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Original Research Article

A prospective comparative study to evaluate the efficacy and safety of mifepristone with misoprostol over misoprostol alone in induction of labour

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ABSTRACT

Background: The clinical requirement for induction of labour arises from circumstances in which it is predicted that the outcome of the pregnancy will be better if it is artificially interrupted rather than being left to follow its natural course. The combination of Mifepristone and Misoprostol is now an established and highly effective and safe method for second and third trimester termination of pregnancy and also significantly reduces the induction delivery interval, has fewer side effects and complications and also reduces the dose of Misoprostol. Hence, an attempt is made in the present study to assess the efficacy of combination of Mifepristone and Misoprostol versus single drug Misoprostol alone for induction of labor.
Methods: A prospective comparative study of 50 cases in each study group, one under Misoprostol induction (group 1) and one under Mifepristone plus Misoprostol induction (group 2) were done and observations made in terms of improvement in Bishop's score, induction-delivery interval and requirement of subsequent doses of Misoprostol.
Results: 64% of the patients were observed with improved Bishop's score. Induction delivery interval was shorter in the group 2 and noteworthy feature is 46% patients did not require even a single dose of Misoprostol after cervical ripening with Mifepristone suggesting that only Mifepristone may be only drug required in future for induction.
Conclusions: Mifepristone with Misoprostol is efficient combination for induction of labour as compared to Misoprostol alone.

Keywords: Induction of labour, Mifepristone, Misoprostol

INTRODUCTION

Induction of labour is perhaps unique in medicine because it seeks to advance a process which in the natural course of events is inevitable unless the pregnancy is terminated by caesarean section or the mother or the fetus ends up in adverse outcome.

Induction of labour is a relatively common procedure. In 2004-05, 19.8% of all deliveries in the UK were induced.[1] Aim of successful induction is to achieve vaginal delivery when continuation of pregnancy is potential threat to the life of mother and unborn baby.

Labor induction is required in 10-20% of the women near term. Medication that ripen the cervix play important role in modern obstetrics.

Mifepristone is an antiprogestin that can be used 24-48 hrs before prostaglandin analogue administration.

Misoprostol is a PGE1 analogue available in a tablet form that is stable at room temperature and inexpensive. It is

formulated for oral use but is effective by vaginal, buccal or sublingual administration for the purposes of abortion.[2]

Mifepristone has been licensed in France and China since 1988, in Great Britain since 1991 and in Sweden since 1992. The optimal dose of Mifepristone as well as of Misoprostol is not known and different regimens are in use, its combination with a prostaglandin up to 63 days of amenorrhea leads to complete abortion in about 95% of pregnancies.[3,4] Mifepristone is an antiprogestogen that blocks the receptors for progesterones and glucocorticoids. It increases the sensitivity of the uterus to prostaglandins and facilitates labor.[5]

The combination of Mifepristone and Misoprostol is now an established and highly effective and safe method for medical method second and third trimester termination of pregnancy. The combination significantly reduces the induction delivery interval and also has fewer side effects and complications and also reduces the dose of Misoprostol. Where Mifepristone is not available or affordable, Misoprostol alone has also been shown to be effective, although a higher total dose is needed and efficacy is lower than for the combined regimen. Therefore, whenever possible, the combined regimen should be used. Efforts should be made to reduce unnecessary surgical intervention for delivery of the fetus.

In India many studies have not been done regarding the use of combination of Mifepristone and Misoprostol for induction of labor. Hence, an attempt is made in the present study to assess the efficacy of combination of Mifepristone and Misoprostol versus single drug Misoprostol alone for induction of labor.

METHODS

Source of data

A prospective comparative study of 50 cases in each study group, one under Misoprostol induction (GROUP 1) and one under Mifepristone plus misoprostol induction (GROUP 2) were done when admitted in the department of obstetrics and gynecology of Rural Medical College and Hospital from 1st September 2012 to 31st July 2014.

Inclusion criteria

- IUFD
- Over 40 weeks of gestation in live fetus.
- All Primi gravida patients
- Singleton fetus with cephalic presentation
- Unfavorable cervix Bishop score < 5
- Normal coagulation profile

Exclusion criteria

- Pregnancy with any medical or surgical complication
- Previous L.S.C.S
- Mal presentation
- Congenital anomaly

Methodology

- At admission, a detailed history was taken regarding relevant medical, surgical and obstetrical information. A vaginal examination was performed to rule out cephalo-pelvic disproportion.
- Gestational age was evaluated by last menstrual period and ultrasound.
- Informed consent was obtained; the patients selected for the study were evaluated initially by modified Bishop's score and admission test for fetal wellbeing. Patients with a modified bishops score <5 and a positive admission test were induced.
- 50 patients in GROUP 1 received 25µg of Per-vaginal misoprostol and repeated for a maximum of 4 doses every 4 hrs as needed.
- 50 patients in GROUP 2 received 200 mg Mifepristone for pre induction cervical ripening and induced with misoprostol per vaginaly after 24 hrs according to Modified Bishop's score and gestational age, repeated for a maximum of 4 doses every 4 hourly as needed.
- Bishop's score was assessed every 6 hours in Misoprostol only group and after 24hrs in Mifepristone + Misoprostol group. If contractions were not adequate, in active phase of labour oxytocin drip was started.
- After administration of drugs, patients were monitored for signs of labour maternal vital signs, fetal heart rate and progress of labour. The fetal heart rate was monitored by electronic fetal heart monitor.
- Oxytocin augmentation and surgical ARM was done in required cases.
- Labour and delivery parameters including, interval from initiation of induction to delivery with misoprostol, mean number of doses of misoprostol until delivery, number of patients requiring oxytocin augmentation, mode of delivery were compared.
- Occurrence of fever, gastrointestinal symptoms, hyper stimulation, post-partum hemorrhage were evaluated. Fetal criteria including presence of thick meconium in the amniotic fluid, fetal distress as defined by abnormal cardio-tocography prompting emergency delivery, APGAR scores at one and five minutes, meconium aspiration, transfer to NICU were evaluated.
- The results observed were subjected to statistical analysis by appropriate test and a 'p' value of < 0.05 was considered as significant.

Observations collected

- Maternal age
- Gestational age

- Indication for induction
- Modified Bishop Score at induction
- Oxytocin augmentation
- Type of delivery
- Induction/Augmentation delivery interval
- Apgar of baby
- Maternal and fetal complications

Modified Bishop's Score (Calder et al)

Table 1: Modified Bishop's score.

	0	1	2	3
Dilatation(cm)	<1	1-2	2-4	>4
Effacement(cm)	>4	2-4	1-2	>1
Station(cm)	-3	-2	-1/0	+1/+2
Consistency	Firm	Average	Soft	
Position	Posterior	Mid-Anterior	-	-

RESULTS

Table 2: Distribution of cases according to age.

Age group (in years)	Number of cases Group 1 n=50(%)	Number of cases Group 2 n=50(%)
≤ 20	2(4%)	3(6%)
21-25	35(70%)	32(64%)
26-30	8(16%)	9(18%)
31-35	3(6%)	4(8%)
>35	2(4%)	2(4%)
Mean age with SD	24.5±4.13	24.78±3.92

Majority of women enrolled in both the group were from same age group (21-25); only up to 8% of patients were elderly (>30yrs) in both the groups.

Table 3: Distribution of postdate pregnancy and intra uterine deaths in two groups.

	Misoprostol (Group 1)		Mifepristone+ Misoprostol (Group 2)	
N=100 Total	**N=50**	**%**	**N=50**	**%**
Post date	40	80%	30	60%
IUD	10	20%	20	40%

In our study 80% of the patients with postdate pregnancy were induced with Misoprostol and 60% in combination group, where as 20% and 40% IUFD patients induced with misoprostol group and combination drug respectively.

Majority of the patients were between 40-42 wks (95% in group I and 93% in group II) which shows almost equal distribution in both the group.

Table 4: Distribution of patients according to gestational age in weeks in post date cases.

Gestational Age (wks)	Misoprostol (Group 1)		Mifepristone + Misoprostol (Group 2)	
	N=40	**Percentage**	**N=30**	**Percentage**
40-40.6	22	55%	08	26.6%
41-42	16	40%	20	66.6%
>42	02	05%	02	6.6%

Table 5: Bishop's score in both the groups.

Bishop score	Misoprostol (Group 1)		Mifepristone + Misoprostol (Group 2)	
	N=50	**Percentage**	**N=50**	**Percentage**
2-3	17	34%	21	42%
4-5	33	66%	29	58%

In the our study 66% of the patients were having bishop's 4-5 in Group 1 and 58% of the patients in combination group were having Bishop's score 4-5.

Mean Bishop's score observed in Group 1 were 4.02±1.09 and 3.84±1.03 in Group 2.

Table 6: Bishop's score 24 hrs after giving Mifepristone in group II.

Bishop Score	Mifepristone (Group 2) Before 24 hrs		Mifepristone+ Misoprostol (Group 2) After 24 hrs	
	N=50	**Percentage**	**N=50**	**Percentage**
2-3	21	42%	01	2%
4-5	29	58%	07	14%
6-8	0	0	10	20%
9-11	0	0	32	64%
Mean bishop's	3.84±1.03		8.54±2.06	

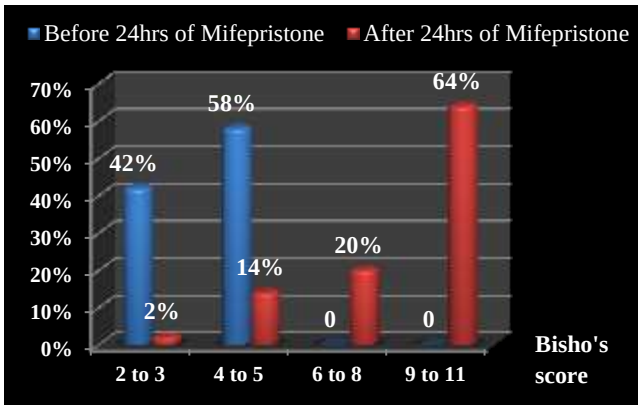

Figure 1: Improvement in Bishop's score after 24hrs of mifepristone.

It was observed that there was significant improvement in the Bishop's score after administrating Mifepristone to

the patients; mean Bishop's 24hrs after mifepristone were 8.54±2.06. This improvement was even proven statistically significant with p value = <0.0001 (Table 6).

Table 7: Induction delivery interval (hours) after first dose of Misoprostol between two groups.

Induction delivery interval after 1st dose of misoprostol	Misoprostol (Group 1)		Mifepristone +Misoprostol (Group 2)	
HRS	**N=50**	**%**	**N=50**	**%**
4-8	14	28%	23	46%
9-12	21	42%	20	40%
13-16	09	18%	07	14%
17-20	04	08%	00	00
21-24	02	04%	00	00
Mean IDI	10.94±3.98		9.34±2.81	

70% patients delivered within 12 hrs of Misoprostol in Group 1; where 86% patients delivered within 12 hrs in combination group where we used Mifepristone as pre-induction cervical ripening, which is proven not much significant with p value= 0.0760.

Table 8: Subsequent dosages of Misoprostol in both the groups.

Dose of misoprostol	Misoprostol (Group 1)		Mifepristone + Misoprostol (Group 2)	
	N=50	**%**	**N=50**	**%**
0	0	0	23	46%
1	07	14%	19	38%
2	29	58%	05	10%
3	14	28%	03	06%
Mean dose required	2.14±0.63		1.4±0.8	

Repeated dose of Misoprostol required in Group 1 was observed to be higher than comparative group as shown in table. Association between requirement of subsequent dose of Misoprostol in both the groups proven statistically significant with p value= <0.0001. Noteworthy feature is 46% patients did not require even a single dose of Misoprostol after cervical ripening with Mifepristone suggesting that only Mifepristone may be only drug required in future for induction.

Table 9: Augmentation of labor required with oxytocin in both the groups.

Augmentation of labor required	Misoprostol (Group 1)		Mifepristone+ Misoprostol (Group 2)	
	N=50	**%**	**N=50**	**%**
Oxytocin	26	52%	42	84%

In present study 84% of the pts required augmentation with Oxytocin in Group 2 where as 52% pts required augmentation in Group 1 which was expected in a course of labor.

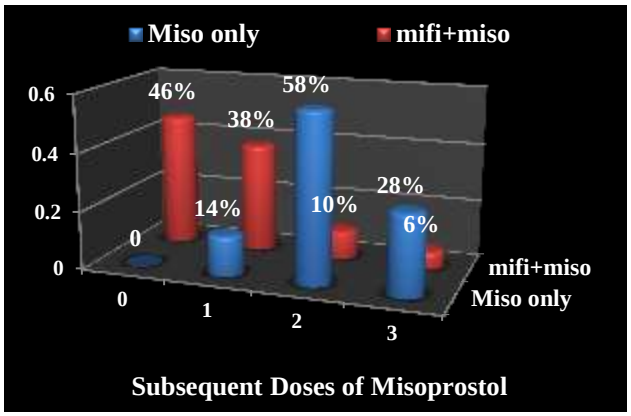

Figure 2: Requirement of subsequent dose of Misoprostol in both the groups.

Table 10: Mode of delivery in both the groups.

Mode of delivery	Misoprostol (Group 1)		Mifepristone + Misoprostol (Group 2)	
	N=50	**Percentage**	**N=50**	**Percentage**
FTND	39	78%	43	86%
LSCS	08	16%	06	12%
FTVVD	03	06%	01	02%

Most of the pts delivered vaginaly (78%) in Group 1 and (86%) Group 2. It was observed that there is 4% reduction in LSCS in combination group, but is not significant statistically.

Table 11: Maternal side effects in two groups.

Maternal side effects	Misoprostol (Group 1)		Mifepristone + Misoprostol (Group 2)	
	N=50	**%**	**N=50**	**%**
Fever	08	16%	03	06%
Vomiting	04	08%	05	10%
Diarrhea	02	04%	03	06%
Traumatic PPH	02	04%	00	00%
Atonic PPH	04	08%	01	02%
Total	20	40%	12	24%

In our observation over all side effects seen to be more with Misoprostol group (40%) and less with combination (24%) not statistically significant but 12% of the pts in Misoprostol group faced consequence like PPH (8% Atonic and 4% traumatic) however only 2% in combination group reported with Atonic PPH, which suggest there is still scope to study further with greater sample size. Out of all neonates born, 85% of the neonates had APGAR score ≥6 at 1 min in Group 1 which was seen to be 83% in Group 2.

Table 12: Neonatal outcome in postdate pregnancies in terms of APGAR score.

Neonatal Outcome	Misoprostol (Group 1)		Mifepristone + Misoprostol (Group 2)	
	N=40	Percentage	N=30	Percentage
APGAR at 1 min				
≥6	34	85%	25	83.33%
<6	06	15%	05	16.6%
APGAR at 5 min				
≥8	38	95%	28	93.33%
<8	02	05%	02	6.66%

Only 5% neonate had APGAR <8 at 5 min in Group 1 and 7% in Group 2 which is statistically insignificant.

Table 13: Indication of NICU admission.

Indication of NICU Admission	Misoprostol (Group 1)		Mifepristone +Misoprostol (Group 2)	
	N=40	%	N=30	%
Meconium aspiration syndrome (MAS)	03	7.5%	02	6.6%
Birth asphyxia	02	05%	01	3.3%
Hyperbillirubinemia	02	05%	02	6.6%
Total	11	17%	05	17%

In our observations, neonatal complications in the Misoprostol group as compared to combination protocol was insignificant as, 7.5% of fetuses suffered from MAS in Misoprostol group and 6.6% in combination group.

Over all rates of NICU admissions in Group 1 and Group 2 was similar.

After analyzing the different observations in the study, we summarize the following results.

a) There was significant improvement in the Bishop's score after administrating Mifepristone to the patients before inducing with Misoprostol.
b) Induction delivery interval after priming cervix with Mifepristone is definitely reduced but not proved statistically significant may be because of sample size taken.
c) Requirement of subsequent dose of Misoprostol is reduced in combination group which is proven statistically significant.
d) This comparative drug therapy has got no difference on mode of delivery and perinatal outcome.

DISCUSSION

As we have summarized the positive results, we are going to discuss similar observations regarding positive results only escaping insignificant observations in discussion.

Similar observations in induction of labor in poor bishop's score of cervix among full term pregnancy with the use of prostaglandins like misoprostol were made by many along with comparative drug of choice being PGE2 gel but limited studies or clinical trials available for pre-induction cervical ripening with RU 486.

A preliminary trial by Cabrol et al, reported successful induction of labor and further using a prospective double blind trial confirmed that mifepristone can be useful in management of intrauterine death.[6] Urquhart et al, showed that mifepristone before prostaglandin induced second trimester termination of pregnancy significantly reduced the induction to abortion interval compared with their controls.[7] Mifepristone in combination with misoprostol is well established in management of early first trimester pregnancy. However, there are limited studies using a combined regimen for inductions of labor in postdate pregnancy and late intrauterine death. Present study is not done to design a new regimen, but to compare those already described in the literature and to assess how the published regimen perform among Indian women who are undergoing induction of labor for late intrauterine death and postdate patients also.

Very limited studies have been put forward for induction of live post term pregnancy with Mifepristone but literature have been mentioned about its effect on cervical ripening in term patients.

It is established practice to use Mifepristone plus Misoprostol regime for termination of pregnancy in 2nd trimester like, Premila W. Ashok et al**,** DianaWebster et al**,** Julia Bartley et al proved that average induction abortion interval is 6-7 hrs.[8-10] They have also been compared with other different dosage protocols of misoprostol which has got significant value regarding the usage of Mifepristone as cervical ripening and abortificient ability.

Optimally people had been using Mifipristone and Misoprostol combination for induction of labor in late intrauterine death and observed IDI, which we also did in our study but we included cases of more than 28wks or term IUD's.

In present study we observed mean IDI 9.34±2.8hrs in all cases whether IUD's or post term pregnancy after pre induction cervical ripening with Mifipristone and compared with mean IDI 10.94±3.98hrs with misoprostol only regimen.

We have observed the effect of Mifepristone on cervix 24hrs pre induction with misoprostol in primi gravida, postdate, singleton pregnancy with no other high risk factor and outcome of study is compared with few similar studies recently done by others authors.

Table 14: The induction to delivery interval of published medical regimens in the management of late IUD.

Reference	Gestation (weeks)	Regimen	Induction to delivery interval (h)
Cabrol et al[6]	18-30	Mifepristone 200mg twice a day for two days	39
Wagaarachchi et al[11]	>24	Mifepristone 200mg oral, 24-48hrs later for 24-34 wks 200µg vaginal misoprostol followed by 200 µg,3hrly x4dose oral and for 34 wks onwards 100 µg is used	8.5
Fairley et al[12]	>24	Mifepristone 200mg, 1st group vaginal/oral 400µg /misoprostol every 4 hourly 2nd group-vaginal 50µg 3 hourly misoprostol	7 10.2
Present study	>28	Mifipristone 200mg f/b misoprostol 50-100 µg every 4hrly	9.34±2.8

In present study 66% pt's included in Group 1 were having mean bishop's score 4.02±1.09 which were induced with misoprostol and outcome observed. In another group where Mifepristone were used as pre induction drug for cervical ripening, mean bishop's score observed was 3.84±1.03.

As expected after 24 hrs of administration of mifepristone 64% of the pt's improved Bishop's up to 11 and 20% up to 10, mean bishop's score observed was 8.54±2.06 and statistically proven significant with chi square value =73.62, df = 3 and 'p' value= <0.0001.

Similar observations are with Wing D.A Fassett Michael J where Bishop's score before administration of mifipristone were unfavorable (<5) and almost 20% pts went in spontaneous labor with favorable Bishop's score (>7).[13]

Shanitha Fathima et al also observed the significant difference in Bishop's score pre and post administration of mifipristone as well as dianoprostone in their study as mean pre induction score 2.32±0.76 and mean post induction score as 7.25±1.75 at 48 hrs.[14]

Athawale R et al also observed pre induction Bishop's <3 in 84% as compared to 58% in placebo group, where Bishop's score improved 24hrs after mifipristone up to >8 in 72% as compared to placebo where Bishop's score remain between 4-8 in 86% pts.[15]

Yelikar K et al observed Mean Bishop's Score at 0 hour (Mean± SD) in study group with mifipristone 2.02±0.749 and 2.16±0.77 with placebo which improved up to 5.0408±1.90with mifipristone administered group and 3.26±1.15 in placebo group.[16]

Hapangama D, Neilson JP, in their study of "Mifepristone for induction of labour" compared to placebo (108 women), Mifepristone treated women were more likely to have a favorable cervix at 48 hours [risk ratio (RR) 2.41, 95% confidence intervals (CI) 1.70 to 3.42]. Effect persisted at 96 hours (RR 3.40, 95% CI 1.96 to 5.92).[17]

Comparison of mean Bishop's score after administration of mifepristone

Table 15: Comparison of mean Bishop's score after administration of mifepristone.

Comparison of Bishop's score after administration of mefipristone	Pre induction Bishop's score	Bishop's score after 24-48 hrs
Wing DA Fassett Michael J[13]	<5	>7
Shanitha Fathima et al[14]	2.32±0.76	7.25±1.75
Athawale R et al[15]	<3	>8
Yelikar K et al[16]	2.02±0.749	5.0408±1.90
Present study	3.84±1.03	8.54±2.06

Induction delivery interval in our study considered from 1st dose of misoprostol instead first dose of mifepristone which is used as pre induction drug for cervical ripening.

It had been a consistent finding that IDI in prime cervix with mifepristone is lesser than misoprostol only in our study as mentioned above which is also seen with placebo or control groups.

In misoprostol only group maximum pt's that is 70% delivered within 12 hrs of 1st dose of misoprostol, mean IDI observed 10.94±3.9 where we can see most of the pt's that is 86% in mifepristone group delivered within 12 hrs. Mean ID 9.34±2.81, which is statistically insignificant (p= 0.0760) but theoretically important and require further study with large scale sample. These significant findings are similar with other studies also.

In terms of requirement of subsequent repeat doses of misoprostol, maximum pt's (58%) required at least 2 doses of misoprostol (50 microgram) in Group 1 whereas maximum pt's (46%) did not require misoprostol at all for induction in Group 2 instead they required augmentation (84%) with Oxytocin which is supposed to be acceptable in terms of normal progress of labour and rest of pts required misoprostol induction. This is also

proven statistically significant with chi square value = 52.597, df= 3 and p = <0.0001.

Table 16: Induction delivery interval is compared with other studies.

Study	Mifepristone IDI in hrs (mean)	Control/ Placebo/ Misoprostol only (IDI hrs)	Dinoprostone (IDI hrs)
Frank J. Chuck[18]	NA	11.4	18.9
Patrick S. Ramsey[19]	NA	23.9	31.1
Howard A. Blanchette[20]	NA	19.8	31.1
David Buser[21]	NA	15.8	24.2
Patrick Rozenberg[22]	NA	14.5	19.2
Wing D A. Fassett Michael J[13]	36.8	44.5	NA
Yelikar K et al[16]	31	35	NA
Shanitha Fathima et al[14]	32	NA	NA
Present study	9.34±2.81	10.94±3.98	NA

Yelikar K et al observed Mean Dose of Misoprostol required (in µg) 40±27.2 as compared to placebo 52±19.46.[16]

In present study mode of delivery seen not get affected much by the induction protocol used, 16% pts required LSCS in Group 1 and 12% in Group 2. This finding is consistent with some other studies also.

As far as the maternal side effects are concerned threatened complication like atonic PPH which did not require surgical intervention, got managed with medical line observed to be in 8% pt's in Group 1 and only 2% in Group 2 which appears to be significant.

Other side complications which really required operative intervention were observed as fetal heart variability, Tachysystole, failure of induction were observed more with Group 1 as 10%, 2% and 2% respectively as compared to Group 2 as there was no case reported as uterine hyper stimulation and only 6% cases with fetal heart variability noted in present study.

Similar observations are with Shanitha Fathima et al case of fetal distress and 1 case of tachysystole observed in mifepristone group (p>0.05 NS), and 1 case in the dinaprostone group (p>0.05 NS).[14]

Yelikar K et al also reported with only one case with Tachysystole in mifepristone+misoprostol in comparison with placebo which is insignificant.[16]

Neonatal outcome in present study observed in the form of APGAR score at 1 and 5 min. In our observation there is no significant difference in APGAR score in both the groups.

In study conducted by Wing D.A Fassett Michael J NICU admission observed was 13.4% with APGAR score <7 at 1min observed in 15.4% pts in Mifepristone only induction protocol, which again was not significant when compared to placebo group.[13]

According to Shanitha Fathima et al also there is no significant difference in perinatal morbidity when Mifepristone compared with Dianoprostone.[14]

CONCLUSION

From our study we finally conclude Mifepristone (RU 486) is a safe and efficient agent for cervical ripening and for initiation of labor when given 24h before labor induction. It appears to reduce the need for augmentation with misoprostol. Mifepristone provides an interesting new alternative for induction of labor at term and can be considered by the obstetricians as a simple and safe method of labor induction. Further study with larger sample size is necessary to formulate its efficacy for postdate patients.

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