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

3

4 Running title: **mode of labour induction and type of delivery**

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43 **Abstract** (150 words; 150 words max)

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45 Since recent research indicates that other modalities are at a minimum non-inferior to the NICE-  
 46 recommended hormonal agent prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), a retrospective cohort study was  
 47 conducted on 1971 consecutive induced singleton pregnancies. Multinomial regression showed  
 48 that the odds ratio (OR) for vaginal delivery with balloon-mediated labour induction (84% vaginal  
 49 deliveries; OR 1.6; 95% CI 0.7-3.5) is similar to the PGE<sub>2</sub> agents propess (81%; OR 1.2; 95% CI 0.68-  
 50 1.98) and prostin (79%; OR 0.99; 95% CI 0.55-1.79) when using triple multi-agent induction as a  
 51 reference. On the other hand, combining propess & prostin (60% vaginal deliveries; OR 0.45; 95%  
 52 CI 0.21-0.96) and attempting quadruple combinations of induction modalities (56%; OR 0.37; 95%  
 53 CI 0.16-0.85) yield significantly poorer outcomes. However, compared to known factors associated  
 54 with increased caesarean section rates, such as increased maternal age, nulliparous pregnancies  
 55 and history of caesarean section, the differential impact of different induction modalities appears  
 56 less pronounced.

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58 **Key Words:** labour induction, prostaglandin E<sub>2</sub>, balloon catheter, parity, vaginal delivery,  
 59 Caesarean section

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63 **Impact statement** (184 words; 200 words max)

64 • What is already known on this subject.

65 Recent published data from controlled clinical trials have shown that other labour-inducing agents,  
 66 including balloon catheters, are as effective as prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) in achieving vaginal delivery.

67 • What the results of this study add.

68 Data from this pragmatic retrospective cohort study support the findings of others that the use of a  
 69 balloon is as effective as PGE<sub>2</sub>. It also demonstrates that regular clinical practice can differ from an  
 70 experimental environment, with patients receiving multiple induction modalities in daily practice.

71 Both the combination of different PGE<sub>2</sub> medications and a quadruple labour induction approach  
 72 are associated with poorer results as measured by the vaginal delivery rate. The data presented  
 73 here also confirms that nulliparous status, maternal age and history of caesarean section are  
 74 associated with reduced odds of achieving vaginal delivery.

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

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

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**83 Introduction**

84 The application of labour induction has been increasing year-on-year and is now applied in  
85 approximately 25% of pregnancies (NHS digital, 2015); in approximately two thirds of cases,  
86 unaided vaginal delivery is achieved (RCOG, 2008). Although induction of labour itself carries risks,  
87 the risk of caesarean delivery is 12% lower with induction compared to expectant management  
88 (Mishanina et al, 2014). Progesterone E<sub>2</sub> (PGE<sub>2</sub>), as a vaginal pessary, gel, or tablet is currently the  
89 recommended mode of pharmacological induction according to National Institute for Health and  
90 Care Excellence Guidelines (NICE, 2008). In a previous study, we and others linked nulliparous  
91 status of a woman with increased use of PGE<sub>2</sub>, and increased risk of caesarean section - despite the  
92 fact that these patients are being administered more doses of PGE<sub>2</sub> (Yogev et al, 2003; Memon et  
93 al, 2011). More recent research has shown that other modalities may be associated with non-  
94 inferior or even better outcomes than PGE<sub>2</sub> for labour induction. For example, a systematic review  
95 found that misoprostol leads to more timely vaginal deliveries compared to PGE<sub>2</sub> (Alfirevic et al,  
96 2015). In another systematic review, Du et al (2017) showed that balloon-assisted induction of  
97 labour is as effective and safe as induction with PGE<sub>2</sub>. The positive evidence for balloons prompted  
98 NICE to publish an Interventional Procedures  
99 Guidance (NICE, 2015). This study aims to investigate how different induction methods for labour  
100 compare in terms of achieving vaginal delivery, using cases from a non-controlled standard clinical  
101 setting, based on local clinical guidelines devised from national published guidance.

102

**103 Materials & Methods***104 Induction guidelines*

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

113 induction in accordance to local guidelines are summarised in Table 1. Due to positive outcomes  
114 published in recent years concerning induction of labour with a balloon, and the interventional  
115 procedure guidance publication by NICE (2015), this modality was introduced in the department  
116 from 2016 onwards; the balloon model used is a Cook Cervical ripening balloon. If the Bishop score  
117 is over 7 then patients are considered eligible for direct artificial rupture of membranes (ARM).  
118 Patients undergoing induction of labour who do not show signs of labour after 24 hours from  
119 insertion of 10mg Propess pessary or after 2 doses of 3mg Prostin pessaries, medical staff assess  
120 and decide on further induction or Caesarean section. Intravenous oxytocin is not commenced until  
121 30 minutes after the 10mg Propess pessary has been removed or six hours have lapsed following  
122 the administration of a 3mg Prostin pessary. Oxytocin is only used in the presence of ruptured  
123 membranes, whether occurred spontaneously or by amniotomy.

#### 124 *Data*

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

133

#### 134 **Results**

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

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

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

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

## 161 **Discussion**

162 When considering the primary variable of interest in relation to induction success, measured by  
163 percentage vaginal delivery (unaided and instrument-aided), three trends can be identified from  
164 the results in Table 3. Firstly, ARM is a very effective induction treatment compared to hormonal  
165 induction, but is only indicated and used in a subset of expectant mothers. Secondly, balloon  
166 catheter induced labour gives very similar outcomes to the use of either propess or prostin. Our  
167 data corroborates with the data published in the systematic review by Du et al on the use of  
168 balloon catheters (2017). Thirdly, it appears that combining the two PGE<sub>2</sub> agents propess and  
169 prostin is counterproductive and associated with lower vaginal delivery rates. Furthermore,  
170 administering quadruple combinations of induction agents (for example propess, balloon,  
171 syntocinon and prostin) also gave poorer outcomes in terms of vaginal delivery rates. This practice  
172 is not in accordance with NICE guidelines and it also increases the risk of uterine hyperstimulation.  
173 This retrospective 'snapshot' of induction of labour has considerable drawbacks compared to a  
174 prospective controlled cohort or (randomised) trial design. These include variability in the choice of  
175 induction agent, often allowed in national guidelines, and inclusion of patients who normally would  
176 not be included in studies - particularly those who have a history of delivery by caesarean section.

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

## 180 **Conclusion**

181 Our data shows that the established predictors, including increased maternal age, nulliparous  
182 pregnancies and history of caesarean section, are associated more significantly with increased  
183 caesarean section than the primary reason or chosen modality for labour induction (when non-  
184 recommended induction methods are not taken into account). In conclusion, our data adds to the  
185 body of evidence that suggests that induction methods other than PGE<sub>2</sub> may just as effective.

186

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188 **Funding disclosure:** None to declare.

189

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

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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

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

288

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

290

291 *Table 3, Multinomial 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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294

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 <sub>2</sub> )	606 / 749	81%	1.16	0.68	1.98
	ARM	192 / 212	91%	2.56*	1.27	5.17
	Prostin (PGE <sub>2</sub> )	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		

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

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