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ORIGINAL RESEARCH

Low Dose Vaginal Misoprostol in the Management of Women with Intrauterine Fetal Death

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Abstract

Objectives: The study was conducted to assess the effectiveness and side effects of vaginal misoprostol (Vagiprost® tablet) in termination of second and third trimester pregnancy complicated with intrauterine fetal death.

Design: A prospective observational cohort study.

Setting: Tanta University Hospital.

Patients: The study was carried out on 324 women with fetal demise in the second and third trimesters. Cases were collected during the period from January 2008 to December 2009.

Intervention: All patients were subjected to history taking, physical examination, Bishop Scoring. Application of 25 µg misoprostol in the posterior fornix of the vagina, this will be repeated every 4 hours over 24 hours. The adverse effects, progress, and outcomes were assessed.

Results: the success rate was 90% and 45% in women with third and second trimesters respectively. The mean induction-termination interval was 8.95 ± 2.63 and 15.3 ± 5.37 hours for women with third and second trimesters respectively. The induction termination interval correlated negatively with the duration of gestation. Approximately, 90% of second trimester and 55% of third trimester women required oxytocin augmentation. The mean value of total required dose of misoprostol was 166.3 ± 7.5 and 120 ± 28.79 µg for women with second and third trimesters respectively.

Conclusion: Vagiprost appears to be a safe, effective, practical, and inexpensive method for termination of third trimester pregnancy complicated with of intrauterine fetal death (IUFD), its effects increase with parity and duration of gestation.

Keywords: misoprostol, vagiprost, induction of labor, intrauterine fetal death, medical management, fetal demise, second and third trimester

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Introduction

According to the World Health Organization, the definition of fetal death (which has also been adopted by the United Nations and the National Center for Health Statistics) is a "death before the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation, 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". For the purpose of statistics, however, fetal deaths are classified according to gestational age, and only pregnancy losses that occur at ≥20 weeks' gestation are categorized as fetal deaths 1 Centers for Disease Control and Prevention, National Center for Health Statistics Web site.[1]

The management of IUFD poses a dilemma. Although a significant number of these patients will spontaneously go into labour within several weeks, many do not. Moreover, after the diagnosis, the social pressures and emotional aspects of delivery are usually considerable, and the medical consequences of postponing delivery can be significant. Unfortunately, the drug most commonly used for induction of labour, oxytocin is frequently ineffective in stimulating the uterus, especially the preterm one. Within the past two decades, prostaglandins (PGs) have provided an alternative method for induction of labour in women with IUFD.[2]

Misoprostol(15-deoxy-16-hydroxy-16-methylPGE1) has been widely used for cervical ripening and labour induction in various pregnancy conditions, at different gestational ages and using different routes of administration and dosing regimens.[3] Although misoprostol is effective and inexpensive, concern has been raised regarding the widespread use of this agent as a primary or adjuvant agent for labour induction.[4] In spite of these concerns, a large body of evidence exists that shows that the use of misoprostol for labour induction is highly efficacious and safe.[5]

Misoprostol is absorbed rapidly when administered orally, vaginally, rectally or intracervically. The vaginal route is advantageous because peak levels are reached slowly and sustained for long and this is associated with fewer side effects.[6,7] The vaginal route is more effective than the oral route.[8–11] The greater bioavailability of vaginal misoprostol probably explains the clinical results. Zieman et al[12] compared the absorption kinetics of misoprostol with oral versus vaginal administration in pregnant women. It was shown that the systemic bioavailability of vaginally administered misoprostol is three-times higher than that of the oral route when determined by area-under-the-curve.[13] The plasma level was sustained for up to 4 hours after vaginal administration.

The aim of this work was: To evaluate the effect of repeated vaginal administration of small doses (25 μg) of misoprostol in termination of pregnancy in cases of second and third trimester pregnancies complicated with IUFD.

Patients

- This study included 324 women recruited from Tanta University Hospital, Obstetrics and Gynaecology department. Cases were collected during the period from January 2008 to December 2009. They were divided into 2 groups:
- Group (1): included 160 cases of 2nd trimester pregnancy ≥20 week gestation, as documented by ultrasound examination and complicated with IUFD.
- Group (2): included 164 cases of 3rd trimester pregnancy, as documented by ultrasound examination, complicated with IUFD.

Inclusion Criteria

- IUFD with gestational age ≤20 weeks, absent spontaneous labour pain and Bishop cervical score <5.

Exclusion Criteria

- Contraindications of misoprostol induction are allergy to prostaglandins, and contraindications to vaginal delivery.

Methods

- All cases were subjected to: -
  - History taking, general, clinical examination, ultrasound examination.
  - Counseling the patient and obtaining written consent.
  - The induction regimen includes application of Vagiprost 25 μg tablet in the posterior fornix of the vagina every 4 hours (up to 6 doses) after determination of Bishop Score before.

Vagiprost (Adwia, El Oubor, Egypt) is licensed in Egypt for Labor induction. The tablet was moistened with moistened with acetic acid before insertion.[13]

- If the cervix is already ripe (Bishop Score ≥ 6) and the first dose does not lead to effective contractions the subsequent dose could be doubled to 50 or 100 µg after 4 hours.
- If no efficient regular uterine contractions occurred after 6 doses, augmentation of uterine contractions was done by oxytocin drip, 4 hours after last misoprostol dose.
- Recording the total dose of misoprostol received and the need for surgical interference to remove the retained placenta.
- The induction trial was considered successful when induction delivery interval was less than 24 hours.
- Failure of delivery within 24 hours is considered "failed trial", but it's not indication to stop the trial ie, the trial will be completed till termination.
- Observation of patients for 24 hours after delivery.
- Any complications during induction and 24 hours after delivery were reported.

Results

- Out of 164 women third trimester pregnant women having IUFD, induction of delivery succeeded in 148 cases (90.24%). Of these 148 cases, 33(20.12%) required 100 µg of misoprostol with induction delivery interval of ≥12 hours, 57 cases (34.76%) needed 125 µg of misoprostol with induction delivery interval of ≥16 hours and 58 cases (35.36%) needed150 µg of misoprostol with induction delivery interval ≥20 hours.
- The induction success rate in second trimester pregnant women having IUFD was approximately 45%. All succeeded inductions needed a total dose of 150 ug misoprostol.
- Failure rate for second trimester pregnant women having IUFD was 55%, of these cases 15% needed 175 µg of misoprostol with induction delivery interval of ≥24 hours, 10% needed 200 µg of misoprostol with induction delivery interval of ≥28 hours, 5% needed 225 µg of misoprostol with induction delivery interval of ≥32 hours, 15% needed 250 µg. of misoprostol with induction delivery interval ≥36 hours and 10% needed 275 µg. of misoprostol with induction delivery interval ≥40 hours.
- Failure rate for third trimester pregnant women having IUFD was 9.75%. All failed induction cases needed 175 µg of misoprostol with induction delivery interval ≥24 hours.
- The most serious complications associated with intra-vaginal misoprostol use for IUFD was premature separation of placenta and postpartum hemorrhage. Surgical interference was resorted to for removal of retained placenta. The rate of Surgical interference was 30% (48 cases) among cases of 2nd trimester IUFD (16 cases needed manual separation and 32 cases needed curettage under general anesthesia). On the other hand, the rate of surgical interference was 5% among cases of 3rd trimester IUFD (8 cases) required manual separation.
- As regards the incident of side effects, they occurred in 30% 2nd trimester pregnant women having IUFD. The most important side effects were fever in 16 cases (10%), fever and diarrhea in 8 cases (5%), nausea and vomiting in 16 cases (10%) and nausea, vomiting and diarrhea in 8 cases (5%). All side effects happened once induction delivery interval ≥34 hours. There were no complications in 3rd trimester IUFD.
- Other results are depicted in the following 4 tables and figures.

Figures (1–4) disclose a significant negative correlation between gestational age and induction contraction interval and between gestational age and induction delivery interval during second and third trimesters respectively.

Discussion

Studies demonstrated that the optimal intravaginal dose of misoprostol is 25 µg taken every 4 to 6 hours. Higher doses or shorter dosing intervals are associated with a higher incidence of side effects, especially hyperstimulation syndrome.[14,15]

The current investigation was conducted to assess the effectiveness of vaginal misoprostol (Vagiprost® tablet) in termination of second and third trimester pregnancy complicated with intrauterine fetal death. The study confirmed the presence of inverse

Table 1. The mean values of parity, induction contraction interval, induction delivery interval and total needed doses of misoprostol (in micrograms) between cases in the 2nd and cases in the 3rd trimesters IUFD.

		Range	Mean ± SD	*P*-value
Age	2nd trimester	17–38	25.09 ± 5.12	0.464
	3rd trimester	17–38	25.53 ± 5.67	
Parity	2nd trimester	0–4	1.900 ± 1.619	0.159
	3rd trimester	0–4	2.150 ± 1.565	
Induction contraction interval	2nd trimester	10–24	15.3 ± 5.37	<0.001
	3rd trimester	5–13	8.950 ± 2.625	
Induction delivery interval	2nd trimester	22–45	30 ± 8.25	<0.001
	3rd trimester	16–28	21.050 ± 3.634	
Total dose (μg)	2nd trimester	150–275	166.3 ± 57.5	<0.001
	3rd trimester	100–175	120 ± 28.79	

Notes: This table shows that there was no significant difference concerning age and parity between both studied groups. In the meantime, the induction contraction interval was significantly longer in women with 2nd trimester IUFD than the parallel value in women with 3rd trimester IUFD. Likewise, the induction delivery interval was significantly longer in women having 2nd trimester IUFD than those having 3rd trimester IUFD. In addition, the average value of total required doses of misoprostol was significantly higher in cases of 2nd trimester IUFD than that in cases of 3rd trimester IUFD.

correlation between parity and induction contraction interval. In addition, inverse relatioship was instituted between parity and induction delivery interval. Furthermore, another significant negative correlation was established between parity and total required dose of misoprostol. These results agree with those of Chittacharoen et al; Caliskan et al and Yilmaz et al.[3,13,16] Meanwhile, that result contradicts that of Auxiliadora de Aquino and Cecatti.[17]

The present study exposed the presence of significant negative correlation between gestational age and induction contraction interval; between gestational age and induction delivery interval and between gestational age and total needed dose of misoprostol. These findings mode with those of Nakintu.[18]

In this study, the induction contraction interval in primipara and second para was significantly lower than that in nullipara. Similarly, the mean of induction contraction interval multiparas was significantly lower than that in nullipara. However, there was no significant difference between the induction contraction interval in primipara, second para and

Table 2. The induction contraction interval in relation to the parity in women with 2nd trimester IUFD.

Induction contraction interval (in hours)	Parity in 2nd trimester		
	0	**1–2**	**3–4**
No of cases	**38**	**64**	**52**
Mean ± SD	20.33 ± 5.39	14.00 ± 3.52	12.50 ± 4.07
Significance (p)	<0.001		
Induction delivery interval (in hours)	Parity in 2nd trimester		
	0	**1–2**	**3–4**
No of cases	**38**	**64**	**52**
Mean ± SD	36.17 ± 7.22	26.33 ± 7.34	25.63 ± 3.81
Significance (p)	<0.001		
Total dose (in micrograms)	Parity in 2nd trimester		
	0	**1–2**	**3–4**
No of cases	**38**	**64**	**52**
Mean ± SD	212.5 ± 46.8	175.0 ± 52.4	137.5 ± 55.1
Significance (p)	<0.001		

Notes: This table shows the mean values the mean value of induction contraction interval, induction delivery interval and total required doses of misoprostol in relation to the parity in weeks of women having second trimester IUFD. Analysis of variance of variables using One-Way ANOVA, revealed a significant difference between the 3 subgroups of parity.

Table 3. The induction contraction interval in relation to the parity in cases of 3rd trimester IUFD.

Induction contraction interval (in hours)	Parity in 3rd trimester		
	0	**1–2**	**3–4**
No of cases	**39**	**64**	**55**
Mean ± SD	10.2 ± 1.48	6 ± 1.32	12 ± 1.22
Significance (p)		<0.001	
Induction delivery interval (in hours)	Parity in 3rd trimester		
	0	**1–2**	**3–4**
No of cases	**39**	**64**	**55**
Mean ± SD	25.2 ± 2.17	22.4 ± 1.52	18.3 ± 2.41
Significance (p)		<0.001	
Total dose (in micrograms)	Parity in 2nd trimester		
	0	**1–2**	**3–4**
No of cases	**39**	**64**	**55**
Mean ± SD	155 ± 20.9	110 ± 13.7	107.5 ± 23.7
Significance (p)		<0.001	

Notes: This table displays the mean values the mean value of induction contraction interval, induction delivery interval and total required doses of misoprostol in relation to the parity in weeks of women having third trimester IUFD. Analysis of variance of variables using One-Way ANOVA, revealed a significant difference between the 3 subgroups of parity.

that in third and fourth para. We found also, that the mean value of induction contraction interval in cases of 2nd trimester IUFD was significantly higher than that in cases of 3rd trimester IUFD. This agrees with the reports of Nakintu;[18] and Bugalho and his colleagues.[19]

The contemporary work shows that the induction delivery interval period in cases of 2nd and 3rd trimesters IUFD in nullipara was significantly higher than the corresponding values in women with previous history of childbirth. Approximately, 80% of patients required total misoprostol doses less than 200 μg to be delivered, and the maximum dose of 275 μg was needed by only in 10% of cases. These results differ from those of other authors.[20,21] The total required dose of misoprostol in cases of 2nd and 3rd trimesters IUFD

Table 4. The rate of induction success in 2nd versus 3rd trimesters pregnancy with IUFD.

	Needed dose of misoprostol	**2nd trimester IUFD**		**3rd trimester IUFD**	
		N	**%**	**N**	**%**
Success	**100**	0	0	33	20.12
(induction delivery interval	**125**	0	0	57	34.76
was less than 24 hours)	**150**	72	45	58	35.37
	Total of success	**72**	**45%**	**148**	**90.24%**
Failure	**175**	24	15	16	9.75
	200	16	10	0	0
	225	8	5	0	0
	250	24	15	0	0
	275	16	10	0	0
	Total of failure	**88**	**55**	**16**	**9.75**
Cases needed oxytocin augmentation		144	**90**	91	**55.49**
Cases not in need of oxytocin augmentation		16	10	73	44.51
Occurrence of side effects		48	**30**	0	0

Notes: This table shows that the induction success rate was 45% in cases of second trimester pregnancy complicated with IUFD, compared with approximately 90% in cases of third trimester pregnancy complicated with IUFD. The difference was highly significant. It is clear shows that: the need for oxytocin augmentation was significantly higher in cases 2nd trimester IUFD than that in 3rd trimester IUFD ($P < 0.05$).

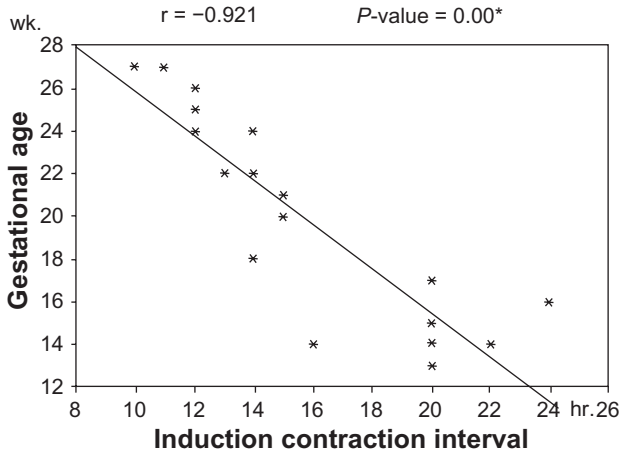

Figure I. Illustrates the correlation between gestational age and Induction contraction interval in cases of second trimester IUFD.

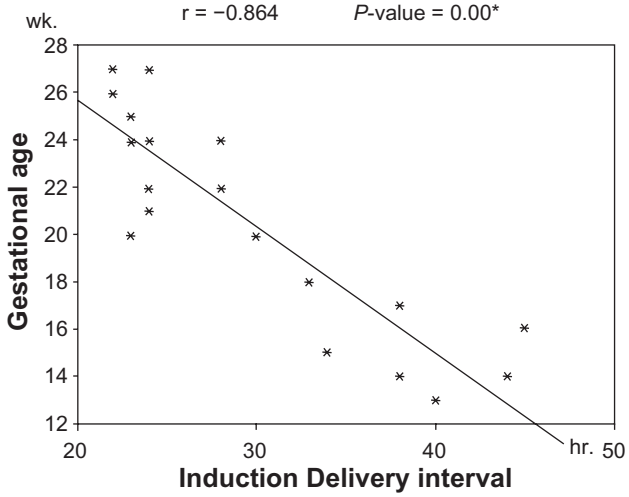

Figure 2. Shows correlation between gestational age and induction delivery interval in cases of second trimester IUFD.

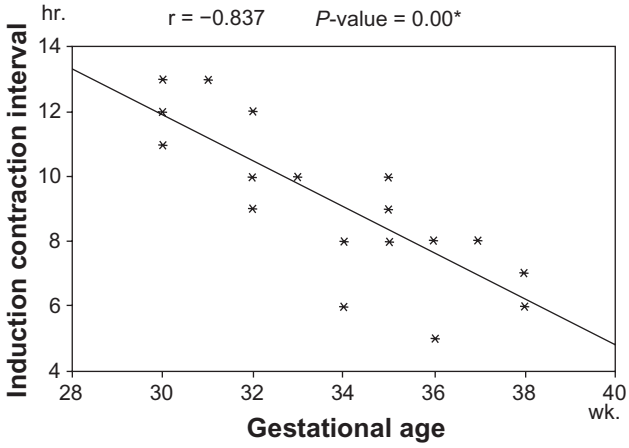

Figure 3. Exhibits the correlation between gestational age and induction contraction interval in cases of 3rd trimester IUFD.

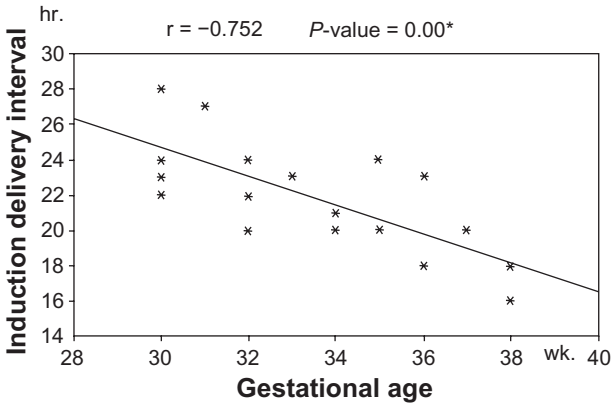

Figure 4. Reveals the correlation between gestational age and induction delivery interval in cases of 3rd trimester IUFD.

in nullipara were significantly higher than that required in parous women. Increased parity has no significant effect on the mean value of the required dose.

The success rate was 45% in cases of 2nd trimester IUFD compared with 90% in cases of the third trimester IUFD. This result agrees with that of many other authors.[22,23] Bugalho et al found that the success rates range from 67 to 100%.[24]

The need for oxytocin augmentation was significantly higher in the 2nd trimester (90% of cases) than that in 3rd trimester cases with IUFD (55% of cases). Nyende[20] found that 20% of his cases required oxytocin augmentation to complete the induction of labour.

The necessity for surgical interference because of retained placenta was 30% in cases 2nd trimester IUFD compared with 5% in 3rd trimester IUFD. Likewise, the occurrence of side effects during induction was significantly higher in cases 2nd trimester IUFD.

As regards complications, we found them in 30% of cases of 2nd trimester pregnant women having IUFD but none in cases of third trimester. The most important side effects were fever in 10%, fever and diarrhea in 5%, nausea and vomiting in 10% and nausea, vomiting and diarrhea in 5%. All side effects happened once induction delivery interval ≥34 hours. Hofmeyr and Gülmezoglu speculated that the most serious complications associated with intra-vaginal misoprostol use for IUFD are premature separation of placenta, postpartum hemorrhage, and rare events such as uterine rupture and amniotic fluid embolism. Gastrointestinal side effects: up to 35% of women will

experience nausea, vomiting, or diarrhea. Pyrexia and shivering: this may occur in up to 7% of women.[25]

Last but not least, we believe that vaginal administration of Vagiprost is a very effective drug for termination of pregnancy in cases of IUFD, its effects increase in direct proportion with parity and duration of pregnancy. Its use is an alternative to other treatments to terminate pregnancy in the second trimester for women with fetal death.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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