

Effect of Intravenous Dexamethasone on Induction of Mid-Trimester Abortion : Randomized Controlled Trial

Original
Article

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ABSTRACT

Background: Medical abortion, the termination of pregnancy through the use of a drug or a combination of drugs, has the potential to reduce complications and to expand access to abortion provided not only by specially trained clinicians but also by other health care providers who may or may not have training in surgical methods of abortion.

Aim: This study aimed to elicit the safety and efficacy of intravenous injection of dexamethasone with vaginal misoprostol for shortening the induction abortion interval in the second trimester of pregnancy.

Materials and Methods: This study was conducted in Ain-Shams Maternity University Hospital where 140 pregnant females were included for induction of second trimester abortion from June 2018 till December 2019.

Results: There was significant statistical difference between the two groups as regard induction-expulsion interval ($P > 0.001$) and length of hospital stay ($P > 0.001$), mean induction-expulsion interval in dexamethasone group was 10.5 hours; while in the control group was 17.5 hours, the mean length hospital stay was 16 hours in the dexamethasone group while it was 23 hours in the control group. There was significant statistical difference between the two groups as regard dose of misoprostol used ($P > 0.001$), mean dose of misoprostol in the dexamethasone group was 800 mcg while it was 1600 mcg in the control group.

Conclusion: It was suggested that use of intravenous injection of dexamethasone with misoprostol was effective in shortening the induction- abortion interval, the length of hospital stay and reducing the misoprostol doses.

Key Words: Corticosteroids, dexamethasone, duration of abortion, induction of abortion, prostaglandins

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INTRODUCTION

Second trimester abortion constitute 10-15% of all induced abortions worldwide and responsible for two-thirds of major abortion-related complications^[1].

Although the majority of abortions are performed in the first trimester, there is still a gradual increase in second-trimester abortion because of the wide scale introduction of prenatal screening programs detecting women whose pregnancies are complicated by serious fetal abnormalities such as cardiovascular and skeletal malformation^[2]. There is a need for evolving a safe and effective method of terminating pregnancy in the second trimester^[3].

Medical abortion, the termination of pregnancy through the use of a drug or a combination of drugs, has the potential to reduce complications and to expand access to abortion provided not only by specially trained clinicians but also by other health care providers who may or may not have training in surgical methods of abortion^[1].

Prostaglandins (PG) play an important role in the regulation of uterine contractility during pregnancy and parturition^[4]. The degree of uterine activity during pregnancy is thought to be regulated by the balance between the intrinsic suppressor, progesterone, and the stimulant oxytocin and prostaglandin^[5].

The PG analogues, besides being suitable for administration by non-invasive routes, have a prolonged action as they are relatively resistant to the initial rapid inactivation in the circulation. Both PGE and PGF analogues are widely used for TOP, although PGE analogues are preferred because of their selective specificity for the myometrium and fewer gastrointestinal side effects^[6]. The most extensively studied PG analogues are carboprost, sulprostone, gemeprost and misoprostol.

Unsafe abortion remains one of the leading causes of maternal death in most of developing countries. Infection rate associated with misoprostol was significantly lower than that with alternative traditional methods. If given

within sufficient frequency, alone can abort a high proportion of pregnancies^[7].

Medical abortion in the second trimester with misoprostol alone has been shown to be effective although misoprostol-only protocols have required higher doses and side effects are more common and the time to complete the abortion is longer^[1].

Glucocorticoids are normally circulating stress hormones; however, in the initiation of labor, a stressful situation, their expression is regulated by placentally derived corticotropin releasing hormone (CRH)^[8].

Liapakis and George 2017^[9] have suggested that (CRH) which has been identified in various organ systems including the female reproductive system, is the principle regulator of the hypothalamic- pituitary-adrenal axis. Some studies showed an increased amount of glucocorticoids receptors on the cervix before the initiation of labor^[5]. Steroid substances produced in the adrenal glands of the human fetus affect the placenta and the membranes and transform the myometrium from the static to the contractile state^[10].

The placenta may play a role in this process because it produces a lot of CRH (corticotropin releasing hormone). The adrenal glands of the fetus do not produce a considerable amount of cortisol until the third trimester. During the last weeks of pregnancy, the cortisol and DHEA-S (dehydroepiandrosterone sulfate) contents of the fetus rise and this leads to an increase in maternal estrogens, a particularly sterol. These results in modification of uterine contractility, stimulation of the membranes to produce more prostaglandins, stimulation to produce C19 steroids from placental adrenaline and increase in the estrogen content. This will disturb the ratio of estrogen to progesterone and will cause expression of contractile proteins. In fact, the increase in CRH near the end of pregnancy confirms the presence of a placental-fetal clock^[11].

A prolonged gestation is more likely to occur when the fetus has congenital adrenal hyperplasia caused by 21-hydroxylase deficiency which may be due to an impaired cortisol production^[12].

One of the methods proposed for the strengthening and speeding up of the labor process (labor induction) is the use of corticosteroids, although the effects of using these substances in the labor process is not well understood^[11].

Moreover, it has been observed that infusion of glucocorticoids into sheep fetuses causes premature birth induction^[13]. In studies carried out, corticosteroids have been employed using extra-amniotic and intravenous methods and in some of these studies, both methods have been proved successful^[13,14].

These studies have prepared the way for bringing up the role of corticosteroids in the speeding up of labor induction in women^[11].

AIM OF THE WORK

The aim of this study is to determine the effect of intravenous dexamethasone on the interval of induction of abortion in second trimester in pregnant women at gestational age 16-24 weeks.

PATIENTS AND METHODS

This randomized controlled study was conducted in Ain-Shams Maternity University Hospital from June 2018 till December 2019 on pregnant women planned to undergo induction of abortion who met the inclusion criteria and exclusion criteria.

This study followed the ethical committee rules of Obstetrics and Gynecology, Ain-Shams University. For all pregnant women in this study, explanation of the study procedures was done and informed written consent was obtained. Any participating women was informed that she had the right to withdraw from the study at any phase without any adverse impact on the medical service she received.

The study included pregnant women with singleton pregnancy, gestational age 16-24 weeks, pregnant women presenting with anhydramnios and women who had viable pregnancy and planned for therapeutic termination of pregnancy for lethal malformations or obstetrical complications needing termination.

However, women who were actively aborting, fetal life negative, congenitally malformed uterus, women with previously scarred uterus or low lying placenta, any contraindication to drug study: severe hypertension, uncontrolled diabetes mellitus or heart disease were excluded from the study.

Methods : The study included 140 pregnant women who were subjected to evaluation that included; a full history taking, physical examination and an ultrasound was done. The study group was selected with regard to inclusion and exclusion criteria.

The patients were randomized into two groups; group 1 (n=70 dexamethasone group) pregnant women who received dexamethasone as dexamethasone sodium phosphate intravenously at a dose of 8 mg intravenous injection 8 and 4 hours before the onset of the medical induction of abortion and the induction of abortion was performed by misoprostol. Group 2 (n=70 control group) pregnant women who received only misoprostol for induction of abortion.

All recruited women received misoprostol for medical induction of abortion as a vaginal dose of 400 mcg every 3 hours for a maximum of 5 doses per day according to Ain-Shams University Maternal Hospital (ASUMH) based on FIGO guidelines^[15].

When the fetus was expelled, oxytocin infusion at a dose of 30 IU/L was to be started. Spontaneous placental expulsion was awaited for 30 minutes. If the placenta was not expelled completely within this time, evacuation was to be performed.

If the fetus was not expelled within the 5 doses, the patient was allowed to rest overnight and started over next morning (second cycle). If failed induction for one week (7 trials of 5 doses per day) hysterotomy was done.

Sample Size Justification: The required sample size has been calculated using the G*Power Software (Universität Düsseldorf, Germany).

The primary outcome measure is the induction of abortion to expulsion of products of conception time.

Currently, there is no adequate information regarding the effect of IV dexamethasone on the outcome measure; therefore, the present exploratory study would target an effect size that would be clinically relevant.

So, it is estimated that a sample size of 64 patients in either study group (total = 128 patients) would achieve a power of 80% (type II error = 0.2) to detect a statistically significant difference between the two groups as regards the induction of abortion to expulsion of products of conception time for a medium effect size corresponding to a Cohen d coefficient of 0.5 using a two-sided unpaired t-test with the test confidence set at a level of 95% (type I error = .05). The effect size (Cohen d) is calculated as follows^[16]:

$$\text{Cohen } d = \frac{\text{Mean of Group 1} - \text{Mean of Group 2}}{\text{Common standard deviation}}$$

The targeted effect size of $d = 0.5$ has been selected as it could be regarded as the smallest effect size that may

be clinically relevant to seek in this exploratory study.

Patient allocation/randomization: Patients will be allocated randomly to either study group using a computer-generated random number list (attached) created with MedCalc© software version 15 (MedCalc© Software bvba, Ostend, Belgium).

STATISTICAL ANALYSIS:

Statistical analysis was performed using Microsoft Excel version 2016 and MedCalc version 7.0. Difference between two independent groups was analyzed using the independent student's t-test and mean difference (MD) with its 95% confidence interval (95% CI) (for numeric normally-distributed variables); Mann-Whitney's U-test and median difference (MedD) with its 95% CI (for numeric non-normally-distributed variables); or chi-squared test (with Yates' continuity correction) and risk ratio (RR) with its 95% CI (for categorical variables). Significance level was set at 0.05.

RESULTS

There were no significant statistical differences between women of both groups regarding the demographics characteristics (Table 1).

There were no significant statistical differences between women of both groups regarding the rates of early vs. late second trimester miscarriages. The total dose of misoprostol (Figure 1), induction-to-expulsion interval (Figure 2) and duration of hospital stay (Figure 3) were statistically highly significant lower in women of group I when compared to women of group II. There were no significant statistical differences between women of both groups regarding the need for a second cycle or the need for surgical evacuation (Table 2).

There were no significant statistical differences between women of both groups regarding post- and pre-abortion hemoglobin difference, blood transfusion and hysterotomy. The rates of fever were higher in women of group II; yet not reached statistical significance. There were no cases of hysterectomy in either group (Table 3).

Table 1: Difference between groups regarding demographics characteristics

	Group I [Dexamethasone Group] (n=70)	Group II [Control Group] (n=70)	MD/RR/MedD (95% CI)	P
Age (years)				
Range	18 – 40	18 – 40	0.22	0.796 ¹
Mean ± SD	26.52 ± 4.96	26.75 ± 5.43	(-1.51 to 1.96)	NS
BMI (kg/m²)				
Range	20 – 38	18.7 – 34	-2.18	0.062 ¹
Mean ± SD	28.45 ± 3.73	26.27 ± 3.46	(-3.38 to -0.97)	NS
Gestational Age (weeks)				
Range	16 – 24	16 – 24	-0.04	0.887 ¹
Mean ± SD	19.67 ± 1.77	19.62 ± 1.77	(-0.63 to 0.54)	NS
Parity				
Nulliparous	10 (14.3%)	9 (12.9%)	1.11	0.805 ²
Multiparous	60 (86.7%)	61 (87.1%)	(0.48 to 2.57)	NS
Previous Miscarriage(s)				
Range	0 – 4	0 – 4	0.0	0.161 ³
Median (IQR)	1 (0 – 1)	1 (0 – 1)	(0.0 to 0.0)	NS

Data presented as range, mean ± SD; frequency (percentage); or range, median (IQR)

1 Analysis using independent student's t-test

2 Analysis using chi-squared test

3 Analysis using Mann-Whitney's U-test

Table 2: Difference between groups regarding miscarriage outcomes

	Group I [Dexamethasone Group] (n=70)	Group II [Control Group] (n=70)	RR/MedD (95% CI)	<i>P</i>
Second-Trimester				
Early	47 (67.1%)	51 (72.9%)	0.92	0.461 ¹
Late	23 (32.9%)	19 (27.1%)	(0.74 to 1.15)	NS
Total Misoprostol Dose (mcg)				
Range	400 – 2800	400 – 3200	800	<0.001 ²
Median (IQR)	800 (800 – 1200)	1600 (1200 – 2000)	(400 – 800)	HS
Induction-to-Expulsion Time (hours)				
Range	9 – 27	9 – 37	6.5	<0.001 ²
Median (IQR)	10.5 (9 – 13)	17.5 (15.5 – 19.5)	(5.5 – 7.5)	HS
Need for Second Cycle	6 (8.6%)	9 (12.9%)	0.67 (0.25 to 1.77)	0.414 ¹ NS
Need for Surgical Evacuation	7 (10%)	10 (14.3%)	0.70 (0.28 to 1.73)	0.439 ¹ HS
Duration of Hospital Stay (hours)				
Range	10 – 31.5	14 – 49	7	<0.001 ²
Median (IQR)	16 (14 – 17.5)	23 (21 – 25)	(6 – 8)	HS

Data presented as frequency (percentage); or range, median (IQR)

1 Analysis using chi-squared test

2 Analysis using Mann-Whitney's U-test

Table 3: Difference between groups regarding blood loss and adverse outcomes

	Group I [Dexamethasone Group] (n=70)	Group II [Control Group] (n=70)	MedD/RR (95% CI)	P
Hb Difference (g/dl)				
Range	0 – 1.6	0 – 1.5	0.05	0.697 ¹
Median (IQR)	0.75 (0.5 – 1.0)	0.8 (0.6 – 1.0)	(-0.1 to 0.1)	NS
Fever	7 (10%)	13 (18.6%)	0.54 (0.23 to 1.27)	0.149 ² NS
Blood Transfusion	2 (2.9%)	3 (4.3%)	1.5 (0.26 to 8.7)	0.999 ² NS
Hysterotomy	3 (4.3%)	4 (5.7%)	1.33 (0.31 to 5.74)	0.999 ² NS
Hysterectomy	0 (0%)	0 (0%)	NE	NE

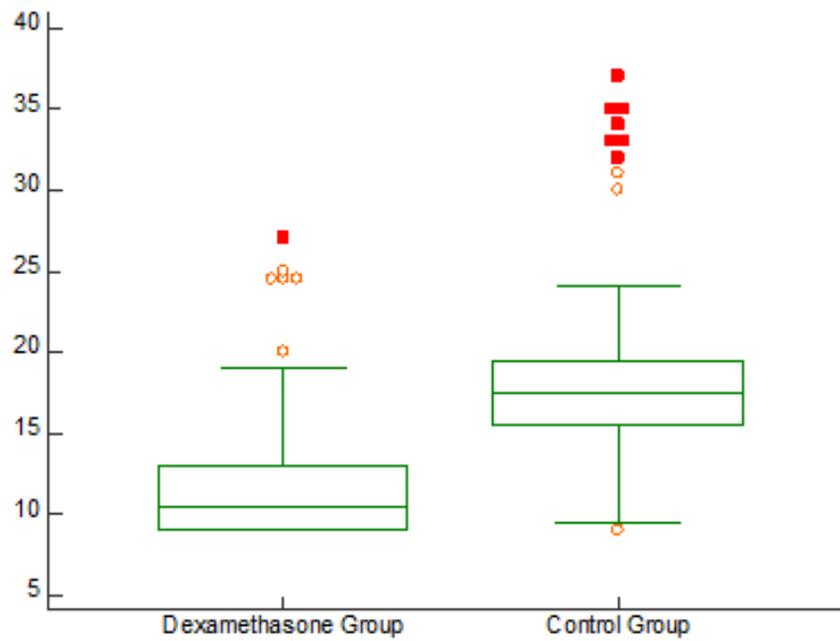


Fig. 1: Box and whisker plot chart showing difference between groups regarding total misoprostol dose

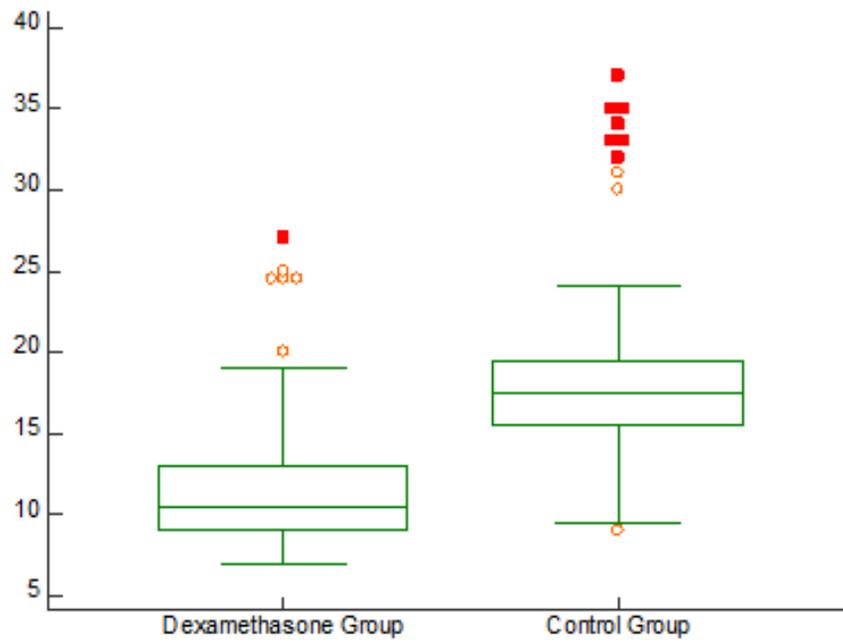


Fig. 2: Box and whisker plot chart showing difference between groups regarding induction-to-expulsion interval

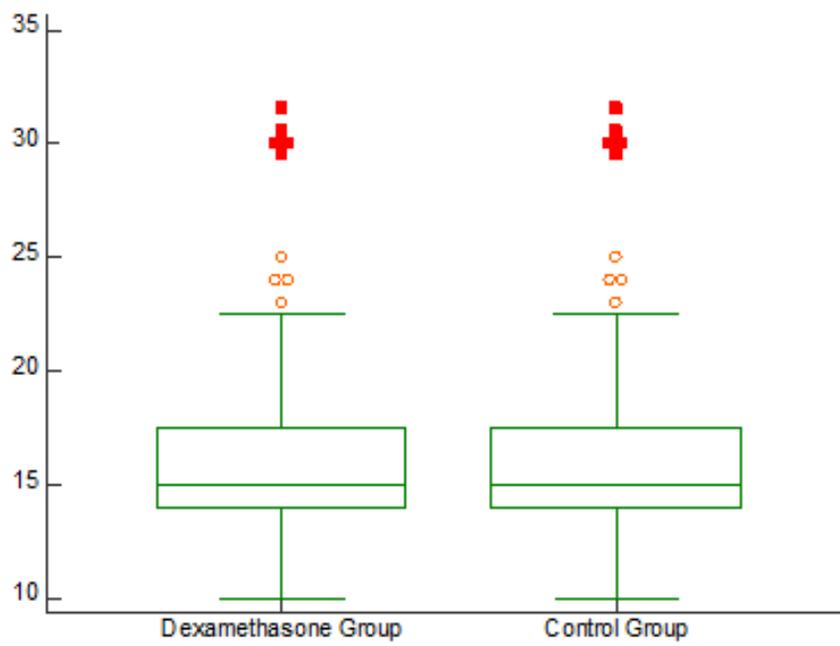


Fig. 3: Box and whisker plot chart showing difference between groups regarding duration of hospital stay

DISCUSSION

In this study, both groups were demographically similar with no statistical difference regarding maternal age ($P=0.0795$), BMI ($P=0.062$), gestational age ($P=0.887$), parity ($P=0.805$) and numbers of previous abortions ($P=0.161$) (Table 1), this means that data in both groups were homogenous.

If the control group included more women who were obese than that in the dexamethasone group, the induction-abortion interval may be longer because they may need more doses of misoprostol and not due to absence effect of dexamethasone in this group.

For the parity on admission, 10 women out of 70 in the dexamethasone group while 9 women out of 70 were nullipara in the control group and the remaining patients were multipara in both groups; this means that data in both groups were homogenous.

If this data showed a big difference in both groups, it would have been thought that the induction-abortion interval may be shorter in the dexamethasone group due to that most of women were multipara, which might have a role in shortening the induction-abortion interval and not due to the effect of dexamethasone on the induction process.

This goes with the results of Attia^[17] study which was conducted in Ain-Shams Maternity University Hospital where 120 pregnant females were included for induction of second trimester abortion. They were divided into two groups each one of 60 female. One group received 12 mg dexamethasone intramuscular injection with onset of the medical induction of abortion by misoprostol and the other group received 3 ml distilled water instead of dexamethasone

In this study, both groups were demographically similar regarding maternal age, gestational age, parity, BMI, numbers of previous abortions and timing of abortion. There was no significant statistical difference; age ($P=0.087$), gestational age ($P=0.913$), parity ($P=0.1.0$), BMI ($P=0.090$), timing of abortion (early or late) ($P=0.547$). The mean age of participating women in the dexamethasone group was 25 years old while it was 26.5 years old in the placebo group. The mean gestational age in the dexamethasone group and the placebo group were 18 weeks. For the parity on admission, 5 women out of 60 in the dexamethasone group while 6 women out of 60 were primigravida in the placebo group and the remaining patients were multigravida in both groups^[17].

The current study (Table2) showed a significant statistical difference between both studied groups as

regard the induction-expulsion interval time from initiation of induction to fetus expulsion (Figure 2) ($P > 0.001$) and the length of the hospital stay (Figure 3) ($P > 0.001$). Where it was found that the mean induction to abortion interval was 10.5 hours in the dexamethasone group while it was 17.5 hours in the control group. Also, the mean stay in hospital was 16 hours in the dexamethasone group while it was 23 hours in the control group. The length of induction to abortion interval was not affected by parity or gestational age.

These results agree with those of Attia^[17] which showed a significant statistical difference between both studied groups as regard the induction-abortion interval time from initiation of induction to fetus expulsion ($P>0.018$) and the length of hospital stay ($P>0.001$). Where it was found that the mean induction to abortion interval was 11.9 hours in the dexamethasone group while it was 18 hours in the placebo group. Also, the mean stay in hospital was 16 hours in the dexamethasone group while was 24 hours in the placebo group. Also, the length of induction to abortion interval was not affected by parity or gestational age.

This result goes with other trials where dexamethasone was used in induction of labor to decrease the interval of induction of labor

Laloha *et al.*^[11] conducted a double blind randomized clinical trial on 172 participants with nulliparity, bishop score of 4 or greater, pregnancy duration in or before 40 weeks then divided into dexamethasone (case) group and control group. The case group received a single dose of 8 mg dexamethasone intravenously and the control group with placebo 2 cc of normal saline, 4 hours before induction was performed by standard protocol using oxytocin so that patient could enter active phase of labor (3 regular contractions in 10 minutes with dilatation of 3-4 cm).

Laloha *et al.*^[11] found that the interval between initiation of labor induction and onset of active phase of labor was significantly shorter in the dexamethasone group than the control group (2.87 ± 0.93 hours vs. 3.80 ± 0.93 hours), respectively ($P>0.001$). They concluded that intravenous dexamethasone reduces the time duration from the induction to the onset of active phase of labor.

Also, Elmaraghy *et al.*^[13] who conducted a study at labor ward of Ain-Shams University Maternity Hospitals on 100 nulliparous women at gestational age 38-42 weeks who were divided into 2 groups; group A (dexamethasone group) $n=50$: 8mg (2ml) amp

dexamethasone sodium phosphate was administered intramuscularly at least half an hour and maximally 6 hours before initiation of labor induction. As well as group B (control group) n=50: (2ml) of distilled water was administered intramuscularly at least half an hour and maximally 6 hours before initiation of labor induction.

El-Maraghy *et al.*^[13] study showed high significant statistical difference in time taken for induction of labor in each group where group A took 3.92 hrs and group B took 6.24 hrs ($P < 0.0001$).

There were many studies conducted on the induction of abortion using a combination of drugs to decrease the induction to abortion interval.

A study by Akkenapally^[18] was conducted by selecting randomly 200 cases attending Family Planning Out-Patient at Jyothi Maternity Center for termination of pregnancy between 14 and 20 weeks. They were divided into 2 groups; group I were given misoprostol 600 mcg inserted in the posterior fornix, followed by 400 mcg sublingually every 3 h until the abortion occurred or up to a maximum of five doses in 24 h. Group II were given mifepristone 200 mg oral dose and then after 24 h admitted and started on misoprostol 600 mcg in the posterior vaginal fornix, followed by 400 mcg sublingually until abortion or a maximum of five doses.

Akkenapally^[18] concluded that the mean induction of abortion interval in group I was 10.67 ± 3.96 h, whereas in group II it was 6.19 ± 2.70 h which was statistically significant lower with a p value >0.01 ; however, among the individual groups (multigravidae and lower gestational age >17 weeks), women had lesser induction of abortion interval.

In the current study, there was no significant statistical difference for the timing of abortion (early from 16-19 weeks and late from 20-24 weeks), 47 women were at early abortion while 23 women were at late abortion in the dexamethasone group. However, 51 women were at early and 19 women were at late abortion in the control group ($P = 0.461$).

If this data showed a big difference in both groups, it would have been thought that the induction-abortion interval may be shorter in the dexamethasone group due to that most of women were in early period of abortion (small gestational age) and not due to the effect of dexamethasone on the induction process.

This results goes with Attia^[17] where 44 women were at early abortion while 16 were at late abortion in the dexamethasone group. However, 41 women were

at early and 19 were at late abortion in the placebo group ($P = 0.547$).

In the present study, there was a significant statistical difference between both groups regarding the dose of misoprostol used (Table 2 and Figure1) $P > (0.001)$. The mean dose of misoprostol in the dexamethasone group was 800 mcg while it was 1600 mcg in the control group. Also, the dose of misoprostol was not correlated to parity and gestational age.

These results goes with Attia^[17] who concluded that the mean dose of misoprostol in the dexamethasone group was 3 doses (600 mcg); while, it was 4 doses (800 mcg) in the placebo group ($P > 0.012$) which was statistically significant. Also, for the need of second cycle of misoprostol, there was no significant statistical difference ($p = 0.491$).

This also goes with Akkenapally^[18] who concluded that the mean dose of misoprostol required in group II (1046 ± 392.71 mcg) was statistically significant lower ($p > 0.01$) compared to group I (1610 ± 511.18 mcg). However, among the individual groups multigravidae and lower gestational age (>17 weeks) women had required lesser misoprostol dose^[18].

It is concluded that mifepristone and misoprostol is now an established and highly effective and safe method for medical method of second trimester abortion. The combination of mifepristone with misoprostol significantly reduces the abortion to induction interval and have fewer side effects and complications as well as reducing the dose of misoprostol; where mifepristone is not available or affordable, misoprostol alone has also been shown to be effective, although a higher total dose is needed and efficacy is lower than for the combined regimen.

Therefore whenever possible, the combined regimen should be used and by comparing this study with the current study, it was found that the study of mifepristone was done on a small number of patients and did not mention any side effects of mifepristone and dexamethasone can be used as a safe and cost effective alternative in shortening the induction-abortion interval in medical induction of abortion rather than mifepristone which is expensive and not available in Egypt.

Moreover, for need of second cycle of misoprostol (Table2), there was no significant statistical difference between both groups ($P = 0.414$). However, it was noticed that 9 women out of 70 in the control group needed second cycle of misoprostol comparing with 6 women only in the dexamethasone group.

Also, this means that patients who received dexamethasone with misoprostol in the dexamethasone group received less doses of misoprostol and few patients of them needed second cycle of induction, so patients in the control group received more doses of misoprostol and also they were more liable for complications of misoprostol (fever and gastrointestinal upset) and prolonged hospital stay.

The current study also showed no significant statistical difference between both groups as regard fever ($P=0.149$). Also, if it was considered that fever is one of the side effects of misoprostol (7 women out of 70 women had fever in the dexamethasone group while 13 women out of 70 in the control group), this will go with that the total number of misoprostol doses used in the control group was more than that used in the dexamethasone group; this difference in doses between both groups was statistically significant. Fever was the most frequently side effect, however, this fever in all of these patients was 38°C or little higher, transient and did not require additional treatment.

Moreover, it was concluded from the current study that use of dexamethasone is not associated with decreasing the need for surgical evacuation. Where it was observed that complete abortion occurred in 63 patients in dexamethasone group and in 60 patients in control group; yet, this was not statistically significant ($P=0.439$).

This goes with the study of Attia^[17] who showed no significant statistical difference between both groups as regard the need for surgical evacuation ($P=0.76$).

Also, the study showed that there was no significant statistical difference between the two studied groups as regard the pre and post induction hemoglobin.

The current study also showed no significant statistical difference between both groups regarding blood transfusion; 2 cases in the dexamethasone group and 3 cases in the control group ($P=0.999$) as well as hysterotomy. hysterotomy; 3 cases in the dexamethasone group and 4 cases in the control group ($P=0.999$).

In contrast to the study of Attia^[17] where no cases needed blood transfusion nor hysterotomy; none of the patients needed hysterectomy.

Taking into consideration all these studies (including the current study), it appears that prescription of dexamethasone can play a role in improving the induction to abortion interval and it is cost effective as regard decreasing total dose of misoprostol used and the length of hospital stay.

CONCLUSION

As a conclusion, the administration of dexamethasone intra-venously (8 mg amp) 8 and 4 hours before the medical induction of abortion by misoprostol (400 mcg intra vaginally every 3hr) appears to be effective as regard shortening the induction-abortion interval (duration between the initiation of induction and expulsion of fetus), the length of hospital stay and decreasing the total dose of misoprostol. Its cost effective and availability are apparent benefits.

CONFLICT OF INTEREST

There are no conflicts of interests.

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