Full length article

Misoprostol vaginal insert (Mysodelle) versus Dinoprostone intravaginal gel (Prostin) for induction of labour

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ABSTRACT

Objective: The aim of this study is the compare the effectiveness and safety of Misoprostol Vaginal Insert (Mysodelle) versus Dinoprostone intravaginal gel (Prostin) for induction of labour.
Study design: We performed a prospective cohort study of the use of misoprostol vaginal inserts (Mysodelle) in the induction of pregnancy and compared it to a historical cohort of women induced with the Dinoprostone intravaginal gel (Prostin) at the Liverpool Women's Hospital, a large UK teaching hospital.
Results: A total of 4102 women were induced between December 2016 and September 2018 of whom 2540 were induced with dinoprostone gel until September 2017. Since October 2017 1562 were induced using misoprostol vaginal inserts (MVI).
The MVI demonstrated a significantly quicker median time to delivery compared with dinoprostone gel (18.2 h versus 21.8 h; $p < 0.0001$). There was a 32% reduced risk of Caesarean section with MVI (7.5% vs 10.9%; RR 0.62 95%CI 0.56–0.84) There was no significant difference in any of the key maternal or neonatal adverse outcomes.
Conclusions: The results of this study suggest that misoprostol vaginal inserts, compared with dinoprostone intravaginal gel, achieve quicker delivery times, and a reduction in caesarean sections with no increased rate of adverse maternal or neonatal outcomes.

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Introduction

Induction of labour rates are increasing worldwide, rising from 9.5% of all deliveries in 1990 in the US to 22.5% in 2006 [1,2]. In the UK. 25% of all labours were induced in 2014 [3] with the number recently reaching up to 40% in some units [4]. The choice of induction methods includes pharmacological and mechanical methods and depends on a range of factors such as cervical and membrane status, cost, maternal factors and obstetrician's experience.

Current guidelines in the UK from NICE state that labour should be induced by vaginal prostaglandin E2 (Dinoprostone), which can be administered by either vaginal gel, oral tablet or controlled pessary [5]. More recently there has been growing evidence that low dose misoprostol may be the most effective prostaglandin for reducing the caesarean section rate following induction of labour [6,7].

In 2013, the Misoprostol vaginal insert (Mysodelle, Ferring Pharmaceuticals, Malmo, Sweden) was licensed and approved in the UK. Mysodelle is a vaginal insert (MVI) that contains 200 micrograms of misoprostol, released at a controlled rate over a 24-h period [8]. To date MVI's appear to be more effective in achieving vaginal births within 24 h with no significant difference in adverse events for mothers and babies when compared to Dinoprostone vaginal inserts (DVI) [8,9]. Despite the effectiveness of MVI in achieving vaginal delivery concerns have been raised over its high rate of uterine hyperstimulation associated with fetal heart rate abnormalities [10].

Most of the literature evaluating the use of MVI compare it to DVI [11,12]. There is limited literature comparing outcomes from induction of labour with the misoprostol vaginal insert compared to Dinoprostone gel. This study aims to report the use of Mysodelle in its first 10 months of use at Liverpool Women's Hospital (8300 deliveries per annum, induction rate of approximately 40%) and compare it to a historical cohort of women who were induced with the then first line induction agent Dinoprostone gel.

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Methods

Data were collected prospectively for women induced with misoprostol vaginal insert between December 2017 and September 2018 (10 months) and compared to a historical cohort of women induced with Dinoprostone gel between December 2016 and September 2017 (10 months). Review of electronic records for mother and baby and hospital pharmacy records was undertaken.

MVI was used as the induction agent of choice for all women with high risk pregnancies who required inpatient induction with intact membranes or low risk women who declined outpatient induction. High risk pregnancies were defined as: small for gestational age fetus, moderate/severe pre-eclampsia, multiple pregnancy, maternal health concerns, preterm <37 weeks or fetal health concerns.

Dinoprostone gel (two 2 mg, 6 h apart) was used for the same indications but also for low risk inpatient inductions of labour and was the induction agent of choice at Liverpool Women's hospital before the introduction of the misoprostol vaginal insert.

Onset of labour was defined by the clinical team as the presence of regular painful uterine contractions. Blood loss was estimated using visual approximations.

The data analysis for this paper was generated using SAS software, Version 9.4 of the SAS System for Windows 9 [13]. Frequency data were compared between groups using chi-squared. Comparison between groups were carried out using Student's t-test. Relative risk was used to calculate adjusted treatment effects. Statistical significance was defined as P < 0.05.

Results

A total of 4102 women were included in this study. Between December 2017-September 2018 a total of 1562 women were induced using MVI. 2540 were induced using Dinoprostone gel during December 2016 and September 2017. All women with a live singleton fetus at the start of labour were included in the analysis.

Age, BMI, ethnicity, parity did not differ between induction method (Table 1). The proportion of women who were induced after 41 weeks was significantly higher in the Dinoprostone gel group versus MVI (p < 0.05). A significantly greater proportion of

women in the MVI treatment group had a modified Bishop's score of less than or equal to 6 (1544 (98.85%)), compared to women in the dinoprostone treatment group (2089 (82.24%)), p < 0.0001. The most frequent (>5%) indications for induction of labour were reduced fetal movements and maternal reasons in in both treatment groups.

The MVI had a significantly quicker median time to delivery 18.2 h compared to 21.8 h following administration of Dinoprostone gel (p < 0.0001). There was a 41% reduction in oxytocin use with MVI compared to Dinoprostone gel. Terbutaline was given to 398 (25.5%) women induced with MVI compared to no women induced with Dinoprostone gel (Table 2).

1446 women (92.5%) induced with MVI achieved a vaginal delivery and 117 women (7.5%) had a caesarean section (Table 2). With Dinoprostone gel a similar rate of vaginal delivery was achieved (2264 women, 89.1%) but 276 women (10.9%) had caesarean sections. There were significantly fewer caesarean sections in women induced with MVI than with Dinoprostone gel (RR 0.68 (0.56–0.84); p = 0.0004). There was no statistical difference in the rate of category one caesarean sections (p = 0.89). There was no significant difference in estimated blood loss, major haemorrhage greater than 1000mls or 3rd and 4th degree tears.

There was no difference in adverse neonatal outcome, including; admission to NICU, Apgar score <7 at 5 min, need for therapeutic cooling or in evidence of Hypoxic Ischaemic Encephalopathy (HIE) between women induced with MVI or Dinoprostone gel (Table 3). A significant difference was seen between the weights of the neonates born in the MVI group compared to the dinoprostone gel group (P < 0.0001, CI -102.23 to – 35.94). There were no stillbirths in either cohort.

Discussion

The findings of this study demonstrate that the misoprostol vaginal insert is more effective than Dinoprostone gel at achieving vaginal delivery following induction of labour. This supports the findings of the EXPEDITE study [8], the first large scale randomised controlled trial published on the misoprostol vaginal insert comparing it to Prostin, a Dinoprostone vaginal pessary.

Caesarean section rates following MVI vary widely in the literature and have been reported to range from 10.1% to 31.1% [8,11,14]. The caesarean section rate with MVI in our study was 7.5% and is the lowest reported rate across the literature in any MVI cohort, despite the MVI group having less favourable Bishop scores. Both arms of this study have a lower caesarean section compared to the EXPEDITE study [8]. The exact reason for this variation in the caesarean section rate following induction with MVI is not clear. Women induced in the different studies may have different baseline characteristics, underlying risk factors and medical complications [14].

A difference in neonatal weights was observed with an average lower weight in neonates induced with MVI compared to dinoprostone gel. This difference may be explained by a greater proportion of women induced for prolonged pregnancy in the dinoprostone group (13.9%) compared to the MVI group (8.5%) and an increased proportion of women induced for fetal growth restriction in the MVI group (12.93% vs 10.43%).

In the EXPEDITE study 10% of women who were given misoprostol vaginal inserts had low-risk inductions. In our cohort misoprostol vaginal inserts were used only for high risk inpatient inductions, a sub-group which would be expected to have a higher caesarean section rate. When examining the differences between our cohort and the EXPEDITE cohort, the main differences seem to be that the population in our study had a lower mean BMI (27.4 vs 33.8), lower proportion of nulliparous women (47.5% vs 65.0%), and higher rate of white women (76.7% vs 38.6%). These factors may go

Table 1

Baseline demographic features of the population. Only inductions with a total % >5% are listed).

	MVI (n=1562)	Dinoprostone gel (n=2540)
Age (years; median, quartiles)	26 (25–33)	29 (25–33)
BMI (kg/m2; median, quartiles)	27.4 (22.7–31.1)	25.7 (22.4–30.6)
White - British	1200 (79.71)	2036 (80.16)
Nulliparous	741 (47.44)	1199 (47.20)
Gestational Age at delivery >41 weeks	133 (8.51)	353 (13.90)
Modified Bishop's score at baseline	n=1544	n=2089
0	147 (9.41)	234 (9.21)
1	216 (13.82)	239 (9.41)
2	299 (19.14)	360 (14.17)
3	297 (19.01)	368 (14.49)
4	267 (17.09)	370 (14.57)
5	215 (13.76)	297 (11.69)
6	103 (6.59)	221 (8.66)
Indication for induction	n=1467	n=1678
Maternal Reason	583 (20.41)	246 (15.75)
Reduced fetal movements	508 (32.52)	489 (19.25)
Prolonged pregnancy	75 (4.80)	284 (11.18)
Fetal growth restriction	202 (12.93)	265 (10.43)
Prelabour rupture of membranes	5 (0.32)	269 (10.59)
Gestational Diabetes	94 (6.01)	125 (4.90)

Table 2

mode of delivery and analgesia by induction agent.

	MVI (n=1562) n (%)	Dinoprostone gel (n=2540) n (%)	RR or p value
Time to delivery (hours; median, quartiles)	18.2 (11.6–27.6)	21.8 (19.0–23.9)	<0.0001
Oxytocin Use	380 (24.3)	1033 (40.7)	0.59 (0.54–0.66); <0.0001
Terbutaline Use	398 (25.5)	0	1295.69 (80.95–20737.24); <0.0001
Vaginal Delivery	1445 (92.5)	2264 (89.1)	0.82 (0.79–0.85); <0.0001
Caesarean Delivery	117 (7.5)	276 (10.9)	0.68 (0.56–0.84); 0.0004
Urgent Caesarean	21 (1.3)	28 (1.9)	1.21 (0.69–2.14); 0.48
Epidural Analgesia	388 (24.8)	798 (31.4)	0.79 (0.71–0.87); <0.0001
Estimated blood loss (ml; mean, SD)	452.06 (404.02)	448.00 (393.35)	–
Estimated blood loss >1000mls	91 (5.8)	134 (5.3)	1.10 (0.85–1.43); 0.45
3rd and 4th degree tears	41 (2.6)	54 (2.1)	1.23 (0.82–1.84); 0.30

Table 3

Neonatal adverse outcomes by induction agent.

	MVI (n=1562) n (%)	Dinoprostone gel (n=2540) n (%)	RR or p value
Stillbirths	0	0	–
Apgar score <7 at 5 minutes	40 (2.6)	75 (3.0)	0.86 (0.59–1.26); 0.46
Neonatal Weight (grams)	3246.77 (508.37)	3315.86 (550.44)	Neonatal Weight (grams)
Infants requiring admission to NICU	127 (8.1)	182 (7.1)	1.13 (0.91–1.41); 0.25
Infants requiring cooling	4 (0.3)	11 (0.4)	0.59 (0.18–1.85); 0.36
HIE grade 3 or more	0 (0.00)	2 (0.1)	0.32 (0.01–6.78); 0.46

some way in explaining the difference seen in the caesarean section rate. However, variation in the clinical practice does affect the rate of caesarean sections [15] and the lower caesarean section rate may reflect a difference in clinical practice in between USA and UK populations.

A systematic review on the use of vaginal misoprostol demonstrated that it is associated with an increased incidence of uterine hyperstimulation [16]. The EXPEDITE study reported a rate of uterine hyperstimulation of 13% with a tocolysis usage rate of 12.2%. Use of tocolysis to prevent adverse outcomes associated with uterine hyperstimulation in our study was very high (25%), almost double the rate of the EXPEDITE study. We attribute this high usage to the increased awareness of obstetricians to the reported potential side effects of MVI and strenuous efforts to ensure that prompt use of tocolysis was used at the earliest sign of hyperstimulation. Despite such high rates of tocolysis use, our study shows no significant increase in adverse neonatal outcomes such as low Apgar score, admission to NICU, need for cooling or HIE. This suggests that the liberal and timely use of tocolytics is able to ensure fetal wellbeing despite concerns about uterine hyperstimulation.

The findings that misoprostol vaginal inserts reduced time to delivery compared to Dinoprostone vaginal insert in the EXPEDITE study has limited generalisability due to stringent inclusion criteria, particularly for cervical unfavorability (modified Bishop score 4 or less). Our confirmatory findings are based on routine clinical practice with a much wider inclusion criteria.

Limitations

This study is a prospective cohort study with comparison to a historical control group from the preceding 12 months and therefore provides real life data on the effect of a change in clinical practice. Accepting the limitations of such study design we do not feel that this should have a large impact on the validity of the results as our clinical practice related to intrapartum and neonatal care did not change over this time period. Unblinded

nature of the study could have influenced clinical decision making on use of tocolytic but we do not feel that it would have positively influenced the use of epidural analgesia or the likelihood of vaginal delivery. Due to variation is practices in different obstetric centres within the UK and internationally, the findings may not be fully generalisable to different centres. This study was performed in a single large maternity unit with high induction rates, therefore the findings may not be directly translatable to smaller units.

An important limitation of this study's impact on clinical practice is the recent decision from Ferring to discontinue manufacture and distribution of Mysodelle.

Conclusion

This study demonstrates real life evidence that use of the MVI, coupled with a liberal use of tocolysis to prevent adverse outcomes from hyperstimulation, significantly improves induction to delivery times, reduces the proportion of women requiring caesarean section, reduces oxytocin use and epidural analgesia with no significant increase in adverse neonatal outcomes.

Declaration of Competing Interest

The maternity unit in which the authors work received financial support from Ferring Ltd in price reduction and midwifery staff costs to support the implementation of MVI into clinical practice. Ferring had no access to the outcome data.

AS has received Honoria for chairing a UK national Mysodelle user group meeting in 2018.

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