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

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\textbf{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.

**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...
increasingly around the world. Therefore, this study
endeavours to develop a consensus around a set of rele-
vant 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 imple-
menting a core outcome dataset for medical and surgical
abortion research [7].

Methods

Literature review

We conducted a literature review of international guide-
lines published from 2007 to 2017 for success and failure
definitions, as well as for failure management. The follow-
ing 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 effi-
cacy 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 mem-
ers of the pharmaceutical industry involved in MToP.
Drawing on the literature search, the group established
consensus definitions of MToP outcome, as well as consen-
sus 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
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 min-
imal bleeding after taking the abortifacient medications as
directed [9]. HAS suggests the administration of additional
doses of misoprostol (400 mg, usually via the oral route) fol-
lowing first misoprostol intake in most first trimester MToP
studies [15]. FIGO recommends additional doses of 600–800
mg 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 dif-
ferentiate 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:

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<tr>
<td>Success</td>
<td>Complete termination of pregnancy without the need for a surgical procedure</td>
<td>Complete termination of pregnancy without the need for a surgical procedure</td>
<td>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</td>
</tr>
<tr>
<td>Failure</td>
<td>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</td>
<td>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</td>
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</table>

Complete abortion

Incomplete abortion

Missed abortion

All products of conception (embryo/fetus, placenta and membranes) are expelled
Although the fetus is expelled, part or all the placenta is retained
Pregnancy where the fetus has died but fetal tissue and placenta are retained in the uterus

Empty boxes correspond to no guideline definitions.
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 3h (maximum two doses) or 600 μg sublingually every 3h (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
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
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...
The length and intensity of bleeding. Aspects such as improving pain management and reducing complications [32,33]. However, future research is needed on 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.

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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Disclosure statement

All authors, except for Sharon Cameron, are members of the external scientific advisory board of Exelgyn. Sharon Cameron was a member until 2016 and ceased thereafter; she has no conflict of interest. Christian Fiala has served on an ad hoc basis as an invited lecturer for Exelgyn and Teva. Teresa Bombas is a member of the board of MSD and HRA and a speaker in conferences/symposia organised by Bayer, MSD, HRA, Gedeon and Exelgyn. Mirella Parachini has served on an ad hoc basis as a consultant for Nordic Pharma. Aubert Agostini is a member of the board at MSD and has served as an investigator for a Nordic Pharma study. Roberto Lertxundi has financial relationships (member of advisory boards, lecturer and/or consultant) with Nordic Pharma, Exelitis, Bayer and Teva. Marek Lubusky has no conflict of interest. Laurence Saya is an employee of Altius Pharma, a consultancy and medical writing company, which received funding from Exelgyn for help with this work. Kristina Gemzell-Danielsson serves or has served on an ad hoc basis as an invited lecturer for Exelgyn, Linepharma and Gynuity, and as an investigator in clinical trials conducted by Concept Foundation/SunPharma.

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References


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

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

<table>
<thead>
<tr>
<th>Outcome of MToP</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Success</td>
<td>Expulsion without the need for additional treatment (repeat MToP, misoprostol alone, or surgical)</td>
</tr>
<tr>
<td>Failure</td>
<td>Ongoing pregnancy</td>
</tr>
<tr>
<td>Need for additional treatment</td>
<td>Situation that is not considered a complication and needs additional treatment, which may be medical (repeat MToP or misoprostol alone) or surgical (aspiration)</td>
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<tr>
<td>Additional treatment needed to complete MToP: incomplete abortion</td>
<td>Heavy or prolonged bleeding; infection; persistent, significant pain</td>
</tr>
<tr>
<td>Complications leading to additional treatment</td>
<td>Woman’s request for additional treatment</td>
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Heavy or prolonged bleeding; infection; persistent, significant pain.


