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Use of Intravenous Sulprostone for the Termination of Pregnancy with Fetal Death in Second and Early Third Trimester of Pregnancy

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استخدام حقن السلبروستون الوريدي لإنهاء الحمل في حالة وفاة الجنين في الثلث الثاني وبداية الثلث الثالث من الحمل

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الملخص: الهدف: دراسة فعالية حقن السلبروستون (نالادور) لإنهاء الحمل في حالة موت الجنين في الاثلوث الثاني وبداية الاثلوث الثالث من الحمل. **الطريقة:** هذه دراسة استعادية ل 97 امرأة حامل تعرضن لوفاة الجنين بين الأسبوع 12-30 من الحمل عولجن بالزرق الوريدي بمادة مضاهية للبروستاجلاندين ، سلبروستون ، من أجل إسقاط الجنين. أجريت الدراسة في قسم النسائية والتوليد بمستشفى جامعة السلطان قابوس في سلطنة عمان. جمعت المعطيات من يناير سنة 2000 إلى بداية ديسمبر سنة 2005. تم البدء بحقن السلبروستون بالوريد بجرعة 15 مايكروجرام/ ساعة إلى أن وصلت الجرعة إلى 240 مايكروجرام/ساعة ، ووصلت الجرعة القصوى إلى 1500 مايكروجرام/يوم كما هو معمول به في القسم. كذلك تم دراسة المعطيات الديمغرافية وعمر الحمل والفترة بين التحريض والإجهاض والحاجة إلى التفريغ والأعراض الجانبية والمضاعفات. **النتائج:** من مجموع الحوامل اللواتي عولجن بالسلبروستون (97) أجهضت 90 منهن خلال 24 ساعة. كان متوسط الفترة بين التحريض والإجهاض 11.9 ± 8.0 ساعة. كان هناك أعراض جانبية قليلة واستطاعت المريضات تحمله بشكل جيد. ولو أن معظم المريضات احتجن إلى تفريغ وكشط لكن فقدان الدم كان قليلا. فقط ست مريضات احتجن إلى نقل الدم ومريضتين إلى بَضْعُ الرَّحِم. **الخلاصة:** وجدنا أن السلبروستون دواء فعال في إنهاء الحمل حين يكون الجنين ميتا في الاثلوث الثاني وبداية الاثلوث الثالث م الحمل.

مفتاح الكلمات: بروستاجلاندين ، سلبروستون ، إنهاء الحمل ، موت الجنين ، عمان.

ABSTRACT ***Objective:*** To study the efficacy of intravenous sulprostone (Nalador) for the termination of pregnancy with fetal death in second and early third trimester of pregnancy. ***Methods:*** This is a retrospective collection and analysis of data from a cohort of 97 women with fetal death between 12-30 weeks gestation treated with intravenous infusion of a prostaglandin analogue, sulprostone, to achieve expulsion of the products of conception. It was conducted in the Department of Obstetrics and Gynaecology, Sultan Qaboos University Hospital, Oman. The data collected was from January 2000 to December 2005. Sulprostone was started as an intravenous infusion of 15µgm/hr and titrated to a maximum of 240µgm/hr to a total dose of 1500µgm/day, as per the departmental protocol. The patients' demographic data, gestational age, induction-expulsion interval, the need for evacuation, side effects and complications were studied. ***Results:*** Out of the 97 women who received sulprostone, 90 aborted within 24 hours. The average induction-expulsion interval was 11.9 ± 8.0 hours. Sulprostone use was associated with few side effects and was well tolerated by patients. Although most of the patients required evacuation and curettage, the blood loss was minimal. Only six out of 97 women required blood transfusions and two patients needed hysterotomy. ***Conclusion:*** We found sulprostone an efficient drug for termination of pregnancy with fetal death in second and early third trimester of pregnancy.

Keywords: Sulprostone; Prostaglandin; Intrauterine fetal death.

Advances in Knowledge

- This is the first study from Oman that analyses use and effect of sulprostone for the termination of pregnancy with fetal death in second and early third trimester of pregnancy.
- The findings of this study confirm the safety of sulprostone for the above mentioned indication.

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Application to Patient care

- This data can be compared with other prostaglandins in recent use, like misoprostol.
- Sulprostone can be safely used for termination of pregnancy in patients with a previous caesarean section.

Termination of pregnancy with intrauterine fetal death in the second and third trimester has always posed a challenge to the obstetrician. Various surgical and medical methods have been used for this purpose. Sulprostone (PGE2 analogue) and misoprostol (PGE1 analogue) are the most widely used prostaglandins for termination of pregnancy. Sulprostone has been the only drug used for termination of pregnancy in our institute since the year 1995.

Most studies used intramuscular sulprostone with or without intravenous sulprostone.[1] A review of the literature shows only a few studies using intravenous sulprostone alone. We undertook this study to find out the safety and efficacy of intravenous sulprostone in cases of termination of pregnancies with second and early third trimester fetal deaths

METHODS

This was an observational cohort study with retrospective data collection and analysis conducted in the Department of Obstetrics and Gynaecology, Sultan Qaboos University Hospital, Muscat, Oman. The data collected was between January 2000 and December 2005. All ninety seven (97) women with a gestational age ranging from 12 to 30 weeks and fetal death, confirmed by ultrasound, were included in this study. Six women with medical complications like hypertension, cardiovascular disease and bronchial asthma were excluded. All 97 women who received sulprostone were included in the analysis. These patients were admitted to the Gynaecology Ward and intravenous sulprostone was started as per the departmental protocol, after confirming normal full blood count and serum electrolytes. Written consent was obtained from all women. None of the patients received cervical priming prior to sulprostone infusion.

Sulprostone is a 16-phenoxy derivative of methylsulphonylamid prostaglandin E2. One ampoule contains 500µgm of active sulprostone in 7.45 mg dried form. The known side effects are nausea, vomiting and diarrhoea. The departmental protocol for use of sulprostone was as follows: the infusion is prepared by adding 500µgm sulprostone to 50 ml of normal saline and the infusion is started via a syringe pump at 1.5 ml/hr (15µgm/hr). The rate is doubled every hour to a maximum of 240µgm/hr and a total dose of 1500 µgm over 24 hours. Medical records were reviewed regarding each patient's age, parity, any previous cesarean section, gestational age, induction-expulsion interval, blood loss, need for analgesia, evacuation, side effects and complications. The induction-expulsion time interval was taken as the primary end point and the others as secondary end points.

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences), Version 10 computer software. A p value <0.05 was considered to be statistically significant. The chi square test was used to test the association of categorised variables; the t-test and ANOVA (Analysis of variance between groups) test were used to test the significance of the difference in induction abortion interval between different groups.

RESULTS

During the six-year period from January 2000 to December 2005, 97 women had induction with sulprostone for fetal death in the second and early third trimester of pregnany. Figure 1 shows the age distribution of the study group. The age ranged from 18 to 42 years with a mean of 28.6 ± 6.0 years.

Eighty-five women were between 12 to 22 weeks of gestation and 12 were at more than 22 weeks. Most of our patients were Omani nationals (86.7%) and the rest were from various other countries.

The primary end point induction-expulsion time interval, was calculated from the start of the sulprostone until the expulsion of the fetus. The average time required for patients of less than 22 weeks gestation was 10.9 ± 8.6 hours and those at more than 22 weeks was 12.0 ± 8.0 hours. This difference was also not found to be statistically significant (p = 0.649). A total of 90 patients expelled the fetus within 24 hours. The longest time taken was 62 hours 25 minutes and the shortest was 1 hour 25 minutes with a mean of 11.9 ± 8.0 hours. Two (2.1%) patients needed repeat doses

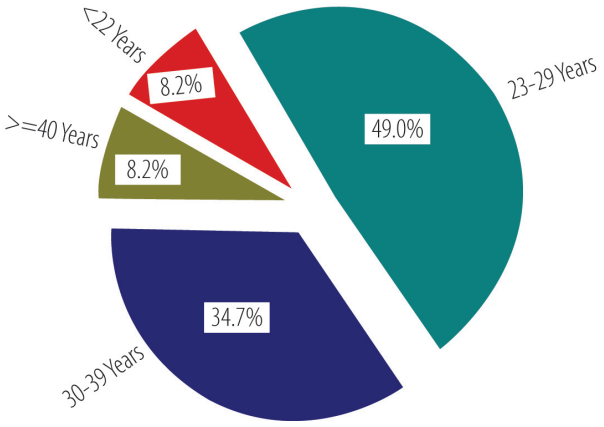

Figure 1: ***Age distribution***

after the initial dose of 1500 µgm.

Twenty-seven women (27.8 %) were nulliparous and five (5.2%) were of parity 8 or more. The highest parity in this study group was 12**.** Figure 2 shows the relationship between parity and the time taken for expulsion. Although nullipara showed the shortest induction-expulsion time and para 8 and above showed the maximum time, this difference was not found to be significant (p = 0.821)

The rate of complete expulsion, defined as the simultaneous passage of the fetus and placenta was 22.7%. Seventy-three women (75.3%) needed evacuation. No relationship was found between complete expulsion rate and age (p = 0.372) or parity (p = 0.643) of the women.

There were 11 (11.3%) patients with previous caesarean sections, including two patients with two previous and one with three previous caesareans. Sixty-seven percent of patients with previous caesarean sections needed evacuation whereas 78% of the group without a previous caesarean needed evacuation; this difference was not found to be statistically significant (p = 0.447). None of the patients with a previous caesarean section had a scar rupture or blood transfusion, whereas five patients without a previous caesarean required a blood transfusion.

The requirement of analgesia in the study group was as follows: 47% of patients required analgesia with pethidine, 42% received no analgesia and the others received diclofenac or midazolam.

The incidence of gastrointestinal side effects was limited and clinically acceptable. Systemic side effects requiring discontinuation of therapy with sulprostone were not observed in this study. Only 3 patients (3.06%) had itching and redness at the intravenous cannula site.

Two women in this group had a hysterotomy. The first patient was a Gravida 2 Para 1 with a previous caesarean section at 14 + weeks gestation and confirmed fetal death. She had a large cervical fibroid (10 cm diameter). She received 2 courses of sulprostone without any response hence a hysterotomy was done.

The second patient was a Gravida 4 Para 2 at 16 weeks gestation, confirmed fetal death, with two previous caesarean sections. After 8 hours of sulprostone infusion the patient complained of severe abdominal pain. A laparotomy and hysterotomy was done. The previous scar was found to be intact.

DISCUSSION

Various medical methods have been described for the expulsion of the fetus in pregnancies with intrauterine fetal deaths: prostaglandin (PG) analogues (misoprostol, gemeprost or sulprostone) [2] with or without antiprogesterone priming (mifepristone). In our institution the PGE2 analogue, sulprostone, is used as a continuous infusion for management of second and early third trimester fetal deaths.

Intravenous, intramuscular and extra amniotic use of sulprostone has been described in the literature. Intramuscular sulprostone has been effectively used for preoperative cervical dilatation in the first trimester with minor side effects, mainly abdominal pain. Antiprogestin mifepristone given orally prior to intramuscular sulprostone facilitates termination of second trimester pregnancies by sulprostone alone without added side effects.[1] Our study did not use mifepristone. Intramuscular sulprostone is no longer recommended for medical abortion due to its association with myocardial infarction.[1]

Kunz et al. in his study of 160 women on second trimester pregnancy termination with intravenous (IV) sulprostone found a mean induction-expulsion interval of 16h 56min. Our primary end point, i.e. induction-expulsion time interval, was 11.9 ± 8.0 hours. Haemorrhage occurred in 6% of our patients compared to 7.5% in Kunz's study.[3]

Jain and Mishell defined 'complete expulsion' as expulsion of both the fetus and the placenta without operative assistance.[4] The rate of complete expulsion in our study was 22.7 % compared to 32% in Jain and Mishell's study. The risk of haemorrhage is 4 in 1,000 at more than 20 weeks.[5] We had five patients who required blood transfusion as a result of excessive bleed-

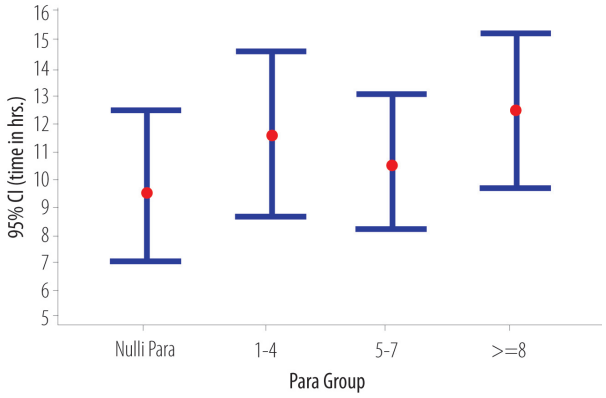

Figure 2: ***Induction-abortion/delivery interval in different parity group***

ing with prolonged retention of the placenta.

Caring for pregnancy with a previous uterine scar is always a challenge. No matter what method is used for termination, there is a greater risk of uterine rupture in these patients than in those women without a scar. Prostaglandins are still a reasonably safe and predictable method of termination of pregnancy even in cases of previous caesarean section. Women should be appropriately counselled about the risks and consequences and supervised closely in labour.[6] Shapira et al., in their study of second trimester abortion by extra-amniotic prostaglandin infusion in 282 women including 35 cases with previous caesarean section, did not observe any case of uterine rupture.[7] There are few case reports of uterine rupture after use of sulprostone with fetal deaths in second and third trimester in a scarred uterus.[6, 8] Out of the 12 women with previous caesarean sections in our study, there was no case of uterine rupture.

Side effects including nausea, vomiting and diarrhea are characteristics of prostaglandin administration and are due to prostaglandin's stimulatory effect on the gastrointestinal tract. Gastrointestinal side effects were minimal in our study. Only 3% patients had itching and redness at the cannula site, which, however, did not warrant a discontinuation of the therapy.

Cardiovascular disease, liver/kidney disease and bronchial asthma are contraindications for the use of sulprostone as suggested by the manufacturer. Cardiac arrests have been reported with bolus dose of IV sulprostone of 30µgm.[9]

Gemund et al. have reported the use of continuous low-dose sulprostone intravenous for pregnancy termination in 30 women with severe preeclampsia and eclampsia.[10] This study, including two patients with a severe deterioration of pulmonary function and one maternal death after induction, does not permit definitive conclusions regarding safety in such patients. Patients with hypertension, heart disease and bronchial asthma were not included in our study.

CONCLUSION

Our study showed that intravenous use of sulprostone was both safe and effective in the termination of pregnancy with fetal death in second and early third trimester of pregnancy; however it requires continuous intravenous access and close monitoring of maternal vital signs.

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