A Retrospective Case–Control Study Evaluating the Role of Mifepristone for Induction of Labor in Women with Previous Cesarean Section

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Abstract

Objective To investigate the role of “mifepristone” for induction of labor (IOL) in pregnant women with prior cesarean section (CS).

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Methods In this retrospective study, all pregnant women with prior CS who received oral mifepristone (400 mg) for IOL (as per clear obstetric indications) [group 1] were compared with pregnant women with prior CS who had spontaneous onset of labor (SOL) [group 2], with respect to incidence of vaginal delivery, CS, duration of labor, and various maternal and fetal outcomes.

Results During the study period, 72 women received mifepristone (group 1) for IOL and 346 had SOL (group 2). In group 1 after mifepristone administration, 40 (55.6 %) women had labor onset, and 24 (33.3 %) women had cervical ripening (Bishop Score ≥ 8) within 48 h. There were no statistically significant differences with respect to duration of labor (p value: 0.681), mode of delivery (i.e., normal delivery or CS— p value: 0.076 or 0.120, respectively), or maternal (blood loss or scar dehiscence/rupture uterus), or fetal outcomes (NICU admission) compared to women with previous CS with SOL (group 2). However,

the need of oxytocin (p value 0.020) and dose of oxytocin requirement (p value 0.008) were more statistically significant in group 1.

Conclusion Mifepristone may be considered as an agent for IOL in women with prior CS.

Keywords Pregnancy · Mifepristone · Induction of labor · Prior cesarean delivery

Introduction

Cesarean section (CS) rates are increasing worldwide [1]. Consequently, the number of pregnant women with previous CS is also increasing dramatically [1, 2]. This is not only leading to a massive escalation in the cost of the obstetric services but also increasing the incidence of previously rare but catastrophic complications of pregnancy (e.g., cesarean scar pregnancy, morbid adherent placenta, uterine rupture, and feto-maternal morbidity) [2]. In addition, the increase in the number of pregnant women with previous CS is posing severe constraint on the already scarce resources in the developing countries [3].

As women with previous CS are increasing, more and more women (with previous CS) are presenting to obstetricians for induction of labor (IOL) due to various obstetrical indications. Even though trial of labor after CS (TOLAC) is a reasonable option in majority of these women [4], still a significant proportion of these women undergo elective repeat CS (ERCS) due to limited options available for IOL in these women, thereby further compounding the dangerous trend of rising rates of CS [1–3].

In addition, IOL is not only associated with decreased rates of successful vaginal delivery (compared to spontaneous labor) but also with the increased rates of catastrophic complications, e.g., scar dehiscence/rupture uterus, and subsequent fetal death and severe maternal morbidity and mortality [4]. Cochrane systematic review on IOL in women with prior CS states that there is lack of information to decide optimal method for IOL in women with previous CS [5]. Another systematic review on IOL in women with prior CS opined that meta-analysis is not possible due to paucity of evidence and advises caution for IOL in women with scarred uterus [6]. There is an ongoing search for an ideal agent for IOL in women with previous CS so as to increase the chances of vaginal delivery and minimize (if not completely eliminate) the chances of scar dehiscence/rupture uterus. This will go a long way in reducing the rates of ERCS, thereby ultimately reducing the overall rising rates of CS.

One such agent under investigation is “mifepristone.” Cochrane systematic review on mifepristone for IOL in pregnant women (without CS) states that there is limited

evidence in support of mifepristone for IOL [7]. However, it was further stated that it was better than placebo in reducing the rates of CS performed for failure of IOL. Also they had presumed theoretically that mifepristone may be advantageous in women with previous CS as it is not an uterotonic and hence may not be associated with over stimulation or rupture uterus, and further research could be initiated in this direction [7].

Hence, we conducted this study for evaluating the role of mifepristone in women with prior CS for IOL with a goal of reducing the rates of ERCS and ultimately, reducing overall CS rates.

Materials and methods

This study is a retrospective analysis of all women with previous one CS who received mifepristone for labor induction, after approval from institutional review board was taken (registration No. ECR/490/Inst/HP/2013) vide letter No. HFW-H-DRPGMC/Ethics/2014.

All the pregnant women (with prior CS) who had received oral mifepristone for IOL from July 1, 2013 to September 30, 2014 were compared with pregnant women with prior CS who had spontaneous onset of labor (SOL) in this pregnancy retrospectively, in the Department of Obstetrics & Gynaecology of Dr. Rajendra Prasad Government Medical College and Hospital, Tanda, Kangra, India. It is a tertiary care teaching hospital catering to the needs of adjoining rural and tribal population, with an average of 8000 deliveries and 2000 CS annually.

All the pregnant women with previous one CS were encouraged and evaluated for TOLAC. Inclusion criteria were singleton pregnancy, previous one low-segment CS (no other uterine scar or previous rupture), and cephalic presentation. Exclusion criteria were interconceptional period less than 18 months, estimated fetal birth weight > 4 kg, premature rupture of membranes/chorio-amnionitis, any evidence of fetal distress at admission, any contraindication for vaginal delivery (cephalo-pelvic disproportion ruled out), and type of uterine incision in prior CS not known.

Pregnant women with prior CS after satisfying the inclusion and exclusion criteria were counseled in detail for IOL, advantages of successful TOLAC, risks associated with failed TOLAC, various agents for IOL, advantages, and concerns regarding the use of mifepristone for IOL. After taking written informed consent, these women received 400 milligrams (mg) of mifepristone orally [two tablets of mifepristone 200 mg each] for IOL for clear obstetric indications (group 1). Subsequently, they were compared with pregnant women with prior one CS willing for TOLAC and presenting with spontaneous onset of labor (SOL) (group 2), retrospectively.

Fig. 1 Total pregnant women during the study period

Labor onset (defined as regular uterine contractions with progressive cervical dilatation and effacement) after mifepristone, was recorded in women in group 1 up to 48 h. Bishop score was assessed after 24 and 48 h of mifepristone administration. If at any time bishop score was ≥ 8 , amniotomy followed by oxytocin infusion was done. If, even after 48 h, neither there was labor onset nor bishop score ≥ 8 , women were again counseled, and as per consent of women, ERCS or IOL with oxytocin, was done.

All the women in labor (group 1 and group 2) were managed as per labor-room protocols. The decisions regarding need for augmentation of labor (with oxytocin), emergency CS, or operative vaginal delivery were taken by the managing team of obstetricians. Women who required oxytocin (Bishop Score ≥ 8 or for augmentation of labor), received low-dose oxytocin infusion (starting at 3 mU/min and every 20 min increments of 3 mU/min, till adequate uterine contractions were established [3–5 uterine

contractions every 10 min with each contraction lasting 30–45 s]). The intraoperative findings (indication of CS, scar dehiscence/scar rupture, blood loss, need for blood transfusion, or peri-partum hysterectomy), and subsequent hospital stay were recorded in all the women who underwent CS for whatsoever indication. Neonatal assessment was done by the attending neonatologist, and admission to NICU was recorded in all the neonates.

Statistical analysis was performed by SPSS 17 software using parametric and nonparametric tests when appropriate. The normality of the distribution was assessed by the Kolmogorov–Smirnov test. Continuous data were analyzed with the *t* test, and categorical variables were analyzed with the Fisher's exact test. *p* value < 0.05 was considered statistically significant. Kaplan–Meier survival analysis was done to estimate the proportion of women who delivered vaginally in either group at any point of time. All women who had CS in this pregnancy were excluded from

Table 1 Demographic characteristics of women

	Group 1 (n = 72)	Group 2 (n = 346)	<i>p</i> value
AGE (in years) ^a	27 (3)	27 (4)	0.285
BMI (in kg/m ²) ^a	21.1 (1.7)	21.1 (1.7)	0.930
Abortion			
One (<i>n</i>)	15	71	0.870
Two (<i>n</i>)	3	5	0.289
Three(<i>n</i>)	0	4	0.979
Previous vaginal delivery (<i>n</i>)	15	72	0.996
Previous successful TOLAC (<i>n</i>)	3	5	0.289
Indication of previous CS (<i>n</i>)			
Acute fetal distress	38	161	0.403
Mal-presentation	15	88	0.504
Failure of induction	10	32	0.329
Non progress of labor	9	65	0.271
POG (in days) ^b	280.1 ± 4.2	273.6 ± 6.5	0.000
Inter delivery interval (<i>n</i>)			
18–24 months	6	39	0.601
24–36 months	19	108	0.503
>36 months	47	199	0.277
Bishop score ^a	7 (3)	7 (2)	0.130
Sex of neonate (<i>n</i>)			
Boy	38	193	0.737
Girl	34	153	0.739
Birth weight (in kgs.) ^a	3.0 (0.25)	2.9 (0.50)	0.148

^a Nonnormal distribution [median {interquartile range}]^b Normal distribution [mean ± standard deviation]

the Kaplan–Meier Survival analysis (as duration of labor could not be calculated in these women due to CS at different cervical dilatations).

Results

As shown in Fig. 1, during the study period, there were a total of 8342 deliveries. A total of 2486 pregnant women had previous CS (29.8 %). Out of these, 1626 had ERCS (896 had either extension of uterine incision or had no record of previous uterine incision; 488 women had previous two or more CS; and 242 had repeat CS for obstetrical indication). Of the remaining 860 eligible women, 312 refused for TOLAC (and had ERCS), 72 women consented for IOL with mifepristone (group 1) for clear obstetrical indications, and 346 had SOL (group 2). and 130 women opted for other methods for IOL (intracervical catheter, synthetic cervical dilators, or oxytocin infusion).

Women in groups 1 and 2 were compared with respect to baseline characteristics, as shown in Table 1. Age, body mass index, abortions (one, two, or three), indication of previous CS, interdelivery interval, Bishop score at first assessment, sex, and

birth weight of the neonate, were not statistically significantly different in these groups. However, period of gestation was statistically significantly different in two groups as shown in Table 1 (280.1 ± 4.2 days vs. 273.6 ± 6.5 days,, respectively, in groups 1 and 2, *p* value 0.000).

In group 1 after the initial dose of mifepristone (orally given two tablets each of 200 mg mifepristone; total 400 mg) within 48 h, 40 women had labor onset, and 24 women had Bishop score ≥ 8 (as per study protocol amniotomy followed by oxytocin infusion for IOL was done). Even after 48 h, eight women neither had labor onset nor favorable bishop score (≥8); of these, all but one woman (in whom ERCS was done) opted for oxytocin infusion for IOL, as shown in Fig. 2.

There was no statistically significant difference with respect to duration of labor in either group (first stage {median [interquartile range]}; 350[353] min in group 1 vs. 292.5 [295] min in group 2, *p* value 0.681; and second stage {median [interquartile range]}; 21.5 [28] min in group 1 vs. 23 [13] min in group 2, *p* value 0.319). Figure 3, shows the Kaplan–Meier Survival Analysis depicting proportion of women delivered in two groups at any point of time (after exclusion of women undergoing emergency CS).

Fig. 2 Pregnancy outcome in group 1 (mifepristone group). Asterisks one woman who opted out of study protocol and requested for CS after 48 h of mifepristone

Fig. 3 Kaplan–Meier Survival Analysis showing proportion of women delivered in two groups at any point of time. Asterisks women with CS excluded from analysis of duration of labor

Mode of delivery (i.e., normal vaginal delivery (NVD), operative vaginal delivery (OVD), and CS) were not statistically significantly different in the two study groups [group 1 (number of women with NVD, OVD, and CS); 40, 13, and 19 vs. group 2 (number of women with NVD, OVD, and CS); 233, 52, and 61; p value 0.076, 0.641 and 0.120, respectively], as shown in Table 2.

No statically significant differences were observed in maternal or fetal outcomes in group 1 versus group 2, in

terms of average blood loss ({median [interquartile range]}; 200 [455] ml vs. 180 [130] ml, p value 0.202), maternal morbidity {scar dehiscence [number of women]; nil out of 72 vs. two out of 346, p value 0.801}, (scar rupture [number of women]; nil out of 72 vs. one out of 346, p value 0.648), {peri-partum hysterectomy [number of women]; nil out of 72 vs. one out of 346, p value 0.648} and (need for blood transfusion [number of women]; {one out of 72 vs. six out of 346, p value 0.835}); and admission to NICU (number of neonates; two out of 72 vs. eight out of 346, p value 0.814). There was no case of maternal or fetal death.

However, statistically significantly more women in group 1 required oxytocin for induction/augmentation of labor compared to group 2 (24 women out of 72 vs. 35 women out of 346, respectively, p value 0.020). In addition, the dose of oxytocin requirement was also significantly more in group 1 compared to group 2 ({mean $\pm$ SD}; 760 $\pm$ 260 mIU/min vs. 540 $\pm$ 130 mIU/ml, respectively, p value 0.008).

Discussion

The rates of IOL in women with previous CS are decreasing drastically worldwide, and the trend is shifting toward ERCS especially whenever any obstetrical indication necessitates termination of pregnancy [1, 2].

Table 2 Maternal and fetal outcomes

	Group 1 (<i>n</i> = 72)	Group 2 (<i>n</i> = 346)	<i>p</i> value
Mode of delivery (<i>n</i>)			
Normal vaginal delivery	40	233	0.076
Operative vaginal delivery	13	52	0.641
Cesarean section	19	61	0.120
Indication of cesarean section (<i>n</i>)			
Acute fetal distress	11	39	0.095
Non progress of labor	8	22	0.069
Duration of first stage of labor (in minutes) ^a	350 (353)	292.5 (295)	0.681
Duration of second stage of labor (in minutes) ^a	21.5 (28)	23 (13)	0.319
Oxytocin requirement (<i>n</i>)	24	35	0.020
Dose of oxytocin required (mIU/min)	760 (260)	540 (130)	0.008
Blood loss (in ml) ^a	200 (455)	180 (130)	0.202
Blood loss (<i>n</i>)			
500–1000 ml	17	58	0.227
>1000 ml	1	6	0.835
Hospital stay (in days) ^a	4 (4)	2 (3)	0.078
Apgar score			
1 min	7 (6–8)	7 (6–8)	0.891
5 min	7 (6–8)	7 (6–8)	0.684
NICU admission (<i>n</i>)	2	8	0.814
Maternal morbidity (<i>n</i>)			
Scar dehiscence	0	2	0.801
Rupture uterus	0	1	0.648
Peri-partum hysterectomy	0	1	0.648
Blood transfusion required	1	6	0.835

^a Nonnormal distribution [median {interquartile range}]

In our study, we observed that mifepristone is associated with favorable outcome in 89 % of women (labor onset in 56 % and cervical ripening 33 %) within 48 h of administration of oral mifepristone. These observations are in accordance with the existing literature where a variable success rate of labor onset at 66–93 % has been observed in pregnant women [8–15]. Also, the effect of cervical ripening after use of mifepristone has been variable ranging from no statistically difference to statistically significant improvement (60–80 % of all cases) [16–20]. However, all these studies except one [11] were conducted in women without previous CS.

There was no observed fetal or maternal side effect of mifepristone. The incidence of intrapartum fetal distress and CS for this indication was not statistically different in two groups. These observations are in accordance with the recent Cochrane meta-analysis which stated that abnormal fetal heart rate patterns are more common after mifepristone compared to placebo but there are no statistically significant differences in terms of Apgar score less than seven at five minutes of birth or increased incidence of CS for fetal distress [7].

However, the need of oxytocin and its dose requirement was statistically significantly more in group 1. This is predominantly because we are comparing pregnant women requiring IOL with women in SOL. This differential requirement of oxytocin (both more in number of women as well as higher dose of oxytocin in those who require it at all) was not found to be associated either with the increased rate of CS or scar dehiscence/rupture uterus.

One of the major apprehensions of using any agent for IOL in women with previous CS is “scar dehiscence/rupture uterus.” A hypothesis was generated by Cochrane systematic review regarding use of mifepristone in women with previous CS for IOL that, as mifepristone is not an uterotonic, chances of scar dehiscence or rupture uterus might not be increased in these women. Our observations are in accordance with their hypothesis, as the indications for emergency CS in both the groups were not statistically significantly different (Table 2). One important point to highlight here is that IOL “per se” is done in women who did not have SOL and hence chances of unsuccessful TOLAC and incidence of CS should be expected to be

much higher (than SOL), with whatsoever method is used for IOL in these women [4].

Mifepristone stimulates labor as naturally as possible, which can be very beneficial especially in women with prior CS. Mifepristone leads to cervical ripening [21, 22] (by stimulating the release of nitric oxide); promotes uterine contractions [23] (by increasing myometrial cell excitability, establishing gap junctions between cells and influx of calcium); and increases the release of prostaglandins by decidual cells [24, 25], without acting as a direct uterotonic. As clearly shown in Fig. 3, Kaplan–Meier analysis shows that after women have labor onset (IOL with mifepristone), the labor closely mimics as that in case of SOL, which could be one of the major reason for preferring mifepristone as an agent for IOL in women with prior CS.

One of the major limitations of our study is that it is a retrospective case–control study. However, in our opinion, this study can provide a platform to plan further randomized controlled trials on this subject. Nonetheless, a well-designed randomized controlled trial is required before mifepristone can be established as an agent for IOL in women with previous CS.

Conclusion

Pregnant women with previous CS requiring IOL for clear obstetrical indications pose a significant challenge to the managing obstetrician due to paucity of available options as well as limited evidence in favor of any method for IOL. Mifepristone may be considered as an alternative agent for the same; however, definite evidence on this issue can only be generated from a randomized controlled trial.

Compliance with Ethical Standards

Conflict of Interest There is no conflict of interest with any individual or organization.

Ethical Statement Compliance with ethical requirements and Conflict of interest Ethical clearance has been taken from ethical committee of Dr. RPGMC Kangra at Tanda (HFW-H-DRPGMC/Ethics/2014) keeping in view the ICMR guidelines (1994) and Helinski declaration (modified 2000). Written informed consent was taken from all the women. Identity of every women is kept as secret. All the women were adequately informed of the aims, methods, and any discomfort it may entail to her and the remedies thereof. Every precaution was taken to respect the privacy of the patient, the confidentiality of the patient's information, and to minimize the impact of the study on her physical and mental integrity and her personality. The patient was given the right to abstain from the study or to withdraw consent to participate at any time of study without reappraisal.

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