ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Effect of Vaginal Isosorbide Mononitrate versus Effect of Vaginal Dinoprostone on Cervical Ripening for Induction of Labor

Walid Abd-ELsalam[1], Youssef Abo-Elwan[1], Fatma Al-Zahraa Sherif[1], &Basem Hamed[1]
[1]Department of Obstetrics and Gynecology, Faculty of Medicine – Zagazig University, Alsharquia, Egypt.

ABSTRACT

Background: Labor induction has risen significantly over the last twenty years. Induction of labor is indicated for either maternal (preeclampsia, pregnancy-induced hypertension) or fetal (pregnancy induced hypertension, preeclampsia, and postdate pregnancy).

Aim of Work: The aim of the study to assess the best method in induction of labor either vaginal Isosorbide Mononitrate or vaginal Dinoprostone.

Patients and Methods: A randomized clinical trial was carried out on 44 full-term pregnant women who were admitted for induction of labor in Zagazig University Hospitals in the period of November 2020 to August 2021. Patients were divided into two groups: Group A included 22 full term pregnant females who received 20mg of intravaginal Isosorbide Mononitrate (Effox20mg, Minapharm). Group B included 22 full-term pregnant females who received 3mg of vaginal Dinoprostone (Dinoglandin E2, Rotabiogen) single dose.
Results: There was little difference between the effectiveness of 20mg of intravaginal Isosorbide Mononitrate and 3mg of vaginal Dinoprostone in induction of labor. The safety profiles of both drugs were similar, but isosorbide mononitrate administration is considered a low-risk method of labour induction for pregnant women at full term. **Conclusions:** This study demonstrated that it is safe to use IMN in induction of labor with less side effects than Dinoprostone as cause of failed induction with Dinoprostone was only due to uterine hyperstimulation that lead to sudden and sever fetal distress, while with IMN there were different causes including fetal distress or 2^{nd} ,3^{rd} degree meconium on AROM. Also, with Dinoprostone there was higher incidence of neonatal admission to NICU after birth than IMN that has no incidence of neonatal admission to NICU
Key words: Cervical ripening, Induction of Labor, Isosorbide, Mononitrate, Misoprostol

INTRODUCTION

Induction of labor (IOL) is the stimulation of uterine contractions during pregnancy before actual labor starts on its own to reach vaginal birth that might be recommended either for the sake of maternal health or for the sake of fetal health [1].

In order to determine if it is essential or not many factors should be taken in consideration such as post-term pregnancy, prelabor rupture of membranes, chorioamnionitis, fetal growth restriction, oligohydramnios, gestational diabetes, gestational hypertension or preeclampsia [2].

Assessment of the cervix and success rate of IOL, depend on some indicators such as; consistency of the cervix, dilatation, position, presentation of the fetal head and its station as known by Bishop score [3].

Several methods aid with IOL, Mechanical methods such as the insertion of a catheter through the cervix into the extra-amniotic space with balloon insufflation; were the initial methods developed to ripen the cervix and induce labor. During recent decades they have been replaced by pharmacological methods such as giving oral or vaginal misoprostol, vaginal dinoprostone, vaginal isosorbide mononitrate or intravenous oxytocin infusion [2].

Vaginal prostaglandin E2 (PGE2) is the indicated method of induction of labor in the absence of any contraindications. PGE2 may be given as a gel, tablet or controlled release pessary and all these preparations appear to have similar efficacies. Each 3 g gel (2.5 ml) contains 1 mg or 2 mg dinoprostone. The gel should be inserted high into the posterior fornix [4].

Side-effects to dinoprostone are rare. The commonest are vomiting, nausea, and diarrhea. Other rarer side-effects include uterine hyperstimulation, fetal distress, maternal hypertension, bronchospasm, backache, rash and amniotic fluid embolism [5].

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

During the recent years, Nitric oxide donors (NODs), like isosorbide mononitrate (IMN), has been studied as an agent for IOL with less side-effects. Also, NODs have a relative relaxant effect on the uterine myometrium. therefore, these are not expected to cause uterine hyperstimulation in contrast to prostaglandins [6].

Isosorbide Mononitrate causes increase in cyclo-oxygenase-2 which stimulates endogenous prostaglandin production in the cervix and also results in cervical ultrastructural reorganization that is the same as spontaneous onset of labor. Isosorbide mononitrate is an FDA approved category C drug; it is cost effective and easily available in the market [7].

Subjects and Methods

Technical design:

An Interventional study, which was performed at Obstetrics and Gynecology Department-Zagazig University Hospitals and Hehya Central Hospital.

Sample size:

Assuming thatmean±SD of time from start of induction to delivery in Dinoprostone group versus Isosorbide Mononitrate group was: 24.2 ±11 Vs 15.5 ±9.16. The sample was calculated to be 44 cases subdivided into (22 in each group) using open Epi with power of test 80% and Confidence Interval 95%.

Inclusion criteria:

Post-date nulliparous or multiparous (> 40 weeks), Singleton viable fetus, cephalic presentation, Patients with Gestational HTN or Preclampsia, Obstetrical indication for labor induction Bishop score <6, and Parity ≤3.

Exclusion criteria:

Parity ≥4, Bishop score >6, Multiple pregnancies, Malpresentation, Patients with previous uterine scar or cesarean section, Contracted pelvis, and Patient refuses induction of labor.

Operational design:

All patients in this study were admitted to the department of obstetrics and gynecology for induction of labor where;

***Detailed complete history including*:**

Full personal history: name, age, occupation, relationship status, special habits, socioeconomic status.

Present history: throughout to exclude any medical or surgical disorder.

obstetric history:

Gravidity and parity, History of previous abortions, dates of deliveries, gestational age which be calculated according to Naegle's rule (a standard way of calculating the due date for a pregnancy when assuming that a gestational age of 280 days at childbirth). The rule estimates the expected date for delivery (EDD) by adding a year, subtracting three months and adding seven days. an obstetric ultrasound was done to confirm gestational age, amniotic fluid, site of the placenta.

Past history:

Medical (diabetes mellitus (DM), hypertension (HTN), deep venous thrombosis (DVT), hypothyroidism or hyperthyroidism), Surgical (history of previous operations), History of drug taking, Previous blood transfusion, and Previous allergy to any drug.

Family history:

Medical disorders (DM & HTN), Congenital fetal malformations, Twins, and Consanguinity.

General examination including:

▪Height, weight, basal metabolic rate (BMI), Vital signs (blood pressure, pulse rate, body temperature and respiratory rate), Colors (jaundice,cyanosis, pallor) and Others (lower limb edema, back).

Abdominal examination:

Inspection:

Contour and size of the abdomen, Fetal movement detection if visible, Localized pulges or grooves, scars, site of the umbilicus,pigmentations, dilated veins, and previous laparotomy scar.

Palpation:

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

eopald'smanoeuver(obstetric palpation):
Fundal level:
Is detected by the ulnar border of the left hand starting from the xiphisternum downwards after centeralization of the uterus.
Fundal grip:
By the palms of both hands, breech was felt as large, soft, irregular, doesn't ballot and continuous with the back.
Umbilical (lateral) grip:
By the palms of the both hands placed on both sides of the umbilicus for detected lie, back, or limbs, amount of liquor.
First pelvic grip:
The right hand is used to grasp the presenting part (head) while the left hand is applying gentle downward pressure at the fundus to steady the fetus. The presenting part cannot be well grasped it it is engaged.
Second pelvic grip:
By the 2 hands are placed in the iliac fossae to confirm finding of first pelvic grip and detect degree of descent.
Auscultation:
The fetal heart sound (FHS) was heard in cephalic presentation below the level of the umbilicus as a tic-tac rhythm.
Local Vaginal examination including: (cervical dilatation, effacement, station, presentation, pelvic adequacy and state of the membranes).
An admission cardiotocography (CTG) was performed to ensure that the fetal heart activity is normal.
If the patient fulfilled the inclusion criteria, she was included in the study.
An informed written consent was obtained from each patient.
Randomization: The patients were randomly assigned in the study using computer generated random number tables. "odd number" for 1st group and "even number" for 2nd group.

1st group (A) (vaginal Isosorbide Mononitrate group):All patients in this group received 20mg of intravaginal Isosorbide Mononitrate (Effox20mg, Minapharm) 6-8 hours apart up to maximum 4 doses or till Bishop score >6 with close monitoring to progression of labor.

2nd group (B) (vaginal Dinoprostone group):All patients in this group received 3mg of vaginal Dinoprostone (Dinoglandin E2,Rotabiogen) single dose with close monitoring to progression of labor.

Augmentation was done in both groups either by artificial rupture of membranes or oxytocin drip.All patients were observed in the labor ward by (WHO PARTOGRAPH) during the first and second stage of labor, closely observed with fetal monitoring through intermittent fetal auscultation by sonicaid or continuous CTG if needed, pulse rate, blood pressure, temperature , antepartum hge , induction of labor time , success rate , failure of induction, incidence of complications including; fetal distress or rupture uterus.

Outcomes:Primary outcomes:Cervical ripening, Change in the Bishop score, Induction to delivery time interval, and No. of vaginal deliveries.Secondary outcomes**:**Neonatal APGAR SCORE at 1 and 5 mins, Rate of admission to NICU, Maternal side effects as: hypotension, headache, PPH and gastrointestinal symptoms.

RESULTS

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute frequencies and were compared using chi square test, monte carlo test and Fisher exact test when appropriate. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests. Independent sample t test was used to compare means when data was normally distributed and Mann Whitney test was used when data is not normally distributed. The level statistical significance was set at $P<0.05$. $p\leq0.001$ was considered as statistically highly significantat $P<0.05$. $p\leq0.001$ was considered as statistically highly significant

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Table (1) Comparison between the studied groups regarding demographic data:

Parameters	**Groups**		**Test**	
	Isosorbide mononitrate group N=22 (%)	**Dinoprostone group** N=22 (%)	t	p
Age (year):				
•Mean ± SD	26.591 ± 2.557	26.091 ± 4.76	0.434	0.667
•Range	21 – 30	19 – 37		

t independent sample t test

Table (1) demonstrated thatthere is statistically non-significant difference between the studied groups regarding age.

Table (2) Comparison between the studied groups regarding presenting symptoms and signs:

Parameters	**Groups**		**Test**	
	Isosorbide mononitrate group N=22 (%)	**Dinoprostone group N=22 (%)**	χ^2	p
Symptoms:				
•Postdate	7 (31.8)	15 (68.2)		
•Eclampsia	0 (0)	1 (4.5)		
•Oligohydramnios	8 (36.4)	2 (9.1)	MC	0.052
•PIH	3 (13.6)	1 (4.5)		
•ROM	4 (18.2)	3 (13.6)		

MC Monte Carlo test *p<0.05 is statistically significant

Table (2) showed that there is statistically non-significant difference between the studied groups regrading presenting symptoms. About 69% of those within Dinoprostone group versus 31.8% within IMN group had no symptoms on admission.

Table (3) Comparison between the studied groups regarding obstetric history:

Parameters	**Groups**		**Test**	
	Isosorbide mononitrate group N=22 (%)	**Dinoprostone group** N=22 (%)	Z	p
Gravidity:				
Median	2	2	-1.503	0.13
Range	1 – 4	1 – 4		
Primigravida	8 (36.4)	6 (27.3)	0.419	0.517
Parity:				
Median	0.5	1	-1.518	0.129
Range	0 – 3	0 – 3		
Abortion:				
Median	0	0	-0.081	0.936
Range	0 – 1	0 – 2		

Z Mann Whitney test

Table (3) demonstrated that there is statistically non-significant difference between the studied groups regarding gravidity, parity or abortion.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Table (4) Comparison between the studied groups regarding vital signs:

Parameters	Groups		Test	
	Isosorbide mononitrate group N=22 (%)	Dinoprostone group N=22 (%)	t	p
•SBP (mmHg)				
Mean ± SD	114.09 ± 11.41	111.36 ± 11.25	0.798	0.429
Range	100 – 140	100 – 160		
•DBP (mmHg)				
Mean ± SD	71.82 ± 10.97	69.09 ± 8.11	0.938	0.354
Range	60 – 100	60 – 100		
•HR (beat/min)				
Mean ± SD	82.59 ± 4.24	80.77 ± 2.51	1.732	0.091
Range	70 – 92	80 – 89		

t independent sample t test

Table (4) displayed that there is statistically non-significant difference between the studied groups regarding heart rate, systolic or diastolic blood pressure.

Table (5) Comparison between the studied groups regarding obstetric investigations:

Parameters	Groups		Test	
	Isosorbide mononitrate group N=22 (%)	Dinoprostone group N=22 (%)	χ^2	p
•Ultrasound:				
Normal	14 (63.6)	20 (90.9)	Fisher	0.069
Oligohydramnios	8 (36.4)	2 (9.1)		
•Admission CTG:				
Reactive	22 (100)	22 (100)	Fisher	>0.999

χ^2 Chi square test

Table (5) clarified that there is statistically non-significant difference between the studied groups regarding result of obstetric ultrasound. CTG was reactive among patients within both groups.

Table (6) Comparison between the studied groups regarding result of first local examination:

Parameters	Groups		Test	
	Isosorbide mononitrate group N=22 (%)	Dinoprostone group N=22 (%)	t/ χ^2	p
Effacement				
Mean ± SD	45.0 ± 14.14	38.24 ± 9.51	1.602	0.121
Range	20 – 60	30 – 60		
Cervix dilatation				
•Closed cervix	2 (9.1)	5 (22.7)	0.001	0.973
•Multiparous cervix	12 (54.5)	11 (50)		
•Dilated <3 cm	8 (36.4)	6 (27.3)		
Head station:	N=22	N=22		
•-2	2 (9.1)	7 (31.8)	3.475	0.062
•-1	14 (63.6)	12 (54.5)		
•Zero	6 (27.3)	3 (13.6)		

t independent sample t test *p<0.05 is statistically significant χ^2 chi square test

Table (6) showed that there is statistically non-significant difference between the studied groups regarding result of initial cervical examination in the form of effacement, cervical dilatation or head position.

Table (7) Comparison between the studied groups regarding time needed for progress of labor:

Time (hour)	Groups	Test

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

	Isosorbide mononitrate group N=22 (%)	Dinoprostone group N=22 (%)	t	p
•Time for induction to augmentation (hr)				
Mean ± SD	3.85 ± 1.55	4.0 ± 1.72	-0.29	0.773
Range	2 – 7.5	1.5 – 8		
•Induction to delivery interval (hr)				
Mean ± SD	6.66 ± 2.37	6.5 ± 2.26	0.228	0.821
Range	1.5 – 10	3 – 12		

t independent sample t test

Table (7) demonstrated that there is statistically non-significant difference between the studied groups regarding duration between first dose till augmented dose, progression in Bishop score or time from induction till delivery

Table (8) Comparison between the studied groups regarding mode of delivery:

Parameters	Groups Isosorbide mononitrate group N=22 (%)	Dinoprostone group N=22 (%)
Mode:		
•Vaginal delivery	16 (72.7)	18 (81.8)
•CS		
	6 (27.3)	**4 (18.2)**
p	0.721	
•CS due to fetal distress	2 (50)	4 (100)
•CS on pt request		
•CS due to 2nd – 3rd degree meconium after AROM	1 (0)	0 (25)
	3 (50)	0 (25)

Table (8) clarified that there is non-significant difference between the studied groups regarding outcome

Table (9) Comparison between the studied groups regarding NICU admission:

Parameters	Groups Isosorbide mononitrate group N=22 (%)	Dinoprostone group N=22 (%)	Test χ^2	p
NICU:				
No	22 (100)	20 (90.9)	Fisher	0.488
Yes	0 (0)	2 (9.1)		

χ^2 Chi square test

Table (9) demonstrated that there is statistically non-significant difference between the studied groups regarding need for NICU admission.

Table (10) Comparison between the studied groups regarding outcome of induction:

Parameters	Groups Isosorbide Mononitrate group N=22 (%)	Dinoprostone group N=22 (%)	Test χ^2	p
Outcome:				
•Success	16 (72.7)	18 (81.8)	Fisher	0.721
•Failure	**6 (27.3)**	**4 (18.2)**		

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Cause of failure:		
•Uterine hyperstimulation	0 (0)	4 (100)
•Meconium on AROM		
•Fetal distress without hyperstimulation	3 (50)	0 (0)
•Patient request	2 (33.3)	0 (0)
	1 (16.7)	0 (0)

χ^2 Chi square test

Table (10) showed that there is statistically non-significant difference between the studied groups regarding outcome. Six patients within IMN group versus four within Dinoprostone group showed failure of induction.

DISCUSSION

IOL means is the stimulation of uterine contractions during pregnancy before labor begins on its own to achieve a vaginal birth that might be recommended either for the sake of maternal health or for the sake of fetal health [1].IOL rates recently increased using various methods either mechanical methods or pharmacological methods.

In this study, comparison was held between two recent pharmacological methods: IMN &Dinoprostone. Comparison between the effect of IMN and Dinoprostone on cervical ripening for IOL, 44 subjects were included in this study sub divided into 2 equal groups; 22 subjects in each group as the following: 1st group (A) (vaginal Isosorbide Mononitrate group):All subjects in this group received 20mg of intravaginal Isosorbide Mononitrate (Effox20mg, Minapharm) 6-8 hours apart up to maximum 4 doses or till Bishop score >6 with close monitoring to progression of labor.

2nd group (B) (vaginal Dinoprostone group):All subjects in this group received 3mg of vaginal Dinoprostone (Dinoglandin E2, Rotabiogen) single dose with close monitoring to progression of labor.In this study; there was statistically non-significant difference between bothgroups regarding demographic data (age) of the studied subjects.No significance difference also regarding obstetric history including:Gravidity, parity and number of abortions using Z Mann Whitney test.

Also, no significance difference regarding vital signs including systolic and diastolic blood pressure and heart rate.In the current study; the mean duration from time of start of induction till the time augmentation was started in 1st group 3.85±1.55 and 2nd group 4.0±1.72 with P value 0.773. while the mean of induction to delivery interval was 6.66 ± 2.37 in 1st group & 6.5 ± 2.26 in 2nd group.

Another study was held in Mashhad, Iran regarding IMN the mean of induction to delivery time was 18.60±2.75, that differs from the current study that it is longer [8], in another study held in new Delhi, India; the mean duration was 9.7±5.28, that is close to our results. [9].

While in [10] in contrast to this study, The mean change in modified Bishop score from recruitment to hospital admission was significantly greater in the IMN group as compared with the placebo group [mean difference of 0.65 (95% CI 0.14, 1.17, P = 0.013).

The same results in another study held in university of Aachen, Germany regarding Dinoprostone; confirmed that controlled-release dinoprostone was associated with a significantly high rate of cervical ripening (OR 3.99 ,95% CI 2.71–5.86; P-0.0001) [11].

Regarding mode of delivery; in this study in 1st group 72% of the subjects had vaginal deliveries while 28% underwent CS, in 2nd group 81% of the subjects had vaginal deliveries while 19% underwent CS for different causes.

Results close to the current study,[10], IMN was administrated to 177 subjects in which 64% had vaginal deliveries, while 36% had CS, but in ***(Lotfalizade et al.,[8])***. 80% of the subjects had vaginal deliveries, while only 20% had CS, which completely agrees with our study.

In a systematic review and meta-analysis held in China, A total of 95 studies (n = 16 311 women) contributed to the analysis of cesarean section: 4841 (29.7%) were assigned to vaginal dinoprostone[12], and that was a little bit higher than our results.

In contrast to our study, in an older study, the incidence of CS, failed induction of labor, and inadequate cervical ripening in subjects undergoing IOL was 55% [13].***(Y.Daykan et al., [14])*** , stated

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

that 12% of the subjects receiving dinoprostone whether nullipara or multipara failed vaginal delivery and had CS.

In our study, causes of failed induction was different in each group, in 1st group: IMN group (3=50%) recorded cases had CS due to 3rd degree meconium on artificial rupture of amniotic membranes (AROM), while (2=33%) recorded cases due to fetal distress recorded while close monitoring of the fetus using sonicaid or CTG, only (1=17%) recorded case had CS due to refusal to continue trial.

While in 2nd group: Dinoprostone group the (4=100%) recorded cases had uterine hyperstimulation accompanied with non-reassuring fetal heart rate and CTG.

The same near results as in ***(Mohamed and Indra, [15])***, only (4=5%) recorded case had CS due to fetal distress after IOL with IMN. While in contrast, the most common indications for cesarean section in a study held in India was acute fetal distress (77.7%) [16].

Data on safety from more than one trial were amalgamated in a meta-analysis by [17]. Rates of uterine hypertonus with FHR changes were similar in controlled-release dinoprostone to rates with other prostaglandin E2 products (OR 1.19, CI 0.58–2.54) [11].

The same results were concluded in a systemic review and meta-analysis study showed that out of number of subjects receiving Dinoprostone (13) subjects had uterine hyperstimulation with non-reassuring changes in FHR [18].

In this current study there was non-significant difference between the two study groups regarding fetal out come and neonatal NICU admission as in 1st group there was no neonatal NICU admission after delivery whether vaginal or CS and only (2=9%) neonates were admitted to NICU after delivery regardless mode of delivery.

The same results as in ***(Mohamed and Indra, [15])***, assessment of the newborn have not shown any adverse effects of vaginal IMN treatment or needed NICU admission.

In contrast, the mean percentage of neonatal admission to NICU was 10.2% [10].***(David et al., [13])***, stated the same results as in our study as 6.3% needed NICU admission and also mean of 13 days at NICU before discharge.

CONCLUSION

This study demonstrated that it is safe to use IMN in induction of labor with less side effects than Dinoprostone as cause of failed induction with Dinoprostone was only due to uterine hyperstimulation that lead to sudden and sever fetal distress, while with IMN there were different causes including fetal distress or 2nd ,3rd degree meconium on AROM. Also, with Dinoprostone there was higher incidence of neonatal admission to NICU after birth than IMN that has no incidence of neonatal admission to NICU.

Funding: No funding was received for this study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

References:

1. **Acuña-IzcarayAgustín, Sánchez-AngaritaEfraín, Plaza Vicente, Rodrigo Gustavo, de Oca Maria Montes, GichIgnasi**: Quality assessment of asthma clinical practice guidelines: a systematic appraisal. Chest 2013;144 (2):390–7.
2. **Foureur M, Ryan CL, Nicholl M, Homer C:** Inconsistent evidence: analysis of six national guidelines for vaginal birth after cesarean section. Birth 2010: (37) 1 : 3-10.
3. **Ekerhovd E, Bullarbo M, Andersch B and Norstrom A:** vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening at term: a randomized controlled study. AM J. OBSTET. GYNECOL. (2003) 189 :1692-7.
4. **Macones GA, Hankins GD, Spong CY, Hauth J, Moore T:** The 2008 National Institute of Child Health and Human Development work shop Report on Electronic Fetal Monitoring: J ObstetGynecol Neonate Nurs2008 ; 37 :510-5.
5. **GЄulmezoglu AM, Crowther CA, Middleton P**. Induction of labor for improving birth outcomes for women at or beyond term. Cochrane Database Syst Rev 2006.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

6. **KellyAJ, Munson C, Minden L**. Nitric oxide donors for cervical ripening and induction of labor. Cochrane Database Syst Rev2011;(6):Cd006901. doi: 10.1002/14651858.CD006901.pub2. [PubMed: 21678363].
7. **Bullarbo M, Orrskog ME, Andersch B, Granstrom L, Norstrom A, Ekerhovd E:** outpatient vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening and induction of laborpostterm a randomized controlled study AM J ObstetGynecol 2007 : 196 (1) 500 – 5
8. **Lotfalizade, M., KhademGhaebi, N., GolhasaniKeshtan, F., TaghipourBazargani**, V. (2018). Comparison of Isosorbide Mononitrate Versus Misoprostol in Cervical Ripening at Term Before Induction of Labor: A Clinical Trial. *Women's Health Bulletin*, 5(3), 1-6. doi: 10.5812/whb.12248
9. **Kavita Agarwal,Aruna Batra, Achla Batra, Anjali Dabral, Abha Aggarwal 2012:** Evaluation of isosorbide mononitrate for cervical ripening prior to induction of labor for post-dated pregnancy in an outpatient setting.
10. **Bollapragada S, MacKenzie F, Norrie J, Eddama O, Petrou S, Reid M, Norman J:** Randomised placebo-controlled trial of outpatient (at home) cervical ripening with isosorbide mononitrate (IMN) prior to induction of labour – clinical trial with analyses of efficacy and acceptability. TheIMOP Study. BJOG 2009; 116:1185–1195.
11. **Werner Rath2005:**A clinical evaluation of controlled-release dinoprostone for cervical ripening – a review of current evidence in hospital and outpatient settings.
12. **Chen W, Xue J, Peprah MK, Wen SW, Walker M, Gao Y, Tang Y:** A systematic review and network meta-analysis comparing the use of Foley catheters, misoprostol, and dinoprostone for cervical ripening in the induction of labour. BJOG 2016;123:346–354
13. **David Buser, Gerardo Mora, and Fernando Arias:** A Randomized Comparison Between Misoprostol and Dinoprostone for Cervical Ripening and Labor Induction in Patients withUnfavorable Cervices 1997.
14. **YairDaykan, Tal Biron-Shental, Daniella Navve, Netanella Miller, Mor Bustan and Rivka Sukenik-Halevy:** Prediction of the efficacy of dinoprostone slow releasevaginal insert (Propess) for cervical ripening: A prospective cohort study J. Obstet. Gynaecol. Res. Vol. 44, No. 9: 1739–1746, September 2018
15. **Mohamed Furukan Mohamed Rameez and Indra Malik Rodrigo Goonewardene:** Nitric oxide donor isosorbide mononitrate for pre-induction cervical ripening at 41 weeks' gestation: A randomized controlled trial. *J. Obstet. Gynaecol. Res. Vol. 33, No. 4: 452–456, August 2007*
16. **Kriti Singh, Sujata Deo, S P Jaiswar, Rashmi Singh, Sushma Sinha:** Intravaginal Isosorbide Mononitrate and Misoprostol Versus Misoprostol Alone For Induction Of Labour 2020
17. **Karen Hughes, Mark A Bellis, Katherine A Hardcastle, Dinesh Sethi, Alexander Butchart, Christopher Mikton, Lisa Jones, Michael P Dunne:**The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis, The Lancet Public Health, Volume 2, Issue 8 (2017), Pages e356-e366.
18. **Lixia Zhu, Cong Zhang, Fang Cao, Qin Liu, Xing Gu, Jianhao Xu, Jianqing Li:** Intracervical Foley catheter balloon versus dinoprostone insert for induction cervical ripening A systematic review and meta-analysis of randomized controlled trials (2018) 97:48.