



Dosing interval between mifepristone and misoprostol in second and third trimester termination

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Received: 22 October 2018 / Accepted: 12 December 2018 / Published online: 21 December 2018
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Abstract

Objective To compare several strategies for second trimester labor induction for termination of pregnancy (TOP) using misoprostol and mifepristone and to determine which one is more effective in accelerating the time to delivery.

Method This was a retrospective study in which pregnancies that underwent second and third trimester TOP due to fetal anomalies between 2007 and 2017 were classified into a group that received misoprostol alone, a group that received mifepristone followed by misoprostol on the same day, one where misoprostol was given 1 day after mifepristone and one where the medications were administered 2 days apart. The primary outcome measure was the induction to delivery interval.

Results 481 pregnancies fulfilled the inclusion criteria. In 140 cases, mifepristone was not administered. 341 women received mifepristone prior to induction, which was administered on the day of induction in 85 cases, and 1 or 2 days prior to induction in 140 and 19 cases. Median time interval between first induction and delivery was 15.0 (IQR 10.0–24.1) h in case no mifepristone was given and 13.2 (9.7–18.2) h if mifepristone was given on the same day and 9.3 (6.6–14.9) and 10.5 (7.2–22.3) h, if mifepristone was given 1 or 2 days prior to induction. After 24 h, the proportion of terminated pregnancies in each of the four groups was 75.0, 83.5, 93.2 and 78.9%.

Conclusion A 1 day interval between mifepristone and misoprostol is more effective in second and third trimester TOP compared to other strategies in terms of reducing the induction to abortion interval.

Keywords Mifepristone · Misoprostol · Induction · Termination of pregnancy

Introduction

Termination of pregnancy (TOP) remains one of the most common procedures in obstetrics and gynaecology [1]. Sedh et al. estimated that in the period 2010–2014 the global abortion rate was 35 per 1000 women aged 15–44 years [2]. In Germany, the Statistical Office reports on about 100,000 terminations per year. The vast majority of these cases are related to social reasons and only in about 4%, termination is carried out due to a fetal defect causing severe maternal distress. These pregnancies are generally terminated in the second and third trimester. Figures from other countries indicate a similar distribution [3].

TOP in the late second and third trimester is usually done medically, predominantly with the use of misoprostol [4–6].

Several work groups have examined the optimal drug regime and corresponding length of induction [1, 6–8]. In a previous study of our group, we found an average time interval between first induction and delivery of about 16 h. In this cohort, women received 400 µg misoprostol every 4–6 h until relevant contractions were recorded [9]. The average induction time was shortened by about a third if mifepristone was given prior to induction. Others have shown a similar effect and reported that more than 90% of the women delivered within 24 h with fewer adverse side effects compared to an induction without prior mifepristone [5].

Mifepristone is a 19-nor steroid that acts as a competitive progesterone-receptor antagonist and a glucocorticoid-receptor antagonist and primes the myometrium and cervix for prostaglandin activity. This approach is based on the evidence that pre-treatment with mifepristone enhances the stimulatory effect of misoprostol on uterine muscle, resulting in increased amplitude and frequency of uterine contractions [10–12]. In general it is recommended to give mifepristone 1–2 days prior to induction. However, other

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study groups have shown that a shorter time interval between mifepristone and misoprostol may also be effective [13–15].

In this study we examine the time interval between first induction and delivery if mifepristone not given or if it is administered on the same day or 1 or 2 days prior to the first induction.

Methods

This monocentric, retrospective study consists of singleton pregnancies that were terminated by induction of labor with misoprostol between 2007 and 2017. The pregnancies were terminated on the basis of present or expected severe maternal distress due to fetal abnormalities (German criminal law §218a, second paragraph). Termination of pregnancy based on personal choice, surgical terminations, cases with a change of the drug regime during the induction, cases with previous cesarean section and induction of labor with other drugs than misoprostol was excluded from this study.

Before 2011, induction of labor was carried out only with misoprostol without the prior use of mifepristone. From 2011, every women who opted for termination of pregnancy received mifepristone prior to induction. At the beginning, we gave mifepristone 2 days prior to induction but we changed this policy due to logistic problems. We carried on with administration of mifepristone 1 day prior to induction or at the same day (3–5 h before induction). The decision was not based on any medical aspects but only on the patient's travel distance to the hospital.

Induction was carried out with 400 mg misoprostol (200 mg vaginally and 200 mg orally at the same time) repeated every 4–6 h until relevant contractions were recorded. Throughout the induction, all women stayed in hospital. If a live born neonate was expected, predominantly in pregnancies after 23 weeks' gestation, an intra-cardiac fetocide with potassium chloride was done prior to induction.

All patients were consented about the off-label-use of misoprostol and mifepristone.

In each case, maternal and pregnancy characteristics, the induction interval between first application of misoprostol and delivery were recorded into a database. Furthermore, we added to the database if and when mifepristone was given.

Some of the cases were used in our two previous studies about termination of pregnancy but none of these studies focused on the effect of the time interval between mifepristone and misoprostol [9, 16].

The ethical committee of Tübingen, Germany approved this study (530/2018BO2).

Statistical analysis

Women were classified into four groups: group 1 did not receive mifepristone, group 2 received mifepristone on the same day and in group 3 and 4, women received mifepristone 1 or 2 days prior to induction. Time interval between first induction with misoprostol and delivery (cut of the umbilical cord) was considered as main outcome parameter. Results are given as median and 25th–75th interquartile range.

Uni- and multivariate regression analysis was used to determine significant covariates that influenced the induction time.

A Chi square test was used to examine if the induction time is shorter in cases with mifepristone prior to induction compared to women without prior mifepristone.

The level of significance was set at a *p* value of 0.05.

Results

The search of the database identified 481 pregnancies. Median maternal and gestational age at the time of TOP was 33.1 years and 18.3 weeks' gestation. Further pregnancy characteristics are shown in Table 1. Table 2 summarizes the reason for termination of pregnancy. In the majority of the cases, there was a chromosomal defect.

In 140 cases, mifepristone was not administered. 341 women received mifepristone prior to induction, which was administered on the day of induction in 85 cases, and 1 or 2 days prior to induction in 140 and 19 cases, respectively.

Table 1 Summary of pregnancy characteristics

	No mifepristone	Mifepristone		
		At the day of induction	1 Day prior to induction	2 Days prior to induction
<i>n</i> (%)	140 (29.1)	85 (17.7)	237 (49.3)	19 (4.0)
Maternal age in years, median (IQR)	33.0 (28.8–38.0)	32.6 (28.6–36.2)	33.5 (29.5–37.4)	30.6 (26.5–35.0)
Gestational age in years, median (IQR)	19.0 (15.3–21.8)	19.4 (15.7–21.3)	17.7 (14.7–21.6)	17.6 (14.4–20.6)
Gravida, median (IQR)	2 (1–3)	2 (0–1)	2 (1–3)	2 (1–4)
Para, median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
BMI in kg/m ² , median (IQR)	23.9 (21.2–26.6)	24.1 (21.8–26.9)	23.8 (21.9–27.0)	25.6 (23.5–29.0)

Table 2 Indication of termination of pregnancy

Indication for termination of pregnancy	No mifepristone	Mifepristone		
		At the day of induction	1 Day prior to induction	2 Days prior to induction
Aneuploidy, <i>n</i> (%)	57 (40.7)	40 (47.1)	118 (49.8)	9 (47.4)
Cardiac defect, <i>n</i> (%)	7 (5.0)	3 (3.5)	13 (5.5)	0 (0)
Nonimmune fetal hydrops, <i>n</i> (%)	7 (5.0)	5 (5.9)	2 (0.8)	1 (5.3)
Neural tube defect, <i>n</i> (%)	14 (10.0)	10 (11.8)	14 (5.9)	0 (0)
Neuromuscular or skeletal anomaly, <i>n</i> (%)	17 (12.1)	4 (4.7)	8 (3.4)	2 (10.5)
Renal defect, <i>n</i> (%)	12 (8.6)	3 (3.5)	25 (10.5)	3 (15.8)
CNS anomaly, <i>n</i> (%)	10 (7.1)	8 (9.4)	13 (5.5)	2 (10.5)
Syndromes and other diseases, <i>n</i> (%)	16 (11.4)	12 (14.1)	44 (18.5)	2 (10.5)

Median time interval between first induction and delivery of the fetus was 15.0 (IQR 10.0–24.1) h in case no mifepristone was given and 13.2 (9.7–18.2) h if mifepristone was given on the same day and 9.3 (6.6–14.9) and 10.5 (7.2–22.3) h, if mifepristone was given 1 or 2 days prior to induction, respectively.

Uni- and multivariate linear regression were used to examine the covariates that influenced the time interval between first induction and delivery (Table 3). Significant covariates resulting in an increasing induction time interval were increasing gestational age (OR 0.146, $p < 0.0001$) and the presence of a nonimmune fetal hydrops (OR 0.095, $p < 0.024$). The only covariate that resulted in a reduction

of the induction time was the use of mifepristone prior to induction. However, only administration on the same day or 1 day prior to induction had a significant influence (on the same day OR – 0.317, $p = 0.002$; 1 day prior to induction, OR – 0.149 $p < 0.0001$).

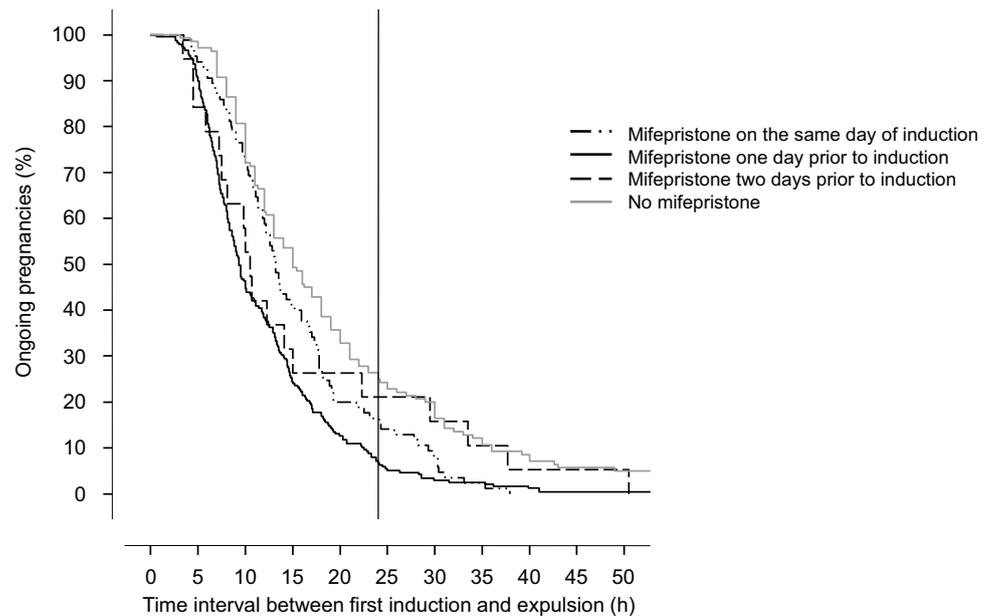
Figure 1 shows the proportion of terminated pregnancies according to time starting from first induction. 12 h after the first induction, the proportion of terminated pregnancies in each of the four groups was 33.6, 41.2, 61.6, and 57.9% respectively. After 24 h, these rates were increased to 75.0, 83.5, 93.2, and 78.9%. The proportion of terminated pregnancies after 24 h was significantly higher if mifepristone was administered 1 day prior to induction compared to the

Table 3 Uni- and multivariate regression analysis for the prediction of the time interval between first induction and delivery of the fetus

Covariate	Univariate		Multivariate	
	OR	<i>p</i>	OR	<i>p</i>
Maternal age in years	– 0.145	0.001	– 0.040	0.368
Gestational age in years	0.198	< 0.0001	0.146	0.006
Gravida in <i>n</i>	– 0.204	< 0.0001	– 0.100	0.144
Para in <i>n</i>	– 0.234	< 0.0001	– 0.128	0.062
BMI in kg/m ²	0.40	0.386		
Fetal defect				
Aneuploidy	0		0	
Cardiac defect	0.068	0.143		
Nonimmune fetal hydrops	0.164	< 0.0001	0.095	0.024
Neural tube defect	0.075	0.110		
Neuromuscular or skeletal anomaly	0.091	0.052		
Renal defect	0.006	0.903		
CNS anomalies	0.036	0.446		
Syndromes and other diseases	0.062	0.197		
Fetocide	0.130	0.004	0.047	0.380
Mifepristone administration				
No mifepristone	0		0	
Mifepristone on the same day of induction	– 0.154	0.002	– 0.149	0.002
1 Day prior to induction	– 0.348	< 0.0001	– 0.317	< 0.0001
2 Days prior to induction	0.072	0.116		

Bold values indicate a significance difference ($p < 0.05$)

Fig. 1 Proportion of ongoing pregnancies after induction of labor with misoprostol. Mifepristone was either not given or administered on the same day or 1 or 2 days prior to misoprostol



three other groups (Chi square test 1 day prior to induction vs. no mifepristone: $p < 0.0001$, vs. mifepristone on the same day $p = 0.008$, vs mifepristone 2 days prior to induction $p = 0.025$).

Discussion

Main finding of our study

In this study we have shown that mifepristone shortens the induction time until delivery but the extent depends on when mifepristone is given. If mifepristone is administered 1 day prior to induction, delivery occurs in more than 90% of the cases within 24 h after the first induction. If mifepristone is given on the same day or 2 days before induction, the effect is less pronounced.

Comparison with previous studies

Misoprostol remains the mainstay of second trimester TOP. To expedite the induction time, it was proposed to administer mifepristone prior to misoprostol [4, 8]. However, a consensus about the best time interval between the two drugs has not yet been reached. Shaw et al. summarized the body of knowledge up to 2013 [17]. Only three randomized controlled studies directly compared the induction of a policy where misoprostol is given one prior to induction with misoprostol against a 2-day interval between the two drugs. The authors found that mifepristone a day prior to misoprostol was slightly more effective than a 2 day policy (weighted average of 7.3 h vs. 6.8 h). In contrast

with these studies, we have compared several different timing strategies between mifepristone and misoprostol versus induction with misoprostol alone. We found that if mifepristone is given 1 day prior to induction, the time interval between induction and delivery was significantly shorter and the reduction was more pronounced than with any other timing strategy. A 2-day interval did not result in a shorter induction interval compared to induction with misoprostol alone. We assume that the “2 days interval” group was too small to reach significance. Administration of mifepristone on the same day as misoprostol was less effective than the non-simultaneous administration. In a more recent study, Abbas et al. compared the simultaneous administration of mifepristone and misoprostol versus a 1 day time interval between the two drugs. With the latter drug regimen, significantly more pregnancies were terminated within 24 h after the first induction (94% vs. 85%) [18]. These results are consistent with our findings. In the 2 corresponding groups of our study, 93% and 84% of the pregnancies were terminated within 24 h.

Mifepristone combined with misoprostol is one of the drugs listed as essential medicines by the WHO [19]. Its usefulness along with misoprostol in first trimester TOP and for the management of early pregnancy loss has been demonstrated by extensive studies [10]. Several professional bodies recommend its use in early TOP as well as for the purpose of cervical priming before surgical termination [7]. Moreover, deriving on the available first and second trimester data, mifepristone has been investigated against placebo in induction of labor in the third trimester and at term with promising results [20, 21]. Further research on this topic is warranted.

Limitations of our study

The main limitation of our study is its retrospective character. However, we only changed the time interval between mifepristone and misoprostol, all other aspects of the treatment (dosage and route of administration) remained the same during the study period, which allowed us to compare the timing strategies.

Conclusion

Our study has shown that TOP with mifepristone 1 day prior to misoprostol is more effective than any other timing strategy between these two drugs. This should be the preferred method for any medically induced termination of pregnancy in the second trimester.

Author contributions NP: data collection, manuscript writing and editing. JB: data collection. MH: data collection, manuscript writing and editing. HA: manuscript writing and editing. PW: manuscript writing and editing. KOK: conceptualization, project development, formal analysis, manuscript writing and editing.

Funding No funding.

Compliance with ethical standards

Conflict of interest All authors declare that there is no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This is a retrospective study that was approved by the local ethical committee (530/2018BO2).

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