A comparative study of mifepristone alone versus mifepristone and misoprostol for induction of labor in intrauterine fetal death

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Abstract

Purpose: Late intrauterine death is an unwanted consequence of pregnancy. The estimated global still birth rate is 18.9 per 1000 births. For a physician confronted with IUFD the management poses a dilemma as to which regimen to follow for effective and safe delivery of the dead fetus. This problem is magnified in cases where prostaglandins are contraindicated but the various methods described and followed worldwide incorporate the use of prostaglandins for induction of labour. This study was conducted to show the efficacy and safety of medical management using mifepristone alone for induction of labor.

Methods: We included 60 patients with late IUFD and divided the patients randomly into two groups each containing 30 patients. Group I was given only mifepristone at a dose of 200mg three times a day for two days while Group II was given a combination of mifepristone and misoprostol.

Results: In Group I, 19 patients with previous cesarean were included. The success rate was 90% in group I and 96.6% in Group II. The mean induction to delivery interval was 48.63±25.1 hrs in group I while it was 68.87±21.1 hrs in group II. 3.2% of patients in group I had side effects while 70% of patients in group II had side effects in the form of nausea, vomiting, fever and shivering.

Conclusion: Thus use of mifepristone alone provides a good alterative regimen in the management of late intrauterine fetal death.

Keywords: Intrauterine fetal death, Mifepristone, Misoprostol, Previous cesarean section

Introduction

Every woman wants to have a healthy baby when she becomes pregnant. Unfortunately, some women have intrauterine fetal death, which is the most unwanted consequence of a pregnancy. When intrauterine fetal death (IUFD) occurs, spontaneous expulsion may take several weeks.

According to the 2003 revision of the procedures for coding cause of fetal death under ICD-10, the national centre for health statistics defines fetal death as "death prior to the complete expulsion or extraction from its mother of a product of human conception, irrespective of the duration of pregnancy and which is not an induced termination of pregnancy. The death is indicated by the fact that after such expulsion or extraction, the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscles. Heart beats are to be distinguished from transient cardiac contractions and respirations are to be distinguished from fleeting respiratory efforts or gasps".[1,2] For statistical purposes, fetal losses are classified according to gestational age. A death that occurs prior to 20 weeks gestation is usually classified as a spontaneous miscarriage and those occurring after 20 weeks constitute fetal demise or stillbirth.[3]

Management of fetal death in utero has changed dramatically from earlier recommendations that regarded the event as a medically innocuous condition to be managed conservatively except under life-threatening circumstances, with 75% of women delivered within two weeks after fetal demise. When a dead fetus has been in utero for 3-4 weeks, fibrinogen levels may drop, leading to a coagulopathy. Early recognition and induction of labour can prevent life threatening complications like coagulopathy to a great extent.[2] Due to the advent of newer agents for effective cervical ripening and uterine contraction, the management of stillbirth has become more proactive.[4]

Out of the various modalities for induction of labour in pregnancy after intrauterine fetal death, mifepristone and misoprostol are thought to be safest for women apart from being cost effective and evidence based.[5]

Common side effects of misoprostol are fever, nausea, vomiting, dizziness, diarrhoea and headache. The most serious side effect associated with the use of misoprostol is uterine hyperstimulation which can lead to uterine tachy-systole and uterine rupture.[6]

The prevalence of women with uterine scars has increased worldwide in the past decades due to higher rates of cesarean deliveries. Though various modalities of treatment have been suggested for termination of pregnancy, a suitable method for induction of labour in previous cesarean cases is yet to be ascertained.

The present study is an endeavour to study the effect of mifepristone alone in induction of labour in scarred as well as unscarred uterus to determine its success and risk-benefit ratio.

Materials and Method

This study was a prospective clinical study comprising of sixty antenatal women at gestational age greater than 24 weeks admitted in the Department of Obstetrics and Gynaecology, Pt. B.D. Sharma PGIMS, Rohtak with intrauterine fetal death or gross congenital malformation requiring termination of pregnancy.

Women with singleton pregnancy, gestational age more than twenty four weeks and not in labour were included in the study after ultrasonographic confirmation of intrauterine fetal death or lethal fetal malformation.

Women in labour, with multiple pregnancy, history of long term corticosteroids intake, on concurrent anticoagulants, bleeding disorders, chronic liver disease, chronic adrenal failure and inherited porphyrias were excluded from the study.

All women were subjected to detailed history, clinical examination and investigations like complete haemogram, liver function test, renal function test and coagulation profile study before starting the treatment. Ultrasonography was done in all patients to confirm intrauterine fetal death or congenital fetal malformation.

After obtaining informed written consent from for termination of pregnancy, patients were alternatively divided into two groups each comprising of thirty patients.

Patients in Group A received tablet mifepristone 200mg orally thrice a day for two days. Group B patients received tablet mifepristone 200mg orally followed after forty eight hours by tablet misoprostol per vaginum, the dose of which was decided according to the labour ward protocol considering the period of gestation and parity of the patient. A per vaginal examination was done before administration of each dose of the drug to assess the Bishop score in group B. In both the groups, uterine contractions were monitored and the next dose of the drug was omitted once the woman progressed into established labour.

Patients who did not deliver within forty eight hours of the last dose of drug were regarded as failures. At the end of the study, data was collected and analysed by Chi-square analysis.

Results

Comparison of parity as shown in Table 1 depicts that in tablet mifepristone has been used in increasing parity with successful outcome in study group (p=0.002). The difference in mean period of gestation between the two groups was statistically not significant (p=0.818).

Table 1: Characteristics of the study groups

Characteristics	Group I (n=30)	Group II (n=30)	p value
Parity			0.002
P0	7(23.3%)	20(66.6%)	
P1	19(63.3%)	5(16.6%)	
P2	3(10%)	4(13.3%)	
P3	1(3.33%)	0	
P4	0	1(1.6%)	
Mean period of gestation	30.36±5.7	30.06±4.27	0.818

Table 2 represents that 16 out of 30 women in study group had one cesarean section while three women had previous two cesarean sections. Out of these, 15 women with previous one cesarean section and 2 women with previous two cesarean section had successful vaginal delivery. While no woman with previous cesarean section was included in control group due to known risk of uterine rupture in scarred uterus with use of misoprostol.

Table 2: Number of cases with previous cesarean section who delivered vaginally

No. of previous cesarean section	Group I (Study)		Vaginal Delivery	
	Number	Percentage	Number	Percentage
1	16	53.33%	15	93.75%
2	3	10%	2	66.66%
Total	19	63.33%	17	89.47%

This observation becomes all the more significant in the present scenario where the number of cesarean sections being done is increasing and we are yet to find a safe and equally effective method for terminating pregnancy in woman with scarred uterus.

The mean duration for onset of labour in shown in Table 3. Labour initiated earlier in study group as compared to control group (39.47±21.7h vs 61.83±2.5h, p <0.0001). The mean induction to delivery interval in Group I and Group II was statistically very significant (48.63±25.1h vs 69.87±21.1h, p=0.001). Oxytocin infusion to establish good contractions and completion of termination was required in one patient in Group I and 20% of patients in Group II (p=0.044). Two patients in Group II required ovum evacuation due to retained products of conception while there were no patients with retained products in group I. Success rate was 90% in Group I and 96.6% in Group II (p=0.301).

Table 4: Average induction to delivery interval of medical regimens using mifepristone and misoprostol compared with mifepristone only regime

Reference	POG (weeks)	Regimen	Induction to delivery interval (hours)
Wagaarachchi et al[10]	>24	Mifepristone 200mg orally followed after 24-48 by vaginal misoprostol at a dose of 200 g every 3 hourly for a total of 4 doses. 34 wks onwards 100 g was used	36 + 8.5 = 44.5
Fairley et al[11]	>24	Mifepristone 200mg, followed after 36 hrs by vaginal/oral misoprostol 400 g every 4 hrly	36+ 7 = 44
Väyrynen et al[12]	21- 42	Mifepristone 200 mg followed by misoprostol 25 mcg 4 hrly	19+12.8 = 31.8
Gandhi et al[13]	20- 42	Mifepristone 200 mg followed by misoprostol 50- 200 mcg 6 hrly	48+10.5 = 58.5
Padayachi et al[9]	>26	Mifepristone 200 mg 12 hrly for 3 days	39.6
Cabrol et al[8]	18-30	Mifepristone 200mg twice a day for two days	39
Present study	>24	Group 1- Mifepristone 200 mg 8 hrly for 2 days Group 2- Mifepristone 200 mg followed after 48 hrs by misoprostol according to gestational age	Group 1-48.63 Group 2-69.87

Discussion

Several methods of induction of labour following late intrauterine fetal death have been described in literature. However, there are very limited studies to describe the method of termination in late IUFD in cases where tablet misoprostol is contraindicated, especially in cases with previous cesarean section. The incidence of encountering such patients is increasing in modern day practice, therefore there is an imperative need for designing a method which is suitable, safe and comparable to the methods of termination described in literature. A preliminary trial by Cabrol et al in 1985 on 11 women with IUFD at mean gestational age of more than 18 weeks, using mifepristone at dose of 200 mg twice a day for two days reported successful induction of labor in 81% of women with mean induction to delivery interval of 39±12.5 hours. No side effects were reported.(7) Another double blind control study was conducted by Cabrol et al in 1990 on 48 women with IUFD at gestation more than 16 weeks using mifepristone 200 mg three times a day for 2 days. They reported a success rate of 63% with good tolerance.(8) Thereafter, Padayachi et al in 1988, described a similar study on 12 women with IUFD at gestational age of more than 26 weeks. They reported a success rate of 66.66% with mean induction to delivery interval of 39.6±4.5%.(9) Since then, no new study without incorporating prostaglandin analogue has been described and method for termination of pregnancy in second and third trimester with IUFD without using prostaglandin analogue has not been formulated, imposing a challenge for clinicians to deal with patients presenting with late IUFD or lethal malformations in women with scarred uterus.

Hence, we have come up with a novel method of termination of pregnancy which is comparable with time tested method of combined use of mifepristone and misoprostol for termination of IUFD and is especially beneficial for patients in whom misoprostol is contraindicated. The induction to delivery interval of published medical regimens in the management of late IUFD are shown in Table.

Induction to delivery interval is calculated from the time of administration of the first dose of mifepristone to the complete expulsion of fetus and placenta.

The IDI in our study group is comparable with that of studies described in Table 4. In these studies, a time lag of 36 to 48 hrs is present between the two drugs, hence increasing IDI. As described by Wagaarachchi et al, this time lag was difficult for some women to accept. Over 76% of women in his study opted for induction with misoprostol within 24 hrs of mifepristone.(10) This problem is being encountered in our daily practice when patient presenting with IUFD is given a tablet of mifepristone and asked to wait for two days. During this time the patient cannot be sent home and apparently patient is not being given any drug to initiate contractions. This adds on to the frustration of the patient. This problem has been overcome in our proposed drug regimen along with reduction in induction to delivery interval.

The side effect rate of our study group is 3.2% which is significantly lower as compared to studies done earlier as well as our control group. Waagarachchi et al had a 7.2% side effect rate.(10) For optimum results using combined regimen there should be a fine balance between the dose, route of administration, induction to delivery interval and side effects. Commonly encountered side effects are gastrointestinal effects like

nausea, vomiting or others like fever with or without chills. Though these side effects are mild in nature and are usually relieved by symptomatic treatment but cause discomfort to the patient. There was no case of retained products of conception in our study group. Similar studies done in the past by Padayachi et al[9] and Cabrol et al[8] have shown similar results. The incidence of RPOC's in our control group was 6.6% which is comparable with similar a study by Wagaarachchi et al.[10] These cases were managed by ovum evacuation. A possible reason for this could be mechanism of action of mifepristone. Though the exact mode of action of mifepristone in inducing in late pregnancy is unclear, but according to various studies, mifepristone causes blockage of progesterone receptors directly leading to endometrial decidual degeneration, cervical softening and dilatation with release of endogenous prostaglandins. This may be responsible for complete shedding of placenta and membranes.

Conclusion

Late intrauterine death is an unwanted consequence of pregnancy. For a physician confronted with IUFD the management poses a dilemma as to which regimen to follow for effective and safe delivery of the dead fetus especially in women with scarred uterus. This problem is magnified in cases where prostaglandins are contraindicated but the various methods described and followed worldwide incorporate the use of prostaglandins for induction of labour. This study was conducted to evaluate the efficacy and safety of medical management using mifepristone alone for induction of labour. In this study we found that with mifepristone only regimen, several essential parameters like side effect profile, induction to delivery interval and length of hospital stay had better outcome when compared to use of mifepristone and misoprostol in combination. Moreover this method has come up as the method of choice in patients with contraindications for misoprostol, especially in women with previous cesarean section. We thus conclude that use of mifepristone alone provides a good alterative regimen in the management of late intrauterine fetal death as compared to the combined use of mifepristone and misoprostol, especially in women with previous cesarean section.

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