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Induction of labour using prostaglandin E2 as an inpatient versus balloon catheter as an outpatient: a multi-centre randomised controlled trial

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Abstract

Objective

To compare clinical outcomes following induction of labour (IOL) using a balloon catheter and going home, versus prostaglandin (PG) as an inpatient.

Design

Randomised controlled trial

Setting

Eight Australian maternity hospitals.

Population

Women with uncomplicated term singleton pregnancies undergoing IOL for low-risk indications including post-term, advanced maternal age, 'social' reasons

Methods

Between September 2015 and October 2018, 347 women were randomised to a balloon outpatient and 348 to a PG inpatient group. PG group received Dinoprostone, either 2mg gel or 10mg controlled-release tape. Balloon group had a double-balloon catheter inserted and went home.

Main Outcome Measures

The primary outcome was a composite neonatal measure comprising nursery admission, intubation/cardiac compressions, acidemia, hypoxic ischaemic encephalopathy, seizure, infection, pulmonary hypertension, stillbirth or death. Clinical and process outcomes are reported.

Results

There were no statistically significant differences in the primary outcome comparing balloon with PG (18.6% vs 25.8%; RR=0.77, 95% CI 0.51-1.02; p=0.070), cord arterial pH<7.10 (3.5% vs 9.2%; p=0.072), nursery admissions (12.6% vs 15.5%; p=0.379), neonatal antibiotic use (12.1% vs 17.6%; p=0.103), or mode of birth. Nulliparous women in the balloon group had lower rates of the primary outcome (20.4% vs 31.0%;p=0.032); Parous women were less likely to have an unassisted vaginal birth (77.6% vs 92.3%; p=0.045).

Conclusions

Balloon catheters may be a superior method of cervical priming for nulliparous women, whereas this may not be the case for parous women. It is feasible that nulliparous women go home after commencing balloon catheter IOL, and the likelihood of adverse outcomes is low.

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Keywords

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Trial Register Number

ANZCTR (UTN: U1111-1151-5383).

Tweetable abstract

Multi-centre trial shows outpatient induction using balloon catheter is safe and feasible for nulliparous women

Introduction

Induction of labour (IOL) is a very common obstetric intervention. In high income countries approximately one in four women are induced.[1] Protocols for IOL commonly include hospital admission, and cervical priming using pharmacological means with prostaglandin (PG) tablets or vaginal gel or controlled-release tape, or mechanical means using a single or double balloon catheter. Once the cervix is more favourable, an amniotomy is performed and Syntocinon infusion commenced.[2]

For women undergoing pharmacological priming, PG can occasionally result in uterine hyperstimulation leading to fetal distress.[3] As such, most clinical practice guidelines recommend women undergoing PG IOL remain in hospital[2] with access to continuous maternal/fetal monitoring and immediate operative birth.[4] This often results in a relatively long hospital stay before an amniotomy and commencement of Syntocinon occurs.

In contrast, women undergoing balloon catheter IOL are less at risk of uterine hyperstimulation and fetal compromise, as the balloon mechanically 'ripens' the cervix.[5] Given this potential safety advantage, some maternity services use balloon catheters routinely for IOL whilst others use them in specific circumstances (e.g. if previous caesarean section (CS), or increased risk of fetal distress). Although balloon catheter is a safe and effective method of IOL[5] whether it confers any advantage when used in an outpatient setting is unknown. The Cochrane review appraising outpatient IOL[6] did not include any studies of balloon catheters for IOL, and a Foley balloon catheter was in only one included trial in the Cochrane review "Outpatient versus inpatient IOL for improving birth outcomes".[7]

A change in practice to outpatient balloon catheter for low-risk IOL indications could reduce in-hospital length of stay by many hours. Commencing an IOL at home may also result in a superior healthcare experience, reduced costs, and improved maternal and perinatal outcomes. We undertook a randomised controlled trial (RCT) to compare the clinical, healthcare experience and economic outcomes of outpatient balloon catheter versus inpatient PG IOL at term.

Methods

Study Design

A multi-centre, non-blinded, pragmatic, RCT was undertaken across eight Australian maternity hospitals (Mater Mothers, Royal Brisbane and Women's, Ipswich, Caboolture, Cairns, Toowoomba, Mackay, Tweed) between September 2015 and October 2018. The study was designed to compare the use of outpatient balloon-catheter cervical priming IOL with inpatient PG (Dinoprostone) vaginal gel or tape. The trial was granted ethics approval, and prospectively registered with the ANZCTR (UTN: U1111-1151-5383). The consumer advocacy group, Maternity Choices Australia, were engaged during trial development and reviewed the protocol and the proposed healthcare experience measures. An IOL core outcome set was not used, as this was not available at the time. There was no external funding source for this study.

Participants

Women with live singleton pregnancies, cephalic presentation, ≥37+0 weeks, undergoing IOL for low-risk indications including post-term, 'social' or 'elective' reasons, and advanced maternal age (≥40 years) were eligible to participate. Exclusion criteria included major congenital abnormality, clinical suspicion or ultrasound diagnosis of small for gestational age, previous CS, cervical priming not required (modified Bishops score (MBS) ≥ 7), high head (≥4/5 palpable abdominally), residing >60 minutes from hospital, or any contraindication to vaginal birth. Women considered potentially eligible by the attending clinician were first provided written and video information about the study. They were then approached by a research midwife after a decision about IOL had been made. Participants provided verbal then written consent.

Randomisation and blinding

Randomisation was according to a computer-generated random allocation list using variable block randomisation in a 1:1 allocation, stratified by participating centre. Sealed sequentially numbered opaque envelopes were prepared for each participating centre. Women were not randomised until approximately one day prior to their booked IOL, when the research midwife opened the next numbered envelope and informed the woman of her allocation by telephone. Neither clinicians nor participants were blinded as to the group allocation.

Procedures

On the day of their IOL, women who had a MBS ≥ 7 were excluded from the study as they did not require cervical priming. Women randomised to the PG group were admitted to hospital. A pre-PG CTG was performed and then PG, either as 2mg Dinoprostone vaginal gel (Prostin) or 10mg Dinoprostone controlled-release vaginal tape (Cervidil), was administered by the midwife or doctor. A post-PG CTG was performed for at least 30 minutes until assessed to be normal and the woman remained an inpatient until birth. Women randomised to the balloon group were not admitted to hospital. A pre-balloon CTG was performed and a double-balloon catheter (CRB plus stylet; Cook Medical, Bloomington, US) placed by a midwife or doctor by inserting it through the internal cervical os as part of a vaginal examination; 80mls of saline was then instilled into the cervical and vaginal balloons. A post-balloon CTG was not routinely performed. After 30 minutes of observation, the woman received written information about reasons to return earlier and how to call hospital, and discharged home for approximately 12 hours.

For women in both PG and balloon groups, early clinical review occurred if vaginal bleeding, fluid loss, onset of regular painful contractions, balloon expulsion, or if the woman required stronger pain relief. Otherwise, women were reviewed the following morning in birth suite, approximately 12 hours after commencement of cervical priming. At subsequent review, an amniotomy was attempted (irrespective of the MBS), and a Syntocinon infusion commenced as soon as possible. In the event that amniotomy was not technically possible, a dose of PG gel was administered followed by an attempt at amniotomy 6 hours later. If this was again unsuccessful, another dose of PG gel was administered. If at the subsequent review, amniotomy was still not possible and there remained a clear indication for delivery, CS was offered.

Outcomes

The primary outcome measure was a composite measure of neonatal outcomes comprising one or more of: admission to a neonatal special care or intensive care nursery, need for intubation and/or external cardiac compressions at birth, neonatal acidemia at birth (defined by cord arterial pH <7.10), hypoxic ischaemic encephalopathy, neonatal seizure, neonatal infection (as defined by neonatal antibiotic administration), persistent pulmonary hypertension of the newborn (PPHN), stillbirth or neonatal death. Secondary outcomes included clinical outcomes (mode of birth, intrapartum analgesia, pain scores with insertion of balloon catheter/PG and amniotomy, maternal and/or neonatal infection, meconium liquor, uterine hyperstimulation, cord prolapse, rupture of membranes, use of Syntocinon), process outcomes (discharged home, hours at home, return to birth suite earlier than scheduled, duration of labour, length of stay), healthcare experience (assessed using a validated questionnaire), and healthcare costs. Clinical and process outcomes are reported here.

Statistical analysis

A sample size of 2500 was calculated to detect a 31% reduction in the composite neonatal outcome measure from 10.0% to 6.9%, with a power of 80% and a type 1 error of 0.05. These assumptions were derived from the reduction in arterial cord pH <7.1, nursery admissions and serious neonatal morbidity reported in the relevant Cochrane review [5], and a recent RCT of outpatient mechanical versus inpatient pharmacological cervical ripening[8]. All participants who received their allocation have been included in the analysis. A-priori subgroup analyses assessed outcomes by parity (nulliparous, parous women), and for women with more (MBS 4-6) and less (MBS 0-3) favourable cervixes at the start of their IOL. The chi-squared and Fisher exact tests were used for categorical outcomes, and Student's t-test and Mann-Whitney *U* tests for data measured on a continuous scale. Relative risks (RR) with 95% confidence intervals, have been presented for the primary outcome, and comparisons deemed statistically significant at the 0.05 level. Analyses were undertaken using StataSE 10.1 (StataCorp, College Station, Texas, USA). A Data and Safety Monitoring Committee (DSMC) was established prior to trial commencement with specified terms of reference including a planned interim analysis after 700 women to assess safety, efficacy and futility.

After the interim analysis, the DSMC advised that recruitment should cease. They noted the slow rate of recruitment, and large attrition from consent-to-randomisation and randomisation-to-intervention. Analysing the very low rates of selected serious adverse events (postpartum haemorrhage >1500mL, cord prolapse, admission to neonatal intensive care, cord arterial pH <7.00, hypoxic ischaemic encephalopathy, stillbirth/neonatal death), it was deemed continuation of the trial was not viable.

Results

Between 1 September 2015 and 31 October 2018, 1965 women were assessed for eligibility across the eight sites, of whom 1060 consented to participate. Between consent and randomisation 365 women gave birth, and 695 women were randomised: 347 into the balloon catheter outpatient (balloon) group and 348 to the prostaglandin inpatient (PG) group. The analysis includes data from the 215 women in the balloon group who received the allocated intervention, and 233 in the PG group. Data were not collected from women who did not receive the allocation, the majority of whom either gave birth prior to the intervention, or did not require cervical priming (MBS ≥ 7). (Figure 1).

The baseline characteristics of women randomised to the balloon and PG groups were comparable with respect to parity, age, BMI, ethnicity, gestation, IOL indication, and MBS at the start of the IOL. Overall more women were nulliparous (71.9%), Caucasian (81.7%), and undergoing IOL for prolonged pregnancy (71.4%). For women randomised to the PG group, gel (69.2%) was used more commonly than tape, and most (71.8%) required 1 dose. (Table 1).

Amongst women who received a treatment allocation, there was a trend toward a lower composite neonatal (primary) outcome in the balloon group compared to the PG group, however the difference did not reach statistical significance (18.6% vs 25.8%; RR=0.77, 95%CI 0.51-1.02; p=0.070). There were also no statistically significant differences in any of the component measures (Table 2).

No statistically significant differences were shown in the mode of birth or indications for instrumental and CS between the balloon versus PG groups. (Table 2). There were also no statistically significant differences in analgesic use, postpartum haemorrhage rates, maternal antibiotic use, rates of cord prolapse or undiagnosed breech after commencement of the IOL. The incidence of meconium stained liquor did not differ statistically, and there was no difference in the rates of low Apgar score (<7) at 5 minutes or mean cord arterial pH. Uterine hyperstimulation occurred exclusively in the PG group (3.0% vs 0%; p=0.029). (Table S1).

The majority (86.5%) of women randomised to the balloon group went home and remained at home for a mean period of 12.3 hours. A similar proportion of women in the balloon and PG groups returned to birth suite earlier than planned. Of those who returned earlier-than-scheduled, the most common reasons in the balloon group were pain (35.5%), balloon expulsion (17.7%), and labour (16.7%). For women in the PG group the most common reasons were labour (38.5%), pain (21.5%), and rupture of membranes (21.5%). One parous woman in the balloon group gave birth before arrival to hospital, and without any adverse consequences. (Table S2).

The length of hospital stay was shorter for women in the balloon group compared to the PG group (p=0.039). Although the time from start of IOL until birth did not differ between the groups, the time from start of IOL until ruptured membranes was shorter in the balloon group (p=0.022), but the time from ruptured membranes until birth was longer (p=0.021). Significantly more women in the balloon group had their membranes artificially ruptured (88.9% vs 71.2%; p<0.001) and were administered a Syntocinon infusion (86.9% vs 66.5%; p<0.001). Women reported higher median pain scores with insertion of a balloon catheter compared PG gel or tape (p=0.002), but lower scores at the time of amniotomy (p=0.007). (Table S2).

In subgroup analyses, nulliparous women (n=312) in the balloon group had lower rates of the composite neonatal outcome than those in the PG group (20.4% vs 31.0%; RR=0.66, 95%CI 0.45-0.97; p=0.032) and less use of neonatal antibiotics (14.0% vs 23.9%; p=0.026). For parous women (n=136), those in the balloon group were more likely to give birth by CS (17.2% vs 5.1%), and less likely to have an unassisted vaginal birth (77.6% vs 92.3%; p=0.045). (Table 3). For women with a more favourable cervix (MBS 4-6) at the start of their IOL (n=217), the balloon group were also more likely to give birth by CS (31.1% vs 20.2%), and less likely to have an unassisted vaginal birth (53.8% vs 72.1%; p=0.021). In a post-hoc analysis to explore the relationship between parity, cervical favourability and mode of birth, the likelihood of CS was no different amongst nulliparous women with either a favourable or an unfavourable cervix. There was also no statistically significant difference in the likelihood of CS for parous women with an unfavourable cervix. However, amongst parous women with a favourable cervix, those in the balloon group had higher rates of CS than those in the PG group (21.2% vs 2.4%; p=0.009).

Discussion

Main Findings

For women undergoing IOL for low-risk indications at term, a protocol of balloon catheter insertion and then going home was not associated with a statistically significant difference in the primary outcome measure of adverse neonatal outcomes, compared to a protocol of PG administration as an inpatient. A trend was shown toward lower adverse neonatal outcomes overall in the balloon group (comprising less neonatal antibiotic administration, less neonatal acidaemia, fewer nursery admissions) but no difference was shown in mode of birth. In subgroup analysis by parity, however, nulliparous women undergoing outpatient balloon priming experienced significantly fewer adverse neonatal outcomes, and parous women had an increased likelihood of birth by CS.

Strengths and limitation

This study is both the largest RCT of IOL using a double-balloon catheter, and the largest RCT of outpatient IOL ever undertaken. Recruitment was ceased early in response to the interim analysis, but it was only upon study-close that it became apparent not all nursery admissions had been recorded correctly and not all exclusions were correct. Statistically significant differences in some outcomes may have been apparent had the trial continued. HREC required randomisation to occur at least 24 hours prior to IOL. By the time of IOL, 24 women had withdrawn consent, and another 223 randomised women were ineligible and did not receive the allocated intervention, most commonly because they had given birth or did not require cervical ripening. Their data were not collected and have not been included (although a formal ITT analysis, inclusive of missing data, was undertaken. Table S3). What appears to be a high drop-out rate, is actually a function of the timing of randomisation. We acknowledge this is not strictly ITT. However, every woman who met the inclusion criteria and received an allocated intervention has been analysed as per her treatment allocation, and therefore in accordance with ITT principles. There is no obvious reason why the randomisation / allocation to outpatient-balloon or inpatient-PG arms would result in a woman labouring before her planned IOL. Furthermore, there is no biologically plausible reason for there to be a difference in outcomes amongst those who were allocated but never received an intervention. We contend that the risk of selection bias is not inflated, and that any differences amongst those who were allocated but did not receive the intervention, should be random.

As a pragmatic trial, many elements of care were not prescribed. Consequently, outcomes such as neonatal antibiotics, nursery admission and analgesia will have been influenced by individual clinical decision-making and local policies. Arterial cord blood gases were not collected routinely and therefore acknowledge that the observed differences in neonatal acidemia may be impacted by a sampling bias. Centres could choose whether to use Dinoprostone gel or tape. A single dose of PG was directed but this varied across the eight sites from 32% to 100%. Similarly, use of Syntocinon following amniotomy ranged from 53% to 85%, despite the protocol recommending immediate Syntocinon for all. Nevertheless, for women randomised to the balloon group, the trend toward a lower composite neonatal outcome for nulliparous women was consistent across all sites, as was the trend toward more CS for parous women. These trends were seen regardless of whether gel or tape were used. We also recognise that this trial has appraised the use of a double-balloon catheter versus PG intravaginal gel or tape, and adopted a protocol of early amniotomy and early Syntocinon administration.[19] Given the large degree of clinical variation in approaches to IOL, care should be taken in applying these findings to local practice. The subgroup analyses were pre-specified and, although specific outcomes are statistically significant, the numbers are small. Adverse outcomes for women who went home with a balloon were rare (one parous woman gave birth before arrival to hospital), however, we are reporting outcomes for only 179 outpatient-managed women and this is insufficient to prove safety. Finally, we acknowledge the study has attempted to concurrently address questions of method of priming and location of care. It should not be assumed that results would be similar had both methods been compared in an inpatient or outpatient setting, or if Foley catheter or other PG had been used, and future researchers should consider these comparisons.

Interpretation

Balloon catheters and PG gel/tape have different mechanisms of action. In the balloon group, amniotomy was almost always possible following initial priming, and uterine hyperstimulation did not occur (consistent with previous studies[5]). In the PG group, the time to rupture of membranes was more prolonged and almost 30% required additional cervical priming, but then fewer women required Syntocinon and the time from ruptured membranes to birth was shorter. The more localised action of the balloon catheter may explain the lack of uterine activity, the infrequency of spontaneous rupture of membranes, and greater need for Syntocinon. Mechanical methods of IOL are thought to cause a release of endogenous PG within the cervix and decidua[9] and there is likely to be some variation in the amount that is released. For example, IOL using larger volume single-balloon catheters is associated with a shorter IOL-to-delivery interval than when smaller volumes are used.[10,11] The degree of PG release and the effectiveness of priming may therefore reflect the amount of cervical pressure generated by the balloon. If true, this may help explain how balloon catheter priming was associated with a higher chance of CS for parous women, and specifically those who already had a more favourable cervix. In these scenarios where the cervix is more "stretchy" or "elastic", the balloon catheter is possibly less effective at releasing endogenous PG with the same volume of fluid. In parous women, differences in the subepithelial structure of the cervix (elastin, collagen, smooth muscle), might make mechanical stretching of the cervix even less effective at generating cervical pressure, and releasing endogenous PG. Perhaps this is why we have observed mode of birth differences specifically for parous women with a more favourable cervix, and not nulliparous women.

The neonatal outcomes were also different for nulliparous and parous women. The data presented supports the preferential use of a balloon catheter specifically for nulliparous women. Similar to Pennell et al,[12] we observed a trend towards increased neonatal acidaemia with use of PG (9.2% vs 3.5%; p=0.072). Presumably the fetus with unrecognised reduced uteroplacental sufficiency is less able to tolerate frequent low amplitude/frequency contractions

commonly seen with pharmacological priming. For nulliparous women receiving PG, this period of priming and uterine activity is likely to be more prolonged, and the potential for fetal compromise greater, compared with parous women for whom labour is quicker. The difference in the composite neonatal outcome, was also driven by a greater use of neonatal antibiotics in the PG group. This might indicate more infectious morbidity associated with more vaginal examinations when PG is used. The diagnosis of sepsis in a newborn, however, is challenging and clinical guidelines[13] support administration of antibiotics to babies who are depressed at birth be it as a result of possible sepsis, hypoxia/acidaemia or other causes. Hence the additional use of neonatal antibiotics in the PG group may imply more than just presumed infection. It is therefore plausible that pharmacological priming in nulliparous women is associated with more adverse neonatal outcomes, compared with mechanical priming.

Our results suggest outpatient balloon IOL is feasible. Of the women randomised to the balloon group, 87% went home, and 74% of those who went home stayed at home until their planned review. Just 6% of those who went home returned because of labour. This contrasts with the findings of a 2014 study of outpatient PG IOL,[14] where 78% went home, 62% remained at home until the next morning, and one in three women returned in labour. In subsequent studies these authors reported that women who went home were more satisfied[15] but the approach was unlikely to be cost-effective.[16] Balloon catheters present as a more appropriate method of cervical priming for outpatient IOL. It is likely that more women could go home and stay home and therefore be cost-effective, and that adverse outcomes related to uterine activity would be less common. In a retrospective analysis of 1905 low-risk women undergoing inpatient single-balloon catheter IOL,[17] the authors hypothesised that no adverse events would have occurred had those women commenced cervical priming as an outpatient. Level-1 evidence[5] already affirms the safety of balloon IOL, and our study adds weight to these findings. There are however a relative paucity of prospective trials of outpatient cervical priming using balloon catheters.[18] Our results would support outpatient balloon cervical priming for nulliparous women undergoing IOL for low-risk indications, but more data are needed to monitor the safety of this approach.

Conclusion

This study supports the position that balloon catheters are a superior method of cervical priming for nulliparous women, but cautions clinicians using balloon catheters for parous women especially when priming a more favourable cervix. It also provides reassurance that a practice of nulliparous women going home after commencing a balloon catheter IOL is feasible, and the likelihood of adverse outcomes is low.

Disclosure of interests

We declare no competing interests. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

MB designed the study, supervised the undertaking of the trial, undertook the analysis and wrote the first draft of the manuscript. KG provided detailed statistical advice during the design, assisted with data analysis and has given editorial feedback to versions of the manuscript. VF and SK provided input into the study design, and provided advice during the running of the trial, and have given editorial feedback to versions of the manuscript

Details of ethics approval

The trial was granted ethics approval from the Mater Health Services Human Research Ethics Committee on 6 March, 2014 (HREC/14/MHS/20).

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References

1. World Health Organisation. *WHO Recommendations for Induction of Labour.* Geneva: Department of Reproductive Health and Research;2011.
2. ACOG. ACOG Practice Bulletin No. 107: Induction of labor. *Obstet Gynecol.* 2009;114(2 Pt 1):386-397.
3. Kelly AJ, Malik S, Smith L, Kavanagh J, Thomas J. Vaginal prostaglandin (PGE2 and PGF2a) for induction of labour at term. *Cochrane Database Syst Rev.* 2009(4):CD003101.
4. MIMS Australia. MIMS Medicines Product Information. In. Sydney: CMP Medica Australia; 2014.
5. Jozwiak M, Bloemenkamp KW, Kelly AJ, Mol BW, Irion O, Boulvain M. Mechanical methods for induction of labour. *Cochrane Database Syst Rev.* 2012(3):CD001233.
6. Vogel JP, Osoti AO, Kelly AJ, Livio S, Norman JE, Alfirevic Z. Pharmacological and mechanical interventions for labour induction in outpatient settings. *Cochrane Database Syst Rev.* 2017;9:CD007701.
7. Kelly AJ, Alfirevic Z, Ghosh A. Outpatient versus inpatient induction of labour for improving birth outcomes. *Cochrane Database Syst Rev.* 2013(11):CD007372.
8. Henry A, Madan A, Reid R, Tracy S, Austin K, Welsh A et al. Outpatient Foley catheter versus inpatient prostaglandin E2 gel for induction of labour: a randomised trial. *BMC Pregnancy Childbirth.* 2013;13:25.
9. Manabe Y, Manabe A, Takahashi A. F prostaglandin levels in amniotic fluid during balloon-induced cervical softening and labor at term. *Prostaglandins.* 1982;23(2):247-256.
10. Levy R, Kanengiser B, Furman B, Ben Arie A, Brown D, Hagay ZJ. A randomized trial comparing a 30-mL and an 80-mL Foley catheter balloon for preinduction cervical ripening. *Am J Obstet Gynecol.* 2004;191(5):1632-1636.
11. Delaney S, Shaffer BL, Cheng YW, Vargas J, Sparks TN, Paul K et al. Predictors of cesarean delivery in women undergoing labor induction with a Foley balloon. *J Matern Fetal Neonatal Med.* 2015;28(9):1000-1004.

12. Pennell CE, Henderson JJ, O'Neill MJ, McChlery S, Doherty DA, Dickinson JE. Induction of labour in nulliparous women with an unfavourable cervix: a randomised controlled trial comparing double and single balloon catheters and PGE2 gel. *BJOG.* 2009;116(11):1443-1452.
13. NICE Guidance. *Neonatal infection (early onset): antibiotics for prevention and treatment.* Manchester, UK: National Institute for Health and Clinical Excellence;2012.
14. Wilkinson C, Bryce R, Adelson P, Turnbull D. A randomised controlled trial of outpatient compared with inpatient cervical ripening with prostaglandin E_2 (OPRA study). *BJOG.* 2015;122(1):94-104.
15. Turnbull D, Adelson P, Oster C, Bryce R, Fereday J, Wilkinson C. Psychosocial outcomes of a randomized controlled trial of outpatient cervical priming for induction of labor. *Birth.* 2013;40(2):75-80.
16. Adelson PL, Wedlock GR, Wilkinson CS, Howard K, Bryce RL, Turnbull DA. A cost analysis of inpatient compared with outpatient prostaglandin E2 cervical priming for induction of labour: results from the OPRA trial. *Aust Health Rev.* 2013;37(4):467-473.
17. Sciscione AC, Bedder CL, Hoffman MK, Ruhstaller K, Shlossman PA. The timing of adverse events with Foley catheter preinduction cervical ripening; implications for outpatient use. *Am J Perinatol.* 2014;31(9):781-786.
18. Diederen M, Gommers J, Wilkinson C, Turnbull D, Mol B. Safety of the balloon catheter for cervical ripening in outpatient care: complications during the period from insertion to expulsion of a balloon catheter in the process of labour induction: a systematic review. *BJOG.* 2018;125(9):1086-1095.
19. Beckmann M, Kumar S, Flenady V, Harker E. Prostaglandin vaginal gel induction of labor comparing amniotomy with repeat prostaglandin gel. *Am J Obstet Gynecol.* 2015;213(6):859.e851-859.

Table 1 Baseline characteristics

	Balloon outpatient n (%)	**PG inpatient n (%)**
Nulliparous	157 (73.0%)	155 (66.5%)
Ethnicity		
Caucasian	172 (81.1%)	194 (84.4%)
Asian	7 (3.3%)	9 (3.9%)
Pacific	6 (2.8%)	6 (2.6%)
ATSI [b]	8 (3.8%)	4 (1.7%)
Other	19 (9.0%)	17 (7.4%)
IOL Indication		
Prolonged pregnancy	151 (70.6%)	169 (73.2%)
Social / elective	24 (11.2%)	25 (10.8%)
Advanced maternal age	10 (4.7%)	9 (3.9%)
Presumed fetal macrosomia	21 (9.8%)	18 (7.8%)
Gestational diabetes (diet control)	8 (3.7%)	10 (4.3%)
Method received		
Balloon Catheter	205 (95.4%)	5 (2.2%)
PG Gel	6 (2.8%)	158 (67.8%)
PG Tape	4 (1.9%)	70 (30.0%)
1 PG dose		163 (71.8%)
2 PG doses		53 (23.4%)
3 PG doses		11 (4.9%)
Age (years) [a]	30 (26-34)	30 (26-34)
Body Mass Index (kg/m^2) [a]	27.1 (23.8-31.3)	27.1 (23.8-32.4)
Gestation at IOL (weeks) [a]	41.0 (40.3-41.4)	41.0 (40.4-41.3)
MBS at start of IOL [a, c]	3 (2-4)	3 (2-4)
MBS ≤ 3 at start of IOL [c]	102 (49.0%)	129 (55.4%)
Dilatation at start of IOL (cm) [a, c]	1 (1-1)	1 (1-1)

[a] median (inter-quartile range)

[b] Aboriginal and/or Torres Strait Islander

[c] modified Bishop's score

Table 2: Composite neonatal outcome and mode of birth outcomes

	Balloon outpatient n (%)	PG inpatient n (%)	RR (95% CI) [a]	p
Primary Outcome [b]	40 (18.6%)	60 (25.8%)	0.77 (0.51, 1.02)	0.070
Arterial pH <7.10	4 (3.5%)	11 (9.2%)	0.38 (0.12, 1.15)	0.072
Admitted neonatal nursery	27 (12.6%)	36 (15.5%)	0.81 (0.51, 1.29)	0.379
Neonatal antibiotics	26 (12.1%)	41 (17.6%)	0.69 (0.44, 1.08)	0.103
Stillbirth /neonatal death	0 (0%)	0 (0%)	-	-
Hypoxic ischaemic encephalopathy	0 (0%)	0 (0%)	-	-
Neonatal seizures	0 (0%)	0 (0%)	-	-
Intubation / cardiac compressions	1 (0.5%)	0 (0%)	-	0.297
Persistent pulmonary hypertension of the newborn	0 (0%)	0 (0%)	-	-
Mode of birth				
CS	70 (32.6%)	60 (25.8%)		
Instrumental	35 (16.3%)	37 (15.9%)		
Unassisted vaginal birth	110 (51.2%)	136 (58.4%)		0.240
Instrument reason				
Slow progress	12 (34.3%)	10 (27.0%)		
Maternal exhaustion	1 (2.9%)	4 (10.8%)		
Fetal distress	20 (57.1%)	21 (56.8%)		0.377
CS reason				
Slow progress	30 (42.9%)	30 (50.0%)		
Failed induction of labour	6 (8.6%)	4 (6.7%)		
Fetal distress	22 (31.4%)	20 (33.3%)		
Failed instrument	4 (5.7%)	2 (3.3%)		
Cord prolapse	1 (1.4%)	0 (0%)		
Undiagnosed breech in labour	3 (4.3%)	3 (5.0%)		
Other	4 (5.7%)	1 (1.7%)		0.730

[a] reference group = prostaglandin inpatient group (PG)

[b] composite measure comprising one or more of: admission to neonatal nursery, need for intubation and/or external cardiac compressions, neonatal acidemia (cord arterial pH <7.10), hypoxic ischaemic encephalopathy, neonatal seizures, neonatal infection (neonatal antibiotic administration), PPHN, stillbirth, neonatal death

Table 3: Subgroup analyses by parity

	Nulliparous n (%)			p	Parous n (%)			p
	Balloon outpatient n (%)	**PG inpatient n (%)**	**RR (95%CI) [a]**		**Balloon outpatient n (%)**	**PG inpatient n (%)**	**RR (95%CI) [a]**	
Primary Outcome [b]	32 (20.4%)	48 (31.0%)	0.66 (0.45-0.97)	0.032*	8 (13.8%)	12 (15.4%)	0.89 (0.39-2.05)	0.795
Arterial pH <7.10	4 (4 .1%)	9 (9.0%)	0.45 (0.15-1.44)	0.168	0 (0%)	2 (10.5%)	-	0.157
Admitted neonatal nursery	21 (13.4%)	29 (18.7%)	0.71 (0.42-1.20)	0.199	6 (10.3%)	7 (9.0%)	1.15 (0.41-3.24)	0.788
Neonatal antibiotics	22 (14.0%)	37 (23.9%)	0.59 (0.36-0.95)	0.026*	4 (6.9%)	4 (5.1%)	1.34 (0.35-5.15)	0.665
Stillbirth /neonatal death	0 (0%)	0 (0%)	-	-	0 (0%)	0 (0%)	-	-
Hypoxic ischaemic encephalopathy	0 (0%)	0 (0%)	-	-	0 (0%)	0 (0%)	-	-
Neonatal seizures	0 (0%)	0 (0%)	-	-	0 (0%)	0 (0%)	-	-
Intubation / cardiac compressions	0 (0%)	0 (0%)	-	-	1 (1.7%)	0 (0%)	-	-
PPHN [c]	0 (0%)	0 (0%)	-	-	0 (0%)	0 (0%)	-	-
Mode of birth								
CS	60 (38.2%)	55 (36.1%)	--		10 (17.2%)	4 (5.1%)	--	
Instrumental	32 (20.4%)	35 (22.6%)	-		3 (5.2%)	2 (2.6%)	-	
Unassisted vaginal birth	65 (41.4%)	64 (41.3%)	-	0.875	45 (77.6%)	72 (92.3%)	-	0.045*

[a] reference group = PG

[b] composite measure comprising one or more of: admission to neonatal nursery, need for intubation and/or external cardiac compressions, neonatal acidemia (cord arterial pH <7.10), hypoxic ischaemic encephalopathy, neonatal seizures, neonatal infection (neonatal antibiotic administration), PPHN, stillbirth, neonatal death

[c] persistent pulmonary hypertension of the newborn

Figure 1 CONSORT flow diagram