



**EFFECT OF MIFEPRISTONE WITH INTRACERVICAL DINOPROSTONE GEL
FOR CERVICAL PRIMING PRIOR TO INDUCTION OF LABOR AT TERM IN
AN UNFAVORABLE CERVIX OF PRIMIGRAVIDA: REVIEW ARTICLE**

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ABSTRACT

Prostaglandin is used for providing an effective method for achieving the induction of labor. On the basis of our study, Misoprostol appears to be an effective agent for the induction and augmentation of labor as compared to the Dinoprostone. The results of labor outcome convincingly prove that in the patients treated with misoprostol, induction interval was shorter and the incidences of caesarean section were reduced.

INTRODUCTION

Human labor is complex process and is characterized by the onset of effective uterine contractions leading to progressive effacement and dilatation of the cervix, resulting in the expulsion of the fetus, placenta and the membrane. The cervix has to play dual role in human reproduction. During pregnancy, it should remain firm and closed allowing the fetus to grow in utero until functional maturity is attained. During labor it should soften and dilate, allowing the fetus to pass through the birth canal. The process by which the cervix become soft, compliant and partially dilated is termed `cervical ripening`. Cervical ripening is thought to be due to combination of biochemical, endocrine, mechanical, and possibly inflammatory events.¹ Induction implies stimulation of uterine contraction before the spontaneous onset of labor with or without rupture membrane.² Induction of cervical ripening is critical to successful induction of labor in a pregnant patient whose cervix has not gone through the ripening process. Cervical ripening allows the uterine contractions to effectively dilate the cervix. . The amount of uterine pressure required to dilate a ripe cervix is thought to be approximately 1600 mm Hg, while the pressure to dilate an unripe cervix is estimated to be greater than 5 times that, or 10,000 mm Hg. Labour induction is indicated when benefits of delivery to mother or fetus outweigh the potential risk of continuing the pregnancy.³ Induction is indicated when the benefits of either mother or fetus outweigh those of continuing the pregnancy. Indication include immediate conditions such as ruptured membranes with chorioamnionitis or severe preeclampsia .The more common indication include membrane rupture without labor, gestational hypertension, non-reassuring fetal status, postterm pregnancy, and various medical conditions such as chronic hypertension and diabetes.² Starting with a favorable cervix ensures the success of labor induction . The goal of cervical ripening is to facilitate the process of cervical softening, effacement and dilatation, thus reducing the induction-to-delivery time. When there is an indication for induction and the cervix in unfavorable, agents for cervical ripening may be used. The status of the cervix can be determined by Bishop pelvic scoring system. An unfavorable cervix has generally been defined as a Bishop score of 6 or less in most randomized trials. If the total score is more than 8 , the probability of vaginal delivery is more likely and is comparable to that after spontaneous onset of labour.¹ The two major techniques for iatrogenic cervical ripening are (1) mechanical interventions, such as insertion of catheters or cervical dilators, and (2) pharmacological such as application of cervical ripening agents (prostaglandins) . Induction of labor is carried out in over 20% of pregnancies on an average in developed countries, indicated to be advantageous for the mother & baby, decrease perinatal morbidity and mortality. Induction between 37-41 weeks has the potential to improve neonatal outcomes. Induction of labor is associated with a doubling in the caesarean delivery rate compared with spontaneous labour.⁴ Therefore; successful labor induction is clearly related to state of the cervix. Pregnant lady with unfavorable cervix, who have not experienced cervical ripening phase prior to labor, present a great challenge with regard to induction of labor . So Bishop's scoring is done to see whether the cervix is favorable or not. In an unfavorable cervix, if induction is done chances of prolonged labor and chance of having cesarean section will be

increased. To reduce cesarean section rate cervical priming is done prior to induction.

LITERATURE REVIEW

The search for glucocorticoid receptor antagonist finally succeeded in early 1980s with development of the 11 β -aminophenyl-substituted 19-non steroid called RU-486 later named Mifepristone. Mifepristone is a pharmacologic antagonist at the steroid receptor.⁵ Given during the follicular phase, its antiprogestin action results in attenuation of midcycle Gn surge from pituitary, slowing of follicular development and delay/failure of ovulation. During the luteal phase, it prevents secretory changes normally brought about by progesterone. Later in the cycle, it blocks progesterone support to endometrium, unrestrained PG release from it, this stimulates uterine contractions. Mifepristone also sensitizes the myometrium to PGs and induces menstruation. If implantation has occurred, it blocks decidualization, conceptus is dislodged, HCG production falls, secondary luteolysis occurs-progesterone secretion decreases and cervix is softened .

In the absence of progesterone (anovulatory cycles, after menopause) it exerts weak progestational activity, induces predecidual changes .The weak antagonistic action is not manifest in the presence of progesterone.

The antiglucocorticoid action of usual doses is also not manifest in normal individuals because blockade of negative feedback at hypothalamic-pituitary level elicits ACTH release, plasma cortisol rises and overcomes the direct antiglucocorticoid action .Amelioration of Cushing's symptoms has been obtained with large doses .

Pharmacokinetics- Mifepristone is active orally but bioavailability is only 25 %. It is largely metabolized by liver by CYP3A4 and is excreted in bile , some enterohepatic circulation occurs.⁶ The mean half-life of Mifepristone is 20 hours .This is longer than that of many natural and synthetic glucocorticoid agonists . Less than 1 % of the daily dose is excreted in the urine, suggesting a minor role of kidney in clearance of the compound .The plasma half-life of Mifepristone results from extensive and strong binding to plasma proteins. Less than 5% of the compound is found in the free form when plasma is analyzed by equilibrium dialysis. Mifepristone can bind to albumin and α_1 -acid glycoprotein but have no affinity to CBG.⁵

In a study conducted by Vidya Gaikwad, Bilsa Mittal, and Mangal Puri in 2014 , 100 patients were included , 50 patients were placed in each group A and B. Tablet Mifepristone 200mg orally was given in group A patients and intracervical gel induction was done in group B patients. Pre induction Bishop's score was noted at beginning to compare improvement in Bishop's score after induction, mode of delivery and induction-delivery interval in both the groups. Rate of successful IOL or vaginal delivery was 84% with Mifepristone and 56% with Dinoprostone. After induction with Mifepristone 94% women had cervical

ripening as compared to 80% with Dinoprostone. 20% Mifepristone treated group required Oxytocin for augmentation as compared to 56% in Dinoprostone. Among the babies, 6% and 14% belonging to Mifepristone and Dinoprostone group respectively, required NICU admissions. In the present study, women who were induced with Mifepristone showed significantly more improvement in Bishop's score than Dinoprostone. Although overall average induction- delivery interval was more in Mifepristone group (29hours) than Dinoprostone group (21hours), vaginal mode of delivery with Mifepristone was more, decreasing the incidence of caesarean section with lesser need for augmentation with Oxytocin. Lesser NICU admissions and maternal complications were noted with Mifepristone. Thus, Mifepristone is a better drug for successful induction of labour as compared to Dinoprostone with a better fetomaternal outcome.⁹

In a study conducted by Rutuja Athawale, Neema Acharya, S. Samal, C. Hariharan in Department of Obstetrics & Gynecology, Jawaharlal Nehru Medical College, India. 100 patients (term) were included. Patients were categorized by BISHOP SCORE at the beginning of induction for comparison of BS, mode of delivery, induction delivery interval (IDI). Women undergoing induction with RU486 (200mg PO) were grouped in one and those with placebo control group into another. Rate of successful IOL or vaginal delivery was 76% in study group and only 36% in control group. After induction with mifepristone for cervical ripening in study group 76% patient who had cervical score <3 on admission had cervical score improved to >8 within 24 hours, whereas in control group 2% female's cervical score was >8. Among the babies, 44% in the control group required baby unit admission as compared to 36% in the study group. In this study, the women who were induced with mifepristone 200 mg per orally showed drastic improvement in cervical score within 24-48 hours and decreased the cesarean rate in the study group and amount of dose requirement of augmentation of labor with Misoprostol or Oxytocin, lesser NICU admission and maternal complication.¹⁰

Shanitha Fathima et al conducted Hospital based, prospective randomized comparative study conducted in Lady Goschen Hospital and Kasturba Medical College, Mangalore in 2013. A total of 100 pregnant women (50 women in the mifepristone group and 50 in the dinaprostone group) at term gestation (37-42 weeks) scheduled for induction of labor were selected for the study. The study demonstrated significant efficacy of mifepristone for cervical ripening and induction of spontaneous labor after drug administration as more women had favorable Bishop's scores at the end of 48h. In this study 66% of women entered labor spontaneously or had a sufficiently ripened cervix within 48h of intake of mifepristone, but there was no difference in time between prostaglandin administration and delivery interval between the groups. There were less no. of caesarean section in the study group but the difference was not statistically significant. Maternal complications and neonatal outcomes were comparable in both the group. Even though, there is a theoretical risk of hypoglycemia in the newborn, the present study showed no difference in the same among the 2 groups. This study concluded that Mifepristone (RU 486) is a safe, efficient and suitable agent for cervical ripening and for initiation of labor when given 48h before labor

induction.¹¹

A literature search of Cochrane database was done by Neilson JP. It includes seven trials that recruited 594 women. All trials compared mifepristone with placebo, except for one that compared mifepristone with no treatment. Compared to placebo, mifepristone treated women were less likely to have an unfavorable cervix at 48 hours (relative risk [RR] 0.36, 95% confidence intervals [CI] 0.2-0.63) or 96 hours (RR 0.39, 95% CI 0.23-0.66). Mifepristone treated women were more likely to have delivered within 48 and 96 hours of treatment than were placebo treated/no treatment women - 48 hours: RR 2.82, 95% CI 1.82-4.36; 96 hours: RR 3.40, 95% CI 1.96-5.92. Mifepristone treated women were less likely to undergo caesarean section (RR 0.71, 95% CI 0.53-0.95). There is little information about fetal outcome; although there was no evidence that neonatal hypoglycemia might be more common after exposure to mifepristone. Similarly, there is little information about maternal side-effects although some nausea and vomiting was reported in one trial. Study concluded that there is insufficient information available from clinical trials to support the use of mifepristone to induce labor. However, available data do show that mifepristone is better than placebo at ripening the cervix, and inducing labor. There is evidence of a possible reduction in the incidence of caesarean section following mifepristone treatment (compared to placebo) that would justify further trials. They found no trials that compared mifepristone with alternative methods of inducing labor e.g. prostaglandins.¹²

Lelaidier C et al evaluate the efficacy and tolerance of Mifepristone in women undergoing induction of labor at term after previous caesarean section. A prospective double blind placebo controlled trial. Thirty-two women at term (after 37.5 weeks' amenorrhea) who had a previous caesarean delivery with a low transverse uterine incision had a clear clinical indication for induction of labor with unfavorable cervical conditions (Bishop's score < 4). They were randomized to receive either 200 mg of mifepristone or placebo on days one and two of a four-day observation period. They found, thirteen women entered spontaneous labor: 11 were treated with Mifepristone and two were in the control group (P < 0.01). Thirteen women, still with an unfavorable cervix on day four needed cervical ripening with vaginal tablets of prostaglandins. Of these, four had received mifepristone and nine the placebo. Mean oxytocin requirements were lower in the mifepristone group (P < 0.01) and the mean time interval between day one and start of labor was also significantly shorter in this group. Mode of delivery and neonatal outcome were similar in both groups. They concluded that Induction of labor is facilitated in term women with prior caesarean section by the use of Mifepristone. This induction agent appears safe and useful with no adverse events on the fetus or mother.¹³

Study done by McGill J, Shetty A to assess the ability of Mifepristone to prime the cervix adequately and induce labor in pregnant women at term; and when Mifepristone alone proves insufficient, to determine whether oral Misoprostol taken 48 h following mifepristone administration is effective in inducing labor. In this prospective study 50 pregnant women at term with an unfavorable cervix were given 400 mg of

Mifepristone orally and allowed to return home. If labor did not start within 48 h, the women were admitted and induction was continued with 50 microgram of Misoprostol, a prostaglandin (PG) E1 analogue, taken orally every 4 h. The 50 controls, who were matched prospectively for parity and pregnancy duration, underwent labor induction according to the routine administration of 3-mg tablets of PGE2 vaginally. They found that in the study group, 66% of the women entered labor spontaneously or had a sufficiently ripened cervix within 48 h of taking Mifepristone. However, there was no difference in time between prostaglandin administration and delivery between the control group and the 34% of women who required Misoprostol in the study group. In the study group, the cesarean section rate was significantly lower among the women whose labor was induced with Mifepristone alone than among those who required Misoprostol. There were no differences overall in obstetric or neonatal outcomes between the study and control groups. They concluded that 400 mg of Mifepristone was effective in inducing cervical changes and labor. Although there were no adverse effects using oral Misoprostol in combination with Mifepristone, labor was more difficult to induce in the women who did not respond to Mifepristone alone, and these women had a higher operative delivery rate.¹⁴

Wing DA et al made a comparative study in 2005. They compare the use of oral Mifepristone with intravenous oxytocin for labor induction in women with prelabor rupture of membranes (PROM) at 36 weeks' or greater gestational age. Sixty-five women with spontaneous PROM were randomly assigned to receive orally administered Mifepristone or oxytocin infusion. Two hundred milligrams of Mifepristone was administered, and subjects were observed for 18 hours, or intravenous oxytocin was administered. They found Thirty-three women received Mifepristone and 32 received Oxytocin. The average interval from start of induction to delivery was 1194.1 +/- 568.7 minutes for Mifepristone-treated subjects and 770.8 +/- 519.9 minutes for oxytocin-treated subjects ($P = .001$, log-transformed data). Of 33 Mifepristone-treated subjects and 32 oxytocin-treated subjects, 25 (78.1%) and 17 (51.5%), respectively, achieved successful induction (defined as vaginal delivery within 24 hours) (relative risk [RR] 0.66, 95% CI 0.45-0.96, $P = .01$). There was more fetal distress in the Mifepristone-treated group (9 vs 2, RR 4.36, 95% CI 1.02-18.66, $P = .02$), and a trend toward more cesarean births (7 vs 3, RR 2.26, 95% CI 0.64-7.99, $P = .19$). Eleven infants of Mifepristone-treated women (33.3%) and 3 infants of oxytocin-treated women (9.4%) were admitted to the neonatal intensive care unit (RR 3.56, 95% CI 1.09-11.58, $P = .02$). They concluded oral Mifepristone administration 18 hours before oxytocin infusion did not improve labor stimulation in women with PROM near term, and was associated with more adverse fetal outcomes.¹⁵

Fassett MJ and Wing DA in 2008 conducted a study to examine the effect of oral Mifepristone on uterine activity in postterm human pregnancies. As part of a randomized, placebo-controlled trial comparing 200 mg oral Mifepristone to placebo for preinduction cervical ripening in women with well-dated pregnancies beyond 41 weeks' gestation with unfavorable cervixes, uterine activity was continuously recorded with external tocodynamometry and contraction frequency tabulated. Ninety-seven women

received Mifepristone and 83 women received placebo. Uterine activity (uterine contractions/hour) was greater in the Mifepristone than in the placebo group between 7 h (8.03 +/- 0.48 vs. 5.90 +/- 0.39, $p = 0.001$) and 24 h (8.53 +/- 0.68 vs. 6.61 +/- 0.46, $p = 0.02$) after dosing. They concluded oral Mifepristone administration to women with pregnancies beyond 41 weeks increases uterine activity in the absence of externally administered uterotonic agents.¹⁶

Berkane N et al in 2005 undertook study to determine the efficacy of Mifepristone for ripening the cervix and inducing labor in term pregnancies. In a double-blind placebo-controlled dose-finding study, 346 women received 50, 100, 200, 400, or 600 mg of Mifepristone or placebo. The main endpoint for efficacy was the number of patients whom labor occurred between 12 and 45 and 54 hours after treatment or who had a Bishop score 6 or greater. Maternal and fetal tolerability was also studied. They found no significant efficacy was observed whatever the dose of Mifepristone. Mifepristone was well tolerated by the mother and fetus. They concluded Mifepristone, at doses up to 600 mg, does not induce labor within 54 hours in patients with unfavorable cervical status.¹⁷

Gallot D et al conducted study in 2004. They compare the mode of delivery in two groups of patients selected by their response after induction of labor with Mifepristone. They studied retrospectively 89 cases of labor induction with viable children after 41 weeks of gestation. Bishop scores were less than 6. Patients were given 200 mg of Mifepristone per day for 48 h. They were retrospectively divided into group 1 (spontaneous onset of labor or premature rupture of membranes before the third day) and group 2 (not in labor by that date). They found the mean Bishop score at inclusion was 3.1 +/- 1.3. Among the 51 patients (53.9%) in group 1, one required prostaglandins and they performed 10 cesarean sections. In group 2, the mean Bishop score at the 3rd day was 4.4 +/- 1.3 ($P < 0.0001$). Twenty-four patients required prostaglandins ($P < 0.0001$) and they performed 17 cesarean sections ($P = 0.01$). The number of cesarean sections increased with the dose of prostaglandins ($P = 0.025$). They observed no maternal or fetal complications. Mifepristone was successful in inducing labor spontaneously in over 50% of pregnancies after 41 weeks of gestation. In the other group, the probability of vaginal delivery was reduced especially when high doses of prostaglandins were required. After the use of Mifepristone, they suggest to shorten the duration of prostaglandin administration (two applications of 2 mg dinoprostone) before performing cesarean section.¹⁸

Wing DA et al conducted study in 2000. They compare the effect of Mifepristone with placebo on cervical ripening before labor induction in prolonged pregnancies. One hundred eighty women with pregnancies beyond 41 weeks and undilated, uneffaced cervixes were assigned randomly to receive Mifepristone 200 mg or placebo and observed for 24 hours. They then gave intravaginal Misoprostol 25 microgram every 4 hours or intravenous oxytocin. They expected 60% of placebo-treated and 80% of mifepristone-treated women to deliver vaginally within 48 hours. Among 180 subjects, 97 received Mifepristone and 83 received placebo. The mean interval (+/- standard deviation [SD]) from start of induction to delivery was 2209 +/- 698 minutes for Mifepristone-treated subjects and 2671 +/- 884 minutes

for placebo-treated subjects ($P < .001$, log-transformed data). Twelve (13.6%) Mifepristone-treated women and seven (10.8%) placebo-treated women delivered vaginally on day 1 ($P = .60$). After 24 hours, the median Bishop score for both groups was 3 (0-11) ($P = .51$). One hundred thirty-one subjects required Misoprostol, 65 (67.0%) were Mifepristone-treated women, and 66 (79.5%) placebo-treated women ($P = .06$). The median (range) oxytocin dose was 871.5 (0-22,174) mU for Mifepristone-treated women and 2021.0 (0-24,750) mU for placebo-treated women ($P = .02$). Seventy-seven (87.5%) Mifepristone-treated women and 46 (70.8%) placebo-treated women delivered vaginally 48 hours after the start of treatment ($P = .01$). There were nine cesareans in the Mifepristone group and 18 in the placebo group ($P = .02$). More nonreassuring fetal heart rate patterns and uterine contractile abnormalities occurred in Mifepristone-treated subjects. There were no statistically significant differences in neonatal outcomes between groups. They concluded Mifepristone had a modest effect on cervical ripening when given 24 hours before labor induction, appearing to reduce the need for Misoprostol and oxytocin compared with placebo.¹⁹

Stenlund PM et al in 1999, study done to evaluate the efficacy of Mifepristone in inducing labor in women with an unripe cervix, its effect on the cervix and on the status of the newborn. In a prospective double-blind study, 36 post-term pregnant women with a Bishop score of 5 or less received either 400 mg mifepristone ($n=24$) or placebo ($n=12$). If, 48 hours after the treatment was started, labor had not begun or the Bishop score was 5 or less, the women were given 0.5 mg prostaglandin E2 intracervically, a treatment which was repeated 12 hours later, if necessary. During the first 48 hours following treatment, 19 (79.2%) of the women treated with Mifepristone and two of the women (16.7%) treated with placebo went into labor. In addition, one and three women, respectively, had a ripe cervix at the end of the 48h period. The overall success rate was thus 83.3% for Mifepristone and 41.7% for placebo ($p=0.008$; OR 14.8; 95% CI 2.1-107.6). The median time from the start of treatment to delivery was also shorter (Mifepristone 36h23' and placebo 53h17'). Treatment with intracervical PGE2 was needed more often after the placebo. The duration of labor, however, tended to be shorter after placebo than after Mifepristone in the women who delivered vaginally. The frequencies of instrumental delivery were similar in both treatment groups. The median Apgar score was slightly lower at 1 minute ($p<0.05$) following Mifepristone treatment, but did not differ at 5 and 10 minutes. There was no difference between the two treatment groups in the umbilical pH at delivery. The results of the present study show that Mifepristone is a simple and effective treatment for inducing labor in post-term women with an unripe cervix.²⁰

Elliott CL et al in 1998, compare the effects of 50 mg or 200 mg of oral Mifepristone with placebo on cervical ripening and induction of labor in primigravid women at term with unfavorable cervixes. This was a double-blind study in which 80 primigravidae at term with a modified Bishop score of 4 or less were randomly assigned to one of three treatment groups. They were assessed at 24-hour intervals for 72 hours, after which labor was induced if it had not occurred spontaneously. Two hundred milligrams of Mifepristone resulted in a favorable cervix (with a Bishop score greater than 6 or in spontaneous labor) in

significantly more women than placebo ($P = .01$). An improvement in cervical ripening was seen in the group given 50 mg of Mifepristone, but this was not statistically significant. There were more cesarean deliveries performed for fetal distress in the group treated with 200 mg of Mifepristone than placebo, but this was not statistically significant and was not associated with any differences between groups in terms of neonatal outcome. They concluded that Mifepristone, a progesterone antagonist, is known to cause softening and dilation of the human early pregnant cervix and an increase in uterine activity. It is theoretically attractive for use as an adjunct in cervical priming and labor induction. In this study, 200 mg of Mifepristone was significantly more likely to result in a favorable cervix than placebo.²¹

Li L et al in 1996 study conducted to determine the efficacy of Mifepristone (RU486) combined with Misoprostol as an induction agent for the initiation of labor in women at term . Study group contained 68 pregnant women at term (gestational age: 38-41 weeks) who had clear clinical indications for labor induction. They received Mifepristone either 150 mg or 200 mg respectively in the first two or three days. The shortening of the cervical length, the change of Bishop Score and the change of the blood serum in estradiol (E2) concentration and progesterone (P) concentration were observed respectively before and after medication. On the fourth day, misoprostol was added from 100 micrograms to 300 micrograms successively. The outcome of labor induction in these women was recorded. They found the cervical length of women who were given Mifepristone was 1-3 cm shorter and Bishop Score was 4-5 higher than those before treatment. The E2 concentration and the P concentration were significantly higher and lower respectively than those before treatment. The cervical ripening ratio was 100.00%. The incidence of the onset of labor was 93.00% and the incidence of vaginally delivery was 80.88% after Misoprostol was given. They concluded that Mifepristone combined with Misoprostol is a safe, efficient, economical and convenient induction agent for initiation of labor in women at term.²²

Su H in 1996 conducted study to evaluate the effectiveness of Mifepristone administered prior to labor induction, and to study its safety for mother and fetus. 124 nullipara, 37-42 gestational weeks, with indications for labor induction were recruited, and randomly allocated into 2 groups. Group A ($n = 62$) was given Mifepristone 50 mg q.12.h. for 2 days, followed by PG05 or oxytocin, while group B ($n = 62$) was were observed for 2 days before labor induction by PG05 or oxytocin. Blood samples were obtained for determination of Mifepristone concentration and hormone levels including estradiol, progesterone, testosterone, cortisol, aldosterone and human placental prolactin at recruitment and immediately after delivery, and umbilical cord blood was collected at the same time. They found Cervical Bishop score increased significantly in the Mifepristone pretreatment group when compared with the control group. 22.58% of the women underwent spontaneous delivery after Mifepristone treatment and 4.84% of the controls followed suit ($P < 0.01$). The oxytocin dose required was significantly less in group a, but the success rate was higher ($P < 0.05$). Side-effects associated with Mifepristone were mild. Maternal serum Mifepristone peak levels ranged from 200 to 700 micrograms/L, with $t_{1/2}$ of 21.7 hr. The concentration of Mifepristone in umbilical blood

was low and stable. The ratio of umbilical/maternal Mifepristone level was 0.25 +/- 0.08. Determination of hormone profiles did not show any significant difference between the 2 groups. They concluded that Mifepristone is an effective inductive agent for cervical ripening and initiation of labor in term pregnancy, and can improve the outcome of labor induction.²³

Double-blind randomized prospective study done by Lelaidier C et al in 1993 to know the value of Mifepristone for induction of labor at term. One hundred and twenty term women (> 37.5 weeks amenorrhea) with unripe cervixes (Bishop < 4) and with a clear clinical indication for labor induction were randomized to receive either Mifepristone (RU 486) or placebo. The patients' regimens consisted of 200 mg of mifepristone on days 1 and 2 over an observation period of 4 days, with labor induction planned for day 4. Within 12 hours after taking the first tablet, fetal distress was diagnosed in 8 patients (3 in the Mifepristone group and 5 in the control group), who underwent immediate cesarean section. These 8 patients could not therefore participate in their survey and have been excluded from the final results. Forty one patients had spontaneous onset of labor, 31 in the Mifepristone group and 10 in the control group ($p < 0.001$). Forty seven patients needed cervical maturation with prostaglandin, 32 from the control group and 13 from the Mifepristone group ($p < 0.001$). Thirteen patients in each group had cervical maturation sufficient for classical labor induction. They noted that patients delivering vaginally needed significantly lower amount of oxytocin in the Mifepristone group and that the mean time interval between day 1 and the onset of labor was also significantly shorter in this group. The high cesarean section rate (32%), which is equivalent in both the placebo and the treated groups, may be attributed to the fact most of the patients in this survey had high risk pregnancies. There was no difference in the occurrence of fetal distress during labor in the 2 groups. Neonatal parameters were similar in both groups. These results establish Mifepristone as an induction agent for the initiation of labor in term women. Though more studies are needed, Mifepristone has shown itself to be safe and appropriate in situations where labor has to be induced in term women.²⁴

Frydman R et al in 1992, study done to determine the efficacy and safety of Mifepristone as an induction agent for the initiation of labor or as a cervical ripening agent in women at term. Study group contained 120 women at term (after 37.5 weeks' amenorrhea) who had clear clinical indications for labor induction. They were randomized to receive either 200 mg of Mifepristone or placebo on days 1 and 2 of a 4-day observation period, with labor induction planned for day 4. Eight patients, three treated with Mifepristone and five receiving placebo, had to be excluded from the survey because they required cesareans for medical reasons (fetal distress or maternal complications) less than 12 hours after taking the first tablet. They found that forty-one subjects entered spontaneous labor, 31 treated with Mifepristone and ten in the control group ($P < .001$). Forty-five needed the cervical maturation with prostaglandins on day 4, 13, of who had received Mifepristone and 32 of who had been given placebo ($P < .001$). Thirteen women treated with Mifepristone and 13 who had taken placebo had mature cervixes sufficient for

classic labor induction with oxytocin and amniotomy. Patients who delivered vaginally needed a much lower amount of oxytocin when Mifepristone had been given, and the mean time interval between day 1 of the survey and the onset of labor was also significantly shorter in this group. They found Mifepristone to be a safe, efficient, and suitable induction agent for initiation of labor in women at term.²⁵

Double-blind study of two different doses of Mifepristone done by Frydman R et al in 1988 to know the effect of 2 different doses of Mifepristone on cervical ripening. Mifepristone (RU486), was administered to 35 patients undergoing a therapeutic interruption of pregnancy during the second and third trimester for maternal or fetal indications. Study test was performed using 150 and 450 mg of Mifepristone as pretreatment prior to prostaglandins. No toxicity or maternal morbidity was recorded. In three patients the onset of labor occurred spontaneously before prostaglandin administration. Mifepristone produced a modification in the consistency of the cervix with a statistical improvement in cervical calibration in the two groups, but the cervical effect was independent of the dose.²⁶

Laffargue F et al in 1988, reports 12 cases of induction of labor which was carried out with the help of RU 486 in the 3rd trimester of pregnancy (mean duration of the pregnancy 34.2 weeks). Nine cases had malformed fetuses and 3 cases had normal infants. In 6 cases out of the 12 delivery took place within 48 hours after RU had been administered by itself and in 3 cases induction with Syntocinon was helped when RU486 was given beforehand. In 3 cases the live-born children showed no secondary ill effects.²⁷

CONCLUSION

There was clearly a superior neonatal outcome in terms of Apgar score and perinatal outcome in misoprostol group. Therefore, misoprostol is cheaper than dinoprostone, easy to administer by intravaginal route and does not require refrigeration. This indicates that misoprostole is a better, effective and safe alternative drug for induction of labor.

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