Long-term reproductive outcome subsequent to medical versus surgical treatment for miscarriage

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BACKGROUND: When compared with the conventional surgical evacuation for the treatment of miscarriage, medical evacuation has been largely accepted as an effective and safe management. However, there is a lack of data on the long-term reproductive outcome of these two treatment modalities, which is crucial in patient counselling. The current study evaluates and compares the long-term fertility and pregnancy outcome following these two treatments.

METHODS: A cohort of 604 women enrolled in a previous randomized controlled trial comparing medical and surgical evacuation for miscarriage were followed up prospectively by telephone interview at a median of 6 (range 4–9) years using a structured questionnaire. RESULTS: A total of 423 women were contacted and four declined to participate (response rate 69.4%). Of these, 261 women (131 medical and 130 surgical evacuations) had attempted to become pregnant since the miscarriage. There were no differences in their baseline characteristics including age, reproductive and contraceptive history. The natural conception rates were the same (97.7%, P = 0.99) and the cumulative pregnancy rates were similar between groups, being 60 and 80% at 12 and 24 months respectively. The median time-to-pregnancy was 8 months in both groups (P = 0.97) and the subsequent live birth rates (85.2 versus 88.2%, P = 0.72) resulting from the immediate pregnancy following previous treatment were similar. CONCLUSIONS: The long-term conception rate and pregnancy outcome are not different following medical or surgical evacuation for miscarriage. Women should be reassured that their long-term fertility potential will not be compromised after medical treatment.

Key words: medical evacuation/miscarriage/reproductive outcome

Introduction

Surgical evacuation of retained product of conception (ERPC) remains the commonest treatment for miscarriage. This policy is based on an assumption that any retained tissue increases the risks of infection and haemorrhage. Over the last decade, nonsurgical approaches have been advocated as an alternative, including diagnosis of complete miscarriage by ultrasound followed by expectant management or medical evacuation of the uterus (Henshaw et al., 1993; Chung et al., 1994; Nielsen and Hahlin, 1995; Hurd et al., 1997; Bagratee et al., 2004). A more conservative approach has been shown to be effective and also carries a lower incidence of both short-term and medium-term complications compared to ERPC in randomized controlled trials (Chipchase and James, 1997; Chung et al., 1999; Wieringa-de Waard et al., 2002a; Coughlin et al., 2004).

Women have also expressed high acceptance and satisfaction towards conservative management without substantial adverse psychological impact (Sahin et al., 2001; Lee et al., 2001; Wieringa-de Waard et al., 2002b; Ngoc et al., 2004). Medical evacuation may also offer economic benefits from the reduction in the number of operations (Hughes et al., 1996; Graziosi et al., 2004). Although most of the recent studies have been focused on the efficacy of various regimens and routes of administration of medical treatment (Pang et al., 2001; Gronlund et al., 2002; Tang et al., 2003; Phupong et al., 2004), little has been reported on the long-term fertility and pregnancy outcomes following these conservative treatment alternatives.

Infertility following miscarriage could be the consequence of tubal damage from infection or intrauterine adhesion either from surgical treatment or secondary to infection. Although concerns had been raised about the infective risks of nonsurgical management (Jurkovic, 1998), published data suggested that medical evacuation resulted in similar or reduced rate of pelvic infection following miscarriage (Chipchase and James, 1997). Hysteroscopic examinations at 6 months post-abortion revealed a low rate of intrauterine adhesions in subjects managed with ERPC but none in those managed with medical evacuation (Tam et al., 2002).

Hence, a non-surgical approach to the management of miscarriage appears to offer the advantage of minimizing unnecessary surgical interventions while maintaining low rates of morbidity from miscarriage. Fertility outcome following conservative management of miscarriage has only been addressed by a few studies of relatively small sample sizes and short
duration of follow-up (Ben Baruch et al., 1991; Blohm et al., 1997; Graziosi et al., 2005). As the subsequent long-term fertility is an important concern in counselling women regarding the choice of management for miscarriage, more data in this area are needed.

Materials and methods

Women who enrolled previously in a randomized controlled trial (Chung et al., 1999) comparing medical and surgical evacuation for miscarriage were followed up prospectively by telephone interview at a median (range) of 6 (4–9) years. A structured questionnaire was used to conduct the telephone interview on the reproductive history following the treatment of previous miscarriages. Details on the desire to become pregnant, contraceptive history, history of infertility, assisted reproductive procedure used to achieve pregnancy, and the outcome of subsequent pregnancy immediately after the index miscarriage were obtained in a telephone interview. This study was approved by the institutional review board.

The medical evacuation misoprostol protocol used to manage miscarriage has been previously described (Chung et al., 1999). Women who were diagnosed with incomplete miscarriage [area of echogenic shadows on transvaginal ultrasound scan (TVS) transverse plane >5 cm², or that of sagittal plane >6 cm²] or missed abortion (intact gestational sac on TVS) were randomized to either medical evacuation with misoprostol or immediate ERPC. In the medical evacuation arm, patients were given misoprostol 400 μg orally every 4 h to a total dose of 1200 μg. TVS was repeated on the following day. Those with an empty uterus (area of echogenic shadows on TVS transverse and sagittal planes ≤5 and ≤6 cm² respectively) after misoprostol treatment were discharged from hospital while those with incomplete evacuation underwent ERPC. Out of the 635 women entered into the randomization, 604 (95.1%) received the assigned treatment. The reasons for deviation from the intention to treat were explained in the previous publication.

From the original cohort, 423 could be contacted but four women declined interview with a response rate of 69.4%. The baseline characteristics of the cohorts available and not available for follow-up were similar in the number of previous live births, termination of pregnancies and miscarriages except that the cohorts available were older (31 versus 33 years; \( P = 0.01 \)). Four patients in the medical evacuation group and six patients in the surgical evacuation group were excluded from analysis because of previous miscarriage, being molar pregnancy, known history of infertility prior to the previous miscarriage, or sterilization during the last miscarriage (Figure 1). A total of 261 women among the responders (61.7%) reported that they had attempted to become pregnant after treatment of the index miscarriages.

The baseline characteristics, previous reproductive history, contraceptive methods and natural conception rate were compared using Mann–Whitney U-test, \( \chi^2 \) and Fisher’s exact test where appropriate by using SPSS 11.0 (SPSS Inc., Chicago, IL, USA). The cumulative pregnancy rates over time were calculated for both groups by using Kaplan–Meier survival analysis and compared using log-rank test (GraphPad Prism™ 4.0; GraphPad Software, Inc. San Diego, USA). The outcome measures were dichotomous as either ‘pregnant’ or ‘not pregnant’ achieved by natural conception over the defined period. The starting point for the calculations was the date of the treatment if the couple did not use any contraception after the miscarriage or the date of cessation of contraceptive methods if the couple practised contraception. The endpoint was the date of the first positive pregnancy or the date 8 months before the delivery of a term pregnancy. For those

Figure 1. Follow-up of patients randomized to medical or surgical evacuation of the retained products of conception.
women who failed to become pregnant by natural conception, the endpoint was the date of the telephone interview. The time-to-pregnancy was calculated from the time the couple attempted to conceive till the endpoint. If pregnancy was obtained by any aid of infertility treatment, the woman was censored from the analysis at the date the treatment began.

Results

Baseline characteristics of the 261 subjects available for analysis and who desired further pregnancy are presented in Table I. A total of 131 were managed by medical evacuation and 130 by immediate ERPC in the index miscarriage. There were no significant differences in the age, numbers of previous live births, termination of pregnancies, miscarriages and methods of contraception used between the two treatment arms (Table I).

The natural conception rates were the same in both groups following the previous treatments for miscarriage (97.7%; P = 0.99). There was no significant difference in the subsequent live birth rate in the immediate pregnancy following previous treatment between the two groups (85.2 versus 88.2%; P = 0.72). The median time-to-pregnancy (interquartile ranges) was 8 months in both medical and surgical groups respectively (not significantly different; P = 0.97) (Table I). One woman in each arm suffered infertility and required ovulation induction to achieve pregnancy.

The cumulative pregnancy rate by natural conception for each group is shown in Figure 2. Women treated by medical evacuation had a fertility rate similar to those treated by standard surgical evacuation (P = 0.92, log-rank test). The cumulative pregnancy rates in both groups at first and second years were ∼60 and ∼80%. With the surgical evacuation as the reference, the hazard ratio for medical evacuation is 0.98 (95% CI 0.76–1.29). A post hoc power analysis shows that the sample size can detect 13 and 12% difference in the pregnancy rate at the first and second years respectively with 80% power at a 0.05 significance level.

Discussion

Previously, research in this area has been confined to short- and intermediate-term complications while very little has been reported on the long-term implications for fertility. To our knowledge, our current study is the only sizeable one in the literature which addresses the issue of fertility from a previous randomized controlled trial. We observed that the long-term fertility and pregnancy outcomes were similar in women managed either by medical or surgical evacuation of miscarriage.

In a previous publication, we examined the occurrence of intrauterine adhesion following the two treatment protocols as a surrogate indicator to reflect the likelihood of long-term fertility problems (Tam et al., 2002). The prevalence of de novo adhesions was much lower than previously reported. This would imply that adverse effects on fecundity in both conservative and surgical evacuations, if any, are minimal. Previous studies which compared fertility after either conservative or surgical management were limited by small sample size. One study included only 14 women who indicated they wanted to become pregnant in one treatment group (Blohm et al., 1997). Another was a follow-up of a non-randomized observational study in which the entry criterion was empty uterus on ultrasound scan, hence not relevant to those with incomplete miscarriage or missed abortion managed with a conservative approach (Ben Baruch et al., 1991). Furthermore, the latter only had 35 cases in the conservative arm. Furthermore, the

### Table I. Baseline demographic parameters and the natural conception rates of the cohorts previously randomized into medical or surgical evacuation

<table>
<thead>
<tr>
<th></th>
<th>Medical evacuation (n = 131)</th>
<th>Surgical evacuation (n = 130)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30 (25–33)</td>
<td>30 (26–33)</td>
<td>0.76</td>
</tr>
<tr>
<td>1</td>
<td>66 (50.4%)</td>
<td>60 (46.2%)</td>
<td>0.64</td>
</tr>
<tr>
<td>≥2</td>
<td>45 (34.4%)</td>
<td>52 (40.0%)</td>
<td></td>
</tr>
<tr>
<td>Number of previous terminations of pregnancies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>91 (69.5%)</td>
<td>96 (73.8%)</td>
<td>0.73</td>
</tr>
<tr>
<td>1</td>
<td>29 (22.1%)</td>
<td>25 (19.2%)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>11 (8.4%)</td>
<td>9 (6.9%)</td>
<td></td>
</tr>
<tr>
<td>Number of previous miscarriages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>89 (67.9%)</td>
<td>90 (69.2%)</td>
<td>0.91</td>
</tr>
<tr>
<td>1</td>
<td>33 (25.2%)</td>
<td>30 (23.1%)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>9 (6.9%)</td>
<td>10 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>Previous treatment complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine perforation</td>
<td>0</td>
<td>2 (1.5%)</td>
<td>0.24*</td>
</tr>
<tr>
<td>PID</td>
<td>4 (3.1%)</td>
<td>2 (1.5%)</td>
<td>0.68*</td>
</tr>
<tr>
<td>Contraception used</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Condom</td>
<td>51 (38.9%)</td>
<td>55 (42.3%)</td>
<td>0.27</td>
</tr>
<tr>
<td>OC pills</td>
<td>3 (2.3%)</td>
<td>1 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Injectable</td>
<td>1 (0.8%)</td>
<td>6 (4.6%)</td>
<td></td>
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<tr>
<td>Safety period or coitus interruptus</td>
<td></td>
<td>1 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Natural conceptions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live birth</td>
<td>128 (97.7%)</td>
<td>127 (97.7%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>109 (85.2%)</td>
<td>112 (88.2%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>17 (13.3%)</td>
<td>14 (11.0%)</td>
<td></td>
</tr>
<tr>
<td>Time-to-pregnancy (months)</td>
<td>8 (4–18)</td>
<td>8 (3–18)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Data are shown in median (interquartile range) or n (%).

*Analysis by Fisher’s exact test.
proportion who attempted to conceive was not clear. The small size in both studies is an obvious limitation in detecting any real difference in the subsequent fertility rate between the two treatment approaches. Recently, Graziosi et al. (2005) reported a cohort of 126 subjects and showed a similar fertility rate after either conservative or surgical treatment for previous miscarriages.

Our present data showed that the median time interval time-to-pregnancy was 8 months in both medically and surgically treated cohorts. The live birth rates and miscarriage rates were also similar between the two groups. However, the time-to-pregnancy seems slightly longer than expected for a normal population with a cumulative natural conception rate after 1 year of 60% in both groups. This could be explained by several reasons.

Firstly, the cohort does not represent a normal population and may have lower fecundity. More than 30% of the women had two or more miscarriages and 30% also had a previous termination of pregnancy. In a recent study which evaluate previous aberrant reproductive outcome and fecundity, time-to-pregnancy doubled after one previous miscarriage compared to that after a previous live birth, and the cumulative pregnancy rate at 12 months was reduced from 86 to 76% after a miscarriage (Hassan and Killick, 2005). This suggests a potential reduction of fecundity after one previous miscarriage irrespective of the treatment received.

Any reproductive data based on recall may be subjected to error and the number of miscarriages may have been under-reported (Wilcox and Horney, 1984; Harlow and Linet, 1989; Kristensen and Irgens, 2000). Since our study groups consisted of an a priori group of women with a high rate of miscarriage, we would expect a higher subsequent miscarriage rate as suggested in the literature (Ben Baruch et al., 1991). Surprisingly, we found a lower rate of miscarriage. The time-to-pregnancy could have been overestimated if some women failed to recall an immediate miscarriage, remembering only a live birth after the previous treatment. Recall bias on the contraceptive history may also introduce error to the calculation of time-to-pregnancy. Time of cessation of contraception may not have been recalled accurately and methods such as coitus interruptus and abstinence are usually poorly documented.

Lastly, only 70% of the cohort were available for the follow-up and the non-responders could have had different fertility and reproductive outcomes. Nonetheless, the previous reproductive history appears similar between the responders and non-responders. Despite the response rate and potential recall bias in the present study, there does not appear to be an adverse impact on fecundity following a non-surgical approach to management compared to surgical evacuation. These findings offer useful information for counselling on the safety and pregnancy rate following medical evacuation of miscarriage.

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References


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