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A Study on Use of Two Doses of Mifepristone Followed by Misoprostol in Pregnancies with Intrauterine Foetal Death in Mid and Late Trimester

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Abstract: ***Objective: To assess the efficacy, safety and acceptability of this new regimen for induction of labour in IUFD in mid and late trimester pregnancies. Design: Observational study. Setting: Umaid Hospital Jodhpur (Rajasthan, India). Methods: A total of 100 women with IUFD of gestational age more than 12 weeks were studied.Once the termination of pregnancy was decided, Tab.Mifepristone 200mg was administered per orally followed again by Tab. Mifepristone 200mg 24 hours later, regardless of gravid status and mode of previous deliveries.48 hours after the second dose of Tab. Mifepristone, Tab Misoprostol was administered per vaginally. For gestational age less than 28 weeks 200mg Misoprostol PV every 4 hours (maximum 4 doses), and for gestational age more than 28 weeks 25mg Misoprostol PV every 4 hours (maximum 4 doses).***

1. Introduction

Pregnancy loss at any gestational age puts a female under an emotional burden, more so when the pregnancy has reached second or third trimester. As the pregnancy advances in females with intrauterine foetal death or with congenitally anomalous foetus, termination becomes more and more challenging as spontaneous delivery may not occur for a longer duration. Moreover, intrauterine foetal death can cause many serious complications to the female like intrauterine infections. As the fetal demise or any congenital anomaly is detected females are given the choice to terminate the pregnancy. The obstetrician is expected to provide the safest termination plan with least side effects.If a woman carries dead fetus in uterus for more than 4 weeks, consumptive coagulopathy and disseminated intravascular coagulation may result(1)

Since ancient times different types of methods for abortion have been used. Surgical abortion was one such method. Different types of herbs, salts, douches and purgatives, were used to terminate pregnancy with intrauterine foetal death, many of which were associated with serious side effects and questionable success rate (2).

The drawbacks of these methods include prolonged labour duration, longer hospital stay and retained products of conception requiring curettage.

In 1980's when Mifepristone became available the scenario changed from surgical to medical methods, and now medical methods of termination of pregnancy is considered method of choice (2).

Mifepristone is an antiprogestogen and is the only one approved for induction of abortion. Progesterone is responsible for maintenance of pregnancy by keeping uterus quiet.It prevents cervical ripening, decreases prostaglandin output from the decidua and prevents uterine contractions. Mifepristone blocks the effects of progesterone and causes damage to vessels, necrosis of decidua and bleeding, which leads to cervical ripening , increased sensitivity of uterus to prostaglandins and converts a quiet pregnant uterus into an spontaneously active one(2).

Misoprostol is the main drug used for medical termination of pregnancy because of the low cost and ease of administration. Its effect is enhanced by prior priming with Mifepristone. Misoprostol induces strong uterine contractions and leads to expulsion of products of conception. Misoprostol has low cost and can be stored at room temperature(2).

Misoprostol has been tried with or without mifepristone for termination of pregnancy in second trimester and is a commonly used regimens for this indication (3).It has been observed that pretreatment with mifepristone before using misoprostol reduces the duration from induction to abortion, anesthesia requirements, and the total dose of misoprostol needed(4).Many side effects of Misoprostol have been listed by the US Food and Drug Administration (FDA) like uterine hyperstimulation, tetany, rupture, maternal shock, maternal death(5).

Out of the many side effects of Misoprostol most worrisome for an obstetrician is uterine hypercontraction and possible risk of uterine rupture. Several reports have also shown that using Misoprostol for termination of pregnancy both in mid and late trimester can cause rupture of uterus both in scarred and unscarred one.(6)(7)(8)

2. Material and Methods

The study is an observational study in the labour room of department of Obstetrics and Gynaecology, Umaid Hospital, Dr. S.N. Medical College Jodhpur.

Pregnancy termination was done strictly following the guidelines of Medical Termination of Pregnancy Act 1972

Once the termination of pregnancy was decided, Tab.Mifepristone 200mg was administered per orally followed again by Tab. Mifepristone 200mg 24 hours later, regardless of gravid status and mode of previous deliveries.48 hours after the second dose of Tab. Mifepristone, Tab Misoprostol was administered per vaginally according to guidelines as follows.

12-26 weeks gestation	More than 26 weeks gestation
200 µg PV every 4-6 hours	27-28 weeks: 100 µg PV every 4 hours > 28 weeks: 25 µg PV every 6 hours

After delivery of fetus, 20IU of oxytocin was administered intravenously in 500ml Ringer's Lactate. The induction to abortion interval was defined as the time interval in hours from administration of Tab Mifepristone to passing the products of conception. Treatment is considered as failure if there is need of surgical evacuation of uterus

Women undelivered after 48 h of misoprostol therapy would receive a transcervical Foley catheter with traction, or high concentration intravenous oxytocin, depending on the cervical status and amniotic membrane integrity.

Table 1: Basic Patient Profile

AGE in years (18-25)	66	66%
AGE in years (26-30)	33	33%
AGE in years (31-35)	1	1%
Gestational Age < 28 weeks	76	76%
Gestational Age > 28 weeks	24	24%
Patients without previous scar	90	90%
Patients with previous 1 scar	8	8%
Patients with previous 2 scar	2	2%
Gravida 1	35	35 %
Gravida 2	22	22 %
Gravida 3	16	16 %
Gravida 4	18	18 %
Gravida 5	5	5 %
Gravida 6	2	2 %
Gravida 9	2	2 %

Table 2

		Range
No of patients delivered with 1 Mifepristone alone	33	2- 38 hours
No of patients delivered with 2 Mifepristone alone	42	26-94 hours (after 1st dose of Mifepristone)
No of patients delivered after using Misoprostol	21	3-69 hours (after 1st dose of Misoprostol)
No of patients requiring laparotomy	4	

Table 3

	Age	Gravidity	Gestational Age
Mean	24.17	2.54	23
Minimum	19	1	13
Maximum	34	9	37

Table 4: Cases Delivered with Single Mifepristone

Less Than 28 Weeks	22	Without Uterine SCAR	21
		With Previous 1 LSCS	1
More Than 28 Weeks	11	Without Uterine SCAR	11
		With Previous 1 LSCS	0

Table 5: Cases Delivered With Two Mifepristone Doses Alone

Less Than 28 Weeks	32	Without Uterine Scar	27
		With Previous 1 LSCS	4
		With Previous 2 LSCS	1
More Than 28 Weeks	10	Without Uterine Scar	10
		With Previous 1 LSCS	0

Table 6: Misoprostol to Delivery Interval

Mean	19.65 hours
Minimum	3 hours
Maximum	69 hours

3. Results

In our study we found that 33 patients out of total 100 delivered with single dose of Mifepristone, and 75 patients out of total 100 delivered with using two Mifepristone doses alone. 21 patients required Tab Misoprostol to deliver. 96% of the patients were successfully delivered using this regimen and 4 patients ultimately required laparotomy. Out of the 4 patients who required laparotomy we found intraoperatively that the pregnancy was located in the rudimentary horn of uterus and it was a failure of diagnosis. So only 1 patient with intrauterine pregnancy was unable to deliver with our regimen and required laparotomy. In our study 10 patients had previous uterine scars and all of them have been successfully delivered vaginally. Out of the 10 patients 6 were delivered with either 1 or 2 doses of Mifepristone and Misoprostol was not needed. Mean induction to delivery interval from 1st dose of Misoprostol was 19.65 hours with a minimum of 3 and maximum of 69 hours. In patients who delivered vaginally minimum hospital duration was 1 day and maximum was 6 days. None of our patients had rupture of uterus.

4. Discussion

We conducted this study to assess the efficacy, safety and acceptability of this new regimen for induction of labour in IUFD. While using Misoprostol particularly in patients with uterine scar an obstetrician is always concerned for the risk of rupture of uterus. In our study we found that 75% of total patients and 60 % of the patients with previous uterine scar delivered with Mifepristone alone and Misoprostol was not at all required. No case of uterine rupture was encountered. Mean duration of hospital stay in our study was found to be 4.5 days which was similar to other studies using different regimen (9).

5. Review of Literature

Roel de Heus et al in their study used only Misoprostol without priming by Mifepristone and found that with a mean gestational age of 24 weeks, the median time from induction to delivery was 16.5 h. They did not find any impact of gestational age on time to delivery, but in patients who have had a previous vaginal birth, time to delivery was twice as short as patients without a previous vaginal birth(10).

Wagaarachchi et al in their study for management of late intrauterine death using Mifepristone and Misoprostol found that the average induction to delivery interval was 8.5 hours. Ninety-five women (98.9%) were delivered within 72 hours of administration of first dose of misoprostol, with 66.7%, 87.5%, 92.7% and 95.8% women delivering within 12, 24, 36 and 48 hours, respectively. Contrary to Roel de Heus et al who used only Misoprostol without priming by Mifepristone no significant correlation was found in induction to delivery interval and parity. They also did not find any significant correlation between mean induction to delivery interval and

maternal age, Bishop's score, birthweight and mifepristone/ misoprostol interval(11).

Stibbe et al found that pre treatment with Mifepristone significantly reduced induction to delivery interval with decreased need for antibiotics and pain relief (12).Similar results were obtained by Nagaria et al in their study(13)

Sharma et al found similar results with decreased induction to delivery interval in Mifepristone pretreated patients. 60% of patients delivered using Mifepristone alone, and rest of the patients had significant improvement in Bishop's score. Parity, gestational age and bishop's score did not affect induction to delivery interval (1)

Basu et al in their study used a flexible regimen, administering Misoprostol 24,48 and 72 hours after giving Mifepristone. Out of 234 women studied they found that No women in the 24-hour group, two women in the 48-hour group and seven in the 72-hour group aborted without giving Misoprostol. Three women in total required surgical evacuation(14).

Nilas et al in their study found that none of the women delivered with Mifepristone alone. Time to abortion was longer in women when Misoprostol was given 1 day after Mifepristone as compared to the women when Misoprostol was administered 2 days after Mifepristone(15).

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