mifepristone 200 mg followed 36 to 48 hours later by misoprostol 800 mcg vaginally, then an additional 400 mcg vaginally every 3 hours [24,32,33].

Recent evidence has suggested that loading doses (> 200 mcg) do not hasten abortion times or improve outcomes. Several studies cited in Table 1 demonstrate the effectiveness of mifepristone 200 mg followed by misoprostol 200 mcg every 3 to 4 hours, with or without a 400 mcg loading dose (Table 1).

Lower doses of misoprostol may also be effective, particularly for greater than 24 weeks of gestation. Some experts note that lower doses may decrease the risk of uterine rupture in a scarred uterus.

Previous World Health Organization recommendations advised re-evaluation of the patient after five doses of misoprostol. If a patient is otherwise doing well, then continue the regimen until complete expulsion, which usually occurs by 48 hours. Studies using an "unlimited dosing" protocol for misoprostol (400 mcg sublingually or buccally every 3 hours, 24–48 hours after mifepristone) for abortions 13 to 22 weeks report high effectiveness, tolerability, and safety. Patients are unlikely to need more than six doses of misoprostol [34,35]. Because most patients will experience complete abortion < 48 hours after the first misoprostol dose, clinical decision-making can be individualized in instances where continued misoprostol dosing is needed past 48 hours. There is no clear safety rationale for a "break" or to stop after five consecutive doses of misoprostol.

2.1.1.2.4. Misoprostol route of administration. Vaginal administration is associated with shorter abortion times compared to oral administration [32,36–39]. Side effect incidence is lower for vaginal use, except for transient fever [39]. Data are more limited for the buccal route. A small study (n = 114) demonstrated little difference in median abortion times comparing buccal and vaginal use (15 vs 12 hours; p = 0.44) [40].

Sublingual administration appears similar in effectiveness to vaginal administration but with a greater side effect incidence [41–43]. Table 3 summarizes select studies comparing misoprostol administration routes in combined regimens.

Evidence regarding patient acceptability is mixed, with one study reporting preference for buccal or sublingual over vaginal and another study finding no difference in acceptability between these routes [37,40]. The most common reasons cited for not liking vaginal administration were pain and inconvenience with insertion [37].

Studies use a range of doses (100–800 mcg per dose), intake routes, and dosing schedules, and many regimens incorporate a higher initial 'loading' dose [48–50]. Several nonoral misoprostol regimens demonstrate effectiveness when used after mifepristone. Insufficient data exist to strongly recommend one regimen over others, but the data seem to support a minimum effective PGE1 dose of 400 mcg for any administration route for a combined regimen.

2.1.1.2.5. Misoprostol-only regimen. If using a misoprostol-only regimen, higher doses (400 and 600 mcg) are more effective [51]. Misoprostol doses of 400 and 600 mcg with either a 4- or 6-hour dosing interval have a similar time to abortion (11–12 hours) [52]. One study (N = 150, 18–30 weeks of gestation) found similar mean abortion times and success rates at 24 and 48 hours when starting with a loading dose (misoprostol 600 mcg vaginally followed by misoprostol 200 mcg vaginally every 6 hours) compared to misoprostol 400 mcg vaginally every 6 hours. Both regimens were more effective than misoprostol 200 mcg every 6 hours [51]. Side effects were more common in the loading dose group, leading authors to conclude that 400 mcg was the preferred dose. Misoprostol-only regimens' effectiveness is included in Table 1.

When a misoprostol 400 mcg dose with dosing 3-hour intervals is compared to the same dose every 6 or 8 hours at 14 0/7 to 22 6/7 weeks of gestation, abortion times are shorter and effectiveness higher (78%–98%) with a 3-hour dosing schedule [53,54].

2.1.2. Effect of gestational duration on success of regimens

Mifepristone in addition to misoprostol results in faster time to complete abortion in all gestational duration ranges [15,16]. Allanson et al. found that mifepristone's effect on time to abortion was similar for pregnancies < 20 weeks of gestation vs 20 weeks of gestation or more [55]. The misoprostol dosing regimen in this study was 600 mcg vaginally, then 400 mcg sublingually every 3 hours. The combined regimen added mifepristone 200 mg 24 hours before the first misoprostol dose.

2.1.3. Medication abortion beyond 24 weeks' gestation

Medication abortion beyond 24 weeks of gestation accounts for a small percentage of abortions, and studies include limited data past 22 to 24 weeks of gestation. Three relevant studies included in this document used misoprostol 200 mcg buccally or vaginally every 3 hours (Table 1) [55,22,20]. Two reported no serious adverse events [20,22]. The third, Allanson et al., reported several adverse events, but the majority were retained placenta (the weeks of gestation of these cases were not noted). Most adverse events occurred in the misoprostol-only group [55].

2.1.4. Alternate agents

Overall, misoprostol appears to be more effective than carboprost (PGF 2α), dinoprostone (PGE2), high-dose oxytocin, and ethacridine lactate when adequate doses are used [21]. Both PGE2 and PGF 2α analogs are expensive and require refrigeration, in contrast to misoprostol, which is inexpensive and stable at room temperature.

Oxytocin is less effective than misoprostol for medication abortion likely due to the paucity of oxytocin receptors at < 20 weeks of gestation. Oxytocin is associated with longer medication to complete abortion intervals compared to mifepristone and PGE1 regimens (11.3 ± 7.4 hours vs 7.0 ± 4.9 hours; p < 0.001) and higher risk of side effects such as hemorrhage [56–58].

Nonetheless, high-dose oxytocin is an option when misoprostol is not available or when there is a desire to avoid prostaglandins [59,60]. Oxytocin requires intravenous access and a potentially more complicated regimen. Several regimens using only oxytocin for medication abortion have been described; one begins with oxytocin 100 units infused over 3 hours followed by 1 hour without oxytocin to allow diuresis for water intoxication prevention, then increased 50 units per 3 hours until fetal expulsion is achieved, to a maximum of 300 units over 3 hours [61].

2.2. What is the safety of medication abortion at 14 0/7 to 27 6/7 weeks of gestation?

2.2.1. Safety

Retained placenta is the most common complication that can occur with medication abortion between 14 0/7 and 27 6/7 weeks of gestation (12%–33%) and can be treated safely with aspiration without subsequent hemorrhage or need for transfusion [62,63]. Studies are too small to determine if this occurs more at certain gestational durations. An RCT found that placental retention rates were reduced to 10% with routine administration of oxytocin 10 units after fetal delivery compared with misoprostol 600 mcg orally or expectant management (29% and 31%, respectively) [64]. After medication abortion with regimens that include misoprostol, it is safe to wait at least 4 hours after fetal expulsion for placental delivery. Using this approach, a retrospective study of second-trimester misoprostol abortion (18–23 weeks of gestation, misoprostol dosed every 6 hours) reported an operative intervention rate of 6% for retained placenta [65]. The majority of these procedures were performed to expedite hospital discharge rather than because of bleeding; waiting and medically managing with ongoing misoprostol dosing for more than 4 hours was not associated with increased morbidity (in contrast to term pregnancy where a delay in