Miscarriage 3

Recurrent miscarriage: evidence to accelerate action

Arri Coomarasamy, Rima K Dhillon-Smith, Argyro Papadopoulou, Maya Al-Memar, Jane Brewin, Vikki M Abrahams, Abha Maheshwari, Ole B Christiansen, Mary D Stephenson, Mariëtte Goddijn, Olufemi T Oladapo, Chandrika N Wijeyaratne, Debra Bick, Hassan Shehata, Rachel Small, Phillip R Bennett, Lesley Regan, Raj Rai, Tom Bourne, Rajinder Kaur, Oonagh Pickering, Jan J Brosens, Adam J Devall, Ioannis D Gallos, Siobhan Quenby

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.[1–4] The latest UK National Institute for Health and Care Excellence guideline on the management of miscarriage and ectopic pregnancy includes 93 recommendations,[1] and the European Society of Human Reproduction and Embryology (ESHRE) guideline on recurrent pregnancy loss has 77 recommendations.[2] 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,[5–34] 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).[2]

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

Lancet 2021; 397: 1675–82

Published Online
April 26, 2021
https://doi.org/10.1016/S0140-6736(21)00681-4

See Editorial page 1597

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

Tommy's National Centre for Miscarriage Research, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK (Prof A Coomarasamy MD, R K Dhillon-Smith PhD, A Papadopoulou MBChB, R Kaur BA, O Pickering DipHE, A J Devall PhD, I D Gallos MD); **Tommy's National Centre for Miscarriage Research, Imperial College London, London, UK** (M Al-Memar PhD, Prof P R Bennett PhD, Prof L Regan MD, R Rai MD, Prof T Bourne PhD); **Tommy's Charity, Laurence Pountney Hill, London, UK** (J Brewin BSc); **Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University, New Haven, CT, USA** (V M Abrahams PhD); **Aberdeen Centre of Reproductive Medicine, Aberdeen, UK** (Prof A Maheshwari MD); **Centre for Recurrent Pregnancy Loss of Western Denmark, Department of Obstetrics and Gynaecology, Aalborg University Hospital, Aalborg, Denmark** (Prof O B Christiansen PhD); **University of Illinois Recurrent Pregnancy Loss Program, Department of Obstetrics and Gynecology, University of Illinois at Chicago, Chicago, IL, USA** (Prof M D Stephenson MD); **Center for Reproductive Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands** (Prof M Goddijn PhD); **UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human**

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.

Reproduction, Department of Sexual and Reproductive Health and Research, WHO, Geneva, Switzerland (O T Oladapo MD); **Department of Reproductive Medicine, University of Colombo, Colombo, Sri Lanka** (Prof C N Wijeyaratne MD); **Warwick Clinical Trials Unit, University of Warwick, Warwick, UK** (D Bick PhD); **Epsom General Hospital, Epsom and St Helier University Hospitals NHS Trust, Epsom, UK** (H Shehata MD); **Birmingham Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK** (R Small RGN); **Division of Biomedical Sciences, Warwick Medical School, University of Warwick, Warwick, UK** (Prof J J Brosens PhD, Prof S Quenby MD); **Tommy's National Centre for Miscarriage Research, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK** (Prof J J Brosens, Prof S Quenby)

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 ultrasonography (preferably three-dimensional transvaginal ultrasound) to assess the uterine cavity.[2] Chromosome testing of pregnancy tissue can be done for explanatory purposes; the recommended test is array-based comparative genomic hybridisation.[2] Some couples might benefit from parental karyotyping.[2,40,41]

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).

Progestogens

Progesterone is essential for the establishment and maintenance of a pregnancy.[42] 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[29] 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).[43] 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.[43,44] 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.[45] Anticoagulant therapy with low-dose aspirin, heparin, or both has been evaluated in four systematic reviews.[14,16,17,34] The studies

Correspondence to:
Prof Arri Coomarasamy, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham B15 2TT, UK
a.coomarasamy@bham.ac.uk

See Online for appendix

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.[35] 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.[36] 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,[36] provide an opportunity to implement standardised women-centred outcome measures,[37] collate data to monitor the consequences of miscarriage, and provide a hub to support research.[38]

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,[39] 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.

in these reviews were mostly of low methodological quality. Results from a Cochrane review published in 2020,[34] and analyses from another Cochrane review[14] 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),[34] compared with aspirin alone, in women with anti-phospholipid 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
β-2-glycoprotein 1	Possibly	Possibly	No data	No data
Hereditary thrombophilia (factor V Leiden, prothrombin genetic variant, *MTHFR* 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.[2] 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.[34] The professional body guidelines recommend the use of low-dose aspirin and heparin in women with antiphospholipid syndrome and recurrent miscarriage.[2]

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.[14] As there is evidence that aspirin therapy could actually increase the risk of miscarriage in women who do not have thrombophilia,[17] 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.[46] 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.[47] Thyroid autoantibodies are linked to miscarriage, even in women without thyroid dysfunction.[48,49]

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.[50–52] Two of the three trials used a thyroid-stimulating hormone threshold of 4·0 mIU/L,[51,52] whereas the third trial used the threshold of 4·5 mIU/L.[50] 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.[53,54] 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.[49,53–57] The three studies analysed for the outcome of livebirth also showed no benefit with levothyroxine treatment (appendix p 6).[53–55] 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.[58] Increased insulin resistance, hyperandrogenism, and obesity are closely linked to polycystic ovary syndrome and all have a substantial effect on reproductive outcomes, including miscarriage.[59–61] 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).[32] An individual patient data meta-analysis, including data from the PregMet2 trial,[62] 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.[63] 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).[10] 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).[10] 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,[64–66] dysregulated cytokines,[67,68] and the presence of antiphospholipid antibodies or other autoantibodies,[69,70] have been linked to miscarriages.

Three systematic reviews evaluated immunological interventions, which included oral prednisolone, intravenous immunoglobulins, lymphocyte immunotherapy, and trophoblast membrane immunisation.[71–73] 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.[74] 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).[18,20,30] 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.[26] 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.[75,76] 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.[77] 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.[77] 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.

Acknowledgments
The Tommy's Charity funds the Tommy's National Centre for Miscarriage Research. JJB holds a Wellcome Trust Investigator Award (212233/Z/18/Z). The funders had no role in the writing of the article or in the decision to submit the paper for publication.

References

1 National Institute for Health and Clinical Excellence. Ectopic pregnancy and miscarriage: diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage. 2019. https://www.nice.org.uk/guidance/ng126 (accessed Apr 20, 2021).
2 European Society of Human Reproduction and Embryology Guideline Group on Recurrent Pregnancy Loss, Bender AR, Christiansen OB, et al. European Society of Human Reproduction and Embryology guideline: recurrent pregnancy loss. *Hum Reprod Open* 2018; **2018:** hoy004.
3 American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 200: early pregnancy loss. *Obstet Gynecol* 2018; **132:** e197–207.
4 Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. *Fertil Steril* 2012; **98:** 1103–11.
5 Aleman A, Althabe F, Belizán J, Bergel E. Bed rest during pregnancy for preventing miscarriage. *Cochrane Database Syst Rev* 2005; **2:** CD003576.
6 Palomba S, Falbo A, Orio F Jr, Zullo F. Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril* 2009; **92:** 1646–58.
7 Lim CE, Ho KK, Cheng NC, Wong FW. Combined oestrogen and progesterone for preventing miscarriage. *Cochrane Database Syst Rev* 2013; **2013:** CD009278.
8 Furber CM, McGowan L, Bower P, Kontopantelis E, Quenby S, Lavender T. Antenatal interventions for reducing weight in obese women for improving pregnancy outcome. *Cochrane Database Syst Rev* 2013; **1:** CD009334.
9 Earl R, Crowther CA, Middleton P. Interventions for hyperthyroidism pre-pregnancy and during pregnancy. *Cochrane Database Syst Rev* 2013; **11:** CD008633.
10 Morley LC, Simpson N, Tang T. Human chorionic gonadotrophin (hCG) for preventing miscarriage. *Cochrane Database Syst Rev* 2013; **1:** CD008611.
11 Reid SM, Middleton P, Cossich MC, Crowther CA, Bain E. Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy. *Cochrane Database Syst Rev* 2013; **5:** CD007752.
12 Yang GY, Luo H, Liao X, Liu JP. Chinese herbal medicine for the treatment of recurrent miscarriage: a systematic review of randomized clinical trials. *BMC Complement Altern Med* 2013; **13:** 320.
13 Brocklehurst P, Gordon A, Heatley E, Milan SJ. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev* 2013; **1:** CD000262.
14 de Jong PG, Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia. *Cochrane Database Syst Rev* 2014; **2014:** CD004734.
15 Carp H. A systematic review of dydrogesterone for the treatment of recurrent miscarriage. *Gynecol Endocrinol* 2015; **31:** 422–30.
16 Areia AL, Fonseca E, Areia M, Moura P. Low-molecular-weight heparin plus aspirin versus aspirin alone in pregnant women with hereditary thrombophilia to improve live birth rate: meta-analysis of randomized controlled trials. *Arch Gynecol Obstet* 2016; **293:** 81–86.
17 Zhang T, Ye X, Zhu T, et al. Antithrombotic treatment for recurrent miscarriage: Bayesian network meta-analysis and systematic review. *Medicine* 2015; **94:** e1732.
18 De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC, Rayco-Solon P. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. *Cochrane Database Syst Rev* 2015; **12:** CD007950.
19 Brown HC, Smith HJ, Mori R, Noma H. Giving women their own case notes to carry during pregnancy. *Cochrane Database Syst Rev* 2015; **2015:** CD002856.
20 Balogun OO, da Silva Lopes K, Ota E, et al. Vitamin supplementation for preventing miscarriage. *Cochrane Database Syst Rev* 2016; **5:** CD004073.
21 Chen H, Fu J, Huang W. Dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history. *Cochrane Database Syst Rev* 2016; **7:** CD008883.
22 Lensen SF, Manders M, Nastri CO, et al. Endometrial injury for pregnancy following sexual intercourse or intrauterine insemination. *Cochrane Database Syst Rev* 2016; **6:** CD011424.
23 Li L, Dou L, Leung PC, Chung TK, Wang CC. Chinese herbal medicines for unexplained recurrent miscarriage. *Cochrane Database Syst Rev* 2016; **1:** CD010568.
24 Boelig RC, Barton SJ, Saccone G, Kelly AJ, Edwards SJ, Berghella V. Interventions for treating hyperemesis gravidarum. *Cochrane Database Syst Rev* 2016; **5:** CD010607.
25 Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. *Cochrane Database Syst Rev* 2017; **6:** CD008991.
26 Rikken JF, Kowalik CR, Emanuel MH, et al. Septum resection for women of reproductive age with a septate uterus. *Cochrane Database Syst Rev* 2017; **1:** CD008576.
27 Morley LC, Tang T, Yasmin E, Norman RJ, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database Syst Rev* 2017; **11:** CD003053.
28 González R, Pons-Duran C, Piqueras M, Aponte JJ, Ter Kuile FO, Menéndez C. Mefloquine for preventing malaria in pregnant women. *Cochrane Database Syst Rev* 2018; **11:** CD011444.
29 Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. *Cochrane Database Syst Rev* 2019; **11:** CD003511.
30 Keats EC, Haider BA, Tam E, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database Syst Rev* 2019; **3:** CD004905.
31 Rao M, Zeng Z, Zhou F, et al. Effect of levothyroxine supplementation on pregnancy loss and preterm birth in women with subclinical hypothyroidism and thyroid autoimmunity: a systematic review and meta-analysis. *Hum Reprod Update* 2019; **25:** 344–61.
32 Sharpe A, Morley LC, Tang T, Norman RJ, Balen AH. Metformin for ovulation induction (excluding gonadotrophins) in women with polycystic ovary syndrome. *Cochrane Database Syst Rev* 2019; **12:** CD013505.
33 Claire R, Chamberlain C, Davey MA, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev* 2015; **12:** CD010078.
34 Hamulyák EN, Scheres LJ, Marijnen MC, Goddijn M, Middeldorp S. Aspirin or heparin or both for improving pregnancy outcomes in women with persistent antiphospholipid antibodies and recurrent pregnancy loss. *Cochrane Database Syst Rev* 2020; **5:** CD012852.
35 van Dijk MM, Kolte AM, Limpens J, et al. Recurrent pregnancy loss: diagnostic workup after two or three pregnancy losses? A systematic review of the literature and meta-analysis. *Hum Reprod Update* 2020; **26:** 356–67.
36 Sandall J, Soltani H, Gates S, Shennan A, Devane D. Midwife-led continuity models versus other models of care for childbearing women. *Cochrane Database Syst Rev* 2016; **4:** CD004667.
37 Smith PP, Dhillon-Smith RK, O'Toole E, Cooper N, Coomarasamy A, Clark TJ. Outcomes in prevention and management of miscarriage trials: a systematic review. *BJOG* 2019; **126:** 176–89.
38 Prior M, Bagness C, Brewin J, et al. Priorities for research in miscarriage: a priority setting partnership between people affected by miscarriage and professionals following the James Lind Alliance methodology. *BMJ Open* 2017; **7:** e016571.
39 Ogasawara M, Aoki K, Okada S, Suzumori K. Embryonic karyotype of abortuses in relation to the number of previous miscarriages. *Fertil Steril* 2000; **73:** 300–04.

40 Franssen MT, Korevaar JC, Leschot NJ, et al. Selective chromosome analysis in couples with two or more miscarriages: case-control study. *BMJ* 2005; **331:** 137–41.

41 Franssen MT, Korevaar JC, van der Veen F, Leschot NJ, Bossuyt PM, Goddijn M. Reproductive outcome after chromosome analysis in couples with two or more miscarriages: index [corrected]-control study. *BMJ* 2006; **332:** 759–63.

42 Coomarasamy A, Devall AJ, Brosens JJ, et al. Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. *Am J Obstet Gynecol* 2020; **223:** 167–76.

43 Coomarasamy A, Williams H, Truchanowicz E, et al. A randomized trial of progesterone in women with recurrent miscarriages. *N Engl J Med* 2015; **373:** 2141–48.

44 Coomarasamy A, Devall AJ, Cheed V, et al. A randomized trial of progesterone in women with bleeding in early pregnancy. *N Engl J Med* 2019; **380:** 1815–24.

45 Brenner B. Inherited thrombophilia and fetal loss. *Curr Opin Hematol* 2000; **7:** 290–95.

46 Alexander EK, Pearce EN, Brent GA, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid* 2017; **27:** 315–89.

47 Stagnaro-Green A, Pearce E. Thyroid disorders in pregnancy. *Nat Rev Endocrinol* 2012; **8:** 650–58.

48 Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. *BMJ* 2011; **342:** d2616.

49 Dong AC, Morgan J, Kane M, Stagnaro-Green A, Stephenson MD. Subclinical hypothyroidism and thyroid autoimmunity in recurrent pregnancy loss: a systematic review and meta-analysis. *Fertil Steril* 2020; **113:** 587–600.e1.

50 Kim CH, Ahn JW, Kang SP, Kim SH, Chae HD, Kang BM. Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. *Fertil Steril* 2011; **95:** 1650–54.

51 Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Alavi Majd H, Azizi F. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. *Eur J Endocrinol* 2017; **176:** 253–65.

52 Nazarpour S, Ramezani Tehrani F, Simbar M, et al. Effects of levothyroxine on pregnant women with subclinical hypothyroidism, negative for thyroid peroxidase antibodies. *J Clin Endocrinol Metab* 2018; **103:** 926–35.

53 Dhillon-Smith RK, Middleton LJ, Sunner KK, et al. Levothyroxine in women with thyroid peroxidase antibodies before conception. *N Engl J Med* 2019; **380:** 1316–25.

54 Wang H, Gao H, Chi H, et al. Effect of levothyroxine on miscarriage among women with normal thyroid function and thyroid autoimmunity undergoing in vitro fertilization and embryo transfer: a randomized clinical trial. *JAMA* 2017; **318:** 2190–98.

55 Negro R, Mangieri T, Coppola L, et al. Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: a prospective study. *Hum Reprod* 2005; **20:** 1529–33.

56 Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *J Clin Endocrinol Metab* 2006; **91:** 2587–91.

57 Negro R, Schwartz A, Stagnaro-Green A. Impact of levothyroxine in miscarriage and preterm delivery rates in first trimester thyroid antibody-positive women with TSH less than 2.5 mIU/L. *J Clin Endocrinol Metab* 2016; **101:** 3685–90.

58 Balen AH, Morley LC, Misso M, et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. *Hum Reprod Update* 2016; **22:** 687–708.

59 Balen AH, Tan SL, MacDougall J, Jacobs HS. Miscarriage rates following in-vitro fertilization are increased in women with polycystic ovaries and reduced by pituitary desensitization with buserelin. *Hum Reprod* 1993; **8:** 959–64.

60 Hamilton-Fairley D, Kiddy D, Watson H, Paterson C, Franks S. Association of moderate obesity with a poor pregnancy outcome in women with polycystic ovary syndrome treated with low dose gonadotrophin. *Br J Obstet Gynaecol* 1992; **99:** 128–31.

61 Ruutiainen K, Seppälä M. Polycystic ovary syndrome: evolution of a concept. *Curr Opin Obstet Gynecol* 1991; **3:** 326–35.

62 Løvvik TS, Carlsen SM, Salvesen Ø, et al. Use of metformin to treat pregnant women with polycystic ovary syndrome (PregMet2): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2019; **7:** 256–66.

63 Oon VJ, Johnson MR. The regulation of the human corpus luteum steroidogenesis: a hypothesis? *Hum Reprod Update* 2000; **6:** 519–29.

64 Fukui A, Fujii S, Yamaguchi E, Kimura H, Sato S, Saito Y. Natural killer cell subpopulations and cytotoxicity for infertile patients undergoing in vitro fertilization. *Am J Reprod Immunol* 1999; **41:** 413–22.

65 Kwak JY, Beaman KD, Gilman-Sachs A, Ruiz JE, Schewitz D, Beer AE. Up-regulated expression of CD56+, CD56+/CD16+, and CD19+ cells in peripheral blood lymphocytes in pregnant women with recurrent pregnancy losses. *Am J Reprod Immunol* 1995; **34:** 93–99.

66 Coulam CB, Goodman C, Roussev RG, Thomason EJ, Beaman KD. Systemic CD56+ cells can predict pregnancy outcome. *Am J Reprod Immunol* 1995; **33:** 40–46.

67 Inagaki N, Stern C, McBain J, Lopata A, Kornman L, Wilkinson D. Analysis of intra-uterine cytokine concentration and matrix-metalloproteinase activity in women with recurrent failed embryo transfer. *Hum Reprod* 2003; **18:** 608–15.

68 Lédée-Bataille N, Bonnet-Chea K, Hosny G, Dubanchet S, Frydman R, Chaouat G. Role of the endometrial tripod interleukin-18, -15, and -12 in inadequate uterine receptivity in patients with a history of repeated in vitro fertilization-embryo transfer failure. *Fertil Steril* 2005; **83:** 598–605.

69 Matsubayashi H, Arai T, Izumi S, Sugi T, McIntyre JA, Makino T. Anti-annexin V antibodies in patients with early pregnancy loss or implantation failures. *Fertil Steril* 2001; **76:** 694–99.

70 Stern C, Chamley L, Norris H, Hale L, Baker HW. A randomized, double-blind, placebo-controlled trial of heparin and aspirin for women with in vitro fertilization implantation failure and antiphospholipid or antinuclear antibodies. *Fertil Steril* 2003; **80:** 376–83.

71 Egerup P, Lindschou J, Gluud C, Christiansen OB. The effects of intravenous immunoglobulins in women with recurrent miscarriages: a systematic review of randomised trials with meta-analyses and trial sequential analyses including individual patient data. *PLoS One* 2015; **10:** e0141588.

72 Wong LF, Porter TF, Scott JR. Immunotherapy for recurrent miscarriage. *Cochrane Database Syst Rev* 2014; **10:** CD000112.

73 Achilli C, Duran-Retamal M, Saab W, Serhal P, Seshadri S. The role of immunotherapy in in vitro fertilization and recurrent pregnancy loss: a systematic review and meta-analysis. *Fertil Steril* 2018; **110:** 1089–100.

74 Duhig K, Chappell LC, Shennan AH. Oxidative stress in pregnancy and reproduction. *Obstet Med* 2016; **9:** 113–16.

75 Musters AM, Repping S, Korevaar JC, et al. Pregnancy outcome after preimplantation genetic screening or natural conception in couples with unexplained recurrent miscarriage: a systematic review of the best available evidence. *Fertil Steril* 2011; **95:** 2153–57.

76 Iews M, Tan J, Taskin O, et al. Does preimplantation genetic diagnosis improve reproductive outcome in couples with recurrent pregnancy loss owing to structural chromosomal rearrangement? A systematic review. *Reprod Biomed Online* 2018; **36:** 677–85.

77 Cui W. Mother or nothing: the agony of infertility. *Bull World Health Organ* 2010; **88:** 881–82.