International Federation of Fertility Societies

Global Standards of Infertility Care

Standard 18

Recurring Pregnancy Loss
Consensus statement

Name	Recurring Pregnancy Loss
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Introduction

The goal of IFFS Practice Standards is to provide policy and decision-makers and the clinical and scientific community with a set of recommendations that can be used as a basis for developing or revising institutional or national guidelines on selected practice recommendations for infertility practice.

The document addresses minimal standards of practice but does not provide rigid guidelines but rather gives recommendations that provide the basis for rationalizing the provision of infertility services in view of the most up-to-date information available.

Because country situations and programme environments vary so greatly, it is inappropriate to set firm international guidelines on infertility practice. However, it is expected that institutional and national programmes will use these guidance documents for updating or developing their own infertility guidelines in the light of their national health policies, needs, priorities and resources. The intent is to help improve access to, quality of, and safety of infertility and assisted conception services. These improvements must be made within the context of users' informed choice and medical safety. Adaptation is not always an easy task and is best done by those well-acquainted with prevailing health conditions, behaviours, and cultures.

Rationale

Pregnancy loss is a distressing condition that affects approximately 20% of all clinically identifiable pregnancies (1). It is reported that approximately 0.5-3.0% of women have a history of recurrent pregnancy loss (RPL) and that 1-2% of second trimester pregnancies miscarry before 24 weeks of gestation (2,3).

Definition

Historically, the presence of three consecutive clinical pregnancy losses has constituted an accepted definition. A clinically identifiable clinical pregnancy loss is defined by presence of ultrasound verified intrauterine pregnancy or histological confirmation of chorionic villi.

However, this ignores the type of pregnancy loss which may occur at a later gestation and postpones the possibility of diagnosable and treatable thrombophilia (4). Both the number and consecutive components of the historical definition have become questionable (5, 6).

Treatments covered by this guidance

This guidance covers the diagnosis and treatment of couples presenting with Recurring Pregnancy Loss as defined above.

Investigation of recurring pregnancy loss

1. Women with recurrent first-trimester miscarriages and one or more second-trimester miscarriage should be screened for antiphospholipid antibodies (4). Two positive tests at least 12 weeks apart for either lupus anticoagulant **(LA)** or anticardiolipin antibodies of IgG and/or IgM is necessary for a diagnosis of antiphospholipid syndrome (APS) (4). Consider a confirmatory step (e.g. using a high phospholipid concentration, platelet neutralizing reagent or LA insensitive reagent) to demonstrate phospholipid dependence. Studies have shown that in patients with pregnancy morbidity, the role of IgM antibodies is unclear and that testing for IgA antibodies is not recommended.

2. Routine testing for peripheral blood natural killer (NK) cells and cytokine tests for recurrent miscarriage are not recommended in clinical practice.

3. Women with second-trimester miscarriage should be screened for inherited thrombophilias including factor V Leiden, prothrombin gene mutation and protein S deficiency.

4. Pelvic ultrasound (US) may be performed to assess for uterine anomalies in all women with recurrent first-trimester miscarriage and is essential for those with one or more second-trimester miscarriages. Ideally, further investigations may be required to confirm suspicion of uterine anomalies using hysteroscopy, laparoscopy or 3-dimensional pelvic US.

5. Although well controlled diabetes mellitus (DM) and treated thyroid dysfunction are not associated with recurrent miscarriage, thyroid function tests (TFTs) and Haemoglobin (Hb) A1c measurements can still be considered when evaluating patients with recurrent miscarriage.

6. Polycystic ovarian syndrome (PCOS) has been historically linked to an increased risk of miscarriage but recent evaluation fails to confirm this (2). Elevated serum luteinizing hormone (LH) or testosterone levels do not predict an increased risk of future pregnancy loss in women with recurrent pregnancy loss.

7. Screening for bacterial vaginosis in high-risk patients with a history of second-trimester miscarriage or spontaneous preterm labour is recommended.

8. Toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and HIV (TORCH) screening is unhelpful and is not recommended when investigating recurrent miscarriage as infections by these agents are not capable of persisting in the genital tract without detection or causing sufficient symptoms to disturb the patient.

9. Peripheral blood karyotyping of both partners should be performed where testing of products of conception reports unbalanced structural chromosomal abnormalities (7) or based on individualised risk assessment (8).

Management

Patients with idiopathic RPL do not benefit from futility treatment interventions such as aspirin, heparin or immunomodulation therapy (2, 4). Approximately 70% of couples will succeed to livebirth without treatment when regular ultrasound support either in a specialised RPL clinic or an early pregnancy unit is provided (9, 10). Increasing maternal age and number of losses reduce the success rate.

In patients with known APS and RPL, antenatal administration of aspirin and heparin is recommended throughout pregnancy and should begin as soon as possible. A risk assessment for venous thromboembolic disease should be made and thromboprophylaxis with heparin prescribed for 8 weeks following delivery. The role of aspirin alone in the low risk assessment group can reduce the occurrence of pre-eclampsia and fetal growth restriction and is associated with a greater than 60% livebirth rate (4).

Consensus statements for practice

1. Following recurring pregnancy loss, it is important to offer the couple **appropriate preconceptual investigation** and then **early pregnancy support** and **empathic care** in a subsequent pregnancy.

2. The **aetiology remains unknown in more than 50% of couples** with RPL despite a thorough evaluation and is therefore classified as idiopathic.

3. Couples with **idiopathic recurrent miscarriage** have a **high chance of a successful outcome without intervention**.

4. Women with **RPL and APS** should be **treated with aspirin and heparin** during and after pregnancy and have a full risk assessment performed for venous thromboembolic disease in early pregnancy.

5. **Anatomical uterine distortion** may have a causal role but the evidence base for surgical intervention and correction is weak.

6. **Chromosomal assessment of products of conception** may yield useful prognostic information, however, in view of the expense of this test its routine use in resource poor environments is not routinely recommended.

7. **Parental karyotyping** may reveal balanced translocations in 2-4% patients which may be of limited clinical relevance. This test is commonly used but given its relatively high cost and relatively low yield, its routine use in resource poor environments is not recommended.

8. There is no compelling evidence currently available to support other investigation or treatment options.

References

1. National Institute for Health and Clinical Excellence (NICE). CG154 Ectopic pregnancy and miscarriage, London; 2012.

2. Royal College of Obstetricians and Gynaecologists (RCOG). The investigation and treatment of couples with recurrent first and second-trimester miscarriage. London: RCOG; 2011.

3. Jauniaux E, Farquharson RG, Christiansen OB, Exalto N. Evidence based guidelines for the investigation and medical treatment of recurrent miscarriage. Human Reproduction, 2006, 229, 2216-22.

4. Keeling et al, British Committee for Standards in Haematology (BCSH). Guidelines on the investigation and management of antiphospholipid syndrome British Journal of Haematology, 2012, 157, 47-58.

5. Jaslow CR, Carney JL, Kutteh WH. Diagnostic factors in 1020 women with two versus three or more recurrent pregnancy losses. Fertility and Sterility, 2010, 193, 1234-43.

6. Boogard E, Cohn D, Korevaar JC, Dawood F, Vissenberg R, Middeldorp S, Goddijn M and Farquharson RG. Number and sequence of preceding miscarriages and maternal age for the prediction of antiphospholipid syndrome in women with recurrent miscarriage, Fertility and Sterility, 2013, 99, 188-92.

7. Kavalier F. Editorial: Investigation of recurrent miscarriages. British Medical Journal, 2005, 331, 121-22.

8. Boogaard E, Hermens RP, Verhoeve HR, Kremer JA, van der Veen F, Knegt AC, Goddijn M. Selective karyotyping in recurrent miscarriage: are recommended guidelines adopted in daily clinical practice? Hum Reprod. 2011, 26, 1965-70.

9. Brigham S, Conlon C, Farquharson R. A longitudinal study of pregnancy outcome following idiopathic recurring miscarriage. Human Reproduction, 1999, 14, 2868-71.

10. Lund M, Kamper-Jørgensen M, Nielsen HS, Lidegaard Ø, Andersen AM, Christiansen OB. Prognosis for livebirth in women with recurrent miscarriage: what is the best measure of success? Obstetrics and Gynecology, 2012, 119, 37-43.

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