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Sporadic miscarriage: evidence to provide effective care

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Summary

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

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

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

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

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 ≥25 mm, or an embryo with a crown rump length of ≥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.

Introduction

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

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

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

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

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

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

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[5-10] and 12 on the management of miscarriage[11-22] 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,[23] the European Society of Human Reproduction and Embryology (ESHRE) guideline on the management of recurrent pregnancy loss,[24] and the American College of Obstetricians and Gynecologists guideline on early pregnancy loss.[25]

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.

Diagnosis of miscarriage

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

Whilst risk prediction can provide helpful information, the diagnosis of miscarriage requires transvaginal ultrasonography. However, a systematic review found much variation in the ultrasound criteria used and there was significant uncertainty in the diagnostic accuracy, as shown by the large confidence intervals around sensitivity and specificity estimates.[26,27] There was no uniform agreement over what criteria should be used to make a diagnosis of miscarriage.[26] For example, the American College of Radiology (ACR) considered the presence of an empty gestation sac with mean sac diameter (MSD) ≥16 mm or an embryo of crown-rump length (CRL) ≥5 mm with no heartbeat to be diagnostic of a miscarriage.[28] On the other hand, the Royal College of Obstetricians and Gynaecologists (RCOG) in the UK used cut-off values for MSD of ≥20 mm and a CRL of ≥6 mm.[29] The diagnostic uncertainties meant there was a risk of initiating treatment erroneously, resulting in the 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
Symptoms and Signs							
Nausea and vomiting	9964 (9)	42·5	30·1	0·6	1·9	9·7 (9·0, 10·4)	25·2 (24·0, 26·6)
Bleeding (light)	4390 (1)	22·9	74·5	0·9	1·1	13·2 (11·4, 15·4)	15·6 (14·9, 16·3)
Bleeding (heavy)	3382 (1)	5·7	97·5	2·3	1·0	28·8 (20·4, 39·0)	14·6 (14·2, 14·9)
Bleeding (any)	11,936 (11)	43·2	83·1	2·6	0·7	31·1 (29·3, 33·0)	10·7 (10·1, 11·3)
Abdominal pain	341 (1)	27·4	69·5	0·9	1·0	13·7 (9·8, 18·8)	15·5 (13·7, 17·6)
Bleeding and abdominal pain	3679 (2)	20·4	96·6	6·0	0·8	51·3 (45·0, 57·5)	12·6 (12·2, 13·2)
Ultrasound markers							
Fetal size in the absence of heart activity							
CRL ≥5mm	659 (2)	22·8	96·8	7·1	0·8	55·6 (32·3, 76·8)	12·4 (11·0, 12·9)
CRL ≥6mm	659 (2)	11·0	99·2	13·7	0·9	70·7 (25·1, 94·5)	13·7 (13·3, 14·1)
CRL ≥7mm	659 (2)	3·6	100	∞	1·0	∞	14·5 (14·4, 14·7)
Gestational sac diameter in the absence of a fetal pole							
GSD ≥16mm	1193 (3)	27·1	96·7	8·2	0·8	59·1 (45·9, 71·0)	11·7 (11·3, 12·2)
GSD ≥20mm	1244 (3)	23·7	98·0	12·1	0·8	68·1 (51·5, 81·1)	12·1 (11·7, 12·5)
GSD ≥20mm + no yolk sac	281 (3)	32·2	100	∞	0·7	∞	10·7 (9·6, 12·0)
GSD ≥25mm	1497 (5)	14·3	100	∞	0·9	∞	13·2 (12·9, 13·4)
Biochemical markers							
Serum progesterone in women with pain or bleeding							
Progesterone <10 ng/mL	4689 (9)	66·5	96·3	18·0	0·4	76·1 (55·9, 88·8)	5·8 (4·2, 8·1)
Progesterone <15 ng/mL	5128 (9)	83·3	87·5	6·7	0·2	54·0 (40·2, 67·4)	3·1 (1·6, 6·6)
Progesterone <20 ng/mL	4348 (8)	85·7	66·6	2·6	0·2	31·1 (20·5, 44·3)	3·7 (1·7, 7·7)
Serum progesterone in women with pain or bleeding and inconclusive USS							
Progesterone <5 ng/mL	1998 (5)	74·6	98·4	45·4	0·3	88·9 (55·7, 98·1)	4·4 (2·1, 9·1)

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

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

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

Prevention of miscarriage in women with early pregnancy bleeding

First trimester vaginal bleeding is common, with reported prevalence ranging between 7 and 24%.[35-39] Bleeding in early pregnancy increases the risk of a miscarriage (Table 1). We found six systematic reviews reporting on four classes of interventions to prevent miscarriages in women with early 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

	Miscarriage			Live birth		
Type of intervention	**Number of participants (trials)**	**Risk ratio [95% CI]**	**Quality of evidence**	**Number of participants (trials)**	**Risk ratio [95% CI]**	**Quality of evidence**
Progesterone						
Progestogen vs placebo or no treatment						
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
hCG						
hCG vs placebo or bed rest						
Women with early pregnancy bleeding	303 (3)	0·66 [0·42, 1·05]	LOW	235 (2)	1·02 [0·92, 1·13]	LOW
Uterine muscle relaxants						
Uterine muscle relaxant drugs vs no treatment						
Women with early pregnancy bleeding	170 (1)	0·25 [0·12, 0·51]	LOW	-	-	-
Bed rest						
Bed rest vs no treatment						
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.

Progestogens

The pivotal role of progesterone in the maintenance of a successful pregnancy is well established.[40] In view of this, progesterone supplementation has been investigated as a treatment to stop a miscarriage in women with early pregnancy bleeding.[41]

Three systematic reviews, using different types, doses and regimens of progestogens in women with early pregnancy bleeding, have reported on miscarriage and live birth outcomes. The totality of evidence, including all types of progestogens, showed a reduction in miscarriage (RR 0·80; 95% CI 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 progestogens used in the trials were dydrogesterone, a synthetic oral progestogen, and micronized vaginal progesterone, which has identical molecular structure to natural progesterone hormone.

Dydrogesterone was associated with an increase in live birth rate (RR 1·16, 95% CI 1·03 to 1·30). However, the two studies of dydrogesterone that reported on live birth outcome were small and of poor quality.[42,43] Both were single centre, open-label studies without placebo control. One of the studies did not randomise participants, but instead allocated patients to dydrogesterone on Saturdays, Mondays and Wednesdays, and to no treatment on Sundays, Tuesdays and Thursdays.[42] The other trial was not only a single-centre, but also a single-author study, with very little description of the trial methods, and thus its quality could not be fully assessed.[49] Thus the effectiveness evidence from these trials is not reliable. Futhermore, as dydrogesterone is a synthetic drug that has a molecular structure different to natural progesterone, there is a need to unequivocally demonstrate short-term and long-term safety before its use can be considered in clinical practice. There is evidence from a case-control study that dydrogesterone use may be associated with congenital cardiac defects.[44]

Vaginal micronized progesterone was associated with an increase in live birth or ongoing pregnancy rate (RR 1·04; 95% CI 1·00 to 1·08); the evidence was primarily from a large UK-wide high quality placebo-controlled trial, the PRISM Trial which contributed 4,038 (93%) participants to the total of 4,345 participants.[45] A pre-specified subgroup analysis in this large trial explored the effects of progesterone in women with the dual risk factors of early pregnancy bleeding and a history of one or more previous miscarriage(s), and found an increase in live birth rate with progesterone (RR 1·09, 95% CI 1·03-1·15; NNT 18).[46] A pooled analysis confirmed this subgroup effect (Table 2). There was no evidence of any safety concerns from the use of natural progesterone.[45,47] A health economic analysis found progesterone in women with early pregnancy bleeding and one or more previous miscarriage had 'economic dominance', meaning it was more effective and less costly, compared with placebo.[48] Progesterone treatment can therefore be considered for women with early pregnancy bleeding and a history of one or more previous miscarriages.[46] Women should be presented with the available evidence to make an informed decision.[46] The recommended treatment regimen is vaginal progesterone, 400mg twice daily, started when a woman with a history of one or more previous miscarriages presents with vaginal bleeding in early pregnancy, and continued to 16 weeks of gestation.[46]

Human chorionic gonadotropin (hCG)

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

There is very limited evidence on the effects of uterine relaxants[10] or bed rest,[49] but the available evidence does not support their use (Table 2).

Management of miscarriage

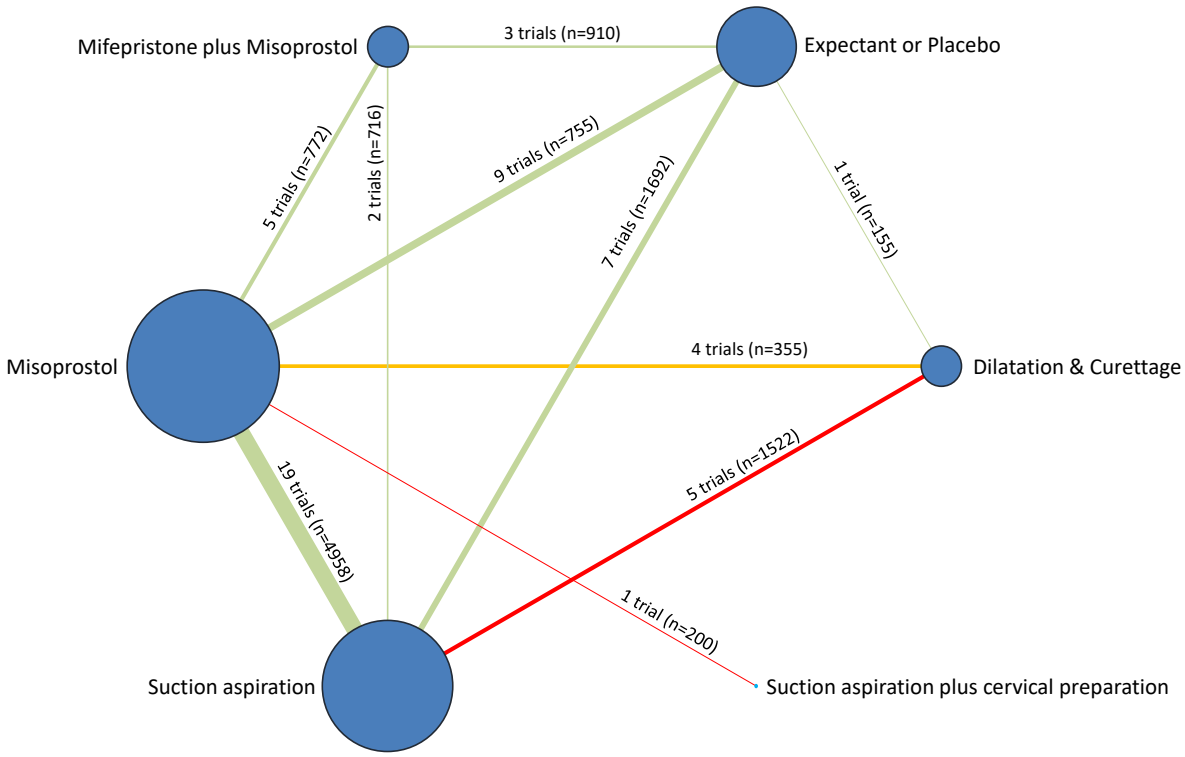
Miscarriage can be managed expectantly, medically with tablets, or surgically. Although historically women with miscarriage had a surgical procedure, there are now alternative options. Expectant management means waiting for natural expulsion of pregnancy tissue. Medical methods of management of miscarriage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

We have recently completed a Cochrane network meta-analysis evaluating six approaches for managing miscarriage.[50] The network meta-analysis included 70 trials with 15,830 participants (Figure 1). The trials included women in hospital settings with missed miscarriage (23 trials), incomplete miscarriage (13 trials), and both types of miscarriage (12 trials). Relative effects from the network meta-analysis of 56 trials (11,311 women) showed that all active interventions were more likely to result in the completion of miscarriage when compared with expectant management or placebo (Table 3). The most effective method for achieving the completion of a miscarriage was suction aspiration with cervical preparation compared with expectant management (RR 2·10, 95% CI 1·44 to 3·06, *very low certainty evidence*). This was followed by dilatation and curettage (RR 1·45, 95% CI 1·25 to 1·68, *low certainty evidence*), suction aspiration alone (RR 1·40, 95% CI 1·26 to 1·56, *low certainty evidence*), mifepristone plus misoprostol combination (RR 1·36, 95% CI 1·17 to 1·59, *moderate certainty evidence*) and misoprostol alone (RR 1·29, 95% CI 1·15 to 1·44, *low certainty evidence*).

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

Our recommendation is that women should be presented with the available evidence and should be supported to choose the miscarriage management approach that suits their needs and preferences. If a woman with a missed miscarriage chooses to have surgery, suction aspiration with cervical preparation should be recommended, but if she chooses to have the medical management, a combination therapy with mifepristone and misoprostol should be recommended. Women with incomplete miscarriage have over 90% chance of completing the miscarriage without medical intervention,[50] as the process of expelling pregnancy tissue has already started. Expectant management is therefore recommended as the first-line option for women with incomplete miscarriage, provided there is no evidence of excessive bleeding or intrauterine infection.

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



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

Table 3. Summary of findings of various miscarriage management approaches for the outcome of 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
Suction aspiration plus cervical preparation	Not reported by included studies	-	2·10 (1·44 to 3·06)	⊕⊖⊖⊖ VERY LOW[a]	2·10 (1·44 to 3·06)	⊕⊖⊖⊖ VERY LOW[b]	647 per 1,000	1,359 per 1,000	712 more per 1,000 (from 285 more to 1,333 more)
Suction aspiration	1·27 (1·08 to 1·48)	⊕⊕⊕⊖ MODERATE[c]	1·63 (1·37 to 1·94)	⊕⊕⊕⊖ MODERATE[d]	1·40 (1·26 to 1·56)	⊕⊕⊖⊖ LOW[e]	647 per 1,000	906 per 1,000	259 more per 1,000 (from 168 more to 362 more)
Dilation plus curettage	1·25 (1·12 to 1·39)	⊕⊕⊕⊖ MODERATE[f]	1·50 (1·27 to 1·78)	⊕⊕⊖⊖ LOW[g]	1·45 (1·25 to 1·68)	⊕⊕⊖⊖ LOW[e]	647 per 1,000	938 per 1,000	291 more per 1,000 (from 162 more to 440 more)

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

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

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

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

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

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

f Direct evidence downgraded -1 due to substantial imprecision

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

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

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

Antibiotic prophylaxis for surgical management of miscarriage

Infection can be a serious consequence of surgical management of miscarriage, in particular in low- and middle-income countries (LMICs).[52] Pelvic infection can result in sepsis and death,[53] as well as long-term consequences from pelvic scarring, including increased rates of ectopic pregnancy and infertility.[54]

A meta-analysis of antibiotic prophylaxis before surgical management of miscarriage found a reduction in pelvic infection (RR 0·56, 95% CI 0·35 to 0·89).[11] Most of the data were from LMICs.[11,52,55-57] The largest trial to contribute data to this analysis was also a high quality trial; it used oral doxycycline 400 mg and oral metronidazole 400 mg two hours before surgery.[57] We recommend the use of prophylactic antibiotics before miscarriage surgery, particularly in LMIC settings.

Organisation and delivery of emergency early pregnancy care

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

We carried out a literature review to evaluate the effectiveness, women's views and cost-effectiveness of the EPUs as a model of organisation of care. We found six observational studies reporting clinical outcomes from an EPU model of care compared with data from the same hospitals before the EPU service was introduced.[58-62] Three studies reporting health economic evidence were also identified.[61-63] Relative effects from the studies showed that the EPU model of care was more likely to result in lower number of hospital admissions (4 studies, 1,323 women; RR 0·48, 95% CI 0·37 to 0·61), lower number of re-admissions to hospital (3 studies, 4,950 women; RR 0·76, 95% CI 0·61 to 0·95) and lower rates of surgery (2 studies, 573 women; RR 0·35, 95% CI 0·17 to 0·71). Two studies estimated the annual savings from establishing an EPU service to be £109,440 in the UK setting[63] and Australian $257,617 in the Australian setting.[62] Another study estimated cost savings to be up to €657 per woman.[61]

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

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

Global perspectives

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

There are several key elements that are required to establish a successful EPU service. These include an availability of resources such as drugs and ultrasound machines, an ability to efficiently process blood tests such as hCG and progesterone, training of individuals to be confident and competent in early pregnancy ultrasound scanning, training in breaking bad news and provision of psychological support. These resources are limited in LMICs. For example, a survey among 232 gynaecologists in Nigeria published in 2014 found that only 24% had formal training in transvaginal ultrasound scanning and that over 90% felt that the lack of the capacity for transvaginal ultrasound scanning was the most important obstacle against achieving effective care for women with miscarriage.[69] There is particular scarcity in ultrasound provisions in rural areas in many low resource settings. In sub-Saharan Africa, 30% of women in urban settings receive an obstetric ultrasound, but in rural areas this falls to 6%.[70] In South Africa, the urban to rural gap is again demonstrated with 68% of women in urban areas receiving pregnancy ultrasound, and only 18% in rural areas.[70]

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

and ultrasound machines remains a considerable barrier to service provision in many low resource settings.[71] Potential solutions include competency-based training programs in ultrasonography,[72] and the provision of innovative hand-held ultrasound machines.[73]

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

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

Discussion

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

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

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

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

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

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

Contributors

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

Declaration of interests

The authors have no conflicts of interest to declare.

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