INTRODUCTION

Miscarriage is defined as the spontaneous loss of pregnancy less than 20 weeks gestation. The American College of Obstetricians and Gynecologists (ACOG) estimates it is the most common form of pregnancy loss***.(NICE,2012)***

The miscarriage rate is roughly 15-20% and it is the most common complication of early pregnancy in humans ***(Storck and Inc, 2011).***

Missed abortion in the 1st trimester is characterized by the arrest of embryonic or fetal development. The cervix is closed and there is no or only slight bleeding. Ultrasound examination shows a fetus without cardiac activity ***(Danielsson et al., 2007).***

A single dose of 800µg vaginal misoprostol may be offered as an effective, safe and acceptable alternative to the traditional surgical treatment for this indication. Alternatively 600µg misoprostol can be administered sublingually ***(Danielsson et al., 2007).***

National Institute for Health and Care Excellence (NICE) recommends 800 mcg of Vaginal misoprostol for missed abortion ***(Huchon et al., 2016).***

The standard management of miscarriage for >50 years has been surgical evacuation of the retained products of conception (ERPC) because of the fear of hemorrhage and sepsis .***(Bagratee et al., 2004).***

However, ERPC is associated with risks of anesthesia, hemorrhage, infection, cervical trauma, uterine perforation and intrauterine adhesions.***(Bagratee et al., 2004).***

Medical abortion became an alternative method of abortion with the availability of prostaglandin analogues in the early 1970s and the anti-progestin mifepristone in the 1980s ***(Chai and Ho, 2013).***

The most common early first-trimester medical abortion regimen consisted of mifepristone in combination with administration of misoprostol. The complete abortion rate was up to 95% in gestations up to 63 days ***(Chai and Ho, 2013).***

However, Mifepristone is expensive and not registered in many countries ***(Ngoc et al., 2011).***

The complete abortion rate with a single dose of vaginal misoprostol moistened with water is only 72% in an early study ***(Jain et al., 2002).***

With repeated doses (up to 3) of vaginal misoprostol alone, the success rate is only 65% when using dry misoprostol

and 85% when using vaginal misoprostol moistened with water ***(Ngai et al., 2000).***

The use of letrozole pretreatment followed by vaginal misoprostol in the first trimester abortion is more effective than misoprostol alone ***(Lee et al., 2011)b***.

The regimen of 2 days of letrozole 7.5 mg daily combined with vaginal misoprostol 800 mcg is associated with a complete abortion rate of 80% in subjects with gestation less than 63 days. In subjects with gestation less than 49 days, the complete abortion rate was higher (87.5%), ***(Lee et al., 2011)b.***

Misoprostol is a prostaglandin E1 analogue that has been approved by the Food and Drug Administration (FDA) to be taken orally for the prevention and treatment of gastric ulcers associated with the use of non-steroidal anti-inflammatory drugs ***(Alisa et al., 2001).***

It has also become an important drug in obstetrical and gynecologic practice because of its utero-tonic and cervical ripening actions ***(Weeks et al., 2005).***

Misoprostol is useful for elective medical abortion, cervical ripening before surgical abortion, evacuation of the uterus in cases of embryonic or fetal death, and induction of

labor.It may also be used to treat and even prevent postpartum hemorrhage ***(Weeks et al., 2005).***

Progesterone maintains the uterus in a quiescent state by inducing hyperpolarization of the membrane of the myometrial cells, and a greater change in electric potential is necessary before contractions can occur ***(Chai and Ho, 2013).***

Mifepristone is an anti-progestin that binds to the progesterone receptors and prevents endogenous progesterone from exerting its effects.It can also increase the sensitivity of the uterus to prostaglandins ***(Chai and Ho, 2013).***

The new third generation aromatase inhibitors agentscommercially available include two non-steroidal preparations, anastrozole and letrozole and a steroidal agent, exemestane ***(Mitwally and Casper, 2005).***

Letrozole has a short half-life (around 2 days) and it clears rapidly from the body ***(Mitwally and Casper, 2002).***

Letrozole is a highly specific non-steroidal aromatase inhibitor that initially was approved for use in postmenopausal women with breast cancer to suppress estrogen production ***(Winer et al., 2002).***

Letrozole is a highly potent third generation and selective AI that inhibits the enzyme activity of intracellular aromatase at the major sites where it is found, resulting in almost complete suppression of whole body aromatization ***(Bhatnagar, 2007)***.

In a study done by ***Tang*** and his colleagues 40 patients who requested termination of pregnancies up to 63 days medical miscarriage was performed with letrozole seven and half milligram daily for two days followed by 800 microgram vaginal misoprostol in 20 subjects and letrozole seven and half milligram combined with 200 mg mifepristone in another 20 subjects***(Tang et al., 2011)***.

In this study, the regimen of letrozole and misoprostol shows a complete miscarriage rate of 80%. While for those with the regimen of letrozole combined with mifepristone the complete miscarriage rate was 71.4%.

The conclusion of this study suggests that a regimen of letrozole and misoprostol may be useful in medical miscarriage, but the combination with mifepristone is less effective and takes longer.

AIM OF THE WORK

Comparing 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:

In women with missed miscarriage in the first trimester undergoing indction of abortion does pre-treatment with letrozole before misoprostol lead to abortion rate similar to that of misoprostol alone?

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)
- Occurance of Septic Abortion on top of Missed or Incomplete Abotion
- Minor side effects (fever,rigors, nausea, vomiting)

Patient's compliance and adherence to treatment

Hemoglobin and hematocrit deficit

MISCARRIAGE

While miscarriage is a term for early pregnancy loss, it is also frequently known in medical literature as spontaneousabortion ***(Farquharson et al., 2005).***

Before the 1980s, health professionals used the phrase "spontaneous abortion" for a miscarriage and **"**induced abortion" for a willful termination of the pregnancy ***(Moscrop, 2013).***

Those born before 24 weeks of gestation rarely survive***(Mohangoo et al., 2013).***

However, the designation "fetal death" applies variably in different countries and contexts, sometimes incorporating weight, and gestational age from 16 weeks in Norway, 20 weeks in the US and Australia, 24 weeks in the UK to 26 weeks in Italy and Spain***(Li et al., 2012).***

A fetus that died before birth after this gestational age may be referred to as a **stillbirth*****(Li et al., 2012).***

In the late 1980s and 1990s, doctors became more conscious of their language in relation to early pregnancy loss. Some medical authors advocated change to use of "miscarriage" instead of "spontaneous abortion" because

they argued this would more respectful to women's feelings and help ease a distressing experience***(Farquharson et al., 2005).***

The most common symptom of a miscarriage is vaginal bleeding. However, light vaginal bleeding is relatively common during the first trimester of pregnancy and does not necessarily indicate a miscarriage ***(Graciaet al., 2005).***

Bleeding during pregnancy may be referred to as a threatenedmiscarriage. Of women who seek clinical treatment for bleeding during pregnancy, about half will miscarry ***(Graciaet al., 2005).***

Epidemiology:

Determining the precise prevalence of miscarriage is not possible, because a large number of miscarriages occur before pregnancies become established and before women are aware they are pregnant. In addition, women with bleeding in early pregnancy may attend for medical care more often than women not experiencing bleeding***(Avalos et al., 2012).***

The prevalence of miscarriage increases with the age of the mother and the father***(Kleinhaus et al., 2006).***

Causes:

Miscarriage may occur for many reasons, not all of which can be identified. Some of these causes include genetic, uterine, or hormonal abnormalities, reproductive tract infections, and tissue rejection***(Tabor and Alfirevic, 2010).***

Miscarriage caused by invasive prenatal diagnosis,chorionic villus sampling (CVS) and amniocentesis is rare (about 1%)***(Agarwal and Alfirevic, 2012).***

First trimester:

Most clinically apparent miscarriages occur during the first trimester***(Storck, 2012).***

The National Institutes of Health report that "around half of all fertilized eggs die and are lost (aborted) spontaneously, usually before the woman knows she is pregnant***(Storck, 2012).***

Chromosomal abnormalities are found in more than half of embryos miscarried in the first 13 weeks. This is more likely to have been the cause in the case of a woman suffering repeated miscarriages, or if one of the parents has a child or other relatives with birth defects. Genetic problems are more likely to occur with older parents***(Wahabi et al., 2007).***

Progesterone deficiency may be a cause. Women diagnosed with low progesterone levels in the second half of their menstrual cycle (luteal phase) may be prescribed progesterone supplements, to be taken for the first trimester of pregnancy***(Wahabi et al., 2007).***

However,no study has shown that general first-trimester progesterone supplements reduce the risk ***(Bukulmez and Arici, 2004).***

Second trimester:

Second trimester losses may be due to uterine malformation, uterine fibroids or cervical problems***(Peng et al., 2006).***

Risk factors:

1. <u>Multifoetal pregnancy:</u>

Pregnancies of more than one fetus are considered at increased risk, the more fetuses in the womb, the higher the risk***(Kapp et al., 2007).***

2. <u>Inter-current diseases:</u>

- **Diabetes mellitus**:

The risk of miscarriage is increased in women with poorly controlled insulin dependent diabetes mellitus***(Mills et al., 2008).***

- **Polycystic ovary syndrome**:

Which may increase the risk of miscarriage, but this is disputed***(Boomsma et al., 2008).***

- **Hypothyroidism**:

Severe cases of hypothyroidism increase the risk of miscarriage. The presence of anti-thyroid autoantibodies is associated with an increased risk***(Boogaard et al., 2011).***

- **Vertically transmitted infections**:

Certain vertically transmitted infections (such as Rubella and Chlamydia) increase the risk of miscarriage***(Hertzen et al., 2009).***

- **Autoimmune disease:**

Some research suggests autoimmunity as a possible cause of recurrent or late term miscarriages. Autoimmune disease occurs when the body's own immune system acts against itself. Therefore, in the case of an auto-immune induced miscarriages the woman's body attacks the growing fetus or prevents normal pregnancy progression***(Gleicher et al., 2007).***

Further research also has suggested that autoimmune disease may cause genetic abnormalities in embryos which in turn may lead to miscarriage***(Weiner et al., 2006)***.

3. Age:

The age of the mother is a significant risk factor. Miscarriage rates increase steadily with age, with more substantial increases after the age 35***(Bray et al., 2006).***

4. Exercise:

Most types of exercise (with the exception of swimming) correlated with a higher risk of miscarrying prior to 18 weeks***(Madsen et al., 2007).***

5. Loop electrosurgical excision procedure (LEEP)

Women with a time interval from LEEP to pregnancy of less than 12 months were at significantly increased risk for spontaneous abortion***(Conner et al., 2013).***

6. Antidepressants

Especially paroxetine and venlafaxine can lead to a miscarriage***(Nakhai et al., 2010).***

Diagnosis:

A miscarriage may be confirmed via obstetric ultrasound and by the examination of the passed tissue. When looking for microscopic pathologic symptoms, one looks for the products of conception. Microscopically, these include villi, trophoblast, fetal parts, and background gestational changes in the

endometrium. As many as half the embryos miscarried have a chromosomal abnormality. When chromosomal abnormalities are found in more than one miscarriage, genetic testing of both parents may be done***(RCOG, 2011)a.***

The physical symptoms of a miscarriage vary according to the length of pregnancy:

At up to six weeks only small blood clots may be present, possibly accompanied by mild cramping or period pain***(Weng et al., 2008).***

At 6 to 13 weeks a clot will form around the embryo or fetus, and the placenta, with many clots up to 5 cm in size being expelled prior to completion of the process. The process may take few hours or be on and off for few days. Symptoms vary widely and may include vomiting and loose bowels***(Weng et al., 2008).***

At more than 13 weeks the fetus may be passed easily from the uterus, however, the placenta is more likely to be fully or partially retained in the uterus, resulting in an incomplete miscarriage***(Weng et al., 2008).***

The physical signs of bleeding, cramping, and pain may be similar to an early stage abortion, but sometimes more severe and labor-like***(Weng et al., 2008).***

Ultrasound criteria:

Miscarriage should be diagnosed only if any of the following criteria are met upon ultrasonography visualization: ***(Doubilet et al., 2013)***.

- Crown-rump length of at least 7 mm and no heartbeat.
- Mean gestational sac diameter of at least 25 mm and no embryo.
- Absence of embryo with heartbeat at least 2 weeks after an ultrasound scan that showed a gestational sac without a yolk sac.
- Absence of embryo with heartbeat at least 11 days after an ultrasound scan that showed a gestational sac with a yolk sac.

In addition, signs upon ultrasonography that are suggested to be suspicious for miscarriage, but not diagnostic of it include: ***(Doubilet et al., 2013)***

- Crown–rump length of less than 7 mm and no heartbeat.
- Mean gestational sac diameter of 16–24 mm and no embryo.
- Absence of embryo with heartbeat 7–13 days after an ultrasound scan that showed a gestational sac without a yolk sac.
- Absence of embryo with heartbeat 7–10 days after a scan that showed a gestational sac with a yolk sac.