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ORIGINAL ARTICLE

COMPARISON OF THE EFFICACY OF PROSTAGLANDIN E2 VAGINAL TABLET VERSUS GEL FOR THE INDUCTION OF LABOR AT TERM: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: Prostaglandin E2 in different forms has been widely used for induction of labor in women with an unfavorable cervix. No significant differences have been noticed between prostaglandin E2 tablets versus gel for induction. The aim of this study was to compare vaginal prostaglandin E2 tablet of 3mg with an increased dose of gel i.e 2mg given both to primigravidas, multigravidas as well as grand multigravidas, regarding any differences in mode of delivery, induction delivery interval and any adverse maternal and fetal outcomes.

Materials & Methods: A randomized control trial was conducted at the department of Gynecology and Obstetrics of Qazi Hussain Ahmad medical complex over 6-month period from July to December 2021. One hundred and seventy-nine women, who met the inclusion and exclusion criteria, were randomly divided into two groups. Patients in group A were induced with Prostaglandin E2 tablet of 3mg and those in group B received vaginal gel of 2mg. Drug was kept in posterior fornix of vagina at 6 hourly intervals with pre and post induction CTG and fetal heart rate recorded. A maximum of 2 doses of each formulation was given. Primary outcome measures were mode of delivery and induction delivery interval. Secondary outcome includes adverse maternal and fetal outcomes, in terms of postpartum hemorrhage, uterine hyper stimulation and fetal distress.

A structured questionnaire was used to collect the relevant information of the patient. After data collection and analysis by using MS Office & SPSS 20, the results were finally presented in tables & figures.

Results: One hundred and seventy-nine women were randomly divided into two groups. Among both groups, no difference was found between modes of delivery i.e. normal vaginal deliveries and c section with increasing parity. Also it was found that parity has no significant impact with respect to the number of doses required of each formulation for inducing labor and modes of delivery with a P-value (0.136 & 0.583) and (0.421 & 0.123) between single and double dose of tablet and gel and among the patients delivered by NVD and C-section respectively. However, a statistically significant difference was found in induction delivery interval with a p-value of 0.02 &0.001 respectively between parity and time duration (≤12hrs & >12hrs). A consistent result was found between both formulations for adverse maternal and fetal outcomes in terms of fetal distress, postpartum hemorrhage and uterine hyper stimulation respectively.

Conclusion: We have concluded that Primi and multi gravidas are more likely to have a shorter induction delivery interval i.e. ≤ 12 hours in the group A versus the group B while grand multigravidas are more likely to have a shorter induction delivery interval with the gel. However, no significant differences in the number of doses, mode of delivery and adverse maternal and fetal outcomes was found between the two groups.

KEY WORD: Prostaglandin E2; Dinoprostone gel; Induction of labor; Bishop Score.

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INTRODUCTION

Induction of labor (IOL) is the process of artificially stimulating the uterus with the aim of achieving the vaginal delivery before the spontaneous onset of labor.[1]It is common and acceptable procedure now as it has been repeatedly justified by satisfactory results. Bishop score is the system most widely used to assess the cervix and decide for the need of induction of labor.[2] It has become a frequent

intervention in obstetrics with a current rate exceeding 20% of births.[3]

Induction of labor is undertaken when the termination of pregnancy has a better outcome for the mother and /OR her baby instead of waiting for spontaneous onset of labor.[4] Nice guidelines recommend that women with uncomplicated pregnancies should usually be offered induction of labor between 41+0and 42+0wks to avoid risks of prolonged pregnancy.[5]As a strong evidence exist for adverse fetal outcomes for continuing pregnancy beyond 41 weeks and induction at this time is not associated with increased risk of adverse fetal outcomes ,assisted vaginal deliveries and c sections.[6] Established indications include prolonged pregnancy, pre-labor rupture of membranes, concerns about fetal well beings (intrauterine growth retardation, Twin pregnancies) and maternal medical disorders (diabetes, pre-eclampsia, obstetric cholestasis).[4]

Various methods reported in literature for, labor induction include mechanical, non-pharmacological and pharmacological methods. Pharmacological methods, includes prostaglandin E2, misoprostol, mifepristone and combination of oxytocin with mechanical method.[7] Prostaglandins are commonly used agent for the cervix ripening and labor induction at term.[8] They have been found to be a safe and efficacious preparation for induction and National Institute Of Health And Clinical Excellence (NICE) recommends it as a preferred method for induction of labor[9] Synthetic prostaglandins works by mechanism similar to physiological cervical ripening and it also enhances the myometrial sensitivity to oxycitocin.[10] vaginal Prostaglandin E2 is available as tablet of 3mg , gel formulations in 1mg/2mg preparations[11]and controlled release vaginal pessary of 10mg that releases 0.3mg of dinoprostone per hour.[12]

Induction of labor should be performed only in cases with a clear medical indication for it, and the expected benefits outweigh the potential harm.[13] Induction have a significant impact on the women health, their birth experiences, babies and even on the labor ward and its staff.[14]

Induction of labor is not risk free, several maternal and fetal risks are documented with induction of labor regardless of indication for induction.[15] Some of them are increased operative delivery rates, high rates of epidural analgesia, low Apgar score at birth and after five minute.[16] As prostaglandins E2 are recommended by NICE for IOL, we want to compare the two commonly available formulations the tablet of 3mg and gel of 2mg in both primigravidas and women of increased parity for any differences in mode of delivery, induction delivery interval and adverse maternal and fetal outcomes.

MATERIALS AND METHODS

A randomized control trial was conducted at the department of Gynecology and Obstetrics of Qazi Hussain Ahmad medical complex over 6-month period from July to December 2021, after an institutional ethical committee approval. A total of n=179 patients at term were included with strict inclusion and exclusion criteria. Patients who needed IOL either due to postdated pregnancies or due to maternal or fetal indications with poor bishop score i.e. ≤6 were enrolled while those with multiple pregnancies, mal-presentation, history of cesarean section and uterine surgeries were excluded.

Randomization was done by making envelopes that appeared to be identical and were sealed to prevent tampering. After confirmation of trial entry details, the trainee medical officer has allocated the study number by taking the next sequentially numbered envelope. The study drug given to group A is Glandin E2 vaginal tablet contains 3mg dinoprostone in a single dose packing and group B is Glandin E2 gel contains 2mg dinoprostone, a thick clear gel in a sterile opaque syringe. Both formulations were stored at 2 to 8^0C. Patient was assigned the formulation after randomization. Prior to the administration of both study drugs, fetal cardiogram was performed for 20 minutes provided that fetal heart rate pattern was within normal limits. If the initial bishop was less than or equal to 6 than the study drug assigned to that was administered in the posterior fornix of vagina. Post induction CTG was done for 30 minute after dose administration followed by hourly fetal hearts auscultation for 1 minute. Patient was reassessed after 6 hours' in case of no improvement in Bishop score, dose was repeated with reassessment after another 6 hours' interval with pre and post induction CTG and hourly fetal hearts rates records, but if more than 7 than patients in both the groups will be transferred to the delivery suite for amniotomy. Syntocinon augmentation of the labor was done by the attending obstetrician based upon the labor ward guidelines. If after 2nd assessment that is after 6 hours of the 2nd tablet, bishop was ≤ 6 then cesarean section will be performed by labeling the patient as failed induction. During induction in case of fetal distress i.e. pathological CTG or passage of meconium emergency Lscs was proceeded. Patient was also monitored for uterine hyper stimulation and primary postpartum hemorrhage.

A structured questionnaire was used to collect the relevant information of the patient. After data collection, data was analyzed by MS Office & SPSS 20. Finally, results were presented in the following tables & figures:

RESULTS

The baseline maternal characteristics for both groups were similar for gestational age at induction and bishop score.

Among the total 179 patients, 87 were Primigravidas

,70 were Multigravidas and 22 were Grand multigravida's. Patients assigned in group A (prostaglandin E2 tablet) and in group B (prostaglandin E2 gel) were 54 % and 46% respectively.

Major indications for IOL were postdated pregnancies, pre-labor rupture of membranes and hypertension in pregnancy.

As P Value > 0.05, There Was Not Statistically Association Between No. Of Doses and parity [PG (P=0.517), MG(P=0.757) and GMG (P=0.746)]

There was a statistically significant difference between Parity (Primi Gravida, Multigravida and Grand multigravida) with Time Duration (≤12hrs & >12hrs) with p-value of 0.02 & 0.001 respectively

Based upon chi square test application on this 2x3 table with 2 degree of freedom; the calculated p value found was 0.222; more than thesignificant p-value (0.05); thus the null hypothesis was not rejected and the results are not significant and thus having no association between formulations and indications for C-section

There was no statistical association between parity, and the number of doses of both formulations with P-value of > 0.05. (Table 3).

Table 1: Formulation given and parity of the patient

Total No. of patients n= 179	Parity		PGE_2 Tablet		PGE_2 GEL	
	n	%	n=96 n	54% %	n=83 n	46% %
PG	87	49%	62	65%	25	30%
MG	70	39%	24	35%	46	55%
GMG	22	12%	10	10%	12	15%

PG(primigravidas) MG (multigravidas) GMG (grand multigravidas)

Table 2: Indications for the induction of labor

Indications of induction	n	%	PG		MG		GMG	
			n	%	n	%	n	%
Post dated pregnancy	48	27%	22	25%	20	28%	6	27%
Pre labour rupture of membranes	52	29%	36	41%	13	19%	3	14%
Hypertension in pregnancy	48	26%	13	15%	23	33%	12	55%
Oligo hydromious	18	10%	7	8%	11	16%	0	0%
Decrease fetal movements	10	6%	6	7%	3	4%	1	4%
Obstetric cholestasis	3	2%	3	4%	0	0%	0	0%

Table 3: No of Doses given and the parity of the patient.

No. of Doses	PG					MG					GMG				
	TAB		GEL		p-value	TAB		GEL		p-value	TAB		GEL		p-value
	n=62	72%	n=25	28%		n=24	34%	n=46	66%		n=10	45%	n=12	55%	
Single Dose	27	44%	9	36%	0.517	15	62%	27	59%	0.757	6	60%	8	67%	0.746
Double Dose	35	56%	16	64%		9	38%	19	41%		4	40%	4	33%	

Table 4: Labor outcomes along with the number of doses.

parity	NVD n=125 70%									C/SECTION n=54 30%								
	TAB n=66 69%				p	GEL n=59 71%				P	TAB n=30 31%				p	GEL n=24 29%				P
	Single Dose n=36 55%		Double Dose n=30 45%			Single Dose n=34 58%		Double Dose n=25 42%			Single Dose n=12 40%		Double Dose n=18 60%			Single Dose n=10 42%		Double Dose n=14 58%		
	n	%	n	%		n	%	n	%		n	%	n	%		n	%	n	%	
PG	18	50%	21	70%		5	15%	6	24%		9	75%	14	78%		4	40%	10	71%	
MG	14	39%	5	17%	0.136	21	62%	15	60%	0.583	1	8%	4	22%	0.421	6	60%	4	29%	0.123
GMG	4	11%	4	13%		8	23%	4	16%		2	17%	0	0%		0	0%	0	0%	

There were no differences in mode of deliveries (NVD and C section) as p > 0.05 respectively.

Table 5: Induction delivery interval

Parity	≤12hrs				p	>12hrs				p
	TAB		GEL			TAB		GEL		
	n=47 49%		n=36 43%			n=49 51%		n=47 57%		
	n	%	n	%		n	%	n	%	
PG	28	46%	7	28%		34	54%	18	72%	
MG	15	63%	21	46%	0.020	9	37%	25	54%	0.001
GMG	4	40%	8	67%		6	60%	4	33%	

Table 6: Adverse maternal and fetal outcomes

Adverse outcomes	PGE 2 Tab		PGE 2 Gel	
	n	%	n	%
Fetal distress	7	7.2%	4	4.8%
Uterine hyperstimulation	0	0%	0	0%
Primary PPH	0	0%	0	0%

Table 7: Indications of c section

Indication for C/ Section	Tablet		Gel		p
	n=30 31%		n=24 29%		
	n	%	n	%	
Failed Induction	17	18%	10	12%	
Failed to Progress	6	6%	10	12%	0.222
Fetal Distress	7	7%	4	5%	

There was no statistical difference (P-value >0.05) regarding modes of delivery i.e. NVD and C-Section; with prostaglandin E2 tablet and gel with regards to parity.

Among those patients who delivered NVD; there was no statistical difference based on Chi-square test and P-Values of 0.136 and 0.583; between single & double doses for tablet or gel formulations. Similarly, there was no significant association between parity and number of doses for both formulations on the rate of caesarean sections. Moreover, caesarean section rates showed no statistical significant difference with single and double doses with P-values of 0.421 and 0.123 respectively. Furthermore, a statistically significant difference was found between parity and induction delivery interval of ≤12 hours and >12 hours for both tablet and gel groups respectively.

Additionally, prostaglandin E2 tablet and gel showed no significant difference regarding C-Section; P-value 0.222; and thus revealed no association between the formulations and indications for the C section.

DISCUSSION

In our study, for the induction of labor; the prostaglandin E2 tablet and gel; showed no differences regarding mode of delivery, and number of doses. Moreover, in our study; approximately 68.75% revealed NVD among the primary, multi-gravidas; and grand-multigravidas. Furthermore, in tablet group among primigravidas; 62.90% showed NVD in our study whereas in studies of Mizrachi et al. 2016 it was 60.69% respectively, while Shetty et al.[17] reported 50.3% rates of vaginal deliveries which were inclusive of 15.4% instrumental deliveries, thus higher spontaneous vaginal delivery rate showed in our study. In contrast in study of Obeidat et al.[18] NVD reported in 62.6% whereas among primigravidas and multigravidas' normal vaginal delivery was reported in 42.8%

and 86.5% respectively as compared to 79.16% in multigravidas in our study, hence their results were not consistent with that of our study. We came up with similar results in prostaglandin E2 tablet group for caesarean section i.e. 31% and 34% by Shetty et al. respectively. Whereas as a 25% rate for caesarean was reported by Blance et al.[19]

In a study conducted internationally, by Jozwick et al.[20] reported total vaginal deliveries among 80% of study participants and among them 67% had spontaneous and 13% had instrumental vaginal deliveries with prostaglandin E2 gel; whereas in our study the spontaneous vaginal deliveries showed 68% prevalence and thus our findings were consistent with study of Jozwick et al. In our study, among prostaglandin E2 gel group; 29% of cases ended with caesarean section; included who failed to progress in second stage; whereas caesarean section was reported in 20% of cases in both studies performed by of Jozwick et al. and Blance et al. respectively. In our study, there were no statistical differences among the different modes of delivery i.e. NVD and C section (P-value >0.05).

The reported rate of postpartum hemorrhage revealed with prostaglandin E2 gel was 9% and 6.6% while that of uterine hyperstimultion was 3% and 6.6% in study of Jozwick et al. and Blance et al. respectively. Whereas with prostaglandin E2 tablet, they had reported PPH in 5.7% and uterine hypertension in 4.2% respectively. However, in our study none of the patients had any adverse maternal outcomes of PPH and uterine hyper stimulation and showed a consistent result with Shetty et al. for uterine hyper stimulation i.e. none with tablet and 0.7% with gel respectively. The presence and observations of secondary outcomes might be due to the application of less doses of Prostaglandin E2 gel i.e. 1mg dose with total of up to five doses after every 6 hours-time as compared to our study; in which 2mg were given for two doses with same 6 hours-time (Jozwick et al.). Among secondary outcomes, for fetal distress results of our study in both tablet and gel group of 7.2% and 4.8% are consistent with Shetty et al. but higher rates were reported by Blance et al. and Obeidat et al. i.e.15.1% and 17.2% respectively with tablet and 17.2% in gel group.

In our study; 51% of the patients in the tablet group while 56% in the gel group had delivered in > 12hrs of start of induction. Whereas in study of Shetty et al. had reported 60.4% and 56.2% respectively. Moreover, in tablet group among primigravidas and multigravidas 46% and 63% vs 28% and 46% in the gel group delivered in < 12 hrs. However, with dinoprostone gel, young et al.[21] reported 28% and 46% of deliveries among the Primi and multigravidas in <12hrs. In our study, the results showed statistical differences for different formulations with respect to parity and time duration (P-value 0.02 & 0.001).

CONCLUSION

We have concluded that Primi and multi gravidas are more likely to have a shorter induction delivery interval i.e. ≤12 hours in the tablet group versus the gel while grand multigravidas are more likely to have a shorter induction delivery interval with the gel.

However, no significant differences in the number of doses, mode of delivery and adverse maternal and fetal outcomes was found between the two groups.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	NP, SN
Acquisition, Analysis or Interpretation of Data:	NP, SN, TB, MP
Manuscript Writing & Approval:	NP, SN, TB, MP

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.