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Intrapartum care

Induction of labour with retrievable prostaglandin vaginal inserts: outcomes following retrieval due to an intrapartum adverse event

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Objective To assess adverse event (AE) resolution, delivery mode and neonatal outcomes after misoprostol or dinoprostone vaginal insert (MVI or DVI) retrieval due to AE during induction of labour (IOL).

Design Randomised, double-blind trial, EXPEDITE.

Setting Thirty five obstetric departments, USA.

Population Consisted of 1358 pregnant women with modified Bishop score ≤4 eligible for pharmacological IOL.

Methods *Post hoc* analysis.

Main outcome measures AEs prompting insert retrieval, times to AE resolution, delivery, delivery mode and neonatal intensive care unit (NICU) admissions.

Results 77/678 (11.4%) and 27/680 (4.0%) women had MVI and DVI retrieved due to AE, respectively ($P < 0.001$). The most common AEs prompting retrieval were uterine tachysystole with fetal heart rate (FHR) involvement and category II/III FHR pattern. Time to AE resolution varied for both treatments depending on the type of AE. For uterine tachysystole with FHR involvement, median resolution times were 1 hour 34.5 minutes ($n = 36$) and 8.5 minutes ($n = 8$) for MVI and DVI, respectively. Caesarean delivery occurred in a high proportion of women with insert retrieved due to AE (MVI: 44/77 (57.1%); DVI: 19/27 (70.4%)); the majority of caesareans were performed at least several hours after insert retrieval. Median times from retrieval to any delivery were not increased for women with insert retrieved due to AE. NICU admissions were 8/77 (10.4%) and 1/27 (3.7%) for MVI and DVI, respectively ($P = 0.440$).

Conclusions AEs leading to insert retrieval were primarily uterine tachysystole with FHR involvement and category II/III FHR patterns. Insert retrieval due to an AE did not prolong time to delivery for either prostaglandin insert.

Keywords Caesarean delivery, dinoprostone vaginal insert, induction of labour, intrapartum adverse events, misoprostol vaginal insert, neonatal outcomes.

Tweetable abstract Induction with prostaglandin vaginal inserts: outcomes following retrieval due to intrapartum adverse event.

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Introduction

Cervical ripening and labour induction with prostaglandins (misoprostol or dinoprostone) are common procedures in today's obstetric practice. The overall rate of labour induction in the European Union (EU) and United States (USA) is reported to be in the range of 20–25%.[1,2] With over 9 million births annually in these regions, at least 1.8 million women undergo labour induction.[1,2] The majority of these women are likely to be exposed to prostaglandins, as prostaglandin methods feature prominently in the recommendations of various national guidelines.

Trial registration: This trial has been registered in the clinical trial register clinicaltrials.gov, registration number NCT01127581.

Cochrane Pregnancy and Childbirth Group review authors with an interest in labour induction have identified five primary outcomes as being most representative of the clinically important measures of effectiveness and complications of products used for induction of labour (IOL). Four of these outcomes are directly related to safety: (i) serious neonatal morbidity and perinatal death; (ii) serious maternal morbidity or death; (iii) uterine hyperstimulation (tachysystole or hypertonus) with FHR involvement; (iv) caesarean delivery.[3] The first two outcomes, although arguably the most clinically relevant, are not precisely defined and, due to their low incidence and potential for confounding causative factors, are impractical as endpoints for clinical research in prospective trials. Sample sizes required to detect an important change in their incidences are estimated to be around 60 000 and 150 000 subjects, respectively.[4] Nevertheless, even low incidences yield substantial numbers when applied to a large population, and so remain important, not only for an individual but also from a public health perspective. In clinical research, uterine hyperstimulation with FHR involvement and caesarean deliveries are both measurable and well-recognised safety outcomes for a cervical ripening and labour induction procedure.

To support decision making and clinical management during IOL, the purpose of the current investigation is to assess the utilisation of retrieving misoprostol or dinoprostone vaginal inserts (MVI or DVI, respectively) in cases of intrapartum adverse events (AEs), including uterine hyperstimulation (referred to as uterine tachysystole) with FHR involvement and subsequent events experienced by women enrolled in the EXPEDITE trial.[5]

Methods

This investigation is a *post hoc* analysis of the Phase III trial, EXPEDITE (clinical trial registration at www.clinicaltrials.gov identifier NCT01127581). The primary publication contains a detailed description of the study protocol and eligible study population.[5] For a list of other investigators involved in the trial, see Appendix S1. In brief, the EXPEDITE trial was a randomised, multicentre, double-blind study conducted in the USA which compared MVI (Misodel®, Misopess®, Misodelle®, Myspess®, Ferring Pharmaceuticals) with DVI (Cervidil®, Propess®, Ferring Pharmaceuticals) for IOL in women at term gestation. MVI releases misoprostol at a mean rate of 7 microg/hour and DVI releases dinoprostone at a mean rate of 0.3 mg/hour over a period of 24 hours.[6,7] Women enrolled into the study were pregnant at ≥36 weeks 0 days gestation; parity ≤3; baseline modified Bishop Score (mBS) ≤4; aged ≥18 years with a single, live, vertex fetus; body mass index (BMI) ≤50 kg/m^2; and candidates for pharmacological IOL. Women with a uterine scar or with a fetus showing signs of distress were not eligible for enrolment.

Prespecified reasons for vaginal insert retrieval

Investigators recorded the primary reason for insert retrieval as either (i) retrieval due to AE necessitating discontinuation of the study drug (these AEs were strictly defined); (ii) the retrieval of the insert at the investigator's discretion; for example, if there was an occurrence of an uterine tachysystole or category II FHR pattern event that did not qualify as an AE according to prespecified definitions; (iii) onset of active labour with prespecified definition; (iv) being *in situ* for 24 hours; (v) vaginal insert fell out; (vi) retrieval at maternal request or (vii) 'other' reason. Characteristics of FHR decelerations were defined according to American College of Obstetrics and Gynecology (ACOG)[8] and Macones et al.[9] Active labour was defined in line with the ACOG guidelines current at the time of the trial conduct.[10] For the current investigation, women were categorised as having the vaginal insert retrieved due to either (i) AEs (as defined previously) or for a reason other than AE, i.e. a composite of reasons (ii)–(vii) above.

Intrapartum adverse events leading to vaginal insert retrieval

The following parameters were assessed for women with the vaginal insert retrieved due to an AE: incidence of AE leading to retrieval, type of AE, time from vaginal insert administration to onset of AE and time from insert retrieval to AE resolution. Start and stop times for AEs were recorded during the trial.

Clinical outcomes

Clinical outcomes assessed were: mode of delivery (vaginal or caesarean); time from insert retrieval to delivery; incidence of low Apgar score (<7) at 5 minutes; and incidence of admission to neonatal intensive care unit (NICU). For context, these clinical outcomes are also presented for women who had either MVI or DVI retrieved for a reason other than AE by treatment group.

Statistical analysis

A two-sided Fisher's exact test was used to compare the primary reason for insert removal (difference between treatment groups in incidence of AE as primary reason for retrieval versus all other reasons) and the difference between treatment groups in the rates of NICU admission after the insert had been retrieved due to AE. A two-sided Wilcoxon rank sum test was used as a non-parametric analysis to compare time from insert administration to onset of AE and time from insert retrieval to AE resolution. A multiple logistic regression analysis was conducted to identify whether there were characteristics or baseline factors which may have predisposed women to have insert retrieval due to an AE, by regressing the insert retrieval due to an AE (Yes/No) using a backwards selection on the

following regressors: induction agent (MVI versus DVI), maternal age (years), race (African-American versus other), parity (nulliparous versus parous), gestational age, baseline BMI, height, weight, induced for post-date gestation (>40 weeks), induced for maternal reason, induced for fetal reason, induced for elective reason, baseline mBS, baseline membrane status (intact versus ruptured), Group B *Streptococcus*-positive status and pooled sites.

Descriptive statistics including 95% confidence intervals (CIs) are provided by treatment group for the incidence of AEs and clinical maternal and neonatal outcomes for women who had MVI or DVI retrieved due to an AE or for reasons other than AEs.

Results

In all, 678 women received MVI and 680 women received DVI. The primary outcomes and the study population of the EXPEDITE trial have been published previously.[5]

Primary reasons for vaginal insert retrieval

Table 1 provides the primary reasons for vaginal insert retrieval. Onset of active labour was the most common reason for insert retrieval in both the MVI and DVI treatment groups. In all, 77/678 women (11.4%) in the MVI group and 27/680 (4.0%) women in the DVI group had the study drug insert removed due to an intrapartum AE ($P < 0.001$). The most frequent AEs leading to MVI retrieval were uterine tachysystole with FHR involvement (36/678 (5.3%)) and category II/III FHR pattern AE (22/678 (3.2%)). The most frequent AEs leading to DVI retrieval were category II/III FHR pattern (13/680 (1.9%)) and uterine tachysystole with FHR involvement (8/680 (1.2%)).

Subgroup baseline clinical characteristics

The subgroups were based on the primary reason for insert retrieval. The original treatment stratification of the trial was according to parity (60% nulliparous, 40% parous). Demographics and baseline characteristics of maternal age, parity, gestational age, BMI, and mBS were similar for women with the insert retrieved due to AE and for those with the insert retrieved for a reason other than AE within the MVI and DVI groups (Table 2). Medical conditions as the primary reason for IOL, in particular hypertensive disorders, were more common for those with the insert retrieved due to AE in the DVI group. The multiple logistic regression analysis showed that the induction agent, DVI or MVI, was the only significant predictor of an AE as the primary reason for insert retrieval ($P < 0.001$), with a higher frequency in those assigned to the MVI group compared with those who had received DVI. None of the baseline clinical characteristics or demographics was shown to be a predictor of an AE as the primary reason for insert retrieval.

Table 1. Primary reason for vaginal insert retrieval (intent to treat/safety population)

Primary reason for retrieval, *n* (%)	MVI (*n* = 678)	DVI (*n* = 680)
Intrapartum AEs*	77 (11.4)	27 (4.0)
Uterine tachysystole† with FHR involvement‡	36 (5.3)	8 (1.2)
Category II/III FHR pattern AE‡	22 (3.2)	13 (1.9)
Uterine tachysystole† or uterine hypertonus	8 (1.2)	2 (0.3)
Meconium in amniotic fluid	5 (0.7)	2 (0.3)
Other AEs§	6 (0.9)	3 (0.4)
Reasons other than intrapartum AE	601 (88.6)	653 (96.0)
Onset of active labour	297 (43.8)	232 (34.1)
Vaginal insert *in situ* for 24 hours	88 (13.0)	219 (32.2)
Vaginal insert fell out	104 (15.3)	129 (19.0)
Non-AE category II FHR¶	58 (8.6)	35 (5.1)
Non-AE uterine tachysystole¶	36 (5.3)	7 (1.0)
Maternal request	6 (0.9)	10 (1.5)
Other	12 (1.8)	21 (3.1)

One DVI subject had two AEs listed as reasons for vaginal insert retrieval (category II FHR and uterine hypertonus).
*$P < 0.001$ between treatment groups; two-sided *P*-value was obtained from a Fisher's exact test of difference in incidence of IPAE as primary reason for removal versus all other reasons for insert retrieval.
†Uterine tachysystole was defined as uterine activity of more than 5 contractions in a 10-minute window, averaged over three consecutive 10-minute periods (i.e. ≥18 contractions in 30 minutes, with each 10-minute period having at least 6 contractions). The contractions must have been of adequate intensity and duration, i.e. moderate intensity and duration ≥45 seconds, in order for the uterine activity to be characterized as tachysystole.
‡FHR involvement was defined as late decelerations, bradycardia or prolonged decelerations. Characteristics of decelerations were defined according to ACOG 2009[8] and Macones et al.[9]
§Antepartum haemorrhage, *n* = 1 for MVI; arrested labour, *n* = 1 for DVI; puerperal pyrexia, *n* = 1 for MVI; premature separation of placenta, *n* = 1 for MVI; oedema genital, *n* = 1 for DVI; hypertension, *n* = 1 for MVI; superventricular tachycardia, *n* = 1 for DVI; fetal malpresentation, *n* = 2 for MVI.
¶Retrieval was at the discretion of the treating clinician taking into account the clinical situation (i.e. when the event did not fit into the strictly defined AE category as described above).
AE, adverse event; DVI, dinoprostone vaginal insert; FHR, fetal heart rate; MVI, misoprostol vaginal insert.

Time frame for intrapartum adverse events leading to vaginal insert retrieval

The overall median time from vaginal insert administration to onset of the AE leading to retrieval was shorter for women induced with MVI than for women induced with DVI (6 hours 45 minutes versus 9 hours 41 minutes, respectively; $P = 0.002$). The median time from insert

Table 2. Demographic and baseline characteristics

	MVI (n = 678)		DVI (n = 680)	
	Insert retrieved due to intrapartum AE (n = 77)	Insert retrieved due to reason other than intrapartum AE (n = 601)	Insert retrieved due to intrapartum AE (n = 27)	Insert retrieved due to reason other than intrapartum AE (n = 653)
Maternal age, years	27.1 ± 6.60	26.0 ± 5.91	24.8 ± 5.54	25.9 ± 5.94
Nulliparous	55 (71.4)	386 (64.2)	20 (74.1)	431 (66.0)
Gestational age, days	277.4 ± 9.31	276.5 ± 9.24	275.9 ± 9.52	277.5 ± 8.99
BMI, kg/m^2*	33.4 ± 5.28	33.8 ± 6.60	34.9 ± 6.44	34.0 ± 6.61
mBS	2 (0–5)	2 (0–5)	2 (0–4)	2 (0–6)
Primary reason for induction				
Medical reason	38 (49.4)	348 (57.9)	19 (70.4)	351 (53.8)
Hypertension	4 (5.2)	75 (12.5)	7 (25.9)	79 (12.1)
Pre-eclampsia	2 (2.6)	69 (11.5)	4 (14.8)	55 (8.4)
Oligohydramnios	6 (7.8)	55 (9.2)	1 (3.7)	59 (9.0)
Diabetes	7 (9.1)	41 (6.8)	0 (0)	43 (6.6)
Intrauterine growth restriction	9 (11.7)	26 (4.3)	2 (7.4)	33 (5.1)
Other medical reasons	10 (13.0)	82 (13.6)	5 (18.5)	82 (12.6)
Post-date gestation (>40 weeks)	28 (36.4)	182 (30.3)	7 (25.9)	220 (33.7)
Elective	11 (14.3)	71 (11.8)	1 (3.7)	82 (12.6)

The subgroups determined by primary reason for insert retrieval were not prespecified in the study protocol, therefore, any subgroup comparisons between treatment groups should be interpreted cautiously.
*BMI was based on term gestation maternal weights.
Data are n (% subgroup), mean ± standard deviation or median (range). AE, adverse event; BMI, body mass index; DVI, dinoprostone vaginal insert; mBS, modified bishop score; MVI, misoprostol vaginal insert.

retrieval to AE resolution, although longer for the MVI group compared with the DVI group, was not significantly different (1 hour 39 minutes versus 47 minutes, respectively; P = 0.452). However, the type of AE affected the time from insert retrieval to AE resolution. The median times from insert retrieval to resolution of uterine tachysystole with FHR involvement were 1 hour 34.5 minutes for women induced with MVI and 8.5 minutes for women induced with DVI, whereas the median resolution times for category II/III FHR pattern AE were considerably longer for both treatments: 2 hours 47 minutes and 1 hour 27 minutes, respectively. For the MVI and DVI induction groups, Figures S1 and S2 depict flow diagrams for women with vaginal insert retrieval for each type of AE, including time from insert retrieval to AE resolution, mode of delivery and subsequent neonatal outcomes.

Caesarean deliveries

The majority of women with insert retrieved due to AE were delivered by caesarean in both treatment groups (MVI: 44/77 (57.1%); DVI: 19/27 (70.4%)); however, this outcome represents a relatively small proportion of women in either treatment group for the overall study population (6.5% (44/678) and 2.8% (19/680), respectively).

Caesarean delivery rates after specific AEs necessitating insert retrieval are listed in Table 2, and are shown in Figures S1 and S2. The primary reasons for caesarean deliveries for each subgroup are listed in Table 3.

Time to caesarean delivery

Median times from insert retrieval to caesarean delivery are presented in Table S1. The majority of caesarean deliveries were performed at least several hours after insert retrieval due to AE (Figure 1).

Time to vaginal delivery

Median times from insert retrieval to vaginal delivery in both groups were similar for women who had the insert retrieved due to AE compared with those who had the insert retrieved due to reasons other than AEs (Table S1).

Neonatal outcomes

No neonatal deaths were reported during the study. A total of 8/77 (10.4%) and 1/27 (3.7%) neonates of women with the insert retrieved due to AE were admitted to NICU in the MVI and DVI groups, respectively (P = 0.440). In context, 53/601 (8.8%) and 70/653 (10.7%) neonates of women in the MVI and DVI groups with the insert retrieved for a reason other than AE were admitted to NICU. All neonates were discharged from NICU in good health.

For neonates of women with insert retrieved due to AE, low Apgar score (<7) at 5 minutes occurred in 4/77 (5.2%)

Table 3. Safety outcomes

	MVI (*n* = 678)				DVI (*n* = 680)			
	Retrieved due to intrapartum AE (*n* = 77)		Retrieved due to reason other than intrapartum AE (*n* = 601)		Retrieved due to intrapartum AE (*n* = 27)		Retrieved due to reason other than intrapartum AE (*n* = 653)	
	n (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI
Uterine tachysystole requiring treatment (without FHR involvement)	10 (13.0)	6.4, 22.6	15 (2.5)	1.4, 4.1	1 (3.7)	0.1, 19.0	8 (1.2)	0.5, 2.4
Uterine tachysystole with FHR involvement	41 (53.2)	41.5, 64.7	29 (4.8)	3.3, 6.9	8 (29.6)	13.8, 50.2	10 (1.5)	0.7, 2.8
Category II FHR pattern AE	41 (53.2)	41.5, 64.7	128 (21.3)	18.1, 24.8	18 (66.7)	46.0, 83.5	157 (24.0)	20.8, 27.5
Category III FHR pattern	4 (5.2)	1.4, 12.8	5 (0.8)	0.3, 1.9	0 (0.0)	0.0, 12.8	5 (0.8)	0.2, 1.8
Tocolysis use	36 (46.8)	35.3, 58.5	47 (7.8)	5.8, 10.3	7 (25.9)	11.1, 46.3	21 (3.2)	2.0, 4.9
Meconium in amniotic fluid	15 (19.5)	11.3, 30.1	105 (17.5)	14.5, 20.7	5 (18.5)	6.3, 38.1	87 (13.3)	10.8, 16.2
Instrumented vaginal delivery during first hospitalisation	4 (5.2)	1.4, 12.8	39 (6.5)	4.7, 8.8	0 (0.0)	0.0, 12.8	35 (5.4)	3.8, 7.4
Caesarean delivery*	44 (57.1)	45.4, 68.4	132 (22.0)	18.7, 25.5	19 (70.4)	49.8, 86.2	165 (24.3)	22.0, 28.8
Primary reason for caesarean delivery								
Arrest of dilation or failure to dilate	8 (10.4)	NA	50 (8.3)	NA	2 (7.4)	NA	83 (12.7)	NA
Category II/III FHR pattern AE	19 (24.7)	NA	46 (7.7)	NA	14 (51.9)	NA	30 (4.6)	NA
Arrest of descent or failure to descend	2 (2.6)	NA	22 (3.7)	NA	2 (7.4)	NA	26 (4.0)	NA
Uterine tachysystole with FHR involvement**	9 (11.7)	NA	5 (0.8)	NA	0 (0.0)	NA	0 (0.0)	NA
Uterine rupture	1 (1.3)	NA	0 (0.0)	NA	0 (0.0)	NA	0 (0.0)	NA
Other AE	4 (5.2)	NA	4 (0.7)	NA	1 (3.7)	NA	10 (1.5)	NA
Other (elective/lack of efficacy; non-AE)	1 (1.3)	NA	5 (0.8)	NA	0 (0.0)	NA	16 (2.5)	NA
Minute 5 Apgar score low (<7)	4 (5.2)	1.4, 12.8	10 (1.7)	0.8, 3.0	0 (0.0)	0.0, 12.8	7 (1.1)	0.4, 2.2
Neonatal ICU admission	8 (10.4)	4.6, 19.4	53 (8.8)	6.7, 11.4	1 (3.7)	0.1, 19.0	70 (10.7)	8.5, 13.3
Neonatal IV/IM antibiotic use	2 (2.6)	0.3, 9.1	45 (7.5)	5.5, 9.9	2 (7.4)	0.9, 24.3	64 (9.8)	7.6, 12.3
Neonatal respiratory events	9 (11.7)	5.5, 21.0	48 (8.0)	5.9, 10.4	0 (0.0)	0.0, 12.8	61 (9.3)	7.2, 11.8
Postpartum haemorrhage	3 (3.9)	0.8, 11.0	39 (6.5)	4.7, 8.8	0 (0.0)	0.0, 12.8	40 (6.1)	4.4, 8.2
Chorioamnionitis	0 (0.0)	0.0, 4.7	38 (6.3)	4.5, 8.6	2 (7.4)	0.9, 24.3	57 (8.7)	6.7, 11.2

The subgroups determined by primary reason for insert retrieval were not prespecified in the study protocol; therefore, any subgroup outcome comparisons between treatment groups should be interpreted cautiously.
*Percentage based on those who delivered during first hospitalisation.
**FHR involvement was defined as late decelerations, bradycardia or prolonged decelerations.
NA, 95% CIs not available for each specific reason for caesarean delivery due to interdependence of data.
AE, adverse event; CI, confidence interval; DVI, dinoprostone vaginal insert; FHR, fetal heart rate; ICU, intensive care unit; IM, intramuscular; IV, intravenous; MVI, misoprostol vaginal insert.

and 0/27 (0%) for the MVI and DVI groups, respectively. In context, 10/601 (1.7%) and 7/653 (1.1%) of neonates in the MVI and DVI groups with the insert retrieved for a reason other than AE had low Apgar score (<7) at 5 minutes.

Other clinical outcomes

Other safety outcomes are presented in Table 3.

Discussion

The aim of this current investigation is to understand better the clinical implications of stopping prostaglandin administration by retrieving a prostaglandin vaginal insert during the labour induction process when an important complication occurred, as protocol stipulated, in the EXPEDITE trial. The Phase III trial EXPEDITE studied the retrievable vaginal inserts, MVI and DVI, in a randomised double-blind fashion, from which data have been extracted for this *post hoc* investigation.

Main findings

Significantly more women induced with MVI experienced AEs that required protocol-specified insert retrieval compared with DVI. AEs that required retrieval were more likely to occur sooner after the start of induction with MVI than DVI. The most frequent AEs prompting retrieval in

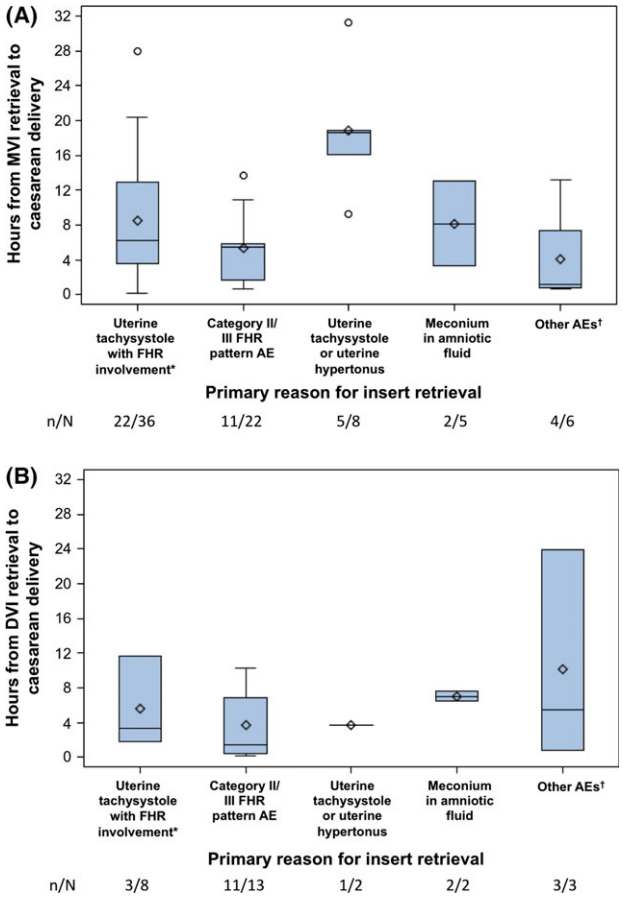

Figure 1. Median time from insert retrieval to caesarean delivery for women with intrapartum AEs necessitating insert retrieval. (A) MVI treatment group, in which 44/77 women had a caesarean delivery after MVI was retrieved due to an intrapartum AE. (B) DVI treatment group, in which 19/27 women had a caesarean delivery after DVI was retrieved to an intrapartum AE. *n/N*, number of caesarean deliveries per subgroup. Lowest box edge represents the 25th percentile, the middle line represents the median and the top box edge represents the 75th percentile. The whiskers represent minimum and maximum values, not including outliers. Observations outside 1.5× the interquartile range were defined as outliers. ○, outliers; ◇, mean values for each group. *FHR involvement was defined as late decelerations, bradycardia or prolonged decelerations. †Antepartum haemorrhage, $n = 1$ for MVI; arrested labour, $n = 1$ for DVI; puerperal pyrexia, $n = 1$ for MVI; premature separation of placenta, $n = 1$ for MVI; oedema genital, $n = 1$ for DVI; hypertension, $n = 1$ for MVI; superventricular tachycardia $n = 1$ for DVI; fetal malpresentation $n = 2$ for MVI. AE, adverse event; DVI, dinoprostone vaginal insert; MVI, misoprostol vaginal insert.

both treatment groups were category II/III FHR patterns and uterine tachysystole with FHR changes.

Category II/III FHR patterns may be less frequently drug-related, as evidenced by most women who had retrieval due to a category II/III FHR pattern AE were delivered by caesarean for the same reason. Having to remove an insert due to a category II/III FHR pattern may thus indicate the presence of a fetus responding unfavourably to effective uterine contractions. Category II/III FHR pattern as the primary reason for caesarean delivery was more frequent among women with insert retrieved due to AE than among those with retrieval for reasons other than AE: 19/77 women (24.7%) versus 46/601 (7.7%) for MVI and 14/27 (51.9%) versus 30/653 (4.6%) for DVI even if most caesareans took place many hours after the insert removal.

Retrieval of DVI at the occurrence of uterine tachysystole (hyperstimulation) with FHR changes was associated with a rapid resolution of the event; in the DVI group, there were no caesarean deliveries due to uterine tachysystole with FHR changes, no indication of neonatal morbidity, and no increase in duration of time to delivery compared with those exposed to DVI with the insert removed for a reason other than AE.

Managing cases of uterine tachysystole with FHR changes is more challenging for misoprostol than dinoprostone due to the longer half-life of misoprostol (approximately 40 minutes for misoprostol[7] compared with approximately 3 minutes for dinoprostone[6]). However, the prescribing information for the MVI states that, among other reasons for retrieval, the insert should be retrieved if uterine contractions are prolonged or excessive and if there is evidence of fetal compromise. Whether the opportunity to stop misoprostol administration in such cases, as is possible with MVI retrieval, offers a safety advantage over intermittent administration of larger, non-retrievable doses of misoprostol is a relevant hypothesis but would require comparison in a head-to-head clinical trial.

Strengths and limitations

The primary strength of the investigation is the design of the EXPEDITE trial upon which the analyses were extracted: a large, prospective, multi-centre, randomised, double-blind trial conducted according to stringent regulatory requirements. Definitions of key events such as uterine tachysystole with FHR involvement were prespecified. Moreover, data collection was closely monitored and, critical for the current analyses, AEs were recorded with start and stop times.

The limitations are that these analyses were conducted *post hoc* and the EXPEDITE trial was not designed or powered to study the subgroup analyses which are the focus of this investigation. As such, the results must be interpreted cautiously, particularly as the subgroups of interest (those who had experienced a predefined AE that required retrieval) made up less than 10% of the total study population and were defined by post-treatment characteristics. Furthermore, as these analyses were exploratory, all analyses have been presented without adjustment for multiple comparisons. Another limitation inherent in the conditions for the investigation is that it is not possible to know what the maternal and neonatal outcomes would have been without the possibility to retrieve the induction agent.

Finally, although there were strict definitions for AEs necessitating insert retrieval that were prespecified in the EXPEDITE trial protocol, these definitions are not necessarily the same as those used in other trials or consistent with those applied in various local guidelines.

Interpretation

To our knowledge, no previous publication has reported on the course of women undergoing IOL and their neonates following retrieval of a prostaglandin insert after the onset of an AE necessitating its removal. Information on AE times-to-resolution, caesarean deliveries and neonatal outcomes are lacking in the literature. In a Cochrane systematic review on the use of vaginal misoprostol for cervical ripening and IOL, incidences for uterine hyperstimulation with FHR changes are reported with a range of 0–42%.[3] The wide incidence range probably reflects differences with regard to dose, frequency of dosing, inclusion criteria and how uterine hyperstimulation with FHR changes were assessed. It is also possible that varying degrees of data monitoring have an impact on the recorded reporting rate of the events. The incidence of uterine tachysystole with FHR involvement that prompted removal of MVI, using a strict definition, was 5.3% in our investigation of the EXPEDITE data. This figure cannot be compared directly with the incidence figures in the Cochrane review as there is no information in the review on the incidences that prompted any kind of intervention, e.g. tocolysis, withholding of scheduled next dosing, oxygen administration, caesarean delivery, etc., which could have been used as a surrogate for comparison.

Overall conclusions

Overall, fewer than 10% of the EXPEDITE trial population had AEs necessitating MVI or DVI retrieval; these were significantly more common in women induced with MVI. The most frequent AEs leading to insert retrieval were uterine tachysystole with FHR involvement and category II/III FHR patterns. MVI or DVI retrieval due to AE did not lengthen time to delivery and did not increase the rate of NICU admissions compared with women whose inserts were removed for reasons other than AE.

Disclosure of interests

Full disclosure of interests available to view online as supporting information.

Contribution to authorship

All authors critically reviewed and amended multiple drafts of the manuscript concept, outline and full manuscript, and approved the final draft of manuscript. In addition to this, OR analysed and interpreted the data, developed manuscript concept, outline and full manuscript; DT conducted the statistical analysis, analysed and interpreted the data, and developed manuscript concept; BP designed the trial, analysed and interpreted the data, and developed manuscript concept; DW was a clinical investigator for the trial, and collected, analysed and interpreted the data.

Details of ethics approval

The relevant Independent Ethics Committees or Institutional Review Boards approved the protocol, participant consent form, information sheet, and study brochure at each of the 35 sites prior to September 2010 when enrolment commenced. The study was performed in accordance with the ethical conduct standards that had their origin at the Declaration of Helsinki and with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Tripartite Guideline on Good Clinical Practice and United States Food and Drug Administration regulations.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow diagram for women with MVI retrieved due to adverse event.

Figure S2. Flow diagram for women with DVI retrieved due to adverse event.

Table S1. Median exposure time and time to events

Appendix S1. List of participating sites and principal investigators. ■

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Induction of labour: many choices, but still in search of the perfect protocol

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In this paper the investigators carry out a secondary sub-analysis of adverse event management of a randomised controlled trial of induction of labour, comparing retrievable preparations of misprostol [Prostaglandin E_1 (MVI)] and dinoprostone [Prostaglandin E_2 (DVI)]: two different agents with different potencies, half lives, and release times. Significantly more women receiving MVI had adverse events requiring removal of the insert and the events occurred in a shorter time. Resolution of tachysystole with fetal heart rate involvement after removal was quicker for DVI. Interestingly, the time for resolution of fetal heart rate abnormalities alone was greater than those associated with tachysystole. There was no difference in NICU admissions between the two arms of the study and all neonates were discharged from the NICU in good condition. Although a small overall proportion of both groups, each had a high percentage of caesarean deliveries after removal [MVI 44/77 (57.1%) and DVI 19/27 (70.4%)]. There was a similar time to vaginal delivery for those who had an insert removed.

Induction of labour is a common procedure with an obvious primary goal and a need for a robust safety profile. This being a study of adverse events, it is of clinical value. Elements considered in the choice of technique for induction include patient population, local logistical factors, and cost. There is a cornucopia of choice of technique for the obstetric provider including mechanical agents, low dose oxytocin intravenous infusion, and both oral and vaginal medications. Each comes with an individual silhouette regarding patient comfort, suitability for outpatient management, requirement for fetal monitoring, and provider control. It is the latter issue that can be a significant disadvantage of medications as, once taken, they may not be practically reversed in the occurrence of an adverse event. Hence the allure of a medication delivered by vaginal insert, as unwanted effects may be potentially abrogated by removal of the insert.

The most significant finding of this study may be the high rate of caesarean delivery in both groups after removal of the insert. Percentages here of 57 and 70 seem to question the whole principle of the use of a vaginal insert in this setting. Timing to onset of, duration of, and timing to resolution of adverse events are of interest for each preparation but are of limited clinical value. It is a little surprising to see dinoprostone having a higher caesarean delivery rate after removal of insert. This, as well as many of the other adverse event statistics are hard to explain scientifically in terms of the half life of either drug.

The negative delivery outcome statistics appearing to question the use of vaginal inserts in this application; one may ask whether this was a study of drug safety profile or an investigation of the insert delivery system? Suggestions for further study may include investigation of two different doses of misoprostol, both delivered by the insert method, or a comparison of the same dose of either of the drugs delivered transvaginally as either tablet or insert.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.