Title of the Protocol: Use of Ulipristal Acetate in Induction of Second Trimestric Missed Abortion in Women with Previous Caesarian section: Randomized Controlled Trial.

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Background

Miscarriage is a common event in a woman's life. Approximately 20% of clinically recognized pregnancies end in a miscarriage [1] Most miscarriages occur before 12 weeks and it has been estimated that only 2–3% of pregnancies end spontaneously in the second trimester. Second-trimester pregnancy loss has been defined as miscarriage diagnosed between the duration of gestation of 12–24 weeks [2]. According to the World Health Organization, miscarriage is defined as the premature loss of a fetus at < 22weeks of the pregnancy and weighing < 500 g. [3]

Medical management of miscarriage and induced abortion has become the gold standard in clinical practice. However, the treatment of second trimester miscarriage has been addressed in only few research studies. In a recent systematic review of medical treatments for incomplete miscarriage, no randomized trials focused specifically on the treatment of miscarriage beyond 13 week´s gestation were identified [4]. Thus the clinical practice on the treatment of late miscarriages is mainly based on the knowledge derived from studies on second trimester induced abortion. [6]

Medical abortion is the termination of pregnancy with use of medications to induce a process similar to a miscarriage. It is an alternative to aspiration curettage. Use of a combination of mifepristone (an antiprogesterone) and misoprostol (a prostaglandin) is the primary method of medication abortion used according to the American College of Obstetricians and Gynecologists . [7]

Ulipristal is a selective progesterone receptor modulator (SPRM) with primarily antiprogestin activity. Due to its antiprogestin activity it is highly effective for use in emergency contraception. It's primary mechanism of action is delay of ovulation, but endometrial effects that may affect implantation may also contribute to efficacy. [9]

A Cochrane review demonstrated that medical abortion in the second trimester (13–28 weeks) using the combination of mifepristone and misoprostol appeared to have the highest efficacy and shortest abortion time interval compared to other medical regimens. [10

Mifepristone may be used in combination with misoprostol to decrease the induction-to-abortion interval and minimize pain. By opposing the activity of progesterone, mifepristone elicits a variety of effects that make the uterus more susceptible to abortion. These effects include cervical dilation, decidual necrosis, increased endogenous prostaglandin production, and increasing uterine sensitivity to exogenously administered prostaglandin. Mifepristone administration gradually elicits a five-fold increase in sensitivity to prostaglandin 24 to 48 hours after its administration [11]. The synergy between mifepristone and prostaglandin permits greater efficacy of prostaglandin at lower doses, potentially minimizing side effects [12].

The improved efficacy with mifepristone was best illustrated in a randomized trial that compared second-trimester abortion with misoprostol (buccal 400 mcg, then 200 mcg every six hours) preceded by either mifepristone (oral 200 mg) or placebo (oral vitamin C).Women in the mifepristone group had a significantly shorter median procedure time (10 versus 18 hours). In addition, the mifepristone group had a non significant association with lower rates of retained placenta (3.1

versus 6.3 percent) and analgesic requirements (27.2 versus 39.3 mg morphine). Side effects were similar between groups. [13].

What is already known on this subject? AND What does this study add?

Ulipristal acetate (UPA) is a selective progesterone receptor modulator approved for use as an emergency contraceptive and for preoperative treatment of uterine fibroids. It has not been used as an abortifacient drug in previous studies. However, due to its antiprogestin activity, like its family member Mifeprostone, it could be effective if it is used alongside Misoprostol according to FIGO guidelines for induction of abortion. This may decrease the time taken for patients to abort, may increase the success rate of having a complete abortion thus decreasing the need for aspiration& hysterotomy. All this, would lead to less morbidity, shorter hospital admission stay, better psychological wellbeing for patients and a decrease in all hospital costs

The aim of this work is to assess the effectiveness and safety of Ulipristal Acetate in the management of 2nd trimestric missed abortion along with misoprostol in pregnant women with previous caesarean section versus the use of misoprostol only with placebo as regards the time needed for abortion.

Research Question

In pregnant women with 2nd trimestric missed abortion with previous caesarean section , does Ulipristal Acetate decrease the time interval to achieve abortion when combined with Misoprostol in comparison to Misoprostol alone?

Hypothesis

In pregnant women with 2nd trimestric missed abortion with previous caesarean section , Ulipristal Acetate may decrease the time interval to achieve abortion when combined with Misoprostol in comparison to misoprostol alone.

Methods

Study Design

Type of Study: A Randomized Controlled Trial.

Study Setting: Ain Shams University Maternity Hospital.

Study Period: Starting from January 2019 to January 2020.

Participants

Study Population: Women with 2nd trimestric missed abortion with previous caesarean section undergoing medication abortion attending either outpatient clinic or emergency room

Eligibility Criteria:

Inclusion Criteria:

- Women with 2nd trimestric missed abortions
- Gestational age 13-26 weeks.
- Women with a previous caesarian section scar,(Para-1CS till Para-4CS).
- Women counseled and chose medication abortion rather than surgical evacuation

Exclusion Criteria:

- Women with an accompanying medical disorder such as: Preeclampsia, DM or Heart disease.
- Primigravida women or non scarred uterus.
- Women with previous myomectomy or hysterotomy scar or upper segment caesarean section scar.

- Induction of abortion in women with congenital fetal malformations or positive fetal pulsations due to medical disorder
- Women with placenta previa.
- Allergy or contraindications to either Ulipristal acetate or Misoprostol.
- Women with inevitable abortion in the form of vaginal bleeding or uterine contractions.

All women who met the inclusion criteria will be assessed.

This assessment will include:

Detailed History:

Personal history (Maternal age, weight, height).

Obstetric history . Gravidity, Parity, previous operative delivery.

Any associated complication during pregnancy.

Menstrual history (Last menstrual period).

Maternal medical history (Hypertension & Coagulopathies).

Physical Examination:

i. **General examination**: a. Vital signs b. Chest and heart examination

ii. **Abdominal examination**: a. Gestational age b. Fetal weight, amount of liquor, fetal lie and presentation, fetal heart sounds c. Uterine contractions and scar of previous surgeries

iii. **Vaginal examination** to detect cervical dilatation, consistency, position and length.

Investigations:

CBC ,Liver Function, Kidney function, Random blood sugar, Prothrombin time (PT)

Obstetric ultrasound study: For assessment of gestational age, fetal life, implantation site of the placenta and fetal weight.

Interventions

The study sample, will be divided into two groups as follows:

Group A: will receive Ulipristal acetate 30mg, starting misoprostol 12 hours later 100µg every 6 hours buccal according to FIGO guidelines 2017.

Group B: will receive placebo tablet then 12 hours later start misoprostol 100µg every 6 hours buccal according to FIGO guidelines 2017.

Then women in both groups will have rest for 24hours after 5 doses of misoprostol

and restart misoprostol-only in both groups with the same above regimens, repeating the same sequence for two weeks unless there is excessive bleeding or infection. If failed, patient will proceed to hysterotomy.

Primary outcome

1. Induction-to-abortion interval time.

Secondary outcome

1. Success rate for complete evacuation between both groups.
2. Occurrence of side effects: i) Nausea ii) Vomiting iii) Fever iv) Pain, between both groups.
3. Rate of uterine rupture between both groups.

4. Amount of blood loss, as a comparison between both groups.
5. Rate of hysterotomy between both groups.

Sampling Method:

Sample Size: A pilot sample was used primarily, to accurately calculate the main study sample. According to Julious SA. [6], a pilot sample size of 24 (12 per arm) was used. The objective is not to prove superiority of the treatment but to test trial procedures and processes and to get estimates of parameters for the main trial sample size calculation. Women fulfilling the inclusion criteria and consenting were randomly assigned to either group

Randomization, Allocation and Concealment:

A computer generated list via MedCalc® Software, version 13.2.2 will be used for randomization, assigning each participant number to either study group using sequentially numbered, otherwise identical, sealed envelopes (SNOSE), each

containing a 2-inch by 2-inch paper with a written code designating the assigned group. These papers were placed in a folded sheet of aluminum foil fitted inside the envelope. To ensure concealment, efforts will be taken to assure absence of any detectable differences in size or weight between intervention and control envelopes. Envelopes will be chosen to be opaque and lined inside with carbon paper. Envelopes will be opened sequentially after writing the subject's tracking information on the envelope so that the carbon paper served as an audit trail. At the time of procedure, the

responsible investigator will open the envelope to reveal the assignment, and she will introduce the planned method.

After enrollment, the cases will be randomly allocated into two groups:

- **Group A(n=30):** Will be the case group, it includes cases who will receive Ulipristal Acetate plus Misoprostol.
- **Group B(n=30):** will be the control group, it includes cases who will receive Misoprostol only plus a structurally similar placebo drug manufactured at Ain Shams Pharmacology department.

Ethical Considerations:

The nature and scope of the clinical study will be explained in a form understandable to the patient and an informed consent document, in Arabic language, contains all locally required elements and specifies who informed the patient, will be provided and the patient must give written consent. Patients should be counseled that medication abortion takes longer and that they may have a greater awareness of blood loss and passage of pregnancy tissue with high risk of rupture uterus (0.3%)[16] and blood transfusion. The study protocol and patient informed consent will be reviewed and approved by the Ethics Committee of the Obstetrics and Gynecology Department Ain Shams University.

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