DOES MISOPROSTOL FOR INDUCTION OF LABOR INCREASE THE RISK OF UTERINE RUPTURE?

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ABSTRACT

Background: Misoprostol is a synthetic prostaglandin E1 analogue which is now commonly used for induction of labor. Hyperstimulation is a complication of misoprostol that may lead to uterine rupture.
Objective: To find the association between misoprostol exposure for induction of labor with uterine rupture.
Methods: Case were all women who delivered in Sardjito and affiliate Hospitals from January 2007 to November 2012 with the diagnosis of uterine rupture. Controls were taken randomly from the same hospital. Chi square test and logistic regression model were used for statistical analysis.
Result and Discussion: There were 53 cases of uterine rupture and 199 controls. The incidence of uterine rupture was 53 over 64,244 deliveries or 0,08%. Risk of of uterine rupture associated with misoprostol exposure was 1, 09 (CI 95% 0,52-2,2), while that of oxytocin exposure was 0,80 (CI 95% 0,35-1,85). Logistic regression analysis showed that the highest risk factor associated with uterine rupture was fetal weight > 3500 (OR 3,46; 95% CI 1,48-8,56) followed by parity (OR 2,56;95% CI 1,019-6,465) and vacuum extraction (OR 2,45;95% CI 0,94-6,39).
Conclusion: There was no association between misoprostol exposure with uterine rupture. Fetal weight > 3500 gram, Parity more than 3, and vacuum extraction increased the risk of uterine rupture associated with misoprostol use.

Keywords: Misoprostol, induction of labor, uterine rupture, fetal weight, parity.

ABSTRAK

Latar belakang: Misoprostol adalah analog prostaglandin E1 sintetik yang sekarang banyak digunakan untuk induksi persalinan. Hiperstimulasi merupakan salah satu komplikasi induksi persalinan dengan misoprostol yang dapat mengakibatkan ruptur uterus .
Tujuan: Untuk mengetahui hubungan antara penggunaan misoprostol untuk induksi persalinan dengan kejadian ruptur uterus.
Metode : Kasus adalah semua ibu melahirkan di RS Sardjito dan RS afiliasi dari Januari 2007 sampai November 2012 yang mengalami ruptur uteri. Sebagai kontrol adalah ibu melahirkan di rumah sakit yang sama yang tidak mengalami ruptur uteri yang diambil secara random dengan perbandingan 1:4. *Chi square* test dan *logistic regression model* digunakan untuk analisis statistik.
Hasil dan Pembahasan : Terdapat 53 kasus ruptur uterus yang memenuhi kriteria kelayakan dan 199 kontrol. Insidensi ruptur uteri adalah 53 dari 64.244 persalinan atau 0,08%. Risiko ruptur uteri yang berhubungan dengan pemakaian misosprostol adalah 1, 09 (CI 95% 0,52-2,2), sedang yang berhubungan dengan pemakaian oksitosin adalah 0,80 (CI 95% 0,35-1,85). Analisis regresi logistik menunjukkan bahwa faktor risiko terbesar yang berhubungan dengan kejadian ruptur uteri adalah berat janin > 3500 (OR 3,46; 95% CI 1,48-8,56) disusul dengan paritas (OR 2,56;95% CI 1,019-6,465) dan ekstraksi vakum (OR 2,45;95% CI 0,94-6,39).

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Kesimpulan: Tidak ada hubungan antara pemakaian misoprostol dengan kejadian ruptur uterus, tetapi berat janin > 3500 gram, paritas lebih dari 3, dan ekstraksi vakum menaikkan risiko ruptur uteri.

Kata kunci: Misoprostol, induksi persalinan, ruptur uteri, berat janin, paritas

INTRODUCTION

Misoprostol, a prostaglandin E1 analog, was first approved by the Food and Drug Administration (FDA) for the treatment of gastric ulcers, but it is now important in obstetric practice because of its uterotonic and cervical ripening actions. It has been now used widely to induce labor in term pregnancy and also to prevent postpartum hemorrhage.[1] It is very effective for induction of labor either in premature rupture of membrane[2], postdate pregnancy[3] and pregnancy induced hypertension.[4] It has also been used to induce labor in women with a history of previous cesarean section but the risk of rupture is still controversy.[5]

Although the use of misoprostol for induction of labor has been widely recognized, but there is no consensus about the optimum dose, frequency and route of administration for its safety.[6] The recommended dose was 25 µg given not less than 3-4 hourly.[7]

Hyperstimulation is one of the side effects of misoprostol can cause uterine rupture. There are several case reports of uterine rupture in women induced with misoprostol, especially with the history of secarea section.[8]

Several studies and reviews have been conducted to assess the effectiveness and safety of misoprostol but until now there has been no research with large scale that examines incidence of uterine rupture associated with misoprostol induction. The use of misoprostol induction in pregnant women is still off label, because the data security is still lacking.[9]

The purpose of the recent stdudy was to find out wether misoprostol was assiciated with the risk of uterine rupture in women using misoprostol for induction of labor.

MATERIALS AND METHOD

Case control designed was used for the study. Data were taken from medical records for 5 years from January 2007 to November 2012 in Sardjito Hospital and 5 affiliated Hospitals located at the Province of Jogjakarta and Central Java.

Cases were all pregnant women with gestational age more than 28 weeks with uterine rupture due not to trauma. These were obtained from medical records with a diagnosis code ICD 071.1 (International Classification of Diseases and related health problems) 10th revision version for 2007). Hospitals that data have not been computerized they were gathered manually was recorded from the delivery room. Controls were those who gave birth without uterine rupture and were taken randomly from the same hospital with a ratio 1:4. Those who had rupture due to trauma were excluded.

Data were processed using SPSS version 16 using chi-square test and logistic regression models for statistical analysis.

RESULTS AND DISCUSSION

There were a total of 64,244 of deliveries during 5 years periode in the study hospitals. Fifty-three of them had uterine rupture and met the inclussion criteria (gestational age more than 28 completed weeks). Twelve from 53 cases of uterine ruptures were associated with misoprostol use. None of them had a history of cesarean section. A total of 199 deliveries were

taken as control. A total of 252 samples then used for further analysis.

There were 54 women who were induced with misoprostol (21,4%), 44 were exposed to oxytocin (17,5%), 23 to vacuum extraction (9,1%) and 53 (21 %) women had uterine rupture (Table 1).

Table 1. Characteristics of Patients

Variable	Frequency	Percent
Age (years)		
> 35	44	17.5
≤ 35	208	82.5
Parity		
> 3	26	10.3
≤ 3	226	89.7
Fetal weight (g)		
> 3500	25	9.9
≤ 3500	227	90.1
Misoprostol-induced		
Yes	54	21.4
No	198	78.6
Exposure to oxytocin		
Yes	44	17.5
No	208	82.5
Vacuum extraction		
Yes	23	9.1
No	229	90.9
Uterine Rupture		
Yes	53	21
No	199	79

The association between misoprostol and uterine rupture was the main interest to investigate, as shown on table 2. It seemed that the exposure of misoprostol did not increase the occurrence of uterine rupture. Uterine rupture is a catastrophic condition potetially leading to death both for mother and fetus if not promptly and adequately managed. The incidence of uterine rupture during 5 years period in this study was 0.08 % (8 per 10,000 deliveries). It was similar with other reports that ranged from 0.07% to 0.17%.[10] The incidence was even lower for the unscarred uterus, 0.007% (0.7 per 10,000 deliveries) but it was much more higher for the scarred uterus.[11]

Table 2. Exposure of misoprostol to uterine rupture

Variable	Rupture	No rupture	OR (CI 95%)	P value
Misoprostol Yes	12	42	1, 09 (0,52-2,26)	0,80
Misoprostol No	41	157		

The rate of uterine rupture was much higher in an attempt to do a vaginal delivery after cesarean section if misoprostol is used. One study showed that there were four out of 41 patient underwent uterine rupture.[12] Other study found that the uterine rupture rate for patients attempting vaginal birth after cesarean section was significantly higher 5.6% in those who received misoprostol, than in those who did not, 0.2%.[13]

This present study showed that induction of labor using misoprostol did not increase the rate of uterine rupture because none of our patients induced by misoprostol had a history of previous cesarean section. In addition to history of scarred uterus, doses of misoprostol might also influence the occurrence of uterine rupture. The use of 100 µg gave rise to 2 out 29 patient undergoing uterine rupture (6.89%) compared to none among 28 patients induced by Folley catheter.[14] Another study found that there were two cases out of 64 women of who had uterine rupture induced with 100 µg compared to none when induced with 50 µg.[15] As our data on the dose of misoprostol were incomplete then the effect of dose on the occurrence of uterine rupture couldn't be analyzed.

Further analysis demonstrated that fetal wight increased significantly the rate of uterine rupture, followed by vacum extraction and parity more than three although they were not statistically significant (Table 3). Oxytocin exposure and maternal age did not have any effect on the occurrence of uterine rupture.

Table 3. Bivariate analysis showing variables potential to induce uterine rupture.

No	Variables	Ruptur	No ruptur	OR (CI 95%)	p
1	Oxytocin exposure:				
	Yes	8	36	0.80 (0.35-1.85)	0.61
	No	45	163		
2	Vacuum Extraction:				
	Yes	8	15	2.18 (0.87-5.46)	0,09
	No	45	184		
3	Maternal age (years):				
	> 35	11	33	1.31 (0.61-2.82)	0.47
	≤ 35	42	166		
4	Parity				
	> 3	9	17	2.19 (0.91-5.24	0.07
	≤ 3	44	182		
5	Fetal weight				
	> 3500 gr	11	14	3,46 (1,46-8,16)	0,03
	≤ 3500 gr	42	185		

To find out variables that gave the greatest influence on the occurrence of uterine rupture, a multivariate logistic regression model was caried out. It was shown that fetal weight more than 3500 g, parity more than three and vaccum extraction were consistently related to uterine rupture. (Table 4).

Table 4. Multivariate analysis of variables potentially induce uterine rupture

Variabel	OR	CI (95%)	p
Misoprostol induction			
Yes	1.15	0,53-2,49	0,71
No	1		
Parity			
> 3	2,56	1,02-6,46	0,04
≤ 3	1		
Fetal Weight			
> 3500 gr	3,56	1,48-8,56	0,01
≤ 3500 gr	1		
Oxytocin exposure			
Yes	0,80	0,33-1,92	0,62
No	1		
Vaccum Extraction			
Yes	2,45	0,94-6,39	0,06
No	1		

The cochrane systematic review conducted by Alfirevic found that oral misoprostol was effective for induction of labor, but the data were not big enough to draw a conclusion on the safety of its use.[16] Review conducted by Homfrey and Munzozini concluded that it was not enough evidence to say that misoprostol under the tongue was safe for inducing labor. The authors suggested to do more studies with larger samples.[17]

The main risk factor found in this study was increased fetal weight more than 3,500 grams and it seemed to be clinically and statistically significant. The same result was demonstrated by Jastrow et al. who found that increased incidence of uterine rupture was influenced by increased fetuses fetal weight more than 3500 grams and much higher in fetus weighing more than 4000 grams.[18]

The present study showed that maternal age didn't increased the risk of uterine rupture as the other investigator reported.[19] Oxytocin was not asscociated with the increased risk for uterine rupture and even with hyperstimulation. This might be due to the limitted sample in the study with small dose. Higher dose had been reported to be asscoiated with maternal hyperstimulation but no rupture was encountered.[20]

The risk of getting rupture associated with the use vacuum extraction to deliver baby in this study was 2.45 (95%, 0.94-6.39). which is not statistically significant but clinically important. Five cases who received misoprostol might have ruptured before vacuum extraction was done. Vacuum extraction was claimed to be a risk factor for uterine rupture.[21] Parity more than three increased the rate of uterine rupture by 2.56 fold. This might be attributed to the thinner uterine wall as more child birth took place as proposed by Gardeil.[22]

CONCLUSSION

This study concluded that misoprostol was not asscociated with the incraesed rate of uterine rupture. On the other hand, fetal weight, parity and exposure to vacuum extraction during the second stage were dominant factors attributable to uterine rupture.

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