Miscarriage 2

Sporadic miscarriage: evidence to provide effective care

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This is the second in a Series of three papers about miscarriage

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The physical and psychological effect 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 caregivers. 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. For this Series paper, we have developed recommendations for practice from a literature review, appraisal of 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) 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 it is central to the diagnosis of miscarriage, and be able to provide expectant management of miscarriage, 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 micronised progesterone to improve the prospects of livebirth. We urge health-care funders and providers to invest in early pregnancy care, with specific focus on training for clinical nurse specialists and doctors to provide comprehensive miscarriage care within the setting of dedicated early pregnancy units.

Introduction

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

Pain and bleeding in early pregnancy are distressing to women. Those who have had 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]

Health-care providers strive to avoid diagnostic errors that could have serious consequences.[2,3] A falsely positive diagnosis of miscarriage can result in the unintentional termination of a viable and wanted pregnancy. In 2012, concerns about inaccuracies in miscarriage diagnosis resulted in urgent revisions to the UK National Institute for Health and Care Excellence recommendations.[4] In an effort to tackle the diagnostic challenge, health-care providers often resort to arranging repeated visits and investigations for pregnant women. A clear diagnostic pathway can help to reduce anxiety in 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 might be provided by generalists or specialists, and be offered in emergency care departments or dedicated early pregnancy units. Uncertainties exist about the optimal ways to organise and provide 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 providing emergency miscarriage care and a call to action for improved care and high-quality research in specific areas.

Diagnosis of miscarriage

The risk of miscarriage varies by the presenting clinical symptoms and signs (appendix p 6). For example, the presence of a small amount of bleeding in early pregnancy is not associated with an increase in the risk of miscarriage, whereas heavy bleeding is associated with a substantial risk of miscarriage (appendix p 6). However, the presence of nausea and vomiting, which can be a marker of a healthy concentration of pregnancy hormones, is associated with a low risk of miscarriage (9·7%; appendix p 6). The probability of miscarriage with particular ultrasound features is so high that these findings can be considered to have sufficient accuracy to justify management as miscarriage (appendix p 6). Serum progesterone concentrations can

Search strategy and selection criteria

The recommendations are based on a review of the current literature, appraisal of professional body guidelines, and expert group discussions. For the literature reviews, we searched the Cochrane Database of Systematic Reviews and MEDLINE (from inception until Jan 9, 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 focused on the prevention of miscarriage in women with bleeding and 12 on the management of miscarriage. We reported results for miscarriage and livebirth separately. For the review of professional body guidelines, we reviewed the latest international guidance on the diagnosis, prevention, and management of miscarriage, including the 2019 National Institute for Health and Care Excellence guideline on the management of ectopic pregnancy and miscarriage, the European Society of Human Reproduction and Embryology guideline on the management of recurrent pregnancy loss, and the American College of Obstetricians and Gynecologists guideline on early pregnancy loss. For 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 Series paper. Agreements were reached through consensus.

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 more, or an embryo with a crown-rump length of 7 mm or more with no visible heart activity on transvaginal ultrasonography, is considered to have sufficient accuracy for the diagnosis of miscarriage to justify management as miscarriage
- Prevention of miscarriage in women with early pregnancy bleeding: there is high-quality evidence that vaginal micronised progesterone increases livebirth rates in women with early pregnancy bleeding and a history of miscarriage; there is a 5% absolute rate increase in livebirths with progesterone, when compared with placebo, in women with bleeding and one or more previous miscarriages, and a 15% absolute rate increase in livebirths in women with bleeding and three or more previous miscarriages
- Miscarriage management: surgical management with vacuum suction aspiration after cervical preparation is ranked first among six competing strategies for completing a missed miscarriage; among 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 management approach that suits their needs and preferences
- Organisation and provision of miscarriage care: miscarriage care, given by clinical nurse specialists and medical staff specifically trained in early pregnancy care, can be organised and provided within self-contained early pregnancy units, which are effective and cost-efficient

provide additional information on the viability of a pregnancy (appendix p 6).

Although predicting risk can provide helpful information, the diagnosis of miscarriage requires transvaginal ultrasonography. However, a systematic review[5] found much variation in the ultrasound criteria used and there was substantial uncertainty in the diagnostic accuracy, as shown by the large confidence intervals around sensitivity and specificity estimates.[5,6] The findings showed that there was no uniform agreement on which criteria should be used to make a diagnosis of miscarriage.[5] For example, the American College of Radiology considered the presence of an empty gestation sac with mean sac diameter of 16 mm or more, or an embryo of crown-rump length of 5 mm or more with no heartbeat to be diagnostic of a miscarriage.[7] By contrast, the Royal College of Obstetricians and Gynaecologists in the UK used cutoff values for mean sac diameter of 20 mm or more and a crown-rump length of 6 mm or more.[8] The diagnostic uncertainties meant there was a risk of initiating treatment erroneously, resulting in the potential termination of a wanted pregnancy.

The diagnostic inaccuracies would have been compounded by another source of error: inter-observer variation when measuring crown-rump length and mean sac diameter. In practice, this variation meant that if the mean sac diameter measured 20 mm, it could have been 16 mm, depending on the sonographers' measurements.[9] New stricter diagnostic criteria were therefore developed to minimise the risk of a false positive diagnosis for miscarriage: an empty gestation sac with a mean sac diameter of 25 mm or more or an embryo with crown-rump length of 7 mm or more with no visible heart activity on transvaginal ultrasonography.[8]

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.[10] Strategies to predict the women most at risk of being given a diagnosis of miscarriage at subsequent visits have been developed, but their clinical utility needs evaluation.[11–13] By providing women with information on the probable outcome, the level of anxiety and distress when waiting for diagnostic certainty can hopefully be reduced and expectations addressed.[10] Appropriate training for sonographers doing ultrasound scans in early pregnancy is essential if errors are to be avoided. Furthermore, the ultrasound scan findings should 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%.[14–18] Bleeding in early pregnancy increases the risk of a miscarriage (appendix p 6). We found six systematic

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See **Online** for appendix

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 (appendix p 7).

The pivotal role of progesterone in pregnancy is well established.[19] In view of this role, progesterone supplementation has been investigated as a treatment to stop a miscarriage in women with early pregnancy bleeding.[20]

Four systematic reviews, using different types, doses, and regimens of progestogens in women with early pregnancy bleeding, have reported on miscarriage and livebirth outcomes.[21–24] The totality of evidence, including all types of progestogens, showed a reduction in miscarriage (relative risk [RR] 0·80; 95% CI 0·66–0·97) and an increase in livebirth rate (1·05; 1·01–1·08).[22] The two main types of progestogens used in the trials were dydrogesterone, a synthetic oral progestogen, and micronised vaginal progesterone, which has an identical molecular structure to natural progesterone hormone.

Dydrogesterone was associated with an increase in livebirth rate (RR 1·16; 95% CI 1·03–1·30; appendix p 7). However, the two studies of dydrogesterone that reported on livebirth outcome were small and of poor quality.[25,26] Both were single centre, open-label studies without placebo control. One of the studies did not randomly assign participants, but instead allocated patients to dydrogesterone on Saturdays, Mondays, and Wednesdays, and to no treatment on Sundays, Tuesdays, and Thursdays.[25] The other trial was not only 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.[27] Therefore, 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 show 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 might be associated with congenital cardiac defects.[28]

Vaginal micronised progesterone was associated with an increase in livebirth or ongoing pregnancy rate (RR 1·04; 95% CI 1·00–1·08);[22] the evidence was primarily from a large UK-wide high-quality placebo-controlled trial, the PRISM Trial, which contributed 4038 (93%) participants to the total of 4345 participants in the meta-analysis.[29] A prespecified 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 miscarriages, and found a substantial increase in livebirth rate with progesterone (1·09; 1·03–1·15; number needed to treat 18).[30] This subgroup effect was confirmed in a pooled analysis (appendix p 7). There was no evidence of any safety concerns from the use of natural progesterone.[29,31] A health economic analysis found progesterone in women with early pregnancy bleeding and one or more previous miscarriages had economic dominance, meaning it was more effective and less costly compared with placebo.[32] Progesterone treatment can therefore be recommended for women with early pregnancy bleeding and a history of one or more previous miscarriages.[30] Women should be presented with the available evidence to make an informed decision.[30] The recommended treatment regimen is vaginal progesterone, 400 mg twice per day, 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.[30]

A systematic review identified three small low-quality trials on the effects of human chorionic gonadotropin in women with early pregnancy bleeding.[33] There was no clear evidence of a reduction in miscarriage rate, and there was no evidence of an increase in livebirth rate (appendix p 7). Current evidence, therefore, does not support the use of human chorionic gonadotropin in women with early pregnancy bleeding.

There is very little evidence on the effects of uterine relaxants[34] or bed rest,[27] but the available evidence does not support their use (appendix p 7).

Management of miscarriage

Miscarriage can be managed expectantly, medically with tablets, or surgically. Although historically women who had a miscarriage had a surgical procedure, there are now alternative options. Expectant management means waiting for natural release 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 release of the pregnancy. Surgical methods can involve dilation 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 completed a Cochrane network meta-analysis evaluating six approaches for managing miscarriage.[35] The network meta-analysis included 78 trials with 17795 participants. The trials included women in hospital settings with missed miscarriage (17 trials), incomplete miscarriage (36 trials), and both types of miscarriage (25 trials). Relative effects from the network meta-analysis of 59 trials (12591 women) showed that all active interventions were more likely to result in the completion of miscarriage when compared with expectant management or placebo (figure; appendix p 8). The most effective method for the completion of a miscarriage was suction aspiration with cervical preparation compared with expectant management or placebo (RR 2·12; 95% CI 1·41–3·20, very low certainty evidence; appendix p 8). The next most effective method was dilation and curettage

(1·49; 1·26–1·75, low certainty evidence; appendix p 8), followed by suction aspiration alone (1·44; 1·29–1·62, low certainty evidence; appendix p 8), mifepristone plus misoprostol combination (1·42; 1·22–1·66, moderate certainty evidence; appendix p 8), and misoprostol alone (1·30; 1·16–1·46, low certainty evidence; appendix p 8).

Relative effects from the network meta-analysis of 35 trials (8161 women) did not show important differences among the six approaches for the composite outcome of death or serious complications, such as uterine perforation, and 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 management of miscarriage did not affect subsequent pregnancy rates, with approximately four in five women giving birth within 5 years of the index miscarriage.[36]

Our recommendation is that women should be presented with available evidence and supported to choose the management approach that suits their needs and preferences. If a woman with a missed miscarriage chooses to have surgery, then suction aspiration with cervical preparation should be recommended, but if she chooses to have medical management, a combination therapy with mifepristone and misoprostol should be recommended. Women with incomplete miscarriage have a more than 90% chance of completing the miscarriage without medical intervention,[35] as the process of removing 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.

Antibiotic prophylaxis for surgical management of miscarriage

Infection can be a serious consequence of surgical management of miscarriage, particularly in low-income and middle-income countries (LMICs).[37] Pelvic infection can result in sepsis and death,[38] and long-term consequences from pelvic scarring, including increased rates of ectopic pregnancy and infertility.[39]

A meta-analysis of antibiotic prophylaxis before surgical management of miscarriage found a reduction in pelvic infection (RR 0·56; 95% CI 0·35–0·89).[40] Most of the data were from LMICs.[37,40–43] 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 2 h before surgery.[43] We recommend the use of prophylactic antibiotics before miscarriage surgery, particularly in LMIC settings.

Organisation and provision of emergency early pregnancy care

Emergency early pregnancy care is provided in various settings including primary care, private offices, emergency departments, and dedicated early pregnancy units. Early pregnancy units are emerging as a model of care in many countries (eg, the UK, the Netherlands, Canada, Ireland, and Australia). They are specialist departments that provide care for women with problems in early pregnancy, including miscarriage, ectopic pregnancy, and hyperemesis gravidarum. These units can be staffed by specialist nurses, midwives, sonographers, doctors, and other health-care professionals.

We did a literature review to evaluate the effectiveness, women's views, and cost-effectiveness of the early pregnancy units as a model of organisation of care. We found six observational studies reporting clinical outcomes from early pregnancy units' model of care compared with data from the same hospitals before the early pregnancy unit service was introduced.[44–48] Three studies reporting health economic evidence were also identified.[47–49] Relative effects from the studies showed that the early pregnancy unit model of care was more likely to result in a lower number of hospital admissions (four studies, 1323 women; RR 0·48; 95% CI 0·37–0·61), lower number of re-admissions to hospital (three studies, 4950 women; 0·76; 0·61–0·95), and lower rates of surgery (two studies, 573 women; 0·35; 0·17–0·71). Two studies estimated the annual savings from establishing an early pregnancy unit service to be £109 440 in the UK setting,[49] and AU$257 617 in the Australian setting.[48] Another study estimated cost savings to be up to €657 per woman in the Netherlands.[47]

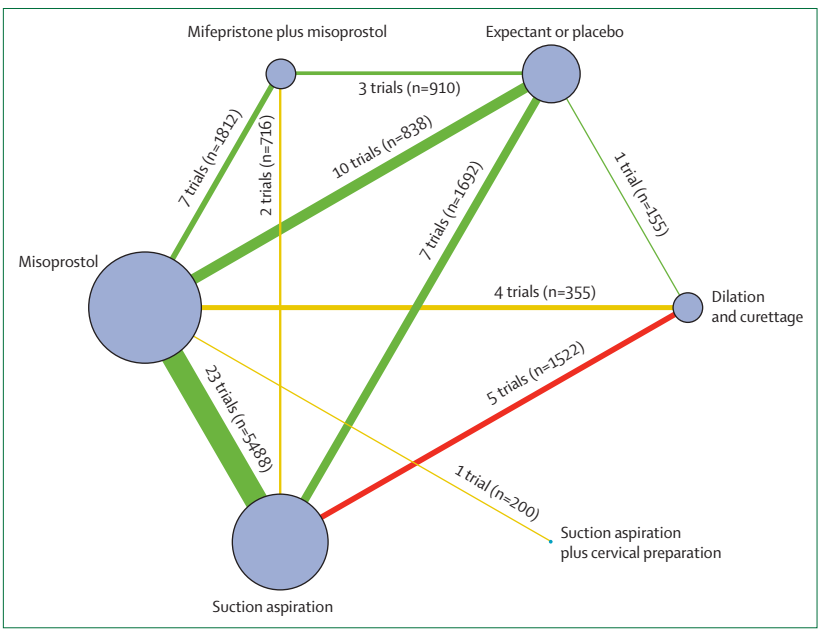

Figure: **Network diagram of studies of miscarriage management for the outcome of completion of miscarriage**

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 proportionally 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 green for moderate certainty evidence, yellow for low certainty evidence, and red for very low certainty evidence.

A qualitative study in the UK found that women valued the care they received in early pregnancy units, 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 early pregnancy unit.[50] The evidence supporting the early pregnancy unit model of care compared with 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 model of care might be cost-effective, at least in high-income country settings. As an early pregnancy unit model is associated with a reduction in hospital admissions, re-admissions and need for surgery and health economic arguments are likely to be in favour of an early pregnancy unit model in LMICs too.

Global perspectives

The availability and accessibility of services for the diagnosis and management of miscarriage varies greatly worldwide. Emergency early pregnancy care is provided in more than 200 dedicated early pregnancy units in the UK.[49] Similar units have now been established in many other countries, including the Netherlands, Canada, Ireland, and Australia.[47,51–54] In the USA, the first early pregnancy unit was established in Denver (CO) in 2013.[54] The concept of a dedicated multiprofessional service for women with early pregnancy complications is now moving to LMICs, such as Nigeria.[55]

There are several key elements that are required to establish a successful early pregnancy unit service. These key elements include an availability of resources (eg, drugs and ultrasound machines), an ability to efficiently process blood tests (eg, human chorionic gonadotropin and progesterone), training of individuals to be confident and competent in early pregnancy ultrasound scanning, training in giving bad news, and provision of psychological support. These resources are scarce 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 more than 90% felt the shortage of availability for transvaginal ultrasound scanning was the most important obstacle against achieving effective care for women with miscarriage.[55] Ultrasound provisions are particularly scarce 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 percentage falls to 6%.[56] In South Africa, the urban to rural gap is again seen with 68% of women in urban areas receiving pregnancy ultrasound, and only 18% in rural areas.[56]

There are a multitude of factors to consider when introducing ultrasound services in LMICs, including patient demographics, disease patterns, geographical factors, cultural beliefs, and availability of sonographer training and ultrasound machines. The availability of appropriately trained practitioners and ultrasound machines is a considerable barrier to service provision in many low resource settings.[57] Potential solutions include competency-based training programmes in ultrasonography,[58] and the provision of innovative handheld ultrasound machines.[59]

Studies that explore the management of miscarriage in LMICs frequently have crossover 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 management of miscarriage; however, arrangements for appropriate clinical follow-up are necessary as there is a risk of incomplete release of pregnancy tissue with this method.[60,61] Manual vacuum aspiration is effective and safe for early pregnancies and is recommended by WHO to replace dilation and curettage.[62] However, a strategic assessment of unsafe abortion in Malawi found that manual vacuum aspiration is used infrequently, with dilation and curettage being used in preference.[63] Reasons suggested for this preference included a shortage of manual vacuum aspiration equipment, equipment being locked up to prevent its use in inducing abortions, and a shortage of trained health-care practitioners. There is a need for improved training and provisions for manual vacuum aspiration.

Women and their partners who are affected by miscarriage in LMICs are often overlooked due to competing health priorities in health-care facilities. 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, which 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 health care for early pregnancy complications is also needed.

Discussion

Sporadic miscarriage is common. Accurate diagnosis of miscarriage is the foundation of an effective early pregnancy service, and relies on high-quality ultrasonography. There is high-certainty evidence that vaginal micronised progesterone increases livebirth rates in women with early pregnancy bleeding and a history of miscarriage. Women who have a miscarriage can choose to have expectant, medical, or surgical management; surgical management with vacuum suction aspiration after cervical preparation is ranked first among six competing strategies for completing a miscarriage. Among the 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 given by clinical nurse specialists and doctors with specialist training in early pregnancy care, in the setting of early pregnancy units, which 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 this 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 among experts when this was necessary.

Most of the available evidence relates to high-income settings, although most miscarriages happen in low resource settings. There is an evidence gap on miscarriage prevalence, consequences, and costs in LMICs that needs 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; as a priority, health-care funders and providers should make these essential supplies universally available.

Miscarriage causes devastation to large numbers of couples in every country; there is silence around miscarriage from women and their partners, health-care providers, policy makers, and funders. We urge all stakeholders to develop and provide a comprehensive miscarriage care service, ideally organised in the setting of a dedicated early pregnancy unit. Urgent research is needed into 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 and review of all sections and agreed to submit the manuscript. The manuscript represents the view of named authors only.

Declaration of interests

We declare no competing interests.

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