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Review Article

Induction of Labour with Prostaglandins: is a Shift from the Traditional Practice Imperative?

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Abstract

Induction of labour is aimed at expediting delivery to optimize maternal/fetal outcome and to achieve vaginal birth. Our study was aimed at determining the success of Induction of Labour using Prostaglandins E2 in terms of cervical ripening and labour onset, to determine the number of doses of Prostaglandins E2 required for accomplishing successful Induction of Labour, to define the relationship between the gestational age and the doses of Prostaglandin E2 required and lastly to seek if any relationship existed between Induction of Labour with Prostaglandins E2 and the mode of delivery. The study was conducted by retrospective analysis of electronic medical records. All the patients who underwent Induction of Labour in Women's Hospital, Doha were included. Those who had previous caesarean and those who had Induction of Labour without prostaglandin as first induction method were excluded. The rate of induction of Labour with Prostaglandins E2 was 10.19% (n = 3465) with a success rate of 91%. Majority of Primigravida required three or four doses of with Prostaglandins E2 for accomplishing successful Induction of Labour (P value of 0.0005 and 0.0009 respectively). On the other hand majority of multigravida required one or two doses of Prostaglandins E2 for successful Induction (P value of 0.02 and 0.006 respectively). There is also a positive association between induction with two or three doses of with Prostaglandins E2 and patients who achieved favorable Bishop Score (P value of 0.001 and 0.005 respectively) and those who entered active labour. 83%the study group achieved vaginal delivery, 17% required Lower Segment Caesarean section. Induction of Labour with two or three doses of Prostaglandins E2 increased the likelihood of having a vaginal delivery (P value of 0.03 and 0.007 respectively). Most of the patients who were induced between 37- 40 weeks of gestation required more doses of with Prostaglandins E2 (P value = 0.04) compared to those who had induction at 40 weeks and beyond. Our study concluded that those who received two or three doses of with Prostaglandins E2 were more likely to achieve a favorable Bishop's score, enter active labour and achieve vaginal delivery. There is no association between Induction of labour with Prostaglandins E2 and the rates of caesarean section. The number of doses of Prostaglandins E2 required for successful Induction of labour increased when induction was carried out at earlier gestational age.

Keywords: *Prostaglandins E2; Induction of Labour; Bishop's Score; Vaginal Delivery; Lower Segment Caesarean Section*

Abbreviations

IOL: Induction of Labour; PG E2: Prostaglandins E2; LSCS: Lower Segment Caesarean Section

Introduction

Induction of labour (IOL) is offered to pregnant women when it is thought that the outcome will be better for the mother or the baby or both if delivery was expedited and chances of vaginal birth were deemed reasonable. Techniques like amniotomy, mechanical dilatation using hydrostatic bag and the use of oxytocin predominated the initial era of IOL. Though they are still used in the current obstetric practice, they could not always guarantee the most optimal results.

The use of prostaglandins in clinical practice for the purpose of IOL emerged in 1960 as a result of work by Sune Bergstrom [1]. The primary use of prostaglandins is cervical ripening with the view of facilitating Induction of Labour with either amniotomy or/and oxytocin. Labour onset after insertion of prostaglandins is a desirable side effect. Therefore, compared to the earlier methods of IOL, the use of Prostaglandins had definitive advantage since they aided both cervical ripening and initiation of uterine contractions. Therefore over the years prostaglandins emerged as the most commonly used pharmacological agent for Induction of Labour.

Two last two decades have seen an over exuberance in the incidence with the literature quoting a number as high as 23.3%in developed countries like USA [2].

There is a wealth of literature addressing the various aspects of IOL using prostaglandins, including maternal and fetal outcome in terms of association with mode of delivery, fetal distress, uterine hyperstimulation, induction to delivery interval and postpartum hemorrhage [3-7] insert citation at the end. Most of these studies that have looked into the outcome had defined success of Induction of Labour with Prostaglandins only in terms of achieving a vaginal delivery. Since the purpose of IOL is to cause a non-labouring woman to go into labour, the efficacy of PGE2 for Induction of Labour should ideally be defined in terms of (i) change in the Bishop Score and, (ii) onset of labour.

Also, after an in-depth review of the existing literature on the various aspects of Induction of Labour with prostaglandins E2,we could conclude that there is no conclusive evidence on the various other cardinal aspects of Induction of Labour like (a) number of doses of Prostaglandins E2 required to achieve successful induction, if they varied according to the parity (b) the relationship between the gestational age and the doses required for successful Induction of labour (c) relationship between Induction of Labour and mode of delivery, (d)whether the outcome varied according to the number of doses received [4,8-11].

Aim of the Study

In our study we aimed to address these important knowledge gaps of induction of labour with prostaglandins E2.

Management of the study group

The decision for Induction of Labour was taken by an experienced senior clinician after cervical assessment using the Bishop score.

1. Prostaglandins E2 vaginal gel (when an abbreviation is first cited in the text, it should be written in full (PGE2) (which comes in 2 mg strength) given as two doses at 8 hour interval (maximum total dose of 4 mg over 24 hours).
2. Prostaglandins E2 vaginal tablets (which comes in 3 mg strength), given as two doses 8 hourly (maximum total dose of 6mg over 24 hours).

   The time interval for giving the divided doses is 8 hours. The dosage regimen was same for both primigravida and multigravida.

Methods

This study was conducted as a part of the quality improvement initiative to review the practice of Induction of labour in Women's Hospital, Doha.

This was a retrospective review of electronic records of all the patients who underwent IOL in Women's Hospital, Doha. The Women's Hospital is one of the largest tertiary obstetric units in Middle East and is responsible more than 17,000 births each year. The study was conducted over a period of 24 months (November 2015 to October 2017).

Those patients who had previous cesarean section and those women who had an IOL without prostaglandin as first induction medication were excluded.

The data was analyzed using 't test' and Pearson's correlation co efficient.

Results

A total of 3465 patients underwent Induction of Labour (i.e. a rate of 10.19%) during the study period, of these, patients, 2025 were primigravida (58%) and 1344 were multigravidas (39%).

The rate of success of Induction of Labour with Prostaglandins E2 was defined in terms of (i) cervical ripening (ii) the number of patients who entered active labour.

Of the total patients who received prostaglandins, 59% of the patients were transferred to labour ward in active labour, 32% of patient achieved favorable cervical score (Bishop's score >/= 6) to proceed with augmentation of labour. This quotes the success rate of Induction of Labour as 91%. Five percentage of the patients were taken from the prelabour ward for Lower Segment Caesarean Section. Indications for the Lower Segment Caesarean Section included presumed fetal compromise, failed induction, patient refusal to continue with induction and suspected abruption placentae.

There is positive association between parity and the number of doses required for successful IOL (primi requiring three or four doses of Prostaglandins E2 for successful Induction of Labour, P value of 0.0005 and 0.0009 respectively) The correlation coefficient being r = 0.63 > and r= 0.68 respectively indicating a moderate positive correlation between the two variables.

On the other hand, the majority of multigravida required only one or two doses of PGE2, P value of 0.02 and 0.006 respectively). Prostaglandins E2 for successful Induction of Labour, P value of 0.0005 and 0.0009 respectively) the correlation coefficient being r = 0.46 and r = 0.55 respectively indicating statistically significant positive correlation between the two variables.

There is also a positive association between induction with two or three doses of PGE2 and patients who achieved favorable Bishop Score (P value of 0.001 and 0.005 respectively) and those who entered active labour; the correlation coefficient being r = 0.70 and r = 0.56 respectively indicating strong positive association.

Sixty seven percent of the patients in the study group achieved normal vaginal delivery, whilst 16% of the patients required instrumental vaginal delivery and 17% delivered by cesarean section. Induction with two doses or three doses of PGE2 increased the likelihood of having a vaginal delivery (P = 0.03, P = 0.007 respectively) (correlation coefficient 0.03 and 0.007 respectively). Also, the association between induction with prostaglandins and the number of patients who went for LSCS from the pre labour ward or from the labour ward were not significant (P value 0.59, 0.63 respectively), i.e. IOL with prostaglandins E2 did not increase the rate of LSCS.

There is a statistically significant association between the number of doses of PGE2 required for successful IOL and the gestational age. Most of the patients who were induced between the gestational age 37 - 40 weeks required 3 doses of PGE2 (correlation coefficient is r = 0.69; P value = 0.04). On the other hand those who had induction at 40 weeks and beyond required only 2 doses of PGE2 (correlation coefficient is r = 0.59; P value = 0.05).

Discussion and Conclusion

International trials which have looked into the various outcome of Induction of labour have failed to draw definitive conclusions. The aim of our study was to contribute to this discussion based on our experiences and results. The various conclusions drawn from our study are as follows.

The rates of IOL in our hospital was 10.19%, which is much lower than most of the units in the developed regions of the world (23.3%in U.S [2] 21.8% in Canada [13] and 29.4% in U.K [12]. The lower rates of induction in our setting could be explained by the following factors.

1. Strict adherence to IOL policies and guidelines
2. Discouraging elective IOL and IOL for non-recognized indications
3. The propensity of the women in Qatar towards avoiding any medical interventions during the pregnancy including IOL.

Patterns of Maternity Care in English NHS Hospitals recommends "Learning lessons from those hospitals that maintain lower induction of labour rates will add value to the quality of care provided". The pattern of IOL represented by our hospital can be used as a benchmark for audit in other obstetric units across the world where rising IOL rates pose significant burden to the healthcare settings.

The low rates as presented by our unit also means that the rates of IOL can be reduced globally by strict adherence to policies and guidelines and by offering IOL only to carefully selected patients who has a definite compelling and convincing reason for IOL [14]. Reducing IOL will have favorable impact on health care statistics in terms of improved patient safety, increased availability of resources, decreased interventions, reduced cost and reduced work load. Also, we recommend strongly against the practice of elective induction of labour for non-recognized maternal or fetal indications.

There is paucity of literature regarding the effects of single versus multiple doses of PGE2 on success of IOL and if the effect varied according to the parity. Our study has concluded that there is positive association between parity and the number of doses required for successful IOL (majority of primi required 3 or 4 doses of PG for successful IOL, P value of 0.0005 and 0.0009 respectively, multigravida required 1 or 2 doses of PGE2, P value of 0.02 and 0.006 respectively).

In our clinical settings, these findings may aid the caretaker to appropriately counsel the patient prior to IOL. Also, it is interesting to note that, the patients who required only one or two doses of PGE2 to enter active labour were mostly multigravidas. Induction of labour in multigravida with repeated doses of prostaglandins pose major concern as it is known to be associated with increased risk of uterine rupture. Many obstetrical units might detain from induction with PG in multi and grand multi owing to this concern. In the Middle East where multiparity and grand multiparity is a common event rather than an exception [15], the findings may mitigate the safety concerns of inducing a multiparous mother as less doses of PGE2 are required for successful IOL.

Our study has shown a positive association between induction with two or three doses of PGE2 and patients who achieved favorable Bishop Score i.e. those patients who received two or three doses were more likely to achieve a favorable Bishop score for further augmentation of labour with amniotomy or oxytocin. (P value of 0.001 and 0.005 respectively). Also, there is a positive association between induction with three doses and the number of patients transferred to labour ward in active labour.ie, those patients who received 3 doses of PGE2 was more likely to achieve successful IOL in terms of entering the active labour.

In a health care setting like ours which caters the obstetric needs of the entire population of the country, we often face shortage of resources in terms of staff and beds. Since IOL is a high risk procedure with many potential risks associated with it, the mother and the baby needs to be monitored closely and continuously, IOL process can strain the health care resources immensely. We concluded in our study that most of the patients who received two or three doses of PGE2 were more likely to achieve cervical ripening or to enter active labour. Therefore, instead of using the PGE2 vaginal tabs or gel every 8 hourly, we can offer the patients 10 mg dinoprostone controlled release pessary (Propess) or sustained-release vaginal insert (Cervidil) or intracervical gel (Prepidil) which are administered every 12 hourly. This will undoubtedly reduce the number of vaginal examination as well as the number of repeat doses. Also, this will significantly reduce the workload on the physicians and midwife.

Randomized controlled trials which compared Dinoprostone slow release pessary (Propess) with gel (Prostin) for induction of labour at term has found no significant differences between the two groups in induction-to-delivery interval, mode of delivery, number of women delivering within 24h and neonatal outcomes [16].

From an economic point of view, the costs of four PGE2 preparations are comparable. Cervidil, the controlled-release gel preparation is more cost effective compared to other prostaglandin preparation due to the following reasons (i) the time to achieve vaginal delivery is shorter, (ii) hospital stay is shorter, (iii) Less frequent requirement of oxytocin without increase in the rate of complications [16], (iv) Also, Cervidil allows easier removal in case of uterine tachysystole with Fetal heart rate changes and requires only a 30-minute delay before the initiation of oxytocin upon its removal compared with an interval of 6 hours for the gel [17], (v) Another merit of cervidil is the fact that it does not require refrigeration unlike dinoprostone, (vi) Cervidil was also associated with decrease in instrumental deliveries [17].

Overall, in the light of the above evidence, we recommend offering the patients Cervidil instead of Dinoprostone in highly demanding health care settings like ours to improve patient care without compromising the quality of care. The introduction of Cervidil will undoubtedly diminish the strain on health resources and allow more compliance to the IOL guidelines.

Criteria for failed labour induction have not been standardized internationally. Our national guidelines defines failed IOL as unfavorable cervix after 2 doses of PGE2 [14]. In the light of our finding that the third dose of PGE2 significantly improved the success of IOL, we suggest to consider revising the existing national and international guidelines to standardize the definition of failed IOL (E.g. failure to achieve a favorable Bishop's score or active labour after 3 doses of PGE2).

There is a huge wealth of international literature which has looked into the association between IOL and LSCS. Few meta-analysis and systematic reviews have suggested that the risk of cesarean delivery following labour induction was significantly lower than the risk associated with expectant management [18-20] especially when it is carried out at term or beyond term [21]. This is in contrast to the statistics for England in 2011/2012 showing an increased rate of emergency caesarean section for those women having an induction of labour compared with those women having a spontaneous labour [22]. There are also other observational study which has concluded that IOL increases the LSCS rates especially if it was carried out for non-recognized [23,24]. The evidence regarding the association of IOL and LSCS in gestational age < 40 weeks is inconclusive [25].

Our study concluded that Induction with two doses or three doses of PGE2 increased the likelihood of having a vaginal delivery (P = 0.03, P = 0.007 respectively). Also, the association between induction with prostaglandins and the number of patients who went for LSCS from the pre labour ward or from the labour ward were not significant (P value 0.59, 0.63 respectively). The number of PGE2 doses did not confound this finding. The patient preference is unlikely to invalidate this finding as the women in Middle East favor IOL than elective LSCS.

We have not specifically looked in our study if the gestational age will confound this conclusion. We suggest further research regarding this draw definitive evidence.

The most common indication for medical induction of labour is prolonged pregnancy [11]. However, for various medical indications, induction may be attempted at different gestational periods.

When we looked into the relationship between gestational age and the number of doses, we could infer that the number of doses of PGE2 required to achieve successful IOL was fewer as the gestational age advances. i.e. most of the patients who had IOL between 37 - 40 weeks required 3 doses (P value 0.04), whereas those who were beyond 40 weeks required just two doses (P value 0.009). The physician can use this information when they counsel the patients against elective Induction of labour at term or earlier [26].

Strengths and Limitations

The data is derived from one of the largest obstetrical service in Middle East. So the large study population will significantly minimize the bias. As extensive sensitivity analyses and scenario analyses showed consistent results, we can conclude that the model is robust against the most influential uncertainties.

Unlike the earlier studies on outcome on IOL, we have aimed to look only into the above given priority outcomes. The fact that we have not matched the patients for their demographics, gestational age, and indications for IOL or Bishop Score may confound our existing findings. So we urge obstetricians worldwide to do more Randomized controlled trials on these priority outcomes to consolidate the evidence to improve the care of Women through appropriate and effective interventions.

Recommendations

1. Offer IOL only for recognized indications to reduce the global burden of IOL.
2. Cervidil can be offered as better alternative for Dinoprostone.
3. To standardize the definition of failed IOL.

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Disclosure of Interests

The authors whose names are listed immediately below certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Contribution of Authorship

Dr Huda Saleh and the members of the Quality and Safety division of Women's Wellness and Research Centre conceived the idea and planned the project as a part of quality improvement. Dr Huda Saleh and Dr Zeena Al Mansouri supervised the project. The members of the Quality and Safety division also contributed to the data collection and computation and analysis of the data. Dr Jis Thomas verified the analysis and took the lead in writing the manuscript. Dr Rati Barman supervised the preparation of the manuscript. Dr Sunday Amu and Dr Abdullah Awad A. Al Ibrahim contributed to the final version of the manuscript.

Details of Ethics Approval

The study was exempted from ethics approval by the Medical Research Council, Hamad Medical Corporation, Doha as it was done as a part of Quality improvement initiative by the Division of Quality and safety, Women's Wellness Research Centre, Hamad medical Corporation, Doha-Qatar.

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