

## Sporadic miscarriage

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# 1 Sporadic miscarriage: evidence to provide effective care

2

3 Arri Coomarasamy, M.D.<sup>1</sup>, Ioannis D Gallos, M.D.<sup>1\*</sup>, Argyro Papadopoulou, M.B., Ch.B.<sup>1</sup>, Rima K4 Dhillon-Smith, Ph.D.<sup>1</sup>, Maya Al-Memar, Ph.D.<sup>2</sup>, Jane Brewin, B.Sc.<sup>3</sup>, Ole B Christiansen, Ph.D.<sup>4</sup>, Mary D5 Stephenson M.D.<sup>5</sup>, Olufemi T Oladapo, M.D.<sup>6</sup>, Chandrika N Wijeyaratne, M.D.<sup>7</sup>, Rachel Small, R.G.N.<sup>8</sup>,6 Phillip R Bennett, Ph.D.<sup>2</sup>, Lesley Regan, M.D.<sup>2</sup>, Mariëtte Goddijn, Ph.D.<sup>9</sup>, Adam J Devall, Ph.D.<sup>1</sup>, Tom7 Bourne, Ph.D.<sup>2,10</sup>, Jan J Brosens, Ph.D.<sup>11,12</sup>, and Siobhan Quenby, M.D.<sup>11,12</sup>8 1. Tommy's National Centre for Miscarriage Research, Institute of Metabolism and Systems  
9 Research, University of Birmingham, UK

10 2. Tommy's National Centre for Miscarriage Research, Imperial College London, UK

11 3. Tommy's Charity, Laurence Pountney Hill, London, UK

12 4. Centre for Recurrent Pregnancy Loss of Western Denmark, Department of Obstetrics and  
13 Gynaecology, Aalborg University Hospital, Aalborg, Denmark14 5. University of Illinois Recurrent Pregnancy Loss Program, Department of Obstetrics and  
15 Gynecology, University of Illinois at Chicago, Chicago, USA16 6. UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and  
17 Research Training in Human Reproduction (HRP), Department of Sexual and Reproductive Health  
18 and Research, World Health Organization, Geneva, Switzerland

19 7. Department of Reproductive Medicine, University of Colombo, Sri Lanka

20 8. Birmingham Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust,  
21 Birmingham, UK

22 9. Center for Reproductive Medicine, Amsterdam UMC, University of Amsterdam, The Netherlands

23 10. KU Leuven, Department of Development and Regeneration, Leuven, Belgium

24 11. Division of Biomedical Sciences, Warwick Medical School, University of Warwick, UK

25 12. Tommy's National Centre for Miscarriage Research, University Hospitals Coventry &  
26 Warwickshire NHS Trust, Coventry, UK27 \* Correspondence to: Dr Ioannis Gallos; Institute of Metabolism and Systems Research, College of  
28 Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK29 Email: [i.d.gallos@bham.ac.uk](mailto:i.d.gallos@bham.ac.uk)

30 Tel: +44(121) 371 8202

31

**32 Summary**

33 The physical and psychological impact of miscarriage is commonly underappreciated. The journey  
34 from diagnosis of miscarriage, through clinical management, to supportive aftercare can be  
35 challenging for women, their partners and care-givers. Diagnostic challenges can lead to delayed or  
36 ineffective care and increased anxiety. Inaccurate diagnosis of a miscarriage can result in the  
37 unintended termination of a wanted pregnancy. Uncertainty about the therapeutic effects of  
38 interventions can lead to suboptimal care, with variations across facilities and countries.

39 We have developed recommendations for practice from a literature review, appraisal of guidelines  
40 and expert group discussions. The recommendations are grouped into three categories: diagnosis of  
41 miscarriage, prevention of miscarriage in women with early pregnancy bleeding and management of  
42 miscarriage.

43 We recommend that every country reports annual aggregate miscarriage data, similarly to the  
44 reporting of stillbirth. Early pregnancy services need to focus on providing an effective ultrasound  
45 service, as this is central to the diagnosis of miscarriage, and be able to provide expectant  
46 miscarriage management, medical management with mifepristone and misoprostol, and surgical  
47 management with manual vacuum aspiration. Women with the dual risk factors of early pregnancy  
48 bleeding and a history of previous miscarriage can be recommended vaginal micronized  
49 progesterone to improve the prospects of live birth. We urge health funders and providers to invest  
50 in early pregnancy care, with specific focus on training for clinical nurse specialists and doctors to  
51 deliver comprehensive miscarriage care within the setting of dedicated early pregnancy units.

52 Keywords: miscarriage, treatment, tests, literature review, models of care

53

**Key messages***Miscarriage diagnosis*

Accurate diagnosis of miscarriage relies on high quality ultrasound scanning and use of validated diagnostic algorithms. An empty gestation sac with a mean sac diameter of  $\geq 25$  mm, or an embryo with a crown rump length of  $\geq 7$  mm with no visible heart activity on transvaginal ultrasonography, is considered to have sufficient accuracy for the diagnosis of miscarriage to justify miscarriage management.

*Prevention of miscarriage in women with early pregnancy bleeding*

There is high quality evidence that vaginal micronized progesterone increases live birth rates in women with early pregnancy bleeding and a history of miscarriage. There is a 5% absolute rate increase in live births with progesterone, when compared with placebo, in women with bleeding and one or more previous miscarriages (RR 1.09; 95% CI, 1.03-1.15), and a 15% absolute rate increase in live births in women with bleeding and three or more previous miscarriages (RR 1.28; 95% CI, 1.08 to 1.51).

*Miscarriage management*

Surgical management with vacuum suction aspiration after cervical preparation is ranked first amongst six competing strategies for completing a missed miscarriage. Amongst medical management strategies, a combination of mifepristone and misoprostol is more effective than misoprostol alone in completing a missed miscarriage. Expectant management is an effective approach for women with incomplete miscarriage. Women should be presented with the available evidence and be free to choose the miscarriage management approach that suits their needs and preferences.

*Organisation and delivery of miscarriage care*

Miscarriage care, delivered by clinical nurse specialists and medical staff specifically trained in early pregnancy care, can be organised and delivered within self-contained early pregnancy units (EPUs). EPUs are effective and cost-efficient.

54

55

**56 Introduction**

57 There are uncertainties about the best approaches to diagnose a miscarriage, prevent a miscarriage  
58 in women with early pregnancy bleeding, manage women with a confirmed miscarriage, and  
59 optimally organise and deliver emergency miscarriage care.

60 Pain and bleeding in early pregnancy are distressing to women. Women who experience these  
61 symptoms are anxious about the fate of their pregnancy, and want to know the risk of a miscarriage  
62 at that moment, and the availability of any treatment that can be offered to reduce their risk. A  
63 miscarriage can also occur without any pain or bleeding. Such a loss, called a missed miscarriage, is  
64 diagnosed by ultrasonography.<sup>1</sup>

65 Healthcare providers strive to avoid diagnostic errors that may have serious consequences.<sup>2,3</sup> A  
66 falsely positive diagnosis of miscarriage can result in the unintentional termination of a viable and  
67 wanted pregnancy. Concerns about inaccuracies in miscarriage diagnosis resulted in urgent revisions  
68 to the UK National Institute for Health and Care Excellence (NICE) recommendations in 2012.<sup>4</sup> In an  
69 effort to tackle the diagnostic challenge, healthcare providers often resort to arranging repeated  
70 visits and investigations for women. A clear diagnostic pathway can help reduce the anxiety to  
71 women by reducing the period of uncertainty. It can also result in a more effective and cost-efficient  
72 early pregnancy service.

73 There are uncertainties about the most effective and safe methods for managing a miscarriage. Each  
74 method carries the potential for complications, such as unplanned surgery or blood transfusion.

75 Emergency miscarriage care may be provided by generalists or specialists, and be offered in  
76 emergency care departments or dedicated early pregnancy units (EPUs). There are uncertainties  
77 about the optimal ways to organise and deliver care.

78 To facilitate evidence-based care, we have developed recommendations for practice from a  
79 literature review, appraisal of existing guidelines, and expert group discussions. The  
80 recommendations are grouped into three categories: 1) diagnosis of miscarriage, 2) prevention of  
81 miscarriage in women with early pregnancy bleeding, and 3) clinical management of a confirmed  
82 miscarriage. We conclude with a proposal for organising and delivering emergency miscarriage care  
83 and a call to action for improved care and high quality research in specific areas.

84 **Box 1:** Methods for literature searches

The recommendations are based on a review of the current literature, appraisal of professional body guidelines and expert group discussions.

*Literature reviews:* We searched the Cochrane Database of Systematic Reviews and MEDLINE (inception until 9 Jan 2020) for systematic reviews specifying or reporting any miscarriage outcome. Any review published before January 2019 was updated with a targeted literature search. Six reviews focussed on the prevention of miscarriage in women with bleeding<sup>5-10</sup> and 12 on the management of miscarriage<sup>11-22</sup> We reported results for miscarriage and live birth separately.

*Review of professional body guidelines:* We reviewed the latest international guidance on the diagnosis, prevention and management of miscarriage, including the 2019 NICE guideline on the management of ectopic pregnancy and miscarriage,<sup>23</sup> the European Society of Human Reproduction and Embryology (ESHRE) guideline on the management of recurrent pregnancy loss,<sup>24</sup> and the American College of Obstetricians and Gynecologists guideline on early pregnancy loss.<sup>25</sup>

*Expert group meetings:* The evidence from the reviews and guidelines was considered by an international group of experts, over the course of several meetings, to formulate the recommendations presented in this article. Agreements were reached through consensus.

85

## 86 **Diagnosis of miscarriage**

87 The risk of miscarriage varies by the presenting clinical symptoms and signs (Table 1). For example,  
88 the presence of a small amount of bleeding in early pregnancy is not associated with an increase in  
89 the risk of miscarriage, whilst heavy bleeding is associated with a substantial risk of miscarriage of  
90 28.8% (Table 1). However, the presence of nausea and vomiting, which can be marker of healthy  
91 levels of pregnancy hormones, is associated with a lower risk of miscarriage (9.7%) (Table 1). The  
92 probability of miscarriage with certain ultrasound features is so high that these findings can be  
93 considered to have sufficient accuracy to justify miscarriage management (Table 1). Serum  
94 progesterone concentrations can provide additional information on the viability of a pregnancy  
95 (Table 1).

96 Whilst risk prediction can provide helpful information, the diagnosis of miscarriage requires  
97 transvaginal ultrasonography. However, a systematic review found much variation in the ultrasound  
98 criteria used and there was significant uncertainty in the diagnostic accuracy, as shown by the large  
99 confidence intervals around sensitivity and specificity estimates.<sup>26,27</sup> There was no uniform  
100 agreement over what criteria should be used to make a diagnosis of miscarriage.<sup>26</sup> For example, the  
101 American College of Radiology (ACR) considered the presence of an empty gestation sac with mean  
102 sac diameter (MSD)  $\geq 16$  mm or an embryo of crown-rump length (CRL)  $\geq 5$  mm with no heartbeat to  
103 be diagnostic of a miscarriage.<sup>28</sup> On the other hand, the Royal College of Obstetricians and  
104 Gynaecologists (RCOG) in the UK used cut-off values for MSD of  $\geq 20$  mm and a CRL of  $\geq 6$  mm.<sup>29</sup> The  
105 diagnostic uncertainties meant there was a risk of initiating treatment erroneously, resulting in the  
106 potential termination of a wanted pregnancy.

107

108 **Table 1.** Accuracy of symptoms, signs and test results for the diagnosis of miscarriage

	Number of participants (studies)	Sensitivity (%)	Specificity (%)	Likelihood ratio (95% CI)		Probability of miscarriage (95% CI)*	
				For positive result	For negative result	Positive test result	Negative test result
<b>Symptoms and Signs</b>							
<b>Nausea and vomiting</b>	9964 (9)	42.5	30.1	0.6	1.9	9.7 (9.0, 10.4)	25.2 (24.0, 26.6)
<b>Bleeding (light)</b>	4390 (1)	22.9	74.5	0.9	1.1	13.2 (11.4, 15.4)	15.6 (14.9, 16.3)
<b>Bleeding (heavy)</b>	3382 (1)	5.7	97.5	2.3	1.0	28.8 (20.4, 39.0)	14.6 (14.2, 14.9)
<b>Bleeding (any)</b>	11,936 (11)	43.2	83.1	2.6	0.7	31.1 (29.3, 33.0)	10.7 (10.1, 11.3)
<b>Abdominal pain</b>	341 (1)	27.4	69.5	0.9	1.0	13.7 (9.8, 18.8)	15.5 (13.7, 17.6)
<b>Bleeding and abdominal pain</b>	3679 (2)	20.4	96.6	6.0	0.8	51.3 (45.0, 57.5)	12.6 (12.2, 13.2)
<b>Ultrasound markers</b>							
<b>Fetal size in the absence of heart activity</b>							
<i>CRL ≥5mm</i>	659 (2)	22.8	96.8	7.1	0.8	55.6 (32.3, 76.8)	12.4 (11.0, 12.9)
<i>CRL ≥6mm</i>	659 (2)	11.0	99.2	13.7	0.9	70.7 (25.1, 94.5)	13.7 (13.3, 14.1)
<i>CRL ≥7mm</i>	659 (2)	3.6	100	∞	1.0	∞	14.5 (14.4, 14.7)
<b>Gestational sac diameter in the absence of a fetal pole</b>							
<i>GSD ≥16mm</i>	1193 (3)	27.1	96.7	8.2	0.8	59.1 (45.9, 71.0)	11.7 (11.3, 12.2)
<i>GSD ≥20mm</i>	1244 (3)	23.7	98.0	12.1	0.8	68.1 (51.5, 81.1)	12.1 (11.7, 12.5)
<i>GSD ≥20mm + no yolk sac</i>	281 (3)	32.2	100	∞	0.7	∞	10.7 (9.6, 12.0)
<i>GSD ≥25mm</i>	1497 (5)	14.3	100	∞	0.9	∞	13.2 (12.9, 13.4)
<b>Biochemical markers</b>							
<b>Serum progesterone in women with pain or bleeding</b>							
<i>Progesterone &lt;10 ng/mL</i>	4689 (9)	66.5	96.3	18.0	0.4	76.1 (55.9, 88.8)	5.8 (4.2, 8.1)
<i>Progesterone &lt;15 ng/mL</i>	5128 (9)	83.3	87.5	6.7	0.2	54.0 (40.2, 67.4)	3.1 (1.6, 6.6)
<i>Progesterone &lt;20 ng/mL</i>	4348 (8)	85.7	66.6	2.6	0.2	31.1 (20.5, 44.3)	3.7 (1.7, 7.7)
<b>Serum progesterone in women with pain or bleeding and inconclusive USS</b>							
<i>Progesterone &lt;5 ng/mL</i>	1998 (5)	74.6	98.4	45.4	0.3	88.9 (55.7, 98.1)	4.4 (2.1, 9.1)



109 CI: confidence interval; CRL: crown rump length; GSD: gestational sac diameter; \* A pre-test probability of 15%  
110 for miscarriage has been assumed for this table. The post-test probabilities are dependent on the pre-test  
111 probabilities which are expected to vary amongst different populations of women.  
112

113 The diagnostic inaccuracies would have been compounded by another source of error: inter-  
114 observer variation when measuring CRL and MSD. In practice this meant that if the MSD measured  
115 20mm, it could have been 16 mm, depending on the sonographer.<sup>30</sup> New stricter diagnostic criteria  
116 were therefore developed to minimise the risk of a false positive diagnosis for miscarriage: an empty  
117 gestation sac with an MSD of  $\geq 25$  mm or an embryo with CRL  $\geq 7$  mm with no visible heart activity on  
118 transvaginal ultrasonography.

119 The new guidelines for the diagnosis of miscarriage come at a cost. The more stringent ultrasound  
120 criteria inevitably lead to a small increase in inconclusive scans and need for follow-up ultrasound  
121 assessments. This diagnostic uncertainty can be distressing for women.<sup>31</sup> Strategies to predict those  
122 most at risk of being given a diagnosis of miscarriage at subsequent visits have been developed, but  
123 their clinical utility needs evaluation.<sup>32-34</sup> It is hoped that by providing women with information on  
124 the likely outcome, levels of anxiety and distress whilst waiting for diagnostic certainty can be  
125 reduced and expectations addressed.<sup>31</sup> Appropriate training for those carrying out ultrasound scans  
126 in early pregnancy is vital if errors are to be avoided. Furthermore, it is best practice for the  
127 ultrasound scan findings to be checked by a second operator before a final diagnosis is made.

128

### 129 **Prevention of miscarriage in women with early pregnancy bleeding**

130 First trimester vaginal bleeding is common, with reported prevalence ranging between 7 and 24%.<sup>35-</sup>  
131 <sup>39</sup> Bleeding in early pregnancy increases the risk of a miscarriage (Table 1). We found six systematic  
132 reviews reporting on four classes of interventions to prevent miscarriages in women with early  
133 pregnancy bleeding: progestogens, human chorionic gonadotropins, uterine relaxants and bed rest

134 (Table 2).

135

136 **Table 2.** Summary effect estimates of interventions to prevent miscarriage in women with early

137 pregnancy bleeding

Type of intervention	Miscarriage			Live birth		
	Number of participants (trials)	Risk ratio [95% CI]	Quality of evidence	Number of participants (trials)	Risk ratio [95% CI]	Quality of evidence
<b>Progesterone</b>						
<b>Progestogen vs placebo or no treatment</b>						
Women with early pregnancy bleeding	4749 (8)	0.80 [0.66, 0.97]	HIGH	4749 (8)	1.05 [1.01, 1.08]	HIGH
Progesterone administered vaginally	4345 (5)	0.89 [0.80, 1.00]	HIGH	4345 (5)	1.04 [1.00, 1.08]	HIGH
Progesterone administered orally	404 (3)	0.59 [0.40, 0.88]	LOW	404 (3)	1.16 [1.03, 1.30]	LOW
Women with early pregnancy bleeding and no previous miscarriages	2261 (2)	0.96 [0.81, 1.12]	HIGH	2261 (2)	0.99 [0.95, 1.04]	HIGH
Women with early pregnancy bleeding and at least 1 previous miscarriage	1829 (2)	0.84 [0.70, 1.00]	HIGH	1829 (2)	1.08 [1.02, 1.15]	HIGH
Women with early pregnancy bleeding and at least 3 previous miscarriages	285 (1)	0.63 [0.43, 0.92]	HIGH	285 (1)	1.25 [1.05, 1.48]	HIGH
<b>hCG</b>						
<b>hCG vs placebo or bed rest</b>						
Women with early pregnancy bleeding	303 (3)	0.66 [0.42, 1.05]	LOW	235 (2)	1.02 [0.92, 1.13]	LOW
<b>Uterine muscle relaxants</b>						
<b>Uterine muscle relaxant drugs vs no treatment</b>						
Women with early pregnancy bleeding	170 (1)	0.25 [0.12, 0.51]	LOW	-	-	-
<b>Bed rest</b>						
<b>Bed rest vs no treatment</b>						
Women with early pregnancy bleeding	64 (2)	1.54 [0.92, 2.58]	LOW	41 (1)	0.48 [0.20, 1.13]	LOW

138 CI: confidence interval; hCG: Human chorionic gonadotropin.

139

140 *Progestogens*141 The pivotal role of progesterone in the maintenance of a successful pregnancy is well established.<sup>40</sup>

142 In view of this, progesterone supplementation has been investigated as a treatment to stop a

143 miscarriage in women with early pregnancy bleeding.<sup>41</sup>

144 Three systematic reviews, using different types, doses and regimens of progestogens in women with

145 early pregnancy bleeding, have reported on miscarriage and live birth outcomes. The totality of

146 evidence, including all types of progestogens, showed a reduction in miscarriage (RR 0·80; 95% CI

147 0·66 to 0·97) and an increase in live birth rate (RR 1·05; 95% CI 1·01 to 1·08). The two main types of

148 progestogens used in the trials were dydrogesterone, a synthetic oral progestogen, and micronized

149 vaginal progesterone, which has identical molecular structure to natural progesterone hormone.

150 Dydrogesterone was associated with an increase in live birth rate (RR 1·16, 95% CI 1·03 to 1·30).

151 However, the two studies of dydrogesterone that reported on live birth outcome were small and of

152 poor quality.<sup>42,43</sup> Both were single centre, open-label studies without placebo control. One of the

153 studies did not randomise participants, but instead allocated patients to dydrogesterone on

154 Saturdays, Mondays and Wednesdays, and to no treatment on Sundays, Tuesdays and Thursdays.<sup>42</sup>

155 The other trial was not only a single-centre, but also a single-author study, with very little description

156 of the trial methods, and thus its quality could not be fully assessed.<sup>49</sup> Thus the effectiveness

157 evidence from these trials is not reliable. Furthermore, as dydrogesterone is a synthetic drug that has

158 a molecular structure different to natural progesterone, there is a need to unequivocally

159 demonstrate short-term and long-term safety before its use can be considered in clinical practice.

160 There is evidence from a case-control study that dydrogesterone use may be associated with

161 congenital cardiac defects.<sup>44</sup>

162 Vaginal micronized progesterone was associated with an increase in live birth or ongoing pregnancy  
163 rate (RR 1.04; 95% CI 1.00 to 1.08); the evidence was primarily from a large UK-wide high quality  
164 placebo-controlled trial, the PRISM Trial which contributed 4,038 (93%) participants to the total of  
165 4,345 participants.<sup>45</sup> A pre-specified subgroup analysis in this large trial explored the effects of  
166 progesterone in women with the dual risk factors of early pregnancy bleeding and a history of one or  
167 more previous miscarriage(s), and found an increase in live birth rate with progesterone (RR 1.09,  
168 95% CI 1.03-1.15; NNT 18).<sup>46</sup> A pooled analysis confirmed this subgroup effect (Table 2). There was  
169 no evidence of any safety concerns from the use of natural progesterone.<sup>45,47</sup> A health economic  
170 analysis found progesterone in women with early pregnancy bleeding and one or more previous  
171 miscarriage had 'economic dominance', meaning it was more effective and less costly, compared  
172 with placebo.<sup>48</sup> Progesterone treatment can therefore be considered for women with early  
173 pregnancy bleeding and a history of one or more previous miscarriages.<sup>46</sup> Women should be  
174 presented with the available evidence to make an informed decision.<sup>46</sup> The recommended treatment  
175 regimen is vaginal progesterone, 400mg twice daily, started when a woman with a history of one or  
176 more previous miscarriages presents with vaginal bleeding in early pregnancy, and continued to 16  
177 weeks of gestation.<sup>46</sup>

178

### 179 *Human chorionic gonadotropin (hCG)*

180 A systematic review identified three small low quality trials on the effects of hCG in women with  
181 early pregnancy bleeding.<sup>5</sup> There was no clear evidence of a reduction in miscarriage rate, and there  
182 was no evidence of an increase in live birth rate (Table 2). Current evidence, therefore, does not  
183 support the use of hCG in women with early pregnancy bleeding.

184 There is very limited evidence on the effects of uterine relaxants<sup>10</sup> or bed rest,<sup>49</sup> but the available  
185 evidence does not support their use (Table 2).

186

187 **Management of miscarriage**

188 Miscarriage can be managed expectantly, medically with tablets, or surgically. Although historically  
189 women with miscarriage had a surgical procedure, there are now alternative options. Expectant  
190 management means waiting for natural expulsion of pregnancy tissue. Medical methods of  
191 management of miscarriage include various regimens of misoprostol, with or without mifepristone.  
192 Misoprostol is a synthetic prostaglandin E1 analogue that induces cervical softening and uterine  
193 contractions. Mifepristone acts as a competitive progesterone and glucocorticoid receptor  
194 antagonist that interferes with the nuclear receptor signalling of progesterone, blocking its actions  
195 and initiating the expulsion of the pregnancy. Surgical methods can involve dilatation of the cervix  
196 and curettage or suction aspiration of pregnancy tissue, with or without the preparation of the  
197 cervix with misoprostol to minimise the risk of injury from cervical dilation.

198 We have recently completed a Cochrane network meta-analysis evaluating six approaches for  
199 managing miscarriage.<sup>50</sup> The network meta-analysis included 70 trials with 15,830 participants  
200 (Figure 1). The trials included women in hospital settings with missed miscarriage (23 trials),  
201 incomplete miscarriage (13 trials), and both types of miscarriage (12 trials). Relative effects from the  
202 network meta-analysis of 56 trials (11,311 women) showed that all active interventions were more  
203 likely to result in the completion of miscarriage when compared with expectant management or  
204 placebo (Table 3). The most effective method for achieving the completion of a miscarriage was  
205 suction aspiration with cervical preparation compared with expectant management (RR 2.10, 95% CI  
206 1.44 to 3.06, *very low certainty evidence*). This was followed by dilatation and curettage (RR 1.45,  
207 95% CI 1.25 to 1.68, *low certainty evidence*), suction aspiration alone (RR 1.40, 95% CI 1.26 to 1.56,  
208 *low certainty evidence*), mifepristone plus misoprostol combination (RR 1.36, 95% CI 1.17 to 1.59,  
209 *moderate certainty evidence*) and misoprostol alone (RR 1.29, 95% CI 1.15 to 1.44, *low certainty*  
210 *evidence*).

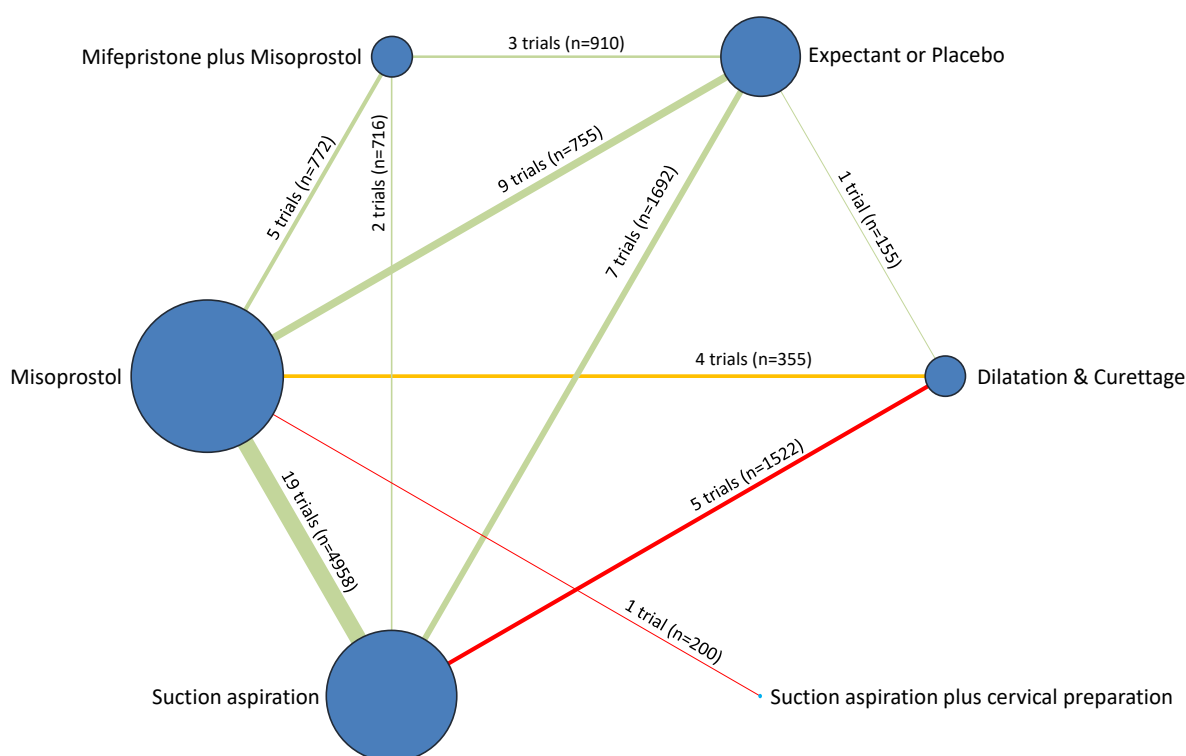
211 Relative effects from the network meta-analysis of 32 trials (7,243 women) did not show important  
212 differences amongst-the six approaches for the composite outcome of death or serious  
213 complications, such as uterine perforation, need for further life-saving procedures including  
214 hysterectomy, blood transfusion or intensive care unit admission. Follow-up of participants from a  
215 large trial of expectant, medical and surgical management showed that the method of miscarriage  
216 management did not affect subsequent pregnancy rates with approximately four in five women  
217 giving birth within five years of the index miscarriage.<sup>51</sup>

218 Our recommendation is that women should be presented with the available evidence and should be  
219 supported to choose the miscarriage management approach that suits their needs and preferences.

220 If a woman with a missed miscarriage chooses to have surgery, suction aspiration with cervical  
221 preparation should be recommended, but if she chooses to have the medical management, a  
222 combination therapy with mifepristone and misoprostol should be recommended. Women with  
223 incomplete miscarriage have over 90% chance of completing the miscarriage without medical  
224 intervention,<sup>50</sup> as the process of expelling pregnancy tissue has already started. Expectant  
225 management is therefore recommended as the first-line option for women with incomplete  
226 miscarriage, provided there is no evidence of excessive bleeding or intrauterine infection.

227

228 **Figure 1.** Network diagram of studies of miscarriage management for the outcome of completion of  
229 miscarriage.



230

231

232 The nodes represent an intervention and their size is proportional to the number of trials comparing this  
 233 intervention to any other in the network. The lines connecting each pair of interventions represent a direct  
 234 comparison and are drawn proportional to the number of trials making that direct comparison. Numbers on  
 235 the lines represent the number of trials and participants for each comparison. The colour of the line is purple  
 236 for high-certainty evidence (there were no high-certainty evidence); green for moderate-certainty evidence;  
 237 orange for low-certainty evidence and red for very low-certainty evidence.

238

239 **Table 3.** Summary of findings of various miscarriage management approaches for the outcome of  
 240 completion of miscarriage

Intervention versus expectant care or placebo	Direct Evidence		Indirect Evidence		Network Evidence		Anticipated absolute effects for NMA estimate		
	RR (95% CI)	Certainty	RR (95% CI)	Certainty	RR (95% CI)	Certainty	Risk with expectant care or placebo	Risk with intervention	Risk difference with intervention
<b>Suction aspiration plus cervical preparation</b>	Not reported by included studies	-	2.10 (1.44 to 3.06)	⊕⊕⊕⊕ VERY LOW <sup>a</sup>	2.10 (1.44 to 3.06)	⊕⊕⊕⊕ VERY LOW <sup>b</sup>	647 per 1,000	1,359 per 1,000	712 more per 1,000 (from 285 more to 1,333 more)
<b>Suction aspiration</b>	1.27 (1.08 to 1.48)	⊕⊕⊕⊕ MODERATE <sup>c</sup>	1.63 (1.37 to 1.94)	⊕⊕⊕⊕ MODERATE <sup>d</sup>	1.40 (1.26 to 1.56)	⊕⊕⊕⊕ LOW <sup>e</sup>	647 per 1,000	906 per 1,000	259 more per 1,000 (from 168 more to 362 more)
<b>Dilation plus curettage</b>	1.25 (1.12 to 1.39)	⊕⊕⊕⊕ MODERATE <sup>f</sup>	1.50 (1.27 to 1.78)	⊕⊕⊕⊕ LOW <sup>g</sup>	1.45 (1.25 to 1.68)	⊕⊕⊕⊕ LOW <sup>e</sup>	647 per 1,000	938 per 1,000	291 more per 1,000 (from 162 more to 440 more)

<b>Mifepristone plus misoprostol</b>	1·59 (1·01 to 2·51)	⊕⊕⊕⊖ MODERATE <sup>c</sup>	1·31 (1·08 to 1·60)	⊕⊕⊕⊖ MODERATE <sup>d</sup>	1·36 (1·17 to 1·59)	⊕⊕⊕⊖ MODERATE <sup>h</sup>	647 per 1,000	880 per 1,000	233 more per 1,000 (from 110 more to 382 more)
<b>Misoprostol</b>	1·72 (1·26 to 2·33)	⊕⊕⊕⊖ MODERATE <sup>c</sup>	1·16 (1·02 to 1·33)	⊕⊕⊕⊖ MODERATE <sup>d</sup>	1·29 (1·15 to 1·44)	⊕⊕⊖⊖ LOW <sup>i</sup>	647 per 1,000	835 per 1,000	188 more per 1,000 (from 97 more to 285 more)

**CI:** Confidence interval; **RR:** Risk ratio; **NMA:** Network Meta Analysis

**GRADE Working Group grades of evidence**

**High certainty:** Very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty:** Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low certainty:** Very little confidence in the effect estimate: The true effect could be substantially different from the estimate of effect

241 *a* Indirect evidence downgraded -3 due to multiple crucial limitations in study design and substantial imprecision

242 *b* Network evidence downgraded -3 due to very low certainty indirect evidence

243 *c* Direct evidence downgraded -1 due to substantial unexplained statistical heterogeneity

244 *d* Indirect evidence downgraded -1 due to substantial unexplained statistical heterogeneity

245 *e* Network evidence downgraded -2 due to moderate certainty direct evidence and incoherence between direct and indirect estimates

247 *f* Direct evidence downgraded -1 due to substantial imprecision

248 *g* Indirect evidence downgraded -2 to limitations in study design and substantial unexplained statistical heterogeneity

250 *h* Network evidence downgraded -1 due to moderate certainty indirect evidence

251 *i* Network evidence downgraded -2 due to moderate certainty indirect evidence and incoherence between direct and indirect estimates

253

254 *Antibiotic prophylaxis for surgical management of miscarriage*

255 Infection can be a serious consequence of surgical management of miscarriage, in particular in low-

256 and middle-income countries (LMICs).<sup>52</sup> Pelvic infection can result in sepsis and death,<sup>53</sup> as well as

257 long-term consequences from pelvic scarring, including increased rates of ectopic pregnancy and

258 infertility.<sup>54</sup>

259 A meta-analysis of antibiotic prophylaxis before surgical management of miscarriage found a

260 reduction in pelvic infection (RR 0·56, 95% CI 0·35 to 0·89).<sup>11</sup> Most of the data were from LMICs.<sup>11,52,55-</sup>

261 <sup>57</sup> The largest trial to contribute data to this analysis was also a high quality trial; it used oral

262 doxycycline 400 mg and oral metronidazole 400 mg two hours before surgery.<sup>57</sup> We recommend the

263 use of prophylactic antibiotics before miscarriage surgery, particularly in LMIC settings.



264

265 **Organisation and delivery of emergency early pregnancy care**

266 Emergency early pregnancy care is currently provided in a variety of settings including primary care,  
267 private offices, emergency departments, and dedicated early pregnancy units (EPUs). Early  
268 pregnancy units are emerging as a model of care in many countries. They are specialist departments  
269 that provide care for women with problems in early pregnancy, including miscarriage, ectopic  
270 pregnancy and hyperemesis gravidarum. They may be staffed by specialist nurses, midwives,  
271 sonographers, doctors and other healthcare professionals.

272 We carried out a literature review to evaluate the effectiveness, women's views and cost-  
273 effectiveness of the EPUs as a model of organisation of care. We found six observational studies  
274 reporting clinical outcomes from an EPU model of care compared with data from the same hospitals  
275 before the EPU service was introduced.<sup>58-62</sup> Three studies reporting health economic evidence were  
276 also identified.<sup>61-63</sup> Relative effects from the studies showed that the EPU model of care was more  
277 likely to result in lower number of hospital admissions (4 studies, 1,323 women; RR 0.48, 95% CI 0.37  
278 to 0.61), lower number of re-admissions to hospital (3 studies, 4,950 women; RR 0.76, 95% CI 0.61 to  
279 0.95) and lower rates of surgery (2 studies, 573 women; RR 0.35, 95% CI 0.17 to 0.71). Two studies  
280 estimated the annual savings from establishing an EPU service to be £109,440 in the UK setting<sup>63</sup> and  
281 Australian \$257,617 in the Australian setting.<sup>62</sup> Another study estimated cost savings to be up to  
282 €657 per woman.<sup>61</sup>

283 A qualitative study in the UK found that women valued the care they received in EPUs, but observed  
284 that improvements were required to ensure that women and their partners receive a streamlined,  
285 informative, supportive and continuous package of care from the point of contact to being  
286 discharged from the EPU.<sup>64</sup> The evidence supporting the EPU model of care over other models of  
287 care is of very low certainty due to the observational nature of studies, but the observed effects for  
288 clinical outcomes are large. The health economic evidence suggests that the EPU model of care may  
289 be cost-effective, at least in high-income country settings. As an EPU model is associated with a

290 reduction in hospital admissions, re-admissions and need for surgery, health economic arguments  
291 are likely to be in favour of an EPU model in LMICs too.

292

### 293 **Global perspectives**

294 The availability and accessibility of services for miscarriage diagnosis and management varies greatly  
295 across the world. Emergency early pregnancy care is provided in over 200 dedicated EPUs in the  
296 UK.<sup>63</sup> Similar units have now been established in many countries, including the Netherlands, Canada,  
297 Ireland, and Australia.<sup>61,65-68</sup> In the USA, the first EPU was established in Denver, Colorado in 2013.<sup>68</sup>  
298 The concept of a dedicated multi-professional service for women with early pregnancy complications  
299 is now spreading into LMICs, for example, Nigeria.<sup>69</sup>

300 There are several key elements that are required to establish a successful EPU service. These include  
301 an availability of resources such as drugs and ultrasound machines, an ability to efficiently process  
302 blood tests such as hCG and progesterone, training of individuals to be confident and competent in  
303 early pregnancy ultrasound scanning, training in breaking bad news and provision of psychological  
304 support. These resources are limited in LMICs. For example, a survey among 232 gynaecologists in  
305 Nigeria published in 2014 found that only 24% had formal training in transvaginal ultrasound  
306 scanning and that over 90% felt that the lack of the capacity for transvaginal ultrasound scanning  
307 was the most important obstacle against achieving effective care for women with miscarriage.<sup>69</sup>

308 There is particular scarcity in ultrasound provisions in rural areas in many low resource settings. In  
309 sub-Saharan Africa, 30% of women in urban settings receive an obstetric ultrasound, but in rural  
310 areas this falls to 6%.<sup>70</sup> In South Africa, the urban to rural gap is again demonstrated with 68% of  
311 women in urban areas receiving pregnancy ultrasound, and only 18% in rural areas.<sup>70</sup>

312 There are a multitude of factors to consider when introducing ultrasound services in LMICs, including  
313 patient demographics, disease patterns, geographic factors, cultural beliefs, and availability of  
314 sonographer training and ultrasound machines. The availability of appropriately trained practitioners

315 and ultrasound machines remains a considerable barrier to service provision in many low resource  
316 settings.<sup>71</sup> Potential solutions include competency-based training programs in ultrasonography,<sup>72</sup>  
317 and the provision of innovative hand-held ultrasound machines.<sup>73</sup>

318 Studies which explore miscarriage management in LMICs frequently have cross-over with abortion  
319 care and so some parallel lessons can be drawn. Medical treatment with misoprostol is commonly  
320 used to treat incomplete abortions and miscarriages. It is an effective, safe, acceptable and  
321 affordable method of miscarriage management; however, arrangements for appropriate clinical  
322 follow-up are necessary as there is a risk of incomplete expulsion of pregnancy tissue with this  
323 method.<sup>74,75</sup> Manual vacuum aspiration (MVA) is effective and safe for early pregnancies and is  
324 recommended by the World Health Organization to replace dilatation and curettage where these are  
325 still practiced.<sup>76</sup> However, a strategic assessment of unsafe abortion in Malawi found MVA is used  
326 infrequently, with dilatation and curettage being used in preference.<sup>77</sup> Reasons suggested for this  
327 preference included a lack of MVA equipment, equipment being locked up to prevent its use in  
328 inducing abortions and a lack of trained healthcare practitioners. There is a need for improved  
329 training and provisions for MVA.

330 Couples affected by miscarriage in LMICs are often overlooked due to competing health priorities.  
331 Access to tests, scans and treatments, which often require specialised and expensive laboratory  
332 facilities are challenges faced by both caregivers and patients. We recommend investment to  
333 improve early pregnancy care in LMICs. This can be achieved through increased provision of  
334 necessary drugs and equipment, increased training in scanning and surgical procedures, and  
335 organisation of effective and efficient care through dedicated early pregnancy units. An awareness-  
336 raising programme to encourage women to recognise and seek healthcare for early pregnancy  
337 complications is also needed.

338

339 **Discussion**

340 Sporadic miscarriage is common. Accurate diagnosis of miscarriage is the cornerstone of an effective  
341 early pregnancy service, and relies on high quality ultrasonography. There is high-certainty evidence  
342 that vaginal micronized progesterone increases live birth rates in women with early pregnancy  
343 bleeding and a history of miscarriage. Women who have a miscarriage may choose to have  
344 expectant, medical or surgical management; surgical management with vacuum suction aspiration  
345 after cervical preparation is ranked first amongst six competing strategies for completing a  
346 miscarriage. Amongst medical management strategies, mifepristone and misoprostol combination is  
347 more effective than misoprostol alone in completing a miscarriage. Expectant management is an  
348 effective approach for women with incomplete miscarriage. Miscarriage care should ideally be  
349 delivered by clinical nurse specialists and doctors with specialist training in early pregnancy care, in  
350 the setting of early pregnancy units. EPU's appear to be effective and cost-effective.

351 We have used the best available evidence to draw our inferences and recommendations, updating  
352 existing reviews, where appropriate, to ensure the information in the series is up-to-date and  
353 evidence-based to the best extent possible. However, there are limitations in the evidence, both in  
354 terms of quantity and quality, and therefore we have relied on consensus amongst experts where  
355 this was necessary.

356 Most of the available evidence relates to high-income settings, although the vast majority of  
357 miscarriages are suffered by women in low-resource settings. There is an evidence gap on  
358 miscarriage prevalence, consequences and costs in LMICs that need to be addressed robustly with  
359 targeted research. We recommend that early pregnancy services document and report monthly  
360 tallies of miscarriages to a national registry, and then every country to report annual miscarriage  
361 data, similarly to the reporting of stillbirth. Such data will facilitate efficient organisation of care,  
362 better allocation of scarce resources, research and international comparisons.

363 An effective emergency pregnancy service needs to be able to support women with expectant  
364 management, and provide medical management with mifepristone and misoprostol, and surgical  
365 management with manual vacuum aspiration. Mifepristone, misoprostol and manual vacuum

366 aspiration kits are not readily available in many resource poor settings; it is a priority for healthcare  
367 funders and providers to make these essential supplies universally available.

368 Miscarriage causes devastation to large numbers of couples in every country; there is silence around  
369 miscarriage, silence from sufferers, healthcare providers, policymakers and funders. We urge all  
370 stakeholders to develop and deliver a comprehensive miscarriage care service, ideally organised in  
371 the setting of a dedicated early pregnancy unit. Urgent research is needed on methods to prevent  
372 and predict women at high risk of physical and psychological morbidity associated with miscarriage,  
373 and to screen for mental health issues after pregnancy loss.

374

375 Contributors

376 All authors participated in the design of the review, literature searches, and assisted with the writing  
377 a review of all sections and agreed to submit the manuscript. The manuscript represents the view of  
378 named authors only.

379

380 Declaration of interests

381 The authors have no conflicts of interest to declare.

382

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387

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