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Comparison of outpatient with inpatient mifepristone usage for cervical ripening: A randomised controlled trial

O. Baev [a,b,*,1], A. Karapetian [a,2], D. Babich [a,**,3], G. Sukhikh [a,b,4]

[a] National Medical Research Center for Obstetrics, Gynecology and Perinatology Named After Academician V.I. Kulakov of Ministry of Healthcare of the Russian Federation, Ac. Oparina str. 4, 117997 Moscow, Russia
[b] Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Healthcare of the Russian Federation (Sechenov University), 8-2 Trubetskaya str., 119991, Moscow, Russia

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ABSTRACT

Purpose: The efficacy and safety of using mifepristone for the preinduction/induction of labour (IOL) as the only method or in combination with others has been confirmed in observational and randomised trials. However, there are currently no studies comparing the efficacy and safety of using mifepristone for the preinduction of labour on an inpatient and outpatient basis.

Objective: To evaluate whether the outpatient use of mifepristone for cervical ripening before IOL at term is as efficient and safe as in inpatients.

Study design: This open-label, prospective, two-arm, non-inferiority randomised controlled trial (ISRCTN26164110) with a 1:1 allocation ratio was conducted in a single tertiary referral hospital. Overall, 322 pregnant women (gestational age: 39–41 weeks; Bishop score < 6, intact membranes, no contraindications for vaginal delivery, and no contraindications for IOL) were included and randomised:162 to the outpatient group and 160 to the inpatient group for cervical ripening with mifepristone. Analyses were performed based on the intention-to-treat principle.

Results: In 16 % and 17 % of the cases, labour began spontaneously within 24–36 h after taking mifepristone tablets. The additional use of prostaglandin E2 or a balloon for cervical ripening occurred equally often in the compared groups. Oxytocin was used more frequently to induce labour in the inpatient group ($P = 0.035$). There was no difference in the length of the interval from the onset of cervical ripening to the onset of labour between the groups (38.6 vs. 38.8 h, $P = 0.900$). The failed induction rate was 1.85 % vs. 0.63 % ($P = 0.346$).
Regional analgesia ($P = 0.011$) and abnormal foetal heart rate patterns ($P = 0.027$) were more common in the inpatient group. In the outpatient mifepristone preinduction group, the average time interval from hospitalisation to discharge was 25 h shorter ($P < 0.001$). No statistically significant differences were observed between the groups in terms of the rates of adverse side effects or perinatal outcomes.

Conclusion: Outpatient cervical ripening with mifepristone reduced the hospital stay duration compared to inpatient ripening, with no difference in efficacy in terms of improvement in the Bishop score, frequency of additional induction method usage, interval from start of preinduction to onset of labour, and labour duration. No differences in the delivery methods, failure rates, or perinatal outcomes were observed. The frequency of adverse effects was low and not related to the setting of the preinduction site. Cervical ripening with mifepristone can be performed on an outpatient basis, because it is as effective and safe as inpatient ripening.

* Corresponding author at: National Medical Research Center for Obstetrics, Gynecology and Perinatology Named After Academician V.I. Kulakov of Ministry of Healthcare of the Russian Federation, Ac. Oparina str. 4, 117997 Moscow, Russia.
** Corresponding author.
E-mail addresses: metod_obsgyn@hotmail.com, o_baev@oparina4.ru (O. Baev), d_babich@oparina4.ru (D. Babich).
[1] https://orcid.org/0000-0001-8572-1971.
[2] https://orcid.org/0000-0001-8555-144X.
[3] https://orcid.org/0000-0002-3264-2038.
[4] https://orcid.org/0000-0002-7712-1260.

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Introduction

In modern obstetrics, labour induction is considered a way to improve maternal and foetal outcomes [1,2]. In this regard, an increase in the frequency of induced labour has been noted worldwide [3–5]. However, some evidence suggests that elective labour induction prolongs hospital stay and may increase costs and resource utilisation [6–8]. Considering these provisions, and also the fact that some women prefer to be at home as long as possible before delivery, outpatient cervical ripening could be a reasonable alternative [9–13].

It is well known that a "ripe" cervix is the most important predictor of success of labour induction. The use of pharmacological agents or mechanical methods to promote cervical ripening before the initiation of the induction process, known as preinduction, is important for successful induction. The preinduction and induction of labour are essentially linked in the same chain; however, they are different. Preinduction is aimed at ripening of the cervix (softening, shortening, and initial dilatation) and consists predominantly of remodelling the connective tissue that constitutes the bulk of the uterine cervix. Induction is the process of stimulating the uterine muscle fibres to initiate contractions. As in the setting of an unfavourable cervix, preinduction requires more time than induction, and it may be beneficial to perform it on an outpatient basis.

Mechanical methods (balloons or dilators) provide dilatation of the cervix; that is, they are preinduction methods. Pharmacological agents, such as prostaglandins and oxytocin, activate the contractile activity of the uterus; therefore, they should be considered as methods of labour induction.

Mifepristone, a 19-norsteroid compound, counteracts progesterone at the receptor level and eliminates its inhibitory effect on uterine tissue, increases the synthesis of prostaglandins, and inhibits the action of prostaglandin dehydrogenase [14–16]. The antiprogestogenic effect of mifepristone promotes cervical ripening by increasing cervical collagenase and prostaglandin synthesis, and enhancing the expression of the extracellular matrix-degrading protease stromelysin-1 [17,18]. To achieve the effect of cervical ripening, a sufficiently long period is required, usually 24–72 h. Given that the action of mifepristone is mainly aimed at ripening the cervix and not stimulating uterine contractions, its use should be considered as a preinduction method.

The efficacy and safety of mifepristone for the preinduction/induction of labour have been confirmed in observational and randomised trials [19–27].

Considering that mifepristone is a means of preinduction, and does not directly induce labour, and that it takes up to 24–72 h to achieve the effect, it seems appropriate and convenient to use it on an outpatient basis. However, there are currently no studies comparing the efficacy and safety of mifepristone preinduction of labour on an inpatient and outpatient basis.

This study aimed to evaluate whether the outpatient use of mifepristone for cervical ripening before the induction of labour at term is efficient and safe.

Methods

We performed an open-label, prospective, two-arm, non-inferiority, randomised controlled trial with a 1:1 allocation ratio at a single tertiary referral hospital (National Medical Research Centre for Obstetrics, Gynaecology, and Perinatology, Moscow) between January 2020 and November 2021. Ethical approval for the trial was obtained from the local Ethics Committee (№ 4,12/04/2018). The study was registered in the ISRCTN registry (ISRCTN26164110) before the enrolment of the first patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria

The inclusion criteria were as follows: Age between 18 and 45 years; singleton live pregnancies; cephalic presentation; gestational age of 39–41 weeks; unripe uterine cervix at the time of enrolment (Bishop's score less than 6); intact membranes; no contraindication for vaginal delivery and labour preinduction with mifepristone, prostaglandin, or oxytocin; indications for labour induction (of which the induction can be postponed for 24–48 h); and informed written consent. Prior to recruitment and randomisation, all eligible women underwent cardiotocography (CTG) to assess foetal well-being and vaginal examination to evaluate their Bishop's score. The Bishop scores were calculated as recommended by the Royal College of Obstetricians and Gynaecologists [28].

Exclusion criteria

The exclusion criteria were as follows: transverse lie or presentation other than cephalic, estimated foetal weight greater than 4500 g or other evidence of cephalopelvic disproportion, premature rupture of membranes, placenta previa or other unexplained vaginal bleeding, previous caesarean section or history of uterine surgery, severe preeclampsia, evidence of chorioamnionitis, severe form of any preexisting medical disease, concerns about the well-being of the foetus, or any medical indication for scheduled caesarean delivery.

The sample size of the study group was calculated based on the previous results showing that the expected success rate (number of women going into spontaneous labour or reaching 8 points on Bishop's scale within 48 h) was 50 % with placebo and 70 % with mifepristone. Based on this, with a 2-sided level of 5 %, 155 patients per group were required to detect a difference with a power of 95 % [52]. Given the possible data loss, 160 patients were scheduled in each group.

Eligible pregnant women who were followed up in our outpatient department and scheduled for delivery at our centre were invited to participate in the study. The women were enroled after obtaining informed consent.

The participants were randomly assigned to either the outpatient or inpatient group based on a list of computer-generated random numbers that were concealed in sequentially numbered, opaque, and sealed envelopes by independent staff members. The envelopes were sequentially opened by the investigator after the participant had completed enrolment and were assigned the corresponding study number. Blinding of healthcare providers to the indications and methods for preinduction was deemed impossible and unethical.

Women randomised to the preinduction of labour group received one tablet of mifepristone 200 mg per os at the time of enrolment. After taking the pill, the women in the outpatient group went home and were advised to return to the maternity unit if uterine contractions, abdominal pain, bleeding, preterm rupture of membranes, or unsatisfactory foetal movements occurred. If the patient did not experience the above symptoms, the patient returned for a second cardiotocographic and vaginal examination 24 h later. In the case of 8 points or more on the Bishop's scale, the woman was referred to the maternity unit for labour induction: amniotomy and, if uterine contractions were absent within 4 h, oxytocin infusion. If the Bishop score was < 8 and the condition of the foetus was satisfactory, the woman received a second tablet of mifepristone and went home for the next 24 h with the same recommendations. After 24 h, the participant was admitted to the maternity unit. Further induction plans were determined based on the Bishop score, according to the local induction protocol. If the Bishop score was 7 or less, a balloon and/or intracervical prostaglandin E2 gel (once) was used. If the Bishop's score was 8 and more – amniotomy and, if uterine contractions were absent within 4 h, oxytocin infusion was administered. In accordance with the local protocol, the induction of labour with oxytocin was considered unsuccessful if contractions did not develop within 4 h or it was not possible to reach the active phase of labour

within 8 h. Foetal conditions were checked before and after the interventions. A preinduction attempt was considered unsuccessful (failed induction of labour) if there was no change in the Bishop's score within 72 h of taking mifepristone.

For inpatient women, the management was similar to that for outpatients; however, they remained in the hospital ward.

Primary outcomes

The primary outcomes included Bishop score improvement (increase in points on the Bishop scale) after 24 and 48 h of mifepristone administration; additional use of prostaglandin E2 and/or mechanical methods for cervical ripening; additional use of oxytocin; interval from cervical ripening start to labour onset; labour duration; operative delivery rate; and the total hospital length of stay.

Secondary outcomes

The secondary outcomes included the rate of adverse effects, failed induction of labour, and neonatal outcomes.

Analyses were performed based on the intention-to-treat principle.

Statistical analysis

A chi square test or Fisher's exact test was performed to analyse the proportions. The unpaired Student's t–test and Mann–Whitney U test were used to compare groups of continuous normally and non-normally distributed variables, respectively. The tests were two-sided, and the statistical significance was defined as $P < 0.05$.

Results

Of the 437 women screened between January 2020 and November 2021, 115 women were excluded because they did not meet the inclusion criteria or provide informed consent. The remaining 326 women were randomised into two groups: 164 women in the outpatient group and 162 women in the inpatient group. Two patients in the outpatient group were lost to follow-up because labour was not performed according to the study protocol. Two patients in the inpatient group discontinued the intervention (one because of a small skin rash similar to an allergic reaction and another refused to continue with the second dose of mifepristone). The analysis included the results of preinduction/induction of labour in 322 women (162 and 160 women) (Fig. 1).

The baseline maternal and pregnancy characteristics and indications for labour induction were similar between the groups (Table 1). In 16 % and 17 % of cases, labour began spontaneously within 24 h after taking mifepristone (RR 0.95; 95 %CI 0.58–1.55, $P = 0.841$). In the remaining observations, there were no intergroup differences in the Bishop score improvement at 24 or 48 h (Table 2).

The additional use of prostaglandin E2 or a balloon for cervical ripening occurred equally often in the compared groups. Oxytocin was used more frequently to induce labour in the inpatient group (Table 2). There was no difference in the length of the interval from the start of cervical ripening to the onset of labour between the groups (38.6 vs. 38.8 h, $P = 0.900$). The failed induction rate was 1.85 % vs. 0.63 % (RR 2.96, 95 % CI 0.31–28.19) ($P = 0.346$).

We found no differences in the mean labour duration and mode of delivery, and there were no cases of postpartum haemorrhage in the compared groups. Regional analgesia and abnormal foetal heart rate patterns during labour were more common in the inpatient group

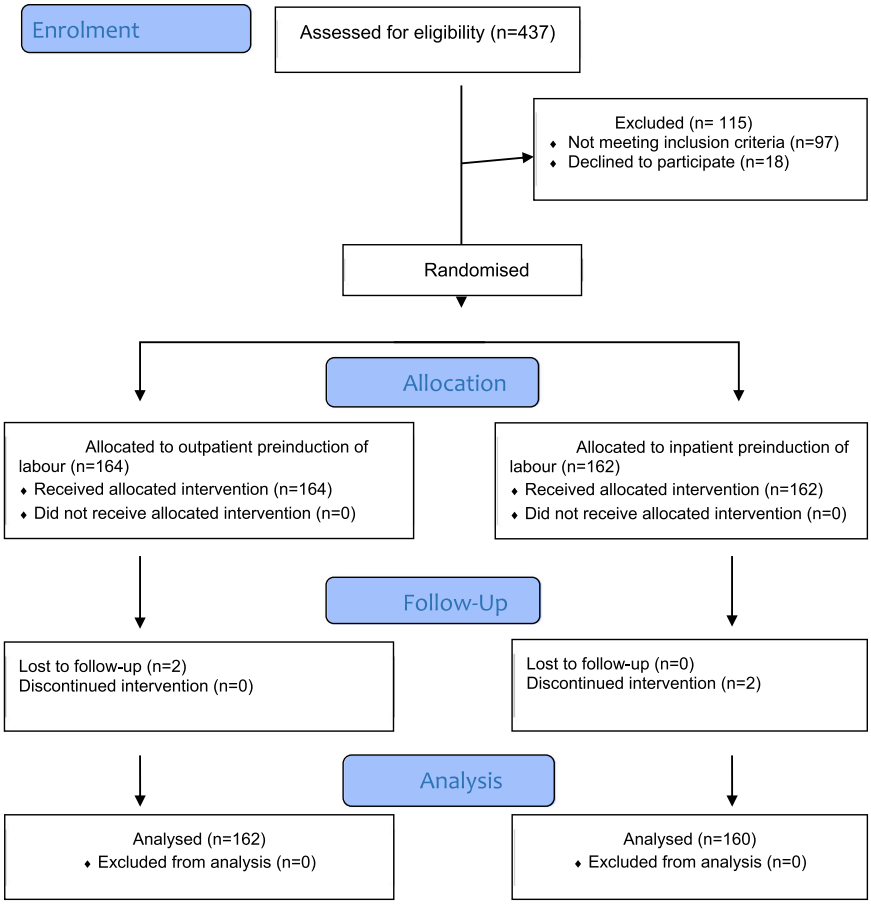

Fig. 1. Patient flowchart according to the CONSORT statement.

Table 1
Participant baseline demographic and clinical characteristics at enrolment.

	Outpatient group n = 162	Inpatient group n = 160	p-value
Maternal age (y)	31.72 ± 7.87	30.86 ± 4.73	0.233
BMI, (kg/m^2)	25.73 ± 3.65	25.98 ± 3.95	0.567
Nulliparous	119 (73.46)	115 (71.88)	0.751
Multiparous	43 (26.54)	45 (28.12)	0.751
Gestational age at enrolment, days	277.28 ± 05.72	278.26 ± 6.45	0.061
Bishop score at enrolment	3 (2–3)	3 (2–4)	0.058
Indications for induction			
Prolonged pregnancy	47 (29.01)	50 (31.25)	0.662
To avoid prolonged pregnancy	19 (11.73)	20 (12.50)	0.832
Foetal macrosomia	44 (27.16)	34 (21.25)	0.216
Diabetes	35 (21.60)	33 (20.63)	0.830
Preeclampsia or arterial hypertension	9 (5.56)	14 (8.75)	0.266
FGR	5 (3.09)	5 (3.13)	0.985
Others	3 (1.85)	4 (2.50)	0.691

Data are presented as mean ± standard deviation, or as n (%), or median (interquartile range).
BMI – body mass index.
FGR – foetal growth restriction.
Others: three cases for symphysiopathy (sacroiliitis) in each group and one for maternal request.

Table 2
Comparison of the outcomes of cervical ripening and induction of labour.

	Outpatient group n = 162	Inpatient group n = 160	*P*-value
Antepartum			
Labour onset without additional agents	26 (16.05)	27 (16.87)	0.925
Bishop's score improvement in 24 h	1 (1–2)	1 (1–2)	0.416
Bishop's score improvement in 48 h	3 (2–4)	3 (1–4)	0.527
Amniotomy for labour induction	14 (8.64)	18 (11.25)	0.435
Additional use of prostaglandin E2	53 (32.71)	48 (30.00)	0.599
Additional use of balloon	56 (34.56)	45 (28.12)	0.213
Additional use of oxytocin	10 (6.25)	21 (12.96)	**0.035**
Interval from cervical ripening start to labour onset, min	2319.50 ± 737.04	2331.43 ± 705.38	0.900
Failed induction of labour	3 (1.85)	1 (0.63)	0.623
Intrapartum			
Regional analgesia in labour	58 (35.80)	80 (50.00)	**0.011**
Abnormal foetal heart rate patterns	11 (6.79)	23 (14.37)	**0.027**
PPH	-	-	
Labour duration, min	434.97 ± 141.25	437.30 ± 148.58	0.888
Mode of delivery			
Vaginal delivery	144 (88.89)	136 (85.00)	0.301
Spontaneous vaginal delivery	140 (86.42)	132 (82.50)	0.332
Operative vaginal delivery	4 (2.47)	4 (2.50)	1.000
Caesarean delivery	18 (11.11)	24 (15.00)	0.300
Operative delivery rate	22 (13.58)	28 (17.50)	0.332
Postpartum			
Total hospital length of stay, min	6344.23 ± 469.14	7848.18 ± 1480.27	**< 0.001**
Neonatal			
Mean birth weight, g	3514.50 ± 410.89	3515.94 ± 405.57	0.975
Birth weight 4000 g and more	22 (13.58)	16 (10.00)	0.320
Apgar score 7 and less at 1 min	12 (7.41)	13 (8.13)	0.810
Apgar score 7 and less at 5 min	1 (0.62)	3 (1.87)	0.370
NICU admission	1 (0.62)	3 (1.87)	0.370

Data are presented as mean ± standard deviation, n (%), or median (interquartile range).

(Table 2). In the outpatient mifepristone preinduction group, the average time interval from hospitalisation to discharge was twenty-five h shorter ($P < 0.001$).

There were no significant differences between the inpatient and outpatient groups in terms of neonatal outcomes (Table 2). There was one case in the outpatient group and three cases in the inpatient group of Apgar score 6 at 1 min and 7 at 5 min (pH level 7.1–7.12). These newborns were carefully examined and followed up for 24–36 h in the neonatal intensive care unit, transferred to the regular unit, and discharged after a normal length of stay.

No serious adverse effects were observed in either group. The rate of side effects was low and did not differ between the groups (Table 3).

Discussion

Our randomised controlled study is the first to use mifepristone on an outpatient basis for cervical ripening at term gestation with a live foetus and was designed to assess whether outpatient mifepristone cervical ripening is as efficient and safe as inpatient mifepristone.

We found that women who underwent outpatient cervical ripening with mifepristone had the same rate of Bishop score improvement as women in the inpatient group at 24 h (1 (1–2) vs. 1 (1–2), $P = 0.416$) and 48 h (3 (2–4) vs. 3 (1–4), $P = 0.527$). This Bishop score improvement was the same as or slightly lower than that reported in other studies [25–27,30–36].

Overall, 16 % of women went into spontaneous labour within 24 h of mifepristone intake, while the rest received additional preinduction methods. There was no significant difference in the frequency of additional prostaglandin E2 gel or balloon use between the outpatient and inpatient groups (67.3 % and 58.12 %, respectively). The frequent use of these additional preinduction methods was due to the need to achieve a high degree of cervical ripening (8 points on the Bishop scale) in accordance with our local protocol. A similar frequency of additional preinduction methods was reported by Sharma et al. (73.3 % of dinoprostone gel) [27] and Wing et al. (67.0 % of misoprostol) [29]. Sujithra et al. reported a lower frequency of dinoprostone gel use (32 %); however, in every fifth case, it was reused twice [35].

A high degree of cervical ripening ensured a high efficiency of labour induction, which was manifested by a low failure rate (1.85 % and 0.62 %) and caesarean section rate (11.11 % and 15.0 %, respectively). An additional advantage of the high degree of cervical ripening was the low rate of oxytocin use for labour induction (6.25 % and 12.96 %, respectively). We assume that this is the lowest rate among the available data (25–90 % in other studies) [19,24,30,31,33,36].

In our study, the mean interval from the start of cervical ripening to labour onset was 38 h and did not differ between the groups. There were no differences in the duration of labour (an average of 7 h). Thus, the interval from the initiation of preinduction to delivery was the same

Table 3
Rate of possible adverse/side effects.

	Outpatient group n = 162	Inpatient group n = 160	*P*-value
Nausea	1 (0.62)	3 (1.87)	0.370
Vomiting	1 (0.62)	3 (1.87)	0.370
Diarrhoea	1 (0.62)	-	
False labour painful contractions	1 (0.62)	1 (0.63)	1.000
Premature rupture of membranes	2 (1.23)	5 (3.13)	0.413
Meconium-stained amniotic liquid	2 (1.23)	-	
Non-reassuring antenatal cardiotocographic patterns	-	-	
Skin rash similar to allergic (case not included into analysis due to the interruption of mifepristone administration)	-	1 (0.63)	

Data are presented as n (%).

(average, 45 h). However, due to antenatal hospitalisation, the total length of hospital stay in the inpatient group was longer by an average of 25.1 h.

One of the important aspects of any labour induction method is the safety of the mother and foetus. This is even more important if the pregnant woman is at home and not in the hospital, where she can receive medical care quickly. Therefore, the presence and frequency of adverse events associated with outpatient cervical ripening should be established to ensure safety.

There are a large number of studies on the safety of mifepristone in connection with its use in pharmacological abortion during early pregnancy. As evidenced by the results of systematic reviews, severe adverse events like blood transfusion, surgical procedures, sepsis and hospitalisation are uncommon (0.03–0.54) and related to complication of abortion and not to medication [37–40]. Haemorrhage occurred more often in patients who received mifepristone and misoprostol (51.44 %) than in those who received mifepristone alone (22.41 %) [41]. As shown by the results of a randomised controlled trial, there were no differences in the adverse side effects between the mifepristone plus misoprostol and placebo plus misoprostol groups for the management of missed miscarriage [42]. Therefore, it can be assumed that the adverse side effects were mainly associated with the use of misoprostol rather than mifepristone.

In a placebo-controlled study, no adverse effects were found in pregnant or non-pregnant women after taking 600 mg of mifepristone to prepare the cervix before abortion or exploratory curettage [17].

In our study, the mifepristone dose was only 200 mg and it was administered no more than twice, which appears to have resulted in a very low frequency and mild degree of adverse effects.

In a study by Hcini et al. [24], upon the use of 600 mg of mifepristone for cervical ripening at or beyond term, only 2 of 108 (1.9 %) patients reported headache and abdominal pain, and no foetal or neonatal side effects were noted. In another study comparing the outcomes of cervical ripening with mifepristone and dinoprostone in 50 women at term pregnancies, there were no differences in neonatal outcomes, including the incidence of hypoglycaemia [35].

Wing et al. [29] in comparison of mifepristone and oxytocin for labour induction in women with prelabour rupture of membranes prematurely terminated the trial due to concerns about the higher frequency of neonates with either suspected or clinical sepsis in the mifepristone arm. The authors concluded that the findings reflected a study design that required an 18-h observation period after mifepristone ingestion and before oxytocin administration. The duration from membrane rupture to the start of induction was longer in the mifepristone group, which likely compounded this clinical outcome.

Compared with oxytocin induction, mifepristone had a longer interval from induction to delivery, but had the advantage of a higher rate of vaginal delivery in women with uterine scars [47].

None of the women experienced premature rupture of membranes in our study, and we found no infectious complications in the mother or foetus. Abnormal cardiotocography patterns occurred on average in 10.6 % of the participants (6.79 % in the outpatient group and 14.37 % in the inpatient group), which is not different from the data obtained in other studies on cardiotocography in labour [43–46]. Sharma et al. did not show any significant increase in caesarean sections for foetal distress or any adverse neonatal outcomes in a study on the effects of mifepristone on full-term pregnancies [27].

A placebo-controlled trial by Berkane et al. with different doses of mifepristone for cervical ripening and labour induction (50–600 mg) did not find statistical differences among groups in terms of acute foetal distress, neonatal hypoglycaemia, jaundice, or respiratory disorders [46]. Similarly, no significant adverse neonatal outcomes were observed.

Confirmation of the safety of outpatient preinduction of labour provides an opportunity for its use to reduce the burden on hospital resources, reduce the cost of care, and improve women's satisfaction. Outpatient Foley catheter induction had a shorter length of hospitalisation from admission to discharge (a 7.17-h difference, 95 % CI, 71.00–77.59) and lower costs of hospitalisation than inpatient inductions [48,49]. A meta-analysis showed that outpatient balloon cervical ripening in low-risk patients was associated with a decreased time from admission to the labour ward until delivery. Moreover, the outpatient group was significantly less likely than the inpatient group to undergo caesarean delivery (21 % vs. 27 %), RR 0.76 (95 % CI 0.59–0.98) [12]. A discrete-choice experiment conducted alongside the OPRA showed that women preferred outpatient cervical ripening more than inpatients. Outpatient cervical ripening at home was more desirable despite the fact that inpatient women were provided with a private room with a private bathroom in the hospital [50]. A significant number of women in the balloon outpatient group reported that they would choose the induction of labour in their next pregnancy and desire the same method as that in the dinoprostone inpatient group [51].

Currently, there are no studies on cost-effectiveness and women's preference for outpatient or inpatient preinduction of labour with mifepristone. However, the reduction in the duration of hospital stay observed in our study suggests cost-effectiveness and promises lesser inconvenience for women in the outpatient group. An evaluation of these outcomes may be a reasonable extension of this study.

A common method of pharmacological preinduction/induction of labour used recently is the use of dinoprostone gels. We found only two studies that directly compared the effectiveness of mifepristone and dinoprostone gels. According to the results of a study by Sah et al. [33], mifepristone was more effective in cervical ripening than dinoprostone gel. The results of a trial by Jindal et al. [25] suggested a better improvement in Bishop's score at the first post-intervention assessment in the dinoprostone group; however, it indicated that oral administration of mifepristone is more convenient and equally safe.

To our knowledge, this randomised trial is the first to compare the outpatient and inpatient use of mifepristone for the preinduction of labour. Future large multicentre international studies are needed to confirm the efficacy of outpatient mifepristone treatment in cervical ripening.

Main strengths of the study

Randomisation and an appropriate sample size contributed to an adequate concealment of allocation, high group comparability, and power for primary outcomes.

Main limitations of the study

This is a single-centre study; therefore, the labour management practices of our local protocol may differ from those of others. The study is not blinded and placebo-controlled, which can lead to some bias. Owing to the rarity of adverse side effects, more observations are needed to reach a conclusion on this outcome.

Conclusion

Outpatient cervical ripening with mifepristone reduced the duration of hospital stay compared to inpatient ripening, with no difference in efficacy in terms of improvement in the Bishop score, frequency of additional induction method usage, delivery method, interval from the start of preinduction to onset of labour, and labour duration.

There were also no differences in the failure rates or perinatal outcomes. The frequency of adverse effects was low and not related to the setting of the preinduction site. Cervical ripening with mifepristone can be performed on an outpatient basis, because it is as effective and safe as inpatient ripening.

Clinical trial registration

The study was registered on ISRCTN registry (ISRCTN26164110) before enrolment of the first patient.

Ethics

Ethical approval for the trial was obtained from the local Ethic Committee of Research Centre for Obstetrics, Gynecology and Perinatology (№4,12/04/2018).

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Author agreement

All authors have seen and approved the final version of the manuscript being submitted. All authors warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Patient Consent for Publication

All patients will provide informed consent for the publication of their data. They will be notified that all records containing names or other personal identifiers will not be used in any written reports or publications.

Informed consent

Informed consent was obtained from all individuals prior to inclusion in the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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