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INTRODUCTION

In the United States (US), mifepristone used together with misoprostol is registered by the Food and Drug Administration (FDA) for termination of intrauterine pregnancy through 70 days' gestation.[1] While medication abortion is safe and effective,[1] current FDA requirements delineated in the Risk Evaluation and Mitigation Strategy (REMS) for mifepristone mandate that it be dispensed in a clinic, medical office, or hospital.[2] Patients then complete the medication regimen outside of the facility. Post-treatment assessment is recommended to ensure the pregnancy is not ongoing, which can take place in person or remotely.[3] While there is little evidence demonstrating that the mandated dispensing requirement improves patient safety, it may pose an insurmountable barrier for people unable to travel to an abortion facility.[4] In addition, hostile policy environments have made abortion nearly unattainable in some US states, a situation that may worsen in the near future as the US Supreme Court considers a case challenging *Roe v. Wade*.[5] The recent passage of Texas Senate Bill 8 (SB 8) bans most abortions after 6 weeks' gestation.[6] While it is still being challenged in court, this law effectively forces people to travel out of state to access care, increasing the travel distance and cost to reach a clinic. These barriers will create delays in accessing care, pushing some patients later in pregnancy before they can obtain the service and preventing others from obtaining a wanted abortion entirely.

Since April 2021 and for the duration of the COVID-19 public health emergency, the FDA is exercising enforcement discretion regarding the in-person dispensing requirement for mifepristone, which allows providers to mail mifepristone to patients or use a mail order pharmacy.[7] Reducing the need for in-person clinical encounters using telehealth and other strategies can improve the patient experience and increase access to abortion earlier in pregnancy.[8] Innovations in abortion provision, particularly those that improve access to early abortion, are essential components of comprehensive reproductive health care, which includes access to the full range of contraceptive options, including emergency contraception.

Currently there are several new models of medication abortion provision that remove required in-person visits and pre-abortion ultrasound, as recommended by professional groups,[9, 10] and are being

implemented globally. These models include implementation of a no-test protocol, mail order, and pharmacy provision; research indicates these models are safe, effective, and acceptable to patients.[8, 11-17] Much of the growth in streamlined options of abortion care stem from the COVID-19 pandemic. As medication abortion service delivery evolves and depends less on in-person visits with a clinician, it is worth considering whether it might be advantageous to patients to have the medications on hand before they need them.

Advance provision of medication abortion pills is an unexplored care model that we believe holds promise and merits further study. Advance provision of mifepristone and misoprostol involves a clinician providing the medications to patients who want to avoid pregnancy but are not pregnant at the time of dispensing. We illustrate here how advance provision of medication abortion pills might work in practice and make the case for studying the model further. This editorial focuses on the US because of the formative research indicating interest in the model there; however, advance provision of medication abortion could have applications in other countries as well.

EXPANDING MEDICATION ABORTION ACCESS HELPS PATIENTS ACCESS CARE EARLIER IN PREGNANCY

Studies performed in the US and other countries demonstrate that medication abortion has a high level of acceptability for most patients seeking pregnancy termination.[18,19] In the US, medication abortions accounted for an estimated 60% of all abortions up to ten weeks' gestation in 2017, up from 45% of eligible abortions in 2014.[20] In a meta-analysis of approximately 4,500 patients who had a medication abortion with mifepristone and misoprostol, over 85% were satisfied with the experience.[21] Some evidence suggests that improved access to mifepristone enables people to obtain abortion earlier in pregnancy and reduces the need for second-trimester abortion.[22] Conversely, studies have shown that abortion restrictions contribute to increases in gestational age at abortion, thereby decreasing eligibility and use of medication abortion.[23, 24]

In the US, policy restrictions have resulted in limited abortion services and clinic closures across the country, increasing the distance people live from the nearest provider.[25] Longer travel distances can increase the cost and logistical difficulty of getting to a clinic, delaying access to timely abortion care and imposing burdens on those with the fewest resources.[26, 27] In particular, Texas' 6-week ban creates an exceedingly narrow window for people to confirm pregnancy and access abortion care, pushing in-state services out of reach for most Texans.[28] During the COVID-19 pandemic, abortion became unattainable for some.[24, 29] Overlapping barriers of policy restrictions, long travel distances, shelter-in-place orders, and the public health risks of travel have left patients with few options.

Even in settings where there is good access to care in the US, there is inevitably some delay between the initial call to the clinic and having an in-person appointment to obtain medication abortion; in settings with restricted access, that delay may be longer. According to a 2014 US national survey of abortion patients, the average wait time between the scheduling call and obtaining an abortion was approximately seven days.[30] For 7% of patients, their wait time exceeded 14 days.[30] For those who do not recognize pregnancy immediately, common even among first-trimester abortion patients,[31,32] the delay to care is compounded and may push some patients beyond the gestational duration limit for medication abortion.[33] Telehealth provision may reduce the scheduling delay, but it introduces a delay associated with mailing the pills, and requires that patients be able to receive the medications by mail. The advance provision model would effectively shorten the time between the decision to have an abortion and obtaining care to zero days.

HOW WOULD ADVANCE PROVISION OF MIFEPRISTONE AND MISOPROSTOL WORK?

Clinicians could screen interested patients for some contraindications to medication abortion prior to pregnancy, while others would need to be evaluated immediately prior to use (see Table). Clinicians could use the screening criteria included in the no-test protocol to exclude patients at higher risk of ectopic pregnancy based on history.[11] Clinicians could also screen in advance for other medical conditions that are contraindications (see Table). These conditions could change over time, and clinicians

could give patients a checklist to help them reassess for these contraindications before using the medications and encourage them to call to discuss any change in their health history.

[Table here, see line 187]

At the time of dispensing, the clinician would provide education on menstrual tracking, pregnancy recognition and testing, how to self-assess for eligibility at the time of pregnancy, how to administer the medications at home, and the necessary follow-up. In particular, the clinician would explain to the patient how to self-assess for ectopic pregnancy risk and gestational duration at the time of pregnancy prior to using the medications (see Table). Patients would be instructed to confirm the pregnancy with a home urine pregnancy test. If they had symptoms suggestive of ectopic pregnancy or if their self-assessed gestational duration was >70 days (or >77 days if that limit is used [34]), patients would be instructed not to take the medications on their own and instead seek care. Clinicians would also inform patients about the warning signs of complications after taking mifepristone and misoprostol, including hemorrhage and infection, as well as how little or no bleeding could be a sign of ectopic pregnancy. This information should be provided both orally and in written format, including pointing patients to online resources. Patients could be encouraged to contact the clinician prior to taking the medications to confirm eligibility according to the no-test protocol and to answer questions.

Clinicians would instruct patients to monitor their pregnancy symptoms after taking the pills, expecting them to dissipate within approximately one week. Clinicians would also encourage patients to use a home urine pregnancy test 4-5 weeks after administering the medications to rule out ongoing pregnancy, including ongoing ectopic pregnancy. Similar to the no-test protocol,[11] patients that have a positive urine pregnancy test would be told to contact a healthcare provider to determine if additional evaluation is needed. Advance provision is envisioned as a complete care model, where the dispensing provider is committed to patient education, screening at the time of use over the phone or by telehealth, and ensuring patients access the necessary follow-up care in case of complications, ongoing pregnancy, or incomplete abortion.

ARE PEOPLE INTERESTED IN RECEIVING ABORTION PILLS IN ADVANCE?

A US nationally representative survey found that people are interested in alternative methods of obtaining medication abortion, including by advance provision.[35] In this national survey of 7,022 self-identified women age 18-49 (English- and Spanish-speaking), nearly half (44%) indicated they supported advance provision of medication abortion, and 22% reported being personally interested in the model.[35] Women who had previously had a medication abortion had over twice the odds (aOR, 2.39, 95% CI 1.51–3.79) of supporting advance provision compared to those who had never had an abortion.[35] Those who reported experiencing two or more barriers to accessing reproductive health care additionally had higher odds (aOR, 1.31, 95% CI 1.08–1.58) of support compared to those who had never experienced a barrier to accessing care.[35]

Almost half (48%) of survey respondents indicated advance provision could benefit women by facilitating abortion earlier in pregnancy.[35] Respondents' concerns about advance provision included that people might take the pills incorrectly (55%), that people would not see a clinician before having the abortion (52%), and that the model could be less safe than the standard of care (42%).[35] It will be important to address these concerns with future research.

In this survey, people were more supportive of and interested in an advance provision model than they were of over-the-counter or online-access models of care.[35] One primary difference between advance provision and other alternative provision models is that advance provision ensures some face-to-face interaction with a health care provider at the time of dispensing, and a certain level of privacy that some people may prefer over other models, such as over-the-counter access in a pharmacy.

Advance provision may also fit the needs of those interested in a late period pill, where patients "bring back their period" by using a regimen of mifepristone and misoprostol without prior pregnancy confirmation.[36] One study found that those with prior abortion experience were more interested in a late period pill than those who had never had an abortion,[36] further supporting that those who have had a prior abortion may be potential candidates for advance provision.

POTENTIAL CHALLENGES AND CONCERNS

In many ways, the advance provision model is similar to the no-test medication abortion protocol. [11] Patients could be encouraged to contact their provider for a telehealth assessment to confirm eligibility according to the no-test protocol immediately before taking the medications. Despite the self-assessment for gestational age and ectopic risk, it is possible that some patients might use the treatment past 70 or 77 days' gestation or with an ectopic pregnancy. Evidence shows that mifepristone neither harms nor helps an ectopic pregnancy,[37] and the no-test protocol may facilitate quicker entry to care if a patient recognizes the relevant warning signs after taking medication abortion, such as having little or no bleeding. Research in the UK suggests that significant adverse events are not more common with the no-test protocol compared to in-person assessment with ultrasound, even though more patients with ectopic pregnancies may be diagnosed after starting treatment with the no-test protocol.[8]

Diversion of the medications to another person is also a possibility. If the person receiving the medications understands how to screen for appropriate use, the risk of harm is low – and might improve access to early abortion. This is an area that will require further discussion among clinicians, advocates, and legal experts to better understand the implications of medication diversion for prescribers and patients.

It is unlikely advance provision could be adopted in all US states. Barriers to adopting advance provision across the US include policy restrictions, such as mandatory ultrasound viewing laws, and other restrictions that require an in-person visit at the time of abortion. Even if advance provision is ultimately not widely scaled up, research on its safety and how patients can use the medications with limited clinician oversight could provide contributory evidence that would inform a future move toward over-the-counter (OTC) availability of mifepristone and misoprostol. As part of its original submission to the FDA requesting approval for OTC availability of levonorgestrel emergency contraception (EC) in 2003, Women's Capital Corporation submitted a literature review of eight articles assessing contraceptive behavior following advance provision of EC in addition to the required label comprehension and actual

use studies.[38] The FDA noted that "having an advanced provision would simulate the access that consumers would enjoy if the product were available OTC," and recognized that these studies complemented the actual use study because they included young people and followed participants for a longer period of time.[38]

CONCLUSION

Despite these challenges and concerns, we see advance provision of medication abortion as an important addition to the menu of options people should have to access early abortion safely – and it is a model that patients are interested in.[35] Evidence of the considerable barriers patients face when accessing facility-based care [26, 27, 39,40] highlights the need to study advance provision, which will allow for a deeper understanding of whether it is worth further investment. Research aims of a future clinical trial should include measuring the proportion of eligible people who are interested in advance provision, and understanding the reasons behind their interest. Among study participants, key outcomes include the proportion of participants who use the medications, whether they contact a clinician before use, acceptability of the model, and clinical outcomes. Relevant clinical outcomes include effectiveness of medication abortion, adverse events, and the incidence and timing of diagnosis of ectopic pregnancy.

While a future landscape of medication abortion may include telemedicine and mail-order pharmacy dispensing, advance provision may be a preferable option for those who would continue to face barriers to care, including those traveling to areas with limited options for safe abortion. Advance provision of medication abortion pills could facilitate improved access to early abortion and should be rigorously studied.

Criteria prescreened by clinician at time of dispensing medications	Criteria self-assessed by patient at time of using medications†	
	Criteria	**Mode of assessment**

• Does not report any of the following risk factors for ectopic pregnancy:
  o Prior ectopic pregnancy
  o Prior permanent contraception or other tubal surgery
  o IUD in place
• Does not report a history of the following:
  o Hemorrhagic disorder or currently taking anticoagulants
  o Chronic adrenal failure
  o Inherited porphyria
  o Allergy to mifepristone or misoprostol
  o Currently taking long-term corticosteroid therapy
	• Pregnancy confirmation	• Home urine pregnancy test

	• Pregnancy location (i.e. assessment of ectopic pregnancy risk)	• Prior to administering medication abortion: Should <u>not</u> ingest mifepristone and contact clinician immediately with presence of unilateral pelvic pain or significant bilateral pelvic pain within the past week or vaginal bleeding or spotting within the past week • After administering medication abortion: Should contact the clinician if experiencing symptoms consistent with ectopic pregnancy, such as little to no bleeding or unusual pelvic pain
	• Gestational duration	• Sure last menstrual period started ≤ 70 days before mifepristone ingestion ‡
	• Confirm that the conditions prescreened for at the time of dispensing have not developed in the interim	• Checklist of questions

Table. Timing of evaluation for contraindications to and eligibility for medication abortion with advance provision of mifepristone and misoprostol*

* Screening criteria are based on the no-test protocol [11]
† Patients could be encouraged to contact the clinician to confirm eligibility before using medications
‡ Clinicians could choose to use an upper limit of 77 days' gestation

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