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Full Length Research Paper

Vagiprost in management of second and third trimester intrauterine fetal death

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The objective of this study is to assess the effectiveness and side effects of vaginal Misoprostol (Vagiprost® tablet) in the termination of second and third trimester pregnancy complicated with intrauterine fetal death. The study design is a prospective observational cohort study in Tanta University Hospital. The study was carried out on 324 women with fetal demise in the second and third trimesters, from January 2008 to December 2009. All patients were subjected to history taking, physical examination, and the Bishop Scoring. 25 µg Misoprostol was applied in the posterior fornix of the vagina and this was repeated every 4 h over 24 h. We assessed the adverse effects, progress, and outcomes. The success rate was 90 and 45% in women in the third and second trimesters respectively. The mean induction-termination interval was 8.95 ± 2.63 and 15.3 ± 5.37 h for women in the 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 in the second and third trimesters respectively. Vagiprost appears to be a safe, effective, practical, and inexpensive method for termination of third trimester pregnancy complicated with intrauterine fetal death (IUFD).

Key words: Misoprostol, vagiprost, induction of labour, intrauterine fetal death, medical management, fetal demise, second and third trimester.

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 (Centers for Disease Control and Prevention, National Center for Health Statistics Web site; Belkin and Wilder, 2007).

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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 (Kochenour, 1987).

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 (Chittacharoen et al., 1997).

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 (Arias, 2000).

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 (Hale and Zinberg, 2001). 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 a long time and this is associated with fewer side effects (Hale and Zinberg, 2001; Gottschall et al., 1997). The vaginal route is also more effective than the oral route. (Ho et al., 1997; Ngai et al., 2002; Bartley and Baird, 2002; Bebbington et al., 2002). The greater bioavailability of vaginal Misoprostol probably explains the clinical results.

Zieman et al. (1997) compared the absorption kinetics of Misoprostol with oral versus vaginal administrations in pregnant women. It was shown that the systemic bio-availability of vaginally administered Misoprostol is three-times higher than that of the oral route when determined by area-under-the-curve (Yilmaz et al., 2007). The plasma level was sustained for up to 4 h after vaginal administration.

The aim of this work is to evaluate the effect of repeated vaginal administration of small doses (25 µg) of Misoprostol (Vagiprost) in termination of pregnancy in cases of second and third trimester pregnancies complicated by IUFD.

PATIENTS AND METHODS

The study included 324 women recruited from the Department of Obstetrics and Gynecology of Tanta University Hospital. Cases were chosen during the period from January 2008 to December 2009. This relatively large number of cases of IUFD in our locality may be attributed to the high incidence of unwanted pregnancy and poor antenatal care services in addition to the fact that induction of abortion is forbidden by law, unless for the sake of maternal safety. Patients 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 the Bishop cervical score <5.
Exclusion criteria: Contraindications of Misoprostol induction are allergy to prostaglandins and contraindications to vaginal delivery as repeated cesarean section, lower genital infections and contracted pelvis.

All cases were subjected to history-taking, general, clinical and ultrasound examination to confirm the diagnosis of IUFD. We counseled the patient and obtained written consent. The induction regimen included application of Vagiprost 25 µg tablet in the posterior fornix of the vagina every 4 h (up to 6 doses) after determination of the Bishop score. Vagiprost (Adwia, El Oubor, Egypt) is licensed in Egypt for Labour induction. The tablet was moistened with acetic acid before insertion (Yilmaz et al., 2007). 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 h. If no efficient regular uterine contractions contractions occurred after six doses, augmentation of uterine contractions was done by oxytocin drip, 4 h after the last Misprostol dose. The total dose of Misoprostol received and the need for surgical intervention to remove the retained placenta were reported. The induction trial was considered successful when the induction delivery interval was less than 24 h. Failure of delivery within 24 h was considered “a failed trial”, but it was not an indication to stop the trial that is, the trial will continue until termination. The failure of medical treatment was diagnosed clinically. Observation of patients was done for 24 h after delivery. Any complications during induction and 24 h 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 an induction delivery interval of ≥12 h, 57 cases (34.76%) required 125 µg of Misoprostol with an induction delivery interval of ≥16 h and 58 cases (35.36%) required 150 µg of Misoprostol with induction delivery interval ≥20 h.

The induction success rate in the second trimester pregnant women having IUFD was approximately 45%. All successful inductions required a total dose of 150 ug misoprostol.

The failure rate for the second trimester pregnant women having IUFD was 55%. Of these cases, 15% required 175 µg of Misoprostol with an induction delivery interval ≥24 h, 10% required 200 µg of Misoprostol with an induction delivery interval ≥28 h, 5% required 225 µg of Misoprostol with an induction delivery interval ≥32 h; 15% required 250 µg of Misoprostol with induction delivery interval ≥36 h; and 10% required 275 µg of Misoprostol with induction delivery interval ≥40 h. The failure rate for the third trimester pregnant women having IUFD was 9.75%. All failed induction cases required 175 µg of Misoprostol with an induction delivery interval ≥24 h.

The most serious complications associated with intra-vaginal Misoprostol use for IUFD were premature separation of placenta, postpartum hemorrhage and increased incidence of operative interference. Surgical intervention was resorted to for removal in the case of retained placenta. The rate of surgical intervention was 30% (48 cases) among cases of 2nd trimester IUFD (16 cases needed manual separation, and 32 cases needed curettage under general anesthesia immediately after medical evacuation of the uterus failed, due to the occurrence of infection and/or if considerable bleeding.

On the other hand, the rate of surgical intervention was 5% among cases of 3rd trimester IUFD (8 cases) required manual separation.

As regards the incidence of side effects, they occurred in 30% of the 2nd trimester pregnant women having IUFD, if surgery is regarded as the side effect of failure of the prostaglandin treatment. So the side effect in 2nd

Table 1. The mean value of age, parity, induction contraction interval, induction delivery interval and total needed doses of Misoprostol (µg) between cases in the 2nd and cases in the 3rd trimester IUFD.

Variable	Trimester	Range	Mean ±SD	P-value
Age	2nd	17-38	25.09 ± 5.12	0.464
	3rd	17-38	25.53 ± 5.67	
Parity	2nd	0-4	1.900 ± 1.619	0.622
	3rd	0-4	2.150 ± 1.565	
Induction contraction Interval	2nd	10-24	1.53 ± 5.37	<0.01
	3rd	5-13	8.950 ± 2.625	
Induction delivery interval	2nd	22-45	3.0 ± 8.25	<0.01
	3rd	16-28	21.050 ± 3.634	
Total dose(in µg)	2nd	150-275	166.3 ± 57.5	>0.01
	3rd	100-175	120 ± 28.79	

This table shows that the success rate was 45.12% for cases of third trimester IUFD compared with 10% for women with IUFD during second trimester. Approximately 90% of second trimester cases needed oxytocin augmentation, compared with 54.88% for cases during third trimester. No side effects were reported for third trimester women compared with the occurrence of minor side effects in 30% for women during the second trimester. The most important side effects were diarrhea, fever and vomiting.

trimester would be doubled. 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 the induction delivery interval exceeded 34 h. There were no complications among cases of the 3rd trimester IUFD.

In cases of second trimester IUFD, we found a highly significant ($P<0.01$) negative correlation ($r= -0.921$) between gestational age and induction contraction interval. Similarly, there was a highly significant ($P<0.01$) negative correlation ($r= -0.864$) between gestational age and other results depicted in Tables 1 to 3.

DISCUSSION

Studies demonstrated that the optimal intravaginal dose of Misoprostol is 25 µg taken every 4 to 6 h. Higher doses or shorter dosing intervals are associated with a higher incidence of side effects, especially hyperstimulation syndrome (Committee on Obstetric Practice, 2000; Bygdeman, 2003).

The current investigation was conducted to assess the effectiveness of vaginal Misoprostol (Vagiprost® tablet) in the termination of second and third trimester pregnancy complicated with intrauterine fetal death. The study confirmed the presence of an inverse correlation between parity and induction contraction interval. In addition, there is an inverse correlation between parity and the induction delivery interval. Furthermore, another significant negative correlation was established between parity and total required dose of Misoprostol. These findings agree with those of Chittacharoen et al. (1997), Caliskan et al. (2005) and Yilmaz et al. (2007). Meanwhile, that result contradicts the finds of Auxiliadora de Aquino and Cecatti (2003).

The present study exposed the presence of significant negative correlation between gestational age and the induction contraction interval; between gestational age and the induction delivery interval and between gestational age and total required dose of Misoprostol (Figures 1 to 4). These findings agree with those of Nakintu (2001).

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 in multiparas was significantly lower than that in nullipara. However, there was no significant difference between the induction contraction interval in primipara, second para and 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 (2001) and Bugalho et al. (1995).

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 delivered, and the maximum dose of 275 µg was needed in only in 10% of cases. These results differ from those of other authors (Ngai et al., 2003; Nyende, 2004). The total required dose of Misoprostol in cases of 2nd and 3rd trimesters IUFD in nullipara were significantly higher than that

Table 2. The induction contraction interval in relation to the parity.

Variable	Parity		
Induction contraction interval (h)	**Parity in 2nd trimester**		
Parity	0	1-2	3-4
Mean ± SD	20.33 ± 5.39	14.00 ± 3.52	12.50 ± 4.07
P value		0.011	
Induction delivery interval (h)			
Parity	0	1-2	3-4
Mean ± SD	155 ± 20.9	175.0 ± 52.4	25.63 ± 3.81
P value		0.002	
Total required dose of Misoprostol (µg)			
Parity	0	1-2	3-4
Mean ± SD	155 ± 20.9	175.0 ± 52.4	107.5 ± 23.7
P value		0.002	
Induction contraction interval (h)			
No. of cases	39	64	55
Parity	0	1-2	3-4
Mean ± SD	10.2 ± 1.48	6 ± 1.32	12 ± 1.22
P value		<0.001	
Induction delivery interval (h)			
Parity	0	1-2	3-4
Mean ± SD	25.2 ±2.17	22.4±1.52	18.3±2.41
P value		<0.001	
Total required dose of Misoprostol (µg)			
Parity	0	1-2	3-4
Mean ± SD	155±20.9	110±13.7	107.5±23.7
P value		<0.001	

This table shows the mean values of induction contraction interval, induction delivery interval and total required dose of Misoprostol in relation to parity in women with second trimester intrauterine fetal death. Analysis of variance using one way ANOVA test revealed significant differences between the three subgroups of parity. The mean values of induction contraction interval, induction delivery interval and total required dose of Misoprostol in relation to parity in women with second trimester intrauterine fetal death. Analysis of variance using one way ANOVA test revealed significant differences between the three subgroups of parity.

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 (Ngai et al., 2003; Fawole et al., 2004). Bugalho et al. (1996) found that the success rates range from 67 to 100%.

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 (2004) 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 when induction delivery interval exceeded 34 h. 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

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

Variable	Total (%) of success	2nd trimester IUFD		3rd trimester IUFD	
		N	%	N	%
Success rate (induction delivery interval < 24 h)	100	0	0	33	20.12
	125	0	0	57	34.76
	150	72	45	58	35.37
	Total of success	72	45	148	90.24
Failure rate	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 requiring oxytocin augmentation		144	90	91	55.49
Cases not requiring oxytocin augmentation		18	10	73	44.51
Cases not requiring oxytocin augmentation		48	30	0	0

This table shows that the success rate was 45.12% for cases of third trimester IUFD compared with 10% for women with IUFD during second trimester. Approximately 90% of second trimester cases needed oxytocin augmentation, compared with 54.88% for cases during third trimester. No side effects were reported for third trimester women compared with the occurrence of minor side effects in 30% for women during the second trimester. The most important side effects were diarrhea, fever and vomiting.

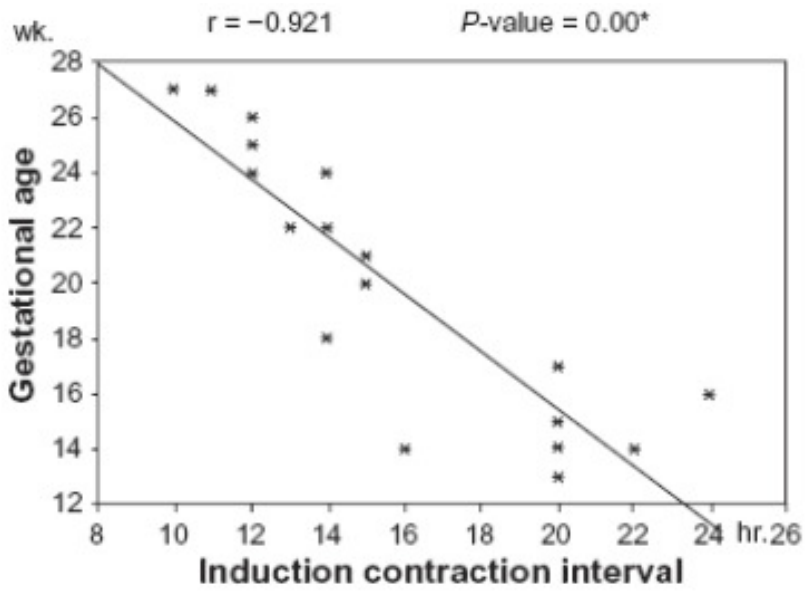

Figure 1. Illustrates the correlation between gestational age and induction contraction interval in cases of second trimester IUFD.

effects: up to 35% of women will experience nausea, vomiting, or diarrhea. Pyrexia and shivering: this may occur in up to 7% of women (Hofmeyr and Gülmezoglu, 2003).

Lastly 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

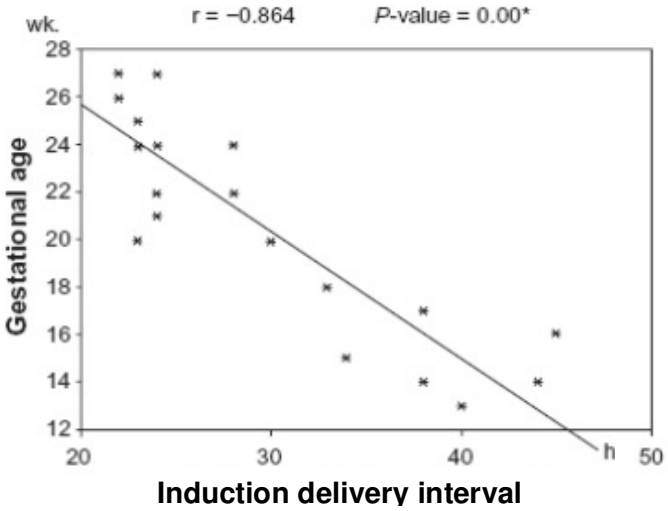

Figure 2. Shows the correlation between gestational age and induction delivery interval in cases of second trimester IUFD.

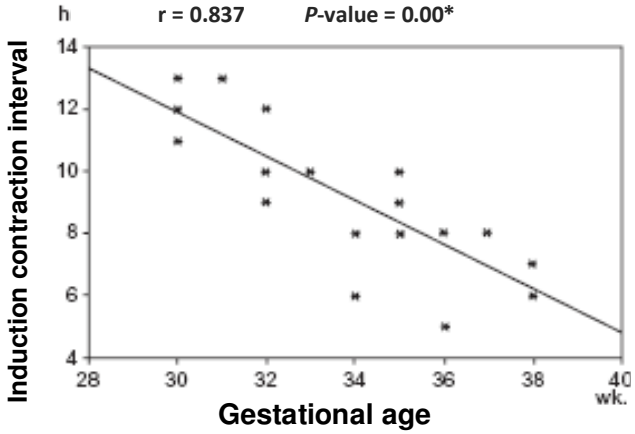

Figure 3. Exhibits the correlation between gestational age and induction contraction interval in cases of 3rd trimester IUFD.

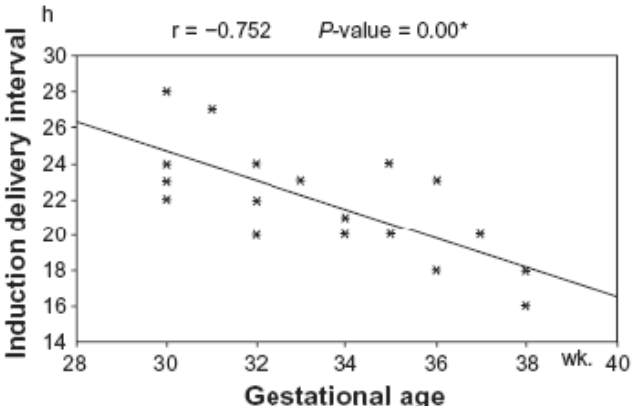

Figure 4. Reveals the correlation between gestational age and induction delivery interval in cases of 3rd trimester IUFD.

pregnancy. Its use is an alternative to other treatments to terminate pregnancy in the second trimester for women with fetal death.

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