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COMPARISON OF PROSTAGLANDIN E_2 GEL AND PROSTAGLANDIN VAGINAL TABLETS FOR INDUCTION OF LABOR

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Abstract:

Objectives. *Our current study was intended to explore the more effective form between vaginal gel and vaginal tablet for induction of labor. This study will help clinician to choose the better drug administering forms.*

Material and Methods: *This was a randomized control trial from January 2013 to June 2013, in Department of Gynecology and Obstetrics, Abbassi Shaheed Hospital, Karachi, through non-probability purposive technique on 218 pregnant females after taking ethical approval. The ethical approval for this study was taken from ethics review committee. Women between 20-45 years of age, bearing single pregnancy with cephalic presentation of the viable fetus, presenting in the labor room after gestational age of 37 weeks (as confirmed by early scan), for labor induction were included in the study. The two groups were Group A, in which women were administered with dinoprostone (PGE 2 analog) gel [1mg/2mg] intravaginally. While Group B participants were administered with dinoprostone tablet [3 mg] intravaginally. Fetal outcomes and the association of labor induction with age was noted. Version 16 of SPSS was used for the data analysis. Descriptive analysis was performed. Chis-square test was used to assess the different with p value of <0.05.*

Results: *In a total of 218 patients, the mean age of females was 32.12±7.69 years in group A and 33.17±7.16 years in group B. Also, the average time from induction to delivery in group A was recorded as 11.88±2.68 hours and in group B as 11.95±2.83 hours. Bishop score of more than 6 was observed in 83(76.1%) from group A and 67(61.5%) females from group B (p =0.019). Correspondingly,88(80.7%) females of group A and 71(65.1%) in group B had 3 uterine contractions of 40 seconds in 10 minutes. 83(76.1%) of females in group A and 67(61.5%)in group B had effective induction (p value =0.019). Age group for women from 41 to 45 years had a significant association (p=0.009) Moreover, this effectiveness when compared among primigravida of both groups, a statistical significance (p value =0.012) was observed.*

Conclusion: *Our study predicted the preeminence role of PGE 2 vaginal gel over PGE 2 vaginal tablets. Vaginal gel was more effective as compared to the oral form for the induction of labor. However, PGE 2 vaginal gel was observed to decline maternal morbidity and mortality significantly, at the same time improving fetal outcome.*

Key Word: *Labor induction, Prostaglandins, dinoprostone, maternal morbidity.*

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INTRODUCTION:

Literature has described the normal time span of a human pregnancy to be around 40 to 41(+3) weeks [1]. Correspondingly, a pregnancy reaching to the 41th week of gestation is termed as prolonged or late term pregnancy [1,2]. The late term pregnancies, in multiple studies have been labeled to cause adverse impacts on the mother and fetus [3,4]. Furthermore, the 0.7 % probability for these adverse events regularly increases up to 5.8%, as the gestation age advances from 37 to 43 (+6) weeks [1]. The common complications seen with pregnancy being prolonged, include meconium aspiration syndrome; neonatal acidosis and less than 7 APGAR score at 5 minutes [1].

Due to the profound negative effects, it is recommended to avoid post term pregnancies and inducing labor artificially, when gestational age reaches to 41 weeks [5,6]. It can be done any time,during 41 to 42 (+6) weeks of gestation, provided there are no contraindication [1]. During this process, the body is exogenously stimulated to initiate labor [7]. Literature has suggested that around 25% of pregnancies move in to the labor with external induction [8,9]. Other than late term pregnancy, several conditions have been associated with the recommendation for inducing labor. Some of them are pregnancy induced hypertension, diabetes mellitus or chronic hypertension in mother, ongoing fetal compromise, chorioamnionitis, premature rupture of membranes and abruptio placenta [10,11]. Moreover, it is also practiced for non-pathological conditions [12]. Although beneficial in many aspects, but artificial induction of labor may result in longer than usual time period of labor and hospital stay, adding to that, the attempt to induce may be failed or end up in the need for caesarian section rather than vaginal delivery [13]. Furthermore, the c section, can be predicated following labor induction, by previous parity history [14]. However, good bishop score and multiparity are linked to the positive outcomes from the induction [15].

Cervical ripening tends to be the 1st stage of labor induction for those with a cervix that is unfavorable. It helps the cervix to become soft, thin and prepare for the labor [16,17]. The two major methods used for the purpose are mechanical and pharmacological [18]. The mechanical methods are the usage of different catheters, for example Foley or Cook, to ripen the cervix [18]. On the other hand, pharmacological agents used are oxytocin, prostaglandin E1 and prostaglandin E2[11]. Despite the fact that all these agents are being widely used with good safety and efficacy, the best among them in terms of safe and effective, is still debatable [11]. The most effective drug is being described to be the one with minimal maternal and fetal compromise while reducing the time of onset and time of different stages of labor [11].

Prostaglandin E2 being one of the agents used for inducing labor, remains the standard of care in many clinical settings [19,20], and its safety profile is well established [21]. Considering the major factors which lead to the use of PGE2 for labor induction, advanced maternal age and low fetal weight are on top of the list [15]. Prostaglandin E2 causes the release of inflammatory cytokines, which initiate the cervical changes in favor of the labor and at the same time induces functional withdrawal to progesterone [22].Prostaglandin E2 acts on four receptors: EP1 and EP3 receptors, through which it augments the level of intracellular calcium and results in improved contractility of uterus; EP2 and EP4 receptors, through which it increases the production of cAMP and ensure an enhanced myometrial relaxation [22]. PGE 2 is available in the different forms, which includes tampon or vaginal insert; vaginal gel; vaginal tablet and cervical gel [19,20].

Although the safety and efficacy for prostaglandin E2 for labor induction has been widely described in previous studies, yet there is a paucity of data on the subject of, which form of PGE 2 is most effective in giving positive results while preserving maternal and fetal health. Our current study intended to explore the more effective form between vaginal gel and vaginal tablet. This study will help clinician to choose the better drug administering form, while at the same time provide data to improve patient awareness in regards of labor induction and drug forms available.

MATERIALS AND METHODS:

This was a randomized control trial. During the period of 6 months from January 2013 to June 2013, the trial was commenced in Department of Gynecology and Obstetrics, Abbassi Shaheed Hospital, Karachi. Data for the study was collected through non-probability purposive technique. The ethical approval for this study was taken from ethics review committee. The sample size was 218.

Women between 20-45 years of age, bearing single pregnancy with cephalic presentation of the viable fetus, presenting in the labor room after gestational age of 37 weeks (as confirmed by early scan), for labor induction due to gestational diabetes or pregnancy induced hypertension; frank leaking at term per speculum inspection; bishop score < 6 on vaginal examination; postdate or post term pregnancy (with respect to early scan) and parity of <6 were

included in the study, On the contrary, women whom had history of previous caesarian section; vaginal birth contraindicated; preterm or pre labor membranes rupture; parity >6; bishop score of > 6; non-reactive CTG and those women who refused to participate were excluded from the study enrollment.

After taking informed consent, the allocation of the group to the study participants was done randomly via lottery method. The two groups were Group A, in which women were administered with dinoprostone (PGE 2 analog) gel [1mg/2mg] intravaginally. While Group B participants were administered with dinoprostone tablet [3 mg] intravaginally. Prior to starting drug administration, careful per vaginal examination was done and bishop score was recorded, then Performa was filled accordingly. Also, to avoid observational bias, same doctor examined the patient every time. After drug administration, fetal cardiogram was recorded for 60 minutes. The drug was administered vaginally after every 6 hours until the cervix became favorable (i.e. bishop score > 6). Furthermore, last bishop score was documented after 18 hours of drug administration in both groups. Women from either group with favorable cervix was taken to labor room for amniotomy. In the mean while portogram and fetal heart rate was continuously documented.

Fetal distress was defined as meconium stained liquor and abnormal fetal heart rate. Similarly, hyperstimulation was defined as prolonged (> 2 minutes) uterine contractions or tachysystole (i.e. 6 or more uterine contractions in 10 minutes). Effectiveness of the drug was declared positive with bishop score of >or equal to 6; occurrence of effective contractions in uterus i.e. 3 contractions for 40 seconds in 10 minutes and neonatal APGAR score at 5 minutes of > 7. On the contrary, failing to achieve these effects was declared as negative in terms of effectiveness. Version 16 of SPSS was used for the data analysis. The presentation of descriptive data analysis was done by mean and standard deviation for quantitative data and frequency and percentage for qualitative data. Conversely, the inferential analysis was done by using chi square test, with level of statistical significance set as 0.05.

RESULTS:

Total 218 women were included in our study. The mean age of females was 32.12±7.69 years in group A and 33.17±7.16years in group B. the average time from induction to delivery in group A was recorded as 11.88±2.68 hours and in group B as 11.95±2.83 hours. During our study, the comparison between two groups on the basis of maternal and fetal outcomes, was executed. In the similar context, bishop score of more than 6 was observed in 83(76.1%) females from group A and 67(61.5%) females from group B and the difference was statistically significant (p value =0.019). Correspondingly, 88(80.7%) females of group A and 71(65.1%) in group B had 3 uterine contractions of 40 seconds in 10 minutes, and the variability of these results in 2 groups was calculated to have statistical significance (p=0.010). The APGAR score was recorded at 5 minutes for all neonates, those whom had score of > 7 were borne to 78(71.6%) in group A and 63(57.8%) females in group B, also the difference in the number was significant (p=0.034).

According to the criteria for effectiveness of the drug form, stated above, 83(76.1%) females in group A and 67(61.5%) in group B were having effective induction. The disparity among groups was calculated to be significant (p=0.019). The effectiveness when stratified with respect to age groups, only age group for women from 41 to 45 years had a significant difference (p=0.009) between the two groups. Moreover, this effectiveness when compared among primigravida of both groups, a statistical significance (p value =0.012). whereas it was insignificant with multigravida females.

Table I: Comparison of Characteristics Between Groups

	Group A	Group B	p-value
	Mean ± SD	Mean ± SD	
Age (Years)	32.12±7.69	33.17±7.16	0.29
Induction to delivery interval time (Hours)	11.88±2.68	11.95±2.83	0.84
Gestational Age (Weeks)	38.39±1.52	38.45±1.47	0.78

Table II: Comparison Maternal and Fetal Outcome Between Groups

Variables	Group A n(%)	Group B n(%)	p-value
Bishop score >6	83(76.1%)	67(61.5%)	0.019
3 contractions in 10 mint of about 40 sec	88(80.7%)	71(65.1%)	0.010
Apgar score >7 at 5 minutes	78(71.6%)	63(57.8%)	0.034
Neonatal admissions in nursery	11(10.1%)	12(11%)	0.82
Perinatal death	6(5.5%)	4(3.7%)	0.52

Table III: Association Of Effectiveness With Age And Gravida In Different Groups

Variables		Group A n=109	Group B n=109	p-value
Overall effectiveness	**Positive**	83(76.1%)	67(61.5%)	0.019
	Negative	26(23.9%)	42(38.5%)	
20 to 30 years of age patients (n=101)	**Positive**	41(75.9%)	28(59.6%)	0.078
	Negative	13(24.1%)	19(40.4%)	
31 to 40 years of age patients(n=74)	**Positive**	22(64.7%)	26(65%)	0.97
	Negative	12(35.3%)	14(35%)	
41 to 50 years of age patients (n=43)	**Positive**	20(95.2%)	13(59.1%)	0.009
	Negative	1(4.8%)	9(40.9%)	
Primigravida (n=99)	**Positive**	31(60.8%)	17(35.4%)	0.012
	Negative	20(39.2%)	31(64.5%)	
Multigravida (n=119)	**Positive**	52(89.7%)	50(82%)	0.23
	Negative	6(10.3%)	11(18%)	

DISCUSSION:

Exogenously initiating labor is being widely performed across the globe, especially in the developed world [11]. Studies have suggested that rather than waiting for spontaneous labor initiation, it is healthier to induce labor artificially as the pregnancy reach 41 weeks, by means of which, meconium stained amniotic fluid and other complications of late term pregnancy can be prevented [24]. While considering induction of labor, the choice of the drug and its form may play a role in the outcomes and must always scrutinize the medical and obstetrical history of patient before selecting the drug [25].

Though the mechanism of action of prostaglandin E2 synthetic analog is very similar to the one produced inside the body [26], yet the different forms of the drug may result in different effects. During our study, we stratified the differences between the two forms of prostaglandin E2, namely vaginal gel and vaginal tablet.

The observed findings in this study showed no statistical significance in difference (p value =0.84) for the time interval needed for delivery following the drug administration. The average time interval recorded for Group B was 11.95±2.83 hours which was given vaginal tablet while that for Group A was 11.88±2.68 hours which was given vaginal gel. A randomized control trial comparing two vaginal preparations of dinoprostone suggested that the two induction procedures (controlled release vaginal dinoprostone pessary or dinoprostone gel) should be considered equivalent as for as ripening of the cervix and initiating labor. In view of this finding, the low bishopscore should be considered an indication to prefer the controlled release devise, since it reduces pain thereby improving the physical and emotional well-being of the parturient. Refrence- A randomized trial between two vaginal preparations of dinoprostone in nulliparous women with an unfavorable cervix. J Matern Fetal Neonatal Med.2011: 24 (5) : 728-731.

Evaluating the maternal and fetal outcomes after induction of labor with PGE 2, our study found a superiority of vaginal gel in results of bishop score, uterine contractions and APGAR score. 83(76.1%) females in group A had bishop score of > 6 while that in group B were merely 67(61.5%) and the difference calculated was significant (p=0.019). In the same way, a standard of 3 uterine contractions of 40 seconds in 10 minutes was achieved by 88(80.7%) women in group A and 71(65.1%) in group B with profound statistical variation (p=0.010) between group A and group B. The neonatal well-being was estimated via APGAR score at 5 minutes and 78(71.6%) females in group A had their babies scored >7 while those in group B were

63(57.8%), also the result had statistical significance (p value = 0.034). Furthermore, neonatal morbidity and mortality was insignificantly different among two groups. A meta-analysis suggested that the need of oxytocin and rate of cesarean section is less encounter while using PGE 2 vaginal insert than while using vaginal or cervical gel [28]. However, Ramsey PS et al. reported no significant variation in respect of APGAR score, birth weight or cesarean section, between the results of vaginally given PGE 2 versus cervically given PGE 2 [29]. Likewise, a retrospective study on women, whose fetuses suffered intrauterine growth retardation were studied, and out of 99 ladies, misoprostol was used in 20 whereas dinoprostone was used in 21 for inducing labor. 14.9% of the pregnant ladies whom were administered dinoprostone required the cesarean delivery while this rate was 5 % in the group with misoprostol administration [30].

The current study intended to elaborate the form of PGE 2 with more effectiveness between vaginal gel and tablet. The basic criteria for positive result was set to be a bishop score of >6; uterine contraction at least 3 of 40 seconds duration in 10 minutes interval and the APGAR score of the newborn to be >7. The number of females from Group A who were able to satisfy the criteria were 83(76.1%), whereas those from Group B were 67(61.5%). The figures are clearly better in Group A when compared to the Group B. On the other hand, Yount SM et al. compared the vaginal insert and cervical gel and concluded that the insert tends to release PGE 2gradually but has a prolong and sustained duration of action [31].A different study stated the rate of release of drug in vaginal insert is 0.3 mg/hour for a period of 20 hours [20]. Additional point to ponder when considering a gel is that a physician is required to administer the drug [19]. On the contrary, the vaginal insert can be easily placed and removed at the time of need [31].

The qualitative approach of our study has assured that we have sampled extensive range of pregnant females. However the study might not be immune from observer and selection bias. Considering the views of our study and to what extent they are related to the variation in dose of PGE 2 formulations will be revealing to discover more facts about the induction of the labor.

CONCLUSION:

Our study predicted the preeminence role of PGE 2 vaginal gel over PGE 2 vaginal tablets. Vaginal gel was more effective as compared to the oral form for the induction of labor. However, PGE 2 vaginal gel was observed to decline maternal morbidity and mortality significantly, at the same time improving fetal outcome.

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