

## Miscarriage 3



# Recurrent miscarriage: evidence to accelerate action

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Women who have had repeated miscarriages often have uncertainties about the cause, the likelihood of recurrence, the investigations they need, and the treatments that might help. Health-care policy makers and providers have uncertainties about the optimal ways to organise and provide care. For this Series paper, we have developed recommendations for practice from literature reviews, appraisal of guidelines, and a UK-wide consensus conference that was held in December, 2019. Caregivers should individualise care according to the clinical needs and preferences of women and their partners. We define a minimum set of investigations and treatments to be offered to couples who have had recurrent miscarriages, and urge health-care policy makers and providers to make them universally available. The essential investigations include measurements of lupus anticoagulant, anticardiolipin antibodies, thyroid function, and a transvaginal pelvic ultrasound scan. The key treatments to consider are first trimester progesterone administration, levothyroxine in women with subclinical hypothyroidism, and the combination of aspirin and heparin in women with antiphospholipid antibodies. Appropriate screening and care for mental health issues and future obstetric risks, particularly preterm birth, fetal growth restriction, and stillbirth, will need to be incorporated into the care pathway for couples with a history of recurrent miscarriage. We suggest health-care services structure care using a graded model in which women are offered online health-care advice and support, care in a nurse or midwifery-led clinic, and care in a medical consultant-led clinic, according to clinical needs.

### Introduction

For couples who have had repeated miscarriages, there are many uncertainties. Women and their partners have uncertainties about the cause of miscarriage (aetiology), the likelihood of recurrence (prognosis), the tests required (diagnosis), and treatments that could prevent a recurrence (therapy). Health-care providers have questions about which investigations are useful for a couple with recurrent miscarriage, how providers can improve outcomes for women at risk of a miscarriage, and about ways to plan, organise, and provide optimal care.

Specialist clinics for recurrent miscarriage often offer different tests and treatments, resulting in couples seeking care in multiple clinics. The wide variation in practice is reflected in professional body guidelines that often have varying, and occasionally contradictory, recommendations.<sup>1-4</sup> The latest UK National Institute for Health and Care Excellence guideline on the management of miscarriage and ectopic pregnancy includes 93 recommendations,<sup>1</sup> and the European Society of Human Reproduction and Embryology (ESHRE) guideline on recurrent pregnancy loss has 77 recommendations.<sup>2</sup> Despite an abundance of guidance, clinical practice is inconsistent and poorly organised.

To accelerate evidence-based care, we have developed recommendations for practice from literature reviews,<sup>5-34</sup> appraisal of guidelines, and a UK-wide consensus conference that was held in December, 2019 (panel), involving women and health-care providers. The recommendations are centred on couples who have had recurrent miscarriage, focusing on relevant investigations

and interventions for the prevention of miscarriage. Finally, we propose a model of care that could be implemented by health-care providers in the UK to standardise the investigations and management of couples with recurrent miscarriage. We conclude with a call for improved care and high-quality research in targeted areas.

### Investigations for recurrent miscarriage

The primary reason for investigating a couple with recurrent miscarriage is to identify any underlying condition for which effective treatment exists, to try to improve outcomes. However, even if an effective treatment is not available, the knowledge of contributory factors for repeated miscarriages, prognostic implications for future pregnancy, acknowledgment of the trauma and distress felt, and the personal quest for answers, can be important for women and their partners. In 2017, the ESHRE guideline development group reviewed the evidence on recurrent miscarriage investigations to explore: (1) whether there was an association between a test result and miscarriage risk; (2) if an association was found, was there evidence that it was contributory to miscarriage risk; (3) whether the test result had any prognostic value; and (4) whether there was evidence that treatment improved outcomes (table).<sup>2</sup>

Associations were found between many test results and miscarriage risk; however, there was little evidence that the associations represented a causative or contributory relationship.<sup>2</sup> Furthermore, there was little evidence of any prognostic value for many tests, and also

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### Key messages

- Investigations for recurrent miscarriage: useful tests for investigating recurrent miscarriage include lupus anticoagulant, anticardiolipin antibodies, thyroid function tests, and transvaginal pelvic ultrasound scan. Chromosome analysis of pregnancy tissue can be done for explanatory purposes. Selected couples can benefit from parental karyotyping.
- Prevention of miscarriage in women at high risk of miscarriage: there is no high-quality evidence that any treatment is useful in preventing miscarriages in women at high risk of miscarriage. There is moderate-quality evidence to suggest that progesterone can increase livebirth rates in patients with recurrent miscarriage, and low-quality evidence that levothyroxine can decrease the risk of miscarriage in women with subclinical hypothyroidism (thyroid-stimulating hormone concentration >4.0 mIU/L). There is low-quality evidence that a combination of aspirin and heparin can increase livebirth rates in women who have antiphospholipid antibodies and a history of recurrent miscarriage.
- Organisation and delivery of miscarriage services: a model of care is needed that addresses the balance between the need for evidence-based management and supportive care while targeting health-care resources appropriately. The appropriate model for a particular country can vary according to the prevailing health-care system, opportunities for service development and reorganisation, and available resources. We propose a graded approach for care for the UK based on the consensus from a UK-wide national conference in December, 2019. The graded approach would entail women are supported with online and preconceptual advice and screened for risk factors following their first miscarriage. After a second miscarriage, women are offered a nurse or midwifery-led service, offering continuity of care, appropriate investigations, and ultrasound scanning for reassurance in a subsequent pregnancy. Following a third or subsequent miscarriage, women are offered a consultant-led service with full panel of investigations and interventions for recurrent miscarriage.

### Search strategy and selection criteria

The recommendations in this Series paper are based on a literature review and appraisal of professional body guidelines. For the literature review, we searched the Cochrane Database of Systematic Reviews and MEDLINE (from inception until Jan 9, 2020) for systematic reviews of randomised controlled trials, specifying or reporting any miscarriage outcome. 30 reviews focused on the prevention of miscarriage in women who were not bleeding. We report results for miscarriage and livebirth separately. For the review of professional body guidelines, we reviewed the latest international guidance on the management and treatment of miscarriage, which included guidelines from the National Institute for Health and Care Excellence on the management of ectopic pregnancy and miscarriage, the European Society of Human Reproduction and Embryology guideline on the management of recurrent pregnancy loss, the American College of Obstetricians and Gynecologists guideline on early pregnancy loss, and the American Society for Reproductive Medicine guideline on recurrent pregnancy loss.

### Progestogens

Progesterone is essential for the establishment and maintenance of a pregnancy.<sup>42</sup> The central role of progesterone in early pregnancy has led clinicians and researchers to hypothesise that progesterone deficiency could be a cause of some miscarriages.

A Cochrane review<sup>29</sup> synthesised ten studies that had used various types of progestogens, including natural progesterone, which was used in the largest and highest-quality trial on this subject that contributed 49% of data to the analysis total of 1684 (appendix p 5).<sup>43</sup> We updated this Cochrane review, and found that the miscarriage rate for women with recurrent miscarriage was reduced and livebirth rate was increased, but these results were not statistically significant (appendix p 5). The livebirth rate was higher for the subgroup of women with a history of three or more miscarriages than the subgroup of women with a history of two or more miscarriages (appendix p 5). There was no evidence of any safety concerns from the first trimester use of micronised vaginal progesterone, which has an identical molecular structure to natural progesterone.<sup>43,44</sup> Micronised vaginal progesterone treatment can therefore be considered for asymptomatic women with recurrent miscarriage, and is likely to be more effective in women with a high number of previous miscarriages.

### Anticoagulant therapy

Thrombophilia, whether acquired (eg, antiphospholipid antibodies) or inherited (eg, factor V Leiden), is associated with vascular thrombosis and adverse pregnancy outcomes such as recurrent miscarriage.<sup>45</sup> Anticoagulant therapy with low-dose aspirin, heparin, or both has been evaluated in four systematic reviews.<sup>14,16,17,34</sup> The studies

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for high-quality evidence of therapeutic benefit for treatments based on test results (table). The tests of value for the investigation of couples with recurrent miscarriage are the measurement of antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies), and thyroid function and pelvic ultrasoundography (preferably three-dimensional transvaginal ultrasound) to assess the uterine cavity.<sup>2</sup> Chromosome testing of pregnancy tissue can be done for explanatory purposes; the recommended test is array-based comparative genomic hybridisation.<sup>2</sup> Some couples might benefit from parental karyotyping.<sup>2,40,41</sup>

### Prevention of miscarriage in women at high risk of miscarriage

Several interventions have targeted asymptomatic women, who have no vaginal bleeding or pelvic pain in early pregnancy, but have other risk factors for miscarriage, such as a history of recurrent pregnancy losses. There were 30 systematic reviews reporting on 12 classes of interventions to prevent miscarriages in asymptomatic women. The key interventions were progestogens, anticoagulants, levothyroxine, metformin, human chorionic gonadotropin, immunomodulatory agents, and micronutrient supplementation (appendix p 5).

### Panel: Three approaches to manage recurrent miscarriage

During a UK-wide consensus conference on miscarriage care in December, 2019, a group of 83 key stakeholders from across the UK met to discuss the development of a standardised national care package for recurrent miscarriage. The conference was funded by Tommy's Charity, with no involvement or sponsorship from any commercial organisations. Key questions about tests, treatments, and organisation of care were presented for discussion, along with a summary of available evidence and guidance. Agreements were reached through consensus.

Three broad approaches to support women with recurrent miscarriage are in use worldwide. In the first model, women receive minimal or no care until they have had three miscarriages. This approach results in missed opportunities for preconception counselling and care, including the opportunity to address bodyweight, smoking, alcohol consumption, and diet, particularly intake of micronutrients such as folate. Couples might not be offered any reasons for the miscarriages, with the only advice being to try again. Mental health following miscarriage is not appreciated or addressed, and dissatisfaction with the service is common. This approach is widely used in the UK National Health Service (NHS); however, it was agreed unanimously at the UK consensus conference that this model is not fit for purpose.

The second model is based on a graded approach. After the first miscarriage, women will be guided to information about miscarriage, resources to address their physical and mental health needs following pregnancy loss, and ways to optimise their health for future pregnancy. This approach could involve patient support groups, online self-help strategies for mental health, weight management, smoking and recreational drugs cessation services, information on appropriate preconceptual folate and vitamin D supplementation, referral to necessary services for management and optimisation of chronic maternal medical conditions (eg, diabetes, hypertension, heart disease, and epilepsy), and screening for mental health issues. Following a second miscarriage, women will be offered an appointment at a miscarriage clinic that could be nurse or midwifery-led, in which tests for full blood count and thyroid function are offered, in addition to addressing lifestyle issues.<sup>35</sup> Referral for specialist care will be arranged if tests are abnormal or if there is a chronic medical or mental health problem. Women will have access to support and early pregnancy reassurance scans in subsequent pregnancies. After a third miscarriage, women will be offered an appointment at a medical consultant-led clinic, in which additional tests and a full range of treatments can be offered. Pregnancy tissue from the third and any subsequent miscarriages

will be sent for genetic testing. Blood tests for antiphospholipid antibodies and a pelvic ultrasound scan (ideally three-dimensional transvaginal) will be arranged and, if necessary, parental karyotyping will be offered depending on the clinical history and the results of the genetic analysis of pregnancy tissue from previous losses. Appropriate screening and care for mental health issues and future obstetric risks, particularly preterm birth, fetal growth restriction, and stillbirth, will need to be incorporated into the care pathway for couples with a history of recurrent miscarriage.

The graded approach takes advantage of online resources and promotion of continuity of care, and could benefit couples who have miscarriages in different resource and health system settings. In the absence of evidence for this approach in the miscarriage context, evidence from other reproductive health areas, such as midwifery-led continuity of care models could provide useful information. A Cochrane review of midwifery-led continuity of care models found several benefits, including fewer preterm births and fewer fetal deaths at less than 24 weeks' gestation.<sup>36</sup> A continuity of care model can integrate care to meet physical and psychological health needs, addressing ongoing concerns and coordination of clinical investigations before and during pregnancy. The model can ensure women and partners know when, where, and how to access the care and help they need, encourage positive lifestyle interventions that might be of benefit, and encourage early referral for relevant investigations in subsequent pregnancies. In addition to the potential effect on subsequent pregnancy outcomes, a continuity approach could increase satisfaction with care,<sup>36</sup> provide an opportunity to implement standardised women-centred outcome measures,<sup>37</sup> collate data to monitor the consequences of miscarriage, and provide a hub to support research.<sup>38</sup>

In the third model, women are seen in a medical consultant clinic after two previous pregnancy losses. A full panel of investigations is often offered from the outset. This model is common in private recurrent miscarriage clinics in the UK and internationally, and in a small number of NHS hospitals in the UK. This model has substantial limitations. Women with two previous miscarriages have a high chance of a future successful pregnancy,<sup>39</sup> and they do not need extensive investigation or treatments; however, the third model makes them susceptible to requesting and receiving interventions that could be of little benefit and have the potential to cause harm. In addition, this approach might not represent an optimal use of finite health-care resources.

The three models were discussed at the UK conference, in which 80 (96%) of 83 participants voted for the graded approach.

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See Online for appendix

in these reviews were mostly of low methodological quality. Results from a Cochrane review published in 2020,<sup>34</sup> and analyses from another Cochrane review<sup>14</sup> are presented in the appendix p 5. Analysis of five trials showed that low-dose aspirin and heparin reduced the

miscarriage rate (relative risk [RR] 0.48; 95% CI 0.32–0.71; low certainty evidence) and increased livebirth rate (1.27; 1.09–1.49; low certainty evidence),<sup>34</sup> compared with aspirin alone, in women with antiphospholipid syndrome and a history of recurrent

	Is there evidence of an association between the test result and miscarriage?	Is there evidence that the association is contributory to miscarriage risk?	Is there evidence that the test result has prognostic value?	Is there evidence that treatment based on test results improves outcomes?
Antiphospholipid antibodies: lupus anticoagulant and anticardiolipin antibodies	Yes	Yes	Yes	Weak evidence
$\beta$ -2-glycoprotein 1	Possibly	Possibly	No data	No data
Hereditary thrombophilia (factor V Leiden, prothrombin genetic variant, <i>MTHFR</i> genetic variant, protein C, protein S, and antithrombin deficiency)	Weak evidence	Unclear	Yes	No
Karyotyping of pregnancy tissue	Yes	Yes	Weak evidence	No
Parental genetic testing	Yes	Yes	Yes	No (however, testing can allow for genetic testing in subsequent pregnancies)
Thyroid function test				
Hypothyroidism	Only for sporadic pregnancy loss	Only for sporadic pregnancy loss	Yes	Yes
Subclinical hypothyroidism	Yes	Yes	Not clear	Not clear
Thyroid antibodies	Yes	Yes	Yes	No
Ultrasonography to diagnose congenital uterine abnormality	Yes	Possibly	No data	Little data
Immune testing (human leukocyte antigen compatibility, human leukocyte antigen class II, human leukocyte antigen-G, KIR and human leukocyte antigen-C, cytokines, and natural killer cells)	Little data	Little data	No data	No data
Anti-HY immunity	Moderate	Yes	Yes	No data
Antinuclear antibodies	Yes	Little data	Unclear	No data
Hormone tests and ultrasound: polycystic ovary syndrome	Yes	Yes	No	Possibly (metformin treatment)
Vitamin D	Possibly	Possibly	Little data	No data
Sperm DNA damage test	Moderate	Probably	Unclear	No

Adapted from the European Society of Human Reproduction and Embryology Guideline Group on Recurrent Pregnancy Loss.<sup>2</sup> KIR=killer immunoglobulin-like receptor.

**Table: Evidence summary of investigations for couples with recurrent miscarriage**

miscarriage (appendix p 5). There was no evidence of harm from available data.<sup>34</sup> The professional body guidelines recommend the use of low-dose aspirin and heparin in women with antiphospholipid syndrome and recurrent miscarriage.<sup>2</sup>

There is no evidence to support the use of aspirin and heparin in women with inherited thrombophilia or in women who do not have thrombophilia.<sup>14</sup> As there is evidence that aspirin therapy could actually increase the risk of miscarriage in women who do not have thrombophilia,<sup>17</sup> empirical treatment with aspirin in these women should be avoided.

### Levothyroxine

Treatment of overt thyroid disorders before conception and in pregnancy is universally accepted for reducing adverse pregnancy outcomes, including miscarriage.<sup>46</sup> There is no clear agreement, however, on the management of women with subclinical hypothyroidism or thyroid autoimmunity. There is some evidence that subclinical hypothyroidism is linked to miscarriage.<sup>47</sup> Thyroid autoantibodies are linked to miscarriage, even in women without thyroid dysfunction.<sup>48,49</sup>

We have summarised the evidence from trials investigating levothyroxine treatment, started before conception or in early pregnancy, for subclinical hypothyroidism in women who are trying to conceive. Three trials were identified, and all were of low methodological quality.<sup>50-52</sup> Two of the three trials used a thyroid-stimulating hormone threshold of 4.0 mIU/L,<sup>51,52</sup> whereas the third trial used the threshold of 4.5 mIU/L.<sup>50</sup> Results showed a reduction in miscarriage rate with levothyroxine treatment (appendix p 6). Data for livebirth did not provide a clear finding (appendix p 6).

Based on the available evidence, levothyroxine treatment could be considered for women with subclinical hypothyroidism in whom thyroid-stimulating hormone concentrations are above 4.0 mIU/L. However, further research is needed to generate high-quality evidence for women with subclinical hypothyroidism, particularly in women with mildly elevated thyroid-stimulating hormone concentrations (2.5–4.0 mIU/L).

Small low-quality trials had suggested a benefit with levothyroxine treatment in women with thyroid antibodies but normal thyroid function; however, there is now evidence from two large high-quality trials that

levothyroxine neither reduces miscarriage rates nor increases livebirth rates in women with thyroid antibodies.<sup>53,54</sup> The analysis of data for levothyroxine treatment in women with normal thyroid function but with thyroid antibodies is presented in the appendix (p 6); six studies reporting on miscarriage found no benefit with levothyroxine treatment.<sup>49,53–57</sup> The three studies analysed for the outcome of livebirth also showed no benefit with levothyroxine treatment (appendix p 6).<sup>53–55</sup> Women with normal thyroid function but with thyroid antibodies do not, therefore, require levothyroxine treatment.

### Metformin

Polycystic ovary syndrome is a common endocrine disorder, which affects up to 15% of women of reproductive age.<sup>58</sup> Increased insulin resistance, hyperandrogenism, and obesity are closely linked to polycystic ovary syndrome and all have a substantial effect on reproductive outcomes, including miscarriage.<sup>59–61</sup> As insulin resistance and resulting hyperinsulinaemia are key metabolic features in women with polycystic ovary syndrome, their improvement, through metformin treatment, could improve pregnancy outcomes.

A systematic review of four small low-quality studies showed no difference in miscarriage outcome with metformin, but a suggestion of potential benefit in livebirth outcome (appendix p 6).<sup>32</sup> An individual patient data meta-analysis, including data from the PregMet2 trial,<sup>62</sup> in which metformin was commenced late in the first trimester, showed 18 (5%) of 397 women had late miscarriage in the metformin group compared with 40 (10%) of 399 women in the placebo group (0.43; 0.23–0.79;  $p=0.004$ ). High-quality trials are needed to evaluate the effects of metformin on miscarriage and livebirth rates in women with polycystic ovary syndrome.

### Human chorionic gonadotropin

The placental hormone—human chorionic gonadotropin—is important for the production of progesterone and implantation of the embryo.<sup>63</sup> It has been hypothesised that a suboptimal concentration of human chorionic gonadotropin might therefore affect endometrial receptivity. In view of this, clinicians and researchers have studied the role of human chorionic gonadotropin as a treatment for recurrent miscarriage.

A systematic review of five randomised controlled trials of human chorionic gonadotropin treatment in women with recurrent miscarriage found a reduction in miscarriage (RR 0.51; 95% CI 0.32–0.81; appendix p 6).<sup>10</sup> However, this systematic review included two methodologically weak studies; when these two studies were excluded in a sensitivity analysis, a benefit was not confirmed (0.74; 0.44–1.23).<sup>10</sup> The evidence supporting human chorionic gonadotropin supplementation to prevent recurrent miscarriage therefore is equivocal, and high-quality research is needed.

### Immunotherapy

A fetus has antigens of maternal and paternal origins. The physiological mechanisms that allow a woman to tolerate the paternal antigens are poorly understood; however a dysfunction in immune modulation has been hypothesised to be a cause of miscarriage. Various immunological markers, including elevated concentrations of natural killer cells,<sup>64–66</sup> dysregulated cytokines,<sup>67,68</sup> and the presence of antiphospholipid antibodies or other autoantibodies,<sup>69,70</sup> have been linked to miscarriages.

Three systematic reviews evaluated immunological interventions, which included oral prednisolone, intravenous immunoglobulins, lymphocyte immunotherapy, and trophoblast membrane immunisation.<sup>71–73</sup> The studies included in the reviews are small and were of low or moderate quality. None of the interventions studied across the three reviews were associated with a reduction in miscarriages or increase in livebirths. There is therefore insufficient evidence to recommend use of immunotherapy to prevent recurrent miscarriage.

### Micronutrients

Vitamins are essential nutrients required for various bodily functions, including normal metabolism and reproduction. Associations have been found between decreased antioxidant defence and pregnancy outcomes.<sup>74</sup> Vitamins, particularly those with antioxidant effects, have therefore been studied as a means of reducing miscarriage risk.

Three systematic reviews evaluated the affects of micronutrients, including vitamins A, C, and E, folate, and iron, to reduce miscarriage (appendix p 6).<sup>18,20,30</sup> Various micronutrients were combined in different formulations and doses. There was no evidence that any of the regimens reduced the risk of miscarriage.

### Surgical interventions for uterine anomalies

Surgical treatment of uterine anomalies, particularly the division of a uterine septum, is a subject of debate. A systematic review on this subject did not find any randomised trials comparing hysteroscopic septum resection with expectant management.<sup>26</sup> The results of the TRUST trial (Dutch Trial Register NTR1676) are awaited.

### Preimplantation genetic screening

Two systematic reviews have explored preimplantation genetic screening, which is now more commonly known as preimplantation genetic testing for aneuploidy, in women with recurrent miscarriage.<sup>75,76</sup> Neither of the reviews identified randomised trial data. The non-randomised data in these reviews suggested similar livebirth rates between the women having preimplantation genetic screening and those conceiving naturally. The available evidence is therefore insufficient to support preimplantation genetic screening in clinical practice.

### Global perspectives

Childless women face discrimination, stigma, and ostracism in many cultures worldwide.<sup>77</sup> It is not only childless women who are stigmatised, but also women who have not fulfilled their expected role to bear several children. The stigmatisation can be extreme in some countries where childless women are viewed as a burden on the socioeconomic wellbeing of a community, and marriage without children is considered as a loss for the two individuals.<sup>77</sup> This stigmatisation is a heavy burden to carry for women in many low-income and middle-income countries (LMICs).

Despite its great importance and substantial socio-cultural effect, miscarriage prevention is a low priority public health issue in LMICs. Care of affected couples is often overlooked because of competing health priorities, with very few formal services available for women with recurrent miscarriages. There needs to be a minimum service available globally for couples with recurrent miscarriage. Within the LMIC setting, this service can include tests to check for anaemia, thyroid abnormalities, and antiphospholipid syndrome, with appropriate treatment based on the results. There also needs to be a focus on providing prepregnancy counselling and psychological support to couples with repeated miscarriages.

### Discussion

Recurrent miscarriage is a devastating experience for most couples. Couples who have had recurrent miscarriages often go to multiple doctors and many clinics in their search for a cause and remedy for miscarriage. However, there are very few investigations and treatments with clear evidence of benefit. Useful tests for investigating recurrent miscarriage include lupus anticoagulant and anticardiolipin antibodies, thyroid function, and pelvic ultrasonography. Genetic analysis of pregnancy tissue can be done for explanatory purposes, and some couples might benefit from parental karyotyping. There is no high-quality evidence for any treatment to prevent miscarriages in women at high risk of miscarriage. There is some evidence that progesterone could increase livebirth rates in women with recurrent miscarriage, levothyroxine might decrease the risk of miscarriage in women with subclinical hypothyroidism, and a combination of aspirin and heparin could increase livebirths in women with recurrent miscarriage and antiphospholipid antibodies.

The recommendations in this Series paper are based on the best available evidence. We have relied on published systematic reviews, with recommendations reflecting the current state of knowledge. However, there were limitations in the evidence, particularly in the quality of many trials that contributed to the systematic reviews. Furthermore, we have relied on consensus among experts to generate recommendations for questions for which there was little evidence. A model of care is needed that

addresses the balance between the need for evidence-based management and supportive care while targeting health-care resources appropriately. We propose a graded approach. The graded model is based on the consensus of stakeholders in the UK; for other countries, other models of service organisation and delivery could be appropriate. Acceleration of high-quality evidence gathering through the integration of early pregnancy services and specialist recurrent miscarriage clinics across different health-care systems is essential.

We recommend caregivers neither normalise nor over-medicalise recurrent miscarriage care, but individualise care according to women's and their partners' needs and preferences. We have defined the minimum set of investigations and treatments that should be offered to couples who have had repeated miscarriages, and recommend that health-care policy makers and providers make these universally available. Services for couples who have had recurrent miscarriages should not only have their physical support needs at the centre of the programme, but also their psychological support needs.

There needs to be a concerted move away from the current fragmented approach in the delivery of care for couples who have miscarried, and instead have validated and standardised care pathways tailored to the need of couples. Their individualised risk of recurrence should also be established. Dedicated research centres with cross-disciplinary expertise in genetics, developmental and reproductive biology, data science, and clinical research should accelerate the discovery of molecular and cellular drivers of recurrent pregnancy loss, and develop new therapeutic strategies. The agenda should include the development of flexible and responsive trial methodologies to hasten the evaluation of new and existing interventions and treatments.

Research is required on optimal ways to stratify women with recurrent miscarriage, so that therapy and psychological care can be appropriately targeted, and on optimal ways of organising and providing care. New diagnostic tests and effective treatments are needed to improve preconceptual endometrium and sperm. Several treatment questions need answering, which include the role of aspirin and heparin for inherited thrombophilia, levothyroxine for women with mild subclinical hypothyroidism (thyroid-stimulating hormone concentration between 2.5 mIU/L and 4.0 mIU/L), preconception and early pregnancy metformin for women with polycystic ovary syndrome, and human chorionic gonadotropin treatment for women with recurrent miscarriages. Another urgent research priority is the exploration of optimal management approaches for women with mental health illness after miscarriages.

#### 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 views of this paper's authors only.

**Declaration of interests**

We declare no competing interests.

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