

STANDARD TREATMENT GUIDELINES

Management of Recurrent Spontaneous Abortion

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सत्यमेव जयते

**Ministry of Health & Family Welfare
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STG Recurrent Miscarriage

Scope

Definition

Miscarriage is defined as a spontaneous loss of pregnancy before 20 weeks of gestation.

Group to be covered

Women with three or more first trimester and one or more second trimester miscarriage (RCOG Greentop). Early evaluation is considered if fetal cardiac activity was present, women >35 years with two or more abortions and the couple has had difficulty in conceiving.

Group not covered

Two or more losses with one or more live issues.

Burden of the disease

In India, the prevalence of recurrent miscarriage is around 7.4%.

Rationale

Since the true prevalence of recurrent miscarriage is still unknown and the multimodality approach being used at different levels of care by health care workers, this guideline attempts to provide an evidence based platform to investigate and manage women with recurrent miscarriage.

Financial constraints

A number of investigations related to recurrent miscarriage are expensive, so financial constraints do come-up while investigating couple.

Target Users

All levels of healthcare including the primary, secondary and tertiary levels.

Main outcomes

Live pregnancy.

Key clinical issues

Causes, investigations and treatment of couples with recurrent miscarriage (RM).

Collection of evidence

Evidence based existing guidelines which reviewed were Greentop, American Society of Reproductive Medicine, National Clearing House and The Obstetrician and Gynaecologist.

Criteria for referral

At the primary level, a thorough history and examination have to be carried out and the patient has to be referred to the secondary care level for further management. If higher modalities of treatment like surgery is required, the patient should be referred to the tertiary care level.

Background

Introduction

Women with three or more first trimester and one or more second trimester miscarriage are the ones who have to be evaluated for recurrent miscarriage (Greentop Guidelines). It affects 1% of fertile couples (Berry et al 1995). 1-2% of pregnancies miscarry before 24 weeks (RCOG). The mechanism of RM remains poorly understood. The cause remains elusive in 50% of cases even after thorough investigations (TOG).

Causes of recurrent miscarriage

1) Epidemiological factors

- Advanced maternal age, number of previous miscarriages and advance paternal age are independent risk factors for RM.
- The risk is highest if maternal age is >35 years and paternal age >40 years.
- The risk of miscarriage increases after each pregnancy loss reaching almost 30% after two and 40% after three consecutive losses.
- Maternal smoking, alcohol consumption (5 units or more per week throughout pregnancy or 3 or more per week in first trimester), caffeine consumption (3-5 cups per day, obesity, illicit drug use like cocaine (TOG)^(ref)) increase the risk.
- The evidence of the effect of anaesthetic gases in theatre workers is conflicting (RCOG Ref¹²⁻¹³).

2) Acquired and inherited thrombophilias

Acquired thrombophilias are antiphospholipid syndrome (APS), hyperhomocysteinemias and acquired protein C resistance (APCR).

- Antiphospholipid antibody syndrome is the most important treatable cause of RM.
- APL antibodies are present in 15% of RM in comparison to only 2% in women with low risk obstetric history^(RCOG 31-33).

- Inherited thrombophilias include Antithrombin-III, Protein C deficiency, Protein S deficiency (uncommon and strongly thrombogenic), Factor-V Leiden, Prothrombin gene mutation (20210A) (common and weekly thrombogenic).
- The association between fetal loss and inherited thrombophilia depends on the type of thrombophilia and timing of fetal loss ^(Rey et al, Lancet 2003).

3) Genetic causes

- Increased incidence of structural chromosomal anomalies to the tune of 2-5% is seen in couples with RM. These are either balanced reciprocal or Robertsonian translocations ^(RCOG 35,38). All the four factors low maternal age at second miscarriage, history of three or more miscarriages, history of two or more miscarriages in brothers and sisters and history of two or more miscarriages in parents of either partner all increase the probability of carrier status ^(Franssen 2005).
- In couples with RM, chromosomal abnormalities of embryo account for 30-57% of further miscarriages (RCOG 39,40).

4) Anatomic factors

a) Congenital uterine malformations

- Reported prevalence of uterine anomalies in recurrent miscarriage population ranges between 1.8-37.6%.
- Women with arcuate uteri have more second trimester miscarriage and those with septate uteri are more likely to miscarry in the first trimester ^(RCOG 45).

b) Cervical incompetence:

- Essentially a clinical diagnosis, with unknown true incidence, cervical incompetence is a recognized cause of recurrent second trimester abortions.
- The diagnosis is usually suggested by a second trimester miscarriage preceding a spontaneous rupture of membrane or painless cervical dilatation.

5) Endocrine factors

- Current evidence indicate that treated thyroid dysfunction and controlled diabetes mellitus is not a risk factor for RM (RCOG 47,48) and the prevalence of diabetes mellitus and thyroid dysfunction is similar to general population (RCOG 49,50).
- Obesity is also associated with statistically significant increased risk of first trimester and recurrent miscarriage ^(Lashen 2004).
- Hypersecretion of LH, luteal phase defect, increased free androgen index and hyperprolactinemia all have a role in recurrent miscarriage.
- Increased free androgen index appears to be a prognostic factor for a subsequent miscarriage in women with RM (RCOG 55).

6) Immune factors

- There is no clear evidence to support the hypothesis of human leucocyte antigen incompatibility between couples, the absence of maternal leucocytotoxic antibodies or the absence of maternal blocking antibodies^(RCOG).
- A no more than modest association between cytokine polymorphism and recurrent miscarriage has been seen ^(RCOG 61).

- Mannan-binding lectin (MBL) is a C-type lectin that participates in the innate immune defence by activating complement. Low MBL levels are associated with RM and that low MBL is associated with significantly higher miscarriage rate in next pregnancy (20%) (Kilpatrick et al 1995, Cruz et al 2002). However, most women with low MBL do not experience RM.

7) Infective factors

- The role of infection in recurrent miscarriage is unclear. Bacterial vaginosis is consistently associated with recurrent second trimester abortions and preterm delivery, but association with first trimester abortion is inconsistent.

Investigations for recurrent miscarriage

The women with recurrent miscarriage should be looked after by a trained and expert health professional within a dedicated recurrent miscarriage clinic. Clearly written patient leaflets are recommended to provide take home written information.

1) Antiphospholipid antibodies

- For diagnosis, a woman should have two positive tests at least 12 weeks apart of either lupus anticoagulant or anticardiolipin (aCL) IgG/IgM in moderate to high titres (>40 g/l).
- Dilute Russell Viper Venous Test (drVVT) along with platelet neutralization procedure is a more sensitive and specific test than either activated prothrombin times test (aPTT) or kaolin clotting time (KCT). aCL antibodies are detected using ELISA (RCOG 31).

2) Inherited thrombophilias

- Women with any unexplained still birth and two or more second trimester losses should be offered screening (Lavigne LG. Hematologica 2005).
- With only second trimester miscarriage women should be screened for inherited thrombophilias for inherited thrombophilias including Factor V Leiden, prothrombin gene mutation and protein S [D] (Meta-analysis by Rey et al).

3) Anatomic Factors

a) Uterine factors

- Suspected uterine anomalies may further require a confirmation with hysteroscopy, laparoscopy or a 3D ultrasound [✓]. 3D ultrasound in particular has become an accurate, reproducible, non-invasive outpatient method for diagnosis (Saliim et al 2003).

- There is insufficient evidence to assess the effect of uterine septum resection in females with RM and uterine septum to further prevent miscarriage [C].

b) Cervical incompetence

- There is currently no satisfactory objective test to clearly identify cervical weakness in non-pregnant state.

4) Endocrine factors

- Role of estimation of serum progesterone, serum hCG, inhibin and actinin levels is yet to be established.

Recommendations

1. Thorough history and Clinical examination is a must
2. Offer testing for APS with lupus anticoagulant (LAC) and anticardiolipin antibody (aCL) ideally before the next pregnancy (^{HR Wilson 2006 and NGC}) to any woman with history of three or more pregnancy losses <10 weeks or one or more loss of a morphologically normal fetus >10 weeks or one or more premature birth <34 weeks due to severe preeclampsia or placental insufficiency.
3. Offer parental karyotype only when probability of carrier status is >2.2% (^{Franssen 2005}).
4. Do not offer testing for human leucocyte antigen, maternal leucocytotoxic antibodies and maternal blocking antibodies.
5. Do not offer TORCH investigations.
6. Do not offer investigations for hyperhomocysteinemia outside a research protocol.
7. Offer screening for inherited thrombophilias only if other causes have been ruled out, with any unexplained still birth and two or more second trimester losses and if only second trimester miscarriages are present.
8. Offer cytogenetic analysis on products of conception of third and subsequent consecutive miscarriages.
9. Offer parental peripheral blood karyotyping of both partners in couples with RM where testing of products of conception reveal an unbalanced structural chromosomal translocations.
10. Consider pelvic ultrasound in all women with recurrent first trimester miscarriages and with one or more second trimester miscarriages to assess uterine anomalies.

Management of Recurrent Spontaneous Abortion (RSA)

The etiology of RSM is multifactorial. Appropriate treatment continues to be a challenge, and there is need for larger well-planned double-blinded randomized controlled trials or standardized research protocols for the investigations and treatment of RSA to effectively resolve many of the problems which remain a source of dilemma for most treating physicians. The investigation and management of women with recurrent spontaneous abortion should be done in a centre well equipped with readily available facilities for all ancillary investigations and well trained qualified personnel.

The management of RSA depends on the causative factor, though in 75% of the cases the cause remains unexplained, thus only 25% of the women require treatment as per the cause.

Management depends on the time of detection of these cases, before pregnancy and during pregnancy.

Treatment before Pregnancy

1. **Counseling** the couple should be done regarding the investigations and the outcome of the investigations, the treatment plan to be followed, and the outcome of such treatment
2. **Psychological support.** Women with RSA are usually quite anxious and full of uncertainty about the outcome of their next pregnancy. A strong psychological support should be provided and should be dealt with tender loving care all through the period of consultation
3. Those couples with abnormal karyotypes detected during the screening period should be referred to a clinical geneticist, where available, for detailed counseling about the outcome of future pregnancies.
4. **Surgery for detected anatomical disorders (congenital and acquired):**
Hysteroscopic resection of uterine septum preferably using cold scissors rather than cautery or bipolar cutting devices, resection of submucous fibroids, and

treatment of intrauterine adhesions presenting as Asherman syndrome can be undertaken before another pregnancy is embarked upon.

Women who have multiple uterine fibroids with an uterine size more than 14 weeks \varnothing size should be encouraged to secure appropriate treatment (including myomectomy) before embarking on another pregnancy.

However, it should be noted that the exact role of a resection of the uterine septum is still unresolved since there are no published controlled randomized trials of the benefits of surgical correction of uterine abnormalities on pregnancy outcome. Uncontrolled studies have indicated a positive effect on pregnancy outcome.

Evidence

- There is insufficient evidence to assess the effect of uterine septum resection in women with recurrent miscarriage and uterine septum to prevent further miscarriage (**RCOG**)
- 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 (Evidence level II).
- Correction of septate defects in particular may have beneficial effects (live birth rate 83.2%, range from 77.4% - to 90.9%) and should be considered in women with RPL. The primary limitation of existing data is the lack of randomized, controlled therapeutic trials (**ASRM**)
- Because randomized trials in this area are lacking and difficult to conduct, the general consensus is that surgical correction of significant uterine cavity defects should be considered
- 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.(RCOG)

- There are no published randomised trials assessing the benefits of surgical correction of uterine abnormalities on pregnancy outcome. Open uterine surgery has never been assessed in prospective trials but is associated with postoperative infertility and carries a significant risk of uterine scar rupture during pregnancy. These complications are less likely to occur after transcervical hysteroscopic resection of uterine septae; experience from case series appears promising However, before a clear judgement can be made, this procedure must be evaluated in a prospective controlled trial
- In the event of irreparable anatomic uterine abnormalities and RPL, IVF with transfer of embryos to an appropriately selected gestational carrier also may be a clinical consideration(ASRM)

Repair of cervical lacerations: Abdominal Cerclage

Surgical correction of traumatic cervical lacerations should be undertaken before further pregnancies are planned. Transabdominal cerclage can be offered as an alternative treatment for patients presenting with second-trimester miscarriage or early preterm labour who have had unsuccessful transvaginal cerclage because of a short or scarred cervix. A systematic review comparing abdominal with vaginal cerclage has indicated a lower risk of delivery before 24 weeks \circ gestation although the timing of performing transabdominal cerclage before or during pregnancy remains unresolved

5. **Medical treatment:** Endocrine disorders including thyroid dysfunction and diabetes mellitus should be well controlled before another pregnancy is planned. Patients presenting with PCOS should be appropriately managed with medical and surgical methods to achieve regular ovulation, and assisted reproductive technology may be indicated in some of these patients with PCOS.

Treatment during Pregnancy

1. **Psychological support:** Psychological support and tender loving care should be continued all through the pregnancy. The women should be encouraged for more frequent antenatal visits (usually 2 weekly appointments) and should be reassured and to be well supported
2. **Treatment for the thyroid dysfunction** and diabetes mellitus should be continued to ensure that these endocrine disorders are well controlled
3. **Treatment of RSA Patients with Cervical Disorders: Cervical cerclage**

Because of conflicting evidence, the management of women presenting with RSA, usually late in the first trimester, and with second-trimester miscarriages is really difficult for the treating physician who needs to decide on the definitive treatment for such patients.

- A meta-analysis of 4 randomized controlled trials reported that prophylactic cerclage did not reduce the risk of miscarriage or preterm delivery in women at risk of such disorders because of cervical weakness.
- Another meta-analysis on women from 4 randomized controlled trials with a short cervix (<25 mm diagnosed by transvaginal ultrasound examinations) and a history of previous second-trimester miscarriage confirmed that cervical cerclage may reduce second-trimester miscarriages and the incidence of preterm delivery. It has been documented that cervical cerclage may be associated with some minor maternal morbidity.
- Prophylactic cerclage can be applied in women who present with a history of recurrent second-trimester abortions, a history of a typical single second-trimester abortion, or with ultrasound-indicated cervical weakness where a cervical length of 25 mm or less has been detected by transvaginal ultrasound.
- In women with a less specific history, serial cervical ultrasonographic monitoring can be carried out in the index pregnancy and prophylactic cerclage can be performed in women with a short cervix (cervical length of <25 mm).

Evidence

- Cervical cerclage is associated with potential hazards related to the surgery and the risk of stimulating uterine contractions and hence should be considered only in women who are likely to benefit (RCOG)
- Women with a history of second-trimester miscarriage and suspected cervical weakness who have not undergone a history-indicated cerclage may be offered serial cervical sonographic surveillance. (RCOG)
- In women with a singleton pregnancy and a history of one second-trimester miscarriage attributable to cervical factors, an ultrasound-indicated cerclage should be offered if a cervical length of 25 mm or less is detected by transvaginal scan before 24 weeks of gestation. (RCOG)

Treatment of RSA Patients with Antiphospholipid Syndrome

APS, the most frequently diagnosed immunological cause of RSA and the only proven thrombophilia associated with an adverse pregnancy outcome, has also been identified as the most treatable cause of RSM.

LDA & LMWH

- 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%.
- 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.

- A meta-analysis showed the combination of unfractionated heparin and aspirin confers a significant benefit in live births (RCOG, ASRM).
- 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.
- 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 (Evidence level I).

Evidence

- Pregnant women with antiphospholipid syndrome should be considered for treatment with low-dose aspirin plus heparin to prevent further miscarriage (**RCOG**)
- The combination of twice daily unfractionated heparin and low-dose aspirin appears to confer a significant benefit in pregnancies with aPLs and otherwise unexplained recurrent pregnancy loss; comparable efficacy of low molecular weight heparin has not been established (**ASRM,2012**).

Treatment with heparin and LDA should be commenced as soon as a pregnancy test is positive and continued all through pregnancy and into the puerperium with specific breaks. LDA should be stopped at 35 weeks gestation because of some adverse neonatal effects of LDA, and heparin should not be administered during labour and operative obstetric operations because of the risk of hemorrhage.

Glucocorticoids :

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. Corticosteroids administered to women during pregnancy presenting with RSA associated with APS do not improve the live

birth rate compared with heparin and LDA, and such therapy should not be encouraged, especially as corticosteroids are associated with significant fetal and maternal morbidity.

Evidence

- Neither corticosteroids nor intravenous immunoglobulin therapy improve the live birth rate of women with recurrent miscarriage associated with antiphospholipid antibodies compared with other treatment modalities; their use may provoke significant maternal and fetal morbidity (**RCOG**)
- Administration of prednisone does not improve pregnancy rates and may be associated with an increased risk of gestational hypertension and gestational diabetes (**ASRM**)

Treatment of women presenting with RSA associated with inherited thrombophilia

- Role of anticoagulation therapy in the treatment of RSA with hereditary thrombophilia is debatable. Treatment of women presenting with RSA associated with inherited thrombophilia poses many challenges because there is no strong evidence to support the treatment of these patients with aspirin and/or heparin.
- 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. However, there is currently no evidence supporting treatment, because observational research is hampered by poor methodology or inconsistent results. (RCOG,ASRM.. insufficient evidence) .
- Recent meta-analysis showed that the use of LMWH in women with inherited thrombophilia with recurrent pregnancy loss is not indicated.
- 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).

- Although some studies have indicated that heparin may improve live birth rates in women with inherited thrombophilia , a more recent has stated that there was no significant difference in the live birth rate in women with RSA and inherited thrombophilia who have been treated with a combination of aspirin and LMWH or aspirin alone.

4. Luteal support Role of Progesterone

In spite of the fact that progesterone has been identified as being essential for the implantation and maintenance of pregnancy, great controversy still exists about the role of progesterone supplementation in supporting early pregnancy and in the prevention and/or reduction of first-trimester miscarriages/recurrent early spontaneous first-trimester miscarriages.

Treatment of women with unexplained RSA

It should be recalled that in about 50-60% of patients presenting with RSA, in spite of comprehensive investigations, no etiological factor is identified, and these are classified as unexplained or idiopathic RSM. Therapy for these cases of idiopathic RSA remains a great challenge and increases the state of dilemma which the treating physicians confront on a regular basis. Therapy for many of these patients is empirical, the treating physician faces a lot of pressure in deciding on whether to offer some other forms of controversial therapy to these patients. A psychological support and tender loving care should be part of the treatment offered to these patients. Efforts should be made to find an appropriate therapy for patients with idiopathic RSA

- Psychological support: should be offered tender loving care, psychological support as well as dedicated intensive monitoring and comprehensive care and they should be reassured that a successful future pregnancy could be in the range of 75%. Women should be reassured for a successful future pregnancy with supportive care.(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. Few RCT suggested clear benefit of using aspirin for such women. Recent trial failed to support any role of Aspirin in unexplained recurrent miscarriage. Aspirin helps in improving uterine perfusion. 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)
- LMWH: Use of LMWH to prevent miscarriage is not recommended in the absence of antiphospholipid syndrome (Evidence level II).
- The role of low molecular weight heparin and aspirin treatment specifically for the prevention of recurrent miscarriage remains controversial.

Two recent randomized controlled trials reported that low molecular weight heparin and aspirin treatment showed no improvement in the live birth rate among women with unexplained recurrent miscarriage Proper RCT should be done to test the efficacy of this treatment (RCOG)

The combination of twice daily unfractionated heparin and low-dose aspirin appears to confer a significant benefit in pregnancies with otherwise unexplained recurrent pregnancy loss (ASRM).

- Progesterone: Meta-analysis of 4 randomized trials and only 132 women in total showed a statistically significant reduction in miscarriages. Further, the evidence is awaited before making recommendation on use of progesterone in explained miscarriage. (Evidence level III).
- Human chorionic gonadotrophin (hCG): Recent Cochrane review failed to find quality evidence to support use of hCG for preventing miscarriage. 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).
- Steroids: 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. 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. 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 (Evidence level III)

Recent randomized controlled trials have indicated that interventions with the drugs stated above do not improve live birth rates in women with unexplained/idiopathic RSA. As clearly recommended, empirical treatment of patients with unexplained RSM with the drugs stated above should be resisted and discontinued, and restate that in spite of the challenges we face in finding suitable evidence-based therapy for our patients with RSA, we should resist offering empirical treatment.

Summary

- The management of RSA is quite varied and challenging.
- The use of LDA and heparin, an established treatment for APS, has been associated with a live birth rate of 54.674%.
- The role of LDA and heparin therapy in congenital thrombophilia remains controversial.
- Surgical treatment for uterine anatomical disorders requires further studies.
- The management of unexplained or idiopathic RSA remains a clinical dilemma, and although psychological care has been associated with a favorable outcome, the

empirical use of LDA and heparin and/or intravenous immunoglobulin, should be discouraged because available results do not support this line of management.

- There is a need for larger, randomized, double-blinded, multi-centred, placebo-controlled studies to establish an evidence-based basis for the aetiology, diagnosis and treatment of RSA, and the definition of RSA should be standardized in such studies.

One of the major setbacks in the field of the management and research in RSA is the lack of large, well-conducted, double-blinded, randomized, placebo-controlled and preferably multi-centred trials with well-defined objectives and dealing with patients with standardized definitions of RSA.

Treatment	RCOG (2012)	ASRM(2012)	ESHRE(2006)
Aspirin plus heparin therapy for antiphospholipid antibodies	Recommended Evidence Level: 2+ Abortion rate Decreased to 54%	Recommended Live birth rates with 74% vs without 42.9%	Insufficient evidence
Aspirin plus heparin therapy in women with unexplained recurrent abortion	Not recommended	Recommended	-
Resection of uterine septum	Insufficient evidence	Should be considered	-
Supportive care for women with unexplained recurrent miscarriage	Insufficient evidence	Recommended	Recommended

Other Treatment

	RCOG	ASRM	ESHRE
Anticoagulants for hereditary thrombophilias	Insufficient evidence	-	Insufficient evidence
Immunotherapy	Not Recommended	Not Recommended	Insufficient evidence
Progesterone supplementation	Insufficient evidence	Insufficient evidence	-Insufficient evidence
HCG supplementation	Insufficient evidence	-	-
Folic acid supplementation for hyperhomocystenemia	-	-	Insufficient evidence
Vitamin supplementation	-	-	<u>Not Recommended</u>
Steroid treatment	<u>Not Recommended</u>	<u>Not Recommended</u>	<u>Not Recommended</u>
Cervical pessary	<u>Not Recommended</u>	-	-
Serial sonographic surveillance	<u>Not Recommended</u>	-	-

