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The effect of introduction of misoprostol for induction of labour on pregnancy in gravidas with pre-eclampsia

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ABSTRACT

Misoprostol has revolutionized labour induction since the early 1990's, because it is inexpensive and very effective. Eclampsia is common unless the pregnancy can be terminated by induction or by caesarean section. This study was done to determine the impact of Misoprostol used for induction of labour, on the outcome in patients with pre-eclampsia (PE) at the University of the West Indies Kingston Jamaica. This was a retrospective analysis of pre-eclamptic women who were managed before and after the introduction of misoprostol into routine usage for induction of labour. We compared 793 women (controls) in the pre misoprostol era (1986-1991) with 709 in the misoprostol era (1993-1998). Outcome variables were the frequency of mild and severe PE, eclampsia, misoprostol and syntocinon inductions, foetal complications and use of caesarean section (CS). Analysis of frequency of eclampsia, neonatal admissions and CS, during the misoprostol years, was also done to eliminate other confounding variables because of the influence of each era. Logistic regression was used to determine the impact of all variables. In comparison to controls, patients induced in the misoprostol years had a greater incidence of severe PE ($p < 0.05$), neonatal admissions ($p = 0.007$), foetal distress ($p < 0.05$); a higher CS rate ($p < 0.05$); but fewer oxytocin inductions ($p < 0.05$). However, sub group analysis of the misoprostol years alone, showed a reduction in the incidence of CS, eclampsia, and neonatal admissions in women who were induced with misoprostol ($p < 0.05$). Logistic regression revealed a lower odds of CS delivery (OR 0.867, 95% confidence interval .02, .37) using misoprostol. These findings suggest that in patients with PE, induction of labor with Misoprostol had a beneficial effect on pregnancy outcome with a decreased incidence of CS, eclampsia and neonatal admissions, but it has not had a significant impact on the main problems in these patients between the two eras as other factors may be important in the management of these patients independent of misoprostol induction.

Keywords: Misoprostol; Eclampsia; Labour Induction

1. INTRODUCTION

Pre-eclampsia is defined as the occurrence of hypertension in combination with proteinuria, developing after 20 weeks gestation in a previously normotensive non-proteinuric patient. It occurs in approximately 3 to 14 % of all pregnancies worldwide and is the leading cause of maternal mortality in Jamaica [1,2]. Outcome of pregnancies complicated by pre-eclampsia is often good, but this disease is unpredictable, sometimes progressing without warning, from its mild to severe form with devastating maternal and foetal complications. The definitive treatment is delivery of the foetus. If untreated; pre-eclampsia is associated with increased risk to the foetus of; intrauterine growth restriction, stillbirth, and neonatal death [3] and to the mother an increased risk of; eclampsia, severe hypertension, HELLP syndrome (Haemolysis, Elevated liver enzymes, Low Platelets), abruption, cerebral haemorrhage, pulmonary oedema, liver haemorrhage, renal failure. The presence of any of these findings in the mother usually requires immediate delivery of the foetus as conservative management in such cases can result in serious maternal and/or foetal complications [4].

Misoprostol is a prostaglandin E1 analogue originally developed for the prevention of non-steroidal drug induced gastritis. However, with the accumulation of evidence that intra-vaginal administration is an effective alternative to endocervically or vaginally administered prostaglandin E2 preparations for cervical ripening and labour induction, at a much reduced cost, it has since been used extensively worldwide for labour induction [5-7]. Local work done by Fletcher et al in 1993 and 1994 concurred with these findings [8,9]. A meta-analy-

sis of trials done has shown that vaginal misoprostol appears to be more effective in inducing labour than conventional methods of cervical ripening and labour induction [10].

Misoprostol was first used at the University hospital in 1992 and has been the principal induction agent used in patients with an unfavourable cervix, since its introduction [11]. Prior to this time patients with pre-eclampsia requiring delivery, were either delivered by caesarean section or had induction of labour with oxytocin if the cervix was favourable or with dinoprostone, which because of cost was not always available. With the introduction of misoprostol, vaginal delivery could be planned, attempted and achieved in patients with mild or severe pre-eclampsia, regardless of gestational age or cervical Bishop Score as cervical ripening and induction of labour could now be achieved. In theory, we were no longer hampered by the presence of an unfavourable cervix and its associated complication of failed induction. This factor is particularly relevant in preterm patients with severe pre-eclampsia, in whom expeditious delivery is sometimes necessary. Ten percent of pre-eclampsia occurs in pregnancies less than 34 weeks of gestation but it has been shown that fewer than 1/3rd of women with severe pre-eclampsia/eclampsia remote from term; *i.e.* less than 28 to 32 weeks of gestation- with an unfavourable cervix will successfully deliver vaginally [12]. Failed induction is an undesirable complication as it not only increases caesarean section rates but also increases foetal and maternal morbidity and mortality.

The purpose of our study was to primarily determine if the introduction of Misoprostol for induction of labour at UHWI has made a significant difference in the outcome of the patients with pre-eclampsia requiring delivery. Our secondary aim was to see if the use of misoprostol in pre-eclamptic patients, had any influence on pregnancy outcome, such as, a decreased incidence of severe pre-eclampsia, eclampsia or other maternal complications; an improved perinatal outcome; or a decrease in the caesarean section rate.

2. PATIENTS AND METHODS

This retrospective cohort study was conducted at the University Hospital of the West Indies. The pregnancy outcome of all women with pre-eclampsia delivered in this institution in the five years preceding misoprostol's introduction (1986-1991) (Group 1) was compared with the outcome of those delivered during the five years after it came into standard usage (1993-1998) (Group 2). The study was approved by the ethical committee at our institution.

Data was obtained from the labour ward Logbook in which is recorded information about all the patients delivered on the Labour Ward at the University Hospital. All the patients with pre-eclampsia delivered during the two 5 year periods were identified. Initials, registration number, age, parity, gestational age at delivery, labour inductions and method *i.e.* Misoprostol versus Oxytocin, Caesarean Sections done, maternal and foetal complications, neonatal deaths, birth weight, Apgar score and Special Care Nursery (SCN) admissions were all recorded.

The primary outcome variables were the number of patients with a diagnosis of mild and severe pre-eclampsia; misoprostol and oxytocin inductions; eclampsia and other maternal complications such as HELLP syndrome, maternal deaths, ICU admissions and abruption; foetal complications as measured by the amount SCN admissions, APGAR Score, neonatal deaths and intrauterine growth retardation (IUGR); Caesarean Sections and indications such as foetal distress, failure to progress, failed induction and previous C-section. Secondary outcome variables were the amount of cases of eclampsia, SCN admissions and C-Sections in those patients induced with misoprostol.

Values were expressed as means with standard deviations, medians with ranges, or frequencies (per cent) as appropriate. For continuous outcome variables, independent t-tests were used to compare differences in means between periods. Differences in frequencies and proportions for qualitative outcome variables between periods were tested with chi-square statistics. Logistic regression models were constructed to determine the relationship between period adjusting for possible confounding clinical factors and dichotomous outcome variables. The data were analyzed using Stata version 7.0 for Windows (Stata Corporation, College Station TX 77840).

3. RESULTS

Between 1986 and 1991 (Group 1) there were a total number of 709 women (47%) with pre-eclampsia delivered on the labour ward at the university hospital, while between 1993 and 1989 (Group 2) there were 793 women (53%). Demographic data are shown in **Table 1**. Misoprostol was only used for induction in Group 2.

The mean age of the women in was significantly greater in year group 2 than year group 1 but the birth weight and gestational age of preterm deliveries in group 1 was significantly greater than group 2. (**Table 1**).

There was a significant association between the severity of pre-eclampsia (PE) and year group with the greater proportion in group 2 but the proportion of women with severe PE who developed eclampsia was not different according to year group (**Table 1**).

As expected there was significantly less use of Oxyto-

cin in the latter period (63% vs 34% $p < 0.05$). Misoprostol was used to induce 287 women 42 of whom received both oxytocin and misoprostol whilst a total of 364 received oxytocin (**Table 1**).

Table 4 shows the frequency and proportions of eclampsia and other maternal complications. There was no significant difference between the groups and the frequency of eclampsia, maternal death, abruption, HELLP syndrome, or ICU admissions.

Foetal Complications are as shown in **Table 2**. There was a significant association between foetal admissions to the SCN and year group with more admissions in group 2 (24% vs 30% $p = 0.007$) but there was no difference in the proportions of neonatal deaths or IUGR between the two groups. There was also no difference in median Apgar score between the groups.

Table 3 shows the frequency of C-Sections and major indications for C-Section associated with Misoprostol use for induction of labour. There was a significant association between C-Section and year group with more C-Sections being done in Group 2 ($p = 0.000$). There was also a significant association between foetal distress and year group with more cases of foetal distress in Group 2 but no difference in the proportion of failure to progress, failed induction and previous C-Sections between the two groups

However sub analysis of year group 2 showed a significant association between C-Section incidence, eclampsia, and SCN admissions with misoprostol use in the latter 5 years with significantly more C-Sections, eclampsia and SCN admissions in those who were not induced with misoprostol (**Table 4**).

Table 1. Maternal characteristics.

variables	Group 1 Pre-misoprostol (n = 793)	Group 2 After-misoprostol (n = 709)	P value
Age (y)*	26.5 ± 5.3	27.2 ± 6.0	0.02
Parity (median)	0 + 1	0 + 1	
Mild PE	531 (74)	455 (57)	0.000
Severe PE	178 (26)	338 (43)	0.000
Misoprostol	0	287 (37)	
Oxytocin	264 (34%)	100 (13%)	0.000
Eclampsia	31 (4.3)	45 (5.6)	0.250
Abruption	7 (0.9)	17 (2.1)	0.074
HELLP syndrome	3 (0.4)	3 (0.3)	0.891
ICU admission	4 (0.5)	2 (0.2)	0.339
Maternal death	4 (0.5)	3 (0.3)	0.598

*Values are expressed as mean ± standard deviation. Other Values expressed as n (%) of patients unless otherwise stated.

Table 2. Fetal and neonatal parameters.

Variables	Group1 Pre-misoprostol	Group2 After-misoprostol	P value
IUGR	25 (3.5)	24 (3.0)	0.586
Gestational age of preterm deliveries*	32.7 ± 2.9	31.1 ± 3.2	0.003
Birth weight (kg)*	2.8 ± 0.8	2.5 ± 0.8	0.00
SCN Admission	172 (24)	238 (30)	0.007
Neonatal Death	2 (0.2)	4 (0.3)	0.495

*Values are expressed as mean ± standard deviation. Other values expressed as n (%) of patients.

Table 3. C-Section rates and Indications.

Variable	Group 1 Pre-misoprostol	Group 2 After-misoprostol	P value
Caesarean section	218 (30)	328 (41)	0.000
Foetal distress	18 (2.5)	55 (6.9)	0.000
Failure to progress	18 (2.5)	23 (2.9)	0.668
Failed induction	12 (1.7)	15 (1.9)	0.772
Previous c-section	30 (4.2)	33 (4.1)	0.946

Values expressed as n (%) of patients.

Table 4. Outcome in patients seen in the misoprostol years.

Variable	Misoprostol N = 287	No Misoprostol N = 506	P value
Eclampsia	8 (2.7)	37 (7.3)	0.008
C-Section	40 (14)	286 (56)	0.000
SCN admission	58 (21)	180 (35)	0.000

Values expressed as n (%) of patients.

The possible confounding variable of maternal age, gestational age of preterm deliveries and parity were eliminated by a logistic regression which showed that the use of misoprostol lowered the odds of C-Section delivery OR –0.867 [95% confidence interval 0.02, 0.37]. Eliminating these variables, also showed the use of misoprostol was not associated with becoming eclamptic OR 1.52 [95% confidence interval 0.31, 7.28].

4. DISCUSSIONS

Intra-vaginal misoprostol used in patients with severe pre-eclampsia remote from term has been previously confirmed to be effective for labour induction in cases where expeditious vaginal delivery is necessary [13]. However; this is the first study, to our knowledge addressing the impact of labour induction with misoprostol on pregnancy outcome in pre-eclamptic patients. Misoprostol is in fact inexpensive, readily available and very effective in inducing labour even with an unripe cervix. Its use also avoids the performance of caesarean sections in patients who are very ill.

It was thought that fewer patients would develop severe PE since they would have been diagnosed and induced before this developed, however a greater proportion of women had severe pre-eclampsia in the latter 5 years than in the earlier period. This is hard to explain since we do not believe the misoprostol is causing severe pre-eclampsia. However despite this finding, the proportion that went on to develop eclampsia was not different, so in fact fewer women with severe pre-eclampsia, developed eclampsia. This could possibly have been a beneficial effect of misoprostol induction. It is however important to point out that only 37% of the patients in the misoprostol years were induced with misoprostol and in these patients caesarean section, eclampsia and admission to the special care nursery rates were lower than in the 63% not induced with misoprostol. This is an important finding because while it is possible that these patients were not as ill as those not induced with misoprostol, it may be an indication that misoprostol use is beneficial in these patients.

Oxytocin was used with less frequency in the latter 5 years (34 vs. 13%). This concurs with a previous Meta-analysis which shows that the use of misoprostol was associated with a 50 % reduction in the use of oxytocin [14].

Although a decrease in the incidence of caesarean section was expected in the latter years there was a surprising increase, with more caesarean sections being done during the period in which misoprostol was used. This is probably not unexpected as the caesarean section rates in general worldwide have increased over the years. This was however corrected by elimination of the confounding variables which yielded the expected decreased odds of caesarean section delivery in the latter five years, as has been previously noted by others [10]. A high caesarean section rate (80%) has been described in eclamptic patients in other centres in the Caribbean and this has been said to be the best mode of delivery for such patients [15]. However this present study seems to suggest

that misoprostol induction may be a useful alternative to emergency caesarean section in these very ill patients.

The frequency of failure to progress and failed induction was the same in both groups, so the introduction of misoprostol did not have a significant impact as expected and thus show a beneficial effect over the era with oxytocin induction only. There were also significantly more cases of fetal distress in the latter group. An earlier study had found an association between the incidence of fetal distress and Misoprostol when used in doses greater than 25ug [7] and this has been a constant finding of most large studies [10].

The fact that the gestational age at delivery and mean neonatal birth weight were both lower after the introduction of misoprostol is also an important finding. What this implies is that we now have the ability to intervene earlier with induction of labour when severe pre-eclampsia occurs. This could also be a reason for the greater number of special care nursery admissions.

The overall frequency of eclampsia and other maternal complications in the two groups were similar and no improvement was seen in perinatal outcome. The fact that more special care nursery admissions occurred in the latter 5 years even though the mean Apgar scores were similar may be an indication of differences in care in the two eras. However misoprostol induction has been shown to be associated with foetal distress (hyperstimulation syndrome) and increased passage of meconium especially at the high doses used at UWI [7,16].

Pregnancy induced hypertension is the leading cause of maternal mortality in Jamaica and timely delivery is the only way to stop the progress of the condition. It was therefore hoped that the introduction of misoprostol to the obstetric armamentarium would have shown a dramatic difference in this outcome in these patients. This however has not been the case as shown in this study and also as has been demonstrated by the fact that despite the introduction of misoprostol hypertensive disorders still remain the leading cause of maternal mortality [12,17] with no decrease in maternal mortality rates.

The main drawback to studies of this type is the impact of differences in management which could have occurred in the two different time periods which have not been taken into account. These may explain some of the differences seen.

Using the data from one period alone has shown some differences indicating that the introduction of misoprostol may have been beneficial in these patients although the overall impact appears disappointing.

Thus, it can be concluded that the introduction of misoprostol is beneficial to pregnancy out come in patients with pre-eclampsia but has not shown significant improvements between the two eras, as there are other factors which may possibly be involved which need to be identified and corrected. We therefore believe that the introduction of misoprostol to decrease maternal complication rates in these patients must be associated with careful patient selection and close monitoring in labour.

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