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REVIEW

Management of pain associated with up-to-9-weeks medical termination of pregnancy (MToP) using mifepristone–misoprostol regimens: expert consensus based on a systematic literature review

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ABSTRACT

Evidence-based guidelines on the management of pain associated with first-trimester medical abortion are lacking. Most published clinical trials have failed to report on this important aspect of the procedure. The aim of this comprehensive work was to provide clinical advice based on a comprehensive literature review, supplemented by the clinical experience of a group of European experts in case no evidence is available. Pain level ranged from 5 to 8 in 80% of studies where pain was measured on a 0–10 visual analogue scale; severe pain was reported by 20–80% of women. Pain assessment was rarely reported in studies. Pain treatment should be preventive and avoidance of unnecessary uterine contractions should be considered. Analgesic treatment should follow the WHO three-step ladder, starting with the use of NSAIDs and allowing for easily available back-up treatment with weak opioids.

KEYWORDS

Pain; medical abortion; expert consensus

Introduction

According to estimates, approximately 50 million abortions are performed worldwide each year. About one in five pregnancies ended in abortion in 2008 (Sedgh et al. 2012) and 25% did so in 2010–2014 (Sedgh et al. 2016).

Medical abortion became an alternative to surgical abortion for first-trimester pregnancy termination with the availability of prostaglandins in the early 1970s and antiprogesterone modulators in the 1980s (Fiala and Gemzell-Danielsson 2006). Medical methods have grown in popularity, and, in 2016, medical abortion accounted for approximately 64% of induced abortions in France (DREES 2016), 68% of all abortions up to 10 weeks in Portugal (DGS 2016), over 80% in Scotland and over 90% in Sweden for terminations at less than 9 weeks gestation (Socialstyrelsen, Abortion Statistics 2016; NHS 2017), and 20% in Spain for terminations at less than 9 weeks gestation (Ministerio de Sanidad, Servicios Sociales e Igualdad 2016).

The most frequently used drug combination in Europe is mifepristone followed by the prostaglandin analogue misoprostol. This combination is highly effective and associated with few adverse events. Nevertheless, pain is often cited by women as one of the worst features of medical abortion (Dragoman et al. 2016). However, most reports of clinical trials fail to describe pain associated with this treatment in the first trimester (Fiala et al. 2014), and information on this subject is scarce in the literature. Also, no specific or comprehensive guideline exists on pain management in first-trimester medical abortion (Fiala et al. 2014). In view of this, a group of European experts in abortion care performed a systematic literature review on the occurrence, assessment and management of pain associated with medical abortion up to 9 weeks in order to provide best practice guidelines. The review was supplemented by a consensus based on clinical experience of the experts for specific aspects where evidence was lacking.

Methods

A group of clinicians and researchers with extensive clinical experience in the field of medical abortion (MToP) based in several European countries (Austria, Czech Republic, France, Italy, Portugal, Spain, Sweden, United Kingdom) worked together to provide these recommendations. Some of the authors were involved in the original development of medical abortion and/or the introduction of this method in their country. The Expert Group developed a list of clinically important questions regarding pain associated with up-to-9-weeks MToP (Supplementary Appendix 1). This list was prepared before performing the literature analysis.

As a first step, a systematic bibliographic search was done for publications in English up to June 2017. The PubMed

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Supplemental data for this article can be accessed here.

search looked at pain treatment/pain assessment and medical termination of pregnancy (first search: ('pain measurement'[MeSH Terms] OR ('pain'[All Fields] AND 'measurement'[All Fields]) OR 'pain measurement'[All Fields] OR ('pain'[All Fields] AND 'assessment'[All Fields]) OR 'pain assessment'[All Fields]) AND ('abortion, induced'[MeSH Terms] OR ('abortion'[All Fields] AND 'induced'[All Fields]) OR 'induced abortion'[All Fields]); second search: 'pain treatment'[MeSH Terms] OR ('pain'[All Fields] AND 'treatment'[All Fields]) OR 'pain treatment'[All Fields] OR ('pain'[All Fields] AND 'management'[All Fields]) OR 'pain management'[All Fields]) AND ('abortion, induced'[MeSH Terms] OR ('abortion'[All Fields] AND 'induced'[All Fields]) OR 'induced abortion'[All Fields]). In addition, publications cited in the list of references of the publications found during the literature search were used if appropriate.

This search allowed for finding responses to most questions. However, for some questions, few or contradictory information was found. The experts were asked to provide their thoughts and clinical experience during several consensus meetings, taking into account the published evidence, as far as available. All published studies but one referred to pregnancy duration $\leq$63 days.

When discrepancies between the experts appeared, this is clearly stated in this paper.

No meta-analysis was possible due to the paucity and heterogeneity of the data.

Results

Occurrence of pain

According to the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience arising from actual or potential tissue damage (IASP 1979). Clinically, pain is whatever the person says he or she is experiencing whenever he or she says it occurs (McCaffery and Pasero 1999).

During MToP, mifepristone increases uterine contractility and sensitises the myometrium to prostaglandins. The administration of prostaglandins following mifepristone induces uterine contractions by binding to specific receptors on the myometrial cell surface (Bygdeman and Swahn 1985; Christin-Maitre et al. 2000). Abdominopelvic pain during medical abortion is due to uterine contractions (HAS 2010), which are an integral part of the medical abortion process (Bygdeman and Swahn 1985; Fiala and Gemzell-Danielsson 2006; FIGO 2011). Side effects of the pregnancy and medical abortion medications, such as nausea as well as potential psychological distress and anxiety, also contribute to the experience of discomfort. There was no specific pattern regarding pain associated with MToP: it has been described as cramping, pain more severe than menstruation, abdominal pain, etc.

The frequency and intensity of pain associated with MToP is rarely reported in the literature. Only a few studies have directly assessed pain by recording levels of pain or reports of pain as an adverse event, or indirectly via the amount of analgesics used by women (Table 1). As data on pain incidence and intensity are usually impossible to dissociate in published sources, they are presented together in the table.

The occurrence and intensity of pain associated with first-trimester MToP was reported in 15 prospective and two retrospective clinical studies using various mifepristone/misoprostol regimens. The level of pain and proportion of women reporting pain varied in these studies depending upon the study, the gestational age and the MToP regimen.

For pregnancies up to 9 weeks of amenorrhoea, mean pain scores varied from 5 to 8 on a 10-level scale following misoprostol administration (0 = no pain, 10 = worst possible pain) (Singh et al. 2005; Shannon et al. 2006; Livshits et al. 2009), and was 2.5 in a study using a 0–5 scale (Ojha et al. 2012). Severe pain varied hugely between studies and ranged from 20% (Svendsen et al. 2005) to 30% (Singh et al. 2005; Lokeland et al. 2014) to 54% (Cavet et al. 2017) or 80% (Livshits et al. 2009) of women. Mean pain level on day 3, after misoprostol intake, was reported to be 4.7 on a 0–10 visual analogue scale (VAS) for pregnancies up to 12 weeks, with 27% women complaining of severe pain (VAS $\geq$ 8) (Saurel-Cubizolles et al. 2015).

In studies where pain was reported as an adverse event, either spontaneously by women or if they were questioned about it, 79–96% of women reported cramping/pain after misoprostol administration (Westhoff et al. 2000a; Schaff et al. 2002; Raghavan et al. 2012) and 2% (ICMR 2000) to 50% (Spitz et al. 1998; Westhoff et al. 2000a) reported severe abdominal pain. Severe pain for at least one day was reported by 23% of women in one study despite systematic intake of 2 g oral paracetamol at the same time as misoprostol administration (Ravn et al. 2005).

When analysing the occurrence and severity of pain as inferred from the amount of analgesic consumption in women who underwent early medical abortion ($\leq$9 weeks of amenorrhoea), large differences were reported between studies, mainly depending on the local clinical protocol for analgesic provision (Westhoff et al. 2000a, 2000b). Up to 75% of women undergoing first-trimester abortion experienced pain severe enough to require analgesia (Penney 2006). However, the rate of women receiving at least one dose of analgesia for abdominal pain was estimated to be 59% (Ashok et al. 2002) to 68% (Spitz et al. 1998). In addition, WHO step II analgesics (Figure 1) were administered upon request to between 30% (Spitz et al. 1998; Westhoff et al. 2000a) and 74% (Westhoff et al. 2000b) of women having a medical abortion at $\leq$9 weeks of amenorrhoea and 80% of women in the first trimester (Jensen et al. 1999). The use of parenteral opiate analgesia, usually prescribed for severe pain, was reported as 5% of women in one study (Ashok et al. 2002) and 18% in another (Svendsen et al. 2005).

Time to pain occurrence and pain duration are reported in Table 2.

Onset of pain after mifepristone administration and before misoprostol administration has been reported to occur in 11% (De Nonno et al. 2000) to around 40% of patients (WHO 2000; Shannon et al. 2005).

Following misoprostol administration (400–800 μg via oral, sublingual or vaginal route, depending upon the study), time to onset of cramping varied (De Nonno et al. 2000; Singh

Table 1. Occurrence/intensity of first-trimester medical termination of pregnancy-associated pain as reported in clinical studies.

Reference	Country	Study design	Gestational age	MToP regimen	*N*	Outcome
Measured pain						
Singh et al. (2005)	India	Prospective	≤8 weeks of gestation	Mife 200 mg + sublingual Miso 600 μg	40	VAS pain score: 7.1 ± 0.8 70% patients = moderate pain (6–7) 30% = severe pain (≥8)
Svendsen et al. (2005)	Denmark	Retrospective	Up to 63 days of gestation	Mife 200 mg + vaginal Miso 800 μg	423	Moderate to severe: 60%, despite systematic diclofenac 100 mg
Shannon et al. (2006)	Canada	Prospective	<56 days of amenorrhoea	Mife 200 mg + 400 μg oral Miso, 600 μg oral Miso or 800 μg vaginal Miso	971	On 0–10 scale, Oral Miso 400 = 5.8 Oral Miso 600 = 6.2 Vaginal Miso 800 = 6.7
Livshits et al. (2009)	Israel	Prospective	≤7 weeks	Mife 600 mg + oral Miso 400 μg	120	On 0–10 scale = 8 Pain score ≥ 7 = 80%
Ojha et al. (2012)	UK	Prospective	Up to 63 days of gestation	Mife 200 mg + vaginal Miso 800 μg	130	On 0–5 scale, highest pain = 2.5
Lokeland et al. (2014)	Norway	Prospective	Up to 63 days of gestation	Mife 200 mg + vaginal Miso 800 μg	1018	Systematic 50 mg diclofenac + 600 mg paracetamol + 50 mg codeine No pain for 4.2% (5.5% for GA < 49 days, 3.3% for GA = 49–55 days, 3.1% for GA = 56–63 days) Moderate to strong pain experienced by 68.4%
Saurel-Cubizolles et al. (2015)	France	Prospective	4–12 weeks of gestation	Mifepristone 200–600 mg + misoprostol 400–800 μg	453	High level of pain on D3 (0–10 VAS ≥8): 27% Mean pain level of D3: 4.7 (0–10 VAS) Analgesic intake on D1–D5: 85%
Cavet et al. (2017)	France	Prospective	Up to 5 weeks	Not reported (mifepristone + misoprostol)	193	Severe pain (0–10 VAS ≥ 6): 54% Mean pain score (0–10 VAS): 5.6
Pain reported as an adverse event						
Schaff et al. (2002)	USA	Prospective	Up to 9 weeks	Mife 200 mg + oral Miso 400 μg or vaginal Miso 800 μg or oral Miso 800 μg	376	Cramping: vaginal Miso 800 μg: 96% oral Miso 400 μg: 87% Oral Miso 800 μg: 92%
ICMR (2000)	India	Prospective	Up to 28 days of the missed period	Mife 200 mg + 600 μg oral Miso	440	Severe abdominal pain: 2%
Ravn et al. (2005)	Denmark	Retrospective	<56 days of gestation	Mife 400 mg + 400 μg oral Miso	134	Despite systematic prescription of 2 g paracetamol, severe pain: 33%
Raghavan et al. (2012)	Vietnam	Prospective	≤56 days of amenorrhoea	Mife 200 mg + 400 μg oral Miso	2400	Pain: 79% Acceptable or very acceptable pain: 92%
Analgesic consumption						
Jensen et al. (1999)	USA	Prospective	First trimester	Mife 600 mg + oral Miso 400 μg	178	Narcotics: 78.5%
Spitz et al. (1998)	USA	Prospective	≤63 days	Mife 600 mg + oral Miso 400 μg	2121	At least one medication for abdominal pain: 68% Step 2: 29%

(*continued*)

Table 1. Continued.

Reference	Country	Study design	Gestational age	MToP regimen	N	Outcome
Westhoff et al. (2000a)	USA	Prospective	≤63 days of amenorrhoea	Mife 200 mg + vaginal Miso 800 μg	2747	Step 2 analgesics: 79%
Westhoff et al. (2000b)	USA	Prospective	≤63 days of amenorrhoea	Mife 600 mg + oral Miso 400 μg	2121	Step 2 analgesics: 27%
Ashok et al. (2002)	Scotland	Prospective	≤63 days of amenorrhoea	Mife 200 mg + vaginal Miso 800 μg	3146	Oral analgesia: 59% Opiate parenteral analgesia: 5%

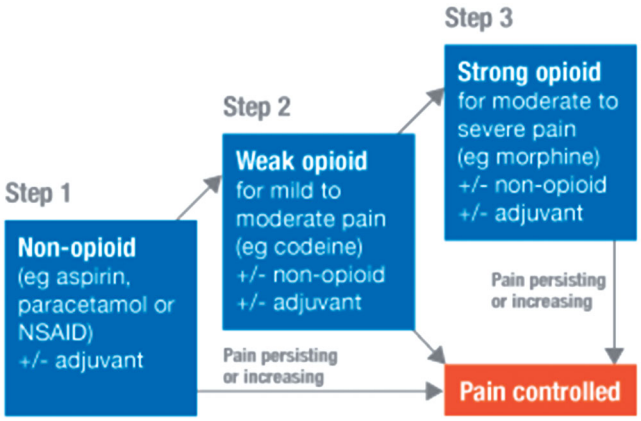

Figure 1. WHO analgesic ladder (Siegel and Bigelow 2018).

et al. 2005; Livshits et al. 2009; Ojha et al. 2012). Lower abdominal pain was reported to peak at 1 and 2 hours after 200 μg oral misoprostol, and at 2 and 3 hours after the same dose administered vaginally (Honkanen et al. 2004). It was also reported to vary according to the MToP setting, with average onset of cramps at 75.6 min (29.4–121.8) for ambulatory patients (moving about until onset of bleeding or passage of products) and 91.7 min (22.2–161.2) for non-ambulatory patients (lying down or reclining with occasional mobilisation) after vaginal administration of 800 μg misoprostol (Ojha et al. 2012).

Duration of pain was reported to last for a minimum of one day following administration of misoprostol (median duration three days) (Shannon et al. 2005), in gestations below 9 weeks of amenorrhoea. Severe pain was reported to last a minimum of one day in 23% of women and 2–3 days in 10% of women (Ravn et al. 2005).

Detailed information provided to women before the procedure, including side-effects, significantly decreased the distress associated with MToP (Kruse et al. 2000). A significant increase in pain was associated with other factors: sociodemographic characteristics (younger age, women living in other places than Asia, unmarried, limited financial support) and reproductive characteristics (low parity, higher gestational age; lower number of previous pregnancies, lower number of previous deliveries, lower number of living children; dysmenorrhoea; retroverted uterus). Increased pain was also associated with a lower mifepristone dose, 200 mg instead of 600 mg, after adjustment for the misoprostol dose (Table 3) (Elul et al. 1999; Westhoff et al. 2000a, 2000b; Abdel-Aziz et al. 2004; Teal et al. 2007; Suhonen et al. 2011; Avraham et al. 2012; Kapp et al. 2013; Saurel-Cubizolles et al. 2015).

Expert group statements on pain occurrence are provided in Table 4.

Pain assessment

According to WHO, pain assessment should be done in all cases, including an initial evaluation and ongoing reassessment. It is imperative to ensure that patients receive safe and effective pain management tailored to their needs (WHO 2007). For women undergoing MToP, this also means that the level of pain must be ascertained (Suhonen et al. 2011).

The paucity of published studies on pain assessment in MToP does not allow a determination of whether systematic assessment of pain is necessary for optimal management of women undergoing MToP, or whether formalised systematic assessment is only required in selected cases. However, the consensus of the Expert Group is that systematic assessment of pain should be undertaken for women as part of future clinical studies of MToP. For clinical practice, pain assessment could be useful even if not systematic.

Regarding pain in general, documenting pain scores as the fifth vital sign (the four others being temperature, pulse rate, respiration rate and blood pressure) should be made mandatory for all patients experiencing pain according to the WHO (WHO 2007). Multiple standardised tools have been developed to help patients measure their level of pain. These include written and verbal forms of numerical rating scales (NRSs) with pain ratings from 0 to 10, where 0 represents 'no pain' and 10 represents 'worst pain imaginable', and a value of 4 or more is often used as a threshold to guide clinical intervention; as well as the VAS with a 100 mm horizontal line from 0 = no pain to 10 = worst imaginable pain, and where 70 mm and above indicates 'severe pain', 0–10 mm 'no pain', 10–30 mm 'mild pain' and 40–60 mm 'moderate pain' (Breivik et al. 2008).

Doctors' assessment of pain experienced by women during MToP correlated strongly with women's own self-assessment of pain (Suhonen et al. 2011). Nevertheless, clinicians' assessment of pain is not feasible for women taking misoprostol at home and it would seem more appropriate to rely on women's reported pain scores or use womens' request as an indicator for (additional) pain medication. This also gives women more involvement in their pain management.

The optimal timing and frequency of pain assessment cannot be determined from the existing medical literature. Mentula et al. demonstrated in a study of pain during second-trimester MToP that women's recall of maximal pain was more intense than same-day self-reports (Mentula et al.

Table 2. Time to occurrence of pain and duration as reported in clinical studies.

Reference	Country	Study	Gestational age	MToP regimen	*N*	Onset	Duration
After mifepristone administration							
De Nonno et al. (2000)	US	Prospective	≤56 days	Mife 200 mg + vaginal Miso 800 µg 24, 48 or 72 h later	2030	Cramping before Miso use: 11% The longer subjects waited to insert misoprostol, the more likely they were to experience early cramping	
WHO (2000)	Armenia, Australia, China, Cuba, Finland, Georgia, Hong Kong, Hungary, India, Russia, Slovenia, Sweden, Tunisia, Vietnam	Prospective	Menstrual delay ≤35 days	Mife 200 or 600 mg + oral 400 µg Miso	1589	Pain after mifepristone: 40%	
Shannon et al. (2005)	US	Prospective	<50 days of amenorrhoea	Mife 200 mg + oral Miso 400 µg	376	Pain before misoprostol: 39.3%	Median duration = 3 days
After misoprostol administration							
De Nonno et al. (2000)	US	Prospective	≤56 days	Mife 200 mg + vaginal Miso 800 µg 24, 48 or 72 h later	2030	Cramps within 1 h: 75% Cramps within 4 h: 95% Mean time to onset = 1.4 h±	
WHO (2000)	Armenia, Australia, China, Cuba, Finland, Georgia, Hong Kong, Hungary, India, Russia, Slovenia, Sweden, Tunisia, Vietnam	Prospective	Menstrual delay ≤35 days	Mife 200 or 600 mg + oral 400 µg Miso	1589	Pain after misoprostol: 80%	
Honkanen et al. (2004)	China, Finland, Hungary, India, Mongolia, Norway, Romania, Singapore; Slovenia, Sweden, Vietnam	Prospective	≤63 days of amenorrhoea	Mife 200 mg + oral 800 µg Miso or vaginal 800 µg Miso	2219	Peak: 1–2 hours after oral Miso Peak: 2–3 hours after vaginal Miso	
Ravn et al. (2005)	Denmark	Retrospective	≤56 days of gestation	Mife 400 mg + oral Miso 400 µg	134		For 33% of women with pain, 1 day with severe pain: 23% 2–3 days with severe pain: 10%
Singh et al. (2005)	India	Prospective	≤8 weeks of gestation	Mife 200 mg + sublingual Miso 600 µg	40	Time to onset = 2 ± 1.2 h after Miso	
Livshits et al. (2009)	Israel	Prospective	≤7 weeks	Mife 600 mg + oral Miso 400 µg	120	1 h after Miso	
Ojha et al. (2012)	UK	Prospective	≤63 days of gestation	Mife 200 mg + vaginal Miso 800 µg	130	Time to onset = 76 min for ambulatory and 92 min for non-ambulatory patients	

2014). Therefore, the Expert Group statement is based on the experts' opinion only.

One of the five cornerstones of the WHO recommendations for patients with acute or chronic pain who require analgesics relies on the fact that analgesics should be prescribed according to pain intensity as evaluated by a scale of intensity of pain (Vargas-Schaffer 2010).

Expert group statements regarding pain assessment are provided in Table 5.

Pain treatment

One important principle guiding the successful management of acute pain is to achieve a level of comfort that allows the patient to function adequately (Wuhrman and Cooney 2011), ideally to avoid or at least relieve suffering.

The most obvious approach is to prevent the occurrence of pain using the most effective and least painful MToP regimen, and allowing MToP to take place in the best conditions. Despite the lack of studies evaluating the impact of the regimen on pain, it may be considered (expert group consensus) that the lowest but still effective dose and appropriate route of the prostaglandin analogue, should be used as MToP pain is caused by uterine contractions induced by the prostaglandin analogue in a dose-dependent way (Fiala et al. 2014).

The goal of pain management is to prevent pain whenever possible by administering analgesics before pain occurs (Wuhrman and Cooney 2011). The pharmacokinetics of the

Table 3. Factors associated with increased/decreased risk for pain and/or analgesic use as reported in clinical studies.

Parameter	Increased risk for pain/analgesic use	Decreased risk for pain/analgesic use
Increasing woman's age		Westhoff et al. (2000a), Abdel-Aziz et al. (2004), Suhonen et al. (2011), Kapp et al. (2013), Saurel-Cubizolles et al. (2015)
Increasing parity		Westhoff et al. (2000a), Westhoff et al. (2000b), Abdel-Aziz et al. (2004) , Teal et al. (2007), Lokeland et al. (2014)
Increasing number of previous pregnancies		Suhonen et al. (2011), Saurel-Cubizolles et al. (2015)
Increasing number of previous deliveries		Suhonen et al. (2011), Kapp et al. (2013)
Increasing number of living children		Abdel-Aziz et al. (2004)
Increasing gestational age	Westhoff et al. (2000a), Westhoff et al. (2000b), Teal et al. (2007), Suhonen et al. (2011)	
Strong pain during normal menstruation/ dysmenorrhoea	Suhonen et al. (2011), Avraham et al. (2012), Kapp et al. (2013), Saurel-Cubizolles et al. (2015)	
Retroverted uterus	Kapp et al. (2013)	
Married		Westhoff et al. (2000a), Abdel-Aziz et al. (2004)
Increased available financial support		Abdel-Aziz et al. (2004)
Asian women		Westhoff et al. (2000a, 2000b)
India		Elul et al. (1999)
Provision of full preliminary information		Kruse et al. (2000)
Decreased mifepristone dosage (200 instead of 600 mg)	Saurel-Cubizolles et al. (2015)	

Table 4. Expert Group Statement regarding pain occurrence.

Question	Expert group statement
Q1. What type of discomfort may be considered as first-trimester MToP-associated pain?	Any discomfort related to medical abortion a woman experiences may contribute to the abortion related pain experience.
Q2. How frequently does first-trimester MToP-associated pain occur? How intense is it?	Most women report pain of a level that requires analgesia, although the occurrence of MToP-associated pain depends on many variables (see Question 4). In addition, there are considerable inter-individual variations.
Q3. When does first trimester-MToP-associated pain occur, and how long does it persist?	MToP-associated pain may infrequently occur after mifepristone intake, but usually starts following administration of misoprostol. MToP-associated pain is related to the onset of contractions, with a peak 1–3 hours following misoprostol administration. A few women may experience pain a few days after expulsion.
Q4. Are there predictive factors for first-trimester MToP-associated pain occurrence or intensity?	Several associations between various factors and pain can be found. However, the predictive value of these factors is insufficient to define pain management for an individual woman.

Table 5. Expert group statement regarding pain assessment.

Question	Expert group statement
Q5. Should pain be assessed during first-trimester MToP process at all?	It is good clinical practice to assess pain during abortion and before and after any pain intervention. It should also be formally integrated into medical abortion clinical studies.
Q6. If pain must be assessed during first-trimester MToP, should this assessment be systematic or selective?	Pain associated with first-trimester MToP should be systematically assessed for women going through the procedure during a clinical study. There was no agreement between the experts regarding the need for a formal assessment in clinical routine. For daily practice, pain assessment could be useful even if not systematic.
Q7. What methods and tools should be used for first-trimester MToP-associated pain assessment?	The method and tool to be used to assess pain associated with up-to-9-weeks MToP might depend on the setting (clinical setting vs. home setting).
Q8. When should first-trimester MToP-associated pain be assessed, how often, and for how long?	In routine practice, for those who think formal assessment is necessary, assessment should be performed before and at an appropriate interval after administration of analgesia. Pain should be regularly and formally evaluated in research studies using formalised tools.
Q9. Does pain assessment help in choosing adequate thresholds for analgesic treatment onset and strength (WHO step)?	The strength of analgesia given should be stepwise according to WHO recommendations. In addition, women should be informed about how to access to additional analgesics and how to use them.

analgesic drug should be taken into account to define the timing for intake, for the analgesic to be active when the first contractions of MToP (and therefore pain) occur. In this respect, it is important to take into consideration the delay in onset of analgesia provided by NSAIDs as compared with the rapid pharmacokinetics of misoprostol, which frequently leads to first contractions (and pain) within a few minutes after intake (Tang et al. 2007). Only one published study compared the administration of prophylactic vs. curative analgesics (ibuprofen 800 mg) for MToP, and found no difference in pain levels between the two analgesic protocols (Raymond et al. 2013). This result is surprising as it contradicts what would be expected based on the pharmacokinetic profile. Therefore, further studies are needed to clarify this

aspect (Kapp et al. 2013). On the other hand, the disadvantages of prophylactic pain administration are likely to be few, and this should therefore be widely offered.

However, prophylactic NSAID administration has been demonstrated to reduce the need for (back-up) opiate injections in women undergoing second-trimester abortion during a randomised study assessing the analgesic efficacy of a prophylactic treatment of diclofenac in comparison with paracetamol in combination with codeine (Fiala et al. 2005).

Although developed initially for cancer pain, the three-step WHO analgesic ladder is currently used worldwide to manage chronic and acute pain (WHO 1986). Analgesics must be given according to the level of the patient's pain and not according to the health care providers' perception of the pain. If a woman says she has pain, it is important to believe her and administer adequate pain relief. The 1986 version of the WHO analgesic ladder proposes that treatment of pain should begin with a non-opioid medication (Figure 1). If the pain is not properly controlled, one should then introduce a weak opioid. If the use of this medication is insufficient to treat the pain, one can begin a more powerful opioid (WHO 1986).

According to WHO, patients with severe pain can start with step 3, and morphine is still the first choice for severe pain (WHO 2007).

There is insufficient data to determine the optimal analgesic to be used for pain associated with first-trimester MToP. One study found NSAIDs to be effective in the second trimester, and this even shortened the time interval to expulsion and reduced women's requests for opiate analgesia (Fiala et al. 2005). In addition, NSAIDs were demonstrated not to have any negative impact on efficacy of medical abortion or the duration of the procedure (Creinin and Shulman 1997; Avraham et al. 2012).

The analysis performed by Jackson et al. in 2010 found only one study of analgesics during first-trimester MToP using the mifepristone + misoprostol regimen (see below, Livshits et al. 2009) (Jackson and Kapp 2011). This prospective, double-blind, randomised study assessed the efficacy of ibuprofen in comparison with paracetamol in 120 women who underwent first-trimester MToP, using 600 mg mifepristone followed by 400 μg misoprostol orally two days later. Ibuprofen 400 mg was found to be significantly more effective ($p < .0001$) than paracetamol 500 mg for pain reduction, with a mean ± standard deviation decrease in pain scores of 2.7 ± 1.4 for paracetamol (mean initial score = 8.3 ± 1.6, mean score after analgesia = 5.7 ± 1.9) vs. 4.8 ± 1.5 for ibuprofen (mean initial score = 8.2 ± 1.7, mean score after analgesia = 3.4 ± 2.0) on a 11-point numeric pain scale (0 = no pain to 10 = most severe pain) (Livshits et al. 2009).

A prospective, comparative, randomised, double-blind study was undertaken to determine the efficacy of prophylactic administration of ibuprofen vs. placebo on pain relief during medical abortion (Avraham et al. 2012). A total of 61 women who underwent up-to-7-weeks medical abortion received 600 mg mifepristone orally followed by 400 μg misoprostol two days later. They were randomised to receive either 800 mg ibuprofen orally or a placebo simultaneously at the time of misoprostol administration. Pain was assessed using a 0–10 numeric pain scale, and by time and need for another analgesic. Prophylactic ibuprofen was found to be more effective than a placebo on pain prevention, with a significantly lower need for additional analgesia (38% vs. 78%, $p=.001$) and a significantly higher rate of women with no pain (15.5% vs. 5.2%, $p=.05$).

According to WHO (2014) guidelines, NSAIDs have demonstrated effectiveness in treating pain for MToP, and ibuprofen 400–800 mg is recommended (WHO 2014). In contrast, paracetamol alone has been shown to be ineffective at decreasing pain caused by uterine contractions, and therefore is not recommended (Jackson and Kapp 2011; RCOG 2011). However, the combination of ibuprofen and paracetamol was described to provide better analgesia than either drug alone at the same dose, with a smaller chance of needing additional analgesia over 8 hours and with a smaller chance of experiencing an adverse event (Derry et al. 2013).

Patients can manage the pain experience better if they know what to expect. Women who receive a detailed description of the sensations associated with the procedure have less distress than those who were informed only about the procedure itself (Kruse et al. 2000).

In a multisite randomised controlled trial, women undergoing early medical abortion (≤9 weeks) using 200 mg mifepristone and 800 μg misoprostol 1–2 days later (at home), were allocated to receive standard of care (SOC) only ($n = 235$), or SOC and a messaging intervention ($n = 234$). Consenting women were interviewed at the clinic after taking mifepristone and again at their follow-up visit 2–3 weeks later; the intervention group received text messages over the duration of this period. Between baseline and follow-up, the intervention group had less anxiety ($p=.013$) and emotional stress (adjusted for baseline anxiety, $p=.015$) compared to the SOC group. Participants in the intervention group were also more likely to report that they felt very well prepared for the pain ($p=.042$) they experienced (Constant et al. 2014).

In the case of home administration of misoprostol, having a partner or friend present during misoprostol administration was demonstrated to have a significant positive impact on acceptability of the procedure (Kopp Kallner et al. 2012).

In addition to respectful communication, verbal support, and a clear explanation of the procedure, the WHO (2014) guidelines also recommend the presence of a supportive adult with the woman during the process, and the use of a hot water bottle or heating pad (WHO 2014).

In one randomised controlled trial of mid-trimester abortion, a shorter induction to abortion interval was observed in the group that received NSAID. One could therefore hypothesise that sufficient pain relief may increase efficacy of medical abortion through increased relaxation (Fiala et al. 2005).

We have not found any study comparing systematic analgesic treatment with treatment of a selected group of women with existing risk factors for higher pain (see Table 3 for risk factors). Therefore, the Expert Group's statement is based only on experts' opinion; see Table 6.

Discussion

Women opting for medical abortion frequently do so partly because of the perception that it is less painful compared to

Table 6. Expert group statement regarding pain treatment.

Question	Expert group statement
Q10. What is the objective of first-trimester MToP-associated pain treatment?	The objective of first-trimester MtoP-associated pain treatment is to avoid or relieve suffering. In addition, due to increase in relaxation, sufficient pain relief may increase the efficacy of medical abortion.
Q11. Should analgesic treatment be systematic or selective?	Treatment for pain associated with first-trimester MToP should be systematic. In addition, women should have easy access to additional stepwise pain treatment.
Q12. Should analgesic treatment be prophylactic or curative, and at what time should it be taken?	Limited data suggest that prophylactic treatment is not better than only curative, so the best prophylactic treatment is still to be determined. But, expert's recommendation is that best principles would advise giving prophylactic analgesia. In addition, analgesia for breakthrough pain should also be offered and be easily accessible.
Q13. Should analgesic treatment be stepped?	Prophylactic treatment should be used, with NSAIDs as first-line analgesics. Second-line analgesics should be used if the first-line agent is not sufficient, and when pain assessment, is consistent with moderate to severe pain. Women who require step 2 medication should be provided this without delay. According to the WHO, patients with severe pain can start with step 3, and morphine is still the first choice for severe pain.
Q14. Which are the most appropriate pharmacological agents?	There was little evidence in the literature regarding the most appropriate pharmacological agents. Therefore, the experts' consensus is: First line: prophylaxis: ibuprofen, 400–800 mg (use of second line in case of contraindications to NSAIDs) Second line: opioids: codeine, dihydrocodeine or morphine. It should be noted that, in some countries, it is not possible to give morphine to women due to legal restrictions; however, codeine is associated with large individual variations and should be replaced by oral morphine where possible.
Q15. Which pain treatment protocols are best?	There is no solid evidence and very few data regarding analgesic protocols for MToP. NSAIDs efficacy is dose dependent. Ibuprofen is widely used. Paracetamol alone use is not recommended by the WHO.
Q16. What are the non-pharmacological strategies, and what is their importance?	Non-pharmacological strategies include: Having someone present if at home Giving detailed information to women on the procedure Using the lowest effective dose of misoprostol Allowing home intake of misoprostol Ensuring a relaxing and supporting environment

surgical abortion (Tamang et al. 2012). In contrast, the available literature cited above clearly and unanimously confirms that women undergoing early medical abortion frequently experience pain, sometimes even severe. Not surprisingly, satisfaction with medical abortion can be limited by differences between women's expectations of pain and bleeding and their actual symptoms (Slade et al. 1998). This negative experience is shared among women, and it has been shown that fear of adverse physical effects is a reason why women frequently choose surgical abortion (Henshaw et al. 1993; Cameron et al. 1996).

Uterine contractions are an integral and necessary part of medical abortion. But the pain they cause is unnecessary. The available literature provides sufficient evidence to formulate a comprehensive pain management plan; although, this is not yet part of most clinical guidelines for medical abortion.

The first step would be to give unrestricted access to early medical abortion even before the pregnancy can be located (VEMA, very early medical abortion) (Bizjak et al. 2017). It has been shown that pain is lower at an earlier gestational age (Westhoff et al. 2000a, 2000b; Teal et al. 2007; Suhonen et al. 2011), and that VEMA can be offered without a lower gestational limit (Bizjak et al. 2017). Another basic consideration for avoiding pain is to use the least painful MToP regimen including the lowest prostaglandin analogue dose and providing detailed information on the procedure to women beforehand. Medical pain treatment should be based on the WHO three-step ladder, providing sufficient step 1 analgesics (NSAIDs and not paracetamol) and a weak opioid as back-up, all easily accessible.

Pain occurrence is rather well described in the literature; although, there is no consistency at all in the way it is commonly reported. There is a consensus regarding the very high rate of women reporting pain, and the most common time for pain occurrence, which is after misoprostol administration. Predictive factors associated with higher occurrence of pain during first-trimester abortion are also well-described in several publications. Far less published information exists on the measurement of pain, and the Expert Group could not come to a consensus on whether systematic measurement of pain after MToP is necessary in routine practice; although, the stepwise adaptation of analgesic treatment to the level of pain was supported by the whole group. Finally, despite some trends for providing guidelines for pain management, there is not yet any clear analgesic protocol in the literature. The Expert Group emphasises the need to use both the least painful MToP regimen and appropriate analgesics, preventive as curative, with easy access for women to a wide range of appropriate medication.

The fundamental weakness of this study is the small number of published evidence on pain aspects in medical abortion; although, the literature search was exhaustive. Another limiting factor is the lack of objective and verifiable measurement of pain intensity. However, the available evidence concordantly shows that medical abortion is a painful experience

for most women, although with huge individual variations. But fortunately, there are sufficient methods available to prevent and treat pain successfully.

Health care professionals and researchers should give this important aspect the attention it deserves.

Conclusions

This work demonstrated the need to improve knowledge and management of pain associated with medical abortion. Clinical protocols for pain prevention should be established that recommend the least painful MToP regimen and the systematic use of analgesics. Further studies are needed to determine if analgesia should be preventive or curative, as well as drugs and dosages to be used.

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References

Abdel-Aziz E, Hassan I, Al-Taher HM. 2004. Assessment of pain associated with medical abortion. International Journal of Gynaecology and Obstetrics 84:264–265.

Ashok PW, Templeton A, Wagaarachchi PT, Flett GM. 2002. Factors affecting the outcome of early medical abortion: a review of 4132 consecutive cases. BJOG 109:1281–1289.

Avraham S, Gat I, Duvdevani NR, Haas J, Frenkel Y, Seidman DS. 2012. Pre-emptive effect of ibuprofen versus placebo on pain relief and success rates of medical abortion: a double-blind, randomized, controlled study. Fertility and Sterility 97:612–615.

Bizjak I, Fiala C, Berggren L, Hognert H, Sääv I, Bring J, Gemzell-Danielsson K. 2017. Efficacy and safety of very early medical termination of pregnancy: a cohort study. BJOG 124:1993–1999.

Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EK. 2008. Assessment of pain. British Journal of Anaesthesia 101: 17–24.

Bygdeman M, Swahn ML. 1985. Progesterone receptor blockage. Effect on uterine contractility and early pregnancy. Contraception 32:45–51.

Cameron ST, Glasier AF, Logan J, Benton L, Baird DT. 1996. Impact of the introduction of new medical methods on therapeutic abortions at the Royal Infirmary of Edinburgh. BJOG 103:1222–1229.

Cavet S, Fiala C, Scemama A, Partouche H. 2017. Assessment of pain during medical abortion with home use of misoprostol. The European Journal of Contraception & Reproductive Health Care 22:207–211.

Christin-Maitre S, Bouchard P, Spitz IM. 2000. Medical termination of pregnancy. The New England Journal of Medicine 342:946–956.

Constant D, de Tolly K, Harries J, Myer L. 2014. Mobile phone messages to provide support to women during the home phase of medical abortion in South Africa: a randomized controlled trial. Contraception 90:226–233.

Creinin MD, Shulman T. 1997. Effect of nonsteroidal anti-inflammatory drugs on the action of misoprostol in a regimen for early abortion. Contraception 56:165–168.

De Nonno LJ, Westhoff C, Fielding S, Schaff E. 2000. Timing of pain and bleeding after mifepristone-induced abortion. Contraception 62: 305–309.

Derry CJ, Derry S, Moore RA. 2013. Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. Cochrane Database of Systematic Reviews (6):CD010210.

DGS. 2016. Relatorio dos registos das interrupçoes da gravidez dados de; [cited 2018 Mar 12]. Available from: file://C:/Users/Saya/Documents/t%C3%A9l%C3%A9chargements/i010414%20(1).pdf

Dragoman MV, Grossman D, Kapp N, Huong NM, Habib N, Dung DL. 2016. Two prophylactic medication approaches in addition to a pain control regimen for early medical abortion <63 days' gestation with mifepristone and misoprostol: study protocol for a randomized, controlled trial. Reproductive Health 13:132.

DREES. 2016. Etudes et Résultats. Les interruptions volontaires de grossesse en; [cited 2018 Mar 12]. Available from: http://drees.solidarites-sante.gouv.fr/IMG/pdf/er_1013.pdf

Elul B, Ellertson C, Winikoff B, Coyaji K. 1999. Side effects of mifepristone–misoprostol abortion versus surgical abortion. Contraception 59: 107–114.

Fiala C, Cameron S, Bombas T, Parachini M, Saya L, Gemzell-Danielsson K. 2014. Pain during medical abortion, the impact of the regimen: a neglected issue? A review. The European Journal of Contraception & Reproductive Health Care 19:404–419.

Fiala C, Gemzell-Danielsson K. 2006. Review of medical abortion using mifepristone in combination with a prostaglandin analogue. Contraception 74:66–86.

Fiala C, Swahn ML, Stephansson O, Gemzell-Danielsson K. 2005. The effect of non-steroidal anti-inflammatory drugs on medical abortion with mifepristone and misoprostol at 13–22 weeks gestation. Human Reproduction 20:3072–3077.

FIGO. 2011. Working Group on Prevention of Unsafe Abortion and its Consequences; International Federation of Gynecology and Obstetrics. The combination of mifepristone and misoprostol for the termination of pregnancy. International Journal of Gynecology & Obstetrics 115: 1–4.

HAS. 2010. Interruption volontaire de grossesse par méthode médicamenteuse. Argumentaire; [cited 7th May 2018]. Available from: https://www.has-sante.fr/portail/upload/docs/application/pdf/2011-04/

ivg_methode_medicamenteuse_-_recommandations_-_mel_2011-04-28_11-39-11_882.pdf
Henshaw RC, Naji SA, Russell IT, Templeton AA. 1993. Comparison of medical abortion with surgical vacuum aspiration: women's preferences and acceptability of treatment. BMJ 307:714–717.
Honkanen H, Piaggio G, Hertzen H, Bartfai G, Erdenetungalag R, Gemzell-Danielsson K, et al. 2004. WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. II: side effects and women's perceptions. BJOG 111:715–725.
ICMR. 2000. Task Force Study. A multicenter randomized comparative clinical trial of 200 mg RU486 (mifepristone) single dose followed by either 5 mg 9-methylene PGE2 gel (meteneprost) or 600 μg oral PGE1 (misoprostol) for termination of early pregnancy within 28 days of missed menstrual period. Contraception 62:125–130.
ISAP. 1979. International Association for the Study of Pain. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. Pain 6:249.
Jackson E, Kapp N. 2011. Pain control in first-trimester and second-trimester medical termination of pregnancy: a systematic review. Contraception 83:116–126.
Jensen JT, Astley SJ, Morgan E, Nichols MD. 1999. Outcomes of suction curettage and mifepristone abortion in the United States. A prospective comparison study. Contraception 59:153–159.
Kapp N, Whyte P, Tang J, Jackson E, Brahmi D. 2013. A review of evidence for safe abortion care. Contraception 88:350–356.
Kopp Kallner H, Fiala C, Gemzell-Danielsson K. 2012. Assessment of significant factors affecting acceptability of home administration of misoprostol for medical abortion. Contraception 85:394–397.
Kruse B, Poppema S, Creinin MD, Paul M. 2000. Management of side effects and complications in medical abortion. American Journal of Obstetrics and Gynecology 183:S65–S75.
Livshits A, Machtinger R, David LB, Spira M, Moshe-Zahav A, Seidman DS. 2009. Ibuprofen and paracetamol for pain relief during medical abortion: a double-blind randomized controlled study. Fertility and Sterility 91:1877–1880.
Lokeland M, Iversen OE, Engeland A, Økland I, Bjørge L. 2014. Medical abortion with mifepristone and home administration of misoprostol up to 63 days' gestation. Acta Obstetricia et Gynecologica Scandinavica 93:647–653.
McCaffery M, Pasero C. 1999. Pain: clinical manual. 2nd ed. St. Louis (MO): Mosby.
Mentula M, Kalso E, Heikinheimo O. 2014. Same-day and delayed reports of pain intensity in second-trimester medical termination of pregnancy: a brief report. Contraception 90:609–611.
Ministerio de Sanidad, Servicios Sociales e Igualdad. 2016. Interrupcion voluntaria del embarazo. Datis definitivos correspondientes al anà 2016; [cited 2018 Mar 12]. Available from: https://www.msssi.gob.es/en/profesionales/saludPublica/prevPromocion/embarazo/docs/IVE_2016.pdf
NHS. 2017. Information Services Division. Termination of pregnancy statistics year ending December 2016; [cited 2018 Mar 12]. Available from: http://www.isdscotland.org/Health-Topics/Sexual-Health/Publications/2017-05-30/2017-05-30-Terminations-2016-Report.pdf
Ojha K, Gillot DJ, Wood P, Valcarcel E, Matah A, Talaulikar VS. 2012. Clinical outcomes from a prospective study evaluating the role of ambulation during medical termination of pregnancy. Contraception 85:398–401.
Penney G. 2006. Treatment of pain during medical abortion. Contraception 74:45–47.
Raghavan S, Nhu Ngoc NT, Shochet T, Winikoff B. 2012. Clinic-level introduction of medical abortion in Vietnam. International Journal of Gynaecology and Obstetrics 119:39–43.
Ravn P, Rasmussen A, Knudse UB, Kristiansen FV. 2005. An outpatient regimen of combined oral mifepristone 400 mg and misoprostol 400 μg for first-trimester legal medical abortion. Acta Obstetricia et Gynecologica Scandinavica 84:1098–1102.
Raymond EG, Weaver MA, Louie KS, Dean G, Porsch L, Lichtenberg ES, et al. 2013. Prophylactic compared with therapeutic ibuprofen analgesia in first-trimester medical abortion: a randomized controlled trial. Obstetrics & Gynecology 122:558–564.
Royal College of Obstetricians and Gynaecologists (RCOG). 2011. The care of women requesting induced abortion. Evidence-based clinical guideline number 7; [cited 7th May 2018]. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/abortion-guideline_web_1.pdf
Saurel-Cubizolles MJ, Opatowski M, David P, Bardy F, Dunbavand A. 2015. Pain during medical abortion: a multicenter study in France. European Journal of Obstetrics, Gynecology, and Reproductive Biology 194:212–217.
Schaff EA, Fielding SL, Westhoff C. 2002. Randomized trial of oral vs vaginal misoprostol 2 days after mifepristone 200 mg for abortion up to 63 days of gestation. Contraception 66:247–250.
Sedgh G, Bearak J, Singh S, Bankole A, Popinchalk A, Ganatra B, et al. 2016. Abortion incidence between 1990 and 2014: global, regional and subregional levels and trends. Lancet 388:258–267.
Sedgh G, Singh S, Shah IH, Ahman E, Henshaw SK, Bankole A. 2012. Induced abortion: incidence and trends worldwide from 1995 to 2008. Lancet (London, England) 379:625–632.
Shannon C, Wiebe E, Jacot F, Guilbert E, Dunn S, Sheldon WR, Winikoff B. 2006. Regimens of misoprostol with mifepristone for early medical abortion: a randomised trial. BJOG 113:621–628.
Shannon CS, Winikoff B, Hausknecht R, Schaff E, Blumenthal PD, Oyer D, et al. 2005. Multicenter trial of a simplified mifepristone medical abortion regimen. Obstetrics and Gynecology 105:345–351.
Siegel M, Bigelow S. 2018. Palliative care symptom management in the emergency department: the ABC's of symptom management for the emergency physician. The Journal of Emergency Medicine 54: 25–32.
Singh KC, Ummat S, Rajaram S, Goel N. 2005. First trimester abortion with mifepristone and three doses of sublingual misoprostol: a pilot study. The Australian & New Zealand Journal of Obstetrics & Gynaecology 45:495–498.
Slade P, Heke S, Fletcher J, Stewart P. 1998. A comparison of medical and surgical termination of pregnancy: choice, emotional impact and satisfaction with care. British Journal of Obstetrics and Gynaecology 105:1288–1295.
Socialstyrelsen, Abortion Statistics. 2016. [cited 2018 Mar 12]. Available from: http://www.socialstyrelsen.se/statistics/statisticaldatabase/abortionstatistics
Spitz IM, Bardin W, Benton L, Robbins A. 1998. Early pregnancy termination with mifepristone and misoprostol in the United States. The New England Journal of Medicine 338:1241–1247.
Suhonen S, Tikka M, Kivinen S, Kauppila T. 2011. Pain during medical abortion: predicting factors from gynecologic history and medical staff evaluation of severity. Contraception 83:357–361.
Svendsen PF, Rorbye C, Vejborg T, Nilas L. 2005. Comparison of gemeprost and vaginal misoprostol in first trimester mifepristone-induced abortion. Contraception 72:28–32.
Tamang A, Tuladhar S, Tamang J, Ganatra B, Dulal B. 2012. Factors associated with choice of medical or surgical abortion among women in Nepal. International Journal of Gynecology & Obstetrics 118:S52–S56.
Tang OS, Gemzell-Danielsson K, Ho PC. 2007. Misoprostol: pharmacokinetic profiles, effects on the uterus and side-effects. International Journal of Gynecology & Obstetrics 99:S160–S167.
Teal SB, Dempsey-Fanning A, Westhoff C. 2007. Predictors of acceptability of medication abortion. Contraception 75:224–229.
Vargas-Schaffer G. 2010. Is the WHO analgesic ladder still valid? Twenty-four years of experience. Canadian Family Physician 56:514–517.
Westhoff C, Dasmahapatra R, Schaff E. 2000a. Analgesia during at-home use of misoprostol as part of a medical abortion regimen. Contraception 62:311–314.
Westhoff C, Dasmahapatra R, Winikoff B, Clarke S. 2000b. Predictors of analgesia use during supervised medical abortion. Contraception 61: 225–229.
WHO. 1986. WHO's cancer pain ladder for adults; [cited 2018 May 7]. Available from: http://www.who.int/cancer/palliative/painladder/en/
WHO. 2000. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomised trial. BJOG 107: 524–553.

WHO. 2007. Normative guidelines on pain management; [cited 7th May 2018]. Available from: http://www.who.int/medicines/areas/quality_safety/delphi_study_pain_guidelines.pdf

WHO. 2014. Clinical practice handbook for Safe abortion; [cited 5th May 2018]. Available from: http://apps.who.int/iris/bitstream/handle/10665/97415/9789241548717_eng.pdf;jsessionid=51C9C122177E01A8197444A236B24EC9?sequence=1

Wuhrman E, Cooney LF. 2011. Acute pain: assessment and treatment. Medscape; [cited 7th May 2018]. Available from: http://www.medscape.com/viewarticle/735034_4