

# Incidence of pregnancy after expectant, medical, or surgical management of spontaneous first trimester miscarriage: long term follow-up of miscarriage treatment (MIST) randomised controlled trial

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## ABSTRACT

**Objectives** To compare fertility rates after the three methods of managing early miscarriage in women recruited to the MIST (miscarriage treatment) randomised controlled trial.

**Setting** Early pregnancy clinics of acute hospitals in the south west region of England.

**Participants** 1199 women who had had an early miscarriage (<13 weeks) confirmed by scan.

**Intervention** Expectant, medical, or surgical management.

**Main outcome measures** Self reported pregnancy rates and live birth rates.

**Results** Of 1199 women recruited to the trial, 1128 consented to follow-up. Of these, 762 women replied giving pregnancy details (68% response rate). Respondents were representative of the trial participants. The live birth rate five years after the index miscarriage was similar in the three management groups: 177/224 (79%, 95% confidence interval 73% to 84%) in the expectant management group, 181/230 (79%, 73% to 84%) in the medical group, and 192/235 (82%, 76% to 86%) in the surgical group. There was also no significant difference according to previous birth history. Older women and those with previous miscarriages were significantly less likely to subsequently give birth.

**Conclusion** Method of miscarriage management does not affect subsequent pregnancy rates with around four in five women giving birth within five years of the index miscarriage. Women can be reassured that long term fertility concerns need not affect their choice of miscarriage management.

**Trial registration** National Research Register N0467011677/N0467073587.

## INTRODUCTION

For decades the standard treatment of women who experienced an early miscarriage was evacuation of retained products of conception.<sup>1</sup> This was increasingly questioned,<sup>2-4</sup> and now women are usually

offered expectant (watch and wait, no active intervention)<sup>5,6</sup> and medical<sup>7,8</sup> management as well. Trials have suggested that all three methods are probably equivalent in terms of gynaecological infection,<sup>9-13</sup> including the largest trial, which recruited around 1200 women (the miscarriage treatment (MIST) trial).<sup>14</sup>

Little published evidence, however, has assessed the effect of management method on subsequent fertility—a key issue for women and those responsible for their care. One small trial found no significant difference in subsequent fertility rates up to 24 months after an index miscarriage.<sup>15</sup> We examined subsequent fertility rates in women randomised to the three arms of the larger MIST trial. Our primary aim was to establish if the management method for early miscarriage affects subsequent fertility. We also assessed the effects of age, previous miscarriage, and previous birth history.

## METHODS

The methods of the MIST trial are described in detail elsewhere.<sup>14</sup> Briefly, the trial recruited women who had had an early (<13 weeks' gestation) miscarriage between May 1997 and December 2001 from early pregnancy assessment clinics in the south west of England. They were randomly allocated to surgical evacuation of retained products of conception, medical treatment with mifepristone or misoprostol, or both, or expectant management. The clinical and economic results of the trial are reported elsewhere,<sup>14,16</sup> as are women's experiences.<sup>17</sup>

A preliminary survey involving the general practitioners of 99 of the original participants was undertaken to assess ease of contacting women. This achieved a response rate of 79%. Subsequently, in 2005-7, women who completed the original trial and their general practitioners were sent a postal questionnaire; the only exclusions were women who opted out of any follow-up or for whom the original general practitioner advised against follow-up. The two items of primary interest were time to next pregnancy and time to next

**Table 1** | Comparison of respondents and non-respondents to follow-up survey (using data collected as part of original MIST trial protocol). Figures are numbers (percentages) unless stated otherwise

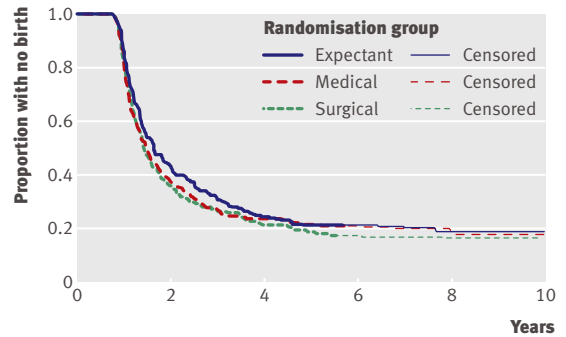
Comparative factor	Respondents	Non-respondents	P value
<b>Randomisation group:</b>			
Expectant	247 (32.4)	147 (34.1)	0.71
Medical	252 (33.1)	145 (33.6)	
Surgical	263 (34.5)	139 (32.3)	
<b>Year entered trial:</b>			
1997	83 (10.9)	46 (10.7)	0.18
1998	210 (27.6)	146 (33.9)	
1999	206 (27.0)	114 (26.5)	
2000	143 (18.8)	68 (15.8)	
2001	120 (15.7)	57 (13.2)	
Mean (SD) age at recruitment (years)	31.2 (6.1)	30.1 (6.7)	
Vaginal bleeding at recruitment	650 (85.4)	360 (83.5)	0.38
Abdominal pain at recruitment	388 (51.1)	243 (56.5)	0.07
Mean (SD) haemoglobin concentration at recruitment (g/l)	132 (9.5)	131 (10)	0.13
Any previous pregnancy loss	269 (35.4)	157 (36.8)	0.65
Any ERPC*	284 (37.3)	156 (36.2)	0.71

\*Evacuation of retained products of conception during management of index miscarriage, irrespective of actual randomised allocation.

live birth. When questionnaire packs were returned “addressee unknown,” we used the Office for National Statistics tracing services to identify the woman’s current health authority information. Health authorities were then requested to forward a pack to her general practitioner for subsequent forwarding. The mailing period extended over two years because of the time delay in obtaining tracing authorisation from all four countries in the United Kingdom. Women’s general practitioners were also asked for details of subsequent pregnancies; women’s replies were used if there were discrepancies between the two.

The questionnaire was sent with a consent form, covering letter, and freepost envelope for return. We estimated from published studies<sup>18-20</sup> that the MIST trial cohort would give 80% power to detect a hazard ratio of about 0.7 in fertility rates between any two of the management methods.

To assess representativeness, we compared respondents and non-respondents (including those not consenting to follow-up) using either  $\chi^2$  test or Student’s *t* test. Kaplan-Meier curves were constructed and log rank tests used to compare fertility rates for the following possible predictors: management method (expectant, medical, surgical); any previous birth after 24 weeks’ gestation (yes, no); previous miscarriages (0, 1, 2,  $\geq 3$ ); and age at recruitment to the MIST trial (<25, 25-29, 30-34, 35-39,  $\geq 40$ ). Significant ( $P < 0.05$ ) predictors were included in a proportional hazards multivariate model. Separate analyses were undertaken for fertility (not shown) and for live births. Quoted denominators vary slightly because of occasional non-response to individual questions. Sensitivity analyses considered how the results might be affected by extreme assumptions about the non-respondents.



**Fig 1** | Time (years) to live birth after index miscarriage classified by type of randomly allocated management method (expectant, medical, surgical)

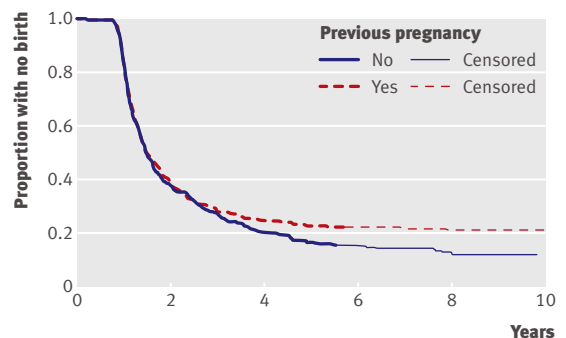
**RESULTS**

Of the 1199 women recruited to the original trial, we sent questionnaires to 1128 women and their GPs. For the 71 remaining we had no consent from the patient or her original general practitioner for such follow-up. Questionnaires providing subsequent pregnancy details were returned for 762 women (68% response rate), from the woman herself, her general practitioner, or both.

With data recorded as part of the original MIST trial protocol, table 1 compares respondents to this follow-up survey with non-respondents (including the 71 not sent a questionnaire as well as those not returning questionnaires). The respondents were broadly representative of the MIST trial population, with no significant differences between respondents and non-respondents.

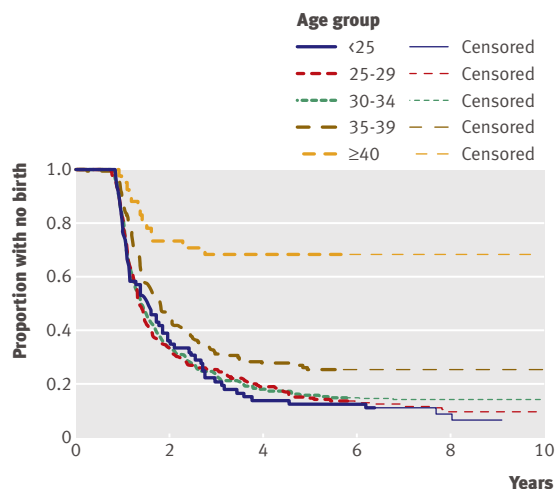
Among the survey respondents, 634/758 (84%, 95% confidence interval 81% to 86%) reported a subsequent pregnancy since the index miscarriage, with 565/689 (82%, 79% to 85%) having a live birth. Time to subsequently giving birth was similar in the three randomised groups (fig 1;  $P = 0.41$ ). Five years after the index miscarriage 177/224 (79%, 73% to 84%) of those who had been randomised to expectant management had given birth, compared with 181/230 (79%, 73% to 84%) in the medical group and 192/235 (82%, 76% to 86%) in the surgical group.

Having had one or more previous pregnancies before the index miscarriage did not significantly



**Fig 2** | Time (years) to live birth after index miscarriage classified by previous pregnancy (yes/no)

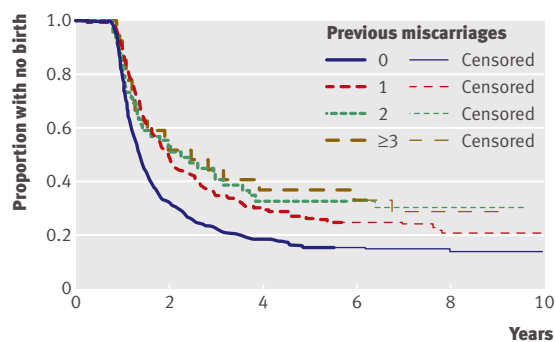
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**Fig 3 | Time (years) to live birth after index miscarriage classified by maternal age**

predict time to giving birth (fig 2;  $P=0.10$ ). Time to subsequent birth, however, was predicted by maternal age (fig 3;  $P<0.001$ ) and having had a previous miscarriage (fig 4;  $P<0.001$ ). Proportional hazards regression confirmed that both age and previous miscarriages were significantly predictive, even when adjusted for each other (table 2). Five years after the index miscarriage, 378/447 (85%) of those women with no previous miscarriage had given birth; the corresponding figures for 1, 2, and  $\geq 3$  previous miscarriages were 122/166 (74%), 33/49 (67%), and 14/24 (58%), respectively. Analysis of time to first pregnancy produced similar findings to that of first birth (results not shown).

The reported results relate only to survey respondents. To illustrate extreme sensitivity analysis scenarios, if none of the non-respondents had given birth within five years of the index miscarriage then the overall percentage having such a birth would reduce from 79.8% to 49.1%; conversely if all the non-respondents had given birth the figure would increase to 87.6%. In both cases there would still be no significant differences between management groups. Significant differences would arise only if the relative birth rate for non-respondents compared with respondents was different within the management groups.



**Fig 4 | Time (years) to live birth after index miscarriage classified by previous miscarriages (0, 1, 2,  $\geq 3$ )**

**DISCUSSION**

In this large study based on a randomised trial we found that the method of management of miscarriage did not affect subsequent fertility, with around 80% of women having a live birth within five years of the index miscarriage. This rate was somewhat lower than that reported in a previous trial that randomised women to expectant or surgical management.<sup>15</sup> Blohm et al surveyed 127 women (28 excluded for various reasons) two to three years after the index miscarriage and obtained an 89% response rate. There was a non-significant difference in subsequent fertility rates up to 24 months after the index miscarriage of about 4% in favour of expectant compared with surgical management.

Previous cohort studies have found subsequent pregnancy rates of about 70%, but over different time scales (undefined,<sup>18</sup> 18 months,<sup>19</sup> five years<sup>20</sup>). The only trial found a 75% rate at 12 months and a 90% rate at 24 months.<sup>15</sup> The rate in our study of about 60% at two years and 80% at five years is comparable but will have been influenced downwards by those respondents (included in our analysis) who did not want to conceive again after their miscarriage. It is likely, however, that our figure of four in five women eventually conceiving is representative of those women included in the original trial as the live birth curve flattens after about six years; women might find this high success rate reassuring in the initial stages after a miscarriage. Our respondents were similar to trial participants in terms of age, previous pregnancy loss, miscarriage type, clinical symptoms, surgical intervention, and management method. It is conceivable that one management method might cause very early future losses that this type of questionnaire study might not detect, but this seems unlikely, given that women would be sensitised to a future pregnancy, have access to the wide availability of pregnancy tests, and would have recorded such losses on the questionnaire.

The low birth rate we observed in older women is not surprising because fertility reduces naturally with age, and some older women would probably not have

**Table 2 | Proportional hazards regression for time to first birth**

Predictor	Hazard ratio (95% CI)	P value
<b>Age group:</b>		
<25	1.00*	
25-29	0.98 (0.74 to 1.31)	<0.001
30-34	0.96 (0.73 to 1.27)	
35-39	0.69 (0.50 to 0.94)	
$\geq 40$	0.21 (0.12 to 0.38)	
<b>Previous miscarriages:</b>		
0	1.00*	0.006
1	0.76 (0.62 to 0.93)	
2	0.68 (0.48 to 0.97)	
$\geq 3$	0.63 (0.40 to 1.01)	

\*Reference category.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

All three of the methods of management of early miscarriage currently offered to women in the UK and elsewhere are probably equivalent in terms of gynaecological infection

Little published evidence has assessed the effect of management method on subsequent fertility—a key issue for women and those who care for them

## WHAT THIS STUDY ADDS

Type of management method does not affect subsequent fertility, with around 80% of women having a live birth within five years of the index miscarriage

planned the index pregnancy nor perhaps want to conceive again. Our results confirm that women experiencing three or more miscarriages might have problems subsequently giving birth and thus need to be investigated for a recurrent cause.<sup>21</sup>

Women can be reassured that after miscarriage their chance of a subsequent live birth is high, irrespective of management method. This information should complement the information that they might want to receive<sup>17</sup> to enable them to choose which management method is personally preferable, bearing in mind the clinical<sup>14</sup> and economic<sup>16</sup> differences.

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**Competing interests:** None declared.

**Ethical approval:** Ethical approval was given by South West MREC in December 2001: MREC/01/6/90.

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