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Recurrent miscarriage

evidence to accelerate action

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1 Recurrent miscarriage: evidence to accelerate action

2

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39

40 Summary

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

46 Caregivers should individualise care according to the clinical needs and women's and partners'
47 preferences. We define a minimum set of investigations and treatments to be offered to couples
48 suffering recurrent miscarriages, and urge healthcare policy-makers and providers to make these
49 universally available. The essential investigations include measurements of lupus anticoagulant,
50 anticardiolipin antibodies, thyroid function, and a transvaginal pelvic ultrasound scan. The key
51 treatments to consider are first trimester progesterone administration, levothyroxine in women with
52 subclinical hypothyroidism and the combination of aspirin and heparin in women with
53 antiphospholipid antibodies. Appropriate screening and care for mental health issues and future
54 obstetric risks, particularly preterm birth, fetal growth restriction and stillbirth, will need to be
55 incorporated into the care pathway for couples with a history of recurrent miscarriage. We suggest
56 health services structure care using a 'graded model' where women are offered online healthcare
57 advice and support, care in a nurse or midwife-led clinic, and care in a medical consultant-led clinic,
58 according to clinical needs.

59 Keywords: recurrent miscarriage, literature review, models of care

60

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.

61

62 **Introduction**

63 The journey for couples who have suffered repeated miscarriages is filled with uncertainties.

64 Women and their partners have uncertainties about the cause of miscarriage (aetiology), the

65 likelihood of recurrence (prognosis), the tests required (diagnosis) and treatments that may prevent

66 a recurrence (therapy). Healthcare providers have questions about which investigations are useful

67 for a couple with recurrent miscarriage, how they can improve outcomes for those at risk of a

68 miscarriage, and about ways to plan, organise and deliver optimal care.

69 Specialist clinics for recurrent miscarriage often offer different tests and treatments, resulting in

70 couples seeking care in multiple clinics. The wide variation in practice is reflected in professional

71 body guidelines that often have varying, and occasionally contradictory recommendations.¹⁻⁴ The

72 most recent UK National Institute for Health and Care Excellence (NICE) guideline on the

73 management of miscarriage and ectopic pregnancy includes 93 recommendations¹, and the

74 European Society of Human Reproduction and Embryology (ESHRE) guideline on recurrent

75 pregnancy loss has 77 recommendations.² Despite an abundance of guidance, clinical practice

76 remains inconsistent and poorly organised. To accelerate evidence-based care, we have developed

77 recommendations for practice from literature reviews, appraisal of guidelines and a UK-wide

78 consensus conference, involving women and healthcare providers. The recommendations are

79 centred on couples who have suffered recurrent miscarriage, focusing on relevant investigations and

80 interventions for prevention of miscarriage. Finally, we propose a model of care that could be

81 implemented by health care providers in the UK to standardise the investigations and management

82 of couples with recurrent miscarriage. We conclude with a call for improved care and high quality

83 research in targeted areas.

84

85 **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 miscarriage¹; the ESHRE guideline on the management of recurrent pregnancy loss²; the American College of Obstetricians and Gynecologists guideline on early pregnancy loss³ and the American Society for Reproductive Medicine guideline on recurrent pregnancy loss.⁴

86

87 **Investigations for recurrent miscarriage**

88 The primary reason for investigating a couple with recurrent miscarriage is to identify any underlying
89 condition for which effective treatment exists to improve outcomes. However, even if an effective
90 treatment is not available, the knowledge of contributory factors for repeated miscarriages,
91 prognostic implications for future pregnancy, and acknowledgement of the trauma and distress
92 experienced and the personal quest for answers, can be important for women and partners. The
93 ESHRE guideline development group reviewed the evidence on recurrent miscarriage investigations
94 in 2017 to explore i) if there was an association between a test result and miscarriage risk, ii) if an
95 association was found, was there evidence that it was contributory to miscarriage risk, iii) if the test
96 result had any prognostic value, and iv) whether there was evidence that treatment improved

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

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115 **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

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

117

118 **Prevention of miscarriage in women at high risk of miscarriage**

119 Several interventions have targeted asymptomatic women, who have no vaginal bleeding or pelvic
120 pain in early pregnancy, but have other risk factors for miscarriage such as a history of recurrent
121 pregnancy losses. There were 30 systematic reviews reporting on 12 classes of interventions to
122 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

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

129

130 *Progestogens*

131 Progesterone is essential for the establishment and maintenance of a pregnancy.³⁷ The central role
132 of progesterone in early pregnancy has led clinicians and researchers to hypothesise that
133 progesterone deficiency could be a cause of some miscarriages.

134 A Cochrane review synthesised 10 studies that had used various types of progestogens, including
135 natural progesterone, which was used in the largest and highest quality trial on this subject that
136 contributed 49% of data to the analysis total of 1,684 (Table 2).³⁸ We updated this review, and found
137 that the miscarriage rate for women with recurrent miscarriage was reduced (RR 0.73; 95% CI 0.54
138 to 1.00) and live birth rate was increased (RR 1.07; 95% CI 1.00 to 1.13), but with borderline
139 significance. The live birth rate was higher for the subgroup of women with a history of three or
140 more miscarriages (RR 1.08; 95% CI 1.00 to 1.15), compared with the subgroup of women with a
141 history of two or more miscarriages (RR 1.01; 95% CI 0.88 to 1.16). There was no evidence of any
142 safety concerns from first trimester use of micronized vaginal progesterone, which has an identical
143 molecular structure to natural progesterone.^{38,39} Micronized vaginal progesterone treatment can
144 therefore be considered for asymptomatic women with recurrent miscarriage, and is likely to be
145 more effective in women with a higher number of previous miscarriages.

146

147 *Anti-coagulant therapy*

148 Thrombophilia, whether acquired (e.g. antiphospholipid antibodies) or inherited (e.g. Factor V
149 Leiden), are associated with vascular thrombosis and adverse pregnancy outcomes such as recurrent
150 miscarriage.⁴⁰ Anticoagulant therapy with low-dose aspirin, heparin or both have been evaluated in
151 four systematic reviews.^{14,16,17,34} Two of these reviews were network meta-analyses.¹⁷ The studies in
152 these reviews were mostly of low methodological quality. Results from a recently published
153 Cochrane review³⁴ and analyses from another Cochrane review¹⁴ are presented in Table 2. Analysis

154 of five trials showed that low-dose aspirin and heparin reduced the miscarriage rate (RR 0.48; 95% CI
155 0.32 to 0.71; low certainty evidence) and increased live birth rate (RR 1.27; 95% CI 1.09, 1.49; low
156 certainty evidence), compared to aspirin alone, in women with antiphospholipid syndrome and a
157 history of recurrent miscarriage. There was no evidence of harm from available data.³⁴ The current
158 professional body guidelines recommend the use of low-dose aspirin and heparin in women with
159 antiphospholipid syndrome and recurrent miscarriage.²

160 There is currently no evidence to support the use of aspirin and heparin in women with inherited
161 thrombophilia or in women who do not have thrombophilia.¹⁴ As there is evidence that aspirin
162 therapy may actually increase the risk of miscarriage in women who do not have thrombophilia¹⁷,
163 empirical treatment with aspirin in these women should be avoided.

164

165 *Levothyroxine*

166 Treatment of overt thyroid disorders pre-conception and in pregnancy is universally accepted for
167 reducing adverse pregnancy outcomes, including miscarriage.⁴¹ There is no clear agreement,
168 however, on the management of women with subclinical hypothyroidism (SCH) or thyroid
169 autoimmunity. There is some evidence that subclinical hypothyroidism is linked to miscarriage.⁴²
170 Thyroid autoantibodies are linked to miscarriage, even in women without thyroid dysfunction.^{43,44}

171 We have summarised the evidence of trials investigating levothyroxine treatment, started
172 preconception or in early pregnancy, for subclinical hypothyroidism in women trying to conceive a
173 pregnancy. Three trials were identified, and all were of low methodological quality.⁴⁵⁻⁴⁷ Two of the
174 three included trials used a thyroid stimulating hormone (TSH) cut-off of 4.0 mIU/L,^{46,47} while the
175 third used the cut-off of 4.5 mIU/L.⁴⁵ Results showed a reduction in miscarriage rate with
176 levothyroxine treatment: RR 0.20 (95% CI 0.05 to 0.76). Data for live birth did not provide a clear
177 finding (RR 1.20; 95% CI 0.82 to 1.75) (Table 2).

178 Based on the available evidence, levothyroxine treatment could be considered for women with
179 subclinical hypothyroidism where TSH levels are above 4.0 mIU/L. However, further research is
180 needed to generate high quality evidence for women with subclinical hypothyroidism, particularly in
181 women with mildly elevated TSH levels (2.5-4.0 mIU/L).

182 Small low quality trials had suggested a benefit with levothyroxine treatment in women with thyroid
183 antibodies, but normal thyroid function; however, there is now evidence from two large high quality
184 trials that levothyroxine neither reduces miscarriage rates nor increases live birth rates in women
185 with thyroid antibodies.^{48,49} The analysis of data for levothyroxine treatment in euthyroid women
186 with thyroid antibodies is presented in Table 2; six studies reporting on miscarriage found no benefit
187 with levothyroxine therapy (RR 0.87; 95% CI 0.70 to 1.07).^{46,48-52} The three studies analysed for the
188 outcome of live birth also showed no benefit with levothyroxine treatment (RR 1.03; 95% CI 0.96 to
189 1.12).⁴⁸⁻⁵⁰ Euthyroid women with thyroid antibodies do not, therefore, require levothyroxine
190 treatment.

191

192 *Metformin*

193 Polycystic ovary syndrome (PCOS) is a common endocrine disorder, which affects up to 15% of
194 women of reproductive age.⁵³ Increased insulin resistance, hyperandrogenism and obesity are
195 closely linked to PCOS and all have a significant impact on reproductive outcomes, including
196 miscarriage.⁵⁴⁻⁵⁶ As insulin resistance and resulting hyperinsulinaemia are key metabolic features in
197 women with PCOS, their improvement, through metformin treatment, could improve pregnancy
198 outcomes.

199 A systematic review of four small low quality studies showed no difference in miscarriage outcome
200 with metformin (OR 1.08; 95% CI 0.52 to 2.26), but a suggestion of potential benefit in live birth
201 outcome (OR 1.41; 95% CI 1.00 to 1.99).³² An individual patient data meta-analysis, including data

202 from the PregMet2 trial⁵⁷, where metformin was commenced late in first trimester, showed 18 of
203 397 (5%) women had late miscarriage in the metformin group compared with 40 of 399 (10%)
204 women in the placebo group (OR 0.43, 95% CI 0.23-0.79; p=0.004). High quality trials are needed to
205 evaluate the effects of metformin on miscarriage and live birth rates in women with PCOS.

206

207 *Human chorionic gonadotropin (hCG)*

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

212 A systematic review of five RCTs of hCG treatment in women with recurrent miscarriage found a
213 reduction in miscarriage (RR 0.51; 95% CI 0.32 to 0.81).¹⁰ However, this review included two
214 methodologically weak studies; when these two studies were excluded in a sensitivity analysis, a
215 benefit was not confirmed (RR 0.74; 95% CI 0.44 to 1.23). The evidence supporting hCG
216 supplementation to prevent recurrent miscarriage therefore remains equivocal, and high quality
217 research is needed.

218

219 *Immunotherapy*

220 A fetus carries antigens of maternal and paternal origins. The physiological mechanisms that allow a
221 mother to tolerate the paternal antigens are poorly understood, but a dysfunction in immune
222 modulation has been hypothesised to be a cause of miscarriage. Various immunological markers,
223 including elevated levels of natural killer (NK) cells⁵⁹⁻⁶¹, dysregulated cytokines^{62,63}, the presence of
224 antiphospholipid antibodies or other autoantibodies,^{64,65} have been linked to miscarriages.

225 Three systematic reviews evaluated immunological interventions, which included oral prednisolone,
226 intravenous immunoglobulins (IVIg), lymphocyte immunotherapy and trophoblast membrane
227 immunisation.⁶⁶⁻⁶⁸ The studies included in the reviews are small and were of low or moderate
228 quality. None of the interventions studied across the three reviews were associated with a reduction
229 in miscarriages or increase in live births. There is therefore insufficient evidence to recommend use
230 of immunotherapy to prevent recurrent miscarriage.

231

232 *Micronutrients*

233 Vitamins are essential nutrients required for various bodily functions including normal metabolism
234 and reproduction. Associations have been found between decreased antioxidant defence and
235 pregnancy outcomes.⁶⁹ Vitamins, particularly those with antioxidant effects, have therefore been
236 studied as a means of reducing miscarriage risk.

237 Three systematic reviews evaluated the effects of micronutrients, including vitamins A, C and E,
238 folate and iron, to reduce miscarriage (Table 2).^{18,20,30} Various micronutrients were combined in
239 different formulations and doses. There was no evidence that any of the regimens reduced the risk
240 of miscarriage.

241

242 *Surgical interventions for uterine anomalies*

243 Surgical treatment of uterine anomalies, particularly the division of a uterine septum, is a subject of
244 debate. A systematic review on this subject did not find any randomised trials comparing
245 hysteroscopic septum resection with expectant management.²⁶ The results of the TRUST trial (NTR
246 1676) are awaited.⁷⁰

247 *Pre-implantation genetic screening (PGS)*

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

254

255 **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.

256

257

258 **Global perspectives**

259 Childless women suffer discrimination, stigma and ostracism in many cultures across the world.⁷⁸ It is

260 not only childless women who are stigmatised, but also women who have not fulfilled their expected

261 role to bear several children. The stigmatisation can be extreme in some countries, where childless

262 women are viewed as a burden on the socioeconomic well-being of a community. Marriage without
263 children is considered as a 'failure of the two individuals'.⁷⁸ This is a heavy burden to carry for
264 women in many low- and middle-income countries (LMICs).

265 Despite its great importance and significant socio-cultural impact, miscarriage prevention remains a
266 low priority public health issue in LMIC. Care of affected couples is often overlooked because of
267 competing health priorities, with very few formal services available for women who suffer recurrent
268 miscarriages. There needs to be a minimum service available globally for couples who suffer
269 recurrent miscarriage. Within the LMIC setting, this can include tests to check for anaemia, thyroid
270 abnormalities and antiphospholipid syndrome, with appropriate treatment based on the results.
271 There also needs to be a focus on providing pre-pregnancy counselling and psychological support to
272 couples who have suffered repeated miscarriages.

273

274 **Discussion**

275 Recurrent miscarriage is a devastating experience for most couples. Couples who have suffered
276 recurrent miscarriages often go to multiple doctors and many clinics in their search for a cause and
277 remedy for miscarriage. However, there are very few investigations and treatments with clear
278 evidence of benefit. Useful tests for investigating recurrent miscarriage include lupus anticoagulant
279 and anticardiolipin antibodies, and thyroid function, and pelvic ultrasonography. Genetic analysis of
280 pregnancy tissue can be performed for explanatory purposes, and some couples may benefit from
281 parental karyotyping. There is no high quality evidence for any treatment to prevent miscarriages in
282 women at high risk of miscarriage. There is some evidence that progesterone may increase live birth
283 rates in women with recurrent miscarriage, levothyroxine may decrease the risk of miscarriage in
284 women with subclinical hypothyroidism, and a combination of aspirin and heparin may increase live
285 births in women with recurrent miscarriage and antiphospholipid antibodies.

286 The recommendations in this article are based on the best available evidence. We have relied on
287 published systematic reviews, with recommendations that reflect the current state of knowledge.
288 However, there were limitations in the evidence, particularly in the quality of many trials that
289 contributed to the systematic reviews. Furthermore, we have relied on consensus amongst experts
290 to generate recommendations for questions for which there was limited evidence. A model of care is
291 needed that addresses the balance between the need for evidence-based management and
292 supportive care, whilst targeting health care resources appropriately. We propose a graded
293 approach. The graded model is based on the consensus of stakeholders in the UK; for other
294 countries, other models of service organisation and delivery may be appropriate. Acceleration of
295 high quality evidence gathering through the integration of early pregnancy services and specialist
296 recurrent miscarriage clinics across different healthcare systems is essential.

297 We recommend caregivers neither normalise nor over-medicalise recurrent miscarriage care, but
298 individualise care according to women's and their partners' needs and preferences. We have defined
299 the minimum set of investigations and treatments that should be offered to couples suffering
300 repeated miscarriages, and recommend that healthcare policy-makers and providers make these
301 universally available. Any service for recurrent miscarriage couples should have not only their
302 physical, but also their psychological support needs at the centre of its programme.

303 There needs to be a concerted move away from the current piecemeal approach in the delivery of
304 care for miscarriage couples, and instead validated and standardised care pathways tailored to the
305 need of couples and their individualised risk of recurrence should be established. Dedicated research
306 centres with cross-disciplinary expertise in genetics, developmental and reproductive biology, data
307 science and clinical research should accelerate the discovery of molecular and cellular drivers of
308 recurrent pregnancy loss, as well as develop new therapeutic strategies. This should include the
309 development of flexible and responsive trial methodologies to hasten the evaluation of new and
310 existing interventions and treatments.

311 Research is required on optimal ways to stratify women with recurrent miscarriage, so that therapy
312 and psychological care can be appropriately targeted, as well as on optimal ways of organising and
313 delivering care. New diagnostic tests and effective treatments are needed to improve pre-
314 conceptual endometrium and sperm. Several treatment questions, including the role of aspirin and
315 heparin for inherited thrombophilia, levothyroxine for women with mild subclinical hypothyroidism
316 (TSH level between 2.5 – 4.0mIU/L), preconception and early pregnancy metformin for women with
317 polycystic ovary syndrome, and hCG treatment for women with recurrent miscarriages, need
318 answering. Another urgent research priority is the exploration of optimal management approaches
319 for women suffering mental health illness after miscarriages.

320 **Contributors**

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

324

325 **Declaration of interests**

326 The authors have no conflicts of interest to declare.

327

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332

333 **References**

- 334 1. Di Renzo GC, Giardina I, Clerici G, Brillo E, Gerli S. Progesterone in normal and pathological
335 pregnancy. *Horm* 2016; **27**(1): 35-48.
- 336 2. Bender Atik R, Christiansen OB, Elson J, et al. ESHRE guideline: recurrent pregnancy loss.
337 *Hum Reprod Open* 2018; **2018**(2): hoy004.
- 338 3. ACOG Practice Bulletin No. 200: Early Pregnancy Loss. *Obstet Gynecol* 2018; **132**(5): e197-
339 e207.
- 340 4. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. *Fertil Steril*
341 2012; **98**(5): 1103-11.
- 342 5. Aleman A, Althabe F, Belizan J, Bergel E. Bed rest during pregnancy for preventing
343 miscarriage. *Cochrane Database Syst Rev* 2005; (2): Cd003576.
- 344 6. Palomba S, Falbo A, Orio F, Jr., Zullo F. Effect of preconceptional metformin on abortion risk
345 in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials.
346 *Fertil Steril* 2009; **92**(5): 1646-58.
- 347 7. Lim CE, Ho KK, Cheng NC, Wong FW. Combined oestrogen and progesterone for preventing
348 miscarriage. *Cochrane Database Syst Rev* 2013; (9): Cd009278.
- 349 8. Furber CM, McGowan L, Bower P, Kontopantelis E, Quenby S, Lavender T. Antenatal
350 interventions for reducing weight in obese women for improving pregnancy outcome. *Cochrane*
351 *Database Syst Rev* 2013; (1): Cd009334.
- 352 9. Earl R, Crowther CA, Middleton P. Interventions for hyperthyroidism pre-pregnancy and
353 during pregnancy. *Cochrane Database Syst Rev* 2013; (11): Cd008633.
- 354 10. Morley LC, Simpson N, Tang T. Human chorionic gonadotrophin (hCG) for preventing
355 miscarriage. *Cochrane Database Syst Rev* 2013; (1): Cd008611.
- 356 11. Reid SM, Middleton P, Cossich MC, Crowther CA, Bain E. Interventions for clinical and
357 subclinical hypothyroidism pre-pregnancy and during pregnancy. *Cochrane Database Syst Rev* 2013;
358 (5): Cd007752.
- 359 12. Yang GY, Luo H, Liao X, Liu JP. Chinese herbal medicine for the treatment of recurrent
360 miscarriage: a systematic review of randomized clinical trials. *BMC Complement Altern Med* 2013;
361 **13**: 320.
- 362 13. Brocklehurst P, Gordon A, Heatley E, Milan SJ. Antibiotics for treating bacterial vaginosis in
363 pregnancy. *Cochrane Database Syst Rev* 2013; (1): Cd000262.
- 364 14. de Jong PG, Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin and/or heparin for
365 women with unexplained recurrent miscarriage with or without inherited thrombophilia. *Cochrane*
366 *Database Syst Rev* 2014; (7): Cd004734.
- 367 15. Carp H. A systematic review of dydrogesterone for the treatment of recurrent miscarriage.
368 *Gynecol Endocrinol* 2015; **31**(6): 422-30.
- 369 16. Areia AL, Fonseca E, Areia M, Moura P. Low-molecular-weight heparin plus aspirin versus
370 aspirin alone in pregnant women with hereditary thrombophilia to improve live birth rate: meta-
371 analysis of randomized controlled trials. *Arch Gynecol Obstet* 2016; **293**(1): 81-6.
- 372 17. Zhang T, Ye X, Zhu T, et al. Antithrombotic Treatment for Recurrent Miscarriage: Bayesian
373 Network Meta-Analysis and Systematic Review. *Medicine (Baltimore)* 2015; **94**(45): e1732.
- 374 18. De-Regil LM, Pena-Rosas JP, Fernandez-Gaxiola AC, Rayco-Solon P. Effects and safety of
375 periconceptional oral folate supplementation for preventing birth defects. *Cochrane Database Syst*
376 *Rev* 2015; (12): Cd007950.
- 377 19. Brown HC, Smith HJ, Mori R, Noma H. Giving women their own case notes to carry during
378 pregnancy. *Cochrane Database Syst Rev* 2015; (10): Cd002856.
- 379 20. Balogun OO, da Silva Lopes K, Ota E, et al. Vitamin supplementation for preventing
380 miscarriage. *Cochrane Database Syst Rev* 2016; (5): Cd004073.
- 381 21. Chen H, Fu J, Huang W. Dopamine agonists for preventing future miscarriage in women with
382 idiopathic hyperprolactinemia and recurrent miscarriage history. *Cochrane Database Syst Rev* 2016;
383 **7**: Cd008883.

- 384 22. Lensen SF, Manders M, Nastri CO, et al. Endometrial injury for pregnancy following sexual
385 intercourse or intrauterine insemination. *Cochrane Database Syst Rev* 2016; (6): Cd011424.
- 386 23. Li L, Dou L, Leung PC, Chung TK, Wang CC. Chinese herbal medicines for unexplained
387 recurrent miscarriage. *Cochrane Database Syst Rev* 2016; (1): Cd010568.
- 388 24. Boelig RC, Barton SJ, Saccone G, Kelly AJ, Edwards SJ, Berghella V. Interventions for treating
389 hyperemesis gravidarum. *Cochrane Database Syst Rev* 2016; (5): Cd010607.
- 390 25. Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in
391 singleton pregnancy. *Cochrane Database Syst Rev* 2017; **6**: Cd008991.
- 392 26. Rikken JF, Kowalik CR, Emanuel MH, et al. Septum resection for women of reproductive age
393 with a septate uterus. *Cochrane Database Syst Rev* 2017; **1**: Cd008576.
- 394 27. Morley LC, Tang T, Yasmin E, Norman RJ, Balen AH. Insulin-sensitising drugs (metformin,
395 rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo
396 amenorrhoea and subfertility. *Cochrane Database Syst Rev* 2017; **11**: Cd003053.
- 397 28. Gonzalez R, Pons-Duran C, Piqueras M, Aponte JJ, Ter Kuile FO, Menendez C. Mefloquine for
398 preventing malaria in pregnant women. *Cochrane Database Syst Rev* 2018; **11**: Cd011444.
- 399 29. Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with
400 recurrent miscarriage of unclear etiology. *Cochrane Database Syst Rev* 2019; **2019**(11).
- 401 30. Keats EC, Haider BA, Tam E, Bhutta ZA. Multiple-micronutrient supplementation for women
402 during pregnancy. *Cochrane Database Syst Rev* 2019; **3**: Cd004905.
- 403 31. Rao M, Zeng Z, Zhou F, et al. Effect of levothyroxine supplementation on pregnancy loss and
404 preterm birth in women with subclinical hypothyroidism and thyroid autoimmunity: a systematic
405 review and meta-analysis. *Hum Reprod Update* 2019; **25**(3): 344-61.
- 406 32. Sharpe A, Morley LC, Tang T, Norman RJ, Balen AH. Metformin for ovulation induction
407 (excluding gonadotrophins) in women with polycystic ovary syndrome. *Cochrane Database Syst Rev*
408 2019; **12**: Cd013505.
- 409 33. Claire R, Chamberlain C, Davey MA, et al. Pharmacological interventions for promoting
410 smoking cessation during pregnancy. *Cochrane Database Syst Rev* 2020; **3**: Cd010078.
- 411 34. Hamulyak EN, Scheres LJ, Marijnen MC, Goddijn M, Middeldorp S. Aspirin or heparin or both
412 for improving pregnancy outcomes in women with persistent antiphospholipid antibodies and
413 recurrent pregnancy loss. *Cochrane Database Syst Rev* 2020; **5**: Cd012852.
- 414 35. Franssen MT, Korevaar JC, Leschot NJ, et al. Selective chromosome analysis in couples with
415 two or more miscarriages: case-control study. *Bmj* 2005; **331**(7509): 137-41.
- 416 36. Franssen MT, Korevaar JC, van der Veen F, Leschot NJ, Bossuyt PM, Goddijn M. Reproductive
417 outcome after chromosome analysis in couples with two or more miscarriages: index [corrected]-
418 control study. *Bmj* 2006; **332**(7544): 759-63.
- 419 37. Coomarasamy A, Devall AJ, Brosens JJ, et al. Micronized vaginal progesterone to prevent
420 miscarriage: a critical evaluation of randomized evidence. *Am J Obstet Gynecol* 2020; **S0002-**
421 **9378(19)32762-0**.
- 422 38. Coomarasamy A, Williams H, Truchanowicz E, et al. A Randomized Trial of Progesterone in
423 Women with Recurrent Miscarriages. *N Engl J Med* 2015; **373**(22): 2141-8.
- 424 39. Coomarasamy A, Devall AJ, Cheed V, et al. A Randomized Trial of Progesterone in Women
425 with Bleeding in Early Pregnancy. *N Engl J Med* 2019; **380**(19): 1815-24.
- 426 40. Brenner B. Inherited thrombophilia and fetal loss. *Curr Opin Hematol* 2000; **7**(5): 290-5.
- 427 41. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid
428 Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the
429 Postpartum. *Thyroid* 2017; **27**(3): 315-89.
- 430 42. Stagnaro-Green A, Pearce E. Thyroid disorders in pregnancy. *Nat Rev Endocrinol* 2012; **8**(11):
431 650-8.
- 432 43. Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between
433 thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. *Bmj* 2011;
434 **342**: d2616.

- 435 44. Dong AC, Morgan J, Kane M, Stagnaro-Green A, Stephenson MD. Subclinical hypothyroidism
436 and thyroid autoimmunity in recurrent pregnancy loss: a systematic review and meta-analysis. *Fertil*
437 *Steril* 2020; **113**(3): 587-600.e1.
- 438 45. Kim CH, Ahn JW, Kang SP, Kim SH, Chae HD, Kang BM. Effect of levothyroxine treatment on
439 in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism
440 undergoing in vitro fertilization/intracytoplasmic sperm injection. *Fertil Steril* 2011; **95**(5): 1650-4.
- 441 46. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Alavi Majd H, Azizi F. Effects of
442 levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid
443 disease. *Eur J Endocrinol* 2017; **176**(2): 253-65.
- 444 47. Nazarpour S, Ramezani Tehrani F, Simbar M, et al. Effects of Levothyroxine on Pregnant
445 Women With Subclinical Hypothyroidism, Negative for Thyroid Peroxidase Antibodies. *J Clin*
446 *Endocrinol Metab* 2018; **103**(3): 926-35.
- 447 48. Dhillon-Smith RK, Middleton LJ, Sunner KK, et al. Levothyroxine in Women with Thyroid
448 Peroxidase Antibodies before Conception. *N Engl J Med* 2019; **380**(14): 1316-25.
- 449 49. Wang H, Gao H, Chi H, et al. Effect of Levothyroxine on Miscarriage Among Women With
450 Normal Thyroid Function and Thyroid Autoimmunity Undergoing In Vitro Fertilization and Embryo
451 Transfer: A Randomized Clinical Trial. *Jama* 2017; **318**(22): 2190-8.
- 452 50. Negro R, Mangieri T, Coppola L, et al. Levothyroxine treatment in thyroid peroxidase
453 antibody-positive women undergoing assisted reproduction technologies: a prospective study. *Hum*
454 *Reprod* 2005; **20**(6): 1529-33.
- 455 51. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment
456 in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical
457 complications. *J Clin Endocrinol Metab* 2006; **91**(7): 2587-91.
- 458 52. Negro R, Schwartz A, Stagnaro-Green A. Impact of Levothyroxine in Miscarriage and Preterm
459 Delivery Rates in First Trimester Thyroid Antibody-Positive Women With TSH Less Than 2.5 mIU/L. *J*
460 *Clin Endocrinol Metab* 2016; **101**(10): 3685-90.
- 461 53. Balen AH, Morley LC, Misso M, et al. The management of anovulatory infertility in women
462 with polycystic ovary syndrome: an analysis of the evidence to support the development of global
463 WHO guidance. *Hum Reprod Update* 2016; **22**(6): 687-708.
- 464 54. Balen AH, Tan SL, MacDougall J, Jacobs HS. Miscarriage rates following in-vitro fertilization
465 are increased in women with polycystic ovaries and reduced by pituitary desensitization with
466 buserelin. *Hum Reprod* 1993; **8**(6): 959-64.
- 467 55. Hamilton-Fairley D, Kiddy D, Watson H, Paterson C, Franks S. Association of moderate
468 obesity with a poor pregnancy outcome in women with polycystic ovary syndrome treated with low
469 dose gonadotrophin. *Br J Obstet Gynaecol* 1992; **99**(2): 128-31.
- 470 56. Ruutiainen K, Seppala M. Polycystic ovary syndrome: evolution of a concept. *Curr Opin*
471 *Obstet Gynecol* 1991; **3**(3): 326-35.
- 472 57. Lovvik TS, Carlsen SM, Salvesen O, et al. Use of metformin to treat pregnant women with
473 polycystic ovary syndrome (PregMet2): a randomised, double-blind, placebo-controlled trial. *Lancet*
474 *Diabetes Endocrinol* 2019; **7**(4): 256-66.
- 475 58. Oon VJ, Johnson MR. The regulation of the human corpus luteum steroidogenesis: a
476 hypothesis? *Hum Reprod Update* 2000; **6**(5): 519-29.
- 477 59. Fukui A, Fujii S, Yamaguchi E, Kimura H, Sato S, Saito Y. Natural killer cell subpopulations and
478 cytotoxicity for infertile patients undergoing in vitro fertilization. *Am J Reprod Immunol* 1999; **41**(6):
479 413-22.
- 480 60. Kwak JY, Beaman KD, Gilman-Sachs A, Ruiz JE, Schewitz D, Beer AE. Up-regulated expression
481 of CD56+, CD56+/CD16+, and CD19+ cells in peripheral blood lymphocytes in pregnant women with
482 recurrent pregnancy losses. *Am J Reprod Immunol* 1995; **34**(2): 93-9.
- 483 61. Coulam CB, Goodman C, Roussev RG, Thomason EJ, Beaman KD. Systemic CD56+ cells can
484 predict pregnancy outcome. *Am J Reprod Immunol* 1995; **33**(1): 40-6.

- 485 62. Inagaki N, Stern C, McBain J, Lopata A, Kornman L, Wilkinson D. Analysis of intra-uterine
486 cytokine concentration and matrix-metalloproteinase activity in women with recurrent failed
487 embryo transfer. *Hum Reprod* 2003; **18**(3): 608-15.
- 488 63. Ledee-Bataille N, Bonnet-Chea K, Hosny G, Dubanchet S, Frydman R, Chaouat G. Role of the
489 endometrial tripod interleukin-18, -15, and -12 in inadequate uterine receptivity in patients with a
490 history of repeated in vitro fertilization-embryo transfer failure. *Fertil Steril* 2005; **83**(3): 598-605.
- 491 64. Matsubayashi H, Arai T, Izumi S, Sugi T, McIntyre JA, Makino T. Anti-annexin V antibodies in
492 patients with early pregnancy loss or implantation failures. *Fertil Steril* 2001; **76**(4): 694-9.
- 493 65. Stern C, Chamley L, Norris H, Hale L, Baker HW. A randomized, double-blind, placebo-
494 controlled trial of heparin and aspirin for women with in vitro fertilization implantation failure and
495 antiphospholipid or antinuclear antibodies. *Fertil Steril* 2003; **80**(2): 376-83.
- 496 66. Egerup P, Lindschou J, Gluud C, Christiansen OB. The Effects of Intravenous Immunoglobulins
497 in Women with Recurrent Miscarriages: A Systematic Review of Randomised Trials with Meta-
498 Analyses and Trial Sequential Analyses Including Individual Patient Data. *PLoS One* 2015; **10**(10):
499 e0141588.
- 500 67. Wong LF, Porter TF, Scott JR. Immunotherapy for recurrent miscarriage. *Cochrane Database*
501 *Syst Rev* 2014; (10): Cd000112.
- 502 68. Achilli C, Duran-Retamal M, Saab W, Serhal P, Seshadri S. The role of immunotherapy in in
503 vitro fertilization and recurrent pregnancy loss: a systematic review and meta-analysis. *Fertil Steril*
504 2018; **110**(6): 1089-100.
- 505 69. Duhig K, Chappell LC, Shennan AH. Oxidative stress in pregnancy and reproduction. *Obstet*
506 *Med* 2016; **9**(3): 113-6.
- 507 70. Rikken JFW, Kowalik CR, Emanuel MH, et al. The randomised uterine septum transection
508 trial (TRUST): design and protocol. *BMC Womens Health* 2018; **18**(1): 163.
- 509 71. Musters AM, Repping S, Korevaar JC, et al. Pregnancy outcome after preimplantation genetic
510 screening or natural conception in couples with unexplained recurrent miscarriage: a systematic
511 review of the best available evidence. *Fertil Steril* 2011; **95**(6): 2153-7, 7.e1-3.
- 512 72. Iews M, Tan J, Taskin O, et al. Does preimplantation genetic diagnosis improve reproductive
513 outcome in couples with recurrent pregnancy loss owing to structural chromosomal rearrangement?
514 A systematic review. *Reprod Biomed Online* 2018; **36**(6): 677-85.
- 515 73. van Dijk MM, Kolte AM, Limpens J, et al. Recurrent pregnancy loss: diagnostic workup after
516 two or three pregnancy losses? A systematic review of the literature and meta-analysis. *Hum Reprod*
517 *Update* 2020; **26**(3): 356-67.
- 518 74. Sandall J, Soltani H, Gates S, Shennan A, Devane D. Midwife-led continuity models versus
519 other models of care for childbearing women. *Cochrane Database Syst Rev* 2016; **4**: Cd004667.
- 520 75. Smith PP, Dhillon-Smith RK, O'Toole E, Cooper N, Coomarasamy A, Clark TJ. Outcomes in
521 prevention and management of miscarriage trials: a systematic review. *Bjog* 2019; **126**(2): 176-89.
- 522 76. Prior M, Bagness C, Brewin J, et al. Priorities for research in miscarriage: a priority setting
523 partnership between people affected by miscarriage and professionals following the James Lind
524 Alliance methodology. *BMJ Open* 2017; **7**(8): e016571.
- 525 77. Ogasawara M, Aoki K, Okada S, Suzumori K. Embryonic karyotype of abortuses in relation to
526 the number of previous miscarriages. *Fertil Steril* 2000; **73**(2): 300-4.
- 527 78. Cui W. Mother or nothing: the agony of infertility. *Bull World Health Organ* 2010; **88**(12):
528 881-2.

529