Introduction

Miscarriage is the most common complication of pregnancy, occurring in 10-20% of clinically recognized pregnancies. Unsafe miscarriage kills approximately 47000 women per year ***(Bagratee et al., 2004).***

The standard management of miscarriage for more than 50 years has been surgical evacuation of the retained products of conception because of the fear of hemorrhage and sepsis secondary to illegal abortion ***(Luise et al., 2002).***

Over the past decade, medical termination of pregnancy in the first trimester gained popularity with the highly effective regimen combining mifepristone and misoprostol ***(Lee et al., 2011)a***.

A medical abortion is one that is brought about by taking medications that will end a pregnancy, medical abortion is not usually an option after nine weeks (or 63 days). After that, surgical abortion is the safest and best option ***(Dudley and Mueller, 2008)***.

Misoprostol, a synthetic analogue of naturally occurring prostaglandin E1, has a uterotonic effect and it can stimulate myometrial contraction and cause cervical ripening and dilatation ***(Chai and Ho, 2013).***

Routes that result in a longer duration of action (i.e. vaginal) also appear to result in greater efficacy compared with oral administration. Similarly, those routes with rapid and significant absorption (i.e. sublingual) also have high

efficacy, but the greater maximum concentration results in more adverse effects **(Creinin and Grossman, 2014)**.

Without pre-treatment with mifepristone the recommended dose of misoprostol for termination of pregnancy before 9 weeks gestation is 3 doses of 800 mcg misoprostol 12-hourly. This regimen is 90% effective. Thus, the efficacy of the treatment is far below the combined treatment with mifepristone and proves that an increased dose of misoprostol cannot compensate for the lack of mifepristone ***(Kallner, 2012).***

Estrogen is important in the maintenance of pregnancy. Aromatase inhibitors, such as letrozole, suppress the peripheral conversion of androgens to estrogens. We have recently shown that the use of letrozole combined with vaginal misoprostol was more effective than misoprostol alone in termination of pregnancy up to 9 weeks' gestation ***(Yeung et al., 2012).***

One study shown that letrozole 7.5 mg given daily for 2 days and then followed by 800 mcg of vaginal misoprostol induce complete abortion in 80% of patients ***(Kallner, 2012).***

The common side effects of letrozole are fatigue and nausea, while of misoprostol are nausea and lower abdominal pain. Most of the side effects, such as nausea, vomiting, fatigue, dizziness, and headache are already present during the pregnancy before administration of treatment and persist after letrozole pretreatment and misoprostol administration ***(Tang et al., 2011)***.

Aim of the Work

Compare the success rate of letrozole and misoprostol versus misoprostol alone for medical termination of first trimester pregnancy.

Hypothesis:

Letrozole can be used as pre-treatment for misoprostol in induction of first trimester miscarriage.

Research question:

Will letrozole pre-treatment before misoprostol improve the outcome of induction of first trimester miscarriage?

Primary outcome:

Incidence of complete miscarriage (complete expulsion of the products of conception with no need for surgical intervention within one week from the first dose of misoprostol).

Secondary outcome:

Need for surgical evacuation of the products of conception

- Incomplete expulsion of the products of conception (incomplete miscarriage).
- Considerable bleeding necessitating immediate surgical evacuation.

Maternal morbidity

- Major side effects (Sepsis, considerable vaginal bleeding leading to hemodynamic instability or necessitating blood transfusion)
- Minor side effects (fever, rigors, nausea, vomiting)

Patient's compliance and adherence to treatment

Hemoglobin and hematocrit deficit

Patients and Methods

Type of the Study:

A prospective double-blind, randomized, controlled trial.

Study Settings:

This clinical trial will be conducted at Ain-Shams University Maternity Hospital in the period between October 2014 and April 2015.

Study Population:

The patients will be recruited from women attending outpatient Obstetric clinic or the emergency room of Ain-Shams University Maternity Hospital.

Sample size justification:

EpiInfo® version 6.0 program was used for calculations of sample size, statistical calculator based on 95% confidence interval and power of the study 80% with α error 5%, According to a previous study ***(Lee et al., 2011)a,*** this study found that the primary outcome measure is the complete miscarriage rate after one week of the first dose of misoprostol. In the study shown that the complete miscarriage rate in the letrozole group combined with misoprostol (86.9%) was significantly higher than that in the

placebo group combined with misoprostol (72.6%). Relative risk: 1.20, 95% confidence interval: 1.03–1.40. The difference in complete abortion rates was 14.3%, thus power is 80%, 160 patients would be required in each group to achieve an alpha error of 5% and a beta error of 10%.

Inclusion criteria:

- Maternal age more than 18 years old (age of legal consent).
- Gestational age less than 64 days gestation.
- Hemoglobin >10 g/dL.
- BMI between 25 kg/m^2 and 35 kg/m^2.
- Missed abortion.

Exclusion criteria:

- Maternal age less than 18 years old.
- Gestational age more than or equal to 64 days.
- Hemoglobin <10 g/dL.
- Fibroid uterus.
- BMI less than 25kg/m^2 and more than 35kg/m^2.
- Coagulopathy.
- Previous attempts for induction of abortion in the current pregnancy.
- Allergy to misoprostol or letrozole.
- Medical disorder that contraindicate induction of abortion (e.g. heart failure).
- Uterine anomalies.
- Molar pregnancy.

Methodology:

Patients that seem to be fulfilling the inclusion criteria will be recruited, then an informed written consent will be taken from every patient before starting the examination to confirm fulfilling all inclusion and exclusion criteria.

Careful and detailed history

a) Personal history:

-Name, age, occupation, residence, socioeconomic status and special habits of medical importance.

b) Obstetric history:

-First day of last menstrual period, estimated gestational age by date.

c) Past history:

-History of diabetes mellitus, hypertensive disorders, cardiac problems, chest diseases, renal diseases, blood diseases or bleeding tendency.

d) Surgical history:

-Previous uterine scars and previous laparotomies

Examination of the patients:

A) General examination:

- Maternal body weight, height and BMI.

$$\text{BMI} = \frac{weight\,(kg)}{(height\,(m))^2}$$

(Romero-Corral et al., 2008)

- Presence of petichae or ecchymosis of the skin to exclude presence of coagulation defect or blood disease.
- Cardiac and chest examination.
- Vital data (blood pressure, pulse, temperature).
- Presence of pallor or jaundice.

B) Abdominal examination:

- Size of the uterus.
- Scar of previous laparotomies.

C) Vaginal examination:

- Cervical assessment includes dilatation, position (posterior, intermediate or anterior), length and consistency (soft, firm or hard).

Investigations:

- Hemoglobin and hematocrit.
- Blood group, RH
- Trans-vaginal ultrasound to confirm missed abortion and to exclude molar pregnancy, fibroid, or uterine anomalies.

Patients not fulfilling the inclusion and exclusion criteria will be dropped from the study and will not be considered as part of the calculated sample size.

Randomization

Patients fulfilling inclusion and exclusion criteria will be divided into two groups.

Group (A):

160 patients will receive misoprostol with letrozole.

Group (B):

160 patients will receive misoprostol with placebo.

Method of randomization

To insure that everyone has the chance of participation, randomization will be guided by computer generated list (MedCalc Software bvba Version 13.2.2, Acacialaan 22, B-8400 Ostend, Belgium), double blinding will be used thus; the primary investigator and the patient will not know whether the patient is receiving the drug or the placebo. Placebo will be the same in size, color, odor and shape of the original drug, the placebo and misoprostol will be put in 160 numbered closed envelopes, letrozole and misoprostol will be put in another 160 numbered closed envelopes according to the computer generated list and an envelope will be allocated to each patient accordingly.

Procedures:

Induction of abortion will be carried according to **FIGO** protocol of induction (**missed abortion** 800µg misoprostol per vagina / 3 hours maximum 2 doses) ***(Gomez et al., 2007).***

Group (A):

Women will receive three tablets of letrozole **(Femara^{R,} NOVARTIS)** as a single dose, each tablet 2.5 mg (total dose 7.5 mg per day) for two days at home and will be told to bring back the empty packs. The third dose will be given on admission to hospital on day three and will be followed by 4 tablets of vaginal misoprostol (200 mcg) **(Misotac^{R},SIGMA)** soaked with saline every three hours up to maximum two doses.

Group (B):

Women will receive three tablets of placebo as a single dose, for two days at home and will be told to bring back the empty packs. The third dose will be given on admission to hospital on day three and will be followed by 4 tablets of vaginal misoprostol (200 mcg) **(Misotac^{R},SIGMA)** soaked with saline every three hours up to maximum two doses.

Women will stay in the hospital for at least 4 hours after the administration of the last dose of misoprostol. Temperature, blood pressure and pulse will be recorded hourly. Side effects, presence of vaginal bleeding and the time of expulsion of tissue mass will be recorded too.

If considerable vaginal bleeding is present but still with good general condition, the patient will be allowed to stay in hospital overnight with close observation.

If the vaginal bleeding affects patient`s general condition (i.e. tachycardia or hypotension) or hemoglobin level decreases by more than 2 gm/dl, surgical evacuation will be done immediately under general anesthesia.

Women will be allowed to go home after the 4 hour observation period if bleeding is not heavy and abdominal pain is not severe.

Upon discharge from hospital, participants will be given diary cards to record the presence of vaginal bleeding and side effects. Patients will be given strict instructions to come back to hospital once they develop rigors, considrable vaginal bleeding, offensive vaginal discharge or fever more than 38ºC.

The follow-up visit will be on day 7 during which a trans-vaginal ultrasound is performed and blood sample is taken for hemoglobin level.

In participants with incomplete or missed miscarriage on day 7 surgical evacuation will be performed under general anesthesia.

Surgical evacuation will also be done at any time over the 7 days follow up period if there is heavy bleeding or on patient's request.

If no emergency or elective curettage is necessary over the 7 days, the outcome of treatment is classified as "complete miscarriage".

Data recording:

1. Vital data (temperature, blood pressure and pulse) during hospital stay.
2. Hemoglobin and hematocrit before treatment and after miscarriage to estimate the decrease in hemoglobin and hematocrit levels.
3. Monitoring minor side effects (fever, rigor, nausea, vomiting and headache).
4. Recording major side effects (considerable vaginal bleeding or sepsis).

5. Patients who received 2 doses of misoprostol and did not abort till seven days after the last dose will be considered failure to induce complete miscarriage, surgical evacuation under anesthesia will be performed.
6. Excessive vaginal bleeding necessitates immediate evacuation under anesthesia.

Statistical Methods

Data will be collected, tabulated, then analyzed using IBM© SPSS© Statistics version 21 (IBM© Corp., Armonk, NY).

Normally distributed numerical data will be presented as mean and SD and differences between the two groups will be compared using the independent-samples Student t test.

Skewed numerical data will be presented as median and interquartile range and inter-group differences will be compared non-parametrically using the Mann-Whitney U test.

Qualitative data will be presented as number and percentage and the chi square test or Fisher's exact test, when appropriate, will be applied for comparison of the two

groups. P-value < 0.05 will be considered statistically significant.

Ethics:

The study will be approved from the Research Ethical Committee of the Department of Obstetrics and Gynecology, Faculty of Medicine, Ain-Shams University.

Informed written consent will be taken from all participants before recruitment in the study, and after explaining the purpose and procedures of the study.

المقدمـــة

يعتبر الإجهاض هو أكثر مضاعفات الحمل شيوعا بحيث يصيب حوالي ١٠-٢٠% من الحوامل . كما يتسبب الإجهاض في وفاة حواالي ٤٧٠٠٠ إمراة سنويا.

خلال أكثر من خمسين عاما كان التفريغ الجراحي هو العلاج الأمثل للإجهاض خوفا من حدوث النزيف المهبلي وحدوث العدوى مع الإنهاء الطبي للحمل .

ولكن وخلال العقد الماضي أصبح الإنهاء الطبي للحمل في الأشهر الثلاثة الأولى وذلك بالجمع بين عقاري الميزوبروستول والميفيبريستون أكثر استخداما ، ولكن الإنهاء الطبي للحمل ليس الخيار الأفضل بعد الأسبوع التاسع للحمل بحيث يعتبر الإجهاض الجراحي أكثر أمانا .

يؤدي الميزوبروستول إلى تحفيز انقباض الرحم كما يؤدي إلى توسيع عنق الرحم ، مما يؤدي إلى الإنهاء الطبي للحمل.

يعطى الميزوبروستول عن طريق المهبل بحيث يكون أكثر فعالية كما يعمل لمدة أطول إذا ما قورن بتناوله عن طريق الفم ، ويمكن تناول الميزوبروستول أيضا تحت اللسان بحيث يكون أسرع امتصاصا وأكثر كفاءة ولكن مع زيادة في حدوث الآثار السلبية للعقار.

أثبتت الدراسات بأن الجرعة الأمثل للميزوبروستول للإنهاء