A COMPARATIVE STUDY BETWEEN THE USE OF INTRAVAGINAL MISOPROSTOL AND INTRAVENOUS OXYTOCIN FOR INDUCTION OF LABOUR AFTER PRE-LABOR RUPTURE OF MEMBRANES AT TERM

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ABSTRACT

Background

Misoprostol is a prostaglandin E1 analogue medication, has been shown to be effective and safe for induction of labor in women with pre-labour rupture of membranes at term.

Objective

The aim of this study is to compare efficacy and acceptability of intravaginal misoprostol with intravenous oxytocin for induction of labor after pre-labour rupture of membranes at term.

Patients and Methods

This study was conducted as prospective randomized trial at the department of Obstetrics and Gynecology in Maternity teaching hospital and Rizgary hospital in Erbil, performed in 2010-2011. The study involved 100 pregnant women with uncomplicated pregnancies at term, with pre-labour rupture of membranes. The women were assigned to receive 50 Microgram of vaginalmisoprostol every 4 hours (50 patients) or oxytocin infusion (50 patients). The patients were selected randomly from the Labour room. The parameter studied were induction to delivery interval, rate of Cesarean section, indications of Cesarean section, neonatal outcomes, maternal complications and maternal satisfaction. The test that used for statistical analysis of variables was t-test.

Results

The two groups were comparable with respect to maternal age, gestational age in weeks, parity and Bishop score. The time interval from induction to delivery was shorter in misoprostol group (7.77±0.88 hours), compared to oxytocin group (9.91±1.02 hours), which is statistically significant (p-value<0.001) and mean difference between them was (2.138 hours). Maternal satisfaction was more in misoprostol group (92%) compared to oxytocin group (62%) which is statistically significant (p-value<0.001). The rate of Cesarean section was (18%) in oxytocin group & (12%) in misoprostol group (p-value=0.401) which is statistically insignificant. No difference of statistical importance seen with regard to indications of C/S, fetal distress, neonatal APGAR score <7, admission to neonatal intensive care unit, fetal weight and sex, and maternal adverse effects of the drugs.

Conclusion

In pre-labour rupture of membranes at term, it is effective, safe and economic to use misoprostol for induction of labour with low cervical Bishop score and is associated with shorter induction to delivery interval compared to oxytocin, with higher maternal satisfaction.

Keywords: *Pre-labour rupture of membranes at term; Induction of labour; Misoprostol; Oxytocin.*

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INTRODUCTION

Premature rupture of membranes (PROM) at term is rupture of membranes prior to the onset of labour at or beyond 37 weeks of gestation. It is a relatively common obstetric event, occurs in approximately 10% of pregnancies. Patients with PROM present with leakage of fluid, and pelvic pressure, but they have no contractions. The interval between membrane rupture and the onset of contraction is referred to as the latency. Some authors advocate there must be a minimum latency (such as 1 hour or 4 hours) for the diagnosis of PROM to stand. At term approximately 75 per cent of women will start labour within 24 hours of membrane rupture. The latency period tends to be longer with decreasing gestational age; at 26 weeks, only half of women are in labour within 1 week; at 32 weeks, half will labour within 24-48 hours [1, 2].

PROM has many risks like, chorioamnionitis, postpartum endomitritis, and neonatal infection. Clinical variables associated with an increased risk for PROM include chorioamnionitis, polyhydramnios, multiple gestation, breech presentations, incompetent cervix, antepartum hemorrhage, previous cervical laceration, and a previous PROM (21% risk of recurrence). Recent intercourse is also known to have precipitated PROM in some patients. Despite a clear association between the mentioned factors and an increased risk for PROM. None of the above-mentioned risk factors are known to be directly etiological [1, 3].

Because there is an increased risk of maternal and /or neonatal morbidity, accurate diagnosis of PROM and appropriate management are important, and despite the relative frequency of PROM, it's management in both preterm and term pregnancies remains controversial. Clear clinical guidelines have not emerged from the research published to date. While some reports favor early induction of labour based upon the fact that the risk of maternal and neonatal infection increases the longer the duration of rupture of membrane, other have shown that expectant management is safer and more successful in achieving vaginal delivery [1 ,4].

Induction of labour (IOL) may be defined as an intervention designed to initiate uterine contractions artificially leading to progressive effacement and dilatation of the cervix and birth of the baby, it is a common procedure and is employed in 15-20% of all term pregnancies in UK. Induction of labour should only follow informed consent by the woman. A detailed vaginal examination (cervical favorability scored according to modified Bishop cervical score) and pelvic assessment should precede induction of labour. In addition to the risks that normally occur with labour and delivery, induction of labor adds the risks of uterine hyperstimulation, fetal distress and a greater liklehood of postpartum haemorrhage. Fetal heart rate (FHR) monitoring should be performed using a high-risk protocol, and a physician able to perform Cesarean section must be informed and available. Induction of labour has many indications (one of them is PROM) and contraindications like placenta previa, transverse fetal lie, etc. [2, 4 ,5, 6, 7].

Oxytocin is used for induction of labour and is a cyclic nona peptide differs by only two amino acide from vasopressin. It is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and is subsequently stored in association with neurophysin 1 in storage granules in the nerve terminal located in the posterior pituitary. Secretion of oxytocin from the neuroscretory nerve ending is regulated by electrical activity of the oxytocin cells in the hypothalamus. Stimuli for its release include, sensory stimuli from the cervix and vagina as well as suckling from the breast. It facilitate birth and breast feeding. Oxytocin is metabolized by hepatic oxytocinases and excreted by biliary and renal system. It is 30% protein bounded and has a half-life of 1.6 minute. Oxytocin has many side effects like uterine spasm and hyperstimulation, which result in fetal distress and uterine rupture. With high intravenous bolus dose nausea, vomiting, arrhythmia, rashes and anaphylactic reaction may occur. It can cause peripheral vasodilatation, maternal hypotention, reflex tachycardia and shock [5, 7, 8, 9].

Prostaglandins (PG) together with eicosanoid which is the name given to a group of 20 carbon unsaturated fatty acids derived principally from arachidonic acid in the cell wall, they are short lived, extremely potent and formed in almost every tissue in the body. Although most of the initial studies used PGF2, this has been entirely superseded by PGE2 and PG analogues, prostaglandin analogues are relatively resistant to metabolism hence have prolonged action [2, 5, 7, 10, 11, 14].

Misoprostol is a synthetic analogue of naturally occurring PGE1. It has approved by the food and drug administration to be taken orally for prevention of gastric ulcer associated with use of nonsteroidal anti-inflammatory drug and is important in obstetrics and gynecology because of uterotonic and cervical ripening effect. It has gastointestinal side effects like diarrhoea,

abdominal pain, nausea, vomiting, dyspepsia and constipation. Gynecological and obstetrical side effects like Spotting, cramps, hypermenorhoea, menstrual disorder, dysmenorhoea, post-menopausal vaginal bleeding, uterine hyperstimulation and rupture with meconium staining of liquor. There are several side effects that is infrequently reported, causal relationship have not been established, these include; body ache, fever, rigor, respireatory, cardiovascular, urinary, and nervous system symptoms. [13, 14 ,15, 16, 17, 18, 21].

The optimal regimen for induction of labour by intravaginal misoprostol has not been firmly established, most clinical trials used 25 to 100 µg prepared from oral tablets and inserted intravaginal. Misoprostol comes in 200 µg tablet, and the desired dose can be prepared in the pharmacy by dividing the tablet, which is then inserted in to the posterior fornix. The most common dose is 50 µg, inserted once or every four to six hours; however, inserting 25µ every 4 to 6 hours in associated with the fewest side effects. The maximum cumulative dosage of misoprostol has not been established, but a total dosage of up to 6000µg has been used safely in one clinical trial [6].

PATIENTS AND METHODS

This study was conducted as prospective randomized trial at the department of Obstetrics and Gynecology in Maternity teaching hospital and Rizgary hospital in Erbil city, Kurdistan region, Iraq. Study population included 100 pregnant women at term with pre-labour rupture of membranes from total number of 19000 deliveries (vaginal deliveries and Cesarean section C/S) per year, performed in 2010-2011.

Inclusion criteria include live singleton pregnancy, cephalic presentation, confirmed rupture of membranes less than 24 hours with clear liquor. Absence of any evidence of infection, no uterine contraction, unripe cervix (Bishop scores <6) and Parity <4.

Exclusion criteria include, evidence of maternal infection, rupture membranes > 24 hours, preterm pre-labour rupture of membranes, post term pregnancy, women with anomalous fetus, pregnancy induced hypertension and pre-eclampsia, diabetes or other medical diseases, history of previous cesarean section or any type of uterine scar, history or evidence of thromboembolism, patient with established labor (bishop score of ≥6), meconium staining liquor, abnormal presentation, parity ≥4, non-reassuring fetal heart rate on CTG, intra uterine fetal death, known hypersensitivity to the drugs, multiple pregnancy, vaginal bleeding, patient`s refusal to participate in the study, and any contraindication to induction of labour.

A thorough history and examination done, including general, abdominal, vaginal speculum examination for amniotic fluid pool in the posterior fornix. Digital vaginal examination to assess the cervix and only women with Bishop scores <6 were included. The consent of the patients was taken for their enrollment in the study and selected for the type of treatment they receive. The patients followed in the first week after delivery for signs and symptoms of endometritis, which include fever, foul smelling vaginal discharge, lower abdominal pain and tenderness. White blood cell count, vaginal swab for culture and sensitivity were performed in patient with the above signs and symptoms.

First group of patients were allocated to induction of labor with misoprostol (N=50) after exclusion of uterine contractions or fetal distress, all patients received an initial 50 microgram of misoprostol (quarter of a 200 microgram tablet – cytotec), placed intravaginaly in the posterior fornix, the women remained in bed for about 2 hours to allow absorption. The dose was repeated every 4 hours up to maximum dose of 200 microgram or until patient developed adequate uterine contractions. Cardiotocography was performed prior to each dose. Patients with an established contraction pattern of > 3 contractions in 10 minutes did not receive a second dose of misoprostol. If no contraction started after 4 doses of misoprostol, the procedure was considered unsuccessful, in these cases the decision for further management was done. 38 cases received 2 doses of misoprostol for adequate uterine contraction to start, 11 cases received 1 dose and 1 case received 3 doses.

Second group of patients (N=50), Oxytocin in 5% dextrose water intravenous infusion was commenced at 2 milli international unit (mlU)/minute and doubled every 30 minutes until 3 contractions in 10 minutes lasting 40-45 seconds is obtained, it's then maintained at this rate. This dose given by diluting 10 unit of oxytocin in 1liter dextrose water, infusion started with 3-4 drops per minute and doubled every 30 minutes. All patients were commenced on Amoxicillin on admission and continued for three days. In both groups when there were no progress of labor after 2-4 hours of adequate uterine contraction or when fetal distress developed emergency cesarean section were decided.

The parameters measured were the mode of delivery, time interval from induction to vaginal delivery, maternal satisfaction, indications for cesarean section and neonatal outcomes (APGAR scores <7, neonatal care unit admission, fetal distress).

The incidence of adverse effect such as uterine hyperstimulation were also noted. Uterine hyperstimulation was defined as six or more uterine contraction in 10 minutes for two consecutive 10 minutes periods or contraction lasting at least 2 minutes [3]. If hyperstimulation suspected then the possible management was to change maternal position, intravenous fluid hydration, oxygen supplementation, cessation of oxytocin infusion in group 2, and removal of the remainder of the misoprostol tablet in group 1. Other side effects of the drugs were also recorded, including nausea, vomiting, fever, rigor, uterine rupture and meconium staining of the liquor. Non-reassuring FHR pattern includes persistent or recurrent episodes of severe (duration >60 seconds, or FHR <70 bpm) variable deceleration, repetitive late deceleration, prolonged fetal bradycardia (baseline <100 bpm for 3 minute or more in the first stage of labor), and combination of decreased beat to beat variability and decelerative pattern. The decision to perform an emergency Cesarean delivery was made immediately whenever a non-reassuring FHR tracing was obtained. Neonatal birth weight and sex were recorded immediately after delivery. Supplementary medical information was obtained from the routine pediatric examination on the first day, and if admitted, from neonatal intensive care unit (NICU). T-test was used for statistical analysis of variables in study groups.

RESULTS

The two study groups were comparable regarding maternal age, gestational age, parity and Bishop scores. There was no statistical significance difference in maternal age between the two groups (p- value= 0.26) with the mean of (26.78±5.132 years) for misoprostol group and (25.54±5.828 years) for oxytocin group. 13 patients (26%) in misoprostol group were primigravida and 37 patients (74%) were multigravida compared with 17 patients (34%) primigravida and 33 patients (66%) multigravida in oxytocin group, with no statistical significance difference between the two study groups (p- value= 0.38). Bishop scores were 4.7±1 in oxytocin group and 4.5±1 in misoprostol group with (p-value = 0.3) which is statistically insignificant, as shown in table 1.

Table 2 show maternal out comes in both groups: 44 patients (88%) delivered by vaginal delivery and 6(12%) delivered by Cesarean section in misoprostol group, while 41 patients (82%) delivered by vaginal delivery and 9 patients (18%) delivered by Cesarean section in oxytocin group, which is statistically insignificant difference(p-value 0.4) Regarding the induction to delivery time interval for vaginal delivery, there was statistically significant difference with (p-value <0.001) between both groups. Mean time interval was (7.77±0.88 hours) for misoprostol, and (9.91±1.02 hours) for oxytocin group (also shown in figure 1), the mean difference between them was 2.138 hours.

46 (92%) patient in misoprostol group were satisfied with their management compared with 31 (62%) patient in oxytocin group with (p-value <0.001) which is statistically significant, satisfaction was assessed by asking the patients about it.

Uterine hyperstimulation rate was the same for both group which was 1 (2%). Nausea reported in 2 cases (4%) in misoprostol group and 1 case (2%) in oxytocin group with (p-value=1) which is statistically insignificant. Vomiting reported in one case (2%) of misoprostol group, with no case of vomiting in the oxytocin group. There was no case of fever and rigor, uterine rupture and endometritis in the first postpartum week in both study group.

Regarding fetal out comes, fetal distress occurred in 2 cases (4%) in misoprostol group & 3 (6%) in oxytocin group (p-value 0.6) which is insignificant. APGAR score under 7 at 5 min was noticed in 2(4%) neonates in misoprostol group and 3 (6%) in oxytocin group with (p-value =0.6) which is statistically insignificant difference. Admission to NCU was for 1 neonate (2%) from misoprostol group & for 2 neonates (4%) from oxytocin group which is statistically insignificant (p-value =0.3). 30 (60%) of neonates were male in misoprostol group compared with 25 (50%) case in oxytocin group with statistical insignificant difference between them (p-value = 0.31). Regarding fetal weight, there was statistically insignificant difference between them (p-value 0.22) with mean (3.406±0.332kg) for misoprostol group and (3.326±0.328 kg) for oxytocin group, as shown in table 3.

The indications for Cesarean section: in misoprostol group, causes of Cesarean section were failure of progress in 4 patients (66.7%%) and fetal distress in 2 patients (33.3%), while in oxytocin group the causes

were failure of progress in 6 patients (66.7%) and fetal distress in 3 patients (33.3%), (p-value = 1) which is statistically insignificant. Meconium staining liquor was responsible for 1case (16.65%) of C/S in misoprostol group and 2 cases (22.2%) in oxytocin group which is insignificant difference. Fetal bradycardia was responsible for 1 case (16.65%) of C/S in misoprostol group and 1 case (11.1%) in oxytocin group which is not a significant difference, as shown in table 4.

Table 1. Characteristics of patients in both study groups.

No.	Variables	Oxytocin N= 50	Misoprostol N=50	P. value
1	**Age (years)***	25.54±5.828	26.78±5.132	0.26
2	**Gestational age in weeks**	39±2	39±2	
3	**Bishop score**	4.7±1	4.5±1	0.3
4	**No. of the pregnancy(s)**			
a.	**Primi gravid**	17(34%)	13(26%)	0.38
b.	**Multi gravid**	33(66%)	37(74%)	

P value < 0.05 is of stastical significance.

Table 2. Maternal outcomes.

No.	Maternal outcomes	Oxytocin No. (50)	Misoprostol No. (50)	P. value	Mean Difference
1.	**Induction to delivery interval (hours)***	9.91±1.02	7.77±0.88	< 0.001	2.138
2.	**Mode of delivery**				
	Normal vaginal	41(82%)	44(88%)	0.4	
	Cesarean section	9(18%)	6(12%)		
3.	**Hyperstimulation rate**	1(2%)	1 (2%)		
4.	**Maternal satisfaction**				
	Yes	31(62%)	46(92%)	< 0.001	
	No	19(38%)	4(8%)		
5.	**Uterine rupture**	0	0		
6.	**Postpartum endometritis**	0	0		
7.	**Nausea**	1(2%)	2(4%)	1	
8.	**Vomiting**	0	1(2%)	1	
9.	**Fever & rigor**	0	0		

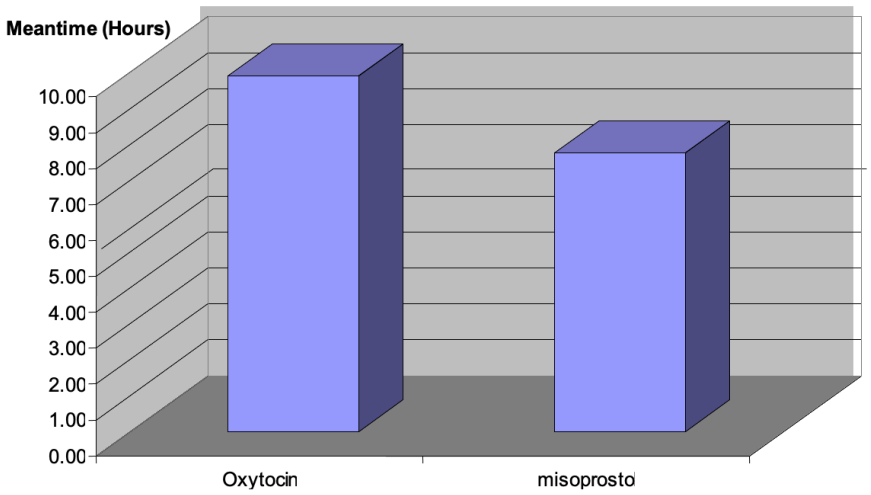

Figure 1. Meantime from induction to delivery in the study groups.

Table 3. Fetal Outcomes.

No.	Parameters	Oxytocin No. 50	Misoprostol NO.50	P-value
1.	**Fetal distress**	3 (6%)	2(4%)	0.6
2.	**APGAR<7**	3 (6%)	2(4%)	0.6
3.	**Admission to NCU**	2(4%)	1(2%)	0.3
4.	**Fetal weight***	3.326±0.328	3.406±0.332	0.22
5.	**Fetal sex**			
a.	**Male**	25(50%)	30(60%)	0.31
b.	**Female**	25(50%)	20(40%)	

Table 4. Indications for cesarean section

No.	Parameters	Oxytocin	Misoprostol	P-value
1.	**Failure of progress**	6 (66.7%)	4 (66.7%)	
2.	**Fetal Distress**	3(33.3%)	2 (33.3%)	1
	Meconium staining liquor	2(22.2%)	1(16.65%)	
	Fetal bradycardia	1(11.1%)	1(16.65%)	

DISCUSSION

Pre labor rupture of membranes at term is a relatively common obstetric event occurs in approximately 8-10% of pregnancies. Evidence support the idea that induction of labor, as opposed to expectant management decrease the risk of chorioamnionitis but there is no evidence that the mode of delivery is affected. Studies following the natural course of PROM at term found an increase perinatal mortality when latent period last longer than 24 hours and this increase in perinatal mortality rises markedly when the latent period last longer than 72 hours [1, 2].

This study is a comparative study between induction of labor with vaginal misoprostol at term in patients with PROM and induction with intravenous oxytocin. 50 patients were selected for induction with misoprostol and another 50 patients were selected for induction with oxytocin.

44 patients (88%) delivered by normal vaginal delivery and 6 (12%) by Cesarean section in misoprostol group, while 41 patients (82%) delivered by NVD and 9 patients (18%) by C/S in oxytocin group (p-value= 0.4) which is statistically insignificant. This result is comparable to the result of a study done by Hannah *et al*, who randomized 5041 women with PROM to induction with oxytocin, vaginal prostaglandin or expectant management, in which the difference in the rate of C/S between induction with Prostaglandin (9.6%) and induction with oxytocin (10.9%) was not statistically significant [12].

The result of this study is not comparable to the result of Nigerian multicenter study, Ezechi *et al* randomized 346 patients with PROM at term to induction with vaginal misoprostol & oxytocin (C/S was 18.6% in misoprostol and 41.3% in oxytocin group) which is statistically significant. This may be due to small sample size in our study or to difference in the guidelines in the hospitals, where the studies were performed [4].

About the interval from induction to vaginal delivery, in misoprostol group the interval was (7.77±0.88 hours) compared to (9.91±1.02 hours) in oxytocin group, (p-value <0.001) which is statistically significant and the mean difference was 2.138 hours. This result is near to the Nigerian multicenter study done by Ezechi *et al*, the time interval was 504±73.8 min. in misoprostol & 627±161.4 min. in oxytocin group (p value= 0.002).[4] The result in this study is also near to the result of study of both Sanchez-Ramos *et al*& Kramer *et al* where the time intervals were longer with oxytocin group [22, 23].

In this study the development of uterine hyperstimulation was similar in both groups (1 patient 2%), this result is similar to the meta analysis done by Lin *et al* in which the risk of uterine hyperstimulation & hypertonus were similar between oxytocin and misoprostol [20]. This result is also near to the study done by Ezechi *et al*, in which uterine hyperstimulation was 3% in misoprostol & 1.2% in oxytocin group (p-value =0.42)[4].

In this study there was no case of postpartum endometritis which is similar to the Nigerian study done by Ezechi *et al,* in which there was no case of puerperal sepsis [4].

In our study there was statistically insignificant difference between the two groups regarding side effects of the drugs like nausea, vomiting, and there was no case of uterine rupture, fever and rigor. This is near to the result of Sanchez-Ramos *et al* in which there was no difference in maternal adverse outcomes between both study groups [22].

About maternal satisfaction it was 92% for misoprostol group and 62% for oxytocin induction group with (p-value <0.001). This result is not comparable to a study done by Hannah *et al* in which there were no significant differences in women`s evaluation of treatment between the two induction groups [12].

About indications for Cesarean section, in 6 patients (66.7%), C/S was done because of failure of progress and in 3 patients (33.3%) because of fetal distress in oxytocin group, while misoprostol group, in 4 patients (66.7%) C/S was done because of failure of progress and in 2 patients (33.3%) because of fetal distress. This result is not comparable to the study done by Ezechi *et al,*in which C/S done for prolonged labor in 9(20%) in misoprostol group and 37 (52.1%) in oxytocin group, but C/S for fetal distress was 4 (12.9%) in misoprostol and 10(14.1%) in oxytocin group, this may be due to different guideline in the hospitals where the studies performed [4].

About the fetal out comes, fetal distress occurred in 3 cases (6%) with oxytocin & 2 cases (4%) with misoprostol group, (p-value= 0.6), which is near to the Nigerian study done by Ezechi *et al* with no significant difference in fetal distress rate (p value=0.42) [4].

APGAR <7 at 5 minute was statistically insignificant between the two groups (p-value 0.6), this result is

similar to a study done by Ozden S *et al*, in which there were no difference between the two groups with regard to 1 and 5 min. APGAR scores [19]. This is also similar to the result of Hannah *et al* with no difference in measures of neonatal morbidity.[12]

Admission to neonatal care unit in this study, was not significantly different between the two groups. This result is comparable to result of both Ozden S *et al* & Hannah *et al*.[12, 19].

In this study there were no significant difference between the two groups with regard to fetal weight and sex. This result is comparable with the result of most studies done by Ezechi *et al*, Hannah *et al*,Ozden S *et al*.[4, 12, 19].

In conclusion, in PROM at term, it is effective, safe, and economic to use misoprostol for induction of labour in patients with low Bishop scores, which is associated with shorter induction to delivery interval compared to oxytocin, and associated with higher maternal satisfaction. The fear of possible effect of liquor amnii on efficacy of misoprostol was not founded.

REFERENCES

1-Tekoaking CNM MPH clinical management of premature rupture of membranes. JNM.1994.39.2.

2- Myles Taylor and Stuart Rundle, Pre labour rupture of membranes, an evidence-based text for the MRCOG, Third edition,2016. 338-344;373-380.

3- Jane E. Norman and Sarah J. Stock. Induction and Augmentation of Labour. Dewhurst's text book of Obstetrics & Gynaecology, ninth edition,2018. 326-335.

4- Oliver C Ezechi M.B.B.S, Olabisi M Loto M.B.Ch.B, Paschal M Ezeobi M.B.B.S et al. Safety and efficacy of misoprostol in induction of labour in prelabour rupture of membrane in Nigerian women. IJRM. 2004, 117 : 449-452. 12.

5- American college of Obstet &gynec. Induction of labour. ACOG technical bulletin.Washington, D.C: ACOG, 1995.217

6- Harman JH,Kim A.Current trend in cervical ripening and labor induction. American family physician 1999;60 (2).

7- Grane J, St.John`s NF . Induction of labour at term. Monteral QC. SOGC Clinical practice guideline 200; 107.

8- Nooh A, Baghdadi S and Raouf S. Induction of labor; How close to the evidence-based guideline are we? O&GJ 2005; 25(5):451-454.

9- Takayanagi yet-al. Pervasive social deficits, but normal partutition, in oxytocin receptor-deficient mice. Proc Nath Acadsci USA.2005.102:16096-101

10- Ragunath M and McEwan AS. Induction of labor. Obstet. Gyn. Rep.M. 2008. 18(1); 1-6.

11- Laurence DR, Bennent PN, Brown MJ. Clinical pharmacology, Edinburgh, Churchill Livingstone, 8th edition. 1997 ;250.

12- Mary E Hannah-et al. Induction of labor compared with Expectant management for pre labor rupture of membranes at term. The new ENGLAND JOURNAL of medicine. 1996; 334(24):1615

13- Templeton A. Review of Labor Induction with Misoprostol: Route of Administration, Efficacy, Safety, and Potential Concerns In:Shannon CS, Winikoff B editors . Misoprostol. Population Council, 2004; 17-23.

14- Sak Oi S,Pak Ch .Prostaglandin for induction of second trimester trimination and intrauterine death .Best practice and research clinical Obstet. & Gyn. 2003;17 (5): 765-775 .

15- Al-Tikreeti R, Muhauder S, The Treatment of Incomplete and Missed Abortion with Oral Misoprostol (accepted for publication in Iraqi postgraduates) MJ 2005;4(4).

16-Motval. NJ. Cytotec (misoprostol) prescribing information. physicians desk references, 47th ed. Medical Economics Inc. 1993;2251-3.

17- Searle. Cytotec (misoprpstol) product information from the American Hospital formulary service. Skokie, IL; 1988 dec. 6.

18- PDR-Cytotec (misoprostol), package leaflet-Searle 2001. 1461.

19- Ozden S, Delikara MN,Avci A,Ficicio gluc. Intravaginal misoprostol vs. expectant management in premature rupture of membranes with low Bishop scores at term. IJ Gyn. & obstet.2002. 77. 115.

20- Lin, Monique G. MD; Nuthalapaty, Francis S. MD; Craver, Alissa R. et al.Misoprostol for labor induction in women with term premature rupture of membranes: A meta- analysis. Obstet. & gyn.2005. 106. 3. 593-601.

21- Wing DA. A benefit –risk assessment of misoprostol for ripening and labor induction. Drug safety 2002 ;25 (9): 665-676.

22- Sanchez-Ramos L; Chen AL; Kaunit ZAM et al Labour induction with intravaginal misoprostol in premature rupture of membranes: a randomized study. Obstet. Gyn.1997. 89:6, 909-12.

23- Kramer RL; Gilson GJ; Morrison DS et al. A randomized trial of misoprostol and oxytocin for induction of labour: safety and efficacy. Obstet. Gyn.1997.89:3. 387-91.