EVIDENCE-BASED MANAGEMENT OF RECURRENT MISCARRIEGER

The following article provides an evidence-based practical guide to managing recurrent pregnancy loss with a focus on issues that are useful for patient management.

Miscarriages can be immensely distressing for couples. While spontaneous miscarriage occurs in 15-20% of all pregnancies, recurrent miscarriage (RM) affects 1% of couples. RM is a challenging problem due to an unknown aetiology in most cases. Couples with RM are often not managed according to the most up-to-date clinical evidence. Ineffective management can be due to under and over diagnosis, resulting in unnecessary tests and costs. In desperation couples may be willing to try non-evidence-based investigations and treatments.

This review is aimed to provide evidence-based and practical guide to manage recurrent pregnancy loss, focusing on issues useful in patient counselling.

Definition
The Royal College of Obstetricians and Gynaecologists (RCOG) defines recurrent miscarriage as three or more consecutive pregnancy losses before 24 weeks gestation. The risk of miscarriage after two consecutive losses is 17-25% and the risk after three consecutive losses is between 25% and 46% and the risk gets worse with increasing maternal age and increasing number of miscarriages.

Additionally, an association is described with subfertility; if the time taken to conceive is longer than three years, then the prognosis for future live birth is worse than if conception has occurred within three years.

Risk factors
Maternal alcohol (>5 units a week), cocaine abuse, excessive coffee (>3-4 cups /day) and smoking are associated with miscarriages. Heavy lifting and night work may also increase the risk.

Pre-pregnant underweight and obesity both are reported as risk factors for miscarriage, although concordance in studies is relatively poor.

Causes, investigations and management

Genetic disorders
Approximately 60-70% of early spontaneous miscarriages are associated with a foetal chromosomal anomaly. The earlier the miscarriage occurs, the greater the likelihood of a foetal chromosome abnormality. A chromosome abnormality was found in >50% of cases with RM in the first trimester versus 20% in second trimester. Parental chromosomal anomalies are present in ~2% of recurrent miscarriages cases. The probability increases to ~5% if the couple has a previous history of stillbirth or a previous child with major congenital abnormality.

Chromosome abnormalities are broadly categorised into numerical or structural abnormalities. In numerical abnormalities (also known as aneuploidy), the total number of chromosomes is more of less than the normal number of 46. Numerical abnormalities account for ~95% of all abnormalities seen in miscarriages and mostly are a chance finding as a result of error during the meiotic process of gametogenesis. These include autosomal trisomies involving chromosomes 16, 21, 22, 13 and 18 (with 47 chromosomes rather than 46), sex chromosome trisomy (47 XXX) or monosomy (45X). Increasing maternal age is a major risk factor for aneuploidy.

The structural abnormalities on the other hand are rearrangements in genetic material of chromosome, when the overall number remains 46. These account for ~5% of chromosomal abnormalities in miscarriages. In these abnormalities, a portion of one chromosome becomes attached to another chromosome (known as translocation). If there is no net gain or loss of genetic material, the individual is carrying a balanced translocation, and these carriers are phenotypically normal. The prevalence of these in the general population is ~1 in 600.

However, during gametogenesis there is a risk.
of gamete having more or less genetic material and the resulting pregnancy may have an unbalanced translocation. Hence, if products of conception show an unbalanced translocation, then parents are offered a karyotype analysis for a balanced translocation, and if found are referred for genetic counselling. However, the risk of a recurrent trisomy is considered non-significant—1%.[17,18]

Karyotype testing for the couple with RM may be considered, especially if there is family history of previous stillbirth or congenital abnormality. The couple must give their informed consent to have the chromosome analysis, as results may have implications for other family members and any information received can no longer be 'unknown'. RCOG advises testing of products of conception of third or subsequent miscarriages to find an unbalanced structural translocation before testing parents, as routine testing for all couples can't be justified. Prevalence of structural chromosome abnormality is relatively low and not treatable at present.[9]

If a genetic abnormality is found in either parent, the couple should be referred to a geneticist for predictive counselling and advice. The range of options would include conservative management, prenatal genetic diagnosis (where a sample of foetal tissue is obtained in early pregnancy to test for chromosomal abnormality with option for termination of affected pregnancy), preimplantation genetic diagnosis (PGD) – an IVF process where only unaffected foetuses are transferred to uterus for implantation/donor gametes etc.[20]

Antiphospholipid syndrome

There is substantial evidence linking antiphospholipid syndrome (APS) to an increased risk of recurrent and late pregnancy loss.[21] APL is diagnosed in patients with thrombosis and/or defined pregnancy morbidity who have persistent antiphospholipid antibodies (aPL). APS is reported in up to 15% of patients with RM.[3]

Clinical criteria for diagnosis of APS include either:

1. Vascular thrombosis – deep vein thrombosis (DVT) and/or pulmonary embolism (PE) but any part of the venous system may be involved, including superficial, portal, renal, mesenteric and intracranial veins. Arterial thrombosis in APS as TIA/stroke or MI is less common,

2. Pregnancy morbidity includes:
   (a) One or more unexplained deaths of a morphologically normal foetus at or beyond the 10th week of gestation
   (b) One or more pre-term births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia or recognized features of placental insufficiency
   (c) Three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation.

Laboratory criteria includes either

1. Lupus anticoagulant (LA: a phospholipid dependent blood clotting test) present in plasma, on two or more occasions at least 12 weeks apart
2. Anticardiolipin (aCL) antibody of immunoglobulin (IgG and/or IgM isotype in serum or plasma, present in medium or high titre (i.e. >40GPL units or MPL units, or > the 99th centile), on two or more occasions, at least 12 weeks apart
3. Anti-b2-glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma (in titre > the 99th centile), present on two or more occasions at least 12 weeks apart. Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria are met. APS has been described as secondary if there is an associated autoimmune disorder, such as systemic lupus erythematosus (SLE) or rheumatoid arthritis association in ~4%, and primary if not.

With regard to pre-eclampsia, placental abruption and foetal growth restriction (FGR), there is an association with APS, but this is less strong than with recurrent pregnancy loss. Women with APS will need consultant-led care in pregnancy and antithrombotics should be used to reduce the incidence of pregnancy complications.

The British Committee for Standards in Haematology (2012) and RCOG recommend treatment with low dose aspirin and LMWH throughout pregnancy, commenced as soon as pregnancy is confirmed. Both low dose aspirin and LMWH are considered safe in pregnancy for this indication.

It is useful to make note of RCOG’s guideline on Thrombosis,[22] in which it says women with previous thrombosis and APS should be offered both antenatal and six weeks of post-partum thromboprophylaxis, and that women with APS and no previous VTE and no other risk factors should be considered for LMWH for seven days postpartum.

Anatomical abnormalities

Congenital uterine malformations such as arcuate uterus (conavity in upper uterine border <1.5cm), bicornuate (internal indentation >1.5 cm and external indentation >1cm), septate (internal septum >1.5 cm and no external indentation, septum may reach unto a normal single cervix) didelphys (2 separate unicominate uterine cavities, or unicominate uterus (single uterine cavity with unilateral single fallopian tube) are reported in 1.8–37% of women with RM.[23] The frequencies of acquired defects (fibroids, adhesions, polyps) are more difficult to determine.[24]

Septate uterus or large submucosal fibroids distorting the cavity are the most common uterine abnormalities associated with early pregnancy loss and would require consideration for treatment.[25] An arcuate uterus, the most commonly reported
abnormality, is a risk factor only for late pregnancy loss and is not associated with early pregnancy loss.\textsuperscript{26} NICE guidance on hysteroscopic metroplasty (resection using trans-cervical hysteroscopic resection technique) of a uterine septum for recurrent miscarriage (ipg 510) 2015 states that the correction of septum can be considered in symptomatic patients, i.e., patients with recurrent miscarriages, while patient selection and treatment should be done by a multi-disciplinary team to optimise appropriate case selection who are most likely to benefit from such treatment. The procedure is considered safe, however some serious but rare complications (uterine ruture in future pregnancies, synechiae-distortion of uterine cavity due to scarring within cavity) have been noted.\textsuperscript{27}

**Hormonal and metabolic factors**

It is generally agreed that maternal endocrine disorders (e.g. diabetes, thyroid dysfunction) should be evaluated and treated.\textsuperscript{28,29,30} As long as thyroid-stimulating hormone (TSH) levels are in the normal range, there is insufficient evidence to recommend routine thyroxine (T4) testing or screening for anti-thyroid antibodies. There has been a lack of consensus regarding the normal upper limit of TSH. Whereas TSH values of 4.0–5.0 mIU/L were once considered normal, a consensus is emerging that TSH values above 2.5 mIU/L are outside the normal range. The Endocrine Society Clinical Practice Guideline (2012)\textsuperscript{31} on management of thyroid dysfunction during pregnancy and postpartum acknowledge an association of subclinical hypothyroidism (women with TSH >2.5 mIU/L and normal T4) with adverse pregnancy outcome; and thyroid replacement may be considered especially in women with thyroid peroxidase antibodies. Only small RCTs are reported demonstrating benefit of T4 replacement in subset of women with subclinical hypothyroidism with anti-TPO antibodies; results of large trial (TABLET) are eagerly awaited and due in latter part of 2017. In women on thyroid replacement therapy before pregnancy, a 30% increase in dose of thyroxine is recommended by four-six weeks of pregnancy. TFT should be checked in each trimester and dose adjusted accordingly. Post-pregnancy, most women need to decrease the dose to the pre-pregnancy dose.

Well-controlled diabetes is not a risk factor for RPL. However, uncontrolled diabetes is associated with increased pregnancy loss.\textsuperscript{1,25,30} Administration of progesterone to women with sporadic miscarriages is ineffective. However, in patients with three or more consecutive miscarriages, empiric progestogen administration may be of some potential benefit.\textsuperscript{31} However a large UK-based RCT (PROMISE Trial 2015)\textsuperscript{32} failed to show a benefit with progesterone replacement (Cyclegest pessaries 400mg BD from conception to 14 weeks). More studies are underway and until further information becomes available, there would be a limited role of progesterone (Cyclegest) replacement to prevent RM.

**Thrombophilia screening**

Inherited thrombophilia is a genetic predisposition increasing the tendency to develop thrombosis and has been evaluated as a potential cause of pregnancy loss. The most common thrombophilias are factor V Leiden, prothrombin gene mutation, protein C deficiency, protein S deficiency and anti-thrombin III deficiency. The combined prevalence in the general population is ~5%. Several studies have reported an increased risk of pregnancy loss in women with inherited thrombophilia; however, significant heterogeneity is attributed to the studies and evidence whether treatment of thrombophilia is effective to improve pregnancy outcome remains uncertain so far.\textsuperscript{33} A case for routine testing for thrombophilia in recurrent early pregnancy loss has not been made. The RCOG advises testing for thrombophilia after second trimester loss, not for recurrent early pregnancy loss. Treatment recommendation is with low dose LMWH starting before eight weeks of pregnancy, continued for the duration of pregnancy.

According to the British Committee for Standards in Haematology (BSSH),\textsuperscript{44} antithrombotic therapy should not be offered to pregnant women based on tests for heritable thrombophilia to prevent pregnancy related complications. Testing for thrombophilia should only be offered to women with personal history of unprovoked thrombosis or provoked with a minor risk factor like travel, and those who have a family history of thrombosis associated with high risk thrombophilia, (antithrombin deficiency or protein C or protein S deficiency). Testing with family history of low risk thrombophilia (heteregeneous factor V Leiden) is not indicated. Women with a previous thrombosis due to a major provoking factor, e.g. surgery or major trauma, would not routinely require prophylaxis or testing. Asymptomatic women with a family history of venous thrombosis should be tested if an event in a first-degree relative was unprovoked, or provoked by pregnancy, COC exposure or a minor risk factor. The result will be more informative if the first-degree relative has a known thrombophilia. Randomised controlled trials of antithrombotic treatment in women with a history of pregnancy complications and thrombophilia are in progress. Until then routine testing or treatment for thrombophilia are not justified.

**Investigations with limited evidence of benefit**

Testing and treatment for Immunologic factors,\textsuperscript{37} chronic endometritis in asymptomatic women and...
treatment for luteal phase deficiency with HCG in routine practice are not justified, and investigation and treatment should be offered under research conditions only.28,29,30

Support
Recurrent miscarriage patients are vulnerable and should receive good clinical supportive care best provided in a RM clinic.5,28,29,30 Couples can be reviewed by one doctor working with a specific protocol, as suggested in this article, so that all patients receive standardised care. All women should be assessed for risk factors (obesity, cigarette, alcohol and excessive caffeine consumption), tests arranged for APS, TFT, diabetic screening and transvaginal ultrasound scan for uterine abnormalities. In late foetal losses, thrombophilia screening should also be arranged.

The couple should be prepared for the fact that in a majority of cases no cause is found. Couples should be encouraged to talk about their fears and anxieties and any misconceptions addressed.

Staff dealing with RM couples should be mindful of the emotional aspects of pregnancy loss. There should be access to counselling and information provision for self-help groups.

Studies have reported high success rate after supportive care in women with unexplained RM. Although clear definition of support is lacking, traditionally it has involved access to early pregnancy clinic and USS for pregnancy assessment every two-to-three weeks in the first trimester.

References
37. RCOG. The Role of Natural Killer Cells in Human Fertility Scientific Impact Paper No. 53 December 2016