Expanding access to medication abortion

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October 2017

UC San Francisco

Limited clinic access

90% of US counties do not have an abortion provider

39% of reproductive age women live in one of those counties

Jones and Jerman, 2017

State restrictions enacted per year

Guttmacher Institute
Medical abortion and access

- Mifepristone approved in 2000
- Mifepristone-misoprostol regimen for medical abortion 95%-99% effective
- Uptake has been slow among non-abortion providing clinicians
- 2005: Only 0.3% of mifepristone-only providers located >50 miles from surgical provider

ACOG 2014; Finer, Obstet Gynecol 2009

US: Medication abortion as proportion of all nonhospital abortions

![Graph showing the increase in medication abortion as a proportion of all nonhospital abortions from 2001 to 2014.](Guttmacher Institute)

Medication abortion

- **Mifepristone**
  - Progesterone receptor blocker
  - Causes lining of uterus to thin, helping to separate pregnancy from uterus
- **Misoprostol**
  - Prostaglandin
  - Causes softening of cervix, uterine contractions

Mifepristone: mechanism of action

- Decidual necrosis and detachment of pregnancy
- Damage to endometrial blood vessels
- Promotes uterine contractions by increasing myometrial cell excitability, establishing gap junctions between cells and influx of calcium
- Increases myometrial response and sensitivity to exogenous prostaglandins
- Stimulates nitric oxide release in the cervix, causing cervical ripening

Spitz, Contraception 2010
Contraindications

→ Chronic adrenal failure: antiglucocorticoid effect may impair action of cortisol replacement
→ Severe asthma not well controlled by therapy: antiglucocorticoid effect may provoke severe attack
→ Confirmed/suspected ectopic pregnancy
→ IUD in place
→ Hemorrhagic disorders or concurrent anticoagulant therapy
→ Inherited porphyrias
→ Allergy to mifepristone or misoprostol: rash, urticaria and facial edema have been rarely reported

US clinical trial – efficacy

→ N=2,121
→ Mifepristone 600 mg, followed 2 days later by misoprostol 400 mcg orally
→ Up to 63 days’ gestation

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Efficacy</th>
<th>Ongoing pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;49 days</td>
<td>92%</td>
<td>1%</td>
</tr>
<tr>
<td>50-56 days</td>
<td>83%*</td>
<td>4%*</td>
</tr>
<tr>
<td>57-63 days</td>
<td>77%*</td>
<td>9%*</td>
</tr>
</tbody>
</table>

*P<0.001 compared to <49 days

Spitz et al., NEJM 1998

US trial – vaginal bleeding

→ Median duration of bleeding or spotting
  → <49 days: 13 days
  → 50-63 days: 15 days
→ 9% reported some bleeding after 30 days
→ 1% reported some bleeding after 60 days
→ 4 blood transfusions (0.2%)

Spitz et al., NEJM 1998

US trial – pain and other side effects

→ Almost all reported pain as part of abortion
→ Severe pain reported more commonly among those 50-63 days' pregnant (53-54%) compared to <49 days (43%, P<0.001)
→ Nulliparous women received more analgesia

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reported</th>
<th>Reported as severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>67%</td>
<td>13%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34%</td>
<td>3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Spitz et al., NEJM 1998
US trial – other adverse effects

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Prevalence reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>32%</td>
</tr>
<tr>
<td>Dizziness, including light-headedness and faintness</td>
<td>12%</td>
</tr>
<tr>
<td>Back pain</td>
<td>9%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9%</td>
</tr>
<tr>
<td>Fever</td>
<td>4%</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>4%</td>
</tr>
<tr>
<td>Viral infections</td>
<td>4%</td>
</tr>
<tr>
<td>Rigors</td>
<td>3%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3%</td>
</tr>
<tr>
<td>Asthenia, leg pain, anxiety, insomnia, anemia, syncope, leukorrhea, sinusitis</td>
<td>2% each</td>
</tr>
</tbody>
</table>

US buccal misoprostol study

- RCT; N=847 with follow-up data and analyzed
- Up to 63 days’ gestation
- Mifepristone 200 mg, followed 24-36 hours later by either (randomized assignment):
  - Misoprostol 800 mcg orally
  - Misoprostol 800 mcg buccally (2 tablets placed in each cheek pouch for 30 minutes, then swallowed)

US buccal miso study – efficacy

<table>
<thead>
<tr>
<th></th>
<th>Oral miso</th>
<th>Buccal miso</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>91.3%</td>
<td>96.2%*</td>
</tr>
<tr>
<td>Ongoing pregnancy</td>
<td>3.5%</td>
<td>1.0%*</td>
</tr>
</tbody>
</table>

*P<0.05 comparing oral and buccal groups

- Success and ongoing pregnancy were similar between groups at <56 days’ gestation
- Success significantly lower (85%) and ongoing pregnancy higher (7.9%) for oral misoprostol compared to buccal route of administration at 57-63 days’ gestation

Winikoff et al., Obstet Gynecol 2008

Buccal miso study – adverse effects

<table>
<thead>
<tr>
<th></th>
<th>Oral miso</th>
<th>Buccal miso</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>69%</td>
<td>75%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>44%</td>
<td>48%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39%</td>
<td>43%</td>
</tr>
<tr>
<td>Fever/chills</td>
<td>36%</td>
<td>48%*</td>
</tr>
<tr>
<td>Headache</td>
<td>39%</td>
<td>41%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>38%</td>
<td>39%</td>
</tr>
<tr>
<td>Weakness</td>
<td>54%</td>
<td>58%</td>
</tr>
</tbody>
</table>

*P=0.001 comparing oral and buccal groups

Winikoff et al., Obstet Gynecol 2008
Medical abortion through 70 days gestation (n=629)

- Mifepristone 200 mg followed 24-48 hours later by misoprostol 800 mcg buccal
- Efficacy
  - 57-63 days gestation: 93.5% (95% CI 90-96%)
  - 64-70 days gestation: 92.8% (95% CI 89-95%)
- Ongoing pregnancy 3% in each group
- No significant difference in efficacy between 9th and 10th week
- High levels of acceptability in both groups (88% reported being satisfied or very satisfied)

Winikoff et al., Obstet Gynecol 2012

Teratogenic potential with ongoing pregnancy

- No evidence that mifepristone alone acts as teratogen
- Exposure to mifepristone alone is not associated with increased risk of birth defects over baseline
- Misoprostol may be teratogenic, especially by causing uterine contractions
- Pregnancy termination should be recommended in cases of failure of regimen
- If woman elects to continue pregnancy, careful ultrasonographic monitoring is recommended

Bernard et al., Epidemiology 2013

Laws and regulations that restrict access to medication abortion

- Requiring providers to follow the protocol described in the (original) FDA-approved label
- Physician-only requirements
- Bans on the use of telemedicine to provide medication abortion
- REMS restrictions on dispensing

Must be provided using FDA protocol
Impact of medication abortion restrictions in Texas

→ Number of visits: at least 3, but generally 4
→ More difficult to access due to:
  → Fewer clinics offering
  → Reduced gestational age limit to 49 days
  → Increased cost at some facilities
→ If have to drive long distance, taking misoprostol in clinic makes it likely she will start abortion while driving

Changes in mifepristone use in 4 states relative to use in 2004

Results: Medication abortions requiring additional intervention

Additional interventions included:
- Repeat misoprostol
- Aspiration
- Blood transfusion
- Hospitalization
- Other abortion-related treatments

New Mifeprex Label - 2016

Regimen: Mife 200 mg oral, miso 800 mcg buccal 24-48 h later
GA limit: 70 days
Location of pill ingestion: Not specified
Required visits: One required (or none?)
Provider: Any “certified” health provider

Sheldon & Winikoff, Contraception 2015
Impact of revised label

- Label now reflects evidence and current accepted standard practice
- In states with laws requiring adherence to FDA-approved label, new label has dramatically increased access
  - Larger population eligible for service
  - Fewer visits
  - More types of clinicians can prescribe drug
- But some laws still tied to old label...

Advanced practice clinicians and medication abortion

- Cochrane review includes 3 studies of mid-level providers and medication abortion (2 RCTs and 1 cohort study; India, Sweden and Nepal)
  - Risk of failure was not different for mid-level providers or doctors (RR 0.81, 95% CI 0.48 to 1.36 from RCTs; RR 1.09, 95% CI 0.63 to 1.88 from observational studies)
  - No complications reported
- WHO recommends that advanced practice clinicians, as well as nurses, can provide medication abortion

18 states ban telemedicine provision of abortion

35 states require that medication abortion be provided by a licensed physician
Safety: Any clinically significant adverse event

<table>
<thead>
<tr>
<th>Telemedicine patients (n=8,765)</th>
<th>In-person patients (n=10,405)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n 16</td>
<td>% (95% CI)</td>
<td>n 33</td>
</tr>
<tr>
<td>0.18% (0.11-0.29%)</td>
<td>0.32% (0.23-0.45%)</td>
<td></td>
</tr>
</tbody>
</table>

Difference in adverse event prevalence: 0.13% (95% CI -0.01% to 0.28%)

Grossman, et al., Obstet Gynecol 2017

Effectiveness of medical abortion

<table>
<thead>
<tr>
<th>Telemedicine</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>99% (N=223)</td>
<td>97% (N=226)</td>
</tr>
</tbody>
</table>

P=0.2


Would recommend to friend

<table>
<thead>
<tr>
<th>Telemedicine (N=213)</th>
<th>Standard (N=217)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90%</td>
<td>83%</td>
</tr>
</tbody>
</table>

P=0.04

Grossman, et al., AJPH 2013

Improved access to medication abortion in rural areas of Iowa after telemedicine

Grossman, et al., AJPH 2013
Gestational age at time of abortion after introduction of telemedicine in Iowa

- 96% of abortions performed at 13 weeks or less
- After the introduction of telemedicine, abortion at >13 weeks decreased slightly from 3.9% to 3.5%
- Controlling for other covariates, clients presenting after TM had a higher odds of having the abortion performed at 13 weeks or less
  - OR 1.46, 95% confidence interval 1.22-1.75

Grossman, et al., AJPH 2013

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Risk Evaluation and Mitigation Strategy (REMS)

- Requirements beyond the label to ensure that the benefits of drug outweigh its risks
- Used for drugs that have known or potential serious risks
- Different for each drug
  - Assessments
  - Medication Guide
  - Communication Plan
  - Elements to Assure Safe Use (ETASU)

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Examples of Drugs with REMS

- Isotretinoin
- Thalidomide
- Parathyroid hormone
- Epoetin
- Truvada
- Flibanserin
- MIFEPRISTONE

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Elements of Mifeprex REMS

- Prescribers must be certified: complete a form attesting that they can
  - assess pregnancy duration
  - diagnose ectopic
  - provide care or refer for incomplete ab or bleeding
- Mifeprex must be dispensed to patients only in clinics, offices, or hospitals by or under supervision of a certified prescriber
- Patients must sign a Patient Agreement Form
Is Mife REMS Justified?

- Mife label does list serious risks
  - Atypical infection
  - Prolonged heavy bleeding
- But these are very rare: ≤0.3% of women have any serious complication
- Mife REMS violates federal regulations regarding ETASU

Raymond et al., NEJM 2017

ETASU Regulations

- Must be commensurate with (mitigate) the specific serious risks listed in the drug labeling
- Cannot be unduly burdensome on patient access to the drug
- Must conform with ETASUs for other drugs with similar serious risks
- Be designed to be compatible with established distribution, procurement, and dispensing systems for drugs with similar risk

Common Sense

- Provider certification is meaningless
  - Criteria can be met by almost any health provider
  - No enforcement
- None of the risks of medical abortion are addressed by dispensing mife in the clinic
  - Label now allows ingestion of mife at home
- Providers can explain the risks of mife to patients without an FDA approved consent form

Is the REMS a barrier to provision?

→ Survey of ACOG Fellows, 2017 (n=1,128)
→ 24% reported performing abortion in prior year
  → 10% provided surgical and medical
  → 4% medical only
  → 9% surgical only
→ If you could write a prescription for Mifeprex and patient could obtain in a pharmacy, would you provide medical abortion?
  → 15% yes
  → 14% not sure
  → Suggests number of medical abortion providers would double
Implications of removing REMS for Mifeprex

- Eliminate burdens of stocking drug
- Allows clinicians to prescribe mifepristone without first registering as an abortion provider
- Allow women presenting unexpectedly to access the drug
- Facilitate telemedicine abortion
- Normalize perceptions about this drug and integrate it into regular health care

Alternative models of obtaining medication abortion

- Internet/ mail order
- Over the counter
- Advance provision of MA drugs
Interest in alternative models of MA (n=7,022)

- Interested in online MA
- Interested in advance provision
- Interested in OTC MA

Interest among women with prior MA (n=164)

- Interested in online MA
- Interested in advance provision
- Interested in OTC MA

Strategies to improve access to medication abortion

- Expand telemedicine provision
- Explore states where APC provision may be possible
- Exert pressure on FDA to remove REMS (research, advocacy, litigation)
- Research on alternative models of obtaining medication abortion
  - Advance provision of MA drugs
  - OTC access

Question 1
Do you currently provide 1st trimester medical abortion with mifepristone and misoprostol?

A. Yes
B. No
Question 2
Would you offer medical abortion to your patients if you could write a prescription for mifepristone and misoprostol, and your patient could obtain both medications at a pharmacy?

A. Yes
B. Maybe
C. No

Question 3
Do you think the safety and efficacy of advance provision of mifepristone and misoprostol should be studied in a clinical trial?

A. Yes
B. No
C. Not sure

Thank you!

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