Title**: Influence of maternal factors and mode of induction on labour outcomes; a pragmatic retrospective cohort study.**

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Abstract (150 words; 150 words max)

Since recent research indicates that other modalities are at a minimum non-inferior to the NICE-recommended hormonal agent prostaglandin E_2 (PGE_2), a retrospective cohort study was conducted on 1971 consecutive induced singleton pregnancies. Multinominal regression showed that the odds ratio (OR) for vaginal delivery with balloon-mediated labour induction (84% vaginal deliveries; OR 1.6; 95% CI 0.7-3.5) is similar to the PGE_2 agents propess (81%; OR 1.2; 95% CI 0.68-1.98) and prostin (79%; OR 0.99; 95% CI 0.55-1.79) when using triple multi-agent induction as a reference. On the other hand, combining propess & prostin (60% vaginal deliveries; OR 0.45; 95% CI 0.21-0.96) and attempting quadruple combinations of induction modalities (56%; OR 0.37; 95% CI 0.16-0.85) yield significantly poorer outcomes. However, compared to known factors associated with increased caesarean section rates, such as increased maternal age, nulliparous pregnancies and history of caesarean section, the differential impact of different induction modalities appears less pronounced.

Key Words: labour induction, prostaglandin E2, balloon catheter, parity, vaginal delivery, Caesarean section

Impact statement (184 words; 200 words max)

- What is already known on this subject.

Recent published data from controlled clinical trials have shown that other labour-inducing agents, including balloon catheters, are as effective as prostaglandin E_2 (PGE_2) in achieving vaginal delivery.

- What the results of this study add.

Data from this pragmatic retrospective cohort study support the findings of others that the use of a balloon is as effective as PGE_2. It also demonstrates that regular clinical practice can differ from an experimental environment, with patients receiving multiple induction modalities in daily practice. Both the combination of different PGE_2 medications and a quadruple labour induction approach are associated with poorer results as measured by the vaginal delivery rate. The data presented here also confirms that nulliparous status, maternal age and history of caesarean section are associated with reduced odds of achieving vaginal delivery.

- What the implications are of these findings for clinical practice and/or further research.

The body of evidence showing favourable results with balloon induction is growing. Furthermore, there are limits to the effectiveness of combining different induction modalities. Maternal and perinatal factors associated with risk of caesarean section further complicate labour induction management.

Introduction

The application of labour induction has been increasing year-on-year and is now applied in approximately 25% of pregnancies (NHS digital, 2015); in approximately two thirds of cases, unaided vaginal delivery is achieved (RCOG, 2008). Although induction of labour itself carries risks, the risk of caesarean delivery is 12% lower with induction compared to expectant management (Mishanina et al, 2014). Progesterone E_2 (PGE_2), as a vaginal pessary, gel, or tablet is currently the recommended mode of pharmacological induction according to National Institute for Health and Care Excellence Guidelines (NICE, 2008). In a previous study, we and others linked nulliparous status of a woman with increased use of PGE_2, and increased risk of caesarean section - despite the fact that these patients are being administered more doses of PGE_2 (Yogev et al, 2003; Memon et al, 2011). More recent research has shown that other modalities may be associated with non-inferior or even better outcomes than PGE_2 for labour induction. For example, a systematic review found that misoprostol leads to more timely vaginal deliveries compared to PGE_2 (Alfirevic et al, 2015). In another systematic review, Du et al (2017) showed that balloon-assisted induction of labour is as effective and safe as induction with PGE_2. The positive evidence for balloons prompted NICE to publish an Interventional Procedures
Guidance (NICE, 2015). This study aims to investigate how different induction methods for labour compare in terms of achieving vaginal delivery, using cases from a non-controlled standard clinical setting, based on local clinical guidelines devised from national published guidance.

Materials & Methods

Induction guidelines

This concerns a retrospective cohort study of pregnant women managed by induction of labour in the maternity unit of a general district hospital in the UK, covering the period mid-July 2015 to end of July 2017. Multiple pregnancies were excluded, as were inductions related to planned terminations. All patients met the criteria for induction of pregnancy as outlined in our local clinical guidelines on induction labour. These guidelines draw from the main national and international literature, National Institute for health and Care Excellence (NICE, 2008, 2011, 2015, 2015); the Royal College of Obstetrics and Gynaecology (RCOG, 2014 & 2015) and the World Health Organisation (WHO, 2011). Some of the key reasons for induction and the primary mode of

induction in accordance to local guidelines are summarised in Table 1. Due to positive outcomes published in recent years concerning induction of labour with a balloon, and the interventional procedure guidance publication by NICE (2015), this modality was introduced in the department from 2016 onwards; the balloon model used is a Cook Cervical ripening balloon. If the Bishop score is over 7 then patients are considered eligible for direct artificial rupture of membranes (ARM). Patients undergoing induction of labour who do not show signs of labour after 24 hours from insertion of 10mg Propess pessary or after 2 doses of 3mg Prostin pessaries, medical staff assess and decide on further induction or Caesarean section. Intravenous oxytocin is not commenced until 30 minutes after the 10mg Propess pessary has been removed or six hours have lapsed following the administration of a 3mg Prostin pessary. Oxytocin is only used in the presence of ruptured membranes, whether occurred spontaneously or by amniotomy.

Data

Data was collected in Microsoft Excel and analysed in SPSS v17. Multinominal regression analysis was conducted, with all variables included as factors in the analysis (all variables listed in Tables 2 & 3). Unaided and aided vaginal deliveries were pooled and compared to births through caesarean section. Trials evaluating success of labour induction often focus on time to delivery and delivery within 24 hours (Faucett et al, 2014; Mishanina et al, 2014). In standard daily practice, clinical parameters such as maternal well-being and foetal monitoring data are used for decision-making on type of induction and whether to proceed with caesarean section; therefore, the time-related outcome measures were not applied in this study.

Results

A total of 1971 deliveries were included in the analyses; no maternal or foetal deaths occurred in this cohort. Table 2 summarises the demographics and obstetric medical history for the patients included. Furthermore, the extent to which each variable is associated with vaginal delivery is determined by multinominal regression analysis. Likewise, the primary reason for induction is summarised in Table 3, with the odds of vaginal delivery again assessed through multinominal regressional analysis. The most common reasons for induction of labour in this cohort were post-term (i.e. > 41 weeks; 18.8%), small for gestational age (SGA; 14.4%) and pre-labour membrane rupture (12.6%) respectively. The mean average maternal age was 30 years (min 13 to max 46 years), and median gravida and parity were 2 and 1 respectively. Mean weight of the newborn child was 3,384 grams; median blood loss was 300 ml. In terms of vaginal deliveries, 1342 (68.1%)

of these were unaided, in 238 (12.1%) cases an extraction technique such as forceps or vacuum had to be applied, and a caesarean section was required in 391 (19.8%) cases. This compares favourably compared to overall caesarean section rates of 26% in the UK in 2013-14.

As identified previously by us and others (Yogev et al, 2003; Memon et al, 2011), parity is strongly linked with increased risk of caesarean section. Young maternal age on the other hand is positively associated with vaginal delivery. A previous caesarean section significantly increases the odds of patients requiring another one in future pregnancies, as confirmed in Table 2.

Only pregnancies with proven abnormal readings on cardiotocograph (CTG) are linked with increased risk of caesarean section. Reduced foetal movement, however, is not associated with any mode of delivery, whereas small for gestational age babies are linked with improved chance of vaginal delivery. Incidentally, there is limited guidance on the best mode of induction for presentations of reduced foetal movement. The RCOG guidance on reduced foetal movements (RCOG, 2011) states: 'the decision whether or not to induce labour at term in a woman who presents recurrently with RFM when the growth, liquor volume and CTG appear normal must be made after careful consultant-led counselling of the pros and cons of induction on an individualised basis'.

Discussion

When considering the primary variable of interest in relation to induction success, measured by percentage vaginal delivery (unaided and instrument-aided), three trends can be identified from the results in Table 3. Firstly, ARM is a very effective induction treatment compared to hormonal induction, but is only indicated and used in a subset of expectant mothers. Secondly, balloon catheter induced labour gives very similar outcomes to the use of either propess or prostin. Our data corroborates with the data published in the systematic review by Du et al on the use of balloon catheters (2017). Thirdly, it appears that combining the two PGE_2 agents propess and prostin is counterproductive and associated with lower vaginal delivery rates. Furthermore, administering quadruple combinations of induction agents (for example propess, balloon, syntocinon and prostin) also gave poorer outcomes in terms of vaginal delivery rates. This practice is not in accordance with NICE guidelines and it also increases the risk of uterine hyperstimulation.

This retrospective 'snapshot' of induction of labour has considerable drawbacks compared to a prospective controlled cohort or (randomised) trial design. These include variability in the choice of induction agent, often allowed in national guidelines, and inclusion of patients who normally would not be included in studies - particularly those who have a history of delivery by caesarean section.

However, conversely these shortcomings contribute to being able to gain an insight into how successful induction of labour is, in terms of vaginal delivery achieved, in a standard district hospital setting.

Conclusion

Our data shows that the established predictors, including increased maternal age, nulliparous pregnancies and history of caesarean section, are associated more significantly with increased caesarean section than the primary reason or chosen modality for labour induction (when non-recommended induction methods are not taken into account). In conclusion, our data adds to the body of evidence that suggests that induction methods other than PGE_2 may just as effective.

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Table 1, Local clinical guideline on choice of modality for induction of labour

Induction – primary reason or circumstances	**First line induction modality**	**Second line induction modality**
Post-term (> 41 weeks)	Prostin or Propess	
Diabetes (gestational, type I, type II)	Prostin	Propess (only > 38 weeks gestation)
Pre-labour rupture of membranes	Prostin	
Small for Gestational Age	Prostin	Propess (only > 38 weeks gestation)
Reduced foetal movement		
Hypertension-related	Prostin	Propess (only > 38 weeks gestation)
Previous Caesarean section	ARM	Prostin or Balloon

Table 2, Multinominal regression analysis of odds ratios associated with vaginal delivery, using caesarean section as reference – demographics and obstetric medical history

Variable	**Category**	**N (vaginal / total)**	**% (vaginal / total)**	**Odds Ratio**	**95% CI (lower)**	**95% CI (upper)**
Maternal age	Under 24	243 / 292	83%	2.26*	1.44	3.56
	24 to 30	538 / 655	82%	1.49*	1.04	2.16
	30 to 35	463 / 574	81%	1.44	1.00	2.09
	35 and over	311 / 408	76%	1		
Gravida	0	539 / 746	72%	1.22	0.73	2.02
	1	491 / 583	84%	1.19	0.75	1.91
	2 or more	525 / 600	88%	1		
Parity	0	677 / 944	72%	0.10*	0.045	0.24
	1	493 / 561	88%	0.44*	0.20	0.95

	2	227 / 251	90%	0.60	0.27	1.35
	3 or more	158 / 173	91%	1		
Previous stillbirth	0	1533 / 1903	81%	1.81	0.55	5.92
	1 or more	22 / 26	85%	1		
Previous CS	0	1511 / 1853	82%	11.37*	6.28	20.60
	1 or more	44 / 76	58%	1		

289 Reference Pseudo R2 = 0.24 (Nagelkerke); *p < 0.05

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291 *Table 3, Multinominal regression analysis of odds ratios associated with vaginal delivery, using*
292 *caesarean section as reference – reason for, and method of induction*

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Variable	**Category**	**N (vaginal / total)**	**% (vaginal / total)**	**Odds Ratio**	**95% CI (lower)**	**95% CI (upper)**
Induction – primary reason	Post-term	279 / 359	78%	0.78	0.517	1.18
	Diabetes	145 / 190	76%	0.85	0.51	1.39
	Pre-labour rupture	192 / 239	80%	1.19	0.70	2.01
	SGA	249 / 279	89%	2.03*	1.20	3.44
	Pre-eclampsia	60 / 83	72%	0.95	0.50	1.82
	Other maternal reason	183 / 235	78%	0.72	0.45	1.15
	Reduced fetal movement	158 / 182	87%	1.47	0.83	2.62
	Other	285 / 356	80%	1		
Induction – method	Propess (PGE_2)	606 / 749	81%	1.16	0.68	1.98
	ARM	192 / 212	91%	2.56*	1.27	5.17
	Prostin (PGE_2)	294 / 371	79%	0.99	0.55	1.79
	Syntocinon (oxytocin)	54 / 74	73%	0.78	0.34	1.76

	Other single or dual method	167 / 196	85%	1.44	0.75	2.79
	Balloon	77 / 92	84%	1.61	0.74	3.48
	Combination propress & prostin	37 / 62	60%	0.45*	0.21	0.96
	Quadruple or more combination	23 / 41	56%	0.37*	0.16	0.85
	Triple combination	99 / 123	80%	1		
Intrapartum foetal problems	None	1017 / 1167	87%	3.50*	1.96	6.25
	Non-reassuring CTG	295 / 357	83%	3.14*	1.68	5.85
	Abnormal CTG	184 / 299	61%	0.98	0.54	1.81
	Other	50 / 73	68%	1		

Reference Pseudo R2 = 0.24 (Nagelkerke); *p < 0.05