Evidence-based management of recurrent miscarriages

Yadava B. Jeve, William Davies[1]
Departments of Obstetrics and Gynaecology, University Hospitals of Leicester, Leicester LE1 5WW, [1]Northampton General Hospital, Northampton, UK

Address for correspondence:
Dr. Yadava B. Jeve, Department of Obstetrics and Gynaecology, University Hospitals of Leicester, Leicester LE1 5WW, UK.
E-mail: drybjeve@gmail.com

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ABSTRACT

Recurrent miscarriages are postimplantation failures in natural conception; they are also termed as habitual abortions or recurrent pregnancy losses. Recurrent pregnancy loss is disheartening to the couple and to the treating clinician. There has been a wide range of research from aetiology to management of recurrent pregnancy loss. It is one of the most debated topic among clinicians and academics. The ideal management is unanswered. This review is aimed to produce an evidence-based guidance on clinical management of recurrent miscarriage. The review is structured to be clinically relevant. We have searched electronic databases (PubMed and Embase) using different key words. We have combined the searches and arranged them with the hierarchy of evidences. We have critically appraised the evidence to produce a concise answer for clinical practice. We have graded the evidence from level I to V on which these recommendations are based.

KEY WORDS: Aspirin, antiphospholipids syndrome, immunotherapy, low molecular weight heparin, recurrent pregnancy loss, recurrent miscarriage, unexplained

INTRODUCTION

Spontaneous miscarriage is a major loss for all pregnant women. It affects 1% of all women.[1] The incidence of spontaneous miscarriage may be much greater than is clinically recognized. Spontaneous miscarriage occurs in 12% to 15% of all pregnancies. Thirty percent pregnancies are lost between implantation and sixth week. Maternal age and previous miscarriages increases risk of subsequent miscarriages.[2] The management of recurrent miscarriages is an unsolved problem; up to 50% of cases of recurrent losses will not have a clearly defined etiology. The investigations and management of recurrent miscarriages is one of the most debated topics. This review is aimed to provide evidence-based approach to manage recurrent pregnancy loss. This review is structured to be clinically relevant.

MATERIALS AND METHOD

Literature search was performed using electronic databases, Embase, and PubMed (1950 to Jan 2014). We have used different keywords and MeSH terms to generate set of results with were combined to generate most relevant results. The evidence was searched using individual subclass of etiology of recurrent pregnancy loss. Different key words were used such as recurrent miscarriage, recurrent pregnancy loss, habitual abortions, pregnancy failures, unexplained, and idiopathic miscarriage; and these words were combined with various factors known to cause or treat miscarriages. The search results were combined and most relevant results were grouped together for critical appraisal. The evidence was sought for all current recommendations as well as all unanswered questions on investigating and managing recurrent miscarriages. The good-quality meta-analysis was critically apprised and accepted. The recommendations are based on evidence. The evidence is graded as (I-IV).

I. High-quality meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a very low risk of bias
II. Meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a high risk of bias or high-quality case–control or cohort studies

III. Well-conducted case–control or cohort studies with risk of confounding, bias
IV. Nonanalytical studies, e.g. case reports, case series
V. Expert opinion

Clinical Guideline

Definition

Recurrent miscarriages are defined as three or more consecutive miscarriages.[1] The Practice Committee of the American Society for Reproductive Medicine[3] defines recurrent pregnancy loss as by two or more failed clinical pregnancies. The risk of recurrent spontaneous miscarriage is much higher in patients with previous losses. The risk of miscarriage after two consecutive losses is 17% to 25% and the risk of miscarrying fourth pregnancy after three consecutive losses is between 25% and 46%. The risk gets worse with increasing maternal age.[4] The evidence suggests higher frequency of spontaneous miscarriages amongst subfertile couples and a higher prevalence of subfertility in women with recurrent spontaneous miscarriages when compared with the general population.[5] Self-reported losses by patients may not be accurate. In one study, only 71% of self-reported clinical pregnancy losses could be verified in hospital records.[6] It is important to define pregnancy as a clinical pregnancy documented by ultrasonography or histo-pathological examination (Evidence level IV).

Investigations

Genetic

The prevalence of chromosome abnormalities in women facing a single sporadic miscarriage is to be 45%.[7] Approximately 50% to 60% of early spontaneous miscarriages are associated with a chromosomal anomaly of conceptus. Most common abnormality is aneuploidy, with autosomal trisomy accounting for more than 50% of chromosomally abnormal abortuses.[8] A strong family history of recurrent miscarriage or genetic anomaly suggests a parental karyotypic abnormality, and a chromosomal analysis of the affected partner is appropriate in the primary evaluation. Chromosomal analysis of the miscarriage offers an explanation in at least 50% of cases.[9] Parental karyotyping is not predictive of a subsequent miscarriage.[10] Routine karyotyping of couples with recurrent miscarriage is not recommended. Cytogenetic analysis may be performed on products of conception to avoid unnecessary evaluation and treatment and because an aneuploid conceptus indicates a somewhat greater likelihood of success with a subsequent pregnancy[10] (Evidence Level III).

Anatomical defects

Women with recurrent pregnancy loss have a 3.2% to 6.9% likelihood of having a major uterine anomaly and 1.0% to 16.9% chance of having an arcuate uterus.[11] Ultrasound is quick, readily available, economical, and lacks radiation. 2D US can only identify about half of the congenital uterine anomalies present, but it has very low false positive rate.[12] Some authors consider that this combination of hysteroscopy and laparoscopy can be the gold standard in evaluating congenital uterine anomalies.[13-16] However, these are invasive tests. Three-dimensional ultrasound by experienced hands is a more accurate than two-dimensional ultrasound and equal to MRI at assessing uterine anomaly.[17] Sonohysterography is a noninvasive, cost-effective method with 95% accuracy in identifying uterine anomalies.[18] MRI is a highly sensitive and specific method available because of its superior ability to reliably visualize complex uterovaginal anatomy.[19] Two-dimensional ultrasound can be used as an initial screening tool. Combined hysteroscopy and laparoscopy, sonohysterography, MRI, and 3D US can be used for a definitive diagnosis (Evidence level II).

Infections

Bacterial vaginosis is a risk factor for preterm delivery and a strong risk factor for late miscarriages.[20] Vaginal swabs should be considered as screening tests during pregnancy in high risk women with previous history of late miscarriages.[21] TORCH test is not recommended (Evidence level II).

Haematological disorders

Acquired thombophilia

Antiphospholipid syndrome (APS) is the only proven thrombophilia that is associated with adverse pregnancy outcomes.[22] Five to fifteen percent of women with recurrent miscarriage have clinically significant antiphospholipid antibody titres, as compared with 2% to 5% of unselected obstetrical patients.[23] Antiphospholipid syndrome (APS) is an autoimmune disease with the presence of antiphospholipid autoantibodies (aPL) formed against the person's own tissues. These autoantibodies interfere with coagulation. Recurrent pregnancy loss will test positive for antiphospholipid antibodies (aPLs), the actual reported range varies between 8% and 42%.[24,25] Laboratory testing for aPL Abs should generally be limited to patients who present with the thrombotic and/or the pregnancy manifestations of the disorder. Weak positive test results for aPL immunoassays are unlikely to have any clinical significance. The two assays that were preferred were the dilute Russell viper venom time (dRVVT) panel, which is widely used in clinical laboratories and is believed to be specific for detecting LA in those patients at high risk of thrombosis,[26] and an LA-insensitive aPTT.[27] Testing positive for aCL Abs does not necessarily mean that a patient has APS. The positive test may be triggered by a preceding infection, such as syphilis, Lyme disease, EBV, CMV, HIV, and hepatitis C virus. These patients do not have LA or elevated Abs against β2GPI.[28] Anti-β2GPI immunoassays are more specific but less sensitive for APS

than aCL Ab assays.[29] The antiphospholipid syndrome should be diagnosed only when two tests performed 12 or more weeks apart are positive (Evidence level I). International Consensus classification criteria for diagnosis of the antiphospholipid syndrome is based on the presence of at least one of the clinical criteria and one of the laboratory criteria.[25,30] Laboratory criteria includes the presence of Lupus anticoagulant (LA) or Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer Anti-β2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA. Clinical criteria include vascular thrombosis or pregnancy morbidity. One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, severe pre-eclampsia or eclampsia, or recognized features of placental insufficiency before 34 weeks gestation and three or more unexplained consecutive spontaneous abortions before the 10th week of gestation are features of pregnancy morbidity. The presence of any one of these clinical features plus abnormal laboratory test diagnose antiphospholipid syndrome (Evidence level I). When a patient has the clinical appearance of APS but negative standard aPL assay results, there is possibility of seronegative APS. Noncriteria tests such as aCL and anti-β2GPI IgA Abs and antiphosphatidylserine Abs may help to clarify the picture[28] (Evidence level II) Ruffatti showed that pregnant women with APS reported that patients with triple aPL Ab-positivity (ie, positivity for LA, aCL, and anti-β2GPI Abs) and/or previous thromboembolism had an increased likelihood of poor neonatal outcomes than patients with double or single aPL Ab positivity and no thrombosis history.[31] However, other study showed that lupus anticoagulant is the primary predictor of adverse pregnancy outcome in aPL-associated pregnancies[32] (Evidence level III).

Inherited Thrombophilia: Antithrombin activity, Protein C activity, Protein S levels, Factor V Leiden (F5), and/or prothrombin G20210A (F2)

Inherited thrombophilias such as factor V Leiden mutation, prothrombin gene mutation (PT 20210A), and deficiencies of natural anticoagulants protein C, protein S, and antithrombin are associated with recurrent miscarriage.[33] The existence of a causal role for heritable thrombophilia and pregnancy failure is controversial.[22] A combination of risk factors, including multiple inherited thrombophilic defects are associated with secondary hypercoagulable states.[34] Case–control studies have shown a modest association (odds ratios of 2 to 3) between recurrent miscarriage and thrombophilias such as the factor V Leiden mutation and the prothrombin G20210A mutation.[35] This association is stronger for fetal deaths, such as stillbirths after 20 weeks' gestation, than for recurrent early losses. Many other large prospective cohort studies have not shown significant associations between thrombophilias and sporadic pregnancy loss.[36-38] However, the strength of the association between inherited thrombophilia and recurrent miscarriage is not very strong, and more importantly, no evidence indicates that the use of anticoagulants improves the chance of live birth in these women.[39] A disadvantage of testing patients with a VTE for thrombophilia is the high costs of testing. Thrmbophilia testing should not be performed routinely in women with recurrent miscarriage except in the context of scientific studies[39] (Evidence level I).

MTHFR mutation

MTHFR (EC 1.5.1.20) is a key enzyme in one-carbon metabolism. The enzyme catalyzes the conversion of 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate, the predominating circulating form of folate.[40] MTHFR gene polymorphisms are commonly associated with hyperhomocysteinemia[41,42] Thus, hyperhomocysteinemia is considered as a risk factor for neural tube defects (NTD)[43,44] and recurrent embryo loss[44,45] Homocysteine levels vary, depending on an individual's state when measured (intake of folic acid, vitamin B12); therefore, it is difficult to achieve representative results. Mild hyperhomocysteinaemia has been identified as a risk factor for arterial disease and venous thrombosis. The evidence is conflicting on hyperhomocysteinaemia as a risk factor for recurrent miscarriage.[46,47] Therefore, testing for MTHFR mutation is not a part of routine evaluation for recurrent miscarriage. (Evidence level II).

Thromboelastography

The test is not recommended as routine investigation for recurrent miscarriage currently as little evidence to support it (Evidence level III). It is argued that thromboelastography identifies a proportion of women with recurrent early miscarriages who are in a pro-thrombotic state outside of pregnancy.[48] Thromboelastography, a "near patient" test of whole blood hemostasis by dynamically assessing the kinetics, strength and stability of the fibrin clot.[49]

Endocrine:

PCO, elevated LH, and insulin resistance

Polycystic ovaries (PCO) is the most commonly identified ultrasound abnormality amongst women with recurrent miscarriages.[50] The prevalence of PCO is 40% among women with recurrent miscarriage; however, polycystic ovarian morphology is not predictive of pregnancy loss amongst ovulatory women with recurrent miscarriage conceiving spontaneously. The ultrasound diagnosis of PCO in women with a history of recurrent miscarriage does not necessarily predict a poor outcome in subsequent pregnancy and therefore it is not recommended[51] (Evidence level III).

It has been reported that hypersecretion of basal LH with or without polycystic ovaries is a risk factor for miscarriage. Women with elevated LH, a frequent feature of the polycystic ovary syndrome, are at increased risk for miscarriage after either spontaneous or assisted conception. However, suppression of endogenous LH release before conception, in women with elevated circulating LH concentrations and a history of recurrent miscarriage, did not improve the live birth rate. Neither an elevated serum luteinizing hormone concentration (>10 IU/l) nor an elevated serum testosterone concentration (>3 nmol/l) was associated with an increased miscarriage rate.[52]

Insulin resistance plays a significant role in recurrent pregnancy loss.[53] Insulin resistance can be independent of polycystic ovarian status. Women with a history of recurrent miscarriage are at an increased risk for insulin resistance during the first trimester of a new pregnancy.[54,55] Recent meta-analysis concluded that insulin resistance is associated with the susceptibility to recurrent miscarriages, and it may contribute to the occurrence of recurrent miscarriages.[56] Therefore, insulin resistance might be one of the direct causes that lead to recurrent miscarriage.[57]

Luteal Phase defect

The shortened luteal phase has been associated with pregnancy loss but the assessment and interpretation of a putative luteal phase defect is problematic. The use of histological and biochemical endpoints as diagnostic criteria for endometrial dating are unreliable (Evidence level III).

Diabetes Mellitus

Evaluation for diabetes is advised with clinical suspicion. Glycated hemoglobin test is advised to screen diabetes. The best test is the oral glucose tolerance test (OGTT), but it is the most expensive, is inconvenient. Fasting plasma glucose would miss people with impaired glucose tolerance. Glycated hemoglobin does not require fasting, and may be the best compromise[58] (Evidence level III).

Thyroid Disorders

Thyroid Function Tests and Thyroid antibody (Thyroid Peroxidase Antibody -TPO) Tests: Recurrent miscarriages are associated with clinical and sub clinical thyroid disorders. Thyroid function tests are recommended based on clinical history while evaluating miscarriages. Evidence is controversial about role of TPO antibodies.[59] Pregnant women with subclinical hypothyroidism or thyroid antibodies have an increased risk of recurrent miscarriage.[60,61] TPO antibody screening is not recommended[62] (Evidence level II).

Immunology

A significant proportion of recurrent pregnancy loss is associated with immune aetiologies.[63] Various mechanisms are suggested. Peripheral natural killer (pNK) and uterine NK (uNK) cells have been associated with reproductive failure. Abnormally functioning immunocompetent cells, including natural killer (NK) cells, in the endometrium, are thought to be responsible and treatment trials including oral prednisolone and intravenous immunoglobulins are now underway.[64] Peripheral immunological dysfunction is observed with recurrent miscarriage.[65] Chronic histiocytic intervillositis is a rare type of placental pathology that is associated with reproductive loss. It is considered to be an immunologic origin.[66] Many studies have suggested that women with recurrent miscarriages have signs of generally exaggerated inflammatory immune responses both before and during pregnancy and signs of breakage of tolerance to autoantigens and fetal antigens.[67] There is neither an adequate standardization of counting uterine NK cells nor consensus as to what constitutes an abnormal level.[64] The prognostic value of measuring pNK or uNK cell parameters is uncertain. Further evidence is required to confirm or refute the role of NK cell assessments as a predictive test for screening women who may benefit from immunotherapy.[68] No immunological test is currently recommended in the recurrent miscarriage work up (Evidence level I).

Male factors

Sperm samples from recurrent pregnancy loss couples have an increase in their sperm DNA fragmentation.[69-71] Meta-analysis showed a significant increase in miscarriage in patients with high DNA damage compared with those with low DNA damage.[72] The associating sperm quality with recurrent pregnancy loss emphasizes the importance of evaluating male factor by tests. Several different tests are available, but no consensus has yet been reached as to which tests are most predictive. Among terminal uridine nick-end labeling assay (TUNEL), sperm chromatin structure assay (SCSA), sperm chromatin dispersion (SCD), and alkaline Comet assays, the alkaline COMET assay showed better prediction for male infertility.[73] A chromosomal abnormality was found in 15.2% men with azoospermia and in 2.3% nonazoospermic men. Male factors abnormality is a significant cause for recurrent pregnancy loss after assisted conception. The number of azoospermic men who needs to be screened to prevent one miscarriage is 80–88 and the number need to screen is 315–347 in the nonazoospermic group.[74] Although there is some evidence of association between DNA defragmentation and recurrent miscarriage, well-designed prospective studies are needed before using these tests in clinical practice.[75] Routine testing for spermploidy (e.g. fluorescence *in situ* hybridization [FISH]) or DNA fragmentation is not recommended (Evidence level II).

Management

Referral to recurrent miscarriage clinic and expert advice help us improve the reproductive outcome

Tender loving care and lifestyle advice

A cause for recurrent miscarriage can be identified approximately 50–60% of the time. There is tremendous psychological impact of recurrent miscarriage.[76] Psychological support in the form of frequent discussions and sympathetic counseling are crucial to the successful evaluation and treatment of the anxious couple. When no etiologic factor is identified, no treatment started at 60% to 80% fetal salvage rate still may be expected. Therefore, couples with unexplained recurrent miscarriage should be offered appropriate emotional support and reassurance[77] (Evidence level III). Obesity,[78] cigarette smoking,[79] alcohol use,[80] and moderate-to-heavy caffeine use[81] may be associated with sporadic miscarriage, but its association with recurrent miscarriage is uncertain. Cigarette smoking has been suggested to have an adverse effect on trophoblastic function and is linked to an increased risk of sporadic pregnancy loss.[82] The Cochrane review concludes that any vitamin supplements prior to pregnancy or in early pregnancy do not prevent women experiencing miscarriage or stillbirth.[83] Lifestyle modification and stress reduction should be emphasized by pointing out that a healthier lifestyle, free from tobacco, alcohol, illicit drugs, and undue stress cannot hurt and may significantly improve the couple's chances for a successful pregnancy (Evidence level III).

Genetic anomalies

In vitro fertilization (IVF) plus prenatal genetic testing is a suggested strategy in the management of couples with chromosomal abnormalities and recurrent miscarriages.[84] It is proposed as a faster method of conceiving a live child than natural conception, at least for translocation carriers with recurrent miscarriages.[85] However, this evidence is being questioned. Systematic reviews showed that there is no conclusive evidence to support prenatal genetic screening for unexplained recurrent miscarriages as well as structural chromosome abnormality.[84,86,87] The new technologies such as trophectoderm-laser-assisted blastocyst biopsy and molecular karyotyping via whole genome amplification and either comparative genomic hybridization (CGH) or single nucleotide polymorphism (SNP) arrays helped to revitalize the concept of preimplantation genetic screening. The evidence from these newer technologies is awaited. Because of the lack of evidence, assisted conception with preimplantation genetic screening as a treatment of recurrent miscarriage is not recommended (Evidence level II).

Anatomical defects

Almost 65% to 85% of patients with bicornuate or septate uteri have a successful pregnancy outcome after metroplasty. However, 59.5% of the patients with such anomalies have a successful subsequent pregnancy without surgery, with a cumulative live birth rate of 78.0%. Further evidence is needed to recommend metroplasty surgery in these women[11] (Evidence level II). The clinical management of pregnancy-loss patients with Asherman syndrome/intrauterine synechiae, uterine fibroids, and uterine polyps is also controversial, and there is no conclusive evidence that surgical treatment reduces the risk of pregnancy loss. Minimally invasive surgeries are the better option for the treatment of structural defects. Cervical incompetence is treated with cervical encirclage; however, the CERVO trial demonstrated no added benefit of circlage.[88] Trans-vaginal Ultrasound examination in subsequent pregnancy is indicated with history of midterm loss due to cervical incompetence, The current data suggest that emergency cerclage is associated with a longer latency and period better pregnancy outcomes when compared with bed rest.[89] (Evidence level III). The accuracy of cervical length in predicting preterm delivery is relatively poor.[90] Compared to the McDonald technique, the Shirodkar technique was more effective in prolonging pregnancy in patients with singleton pregnancies undergoing ultrasound-indicated cerclage[91] (Evidence level III). Cerclage, vaginal progesterone, or pessary are equally efficacious in the prevention of preterm birth in women with a short cervix detected on sonogrphy at the midtrimester in singleton gestation[92,93] (Evidence level II).

Infection

Treatment of asymptomatic abnormal vaginal flora and bacterial vaginosis with oral clindamycin early in the second trimester significantly reduces the rate of late miscarriage and spontaneous preterm birth in a general obstetric population[20,94] (Evidence II).

Endocrine disorders

It is generally agreed that maternal endocrine disorders (e.g. diabetes, thyroid dysfunction) should be evaluated and treated.[95,96] Though elevated LH is associated with increased risk of miscarriage suppression of LH secretion with GnRH agonist prior to ovulation induction yielded no difference in outcome. Hyperprolactinemia may be associated with recurrent pregnancy loss through alterations in the hypothalamic-pituitary-ovarian axis, resulting in impaired folliculogenesis and oocyte maturation, and/or a short luteal phase. Normalization of prolactin levels with a dopamine agonist improved subsequent pregnancy outcomes in patients with recurrent pregnancy loss Hyper-prolactinemia is treated with dopamine agonist.[97] Thyroid disorders can be treated medically to achieve euthyroid status and medications should be modified with pregnancy appropriately. There is lack of consensus regarding the definition of a normal upper limit of TSH. A consensus is emerging that TSH values more than 2.5 mIU/L are outside the normal range.[3]

Thyroid hormone requirement in early pregnancy is higher. The aim is to maintain baseline TSH < 2.5 mU/L. Some evidence suggests association of raised thyroid (TPO) antibodies with recurrent miscarriage.[62,98] Levothyroxine 50 μg daily for the women with raised TPO antibodies with normal TSH is suggested intervention. Observational study suggest TPO Ab-positive status does not have a prognostic value regarding the outcome of a subsequent pregnancy, and empirical thyroxine therapy in those who tested positive did not seem to improve outcome.[59] The thyroid antibodies and levothyroxine study (TABLET) study is a randomized controlled trial of the efficacy and mechanism of levothyroxine treatment on pregnancy and neonatal outcomes in women with thyroid antibodies. This study will help to find the role of thyroxin treatment for women with normal thyroid function tests but raised thyroid peroxidase antibody (TPO) (http://www.controlled-trials.com/ISRCTN15948785/). Until robust evidence is available, thyroxine treatment is not recommended in raised thyroid antibody status with normal thyroid function tests (Evidence level III).

Progesterone supplementation

The progesterone act as immmunomodulator and it shift from proinflammatoryTh-1 cytokine responses to anti-inflammatory Th-2 cytokine response which is more favorable and pregnancy protective.[99,100] Dihydrogesterone is a potential immunomodulator, it produces progesterone-induced blocking factors (PIBF) which is protein produced by pregnancy lymphocyte following exposure to progestorene. PIBF inhibits cell-mediated cytotoxicity and natural killer cell activity. Thus, it is immunoprotective for pregnancy. Administration of progesterone to women with sporadic miscarriages is ineffective.[97,101] However, in patients with three or more consecutive miscarriages immediately preceding their current pregnancy, empiric progestogen administration may be of some potential benefit.[97,101-103] A large multicenter study called promise study (http://www.medscinet.net/promise) is currently underway to assess the benefit of progesterone supplementation in women with unexplained recurrent miscarriages. Most commonly used regime is micronized progesterone tablets 400 mg daily. The route of administration may be either vaginal or oral. The argument for use of progesterone is that there is no evidence of harm and some evidence of benefit, although not coming from huge multicentric trials. The decision should be based on clinician's discretion until strong evidence is available to recommend routine use (Evidence level III).

Metformin

Data on the use of metformin to decrease the chance of miscarriage are contradictory as no adequately powered trials have been published. Insulin resistance is an independent risk factor for spontaneous miscarriage in spontaneous pregnancy. Patients with insulin resistance should be advised to improve their insulin sensitivity through lifestyle change or medical intervention before infertility treatment to reduce their risk of spontaneous miscarriage. Nonrandomized studies have shown that the reduction in insulin levels with metformin in insulin-resistant individuals may reduce miscarriage risk by restoring normal hemostasis and improving the endometrial milieu[104,105] Metformin is not recommended as a treatment of recurrent miscarriage (Evidence level III).

Hematological disorders:

Antiphospholipid syndrome

Low doses of acetylsalicylic acid and low molecular weight heparin (LMWH) are the best solution in women suffering from recurrent spontaneous miscarriage. This treatment combination of low dose aspirin and low molecular weight heparin reduces the miscarriage rate by 54%.[106] The role of low molecular weight heparin and aspirin treatment specifically for the prevention of recurrent miscarriage remains controversial. The meta-analysis showed the combination of unfractionated heparin and aspirin confers a significant benefit in live births. However, the efficacy of low molecular weight heparin plus aspirin remains unproven as LMWH data were based on only two trials. These trials were criticized as studies were not blinded and the randomization procedure had been criticized in one of the trials and inclusion criteria were very different. Third trial showed no significant difference in live birth rate with LMWH treatment versus aspirin or a combination of both versus aspirin in women with recurrent miscarriage.[107] A small trial showed comparable results with LMWH plus aspirin as an alternative to unfractionated heparin and aspirin in the management of recurrent miscarriage secondary to APS.[108] The consensus is combination of low molecular weight heparin and aspirin is superior to aspirin alone in achieving more live births. Therefore, it is recommended treatment for recurrent miscarriages with antiphospholipid syndrome[109,110] (Evidence level I). Glucocorticoids should not be given in antiphospholipid antibodies syndrome without connective tissue disorder. Low-dose prednisone is given when lupus is present and with the advice of rheumatologist. Prednisone does not prevent recurrent fetal death in women with antiphospholipid antibody.[111] Women with a history of thrombosis in whom the antiphospholipid syndrome or a heritable thrombophilia is diagnosed should receive an appropriate dose of unfractionated heparin or low-molecular-weight heparin[23] (Evidence level I). A third trial could not find that heparin/aspirin was better than aspirin alone.

Inherited Thrombophilia

Role of anticoagulation therapy in the treatment of recurrent miscarriages with hereditary thrombophilia is debatable. Few studies suggested low molecular weight heparin therapy during pregnancy may improve the live birth rate of women with second-trimester miscarriage associated with inherited thrombophilia.[112-114] However, there is currently no evidence supporting treatment, because observational research is hampered by poor methodology or inconsistent results.[115] Recent meta-analysis showed that the use of LMWH in women with inherited thrombophilia with recurrent pregnancy loss is not indicated.[116] Women with thrombophilia should be followed closely without routine prophylactic low molecular weight heparin other than for prevention of venous thromboembolism in limited circumstances (Evidence level I).

Hyperhomocysteinemia and MTHFR mutation

High-dose folic acid (5 mg) and vitamin B12 (0.5 mg) once daily has been reported to reduce levels of homocysteine; however, a randomized-controlled trial on the effect of variable doses of both vitamins on pregnancy has yet to be conducted. High-dose folic acid is considered with women with high BMI and diabetes. There is no evidence to support usage of 5 mg folic acid from pre-pregnancy stage purely to reduce the risk of recurrent miscarriage (Evidence level III).

Fibrinolytic anomalies

Activators and inhibitors of the fibrinolytic system are frequently abnormal in recurrent miscarriage.[117] Plasma levels of tissue factor activity, thrombomodulin activity, and procoagulant phospholipids were significantly higher in recurrent miscarriage group.[118] Clinical evaluation of recurrent miscarriage does not include investigating fibrinolytic anomalies. It is limited to the research interest.

Immunotherapy

Both organ-specific and systemic autoimmunity are associated with an increased prevalence of recurrent miscarriage. Immune modulating therapies have been mooted as potential therapeutic strategies. There is no specific immunological test or clinical method, which will predict the need for treatment. Mechanisms of possible efficacy of high dose of intravenous immunoglobulin therapy for recurrent miscarriage may include enhancement of CD94 expression and subsequent suppression of NK cell cytotoxicity.[119] Evidence does not support routine use of intralipid therapy.[120] The Cochrane review analyzed various strategies including paternal cell immunization, third-party donor leukocytes, trophoblast membranes, and intravenous immune globulin. None of these interventions proved beneficial over placebo in improving the live birth rate.[121] This Cochrane review has been widely criticized for not making the necessary sub-analyses between primary and secondary recurrent miscarriage. Meta-analysis showed that IVIG increased the rates of live birth in secondary recurrent miscarriage, but there was insufficient evidence for its use in primary recurrent miscarriage.[122] There is risk of possible complications such as undesirable immune responses and the possibility of transmitting infectious diseases like cytomegalovirus. The risk of transmitting infections disease with intravenous immunoglobulin is extremely small. Most recent systematic review and meta-analysis concludes that NK cell analysis and immune therapy should be offered only in the context of clinical research.[123] The current recommendation is immunotherapy should not be advised.[121] (Evidence level II)

Unexplained recurrent miscarriage

- Psychological support: Stress itself is a risk factor for miscarriage[124] and recurrent miscarriage is a stressful condition so that the vicious cycle can be broken by strong psychological support. Women should be reassured for a successful future pregnancy with supportive care.[125,126] (Evidence level III)
- Aspirin 75 mg OD: Evidence is debatable. There is paucity of evidence to make any recommendation on aspirin for treating recurrent miscarriage in women without antiphospholipid syndrome.[115] Few RCT suggested clear benefit of using aspirin for such women.[127] Recent trial failed to support any role of Aspirin in unexplained recurrent miscarriage.[128] Aspirin helps in improving uterine perfusion.[129] Aspirin is useful in many undiagnosed implantation failure patients. However, in the absence of strong evidence, routine use of Aspirin is not recommended (Evidence level II)
- Progesterone: Meta-analysis of 4 randomized trials and only 132 women in total showed a statistically significant reduction in miscarriages.[130] Further, the evidence is awaited before making recommendation on use of progesterone in explained miscarriage. (Evidence level III)
- LMWH: Use of LMWH to prevent miscarriage is not recommended in the absence of antiphospholipid syndrome (Evidence level II)
- Human chorionic gonadotrophin (hCG): Recent Cochrane review failed to find quality evidence to support use of hCG for preventing miscarriage.[131] A well-designed randomized controlled trial of adequate power and methodological quality is required. Therefore, the use of hCG is not recommended (Evidence level II)
- Steriods: The effect of prednisolone therapy for some women with recurrent miscarriage may be due to altered endometrial angiogenic growth factor expression and reduced blood vessel maturation.[132] The role is mostly limited to recurrent miscarriage with known connective tissue disorders. Rheumatologic advice should be taken

with patients diagnosed having recurrent pregnancy loss and connective tissue disorder. The results from the Prednisolone Trial are awaited; it is a randomized controlled trial of prednisolone for women with idiopathic recurrent miscarriage and raised uNK cells in the endometrium.[133] There is no robust evidence to recommend steroid use for unexplained recurrent miscarriage (Evidence level III)

- Immunoglobulins: IVIG administration for treatment of recurrent miscarriage is not justified outside the context of research as discussed earlier (Evidence level II)
- Intravenous intralipid solution: No evidence of benefit with use of intralipid. Well controlled, large-scale, and confirmatory studies required before it can be recommended for routine use[118,120] (Evidence level III)

CONCLUSION

Recurrent miscarriage is one of most the widely researched areas in medicine. Recurrent miscarriage may be the first presentation of some of the hematological or endocrine disorders. Many investigations such as genetic thrombophilia screening are not based on strong evidence. The management of unexplained miscarriage is a challenge. Role of aspirin and low molecular weight heparin is controversial in genetic thrombophilias. Any form of immunotherapy is not recommended until further evidence is available. We look forward for results of various ongoing multicentre trials to produce an answer.

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