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RESEARCH ARTICLE

MISOPROSTOL INDUCTION OF LABOR IN MULTIPARA PREGNANT WOMEN: A MINI-SURVEY FOR PREDICTORS OF OUTCOME.

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Abstract

Objectives: To evaluate dose-related outcome of induction of labor (IOL) using misoprostol vaginal inserts (MVI) in multipara pregnant women so as to determine the appropriate dose for getting trial success defined as having vaginal delivery (VD) within 24-hr induction-to-delivery (ITD) interval.

Patients & Methods: 644 pregnant women underwent clinical evaluation and vaginal examination to determine Bishop score using the Simplified Bishop Score (SBS). All women received 25 µg MVI only once and were monitored for labor progress as judged by SBS and uterine contractions with fetal heart monitoring. In absence of fetal distress manifestations and membranes were still intact, but uterine contractions occurred <3 times/10 minutes, another MVI was used for a maximum of 6 doses. Uterine contraction augmentation was provided as amniotomy or/and oxytocin infusion started 4-hrs after the last MVI was placed. Study outcomes included trail success rate, number of MVI used, frequency and mode of augmentation and delivery assistance.

Results: 530 women (82.3%) had VD; 159 women without augmentation, 182 women had amniotomy, 105 women received oxytocin drip and 84 women required both. Only 168 women (26.1%) had instrumentally-assisted VD. Mean ITD interval was 10.9±6.3 hr; 492 women had ITD interval <24 hr for a trial success rate of 76.4%. Cesarean section was indicted in 114 women (17.7%). Only 29 women received four, 71 three, 93 two, while 451 women received one MVI, VD rate was significantly ($p<0.00001$) lower among women received higher number of MVI. Statistical analyses defined high MVI dose and BMI as negative, while high parity is a positive significant predictor for trial success. High MVI dose and BMI are positive, while high SBS and high parity are negative significant predictors for long ITD interval. Kaplan-Meier regression analysis defined the appropriate MVI for IOL trial success at a mean dose of 1.5±0.039 (95% CI: 1.4-1.55).

Conclusion: MVI is a satisfactory modality for IOL trial in multipara pregnant women with VD rate of 82.3% and ITD interval of <24-hr in 76.4%. Lower BMI and higher number of previous VD indicate higher possibility of trial success. SBS is appropriate for women selection for trial and follow-up and can predict outcome if combined with BMI, parity and number of MVI used.

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Introduction:-

Spontaneous vaginal birth rates are decreasing worldwide, while cesarean delivery, instrumental births, and medical birth interventions are increasing [1]. Induction of labor (IOL) is a medical procedure used to initiate uterine contractions to achieve delivery [2]. Rates of IOL have increased considerably in the United States as well as around the world and have accounted for >20% of pregnancies [3].

Multiple benefits for IOL allowed for its growing up application, where **Zizzo et al.** [4] detected a decline in stillbirths and perinatal mortality rates with IOL for post-date pregnancies and the risk of interventions as cesarean section (CS) and vacuum extraction (VE) remained stable despite an increase in IOL rate. Also, **Knight et al.** [5] documented that routine use of IOL at 40-wks of gestation instead of 41-42 wks in nulliparous women aged ≥35 years reduced perinatal mortality rates. Moreover, **Gibbs et al.** [6] found elective IOL after 39 weeks of gestation was associated with reduced maternal and neonatal morbidity among obese women.

Methods for IOL may be mechanical, pharmacological or combination of both methods [7]. However, combined mechanical and pharmacological IOL showed no benefit over either method used alone, but may worsen outcome [8]. **Boyon et al.** [9] found double-balloon was as efficient as vaginal prostaglandins.

Misoprostol, a synthetic prostaglandin E1 analog has the ability to mimic the changes of spontaneous labor and has been used as IOL agent [10]. Misoprostol was available as oral, sublingual and vaginal tablets; thirty-seven trials found no statistically significant difference in the primary outcomes between IOL using oral and vaginal misoprostol [11], however, data concerning outcome of sublingual route are limited [12].

Dosing regimen of misoprostol for IOL still represents a challenge; **Zangeneh et al.** [13] found combined use of misoprostol with oxytocin gave similar results to the use of multiple doses of misoprostol for 2nd trimester termination of pregnancy. However, for IOL misoprostol dose-adjustment was not fully evaluated, thus the current study targets to evaluate dose-related outcome of IOL in multipara women so as to determine the appropriate dose for getting trial success defined as having vaginal delivery (VD) within 24-hr induction-to-delivery (ITD) interval.

Design:-
Mini-survey clinical study

Setting:-
Benha University Hospital

Patients & Methods:-

The study protocol was approved by the Local Ethical Committee and included women signed written fully informed consent for study participation and taking prescribed medications. Multipara women at the end of the 3rd trimester, having singleton fetus with vertex presentation and intact membrane were included in the study. All women underwent demographic data collection, history taking including medical and surgical history, obstetric and gynecologic history and prenatal history; then all women had clinical examination. Vaginal examination and Bishop score was determined using the Simplified Bishop Score (SBS) using only dilation, effacement and station (Table 1) as evaluating signs and a SBS of ≥5 indicates that cervix is ripe or favorable for induction and good chances of having VD [14].

Table 1:-The Simplified Bishop Score [14]

Cervical status	Points			
	0	1	2	3
Dilatation (cm)	Closed	1-2 cm	3-4 cm	5-6 cm
Effacement (%)	0-30	40-50	60-70	80%
Station	-3	-2	-1, 0	+1, +2

Exclusion criteria included presence of systemic diseases inducing postdate, multiple pregnancy, previous CS, fetal congenital anomalies, presence of indications for CS concerning fetal position, presentation or maternal liability to complications on IOL, systemic contraindication for prostaglandin therapy. On examination, women with SBS of

<5, premature rupture of membrane, or developed ruptured membrane on arrival to hospital were excluded from the study.

All women had IOL using 25 µg misoprostol vaginal inserts (Vagiprost, Adwia Pharmaceuticals Co., Heliopolis Area, Cairo, Egypt) only once and were monitored for labor progress that was assessed hourly for uterine contractions and fetal heart monitoring half-hourly. In absence of fetal distress manifestations and membranes were still intact, but uterine contractions occurred <3 times/10 minutes, vaginal examination was performed to determine the SBS and accordingly another dosage of misoprostol was used for a maximum of 6 doses. On the start of the active phase of labor, which is defined according to the WHO's definition as dilated cervix to 4 cm with regular contractions [15], fetal surveillance was monitored by CTG and uterine contraction augmentation in the form of oxytocin infusion, or/and amniotomy was started at least 4-hrs after the last MVI was placed. According to recommendations of Royal Collage of Obstetricians and Gynecologists [16], amniotomy was started before oxytocin augmentation (strong recommendation), but augmentation with oxytocin is recommended in women with slow progress due to insufficient contractions. Oxytocin infusion was started by 2 mU/min and increased by 2 mU every 20 minutes until regular uterine contractions occurred.

Study outcomes;-

Primary outcomes:-

1. Trail success rate: success was defined as having VD within 24-hr induction-to-delivery (ITD) interval.
2. Number of MVI used, frequency and mode of augmentation and delivery assistance.
3. Trial failure rate: failure was defined as trial canceling and shifting to CS, irrespective of timing of decision or cause.

Secondary outcomes included the frequencies of meconium-stained amniotic fluid on amniotomy, fetal distress necessitating canceling of trial and development of uterine hyperstimulation that was defined as the occurrence of excessive uterine activity of >5 contractions/10 min associated with a non-reassuring fetal heart rate [17].

Statistical analysis:-

Obtained data were presented as mean±SD, numbers and percentages. Results were analyzed using Chi-square test (X^2 test). Possible relationships were investigated using Spearman's linear regression. Sensitivity & specificity of estimated parameters as predictors were evaluated using the receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC) compared versus the null hypothesis that AUC=0.05. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015) for Windows statistical package. P value <0.05 was considered statistically significant.

Results:-

The study included 762 pregnant multipara women, 118 were excluded and 644 women were included in the study. Patients' enrolment data were shown in table 1.

Table 1:-Enrolment data of studied women

Data		Findings
Age (years)		27.7±2.4
BMI data	Weight (kg)	84.2±5.8
	Height (cm)	163±2.8
	BMI (kg/m^2)	31.7±2
Obstetric history	Gravidity	2.7±0.7
	Parity	1.5±0.6
Simplified Bishop score		6±0.6

Data were shown as mean±SD

During the observation period, after varying number doses of MVI; 530 women (82.3%) had VD, while 114 women (17.7) had CS. Out of women had VD, 159 women (24.7%) required no augmentation, while 371 women (57.6%) required augmentation; 182 women (28.3%) had amniotomy, 105 women (19.8%) received oxytocin drip and 84 women (15.9%) required both amniotomy and oxytocin drip to have VD. Only 168 women (26.1%) had instrumentally-assisted VD. Thirty-eight women had VD after ≥24 hr, while 492 women had induction-to-delivery (ITD) interval <24 hr for a trial success rate of 76.4%. Mean ITD interval was 10.9±6.3; range: 2-33 hr. Meconium-

stained amniotic fluid was detected on amniotomy in 26 women (4%). Indications for CS were no progress of labor despite of repeated doses of misoprostol and augmentation by oxytocin infusion in 49 women showed, fetal distress manifestations in 38 women, ruptured membranes without progress of labor in 17 women and uterine hyperstimulation in 10 women (Table 2, Fig. 1).

Table 2:-Outcome data

Data				Findings
Vaginal delivery	Augmentation	No		159 (24.7%)
		Yes	Amniotomy only	182 (28.3%)
			Oxytocin drip only	105 (16.3%)
			Both amniotomy & oxytocin drip	84 (13%)
			Total	371 (57.6%)
	Instrumentation	No		362 (56.2%)
		Yes		168 (26.1%)
	Initiation of IOL-delivery interval (hr)	<24	Frequency	492 (92.8%)
			Duration	9.6±4.6 (2-21)
		≥24	Frequency	38 (7.2%)
			Duration	27±2.2 (24-33)
		Total		10.9±6.3 (2-33)
	Meconium stained liquor			26 (4%)
Operative delivery	Indications	No progress		49 (7.6%)
		Fetal distress		38 (5.9%)
		Ruptured membrane		17 (2.6%)
		Uterine hyperstimulation		10 (1.6%)
	Total			114 (17.7%)

Data were presented as number with percentages were in parenthesis

Among women had SVD (n=362), 293 women (80.9%) gave birth after receiving only one MVI, 42 women (11.6%) received two MVI, 21 women (5.8%) received three MVI and 7 women (1.9%) responded to the fourth MVI with significantly ($p<0.00001$) lower frequency of SVD among women received higher number of MVI (Fig. 1). On contrary, among women had CS (n=114), 60 had received single MVI (52.6%), 22 women had received two MVI (23.7%), 19 women had received MVI (16.7%) and 13 women (11.4%) had received four MVI with significantly ($p=0.000027$) higher frequency of CS among women received higher number of MVI (Table 3).

Table 3:-Patients' distribution according to received doses misoprostol and mode of delivery

Mode of delivery Number of doses	Spontaneous vaginal delivery (n=362)	Assisted vaginal delivery (n=168)	Operative delivery (n=114)
One-dose (n=451)	293 (65%)	98 (21.7%)	60 (13.3%)
Two-doses (n=93)	42 (45.1%)	29 (31.2%)	22 (23.7%)
Three-doses (n=71)	21 (29.6%)	31 (43.7%)	19 (26.7%)
Fourth-doses (n=29)	6 (20.7%)	10 (34.5%)	13 (44.8%)
P value	<0.00001	0.00044	=0.000027

Data were presented as number with percentages were in parenthesis

The possibility of getting VD showed positive significant correlation with multiplicity of MVI, but negatively correlated with BMI and SBS, and ITD interval showed positive significant correlation with multiplicity of MVI and BMI, while showed negative significant correlation with number of previous VD and SBS. On contrary, the possibility for failure of IOL showed positive significant correlation with BMI and negative significant correlation with multiplicity of MVI and previous VD (Table 4).

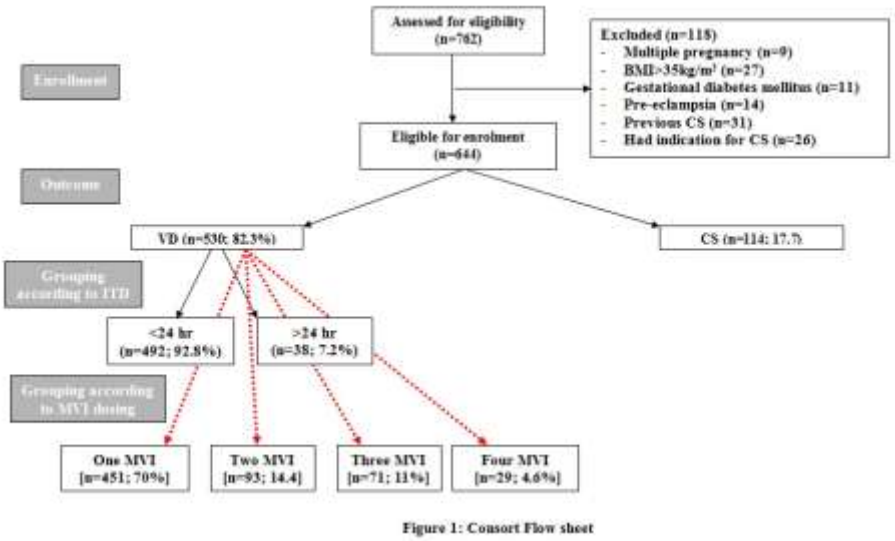

Figure 1: Consort Flow sheet

Table 4:-Correlation between Patients' data and mode of delivery, ITD interval

Variable / Parameter	VD		ITD		CS	
	Rho	p	Rho	p	Rho	p
Misoprostol dose	0.208	<0.001	0.477	<0.001	-0.294	<0.001
Age	0.103	>0.05	0.049	>0.05	-0.064	>0.05
BMI	-0.164	<0.001	0.252	<0.001	0.088	0.026
Parity	-0.068	>0.05	-0.163	<0.001	0.110	0.005
SBS	-0.109	0.006	-0.204	<0.001	0.058	>0.05

VD: Vaginal delivery; ITD: Induction-to-delivery; CS: Cesarean section; Rho: Spearman correlation coefficient; BMI: Body mass index; SBS: Simplified Bishop Score

Verification of parameters correlated with outcome to define predictors for outcome of IOL trial using Regression analysis defined need for high MVI dose and high BMI as negative significant predictors for the possibility of trial success, while were positive significant predictors for the possibility of trial failure. High number of previous VD is a significant positive predictor for trial success. Concerning ITD interval, high ITD dose and BMI are positive significant predictors, while high SBS and high number of previous VD are negative significant predictors for long ITD interval (Table 5).

Table 5:-Regression analysis for predictors of mode of delivery and ITD

VD				ITD				CS			
	Variable	β	p		Variable	β	p		Variable	β	p
M-1	Dose	-0.270	<0.001	M-1	Dose	0.515	<0.001	M-1	Dose	0.226	<0.001
	Parity	0.124	0.001		SBS	-0.139	<0.001		BMI	0.124	0.001
	BMI	-0.124	0.001		BMI	0.154	<0.001	M-2	Dose	0.249	<0.001
M-2	Dose	-0.293	<0.001		Parity	-0.137	<0.001				
	Parity	0.123	0.001	M-2	Dose	0.531	<0.001				
M-3	Dose	-0.307	<0.001		SBS	-0.153	<0.001				
					BMI	0.154	<0.001				
				M-3	Dose	0.560	<0.001				
					SBS	-0.163	<0.001				
				M-4	Dose	0.570	<0.001				

VD: Vaginal delivery; ITD: Induction-to-delivery; CS: Cesarean section; β: Standardized coefficient; M: Statistical model; Dose: Misoprostol dose; BMI: Body mass index; SBS: Simplified Bishop Score

ROC curve analysis determined low BMI with low MVI dose used for IOL and high number of previous VD as significant predictors for the possibility of IOL trial success (Fig 2), while progress on low MVI dose as the only

significant predictor for short ITD interval (Table 6, Fig. 3). Kaplan-Meier regression analysis defined the appropriate MVI for getting IOL trial success at a mean dose of 1.5±0.039 (95% CI: 1.4-1.55) as shown in Fig. 4.

Table 6:-ROC curve analysis for predictors of IOL trial success within short time

	VD			Short ITD interval		
	AUC (±SE)	P	95% CI	AUC (±SE)	P	95% CI
Dose	0.362 (±0.022)	<0.001	0.318-0.405	0.761 (±0.105)	0.018	0.555-0.967
BMI	0.381 (±0.022)	<0.001	0.338-0.425	0.489 (±0.097)	>0.05	0.299-0.680
Parity	0.557 (±0.023)	0.014	0.512-0.601	0.328 (±0.085)	>0.05	0.161-0.494
SBS	0.529 (±0.023)	>0.05	0.483-0.576	0.448 (±0.091)	>0.05	0.269-0.626

IOL: Induction of labor; AUC: Area under curve; CI: Confidence interval; Dose: Misoprostol dose; BMI: Body mass index; SBS: Simplified Bishop Score

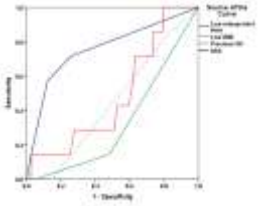

Fig 2:-ROC curve analysis of low MVI, low BMI, previous VD and SBS as predictor for VD

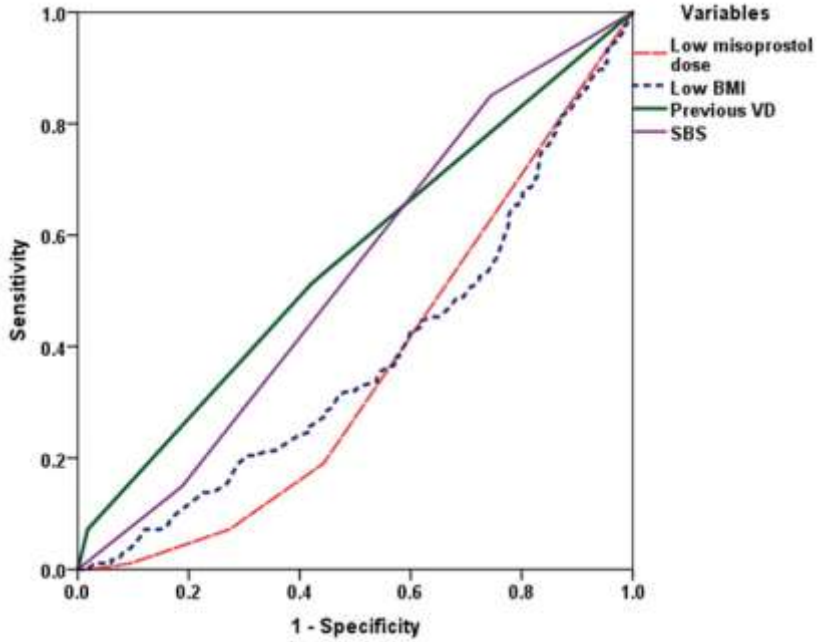

Fig 3:-ROC curve analysis of low MVI, low BMI, previous VD and SBS as predictor for short ITD interval

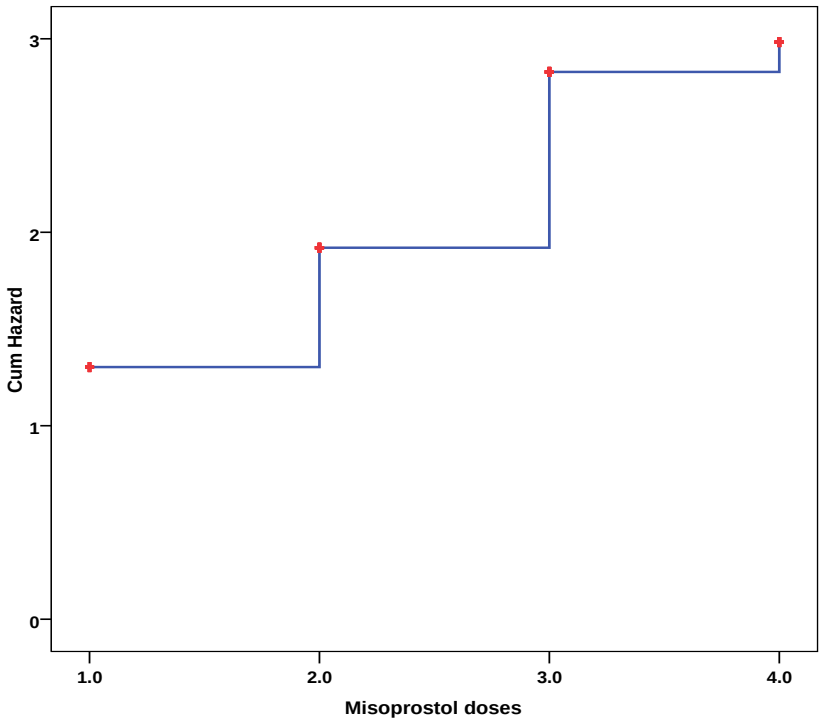

Fig 4:-Kaplan-Meier cumulative hazard curve to determine the appropriate MVI dose for trial success

Discussion:-

The current study relied on simple Bishop score (SBS) for differentiation between women had favorable cervix to be included and women with unfavorable cervix to be excluded from the study depending on the data documented by **Laughon et al.** [14] that SBS, comprised of dilation, station, and effacement, attains a high predictive ability of successful induction as the original score. Reliance on SBS for inclusion and follow-up of women underwent IOL goes in hand with multiple previous studies that assured its efficacy [18, 19, 20].

During the observation period, irrespective of misoprostol dose; 530 women had VD for a rate of 82.3%, of which only 168 women required instrumental assistance and 114 women (17.7%) had CS for varied indications. These figures are superior to that reported by **Mbaluka et al.** [21] who reported an overall induction success rates with misoprostol versus oxytocin were 81% versus 83%, respectively and **Silva et al.** [22] who reported an IOL trial success of 69% using vaginal 25-µg misoprostol tablets, while 31% of the women progressed to CS.

Concerning the induction-to-delivery (ITD) interval, 492 (92.3%) women had VD within <24 hr after initiation of IOL, while 38 (7.2%) women had VD after ≥24 hr for a mean ITD interval of 10.9±6.3; range: 2-33 hr. In line with these figure, **Levine et al.** [8] reported a mean ITD interval of 17.6 hr after MVI. Also, **Garba et al.** [23] found MVI resulted in shorter ITD interval compared to transcervical Foley catheter. Recently, **Grobman et al.** [24] out of a 25-center survey study included 10,677 women had IOL documented that 96.4% of women had reached the active phase by 15 hours.

In support of the efficacy and safety of IOL using MVI, **Liu et al.** [25] reported that MVI appears to be more efficient for IOL than intracervical dinoprostone. Thereafter, **de Paiva Marques et al.** [26] documented that maternal and perinatal outcomes were similar in hypertensive and normotensive women submitted to misoprostol IOL. Also, **Burgos et al.** [27] reported that in comparison to spontaneous onset of labor, IOL using either misoprostol or oxytocin in breech presentation at term is a reasonable and effective option and was not associated with increased perinatal morbidity or CS rates. Moreover, **Navve et al.** [28] reported non-significant difference regarding IOL outcomes using oxytocin, vaginal prostaglandin E2 insert or a transcervical double balloon catheter and **Kawakita et al.** [29] also reported that in women with oligohydramnios and an unfavorable cervix, misoprostol IOL was comparable to prostaglandin E2 IOL.

Moreover, concerning cost/effectiveness of misoprostol IOL, **Bierut et al.** [30] documented that IOL with use MVI generated savings from a hospital perspective in most countries and scenarios, in comparison to alternative technologies.

The effect of misoprostol dose on IOL outcome is heterogeneous, as the trial success is governed by other multiple factors as maternal age and BMI, multiparity especially the frequency of previous VD, and the cervical status as evaluated by SBS. In support of this assumption, **Clouqueur et al.** [12] documented that it is not possible to recommend a specific dosing schedule of misoprostol for IOL. Moreover, statistical analyses for results of the current study defined need for high misoprostol dose and high BMI as negative significant predictors, while high number of previous VD as a significant positive predictor for trial success and short ITD interval.

Furthermore, Kaplan-Meier hazard risk regression analysis defined misoprostol dose of two doses as the appropriate dose for getting trial success and the hazard of trial failure showed stepwise increase with dose. In support of this finding, **Pimentel et al.** [31] in randomized controlled trial comparing a single to multiple dosing of misoprostol, documented that one-dose is an acceptable alternative for IOL, especially for multiparous women and for those with Bishop score > 4 after the first dose.

Data concerning the impact of BMI on IOL trial success go in hand with **Marroquin et al.** [32] who found younger maternal age, lower weight, and lower BMI were associated with successful IOL and **Roloff et al.** [33] who also found obese women required a larger cumulative oxytocin dose to achieve VD during IOL. Also, **Lassiter et al.** [34] reported that as BMI increases, patients undergoing misoprostol IOL have longer ITD, require more doses of misoprostol with longer duration of oxytocin and have higher CS rate and **Prado et al.** [35] reported that pre-induction maternal BMI can affect the chance of achieving a successful VD on IOL.

As regards the predictability of parity for IOL outcome, **Silva et al.** [22] found previous VD was the best predictor of successful IOL with MVI and **Garba et al.** [23] reported that high parity was found to be associated with IOL success. Moreover, **Navve et al.** [28] reported that IOL in multiparous women is safe and successful regardless of the initial BS and **Prado et al.** [35] found increased parity, increases the chance of achieving a successful VD. Recently, in a similar trial, **Levine et al.** [3] documented that in multivariable modeling, nulliparity, BMI at delivery, and height were significantly associated with CS.

Regarding at admission SBS, despite of the negative correlation between SBS and trial success and ITD interval, other statistical analyses excluded SBS as a predictor for both events. In line with these findings, **Navve et al.** [28] reported that BS is not a good predictor for IOL success, nor is it a predictor for maternal or neonatal adverse outcomes and complications. Recently, **Al-Adwy et al.** [36] found posterior cervical angle of >99.5° yielded the best accuracy in predicting successful IOL compared with the cervical length and Bishop score. On contrary to these data, **Silva et al.** [22] and **Garba et al.** [23] found higher Bishop scores were the best predictors of successful misoprostol IOL. However, **Levine et al.** [3] documented that modified Bishop score was significantly associated with CS.

Conclusion:-

Misoprostol vaginal inserts is a satisfactory modality for IOL trial in multipara pregnant women with VD rate of 82.3% and ITD interval of <24-hr in 76.4%. Lower BMI and higher number of previous VD can predict higher possibility of trial success. Simple Bishop Score is appropriate for women selection for IOL trial and follow-up and can predict outcome if combined with BMI, parity and number of MVI used. Statistical analysis defined two MVI as the appropriate cutoff point for prediction of the trial outcome with increased probability for CS on needing higher doses

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