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Original Research

The association between repeated doses of vaginal PGE2 (Dinoprostone, Prostin®) and both maternal and neonatal outcomes among women in the north of Jordan

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Summary

Objective: To evaluate the association between repeated doses of vaginal PGE2 and the maternal and neonatal outcomes for primigravid and multiparous women. *Study design*: A retrospective descriptive study was conducted at a teaching university hospital in Jordan. The study involved 885 women with singleton live fetuses; these women had been admitted to the labor ward for an induction of labor by vaginal PGE2 (Dinoprostone, Prostin®) for different indications from January 2015 to December 2016. The women were classified according to parity into two main groups, namely, primigravid and multiparous. In the primigravid group, the women who had received two or fewer doses of a vaginal PGE2 tablet (3 mg Dinoprostone) were compared with those who had received a PGE2 tablet three times. In the multiparous group, the women who had received one or two doses of half the usual vaginal PGE2 tablet (1.5 mg Dinoprostone) were compared with those who had received the same dose three times. The main outcomes studied were the cesarean section rate and the APGAR score. *Results*: There was a statistically significant association, namely, X^2 (1) = 13.96, P = 0.001, between the repeated doses of PGE2 and the mode of delivery. This indicates that primigravid women who received more than two doses of PGE2 were more likely to have a cesarean section (65.5%, n = 57 out of 87) compared with primigravid women who received two or fewer doses of PGE2 (42.9%, n = 132 out of 308). There was no significant association between repeated doses of PGE2 insertion and admission either to the nursery or the neonatal intensive care unit (NICU) X^2 (1) = 2.11, P = 0.14. Moreover, the results also showed that there was no significant association between repeated doses of PGE2 insertion and the APGAR score X^2 (1) = 0.06, P = 0.88. For multiparous women, there was no statistically significant association X^2 (1) = 2.15, P = 0.14 between repeated doses of PGE2 insertion and the mode of delivery. *Conclusion*: In both groups of primigravid and multiparous women, the third dose of vaginal PGE2 was not associated with a significant increase in maternal or neonatal morbidity. In the primigravid group, despite the third dose of PGE2 being associated with a higher rate of cesarean section in comparison with two or fewer doses of it, nearly a third of the women nevertheless achieved vaginal delivery. In the multiparous group, the third dose of PGE2 was not associated with a higher rate of cesarean sections.

Key words: Induction; Labor; PGE2; Cesarean section.

Introduction

About 20% of all pregnancies will need to be induced at a certain time during the gestation for a particular indication [1], postdate being the commonest indication for induction. There are many methods described and used to induce labor [2, 3]: these include, but are not limited to, Misoprostol, Oxytocin, membrane sweeping or stripping, balloon catheter, nipple stimulation, intercourse and herbal remedies. However, vaginal prostaglandin E2 (Dinoprostone, Prostin®) [4, 5] has been used extensively as the preferred way for induction by most specialized institutions and is considered to be the safest option for the mother and neonate as well as the most effective one to induce vaginal delivery within 24 hours for women with an unfavorable cervix [6-11]. However, there is no full agreement on the ideal dosage of PGE2 that should be used to achieve the optimal outcome [12-14]. Moreover, there is much debate concerning the frequency of PGE2 use, whether there are different regimens for multiparous women [15], and at what point induction of labor has failed and that a cesarean section should be the exclusive and definitive mode of delivery. These issues of uncertainty have been addressed by the Royal College of Obstetricians and Gynaecologists (RCOG) and the National Institute for Health and Clinical Excellence (NICE) guidelines in 2001 and 2008; subsequently, a limited number of studies have briefly explored this area but with contradictory results [16].

The current definition of failed induction by NICE (2008) is a failure to establish labor after one cycle of treatment consisting of the insertion of two vaginal PGE2 tablets (3 mg) or gel (1–2 mg) at 6-hourly intervals, or one PGE2 controlled-release pessary (10 mg) over 24 hours. In this situation, NICE recommends counseling the patient about either continuing the induction process by inserting additional doses of vaginal PGE2 or by performing a cesarean

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section. The paucity of reassuring data about maternal and neonatal safety and the limited information about the success rate of giving birth after exceeding the recommended dose of vaginal PGE2 make this counseling significantly deficient: the final decision still remains extremely difficult. Hence, this dilemma has attracted numerous researchers, including our group, keen to fill this knowledge gap [16-18].

We conducted this study to evaluate the association between repeated doses of vaginal PGE2 and maternal and neonatal outcomes for primigravid and multiparous women. The results can be applied worldwide, especially where there is intention to reduce the alarmingly high rates of cesarean section. The use of additional doses of vaginal PGE2 may be a beneficial way of limiting the steady rise of global cesarean section rates without compromising the wellbeing of mothers and neonates.

Material and Methods

Design

A retrospective descriptive design was used to evaluate the association between repeated doses of vaginal PGE2 (Dinoprostone, Prostin®) and the maternal and neonatal outcomes for primigravid and multiparous women.

Sample and sampling technique

All pregnant women with singleton live fetuses admitted to the labor ward for the induction of labor by vaginal PGE2 for different indications from January 2015 to December 2016 were selected for inclusion in this retrospective study.

Site and setting of the study

This study was conducted at the University Educational Hospital in Irbid Province, which, after Amman, has the second largest metropolitan population in Jordan. The total capacity of this hospital is more than 650 beds, with an impressive occupancy rate of close to 99%. This hospital includes diverse specialties, such as internal medicine, cardiology, orthopedics, pediatrics, neurology, maternity and dermatology.

Data collection procedure

The study method and protocol were approved by the Institutional Review Board (IRB) of the University Hospital (approval number: 49/116/2018). Data was collected from the files of patients admitted for the induction of labor by PGE2 over these two years, 2015 and 2016. The data collected comprised demographic and clinical variables. Demographic variables included age and monthly income while clinical variables included parity, gestational age at the time of induction, indication for induction, the number of PGE2 tablets inserted, the total dose of PGE2 tablets received, the duration of induction, the maternal outcome in terms of the mode of delivery and uterine hyperstimulation and the neonatal outcome in terms of the APGAR score and the NICU admission.

All women included in the study had a Bishop score of 6 or less and were induced by vaginal administration of PGE2 tablets (Dinoprostone, Prostin®). Primigravid women received one tablet of PGE2 (3 mg), while multiparous women received half a tablet (1.5 mg). All our patients were admitted to the labor ward during the process of induction and their Bishop score was assessed again after 6 hours. If the score was 6 or less, the patient was offered another dose of PGE2, but if the score was 7 or more, then ARM was tried and oxytocin infusion started, if indicated. If there was no response after the second dose of PGE2, the patients were counseled regarding the administration of a third dose of PGE2. Some women opted to have a cesarean section while others agreed to continue the process of induction and received a third dose of PGE2.

We classified patients according to parity into two main groups, primigravid and multiparous women. Primigravid women were further subdivided into two groups: The first group included those who had received two or fewer Vaginal PGE2, while the second group included those who had received PGE2 three times. Multiparous women were also subdivided into two groups: The first group were those who had received half a PGE2 tablet (1.5 mg) two times or fewer, while the second group had received the same (half a tablet) three times.

The main study outcomes following insertion of the third dose were the cesarean section rates and the APGAR scores.

Statistical analysis

Descriptive statistics, including frequency, percentages, means, and standard deviations, were used to describe the data. A chi-square was conducted to assess the association between repeated doses of PGE2 and maternal and neonatal outcomes. Significance was considered at $P < 0.05$.

Results

Sample characteristics

There were 898 pregnant women with singleton live fetuses admitted to the labor ward for the induction of labor by vaginal PGE2 for different indications. In 13 files, the data was not complete but the remaining 885 files were used in the analysis. Of these 885 women, there were 395 primigravid mothers admitted during the study period (January 2015 to December 2016) for the induction of labor, comprising almost 45% of the total sample, while there were 490 multiparous mothers admitted for the induction of labor in the same period. The mean age of the women was 28.19 years (SD = 5.37) with an actual range of 15 to 48 years old. The results showed that nearly 71% delivered vaginally (n = 623), 27% by cesarean section (n = 242) and only 2% via instrumental delivery (n = 20).

The mean age for primigravid women was 25.66 years (SD = 3.90) with an actual range of 15 to 42 years old. Almost 49% delivered vaginally (n = 193), 48% by cesarean section (n = 189), and only 3% via instrumental delivery (n = 13). The mean age for multiparous women was 32.20 years (SD = 5.53) with an actual range of 15 to 48 years old. The majority (88%, n = 430) of them delivered vaginally, and almost 11% had a cesarean section (n = 53) while

Table 1. — *Sample characteristics for primigravid and multiparous women (N = 885)*

	The whole sample (N = 885)	Primigravid women 45% (n = 395)	Multiparous women 55% (n = 490)
Age M (SD)	28.19 (5.37)	25.66 (3.90)	32.20 (5.53)
Age range	15-48 years	15-42 years	15-48 years
Mode of delivery N %			
Vaginal delivery N %	623 (71%)	193 (49%)	430 (88%)
Cesarean section N %	242 (27%)	189 (48%)	53 (11%)
Instrumental delivery N %	20 (2%)	13 (3%)	7 (1%)

Table 2. — *Indications for the induction of labor among primigravid and multiparous women (N = 885)*

Indications for induction	N	Percentage %
1-Postdate (41 weeks or more of gestation)	337	38.1
2-Premature rupture of membranes (PROM)	149	16.8
3-Reduced amniotic fluid index	130	14.7
4-Suspected fetal compromise	103	11.6
5-Hypertensive disorders	89	10.1
6-Preterm premature rupture of membranes (P-PROM)	25	2.8
7-A good-size baby in both diabetic and non-diabetic mothers	17	1.9
8-Maternal request	11	1.2
9-Stillbirth	9	1
10-Cholestasis in pregnancy	7	0.8
11-Advanced maternal age	4	0.5
12-Thrombophilic disorders	4	0.5

only 1% had an instrumental delivery (n = 7). The sample characteristics are presented in Table 1.

Table 2 shows that the postdate was the most common indication for induction as it accounted for 38% of the sample (n = 337). The second most common indication for induction was the premature rupture of the membranes (PROM), representing almost 17% of the sample (n = 149). For roughly 15% of the sample (n = 130) and 12% (n = 103), the indications for the induction of labor were reduced amniotic fluid index and suspected fetal compromise, respectively. Nearly 10% (n = 89) had hypertensive disorders.

The association between the repeated insertion of vaginal PGE2 tablets and both maternal and neonatal outcomes among primigravid women

A chi-square test was applied to assess the association between repeated doses of vaginal PGE2 insertion and the mode of delivery among primigravid women. The PGE2 insertion variable was categorized into the following two categories: two or fewer and more than two insertions of one tablet of vaginal PGE2 (3 mg of Dinoprostone, Prostin®). The mode of delivery was categorized into either vaginal delivery or cesarean section. The results showed that there was a statistically significant association, namely, X^2 (1) = 13.96, $P = 0.001$, between repeated doses of PGE2 and the mode of delivery. Interestingly, this indicates that primigravid women who received more than two doses of PGE2 were more likely to have a cesarean section (65.5%, n = 57 out of 87) compared with primigravid women who received two or fewer doses of PGE2 (42.9%, n = 132 out of 308).

The chi-square also indicated that there was no significant association between repeated doses of PGE2 and fetal outcomes. The results showed that there was no significant association between repeated doses of PGE2 insertion and admission either to the nursery or the neonatal intensive care unit (NICU) X^2 (1) = 2.11, $P = 0.14$. Moreover, the results showed that there was no significant association between repeated doses of PGE2 insertion and the APGAR score X^2 (1) = 0.06, $P = 0.88$. The results of the chi-square analysis are presented in Table 3.

The association between the repeated insertion of vaginal PGE2 and both maternal and neonatal outcomes among multiparous women. (Bear in mind that the dose of vaginal PGE2 used in multiparous women is half the usual dose. Each dose consisted of 1.5 mg of Dinoprostone, Prostin®)

A chi-square test was applied to assess the association between repeated doses of PGE2 insertion and the mode of delivery among multiparous women. The results showed that there was in fact no statistically significant association X^2 (1) = 2.15, $P = 0.14$ between repeated doses of PGE2 insertion and the mode of delivery.

The chi-square, however, did reveal that there was a significant association between PGE2 insertion and admission either to nursery or NICU, X2 (1) = 9.36, $P = 0.002$. This showed that multiparous women who received more than two doses of PGE2 were more likely to deliver a baby that needed NICU admission (35.2%, n =19 out of 54). This should be compared with multiparous women who received two or fewer doses of PGE2 and were shown to be

Table 3. — *A chi-square to examine the association between repeated insertion of vaginal PGE2 (3 mg of Dinoprostone, one Prostin® tablet) and both maternal and neonatal outcomes among primigravid women (N = 395)*

	Vaginal PGE2 Insertion		*p* value
Maternal and neonatal outcomes	Two or fewer	More than two	
Mode of delivery			0.001*
Vaginal delivery N %	176 (57.1%)	30 (34.5%)	
Cesarean section delivery N %	132 (42.9%)	57 (65.5%)	
Admission after delivery			0.14
Nursery	232 (75.3%)	72 (82.8%)	
NICU	76 (24.7%)	15 (17.2%)	
APGAR score			0.8
6 and less	36.7 (11.7%)	11 (12.6%)	
7 and more	272 (88.3%)	76 (87.4%)	

* *P* is significant at 0.05, NICU: neonatal intensive care unit, N: Number

less likely to deliver a baby that needed NICU admission (17.7%, n = 77 out of 436). Further analysis was carried out and logistic regression indicated that the Nagelkerke R2 was 0.02; only 2% of the variance in admission units could be explained by the repeated PGE2 insertion.

Moreover, the chi-square also indicated that there was a significant association between PGE2 insertion and the APGAR score, X2 (1) = 14.76, $P = 0.001$. This showed that multiparous women who received more than two doses of PGE2 were more likely to deliver a baby with 6 or less on the APGAR score (24.1%, n = 13 out of 54), compared with women who received two or fewer doses of PGE2 (7.8%, n = 34 out of 436). Further analysis was carried out and logistic regression indicated that the Nagelkerke R2 was 0.04, of which only 4% of the variance in the APGAR score could be explained by PGE2 insertion. The results of the chi-square analysis are presented in Table 4.

Discussion

We reviewed the medical literature in the PubMed database, searching for similar published studies that examine the correlation between exceeded doses of PGE2 for the induction of labor and maternal and neonatal outcomes. The most recent similar study was a retrospective one conducted at Aberdeen Maternity Hospital in the UK in October 2013. It showed that additional doses of vaginal PGE2 for nulliparous women with singleton pregnancies who were induced for being postdate were not associated with higher rates of adverse neonatal or maternal outcomes; nearly half of the women delivered vaginally [16]. An older randomized controlled study, conducted at Singapore General Hospital in 1999, also showed that using vaginal PGE2 three times over 24 hours, 6 hours apart, was more effective for the induction of labor in primigravid women with singleton pregnancies than for a second group taking one tablet of PGE2 over the same duration. However, there was no difference in the cesarean section rates or instrumental deliveries between the two groups. There was also no difference in neonatal outcomes, nor any cases of uterine hyperstimulation requiring treatment [14]. A study carried out in China in 2002 compared the rates of intrapartum cesarean section in (i) women who had a favorable Bishop score and for whom no prostaglandins had been inserted for the induction of labor with (ii) women who had had one or two doses of Prostaglandin for induction and (iii) women who had received three doses of Prostaglandin for the induction of labor. It was found that the third group had the highest rate of emergency cesarean sections, not to mention the impact on maternal and fetal wellbeing [19].

In addition to the aforementioned studies, a clinical survey of obstetric units conducted in England in 2007 showed that more than 86% of medical practitioners regularly used more than the recommended dose of vaginal PGE2, supporting the clinical claim that repeated doses of vaginal PGE2 is safe for both the mother and the neonate [20]. We also conducted our own electronic survey among Jordanian obstetricians in 2018 and asked them, "Do you think that inserting a third dose of Prostin® (3 mg Dinoprostone) for the induction of labor for primigravid women is safe for the mother and the neonate?" As expected, the results confirmed the general, global consensus among professional practitioners about the safety of repeated doses of vaginal PGE2. The response rate was 70.5% as 55 out of 78 responded to the question with either yes or no. The survey showed that 80% of the respondents, (44 out of 55), said that they used vaginal PGE2 above the doses recommended by the NICE guidelines as they felt it was a perfectly safe practice.

Modern obstetrics should be based on a solid body of evidence rather than on a vague clinical sense of what should be done. The evidence should be carefully examined before any current practice is changed. Our study assessed the relation between repeated doses of PGE2 and maternal and neonatal safety. We evaluated the relationship between repeated doses of PGE2, above the recommended dose, for the induction of labor for different indications, as well as the maternal and neonatal outcomes. The results of our study support the clinical sense that additional doses of vaginal

Table 4. — *A chi-square to examine the association between the repeated insertion of vaginal PGE2 (1.5 mg of Dinoprostone, half Prostin® tablet) and both maternal and neonatal outcomes among multiparous women (N = 490)*

	Vaginal PGE2 Insertion		*p* value
Maternal and neonatal outcomes	Two or less	More than two	
Mode of delivery			0.14
Vaginal delivery N %	392 (89.9%)	45 (83.3%)	
Cesarean section delivery N %	44 (10.1%)	9 (16.7%)	
Admission after delivery			0.002*
Nursery	359 (82.3%)	35 (64.8%)	
NICU	77 (17.7%)	19 (35.2%)	
APGAR score			0.001*
6 and less	34 (7.8%)	13 (24.1%)	
7 and more	402 (92.2%)	41 (75.9%)	

* *P* is significant at 0.05, NICU: neonatal intensive care unit, N: Number

PGE2 above the recommended dosage do not increase maternal or neonatal morbidity. This result gives the study the potential to reduce the rate of cesarean sections, as it encourages all professional medical practitioners caring for women admitted to the labor ward for the induction of labor to continue the process of induction for women with unfavorable cervixes by repeating vaginal PGE2 insertion for a third time.

We believe that adopting this policy will increase the number of vaginal births, which in turn will have a direct beneficial effect on patients, enabling them to avoid major surgery along with its potential complications. There will also be an indirect beneficial effect on national health systems as costs and the need for caesarian specialists will be substantially reduced. This potential benefit will be of great importance not only in Jordan but worldwide for, due to many reasons [21], there has indeed been a universal rise in the number of cesarean sections. Particularly in Jordan, the escalating rate of cesarean deliveries is a major concern. For example, Al Rifai found that cesarean section rates have risen over time from 18.2% in 2002, to 20.1% in 2007, and to 30.3% in 2012 [22].

Conclusion

Our study has shown that repeated doses of vaginal PGE2 insertion for the induction of labor above the current recommendations are not associated with increased maternal or neonatal morbidity for both primigravid and multiparous women. But it has also shown that in primigravid women, the risk of cesarean section will increase for women who have received more than two doses of PGE2. In other words, the study supports the need for counseling primigravid women who have had the recommended doses of PGE2 but have not yet shown a response to it. Our study has demonstrated that such women are in fact less likely to have a vaginal birth if they agree to take a third dose of PGE2. There is, however, a nearly 30% chance for such women to deliver vaginally and avoid a cesarean section if they agree to a third dose. At the same time, they can be reassured that a third dose will have no adverse effect on them or on the neonate. By thus focusing on the positive aspects of a third dose of PGE2 in primigravid women, we anticipate a reasonable reduction in cesarean section rates among those primigravid women who had previously been considered failed to be induced. This could be achieved if the current practice changes such that a third dose of PGE2 is administered to all women scheduled for the induction of labor. We are confident that this can be achieved especially when we are reassured by the fact that there was no single case of uterine hyperstimulation in our study. The adoption of this recommendation will have a tremendous effect in hospitals, such as our labor ward unit, where the cesarean section rate is high. For multiparous women, our study showed no significant change in the risk of having a cesarean section or any significant clinical harm from a third dose of PGE2.

Limitations of the Study

Maternal morbidity was not fully assessed in our study other than in cesarean section rates, uterine hyperstimulation and uterine rupture. In fact, we wanted to include the postpartum hemorrhage rate among women in our study as one of the studied variables, but there were difficulties in assessing the exact amount of bleeding, and post-delivery hemoglobin levels were not done routinely for all patients delivered vaginally. Future studies that include a larger number of women and focus more on maternal morbidity might provide better results.

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Conflict of Interest

The authors declare no competing interests.

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