Introduction

Pre-labour rupture of membranes (PROM) is defined as rupture of the fetal membranes with a latent period before the onset of spontaneous uterine contractions. The length of this latent period varies in different definitions, ranging from not being specified up to 8 hours ***(Svigos et al., 2006).***

Approximately 8 percent of pregnant women at term present with PROM. If PROM persists, the risks of infectious complications are greatly increased. Research indicates that induction of labor (IOL) reduces the risk of infection and other complications of PROM at term ***(Mozurkewich et al., 2003).***

The treatment of PROM at term is controversial. Options include expectant treatment or induction with mechanical methods, vaginal prostaglandin (PG), or intravenous (IV) oxytocin ***(Butt et al., 1999).***

In recent years, misoprostol, a prostaglandin E1 analogue, which is relatively cheap, stable at room temperature and is rapidly absorbed both vaginally and orally, has emerged as an alternative induction agent to dinoprostone and oxytocin. It is not licensed for use in pregnancy in most countries, and this has been an issue of much debate ***(Goldberg et al., 2001).***

In the past 15 years, a large number of trials have been reported, which have assessed the efficacy and safety of

misoprostol when used for IOL in the presence of a viable pregnancy. These trials have used both vaginal and oral misoprostol. The potential advantages of the oral route include easy, noninvasive administration and avoidance of unnecessary vaginal examinations, thus the oral route may be preferred by women and caregivers. Systematic reviews of trials of misoprostol have shown it to be more effective than other agents if used vaginally and as effective as other agents if used orally ***(Alfirevic and Weeks, 2006).***

However, definitive data on safety are still lacking. Overall, misoprostol seems to be associated with an increased incidence of uterine hyperstimulation, both compared with dinoprostone and oxytocin ***(Hofmeyr and Lmezoglu, 2003).***

Uterine hyperstimulation may predispose to more serious complications such as uterine rupture and associated maternal and neonatal morbidity and mortality. However, the incidence of adverse effects appears to be dose related, and it is generally accepted that low-dose regimens are safer, but their use may compromise clinical efficacy ***(Alfirevic and Weeks, 2006).***

Aim of the Work

The aim of the study is to compare the efficacy and safety of the use of (25 µg) and (50 µg) of misoprostol solution orally in pre-labor rupture of membranes in term pregnancies.

Patients and Methods

Study Design:

Prospective-controlled double-blind randomized clinical trial.

Study Populations:

The study will include pregnant women attending the casualties of Ain Shams University Maternity Hospital, presenting with pre-labor rupture of membranes, according to inclusion criteria listed below.

Inclusion criteria:

1. Age: 18-40 years old.
2. Gestational age: > 37 weeks.
3. Singleton pregnancy.
4. Presented with pre-labor rupture of membranes.
5. Initial reassuring non-stress test.

Exclusion criteria:

1. Any contraindication to vaginal delivery including malpresentations and prior uterine surgery.
2. Active labor.

3. Antepartum hemorrhage.
4. Major congenital fetal malformations.
5. Contraindication to prostaglandin use e.g. bronchial asthma.

Included women will be subjected to:

1. History taking with emphasis on menstrual dates, history of prior surgery, history of rupture of membranes, history of prior medical disorders or problems in the current pregnancy.
2. Abdominal examination.
3. Cusco speculum examination.
4. Pelvic digital examination and assessment according to modified Bishop score.

Rupture of the membranes is diagnosed by:

1. Definite history of gush of considerable amount of watery fluid with continuity.
2. Vulval pad showing liquor.
3. Sterile Cusco speculum examination showing pooling in the posterior fornix or leakage through the cervical external os.

The included women will be randomized into 2 groups:

1. **Group I:** women who will receive 25 µg misoprostol solution orally every 6 hours till being in active labour (defined by at least 3 uterine contractions per 10 minutes, of, at least, 30 seconds duration, with progressive cervical dilatation).
2. **Group II:** women who will receive 50 µg misoprostol solution orally every 6 hours till being in active labour.

- Misoprostol solution will be given orally for a maximum of 4 doses. If the woman fails to get into the active labor, 6 hours after the fourth dose, oxytocin infusion will be started as per Ain Shams University Maternity Hospital protocols, till satisfactory uterine contractions are reached.
- Women who fail to develop uterine contractions till 12 hours after starting oxytocin infusion and titrating it to the maximum dose will be considered as failed induction of labor, and switched for Cesarean delivery.
- Women who succeded to have uterine contraction after the indution with the oral misoprostol solution, but with unsatisfactory uterine contraction (less than 3 contractions per 10 minutes and less than 30 seconds duration) and with protracted first stage or second stage of labor, oxytocin augmentation is allowed to be given according to our hospital protocols. Oxytocin will not be given before 6 hours after the last dose of misoprostol.

Outcome Measures:

- The primary outcome is the induction-to-delivery interval.
- Secondary outcomes include number of women in active labor within 24 hours of induction, duration of the first and second stages of labor, need for analgesia, intrapartum pyrexia, postpartum pyrexia, postpartum bleeding, need for CS for either failed induction or intrapartum fetal distress, maternal satisfaction, neonatal outcome, Apgar score at 1 and 5 minutes, need for neonatal ICU admission and neonatal sepsis.

Randomization and Blinding:

- Randomization will be performed using a Computer-generated randomization system.
- This trial is a double-blind one. Neither the investigator nor the patient will be aware of the dose of misoprostol given. Drugs will be contained in sealed envelops. Each envelop will contain 4 doses of the misoprostol solution; either of 50 μg misoprostol solution or 25 μg misoprostol solution in a clean well sealed tubes.
- Sealed envelops will be numbered according to the randomization tables.
- Packing, sealing and numbering of the envelops will be performed by a neutral medical personnel.
- Randomization and numbering tables will be hidden from the main investigator till the end of the trial.

Ethical aspects:

- The purposes and procedures of the trial will be explained to all eligible women before recruitment in the trial.
- Included women will be asked to sign an informed consent before participating in the trial.
- Any woman has the right to withdraw from the trial at any stage, without being harmed by this withdrawal concerning medical and ethical management.
- The protocol of the trial is to be approved from the Ethical Committee of Medical Researches in Obstetrics and Gynecology Department, Faculty of Medicine, Ain Shams University.

Drugs:

- The drug given is misoprostol 200 μg tablets (Misotac®, SIGMA pharmaceutical industries, Egypt, S.A.E.).

Sample size justification:

Sample size was calculated using EpiInfo® version 6.0, setting the power (β) at 80% and significance level (α) at 0.05. Our primary outcome is the induction-to-delivery interval. A 4-hour (240 minutes) difference is considered worthwhile difference. Data from a previous study ***(Butt et al; 1999)*** indicated that the standard deviation of induction-to-delivery interval was 382 min (in misoprostol group). Calculation

according to these values produced a minimal sample size of 53 cases. Assuming a drop-out rate of 5%, and a 20% expected rate of Cesarean section, a minimal sample size of 69 cases is produced. Therefore, the total sample size will be 140 cases to be randomized into 2 groups.

Statistical analysis:

Demographic data of included women will be presented as descriptive statistics (using range, mean and standard deviation for metric data, and range, median and interquartile range for discrete data). Demographic data, and primary and secondary outcomes of both groups will be compared using t-test (for quantitative measures), and chi-squared and Fischer's Exact tests (for categorical measures). Microsoft® Excel® (version 2007) and SPSS® for Windows® version 16.0 will be used for data presentation and statistical analysis.

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Oral Misoprostol for Induction of Labor in Pre-labour Rupture of the Fetal Membranes in Term Pregnancies

Protocol of Thesis submitted for Partial Fulfillment of Master Degree ***in Obstetrics and Gynecology***

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PREMATURE RUPTURE OF MEMBRANE AT TERM

Definitions:

Pre-labour or premature rupture of membranes (PROM) is defined as rupture of membranes before the onset of labour irrespective of the gestational age. It could be term or preterm depending on the gestational age it occurred. Membrane rupture that occurs at or beyond 37 weeks of gestation is defined in this study as term PROM (TPROM) ***(Eleje et al., 2010).***

The interval between membrane rupture and the onset of labour is referred to as the ***latency interval***. There is little consensus on how long this interval should be in order to substantiate the judgement that rupture of membranes did not coincide with onset of labour. Currently, a preference for the latency interval of one- hour is required to fulfill the diagnosis of PROM ***(Eleje et al., 2010).***

Classification:

1. Premature rupture of membranes (PROM): when the fetal membranes rupture early, at least one hour before labor has started. ***(Beckmann and Charles, 2010).***
    - Prolonged PROM: a case of premature rupture of membranes in which more than 24 hours has passed between the rupture and the onset of labor ***(DeCherney and Alan, 2013).***

2. Preterm Premature Rupture of Membranes (PPROM): premature rupture of membranes that occurs before 37 weeks.
    - Midtrimester PPROM or Pre-viable PPROM: premature rupture of membranes that occurs before 24 weeks completed gestational age of the fetus. Before this age, the fetus cannot survive outside of the mother's womb ***(Beckmann and Charles, 2014).***

Epidemiology:

The incidence of PROM ranges from about 5% to 10% of all deliveries, and PPROM occurs in approximately 1% of all pregnancies. Approximately 70% of cases of PROM occur in pregnancies at term ***(Gibbs et al., 2008).***

Of all term pregnancies (> 37 weeks) about 8% are complicated by PROM, ***(Cunningham et al., 2014)*** 20% of these become prolonged PROM ***(DeCherney and Alan, 2013).***

About 30% of all preterm deliveries (before 37 weeks) are complicated by PPROM, and rupture of membranes before viability (before 24 weeks) occurs in less than 1% of all pregnancies ***(ACOG, 2013).***

Since there are significantly fewer preterm deliveries than term deliveries, the number of PPROM cases make up only about 5% of all cases of PROM ***(DeCherney and Alan, 2013).***

Signs and symptoms:

Most women will experience a painless gush of fluid that leaks out of the vagina. Sometimes women notice a steady leakage of small amounts of watery fluid rather than a distinct "gush" ***(Beckmann and Charles, 2010).*** Other symptoms include a change in color and consistency of fluid coming out of the vagina, flecks of meconium (fetal stool) in the fluid, or a decrease in the size of the uterus ***(DeCherney and Alan, 2013).***

Pathophysiology:

A) Weakened fetal membranes:

Fetal membranes likely break because they become weak and fragile. This weakening is a normal process that typically happens at term as the body prepares for labor and delivery. But, this can be a problem when it occurs pre-term (before 37 weeks). The natural weakening of fetal membranes is thought to be due to one or a combination of the following. In premature rupture of membranes, these processes are activated too early:

- Cell death: when cells undergo programed cell death, they release chemical markers that are detected in higher concentrations in cases of PPROM.
- Poor assembly of collagen: collagen is a molecule that gives fetal membranes their strength. In cases of PPROM, proteins that bind and cross-link collagen to increase its tensile strength are altered.