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Recurrent miscarriage: evidence to accelerate action

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Summary

Women who have suffered repeated miscarriages often have uncertainties about the cause, the likelihood of recurrence, the investigations that they need, and the treatments that may help. Health care policy-makers and providers have uncertainties about the optimal ways to organise and deliver care. We have developed recommendations for practice from literature reviews, appraisal of guidelines and a UK-wide consensus conference, held in December 2019.

Caregivers should individualise care according to the clinical needs and women's and partners' preferences. We define a minimum set of investigations and treatments to be offered to couples suffering recurrent miscarriages, and urge healthcare policy-makers and providers to make these 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 services structure care using a 'graded model' where women are offered online healthcare advice and support, care in a nurse or midwife-led clinic, and care in a medical consultant-led clinic, according to clinical needs.

Keywords: recurrent miscarriage, literature review, models of care

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 performed for explanatory purposes. Selected couples may 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 may increase live birth rates in patients with recurrent miscarriage, and low quality evidence that levothyroxine may decrease the risk of miscarriage in women with subclinical hypothyroidism (thyroid stimulating hormone level >4·0 mIU/L). There is low quality evidence that a combination of aspirin and heparin may increase live birth 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, whilst targeting health care resources appropriately. The appropriate model for a particular country may vary according to the prevailing healthcare system, opportunities for service development and re-organisation, and available resources. We propose a graded approach for care for the UK, based on the consensus from a UK-wide national conference in 2019. The graded approach would entail women are supported with online, pre-conceptual advice, and screened for risk factors following their first miscarriage; following 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; and following a third or subsequent miscarriage, women are offered a consultant-led service with full panel of investigations and interventions for recurrent miscarriage.

Introduction

The journey for couples who have suffered repeated miscarriages is filled with 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 may prevent a recurrence (therapy). Healthcare providers have questions about which investigations are useful for a couple with recurrent miscarriage, how they can improve outcomes for those at risk of a miscarriage, and about ways to plan, organise and deliver 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 most recent UK National Institute for Health and Care Excellence (NICE) 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 remains inconsistent and poorly organised. To accelerate evidence-based care, we have developed recommendations for practice from literature reviews, appraisal of guidelines and a UK-wide consensus conference, involving women and healthcare providers. The recommendations are centred on couples who have suffered recurrent miscarriage, focusing on relevant investigations and interventions for 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.

Box 1. Methods for literature searches

The recommendations in this article are based on a literature review and appraisal of professional body guidelines.

Literature reviews: We searched the Cochrane Database of Systematic Reviews and MEDLINE (from inception until 9 Jan 2020) for systematic reviews of randomised controlled trials, specifying or reporting any miscarriage outcome. Thirty reviews focussed on the prevention of miscarriage in women who were not bleeding.[5-34] We report results for miscarriage and live birth separately.

Review of professional body guidelines: We reviewed the latest international guidance on the management and treatment of miscarriage, which included guidelines from NICE on the management of ectopic pregnancy and miscarriage[1]; the ESHRE guideline on the management of recurrent pregnancy loss[2]; the American College of Obstetricians and Gynecologists guideline on early pregnancy loss[3] and the American Society for Reproductive Medicine guideline on recurrent pregnancy loss.[4]

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 improve outcomes. However, even if an effective treatment is not available, the knowledge of contributory factors for repeated miscarriages, prognostic implications for future pregnancy, and acknowledgement of the trauma and distress experienced and the personal quest for answers, can be important for women and partners. The ESHRE guideline development group reviewed the evidence on recurrent miscarriage investigations in 2017 to explore i) if there was an association between a test result and miscarriage risk, ii) if an association was found, was there evidence that it was contributory to miscarriage risk, iii) if the test result had any prognostic value, and iv) whether there was evidence that treatment improved

outcomes (Table 1).[2] Associations were found between many test results and miscarriage risk; however, there was limited evidence that the associations represented a causative or contributory relationship.[2] Furthermore, there was little evidence of any prognostic value for many tests, and limited high quality evidence of therapeutic benefit for treatments based on test results (Table 1). The tests of value for the investigation of couples with recurrent miscarriage are the measurement of antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies), thyroid function and pelvic ultrasonography, preferably 3-dimensional transvaginal ultrasound, to assess the uterine cavity.[2] Chromosome testing of pregnancy tissue can be performed for explanatory purposes; the recommended test is array-based comparative genomic hybridization (array-CGH).[2] Some couples may benefit from parental karyotyping.[2,35,36]

Table 1. Evidence summary of investigations for couples with recurrent miscarriage

Test	Is there evidence of 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	Yes	Yes	Yes	Weak evidence

anticoagulant and anticardiolipin antibodies				
Beta-2-Glycoprotein1	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 genetic testing in subsequent pregnancies)
Thyroid function test: hypothyroidism	Only for sporadic pregnancy loss	Only for sporadic pregnancy loss	Yes	Yes
Thyroid function test: subclinical hypothyroidism	Yes	Yes	Not clear	Not clear
Thyroid antibodies	Yes	Yes	Yes	No
Ultrasonography to diagnose congenital uterine abnormality	Yes	Possibly	No data	Limited data
Immune testing (HLA compatibility, HLA class II, HLA-G, KIR and HLA-C, cytokines and NK cells)	Limited data	Limited data	No data	No data
Anti-HY immunity	Moderate	Yes	Yes	No data
Anti-nuclear antibodies	Yes	Limited data	Unclear	No data
Hormone tests and ultrasound: Polycystic ovary syndrome	Yes	Yes	No	Possibly (metformin treatment)
Vitamin D	Possibly	Possibly	Limited data	No data
Sperm DNA damage test	Moderate	Probably	Unclear	No

Adapted from ESHRE guideline on Recurrent Pregnancy Loss (2018).[2]

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, anti-

123 coagulants, levothyroxine, metformin, human chorionic gonadotropin, immunomodulatory agents,

124 and micronutrient supplementation. The key results are presented in Table 2.

125

126 **Table 2.** Summary effect estimates from systematic reviews of treatments to prevent miscarriage in

127 asymptomatic women

	Miscarriage			Live birth		
Type of intervention	**Number of participants (trials)**	**Risk ratio [95% CI]**	**Quality of evidence**	**Number of participants (trials)**	**Risk ratio [95% CI]**	**Quality of evidence**
Progesterone						
Progestogen vs placebo or no treatment						
All women with RM	1684 (10)	0·73 [0·54, 1·00]	MODERATE	1411 (6)	1·07 [1·00, 1·13]	MODERATE
Women with at least 2 previous miscarriages	290 (5)	0·98 [0·64, 1·52]	LOW	207 (3)	1·01 [0·88, 1·16]	LOW
Women with at least 3 previous miscarriages	1334 (4)	0·59 [0·34, 1·01]	LOW	1204 (3)	1·08 [1·00, 1·15]	MODERATE
Anti-coagulants						
Aspirin vs placebo or no treatment						
All women with RM	656 (3)	1·20 [0·90, 1·61]	MODERATE	656 (3)	0·97 [0·90, 1·04]	HIGH
Women with RM + inherited thrombophilia	-	-	-	32 (1)	1·08 [0·63, 1·85]	LOW
Women with RM + APS	40 (1)	1·33 [0·34, 5·21]	LOW	40 (1)	0·94 [0·71, 1·25]	LOW
LMWH vs placebo or no treatment						
All women with RM	650 (4)	0·62 [0·30, 1·29]	LOW	650 (4)	1·31 [0·85, 2·01]	LOW
Women with RM + inherited thrombophilia	-	-	-	-	-	-
Women with RM + APS	-	-	-	-	-	-
LMWH + Aspirin vs placebo/no treatment						
All women with RM	200 (1)	0·92 [0·60, 1·43]	LOW	322 (2)	1·01 [0·87, 1·16]	HIGH
Women with RM + inherited thrombophilia	-	-	-	27 (1)	1·25 [0·74, 2·12]	LOW
Women with RM + APS	-	-	-	-	-	-
LMWH vs aspirin						
All women with RM	104 (1)	1·16 [0·50, 2·70]	LOW	239 (2)	1·08 [0·93, 1·26]	MODERATE
Women with RM + inherited thrombophilia	-	-		36 (1)	1·21 [0·79, 1·87]	LOW
Women with RM + APS	141 (1)	0·49 [0·25, 0·98]	LOW	141 (1)	1·20 [1·00, 1·43]	LOW
Heparin (LMWH or Unfractionated) + Aspirin vs Aspirin						

All women with RM	196 (1)	0·74 [0·49, 1·12]	LOW	327 (2)	1·11 [0·94, 1·30]	MODERATE
Women with RM + inherited thrombophilia	-	-		63 (2)	1·05 [0·73, 1·50]	LOW
Women with RM + APS	1295 (5)	0·48 [0·32, 0·71]	LOW	1295 (5)	1·27 [1·09, 1·49]	LOW
Levothyroxine						
Levothyroxine vs placebo or no treatment						
Women with sub-clinical hypothyroidism	257 (3)	0·20 [0·05, 0·76]	LOW	257 (3)	1·20 [0·82, 1·75]	LOW
Women with thyroid autoimmunity	1427 (6)	0·87 [0·70, 1·07]	HIGH	805 (3)	1·03 [0·96, 1·12]	MODERATE
Metformin						
Metformin vs placebo or no treatment						
Women with PCOS undergoing ovulation induction	748 (4)	1·08 [0·52, 2·26]	LOW	435 (4)	1·41 [1·00, 1·99]	LOW
hCG						
hCG vs control						
All women with RM	302 (5)	0·51 [0·32, 0·81]	LOW	274 (4)	1·15 [0·96, 1·39]	LOW
Micronutrients						
Vitamin C + E vs placebo or no treatment						
Pregnant women	13,346 (4)	0·90 [0·65, 1·26]	MODERATE	-	-	-
Vitamin A + iron + folic acid vs iron + folic acid						
Pregnant women	1397 (2)	0·86 [0·46, 1·62]	LOW	-	-	-
Multivitamin + iron + folic acid vs iron + folic acid						
Pregnant women	94,948 (10)	0·98 [0·94, 1·03]	MODERATE	-	-	-
Multiple micronutrient + iron + folic acid vs iron ± folic acid						
Pregnant women	107,220 (12)	0·99 [0·94, 1·04]	MODERATE	-	-	-
Supplementation with folate vs no treatment or placebo or micronutrients without folate						
Pregnant women	7391 (5)	1·10 [0·94, 1·28]	MODERATE	7001 (3)	0·99 [0·98, 1·01]	MODERATE

RM: recurrent miscarriage; APS: antiphospholipid syndrome; LMWH: low molecular weight heparin

Progestogens

Progesterone is essential for the establishment and maintenance of a pregnancy.[37] 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 synthesised 10 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 1,684 (Table 2).[38] We updated this review, and found that the miscarriage rate for women with recurrent miscarriage was reduced (RR 0·73; 95% CI 0·54 to 1·00) and live birth rate was increased (RR 1·07; 95% CI 1·00 to 1·13), but with borderline significance. The live birth rate was higher for the subgroup of women with a history of three or more miscarriages (RR 1·08; 95% CI 1·00 to 1·15), compared with the subgroup of women with a history of two or more miscarriages (RR 1·01; 95% CI 0·88 to 1·16). There was no evidence of any safety concerns from first trimester use of micronized vaginal progesterone, which has an identical molecular structure to natural progesterone.[38,39] Micronized vaginal progesterone treatment can therefore be considered for asymptomatic women with recurrent miscarriage, and is likely to be more effective in women with a higher number of previous miscarriages.

Anti-coagulant therapy

Thrombophilia, whether acquired (e.g. antiphospholipid antibodies) or inherited (e.g. Factor V Leiden), are associated with vascular thrombosis and adverse pregnancy outcomes such as recurrent miscarriage.[40] Anticoagulant therapy with low-dose aspirin, heparin or both have been evaluated in four systematic reviews.[14,16,17,34] Two of these reviews were network meta-analyses.[17] The studies in these reviews were mostly of low methodological quality. Results from a recently published Cochrane review[34] and analyses from another Cochrane review[14] are presented in Table 2. Analysis

of five trials showed that low-dose aspirin and heparin reduced the miscarriage rate (RR 0·48; 95% CI 0·32 to 0·71; low certainty evidence) and increased live birth rate (RR 1·27; 95% CI 1·09, 1·49; low certainty evidence), compared to aspirin alone, in women with antiphospholipid syndrome and a history of recurrent miscarriage. There was no evidence of harm from available data.[34] The current professional body guidelines recommend the use of low-dose aspirin and heparin in women with antiphospholipid syndrome and recurrent miscarriage.[2]

There is currently 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 may 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 pre-conception and in pregnancy is universally accepted for reducing adverse pregnancy outcomes, including miscarriage.[41] There is no clear agreement, however, on the management of women with subclinical hypothyroidism (SCH) or thyroid autoimmunity. There is some evidence that subclinical hypothyroidism is linked to miscarriage.[42] Thyroid autoantibodies are linked to miscarriage, even in women without thyroid dysfunction.[43,44]

We have summarised the evidence of trials investigating levothyroxine treatment, started preconception or in early pregnancy, for subclinical hypothyroidism in women trying to conceive a pregnancy. Three trials were identified, and all were of low methodological quality.[45-47] Two of the three included trials used a thyroid stimulating hormone (TSH) cut-off of 4·0 mIU/L,[46,47] while the third used the cut-off of 4·5 mIU/L.[45] Results showed a reduction in miscarriage rate with levothyroxine treatment: RR 0·20 (95% CI 0·05 to 0·76). Data for live birth did not provide a clear finding (RR 1·20; 95% CI 0·82 to 1·75) (Table 2).

Based on the available evidence, levothyroxine treatment could be considered for women with subclinical hypothyroidism where TSH levels 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 TSH levels (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 live birth rates in women with thyroid antibodies.[48,49] The analysis of data for levothyroxine treatment in euthyroid women with thyroid antibodies is presented in Table 2; six studies reporting on miscarriage found no benefit with levothyroxine therapy (RR 0·87; 95% CI 0·70 to 1·07).[46,48-52] The three studies analysed for the outcome of live birth also showed no benefit with levothyroxine treatment (RR 1·03; 95% CI 0·96 to 1·12).[48-50] Euthyroid women with thyroid antibodies do not, therefore, require levothyroxine treatment.

Metformin

Polycystic ovary syndrome (PCOS) is a common endocrine disorder, which affects up to 15% of women of reproductive age.[53] Increased insulin resistance, hyperandrogenism and obesity are closely linked to PCOS and all have a significant impact on reproductive outcomes, including miscarriage.[54-56] As insulin resistance and resulting hyperinsulinaemia are key metabolic features in women with PCOS, 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 (OR 1·08; 95% CI 0·52 to 2·26), but a suggestion of potential benefit in live birth outcome (OR 1·41; 95% CI 1·00 to 1·99).[32] An individual patient data meta-analysis, including data

from the PregMet2 trial[57], where metformin was commenced late in first trimester, showed 18 of 397 (5%) women had late miscarriage in the metformin group compared with 40 of 399 (10%) women in the placebo group (OR 0·43, 95% CI 0·23-0·79; p=0·004). High quality trials are needed to evaluate the effects of metformin on miscarriage and live birth rates in women with PCOS.

Human chorionic gonadotropin (hCG)

The placental hormone hCG is important for the production of progesterone and implantation of the embryo.[58] It has been hypothesised that a suboptimal level of hCG might therefore affect endometrial receptivity. In view of this, clinicians and researchers have studied the role of hCG as a treatment for recurrent miscarriage.

A systematic review of five RCTs of hCG treatment in women with recurrent miscarriage found a reduction in miscarriage (RR 0·51; 95% CI 0·32 to 0·81).[10] However, this review included two methodologically weak studies; when these two studies were excluded in a sensitivity analysis, a benefit was not confirmed (RR 0·74; 95% CI 0·44 to 1·23). The evidence supporting hCG supplementation to prevent recurrent miscarriage therefore remains equivocal, and high quality research is needed.

Immunotherapy

A fetus carries antigens of maternal and paternal origins. The physiological mechanisms that allow a mother to tolerate the paternal antigens are poorly understood, but a dysfunction in immune modulation has been hypothesised to be a cause of miscarriage. Various immunological markers, including elevated levels of natural killer (NK) cells[59-61], dysregulated cytokines[62,63], the presence of antiphospholipid antibodies or other autoantibodies,[64,65] have been linked to miscarriages.

Three systematic reviews evaluated immunological interventions, which included oral prednisolone, intravenous immunoglobulins (IVIG), lymphocyte immunotherapy and trophoblast membrane immunisation.[66-68] 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 live births. 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.[69] Vitamins, particularly those with antioxidant effects, have therefore been studied as a means of reducing miscarriage risk.

Three systematic reviews evaluated the effects of micronutrients, including vitamins A, C and E, folate and iron, to reduce miscarriage (Table 2).[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 (NTR 1676) are awaited.[70]

Pre-implantation genetic screening (PGS)

Two systematic reviews have explored pre-implantation genetic screening (PGS), which is now more commonly known as pre-implantation genetic testing for aneuploidy (PGT-A), in women with recurrent miscarriage.[71,72] Neither of the reviews identified randomised trial data. The non-randomised data in these reviews suggested similar live birth rates between those having PGS and those conceiving naturally. The currently available evidence is, therefore, insufficient to support PGS in clinical practice.

Box 2. Three approaches to manage recurrent miscarriage

UK-wide consensus conference: A group of 39 key stakeholders from across the UK met in December 2019 to discuss the development of a standardised national care package for recurrent miscarriage. The conference was funded by the 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 results in missed opportunities for pre-conception counselling and care, including the opportunity to address body weight, smoking, alcohol consumption, and diet, particularly intake of micronutrients such as folate. Couples may not be offered any reasons for the miscarriages, with the only advice being 'try again'. Mental health sequelae 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; 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 signposted 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 could involve patient support groups, online self-help strategies for mental health, weight management, smoking and recreational drugs cessation services, information regarding appropriate pre-conceptual folate and vitamin D supplementation, referral to necessary services for management and optimisation of chronic maternal medical conditions, such as 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, where tests for full blood count and thyroid function are offered, in addition to addressing lifestyle issues.[73] 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, where 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 3-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, as well as promotion of continuity of care, and could benefit couples who lose pregnancies 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 may 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.[74]

A continuity of care model can integrate care to meet physical and psychological health needs, addressing ongoing concerns and co-ordination of clinical investigations before and during pregnancy. It can ensure women and partners know when, where and how to access the care and help they need; encourage positive lifestyle interventions which may be of benefit; and encourage early referral for relevant investigations in subsequent pregnancies. In addition to potential impact on subsequent pregnancy outcomes, a continuity approach may increase satisfaction with care,[74] provide opportunity to implement standardized women-centered outcome measures,[75] collate data to monitor the burden of miscarriage, and provide a 'hub' to support research.[76]

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 National Health Service Hospitals in the UK. This model has significant limitations. Women with only two previous miscarriages have a high chance of a future successful pregnancy.[77] They do not need extensive investigation or treatments; however, the third model makes them vulnerable to requesting and receiving interventions which may be of little benefit and have the potential to cause harm. In addition, this approach may not represent an optimal use of finite health care resources.

The three models were discussed at the UK miscarriage care consensus conference in 2019, where 96% (80/83) of participants voted for the graded approach.

Global perspectives

Childless women suffer discrimination, stigma and ostracism in many cultures across the world.[78] 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 well-being of a community. Marriage without children is considered as a 'failure of the two individuals'.[78] This is a heavy burden to carry for women in many low- and middle-income countries (LMICs).

Despite its great importance and significant socio-cultural impact, miscarriage prevention remains a low priority public health issue in LMIC. Care of affected couples is often overlooked because of competing health priorities, with very few formal services available for women who suffer recurrent miscarriages. There needs to be a minimum service available globally for couples who suffer recurrent miscarriage. Within the LMIC setting, this 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 pre-pregnancy counselling and psychological support to couples who have suffered repeated miscarriages.

Discussion

Recurrent miscarriage is a devastating experience for most couples. Couples who have suffered 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, and thyroid function, and pelvic ultrasonography. Genetic analysis of pregnancy tissue can be performed for explanatory purposes, and some couples may 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 may increase live birth rates in women with recurrent miscarriage, levothyroxine may decrease the risk of miscarriage in women with subclinical hypothyroidism, and a combination of aspirin and heparin may increase live births in women with recurrent miscarriage and antiphospholipid antibodies.

The recommendations in this article are based on the best available evidence. We have relied on published systematic reviews, with recommendations that reflect 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 amongst experts to generate recommendations for questions for which there was limited evidence. A model of care is needed that addresses the balance between the need for evidence-based management and supportive care, whilst 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 may be appropriate. Acceleration of high quality evidence gathering through the integration of early pregnancy services and specialist recurrent miscarriage clinics across different healthcare 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 suffering repeated miscarriages, and recommend that healthcare policy-makers and providers make these universally available. Any service for recurrent miscarriage couples should have not only their physical, but also their psychological support needs at the centre of its programme.

There needs to be a concerted move away from the current piecemeal approach in the delivery of care for miscarriage couples, and instead validated and standardised care pathways tailored to the need of couples and their individualised risk of recurrence should 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, as well as develop new therapeutic strategies. This 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, as well as on optimal ways of organising and delivering care. New diagnostic tests and effective treatments are needed to improve pre-conceptual endometrium and sperm. Several treatment questions, including the role of aspirin and heparin for inherited thrombophilia, levothyroxine for women with mild subclinical hypothyroidism (TSH level between 2.5 – 4.0mIU/L), preconception and early pregnancy metformin for women with polycystic ovary syndrome, and hCG treatment for women with recurrent miscarriages, need answering. Another urgent research priority is the exploration of optimal management approaches for women suffering mental health illness after miscarriages.

Contributors

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

Declaration of interests

The authors have no conflicts of interest to declare.

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