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

Disclosures

I have nothing to disclose
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

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
Safety in humans

⇾ Antiglucocorticoid effect expressed at single doses >400 mg or repeated doses of 200 mg
⇾ No clinical or laboratory signs of adrenal failure observed with chronic administration to people with normal adrenal function
⇾ No mineralocorticoid effect
⇾ Specific drug/food interactions have not been studied but may occur given metabolism by CYP 3A4

Sitruk-Ware, Contraception 2006

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

Sitruk-Ware, Contraception 2006

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>Rigos</td>
<td>3%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3%</td>
</tr>
<tr>
<td>Asthenia, leg pain, anxiety, insomnia, anemia, syncope, leukorrhoea, 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 misoprostol 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>Adverse Effect</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

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: 93.3% (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

→ Unclear if mifepristone alone has teratogenic potential
→ Normal pregnancies have been reported after mifepristone exposure
→ 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

Sitruk-Ware, Contraception 2006

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

Average Monthly Intervention Rate

Sheldon & Winkoff, Contraception 2015

Results: Medication abortions requiring additional intervention

<table>
<thead>
<tr>
<th>Pre-law</th>
<th>Post-law</th>
</tr>
</thead>
<tbody>
<tr>
<td>No additional intervention</td>
<td>95.1%</td>
</tr>
<tr>
<td>Additional intervention</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

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


New Mifeprex Label - 2016

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

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...

37 states require that medication abortion be provided by a licensed physician
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
  
Barnard, Cochrane 2015; WHO 2015

18 states ban telemedicine provision of abortion

Guttmacher Institute

Safety: Any clinically significant adverse event

<table>
<thead>
<tr>
<th></th>
<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</td>
<td>16</td>
<td>33</td>
<td>0.07</td>
</tr>
<tr>
<td>% (95% CI)</td>
<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

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

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)
Examples of Drugs with REMS
- Isotretinoin
- Thalidomide
- Parathyroid hormone
- Epoetin
- Truvada
- Flibanserin
- MIFEPIRSTONE

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

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

Geographic distribution of certified mifepristone physician prescribers in Australia, May 2015
Grossman & Goldstone, Contraception 2015

Geographic distribution of certified mifepristone pharmacist dispensers in Australia, May 2015
Grossman & Goldstone, Contraception 2015
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
- Advance provision of MA drugs
- Over the counter

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?
1. Yes
2. 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?
1. Yes
2. Maybe
3. No

Question 3

Do you think the safety and efficacy of advance provision of mifepristone and misoprostol should be studied in a clinical trial?
1. Yes
2. No
3. Not sure
Thank you!

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