Management of Anembryonic Pregnancy Loss: An Observational Study

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Background: This study was undertaken to determine if expectant management with a longer waiting period is an effective and safe option for women with anembryonic pregnancy.

Methods: Women with an ultrasound diagnosis of anembryonic pregnancy were offered the option of expectant management with a 3-week waiting period or surgical evacuation according to their preference.

Results: A total of 121 women with anembryonic pregnancies participated in the study; 45 of them elected expectant management. The overall success rate was 83.3% in the expectant group and 97.3% in the surgical group. No significant complications were noted in either group.

Conclusion: Expectant management with a 3-week waiting period is an efficacious and safe option with a low risk of infection and hemorrhage. However, it is difficult to predict the exact time period before spontaneous abortion. [*J Chin Med Assoc* 2010;73(3):150–155]

Key Words: abortion, anembryonic pregnancy, expectant management, uterine curettage

Introduction

Pregnancy loss is a common obstetric complication and affects > 30% of conception.[1] The majority of these losses occur in the 1st trimester, including spontaneous abortion, anembryonic gestation and embryonic or fetal death.[2] The prevalence of early pregnancy failure was 2.8% in a study involving 17,810 women at 10–13 weeks' gestation, and anembryonic pregnancies accounted for 37.5% of the pregnancies lost.[3] Loss before the development of an embryo is more likely to be associated with genetic abnormalities than those later in gestation,[4] and imparts a considerable influence on recurring risk in subsequent pregnancies.

Anembryonic pregnancy is defined as a gestational sac (GS) containing no fetal pole with a mean diameter ≥ 15 mm, or a GS < 15 mm not showing any growth in 7 days.[5,6] Dilatation and curettage has been the primary treatment option for early pregnancy loss in many countries since it was first introduced into clinical practice in the 1930s.[7] However, the risks of uterine evacuation, including sepsis, hemorrhage and anesthesia-related complications, have always been of concern to patients. In 1995, Nielsen and Hahlin conducted a small randomized study of expectant and surgical management of early nonviable pregnancies, which suggested that the outcomes were similar, including complications and the need for a second or emergent curettage.[8] Additional studies have supported the role of expectant management as a treatment option in early pregnancy loss; however, reported success rates have ranged widely from 25% to 76%.[9,10]

According to Luise et al's study in 2002, expectant management in patients with anembryonic pregnancies had a less favorable success rate compared to patients with incomplete abortion or embryonic fetal death.[10] Patients with failure of expectant management eventually required surgical evacuation to remove the products of conception. In contrast, based on a randomized trial conducted by Wieringa-de Waard et al, up to 40% of surgeries can be avoided by a waiting period of 7 days, which could be offered to well-informed women.[6] Patients were willing to accept the waiting period with adequate counseling and help.

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The success rate of surgical treatment has been superior to that of expectant management in both reviewed literature and clinical practice. However, expectant management can be justified as an alternative treatment option if the success rate can reach 80%. The purpose of this study was to determine whether or not expectant management with a 3-week waiting period is an effective and safe option for women with anembryonic pregnancy, and if outcomes differ from those of surgical evacuation.

Methods

Subjects

Women presenting to the outpatient clinic and emergency department of Hsinchu Cathay General Hospital (CGH) in Taiwan between July 1, 2008 and June 30, 2009 with anembryonic pregnancy were included in the study. The trial was approved by the Institutional Review Board of Hsinchu CGH (number CT 9813), and all of the subjects gave informed consent.

Diagnosis of anembryonic pregnancy was made when, as seen on transvaginal ultrasound, the mean diameter of the GS was ≥ 15 mm without a visible embryo or the GS was < 15 mm and with no growth in 7 days.[5,6] All of the sonographic scans were performed by obstetricians in Hsinchu CGH using a 6.5-MHz transducer (Aloka Co. Ltd., Tokyo Japan). Endometrial thickness was measured in the sagittal plane from the interface of the endometrium and myometrium across the uterine cavity.

The inclusion criteria were hemodynamic stability, temperature < 37.5°C in the past 24 hours, no history of current serious systemic disease, ≥ 20 years of age, singleton pregnancy, no intrauterine device present, and no contraindication to the use of prostaglandin and ergonovine. Patients were excluded if they were experiencing severe pain, fever or heavy bleeding requiring immediate surgery. Patients could opt out of the study at any time on request.

Protocol

Patients who met the inclusion criteria were informed of the risks and benefits of expectant management and surgical treatment. Patients then elected expectant or surgical management. The patients in the expectant management group were seen in the outpatient clinic on days 14 and 21 for reevaluation before the products of conception were expelled. Once the tissue was passed, patients returned to the outpatient clinic in 7 days and ultrasonography was performed to determine if there was any retained tissue in the uterine cavity. If there was evidence of retained tissue or if the endometrial lining was ≥ 15 mm, then a 200-μg tablet of misoprostol was given 3 times a day orally for the next 3 days (maximum dose, 1,800 μg). Patients with retained tissue were considered a treatment failure.

If the expulsion was still incomplete after taking misoprostol or if expulsion failed to occur after 21 days of expectant management, then surgical uterine evacuation was performed. Patients had 1 scheduled follow-up visit in 7 days, and ultrasonography was performed to assess the endometrial lining.

The symptoms and signs during the waiting period of expectant management before spontaneous loss were thoroughly explained to the patients in the expectant group, who also received a contact phone number in case further care or information was necessary. Emergent admission and surgery were arranged if necessary.

Outcome measures

The primary outcome measure was complete expulsion of the products of conception within 21 days after the diagnosis of anembryonic pregnancy was made. Treatment success was defined as endometrial thickness < 15 mm in the follow-up visit after spontaneous abortion or surgical curettage had been performed. For women with incomplete expulsion or endometrial thickness ≥ 15 mm in both groups, we also determined whether or not additional management with medication improved the overall success rate. The secondary outcomes assessed were the number of patients requiring a second curettage and immediate surgery due to bleeding > 500 mL, and the incidence of pelvic inflammatory disease within 4 weeks after evacuation of uterus and pain severity.

Patients were offered nonsteroidal anti-inflammatory drugs for pain relief. If the pain was unbearable, they were required to return to the clinic, where narcotic or opiate medications were provided if necessary.

Infection was diagnosed if patients presented with lower abdominal pain or leukorrhea, and 1 of any of the following criteria was met: temperature > 38°C, white blood cell count ≥ 11,000/mm^3, and administration of antibiotics within 4 weeks of expulsion, whether by expectant management or surgical evacuation.

Statistical analysis

Statistical analysis was performed using SPSS version 13 (SPSS Inc., Chicago, IL, USA). Student's *t* test, Fisher's exact test and χ^2 test were used to analyze the differences in patient characteristics and outcomes. A p value < 0.05 was considered to indicate statistical significance.

Results

A total of 121 eligible women who presented to Hsinchu CGH between July 1, 2008 and June 30, 2009 were enrolled into this study (Figure 1). There were no significant differences in patient characteristics between the expectant and surgical management groups except for the size of the GS (Table 1). The mean size of the GS in the expectant management group was 2.7 cm, versus 2.1 cm in the surgical management group.

Of the enrolled women, 76 underwent surgical evacuation and 45 elected to have expectant management. The overall success rate of expectant management was 83.3%, compared with 97.3% for surgical evacuation.

Of the 45 women in the expectant management group, 8 withdrew from the study and were excluded from the analysis. Five of these 8 women dropped out on day 7, and the other 3 dropped out on days 6, 9 and 16. All 8 patients subsequently received uterine curettage. Also, 1 patient did not return after being allocated to the expectant management group, so she was excluded as well. In the 36 women who were included for analysis, 22 experienced spontaneous loss within 14 days of diagnosis and 8 within 21 days. Of the remaining 6 patients, 2 expelled the products of conception on days 3 and 4, respectively, but an endometrial thickness ≥ 15 mm was revealed by ultrasound when they returned to the clinic. These 2 patients experienced vaginal bleeding for more than 14 days and were administered oral misoprostol, after which the bleeding stopped within 7 days. In the last 4 patients, ultrasound revealed visible GS on day 21. These 4 women only experienced minimal vaginal spotting; they underwent surgical evacuation and were classified as treatment failure of expectant management.

In the surgical management group, 2 patients required a second curettage due to persistent vaginal bleeding for > 21 days (Table 2) despite the administration

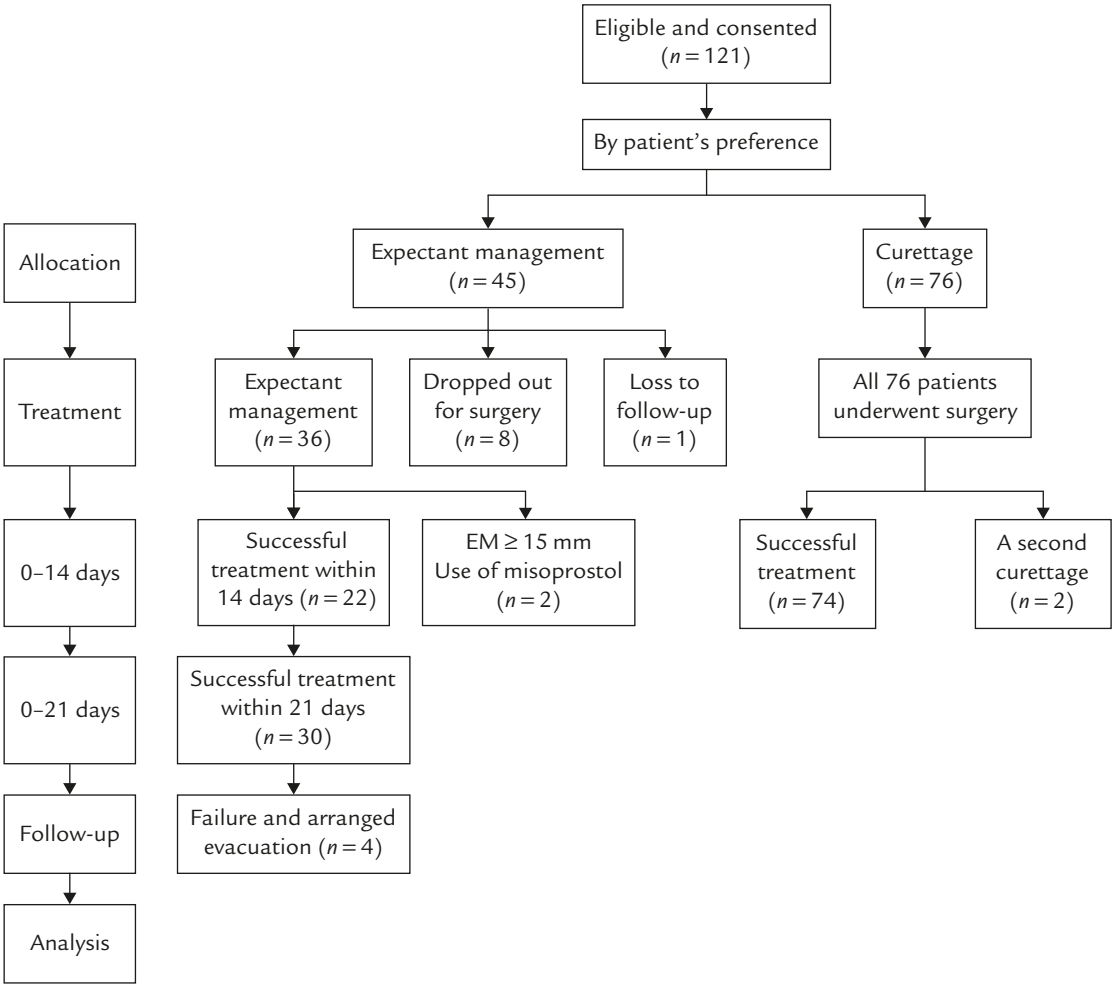

Figure 1. The allocation of patients based on their preferences. EM = endometrial thickness.

Table 1. Patients' characteristics*

	Surgical management ($n=76$)	Expectant management ($n=36$)	$p^{\dagger}$
Age (yr)	32.7 ± 0.5 (26–39)	32.9 ± 0.48 (24–42)	NS
Parity			
0	43 (56.5)	22 (59.4)	NS
≥ 1	15 (40.6)	33 (43.5)	NS
Previous miscarriage	21 (27.6)	3 (8.1)	NS
GS size (cm)	2.1 ± 0.1	2.7 ± 0.2	0.02
Time to return to clinic (d)	6.7 ± 0.3	8.2 ± 0.5	NS
Successful treatment			
EM < 15 mm	74 (97.3)	30 (83.3)	0.013
Vaginal bleeding present	23 (30.2)	17 (47.2)	NS
EM thickness at follow-up (mm)	8 ± 2	6 ± 5	NS

**Data presented as mean ± standard deviation (range) or n (%) or mean ± standard deviation; †success rate was analyzed by Fisher's exact test and differences in patient characteristics analyzed by χ^2 test. GS = gestational sac; EM = endometrial thickness; NS = not significant.*

Table 2. Outcomes*

	Surgical management ($n=76$)	Expectant management ($n=36$)
Successful treatment with EM < 15 mm	74 (97.3)	30 (83.3)
Treatment with medication due to EM ≥ 15 mm after abortion	2 (2)	2 (6.2)
Successful treatment with medication†	4 (97.3)	32 (88.85)
Second curettage	2 (2)	0
Emergent curettage	0	0
Failure of expulsion	–	4 (11.1)
Complications		
Hemorrhage > 500 mL	0	0
Pain requiring opiates or narcotics	0	0
Infection within 4 wk of abortion	5 (6.5)	1 (2.7)
Uterine perforation	0	–
Bleeding status before treatment	23 (30.2)	17 (47.2)
Time to spontaneous abortion (d)‡	–	9.15 ± 2.9 (2–21)

**Data presented as n (%) or mean ± standard deviation (range); †success rate was assessed after patients with incomplete abortion or EM ≥ 15 mm took misoprostol; ‡from time of diagnosis of anembryonic pregnancy. EM = endometrial thickness.*

of misoprostol. Pathological reports revealed residual gestational tissue, and bleeding only stopped on days 5 and 6 after the second operation.

The presence of vaginal bleeding before treatment had no significant effect on the success of expulsion; 47.2% (17/36) of patients in the expectant management group had vaginal spotting, but the success rate reached 83.3% (30/36; $p=0.662$, Fisher's exact test). Three patients with failed expectant management had intermittent vaginal bleeding, but the tissue was not expelled within the 3-week waiting period.

No woman in either group required blood transfusion. No patient in the expectant management group required more than nonsteroidal anti-inflammatory drugs for pain relief, and none of them underwent emergent curettage because of intolerable pain or heavy bleeding. Five patients in the surgical group experienced lower abdominal pain after uterine curettage and received antibiotic treatment. The incidences of pelvic inflammatory disease were 6.5% and 2.5% in the surgical and expectant management groups, respectively.

Discussion

The causes of pregnancy loss vary with gestational age. The expression "blighted ovum" has been replaced

with anembryonic or preembryonic pregnancy loss, defined in terms of developmental biology, and possibly occurs when there are genetic problems.[11] Recently, the management of early pregnancy loss has changed from a surgical approach to conservative treatment. The rate of spontaneous expulsion varies depending on the type of miscarriage; with anembryonic pregnancy, a lower success rate may be due to an intact sac and closed cervix.[12] Rates as low as 24.7% have been reported by Jurkovic et al,[9] whereas Nielsen and Hahlin reported the success rates of expectant management to be 91% for incomplete miscarriage, 76% for missed abortion, and 66% for anembryonic pregnancy.[8] In our study, the success rate by day 14 was 61.1%, consistent with the study of Nielsen and Hahlin. Our success rate reached 83.3% by day 21, indicating that a longer waiting period can reduce the need for surgical evacuation.[6]

Successful outcome in the current study was defined as an endometrial thickness < 15 mm without retained products of conception after natural expulsion or surgical evacuation. If we were to include the 2 patients with endometrial thickness ≥ 15 mm who took misoprostol (after which their bleeding stopped) and the patient with endometrial thickness < 15 mm within 10 days in the expectant group, the overall success rate would be 88.8%. In that case, successful treatment was considered as no need for uterine curettage. According to the systematic review of 18 studies by Geyman et al,[13] expectant management for 1st trimester pregnancy loss has an overall success rate of 93%. The surgical success rate reported by Creinin et al[14] was 98%, which is consistent with our finding.

In Zhang et al's study of 1st trimester pregnancy failure including anembryonic gestation, embryonic or fetal death, incomplete abortion or inevitable spontaneous abortion, misoprostol 800 mg vaginally was given to the women on day 1 and a second dose on day 3 if expulsion was incomplete. By day 3, 71% had experienced complete expulsion; by day 8, the success rate had reached 84%.[15] Immediate administration of medication saves waiting time and its success rate is similar to that of expectant management.

In our study, we used a cut-off value for endometrial thickness of < 15 mm to define treatment success. However, there is evidence to suggest that 15 mm is too stringent.[10,15–17] Patients with endometrial thickness 15–30 mm after misoprostol treatment usually expel the products of conception completely without complications.[17] Creinin et al analyzed 80 women with early pregnancy loss who were treated with misoprostol, and suggested that there was no obvious relationship between increasing endometrial thickness and the need for surgical intervention as none of their patients with endometrial thickness ≥ 15 mm required surgical intervention.[17] Based on literature reports, it would appear that it was not necessary to use misoprostol in our 2 patients with endometrial thickness ≥ 15 mm as spontaneous resolution would likely have occurred. However, the medication may reduce the length of vaginal bleeding. In our surgical management group, 2 patients underwent a second curettage due to prolonged bleeding. When we compared the intrauterine sonographic pattern of these 4 women (2 in the expectant management group; 2 in the surgical management group) with endometrial thickness ≥ 15 mm, the echogenicity was obviously more heterogeneous in the surgical management patients. Bleeding persisted despite the administration of misoprostol. Operative reintervention is indicated in symptomatic abnormal endometrial content.[18]

In this study, mean GS was 2.7 cm and 2.1 cm in the expectant and surgical management groups, respectively. Although GS size was a significantly different factor in the patient characteristics of the 2 groups, the group allocation in the study was based on the requests of the patients rather than on randomization. The 4 patients who had expectant management failure had GS > 3 cm in diameter (3.5, 3.28, 3.54 and 3.1 cm). The presence of a GS that is deformed or flattened, with largest diameter > 5 cm without a detectable embryo, is often an indicator of miscarriage.[19] Due to our small sample size, we could not determine if GS > 3 cm is associated with a higher failure rate of spontaneous expulsion.

There was no increase in complications such as infection or bleeding in the expectant management group, or in the 4 patients with treatment failure during the 3-week waiting period. The 8 patients who dropped out of the expectant management group did so because they lost patience and were tired of waiting. With thorough explanation and adequate consultation, the waiting time for tissue expulsion might be extended on their preference. Retained tissue in the endocervical canal with pain and bleeding sometimes occur in patients managed expectantly, but this did not occur in our study group. In most cases, the tissue can be removed with ring forceps without further treatment.[17] We assumed that anembryonic pregnancy often presents with an empty sac, or only a minimal fetal pole, which allows the small amount of tissue to pass smoothly.

In conclusion, our results indicate that expectant management with a 3-week waiting period is a safe and effective option with a low risk of infection and hemorrhage for the management of anembryonic pregnancy in early gestation. The success rate is higher than previously reported, though lower than for surgical

curettage. Adequate counseling and help are important for women who choose expectant management of pregnancy loss as it is difficult to predict the exact time when expulsion may occur and so the optimal follow-up time is not yet standardized.

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