misoprostol every 3 h in up to five doses to complete the procedure for a woman reporting ongoing symptoms of pregnancy and/or who has only minimal bleeding after taking the abortifacient medications as directed [9]. HAS suggests the administration of additional doses of misoprostol (400 µg, usually via the oral route) following first misoprostol intake in most first trimester MToP studies [15]. FIGO recommends additional doses of 600–800 µg via the sublingual, vaginal or buccal route [5].

A follow-up visit is not necessary from a clinical point of view if expulsion has been confirmed at the time of the procedure [9,16]. It is still recommended by IPPF 14 days after the procedure, to initiate contraception [11]. It is also legally mandatory in some countries (e.g. France) and must be held 2 weeks after misoprostol administration [14].

MToP outcome at a follow-up visit may be complete abortion, incomplete abortion (which can be difficult to differentiate from intrauterine blood clots on ultrasound), missed abortion (persistent but non-developing pregnancy) or ongoing pregnancy [4].

Incomplete abortion

No clear and uniform definition of incomplete abortion exists, nor are there any criteria on how to diagnose it:

Table 2. Management of abortion outcome up to 13 weeks at follow-up: guidelines.

Guideline	Ongoing pregnancy	Incomplete abortion	Missed abortion
WHO [9]	Re-administration of misoprostol or surgery	Expectant management, or Misoprostol 400 µg sublingually or 600 µg orally, or Surgery	
WHO [10]	Uterine evacuation	Expectant management, or Vacuum aspiration, or Misoprostol 600 µg orally, 400 µg sublingually or 400-800 µg vaginally if vaginal bleeding is minimal	Expectant management, or Vacuum aspiration, or Misoprostol
IPPF [11]		Misoprostol 800 µg orally or vaginally	
FIGO [12]	Uterine evacuation	Additional misoprostol 600 µg orally or 400 µg sublingually, or Vacuum aspiration	
RCOG [17]		Vacuum aspiration, or Misoprostol 600 µg orally or 400 µg sublingually	
SFOG [18]		Medical treatment (misoprostol 400 µg sublingually or 600 µg vaginally), or Vacuum aspiration and pretreatment with misoprostol 400 µg sublingually	Misoprostol 800 µg vaginally or 600 µg sublingually, or Vacuum aspiration and pretreatment with misoprostol 400 µg sublingually

Empty boxes correspond to no guideline recommendations.

with or without ultrasound, with or without human chorionic gonadotropin (hCG) testing, with or without gynaecological examination, etc. (Table 2). WHO and FIGO recommend either vacuum aspiration or treatment with misoprostol for incomplete abortion if uterine size is equivalent to a pregnancy of gestational age ≤ 13 weeks [9,12]. The recommended regimen of misoprostol is a single dose given either sublingually (400 µg) or orally (400–800 µg). Misoprostol may also be given vaginally, but this route of administration should be avoided in women with a level of bleeding that might affect absorption of misoprostol [10–12,17,19–21]. Expectant management may also be considered [9,10,20]. Surgical evacuation of the uterus may be carried out at the woman's request or in case of a clinical indication (e.g. haemodynamically unstable situation, heavy or prolonged bleeding, anaemia, suspicion of infection) [10].

Missed abortion

For management of missed abortion independently of prior treatment for MToP, FIGO's 2017 guidelines recommend misoprostol 800 µg vaginally every 3 h (maximum two doses) or 600 µg sublingually every 3 h (maximum two doses) [5]. SFOG guidelines recommend either misoprostol or surgery [18].

Ongoing pregnancy

For ongoing pregnancy (Table 2), WHO, IPPF and FIGO recommend that women be offered a uterine evacuation procedure as quickly as possible [9,11,12]. This is usually done by vacuum aspiration [9,11,12]; however, a second identical course of MToP may also be given if the woman prefers and if the gestational age is still within the approved gestational limit for the drug [18].

Discussion

During the first 20 years of MToP, success was defined as expulsion of the pregnancy without surgical intervention, because most complications (heavy bleeding) or undesired outcomes (ongoing pregnancy, missed or incomplete abortion) were treated surgically. However, the frequency of a surgical intervention in these cases not only depends on

the diagnosis of the outcome but to a large extent on the provider (experience and motivation to perform or avoid a surgical intervention) [22] and the woman being treated. Moreover, this definition is no longer applicable for two reasons:

1. Except for ongoing pregnancy, undesired outcomes are currently defined by widely varying criteria. Therefore, the frequency varies considerably depending on the provider.
2. Recent years have seen a tendency towards fewer surgical interventions to treat undesired outcomes and complications of MToP, because clinical experience has shown that most situations may be handled with medical treatment: additional doses of misoprostol, a repeat course of the combination of mifepristone and misoprostol, or expectant management.

New definitions of MToP outcomes are necessary. However, it will not be possible to compare the rates of success and failure presented in previous literature with the rates found using the new definitions. This should be kept in mind for future meta-analyses.

Diagnosing and managing different outcomes of MToP

The outcome of MToP may be one of the following three situations (Figure 1):

- Success: expulsion without the need for additional intervention.
- Failure: ongoing viable pregnancy.
- Need for additional treatment or expectant management (because of incomplete or missed abortion, a complication, or at the woman's request).

Follow-up assessment

The outcome of MToP can be diagnosed during the procedure and/or during the follow-up visit. The purpose of the visit is to confirm expulsion of the pregnancy and

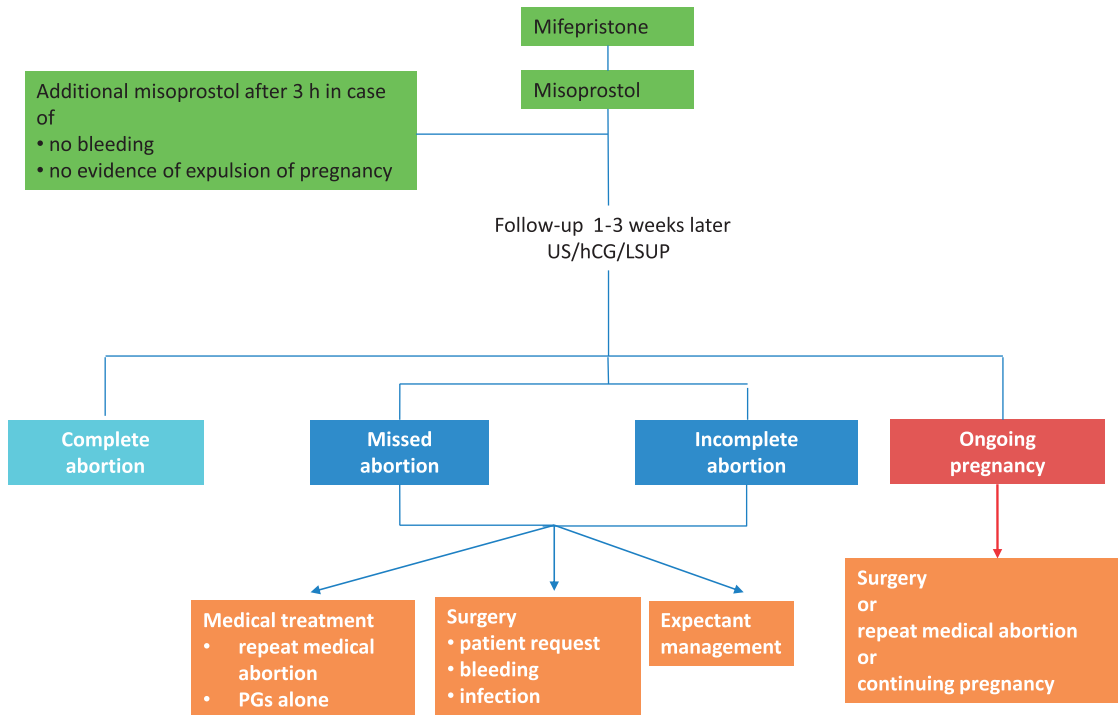


Figure 1. Management of MToP outcome. PG, prostaglandin; US, ultrasound.

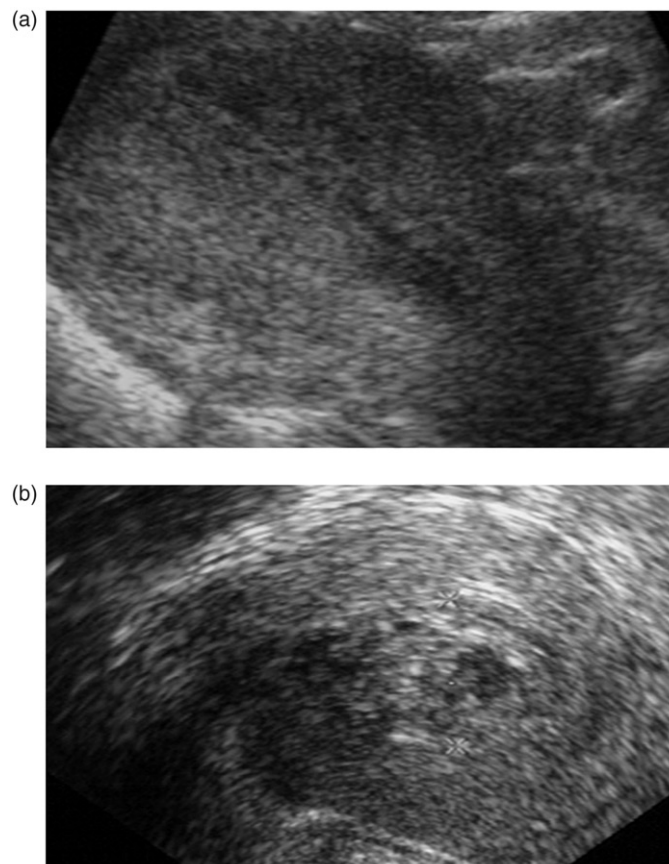


Figure 2. Vaginal ultrasound. (a) Uterine cavity immediately after aspiration of an 8-week pregnancy. (b) Presence of blood clots in the same woman 10 days after surgical abortion.

enable the woman to make an early decision on how to proceed in the rare case of an ongoing pregnancy. The delay between misoprostol intake and the follow-up visit is a trade-off between the woman's interest in knowing the treatment outcome as soon as possible and the reliability of the examination (ultrasound or hCG), which may be

inconclusive if done too early but becomes highly reliable with increasing time.

Early identification of the outcome is important to avoid delay in potentially necessary additional treatment, especially in the case of ongoing pregnancy. Diagnosis of ongoing pregnancy can be done by ultrasound; by

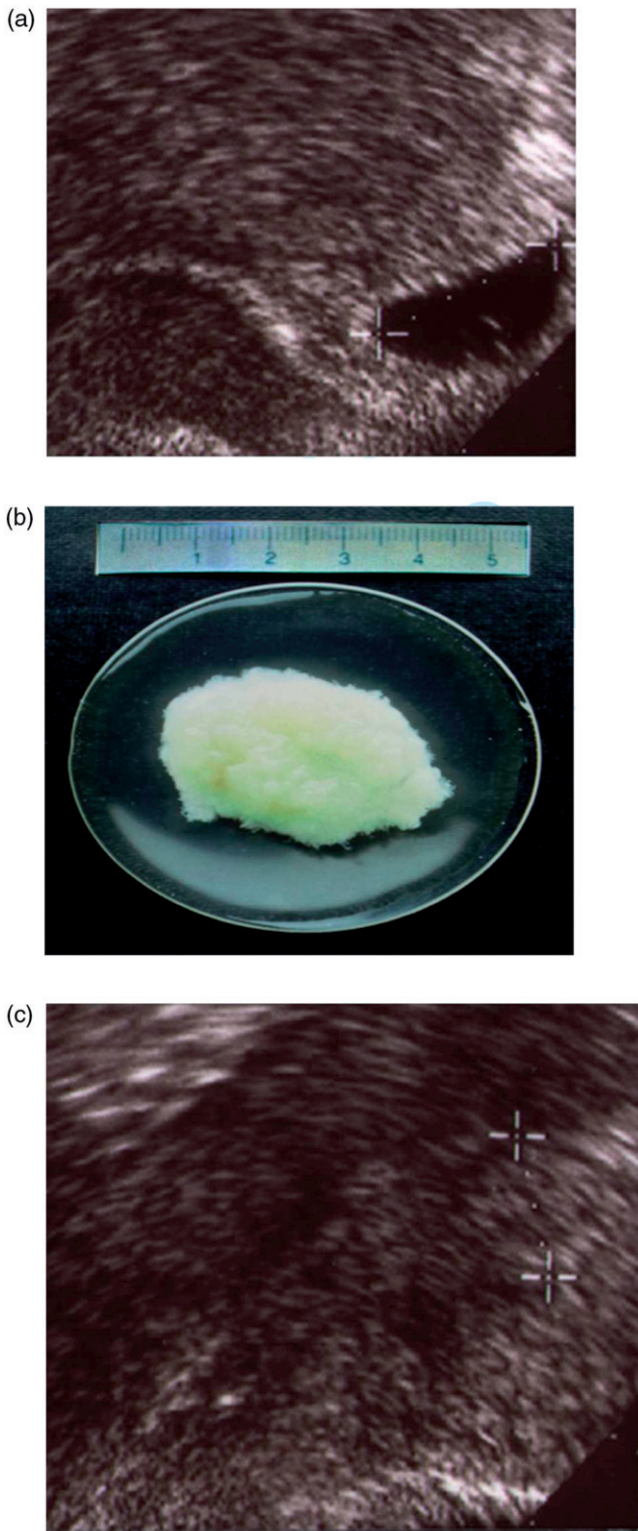


Figure 3. Vaginal ultrasound. (a) Uterus with an intrauterine pregnancy corresponding to 6 weeks after the last menstrual period, with yolk sac visible and serum hCG 32,000 IU/l. (b) Gestational sac of the same woman expelled on day 3. (c) Uterine cavity diameter 12 mm in the same woman 8 days after intake of mifepristone in an MToP procedure. Serum hCG had dropped to 837 IU/l. The gestational sac that was visible in the uterine cavity prior to the procedure is gone.

interpreting a woman's report of signs and symptoms of ongoing pregnancy; by a specially designed, self-performed, low-sensitivity urinary pregnancy (LSUP) test; by serial serum hCG testing; or by serial use of a multilevel pregnancy test [23]. Follow-up can be organised by self-assessment [24], telephone follow-up, or by systematic clinic visits and ultrasound [25].

Ongoing pregnancy

Ongoing pregnancy is arguably the only true failure of treatment. It is easy and unambiguous to diagnose and is a reliable criterion to compare the results from different studies. The rate of ongoing pregnancy is, however, very low following MToP carried out according to recommended guidelines [26]. Treatment of an ongoing pregnancy can be by surgical evacuation, as recommended by most guidelines, or repeat MToP [24]. However, few published data give evidence-based recommendations for the best treatment in such circumstances.

Missed and incomplete abortion

Missed abortion (persistent non-viable pregnancy) and incomplete abortion (remaining residue) are clinical situations that may also need additional treatment. Different recommendations exist for this additional treatment [10]. However, the diagnosis is usually unclear in the published literature and treatment varies widely in clinical practice. Treatment can be surgical (aspiration), medical (additional misoprostol or the repeated combination of mifepristone and misoprostol) or expectant management. These differences make it almost impossible to compare results from different studies, especially since some interventions are classified as failures (e.g. surgical intervention), while other interventions for the same undesired outcome are classified as successes (e.g. additional medical treatment).

The diagnosis of missed abortion uses clinical symptoms in combination with either a post-treatment LSUP test, confirmed by ultrasound or ultrasound alone.

The diagnosis of incomplete abortion is usually based on clinical signs and symptoms (no expulsion; nausea; breast tenderness; enlarged, soft uterus; dilated cervix; prolonged bleeding), and/or elevated hCG levels, and/or ultrasound that may find an echogenic structure in the uterine cavity. However, blood clots frequently look identical to pregnancy residue on ultrasound, and intrauterine blood clots are frequently found in a complete abortion [27]. These two situations may be indistinguishable without histological examination of the tissue (Figures 2 and 3). Therefore, the diagnosis of incomplete abortion should not be based on ultrasound criteria alone but should include hCG testing and/or clinical evaluation [16,28,29]. Also, interventions based on ultrasound diagnosis or a single hCG test alone might be unnecessary.

New definition for outcome of MToP

Based on the above analysis, the expert group suggests the following classification for MToP outcome, as assessed 1–3 weeks after the procedure (Table 3):

- Success: expulsion of the gestational sac with no need for additional treatment (repeat MToP, misoprostol alone, or surgical vacuum aspiration).
- Failure: ongoing pregnancy that can be unambiguously diagnosed.
- Need for additional treatment:
 - To complete MToP: additional treatment can be medical (repeat MToP or misoprostol alone) or surgical (vacuum aspiration). However, a surgical

Table 3. Proposed definitions of outcome of MToP (or medical abortion).

Outcome of MToP	Definition
Success	Expulsion without the need for additional treatment (repeat MToP, misoprostol alone, or surgical)
Failure	Ongoing pregnancy
Need for additional treatment	
Additional treatment needed to complete MToP: incomplete abortion (products of conception are retained but gestational sac/embryo is expelled), missed abortion (persistent non-evolving pregnancy)	Situation that is not considered a complication and needs additional treatment, which may be medical (repeat MToP or misoprostol alone) or surgical (aspiration)
Complications leading to additional treatment	Heavy or prolonged bleeding; infection; persistent, significant pain
Woman's request for additional treatment	

For research protocols, outcomes should be assessed at standardised time points (follow-up including self-assessment).

intervention is invasive, which can greatly impact treatment satisfaction, since a woman who chooses medical treatment often wants to avoid surgery [23].

- To treat a complication: this would include surgery or medical treatment (antibiotics, misoprostol or blood transfusion) for adverse outcomes such as heavy or prolonged bleeding, infection or persistent significant pain, if these outcomes are not associated with missed or incomplete abortion.
- At the woman's request.

Future research

Thirty years after MToP was first marketed in France in 1988, many questions about it have been answered in numerous clinical studies. Its high efficacy and safety have been demonstrated [30], along with the immediate return of ovulation [31] and no negative impact on future pregnancies [32,33]. However, future research is needed on aspects such as improving pain management and reducing the length and intensity of bleeding.

Conclusion

The currently used definitions of success of MToP are inconsistent and provider-dependent. The increasing use of medical treatments in place of surgery makes it necessary to find new definitions for MToP outcomes where the only true failure is verifiable and unambiguous: ongoing viable pregnancy. The new definitions recommended in this review should allow for easier and more reliable comparison of the efficacy of different regimens in the future and should help providers manage MToP outcomes appropriately.

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