นิพนธ์ต้นฉบับ

Termination of second and third trimester pregnancy by misoprostol

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Objective : *To study the efficacy, side effects and adverse effects of intravaginal misoprostol for termination of second and third trimester pregnancies.*

Design : *Prospective descriptive study.*

Setting : *Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University.*

Pateints : *Fifty pregnant women in their second and third trimester with medical indications for termination of pregnancy (intrauterine fetal death in 45 cases, and medical complications in 5 cases).*

Intervention : *One tablet of 200-microgram misoprostol was applied in the posterior fornix every 12 hours, with a maximum of 4 doses. The main outcome measures were the rate of expulsion of the fetuses within 24 and 48 hours, and an average time from induction to expulsion.*

Results : *Expulsion of fetuses occurred within 24 hours in 80 percent (40 cases), within 48 hours in 92 percent (46 cases. Average time from induction to expulsion of the fetus was 14.53 hours. Side effects were minimal. No severe adverse effects occurred. No patient required a blood transfusion.*

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Conclusion : *Intravaginal misoprostol is an effective method for termination of second and third trimester pregnancies. In our study, there are minimal side effects, without any severe adverse effects.*

Key words : *Misoprostol, Termination of pregnancy, Pregnancy.*

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วัตถุประสงค์ : *เพื่อศึกษาประสิทธิภาพ อาการข้างเคียง และภาวะแทรกซ้อนของการใช้ยาไมโสพรอสตอลทางช่องคลอด เพื่อทำให้มีการสิ้นสุดของการตั้งครรภ์ในไตรมาสที่สองและสาม*

รูปแบบการวิจัย : *การวิจัยเชิงพรรณนา แบบไปข้างหน้า*

สถานที่ที่ทำการศึกษา : *ภาควิชาสูติศาสตร์-นรีเวชวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

ผู้ป่วยที่ทำการศึกษา : *สตรีตั้งครรภ์ในไตรมาสที่สองและสาม ที่มีข้อบ่งชี้ในการทำให้การตั้งครรภ์สิ้นสุดลงจำนวน 50 ราย (ทารกเสียชีวิตในครรภ์จำนวน 45 ราย และมีโรคแทรกซ้อนทางอายุรกรรมที่รุนแรงจำนวน 5 ราย)*

วิธีการศึกษา : *เหน็บยาไมโสพรอสตอลขนาด 200 ไมโครกรัม 1 เม็ดทางช่องคลอด ทุก 12 ชั่วโมง จำนวนไม่เกิน 4 ครั้ง ตัววัดที่สำคัญคืออัตราการสิ้นสุดของการตั้งครรภ์ภายใน 24 และ 48 ชั่วโมง และระยะเวลาตั้งแต่ให้ยาจนการตั้งครรภ์สิ้นสุด*

ผลการศึกษา : *การสิ้นสุดของการตั้งครรภ์เกิดขึ้นภายใน 24 และ 48 ชั่วโมงในผู้ป่วยร้อยละ 80 และ 92 ตามลำดับ และระยะเวลาเฉลี่ยตั้งแต่เริ่มให้ยาจนการตั้งครรภ์สิ้นสุด 14.53 ชั่วโมง อาการข้างเคียงที่พบไม่รุนแรง ไม่พบภาวะแทรกซ้อนรุนแรง ไม่มีผู้ป่วยที่ต้องให้เลือด*

สรุป : *การใช้ยาไมโสพรอสตอลทางช่องคลอดเป็นวิธีการที่มีประสิทธิภาพสูงในการทำให้การตั้งครรภ์สิ้นสุดลงในไตรมาสที่สองและสาม อาการข้างเคียงพบน้อย และไม่พบภาวะแทรกซ้อนรุนแรงในกลุ่มผู้ป่วยที่ทำการศึกษา*

The number of pregnant women requiring termination of their pregnancy in second and third trimester is increasing. Major medical indications include intrauterine fetal death, fetal chromosomal abnormalities, lethal fetal structural abnormalities, and life-threatening medical disorders.[1]

Currently accepted methods for termination of second and third trimester pregnancies are associated with certain disadvantages.[1] Surgical procedures, such as dilatation and evacuation or hysterotomy, are associated with a high risk of uterine and cervical injuries, blood and tissue contaminations, and also with anesthetic risks. Intra-amniotic hyperosmotic solution instillations are associated with hyperosmolar crisis, heart failure, peritonitis, septic shock, and disseminated intravascular coagulation. Systemic prostaglandins are associated with fever, diarrhea, and high cost.[2]

Recently, the use of intravaginal misoprostol, a prostaglandin E_1 analogue, was introduced for termination of second and third trimester pregnancies.[2,3,4] The efficacy of misoprostol in a Thai population had not been established. The aim of this study was to assess the efficacy, side effects and adverse effects of intravaginal misoprostol for termination of second and third trimester pregnancies in pregnant Thai women.

Materials and Methods

Pregnant women with medical indications for termination of pregnancy in the second or third trimester were recruited. The indications included intrauterine fetal death and life-threatening medical disorders. All women gave informed consent. Exclusion criteria were (1) previous uterine incision (2) systemic infections (3) asthma , and (4) history of hypersensitivity to prostaglandins. Pelvic examination was performed and Bishop scoring was assessed in all cases. One tablet of 200-mcg misoprostol (Cytotec, Searle) was inserted in the posterior fornix every 12 hours (at 0, 12, 24, 36 hours) until expulsion of the fetus occurred. Meperidine 50 mg was given intramuscularly in cases with moderate to severe pain. Vital signs were monitored every 4 hours, as well as subjective complaints of vomiting and diarrhea. No oxytocic drug was given before expulsion of the fetus. Successful treatment was defined as expulsion of the fetus within 48 hours. The study protocol was approved by the Ethical Committee of the Faculty of Medicine, Chulalongkorn University.

Results

Fifty pregnant women with medical indications for termination of pregnancy in second or third trimester were recruited. The indications included 45 cases of intrauterine fetal death, and 5 cases of life-threatening medical disorders (3 cases of SLE with renal involvement and 2 cases of rheumatic heart diseases). Demographic and obstetric data are summarized in Table 1.

The expulsion of the fetuses occurred within 24 hours in 80 percent (40 cases), within 48 hours in 92 percent (46 cases). Average Bishop score increased from 2.02 before treatment to 3.96 after 12 hours. Average time from induction to

Table 2. Results of treatment.

	Mean	SD
Number of dosages	2.00	1.43
Bishop score at 0 hour	2.02	1.90
Bishop score at 12 hours*	3.96	2.65
Average time to delivery (hours)**	14.53	8.98

* Data from 28 cases terminated after insertion of second tablet.

** Data from 46 cases terminated before 48 hours.

Table 3. Time from induction to delivery.

Time from induction to delivery	Cases	Percent
Less than 12 hours	20	40
12 - 24 hours	20	40
24 - 36 hours	5	10
36 - 48 hours	1	2
More than 48 hours	4	8

Table 4. Number of doses of misoprostol.

Number of dosages	Cases	Percent
1	22	44
2	17	34
3	6	12
4	1	2
Failure after 4 doses	4	8

expulsion of the fetus was 14.53 hours. Details are presented in Tables 2, 3 and 4.

In 46 cases where expulsion of the fetuses occurred within 48 hours, 34 cases were in the second trimester and 12 cases were in the third trimester. The mean duration between start of treatment to expulsion of fetuses were 15.15±8.97 and 12.77±9.15 hours, respectively. The difference did not reach statistical significance. Also in this group, 32 cases had initial Bishop score of less than three, 14 cases had initial scores of three or more. The mean durations between start of treatment to expulsion of fetuses were 16.25±9.38 and 10.56±6.73 hours respectively. There was a statistically

significant difference between the two groups (p=0.047).

Among 28 cases which required more than 1 dose of misoprostol, the initial Bishop scores were compared with the scores at 12 hours using a paired T-test. The mean initial Bishop scores were 1.36±1.10, and were 3.96±2.65 at 12 hours. There was a statistically significant difference between the initial score and at 12 hours (p<0.001).

Meperidine was needed to alleviate uterine pain in 20 cases (40 percent). Other side effects were rare, usually minimal, and required no treatment. Details are presented in Table 5. No severe adverse effects occurred. No patient required a blood transfusion. Curettages were done in 2 cases due to retained placental fragments.

Table 5. Side effects.

Side effects	Cases	Percent Pain
(requiring meperidine)	20	40
Nausea and vomiting	1	2
Diarrhea	0	0
Fever (More than 38.0 C)	2	4

Table 6. Details of 4 cases with failure of treatment after 48 hours.

Case No.	Age (yr)	G	P	Gestational age (weeks)	Indication	Initial Bishop score
1	27	4	2	23	FDU	1
2	30	3	2	39	FDU	0
3	35	2	1	19	FDU	0
4	19	2	1	19	RHD	3

FDU = fetal death in utero RHD = rheumatic heart disease.

Discussion

Misoprostol, a prostaglandin E1 analogue,[5] has been approved by the Food and Drug Administration for the prevention and treatment of peptic ulcer. One of its properties is that it can induce myometrial contraction.[6] Therefore, oral and intravaginal misoprostol were studied by various investigators for termination of second and third trimester pregnancies.[2,3,4] Illegal use of misoprostol as an abortifacient has been widespread in some countries, such as Brazil.[7,8,9,10]

The safety of intravaginal misoprostol in therapeutic doses for termination of pregnancy has been confirmed by several reports.[2,3,4] Use of oral and intravaginal misoprostol for induced abortion with a combined dosage of 16,800 mcg has been reported without severe adverse systemic effects.[7]

Bugalho, et al[3] reported that 200 to 800 mcg of intravaginal misoprostol given every 24 hours were effective for termination of second-trimester pregnancy. Termination of pregnancy occurred within 48 hours in 91.1 percent of the cases. No complications or significant side effects occurred, and none required blood transfusions. There was no difference in efficacy among dosages of 200, 400, 600, and 800 mcg. In 1994,[5] his group also reported that 100-mcg doses of intravaginal misoprostol given every 12 hours was effective for the termination of 72 cases of pregnancy with intrauterine fetal death. Termination of pregnancy occurred within 48 hours in all cases. No severe side effects and no complications were found.

In Jain and Mishell's study,[2] the efficacy of 200-mcg intravaginal misoprostol given every 12 hours was comparable to 20 mg intravaginal prostaglandin E2 for the termination of second trimester pregnancy. But the side effects and the costs were less than in the former group.

The results of our study are comparable with other studies.[2,3,4] Termination of pregnancy within 24 and 48 hours occurred in 80 and 92 percent of our cases, respectively, compared with 91 and 100 percent for the cases in Jain and Mishell's study.[2] Average time from induction to delivery was 14.53 hours, compared with 12 hours in Jain and Mishell's study[2] and 12.6 hours in Bugalho's study.[4]

An initial Bishop score of 3 or more was associated with a shorter duration between the start of treatment and expulsion of the fetuses, while the duration of the pregnancy was not associated. In 28 cases which required more than 1 dosage of misoprostol, the Bishop score increased an average of 2.60 after 12 hours.

Drug disintegration was a problem encountered during our study. In some cases the first tablet was found intact during the time of insertion of the second tablet. Misoprostol is commercially available as oral tablets, and is not specifically prepared for intravaginal use. Some of the vaginal characteristics, such as moisture and vaginal pH, and also the lubricants used during drug insertion, may play an important role in drug disintegration and absorption. Further studies are needed to address this problem.

In conclusion, this study showed that intravaginal misoprostol is an effective, inexpensive, and convenient method for termination of second and third trimester pregnancies.

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