Medication Management of Early Pregnancy Loss

WomanCare GLOBAL academy

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Objectives

By the end of this training program, participants will be able to:

- Explain Early Pregnancy Loss (Miscarriage) and its implications
- Explain options for Medical Management of Early Pregnancy Loss
- Provide an overview of different uterine evacuation methods
- Provide an overview of Medications used to manage EPL
- Explain After-Care
- Provide options for contraception after EPL
- Explain the role of telemedicine in EPL

GLOBAL CHALLENGES

OF EPL

Global Challenges of Miscarriage

1

Globally **23 million** pregnancies are lost before viability every year.

That is **44 miscarriages** per minute – probably higher

15% risk of miscarriage

2

Population prevalence **women with previous miscarriages**

one previous = 10.8%,

two previous = 1.9%,

three or more = 0.7%

3

Increased risk with age of mother (and father)

at the **age of 30**, the risk of miscarriage is one in five (**20%**);

Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss, Quenby S et al. Lancet 2021; 397: 1658–67 .Lancet 2021; 397: 1658–67

Global Challenges of Miscarriage

Other risk factors include:

- Black ethnicity v white,
- Smoking,
- Alcohol,
- Uterine and endometrial abnormalities,
- Chronic illnesses such as diabetes, obesity,
- Vaginal (e.g. bacterial vaginosis) and systemic infections (e.g. malaria),
- Increasing evidence about the role of pollution.

Global Challenges of Miscarriage

- ‘Miscarriage: worldwide reform of care is needed’ - Lancet Series, April 2021
- Partial understanding of the burden
- Numbers not collected accurately, diagnostic criteria not consistent
  - Diagnosis based on hCG or USS?
    - Biochemical pregnancy loss
    - Preclinical pregnancy loss (before identification on USS)
    - Clinical pregnancy loss (after identification on USS)
  - Recurrent miscarriage criteria
    - ASRM – 2 or more failed pregnancies
    - RCOG – 3 or more consecutive including biochemical pregnancies
    - ESHRE – 2 or more, non consecutive

All mean that women can be denied treatments and management options

Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss, Quenby S et al. Lancet 2021; 397: 1658–67 .Lancet 2021; 397: 1658–67

Types of EPL/Miscarriage

Missed abortion

When the pregnancy stops developing, but it (the embryo/ fetus/ embryonic tissue or empty gestation sac) remains in the uterus and the cervical os is closed*
The patient may have pain, bleeding or no complaints. An ultrasound may show an embryo or fetus without cardiac activity, or a fluid-filled sac within the uterus.

Incomplete Miscarriage

When the pregnancy has started to pass out of the uterus and the cervical os is open. The patient complains of bleeding and cramping pain.
An ultrasound may show 'Irregular heterogeneous echoes within the endometrial cavity on TVS **. However, routine ultrasound should not be used to screen for incomplete abortion; ultrasound appearances correlate poorly with retained products of conception (WHO 2023)

Threatened miscarriage

When vaginal bleeding or spotting occurs, but the pregnancy remains alive / viable in the uterus and the cervical os is closed. There may or may not be pain.

*Abortion care guideline. Geneva: World Health Organization; 2022. Abortion care guideline (who.int)
** Doubilet PM, Benson CB, Bourne T, Blaivas M. Diagnostic criteria for nonviable pregnancy early in the first trimester. N Engl J Med 2013; 369: 1443–51.

WHY DOES MISCARRIAGE MATTER?

Why does miscarriage matter?

Health risks

- Vaginal bleeding in early pregnancy is linked to an increased risk of obstetric complications and poor pregnancy outcomes
  - Threatened miscarriage -> increased risk of APH (RR 1.62-2.47), and
  - Increased risk perinatal mortality and low birth weight (RR 2.15 and 1.83)
- With each miscarriage an increased risk of preterm birth
  - Related to damage from curettage, changes to endometrial biome, leading to abnormal placentation

Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss, Quenby S et al Lancet 2021; 397: 1658–67

Why does miscarriage matter?

Long term health risks

- Recurrent miscarriage increases the risks of cardiovascular disease and venous thromboembolism
- Psychological effects of miscarriage grossly underestimated*
  - 18% met criteria for post-traumatic stress
  - 17% moderate to severe anxiety
  - 6% moderate to severe depression

*Farren J, Jalmbrant M, Falconieri N, et al. Posttraumatic stress, anxiety and depression following miscarriage and ectopic pregnancy: a multicenter, prospective, cohort study. Am J Obstet Gynecol 2020; 222: 367.e1–22

Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss, Quenby S et al Lancet 2021; 397: 1658–67

Why does miscarriage matter?

Economic Costs

Direct Costs to health system of miscarriage treatments widely variable with in patient vacuum aspiration creating a high financial burden

- USA MVA outpatient _____ £852
- Inpatient _____ £1729
- Expectant management _____ £380
- Medical management _____ £298
- Esawatini MVA _____ £131
- D&C for incomplete miscarriage ____ £201

For the woman, short term work absences with long term costs unknown.

- UK estimates annual economic cost of miscarriage _____ £417 million

Introducing mifepristone will :

- Increase coverage for post-abortion care for rural women.
- Significantly reduce the cost of managing miscarriage in Malawi.

*Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss, Quenby S et al

UTERINE EVACUATION METHODS

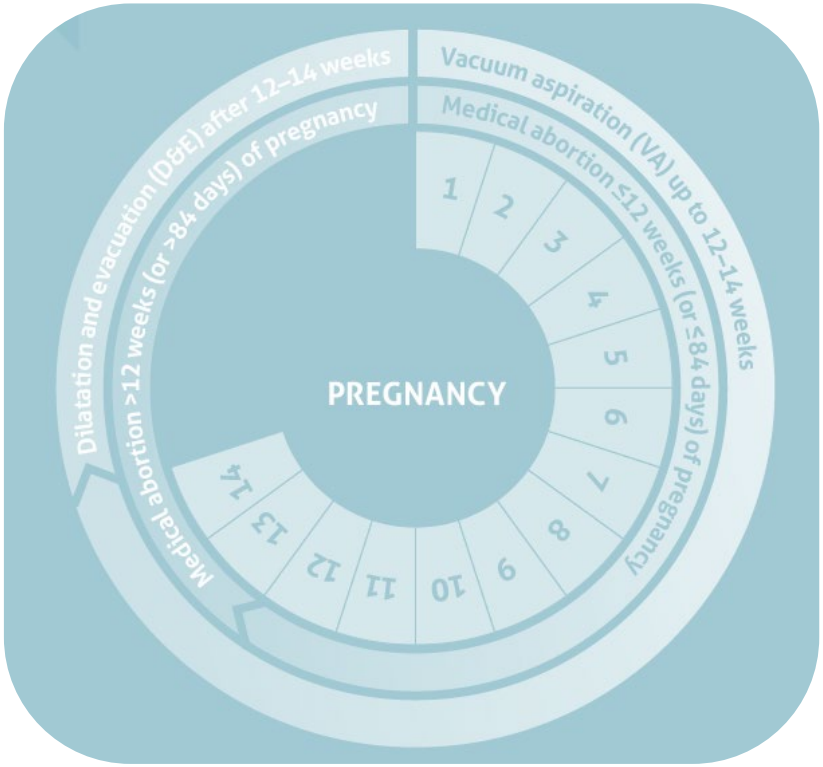
OVERVIEW

Uterine Evacuation Methods Overview

Recommended methods of evacuation by pregnancy duration:

- Medical
- Surgical
  - Vacuum aspiration – up to 14 weeks
  - Manual vacuum aspiration (MVA)
  - Electric vacuum aspiration (EVA)
- Dilation and evacuation (D&E) - after 14 weeks.

VA should replace D&C because D&C is likely to be associated with more complications



Clinical practice handbook for Quality Abortion Care , World Health Organization, 2023

Comparison of Uterine Evacuation Methods < 14weeks

Medical Evacuation	MVA
Avoids surgery.	Minor surgical procedure done in OPD.
Mimics the natural process of spontaneous miscarriage.	Done with the help of instruments by trained provider.
In some settings and gestations it can take place at home.	Takes place in a health facility.
Process takes hours or days to complete, which is unpredictable. women experience bleeding and cramping during this time. IUD can be inserted only after confirming completion which may take more than a week.	Quick procedure, takes less than 15 minutes to complete. Complete evacuation confirmed by examining aspirated products. Intrauterine contraception can be provided at the end of the procedure.
Tablets may cause other side effects such as vomiting, shivering and nausea.	Instrumentation may cause some discomfort.
May require more than one visit to the clinic if bleeding and pain require treatment and to confirm that the pregnancy has passed completely.	Single visit unless there is uterine or cervical injury – risk of injury is small in hands of trained provider.
There is a chance that women may see the products of conception.	Women do not see products of conception.
Timing of process can be women controlled.	Timing of procedure is controlled by the provider and the clinic.

ROLE OF MIFEPRISTONE AND MISOPROSTOL

Mifepristone

Information

- Mifepristone is a synthetic prostaglandin (RU486), with a molecular formula of $C_{29}H_{35}NO_2$: 11β-[p-(dimethylamino) phenyl]-17α-(1-propynyl) estra-4,9-dien-17β-ol-3-one
- It is a steroidal antiprogestogen, antiglucocorticoid and a weak antiandrogen.
- It antagonises cortisol action competitively at the receptor level.
- It was developed in 1980, and is on WHO List of Essential Medicines.

Presentation

- Mifepristone is presented as uncoated yellow, round, flat tablet, scored on one side for oral or vaginal route.
- It is typically used in combination with misoprostol to promote uterine contractions.
- May be administered orally or vaginal.

Medical Uses

- Emergency contraception – within 120 hrs of unprotected intercourse.
- Medical Abortion in first and second trimester of pregnancy.
- Ripening of the cervix.
- Preparation for the action of prostaglandin analogues such as misoprostol on the uterus. Mifepristone potentiates misoprostol.
- Induction of labour in IUD.
- Management of Incomplete Abortion / Miscarriage.
- Treatment of type 2 diabetes or glucose intolerance, due to high cortisol levels (hypercortisolism) in adults with Cushing's syndrome (when surgery is impossible) . Ref 1,2

Mechanism of Action

Mifepristone

- Progesterone receptor antagonist, interferes with the progesterone, blocking its actions and initiating the release of the pregnancy.
- Used combined with misoprostol in a set dosing sequence.

Misoprostol

- Stimulates the uterus to contract and empty by softening the cervix.
- Can be used without mifepristone where this is not available.
- Initially used for protecting the stomach lining.

Contraindications

Mifepristone

- Adrenal suppression (may require corticosteroid);
- Anticoagulant therapy;
- Asthma (avoid if severe and uncontrolled);
- Existing cardiovascular disease;
- Haemorrhagic disorders;
- History of endocarditis;
- Prosthetic heart valve;
- Risk factors for cardiovascular disease

Misoprostol

- Cardiovascular disease;
- Risk factors for cardiovascular disease

Allergies to the medication

Routes of Administration

Oral

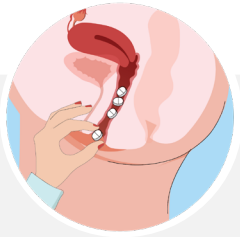
pills are swallowed immediately

Sublingual

pills are placed under the tongue and swallowed after 30 minutes

Buccal

pills are placed between the cheek and gums and swallowed after 20 to 30 minutes



Vaginal

pills are placed in the vagina

Medication Side Effects

Cramping/pain

- occurs in >90% of patients, varies in intensity, peaks after misoprostol dose. Normally no more than 6 hrs and responds to ibuprofen.

Nausea, vomiting, diarrhea, low-grade fever, chills and myalgias

- are common side effects of misoprostol, and usually resolve within 6 hours of use.

Vaginal bleeding

- is usually heaviest within 4-6 hours after misoprostol, often heavier than normal menses and accompanied by the passage of clots.

MEDICAL MANAGEMENT OF EPL

REGIMENS

Options for Medical Management

Expectant *v* Medical *v* Surgical evacuation

Cochrane Review, 2021

- Medical management and surgical evacuation superior to expectant but expectant management successful in 50% or women*
- Medical management successful in over 85% of women and avoids anaesthetic*
- No one is better than another for future pregnancies
- Depends on the woman's own feelings and personal circumstance
- Principles of choice for women with first trimester pregnancy loss

*RCOG PIL, Early Miscarriage 2016

Management of Early Pregnancy Loss

Medical, surgical (vacuum aspiration) and expectant management are all options for **management of missed abortion**. The decision depends on the individual's clinical condition and preference for treatment

MEDICAL TREATMENT OF MISSED ABORTION < 14 WEEKS

REGIMEN TYPE	DOSING INFORMATION			REMARKS
MIFEPRISTONE PLUS MISOPROSTOL (Recommended regimen)	Mifepristone 200 mg PO once	1-2 DAYS BEFORE	Misoprostol 800 µg by any route (B, PV or SL) once	The minimum recommended interval between use of mifepristone and misoprostol is 24 hours.
MISOPROSTOL ALONE (Alternative regimen)	NA		Misoprostol 800 µg by any route (B, PV or SL)	If using this regimen, it should be noted that at gestational ages ≥ 9 weeks, evidence shows that repeat dosing of misoprostol is more effective to achieve success of the abortion process. WHO guidance does not indicate a maximum number of doses of misoprostol.

B: buccal; NA: not applicable; PO: oral; PV: vaginal; SL: sublingual

Management of Early Pregnancy Loss

For clinically stable patients, the three options for **management of incomplete abortion < 14 weeks** are : expectant management, vacuum aspiration, or medical management with misoprostol based on her clinical condition and her preference for treatment.

Misoprostol can be repeated as needed to achieve completion of the abortion process but WHO guidance does not indicate a maximum number of doses of misoprostol to be used.

Recommended regimen for management of incomplete abortion with misoprostol

UTERINE SIZE	MISOPROSTOL REGIMEN (DOSE AND ROUTE)
< 14 weeks uterine size	600 µg oral or 400 µg sublingual
≥ 14 weeks uterine size	400 µg sublingual, vaginal or buccal every 3 hours

Caution must be exercised with maximum number of doses of misoprostol in pregnant women with prior uterine incision and advanced pregnancy (> 14 weeks) to avoid uterine rupture

Why a combination of drugs?

Evidence that the combination of mifepristone and misoprostol

1

Reduced the failure of the gestational sac to spontaneously pass by 7 days

2

Reduced the need for surgical intervention to complete the miscarriage up to and after 7 days, compared to misoprostol alone

3

The use of combination treatment will also reduce the need for surgical intervention so will reduce costs

This has been shown to be a cost-effective treatment in the UK

RCOG, Ectopic Pregnancy and miscarriage: diagnosis and initial management NICE Guideline [NG126] Last Updated 23 August 2023

Efficacy

MISOPROSTOL ALONE

- Across all studies, about 78% of women had complete abortions without recourse to surgery.
- Among groups in which the dose was 800 mcg vaginally, surgical intervention was substantially less common if women were permitted to take at least four doses.
- Moistening of vaginally administered tablets increases absorption rates and is associated with lower surgery intervention.

Efficacy of Misoprostol Alone for First-Trimester Medical Abortion: A Systematic Review. Elizabeth G. Raymond, Margo S. Harrison, Mark A. Weaver, PhD. Obstet Gynecol. 2019 Jan; 133(1): 137–147. doi: 10.1097/AOG.0000000000003017

MIFEPRISTONE PLUS MISOPROSTOL

- Mifepristone potentiates the abortifacient action of misoprostol, resulting in complete abortion in 95% of women through 63 days of gestation and 93% between 64 and 70 days.
- Pre-treatment with mifepristone 200 mg before misoprostol safely, and statistically significantly increased efficacy from 67% to 84%.

Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT. Mifepristone pretreatment for the medical management of early pregnancy loss. N Engl J Med. 2018; 378: 2161-2170

Management of EPL

Missed miscarriage

- 200 mg oral mifepristone, and
- 24-48 hours later, 800 micrograms misoprostol (vaginal, oral or sublingual) unless the gestational sac has already been passed.

Incomplete Miscarriage

- Single dose of misoprostol 600 micrograms (vaginal, oral or sublingual)
- Misoprostol 800 micrograms can be used as an alternative to allow alignment of treatment protocols for both missed and incomplete miscarriage
- Do not offer mifepristone

Abortion care guideline. Geneva: World Health Organization; 2022. Abortion care guideline (who.int)

EXPECTANT MANAGEMENT

Management of confirmed miscarriage

Expectant

'Wait and See'

Importance of patient selection and choice

- Longer time for expulsion and increased risk of retained tissue but most women will not need further treatment.
- If bleeding and pain indicate that the miscarriage has completed during 7 to 14 days of expectant management, repeat urine pregnancy test 3 weeks after miscarriage.
- Offer follow up if no bleeding or persisting and/or increasing bleeding .

Beware:

- Risk of haemorrhage (late 1st trimester), clotting disorders.
- Previous adverse events or traumatic experience associated with pregnancy e.g. stillbirth, miscarriage.
- Signs of infection.

Management of confirmed miscarriage

Threatened

USS confirmed IUP with no previous history of miscarriage?

- Bleeding worsens or persists after 14 days to return for reassessment.

Previous history of miscarriage?

- Offer vaginal micronized progesterone 400mg twice daily until 16 weeks gestation.

Mifepristone and Misoprostol do not terminate ectopic pregnancy.

OPERATIONAL CONSIDERATIONS

Options for Medical Management

Estimation of gestational age

- This is essential even for women having miscarriage.
- Medical management at later gestations should be performed in a healthcare facility because of increased risk of bleeding.
- Gestational age can be reasonably estimated in most cases as the number of weeks and days from the first day of the last normal menstrual period (LMP).
- Perform ultrasound or physical exam if there are doubts about gestation, or suspicion of ectopic pregnancy.

Medical Considerations

Importance of patient selection and choice

Counselling

- Length and extent of bleeding, cramps within 4 hours of taking misoprostol, heavy bleeding for a few hours.
- 2/3 women will complete miscarriage after 2 weeks, 4 in 5 women completed after 4 weeks (Imperial College London data).
- Potential side effects of treatment including pain, diarrhoea and vomiting.
- Offer pain relief (NSAIDs, co-dydramol), anti emetics.

Do they have access to follow up care in case of emergency?

Advise the woman that if bleeding has not started within 48 hours after misoprostol treatment, they should **contact their healthcare professional** to determine ongoing individualised care.

RCOG: provide a urine pregnancy test to take at home 3 weeks after taking drugs

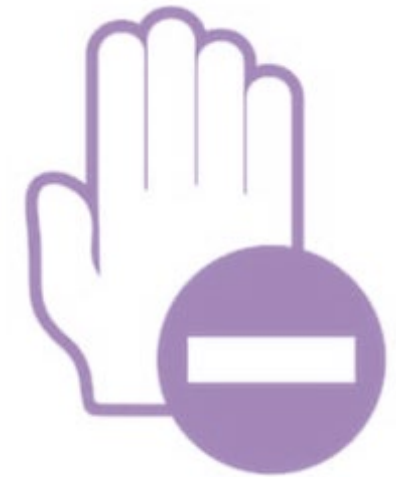
If persistent or heavy bleeding in any circumstance reassess and consider surgical evacuation

- Changing pads more than once every 30 minutes for more than an hour or unable to leave toilet

Medical Considerations

Do not offer anti-D immunoglobulin prophylaxis to women who:

- receive solely medical management for miscarriage **or**
- have a threatened miscarriage **or**
- have a complete miscarriage



Prophylactic antibiotics are not indicated but **check local protocols**

Abortion care guideline. Geneva: World Health Organization; 2022. Abortion care guideline (who.int)

Patient Considerations

1

Take day off work, someone to support the process

2

Childcare arrangements

3

Usually will not see a pregnancy but safe to flush remains or dispose as per her wishes

Operational Considerations

Staff

- Adequate numbers who are trained in counselling and available in case of emergency or follow up questions

Facility

- Enough supplies to enable choice
- Telephone lines open
- Access to emergency assessment, resuscitation and uterine evacuation
- Provision of written information is essential

Follow Up Care

- Women must be informed about 'danger signs' to seek medical advice::
  - Prolonged heavy bleeding or absence bleeding
  - Severe pain not relieved by medication can indicate an ectopic pregnancy
- There is no medical need for mandatory medical follow-up unless the woman wishes to be assessed

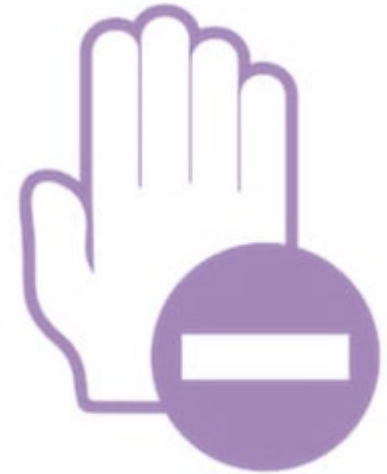
However, it is Important to say "Come back any time"

and have an open door policy

Danger Signs

The patient should reach emergency services if:

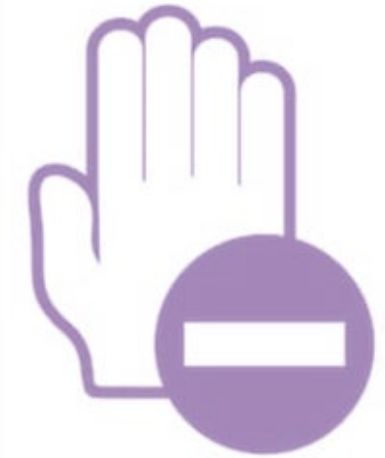
- There is no bleeding within 24 hours of taking misoprostol
- Soak 2 or more maxi-pads for 2 or more consecutive hours
- Unmanageable pain despite taking analgesics prescribed
- Sustained fever >38°C or 100.4°F or onset of fever >24 hours after misoprostol
- Abdominal pain, weakness, nausea, vomiting or diarrhea more than 24 hours after misoprostol



Goodman S, Flaxman G, and the TEACH Trainers Collaborative Working Group.* TEACH Early Abortion Training Workbook, Fifth Edition. UCSF Bixby Center for Global Reproductive Health: San Francisco, CA (2016).

Complications of Medical Management

- If there is no bleeding after taking pills consider
  - A failed procedure (1-2 per 100 women): if confirmed, provider should discuss repeat MA or MVA
  - Ectopic pregnancy: may be asymptomatic or present with minimal bleeding or pain
- If there is heavy or prolonged bleeding after taking MA pills, urgent uterine aspiration may be required to control bleeding
  - Severe bleeding requiring transfusion is seen in less than 1 per 1000
- The need for additional procedure to complete the procedure occurs in 70 per 1000 cases
- Infection is rare (less than 1per 100)



Best Practice in Abortion Care, Royal College of Obstetricians and Gynaecologists, April 2022

Unsuccessful Procedure

The following signs may indicate that process has **not** been successful:

- No bleeding or only slight spotting within 24 hours of taking misoprostol tablets.
- Less than 4 days of bleeding after taking pills.

* British Pregnancy Advisory Service (BPAS). Abortion aftercare. https://www.bpas.org/abortion-care/abortion-aftercare/.

POST EPL CONTRACEPTION

OVERVIEW

Contraception

- Following a spontaneous abortion / miscarriage / EPL , ovulation can return as early as 8–10 days later and usually within one month.
- Starting contraception as soon as possible within the first month is important for women who desire to delay or prevent a future pregnancy.
- All contraceptive options may be considered, but informed choice and the client's wishes are most important.
- Generally, almost all methods can be initiated immediately following a surgical or medical evacuation.

Best Practice in Abortion Care, Royal College of Obstetricians and Gynaecologists, April 2022

Contraception

- Immediate start of contraception after surgical evacuation means it can be started on the same day as the procedure, after the success of the procedure has been confirmed.
- Immediate start of contraception means it can be started after taking the first pill (mifepristone or misoprostol) of the medical regimen, except for IUDs.
- IUDs may be inserted immediately after any uterine evacuation (surgical / medical) has been confirmed as successful, but not after a septic (infected) abortion.
- As with starting any method of contraception, the woman's medical eligibility for her chosen method should be verified.

Best Practice in Abortion Care, Royal College of Obstetricians and Gynaecologists, April 2022

TELEMEDICINE

OVERVIEW

Overview

Telemedicine is a mode of health service delivery where providers and clients, or providers and consultants, are separated by distance.

The interaction may take place in real time (synchronously), using telephone or video link, or asynchronously using a store-and-forward method, when a query is submitted and an answer is provided later (e.g. by email, text or voice/audio message)

Best Practice in Abortion Care, Royal College of Obstetricians and Gynaecologists, April 2022

EPL Services Using Telemedicine

- An alternative to in-person interactions with the health worker to deliver services in whole or in part.
- Telemedicine can be used for assessment of eligibility for medical treatment, counselling and/or instruction relating to the process, providing instruction for and active facilitation of the administration of medicines, and follow-up care
- Telemedicine services should include referrals
  - (based on the woman's location) for medicines (including pain control medicines)
  - for any related care or follow-up care required (including for emergency care if needed)
  - for contraceptive services

Best Practice in Abortion Care, Royal College of Obstetricians and Gynaecologists, April 2022

Self-Management of EPL <12 Weeks

For EPL < 12 weeks (using combination of mifepristone plus misoprostol or using misoprostol only) , self-management is possible as follows:

- self-assessment of eligibility (determining pregnancy duration, ruling out contraindications)
- self-administration of medicines outside a health-care facility without the direct supervision of a trained provider
- self-management of the process
- self-assessment of the success

High Quality counselling and information are pre-requisites of self-management

Session Summary

- Mifepristone + misoprostol, or misoprostol alone are safe and effective treatments for uterine evacuation for early pregnancy loss.
- This method does not require a surgical procedure or availability of a provider.
- Medications can be self-administered successfully supported by good quality counselling and correct information including using telemedicine.
- MVA should be accessible for all women who choose medications if the woman changes her mind or uterine evacuation is incomplete or if there is heavy bleeding.
- High quality EPL services should take into account the burden of disease of EPL and impact on women.

REFERENCES

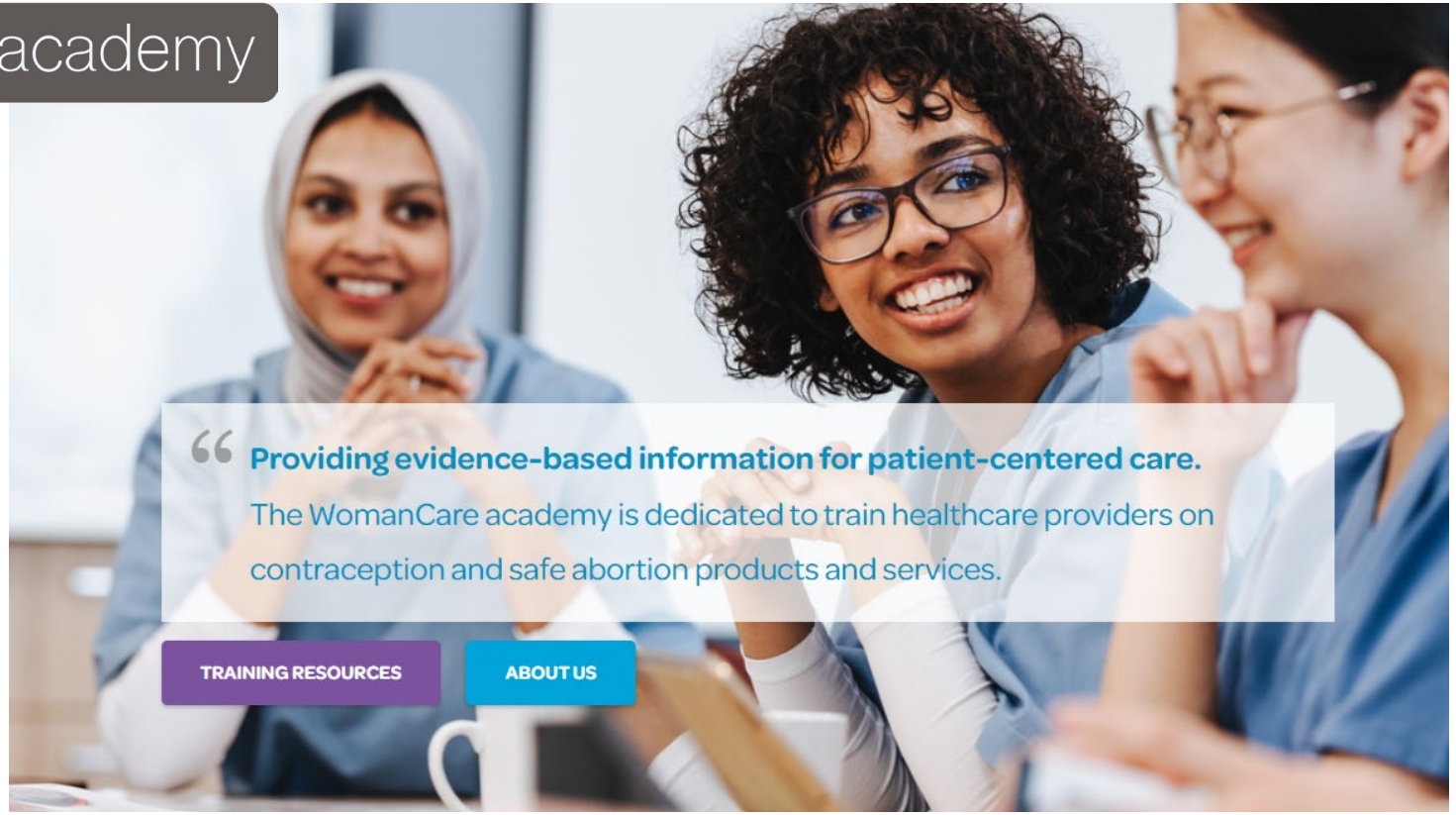
Source Material

- Abortion care guideline. Geneva: World Health Organization; 2022. Abortion care guideline (who.int) Clinical practice handbook for quality abortion care. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO
- RCOG, Ectopic Pregnancy and miscarriage: diagnosis and initial management NICE Guideline [NG126] Last Updated 23 August 2023
- World Health Organization Department of Sexual and Reproductive Health and Research (WHO/SRH) and Johns Hopkins Bloomberg School of Public Health/ Center for Communication Programs (CCP), Knowledge SUCCESS. Family Planning: A Global Handbook for Providers (2022 update). Baltimore and Geneva: CCP and WHO; 2022.
- Lancet Series, 'Miscarriage Matters', April 26th, 2021

Questions, Comments, Or Concerns?

We want to hear about it ...

Training resources: WomanCare Academy



Training resources: WomanCare Academy

Training resources for healthcare providers

Through the WomanCare Academy, we educate a spectrum of healthcare providers: gynecologists, nurses, midwives and others worldwide, to build their skills in delivering high quality, patient-centered care using our contraceptive and safe abortion products.

womancare-academy.org

Training resources: WomanCare Academy

- Training tools for contraception and safe abortion products
  - Implants
  - Emergency contraception
  - Injectable contraception
  - IUDs
  - Medical abortion
  - Surgical abortion
  - Early pregnancy loss management

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