14

Recurrent Miscarriage including Cervical Incompetence

Tracy Yeung and Lesley Regan

INTRODUCTION

The loss of a wanted pregnancy at any stage is a devastating event and especially so in couples with recurrent pregnancy losses. Careful history taking from both partners regarding the general medical health and past obstetric history remains a key to management of these couples. Numerous causes have been implicated in couples with recurrent miscarriage, together with ever-emerging investigations and management options. However, some of the suggested causes have not been consistently shown as the culprit and many of the investigations and treatment options have not been properly evaluated as discriminative and effective. The aim of this chapter is to provide an overview on the causes, investigations and management of couples with recurrent miscarriage and highlight the updated evidence, which is particularly important in streamlining management in areas where resources are limited.

MISCARRIAGE

Miscarriage is the spontaneous loss of a pregnancy before the fetus has reached viability, most commonly defined as before 24 weeks or with a birth weight of less than 500 g (Table 1). Among all clinically recognized pregnancies, ~15% (almost 1 in 6) end in miscarriage[1]. And indeed, approximately 50% of all conceptions are lost and the majority occur before even being noticed.

Sporadic miscarriage is common and the lifetime risk increases with the number of pregnancies a woman has. The chance of having a single miscarriage in one pregnancy is around one in six (16.7%), and increases to 31% with two pregnancies, 42.5% in three pregnancies and over 50% in more than four pregnancies. However, the chance of having consecutive sporadic miscarriages is much less common with 1 in 36 and 1 in 216 women, respectively, having two or three sporadic miscarriages consecutively.

The majority of sporadic pregnancy loss is due to a random fetal chromosomal abnormality[2,3], which increases with increasing maternal age[4]. The vast majority of miscarriages occur *early*, before 12 completed weeks of gestation (first trimester). The incidence of *late* miscarriage (second-trimester pregnancy loss, from 13 to 23 completed weeks) is estimated as 2%[5].

RECURRENT MISCARRIAGE

The most widely accepted definition of recurrent miscarriage is three or more consecutive pregnancy losses, which affects 1% of couples[6]. This is about twice the incidence (1% vs 1 in 216) that would be

Table 1 Definition and prevalence of miscarriages

	Definition	*Prevalence*
Early miscarriage/first-trimester miscarriage	Before 12 weeks	~15% (single sporadic event)
Late miscarriage	Between 13 weeks and 23 completed weeks	~2% (single sporadic event)
Recurrent miscarriage	Three or more consecutive pregnancy losses	~1%

expected by chance alone. A woman's risk of miscarriage has been shown to correlate with the outcome of her previous pregnancies[7–10]. Women with a history of recurrent miscarriage are more likely to have reproductive characteristics (demographics, physical attributes) associated with a poor prognosis for future pregnancy outcome than women suffering sporadic miscarriage[11–13]. In contrast to women with sporadic miscarriage, those with recurrent miscarriage are more likely to lose pregnancies with a normal chromosome complement[2,14]. These all indicate the likelihood of additional pathology in women with recurrent miscarriage other than random chromosomal abnormality of embryos.

RISK FACTORS FOR RECURRENT MISCARRIAGE

Epidemiological factors

Maternal age

Risk of miscarriage increases with advancing maternal age, secondary to the increase in chromosomally abnormal conceptions[15] and decline in ovarian function. The risk increases steeply after 35 years of age from 11% at 20–24 years to 25% at 35–39 years and 93% over 45 years[9]. Advanced paternal age has also been identified as a risk factor with the highest risk in couples with maternal age ≥35 years and paternal age ≥40 years[16].

Previous reproductive history

Reproductive history is an independent predictor of future pregnancy outcome and history of previous miscarriage is the single most important factor[7]. Risk of a further miscarriage increases after each successive pregnancy loss, reaching 45% after three and 54% after four consecutive pregnancy losses[7–9]. However, a previous live birth does not preclude women from experiencing recurrent miscarriage in the future[17].

Environmental factors

Most data on environmental risk factors are based on studies with women having sporadic rather than recurrent miscarriage. The results are conflicting and understandably biased with difficulties in controlling for confounding factors and inaccuracy in quantifying the dose of exposure.

Maternal cigarette smoking has an adverse effect on trophoblast invasion and proliferation and has been suggested to have dose-dependent increased risk of miscarriage, although current evidence is insufficient to confirm the association[18,19]. Heavy alcohol assumption is toxic to the embryo and the fetus and even moderate consumption of ≥5 units per week may increase the risk of sporadic miscarriage[20]. Caffeine consumption has also been implicated with an increased risk of spontaneous miscarriage in a dose-dependent manner with risk becoming significant with more than three cups a day (~300 mg caffeine)[19,21]. Obesity is becoming an increasingly important health problem all over the world. Accumulating evidence has shown obesity is a risk factor for infertility, sporadic and recurrent miscarriage, as well as obstetrics complications and perinatal morbidities[22–25].

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is the most important *treatable* cause of recurrent miscarriage. It refers to the association between antiphospholipid antibodies, most commonly lupus anticoagulant and anticardiolipin antibodies[26,27]. Adverse pregnancy outcomes in APS include:

- Three or more consecutive miscarriages before 10 weeks of gestation.
- One or more morphologically normal fetal losses after 10th week of gestation.
- One or more preterm births before the 34 weeks of gestation due to placental disease.

'Primary APS' affects patients with no identifiable underlying systemic connective tissue disease, whereas APS in patients with chronic inflammatory diseases, such as systemic lupus erythematosus, is referred to as 'secondary APS'.

Worldwide, antiphospholipid antibodies are present in ~15% of women with recurrent miscarriage, compared with <2% in women with a low-risk obstetrics history. Adverse pregnancy outcomes may be due to the inhibition of trophoblastic function and differentiation[28–32], activation of complement pathways at maternal fetal interface resulting in a local inflammatory response[33], and, in later pregnancy, thrombosis of the uteroplacental vasculature[34–36]. Live birth rate in pregnancies with no pharmacological intervention has been reported to be as low as 10%[37].

Genetic factors

Parental chromosomal rearrangements

In around 2–5% of couples with recurrent miscarriage, one of the partners carries a balanced structural chromosomal anomaly, most commonly a balanced reciprocal or Robertsonian translocation[13,38,39] (Figure 1). Carriers of balanced translocation are usually phenotypically normal and unaware of the condition. However, up to 70% of their gametes and thus the conceptions would be abnormal due to unbalanced translocation. This leads to a much higher risk of miscarriage, or rarely resulting in live birth with multiple congenital malformation and/or mental disability.

Fetal aneuploidy and polyploidy (increased or decreased number of chromosomes)

The risk of miscarriage resulting from chromosomal abnormality increases with maternal age. In couples with recurrent miscarriage, chromosomal abnormalities of the embryo account for 35–57% of further miscarriages[2,40]. However, with increasing number of miscarriages, the risk of euploid pregnancy loss increases, suggesting some other underlying pathology accounting for the loss.

Anatomic disorders

Congenital uterine malformations

Congenital uterine malformation is the result of disturbances in Müllerian duct development, fusion, canalization and septal reabsorption. The malformation ranges from the mildest form with slight indentation at the fundus (arcuate uterus) to the most extreme form with complete duplication (uterus didelphys) (Figure 2).

The exact prevalence of congenital uterine anomalies in both the general population and women with recurrent miscarriages is not clear. Wide variation of prevalence from 1.8% to 37.6% have been reported and a recent literature review of uterine anomalies in early and late recurrent miscarriage patients reported a prevalence of 16.7% [96% confidence interval (CI) 14.8–18.6][41]. A retrospective review of reproductive performance in patients with untreated uterine anomalies suggested that these women have high rates of miscarriage and preterm delivery, resulting in a term delivery rate of only 50%[42].

Cervical incompetence

Cervical incompetence is defined as the inability of the cervix to retain a pregnancy, due to a

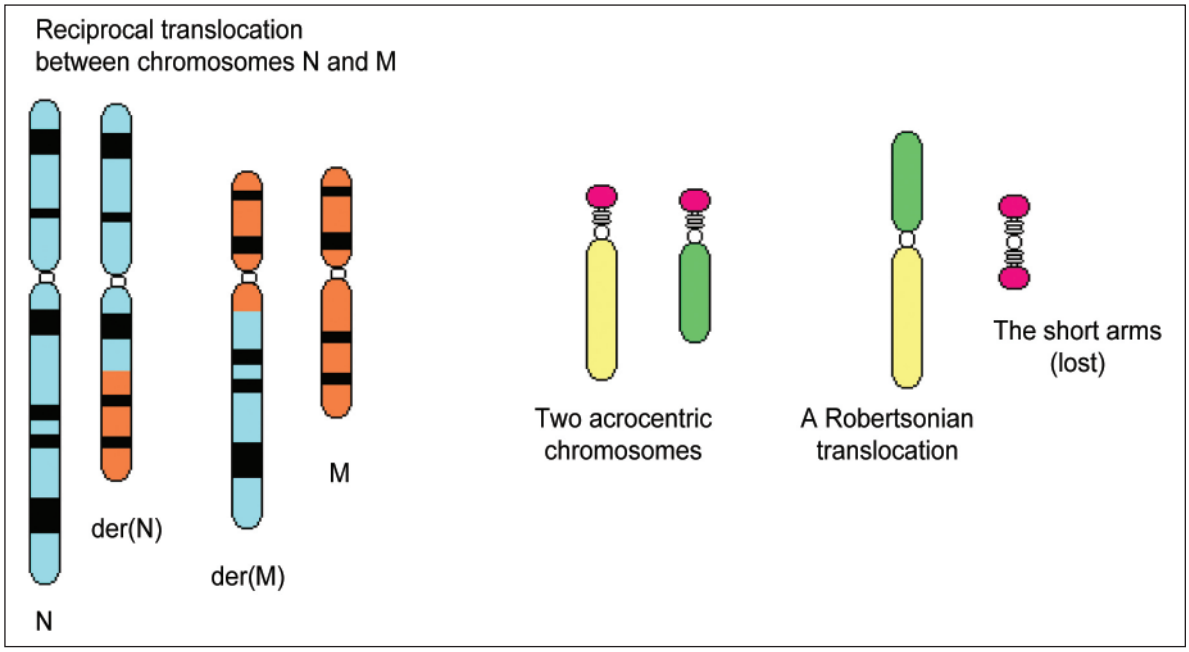

Figure 1 Parental chromosomal reciprocal and Robertsonian translocations. Reprinted with permission of Dr Jonathan Wolfe, Department of Biology, Galton Laboratory, University College London, UK

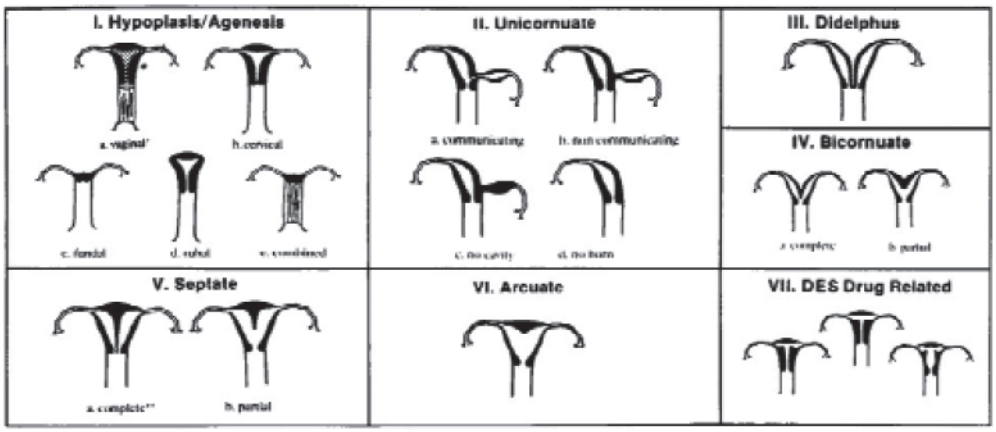

Figure 2 The American Society for Reproductive Medicine classification of Müllerian anomalies. Copyright 2012 by the American Society for Reproductive Medicine. All rights reserved. No part of this presentation may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or by any information storage and retrieval system without permission in writing from the American Society for Reproductive Medicine, 1209 Montgomery Highway, Birmingham, AL 35216.

functional or structural defect, in the absence of contractions or labor. It is a well-recognized cause of late miscarriage but the true incidence is unknown. Epidemiological studies suggest an approximate incidence of 0.5% in the general obstetric population[43] and 8% in women with a history of previous mid-trimester miscarriages[5].

Although some cases involve mechanical incompetence (e.g. congenital hypoplastic cervix, previous cervical surgery or extensive trauma), many women with a clinical diagnosis of cervical incompetence have normal cervical anatomy. The cervix is the main mechanical barrier separating the pregnancy from the vaginal bacterial flora. Many patients who have asymptomatic mid-trimester cervical dilation also have evidence of subclinical intrauterine infection[44]. It is unclear whether this high rate of microbial invasion is the result or the cause of premature cervical dilation.

Fibroids

Uterine fibroids have long been associated with a variety of reproductive problems, including pregnancy loss. Presumed mechanisms include mechanical distortion of the uterine cavity, abnormal vascularization, abnormal endometrial development, endometrial inflammation, abnormal endocrine milieu and structural and contractile myometrial abnormalities[45], any or all of which may impede embryonic implantation. It is well agreed that submucosal fibroids have a negative impact on pregnancy outcomes, whereas subserosal lesions do not[46–51]. The impact of intramural fibroids is more controversial. While initial meta-analyses failed to document a harmful impact[46,47], the most recent meta-analysis reported a reduction of pregnancy and live birth in women with intramural fibroids by 15% and 21%, respectively[48].

Intrauterine adhesions

Intrauterine adhesions (Asherman's syndrome) can result from uterine trauma after vigorous intrauterine curettage or intrauterine infection. This has been implicated in recurrent miscarriage presumably due to the reduced uterine cavity volume as well as fibrosis and inflammation of the endometrium leading to defective implantation and pregnancy loss. Dilatation and curettage (D&C) should only be used judiciously for retained products of gestation and vigorous curettage should be avoided.

Endocrine factors

Systemic endocrine factors

Diabetes and thyroid disease have been associated with sporadic miscarriage but there is no direct evidence that they contribute to recurrent miscarriage. Women with well-controlled diabetes mellitus and treated thyroid dysfunction do not

carry higher risks for recurrent miscarriage[52,53]. The prevalence of diabetes and thyroid dysfunction in women with recurrent miscarriage is similar to that reported in the general population[54,55].

Luteal phase defect and progesterone deficiency

A functional corpus luteum is essential for the implantation and maintenance of early pregnancy, primarily through the production of progesterone, which is responsible for the conversion of proliferative to a secretory endometrium suitable for embryonic implantation. Luteal phase defect, in which insufficient progesterone production results in retarded endometrial development, has long been believed to be associated with recurrent miscarriage. However, there are no accurate and reliable tests to assess the true incidence and effect of luteal phase defect[56].

Infective factors

Any severe infection leading to bacteremia or viremia including malaria can cause sporadic miscarriage but its role in recurrent miscarriage is unclear. Commonly screened infections including toxoplasmosis, rubella, cytomegalovirus, herpes and *Listeria* infections do not fulfill these criteria and routine screening for these disorders is not recommended[57]. Currently, there are no available data to suggest an association between tuberculosis or AIDS with recurrent miscarriage.

Empirical use of antibiotics in pregnancy should be avoided due to lack of evidence of benefit and potential harm with increased risk of cerebral palsy[58].

Inherited thrombophilic defects

The hemostatic system plays a crucial role in both the establishment and the maintenance of pregnancy. The fibrinolytic pathways are involved in the implantation and are important in maintaining an intact placental circulation. The potential role of thrombophilic defects on recurrent miscarriage and later pregnancy complications are presumably caused by an exaggerated hemostatic response during pregnancy, leading to thrombosis of the uteroplacental vasculature and subsequent fetal demise.

Thrombophilias, including activated protein C resistance (APCR) (most commonly due to factor V Leiden mutation), deficiencies of protein C/S and antithrombin III, hyperhomocysteinemia and prothrombin gene mutation, are established causes of systemic thrombosis and have recently been associated with obstetric morbidity (Table 2).

PROGNOSIS FOR HEALTHY PREGNANCY AFTER RECURRENT MISCARRIAGE

The prognosis for healthy pregnancy after miscarriages depends on:

- Age

Table 2 Established causes of systemic thrombosis associated with obstetric morbidity

	Recurrent first-trimester loss	*Recurrent loss before 25 weeks*	*Recurrent late loss >22 weeks*	*Non-recurrent late loss >19 weeks*
FVL	OR 2.01, 95% CI 1.13–3.58	–	OR 7.83, 95% CI 2.83–21.67	OR 3.26. 95% CI 1.82–5.83
APCR	OR 3.48, 95% CI 1.58–7.69	–	–	–
PGM	OR 2.32, 95% CI 1.12 –4.79	OR 2.56, 95% CI 1.04–6.29	–	OR 2.3, 95% CI 1.09–4.87
Protein S def.	OR 14, 95% CI 0.99–218	–		OR 7.39, 95% CI 1.28–42.83
MTHF mutation, protein C def., AT III def.	No definite association			

OR, odds ratio; CI, confidence interval; FVL, factor V Leiden; APCR, activated protein C resistance; PGM, prothrombin gene mutation; *MTHF* mutation, methylene tetrahydrofolate reductase mutation; AT III def., antithrombin III deficiency

- Previous obstetrics history
- Causes of recurrent miscarriage.

A descriptive cohort study in Denmark has shown that for women aged 30–34 years with a history of three first-trimester miscarriages, 66.7% (95% CI 63.7–69.1) achieved a live birth in 5 years after the first consultation. There was a significantly decreased chance of live birth with increasing maternal age and increasing number of miscarriages at presentation[59].

MANAGEMENT OF COUPLES WITH RECURRENT FIRST- AND SECOND-TRIMESTER MISCARRIAGE

History taking

A thorough history of the patient is very important. A lot of information on the likely underlying cause can be gained from focused history taking. Please see Chapter 1 on how to take a basic gynecological history. Specific questions you may want to add:

- *Number of miscarriages and type*: early/late miscarriage, missed miscarriage, vaginal bleeding with or without contractions, signs of infection prior to event. Early miscarriage, especially missed miscarriage is most frequently associated with chromosomal abnormality but may also point to thrombophilia or other factors compromising uterine vascularization.
- *Treatment received*: misoprostol, manual vacuum aspiration and D&C. Likelihood of cervical trauma or uterine adhesions increases with the number of cervical and/or uterine manipulation.
- *Other obstetric history*: number of term and preterm deliveries.
- *Gynecological history*: menorrhagia, dysmenorrhea and dysfunctional bleeding may be signs of fibroids or endometrial polyps.
- *Other gynecological operations*: myomectomy, D&C (explicitly ask about this as they are often not considered as operations by your patient but as 'cleaning of the uterus'), unskilled abortion in the past and any postoperative complications.
- *Contraceptive history*: the risk for deep venous thrombosis (DVT) in women with inherited thrombophilia taking the pill is high.
- *Medical history*: ask about symptoms of hyperthyroidism or diabetes (see Chapter 1). DVT or lung embolism.
- *Family history*: DVT, recurrent miscarriage.

Physical examination

Speculum examination

Look for signs of infection and take a wet mount and genital swab for culture if a cerclage seems likely. See Chapter 1 on how to do a speculum and bimanual examination.

Recommended investigations

Of the many risk factors, *parental karyotype abnormalities, APS, APCR* and *cervical incompetence* are the only established causes of recurrent miscarriage. Limited resources should be directed in identifying these. Taking into consideration the immense suffering of couples with recurrent miscarriage and the significant amount of money spent on traditional treatment or futile biomedical treatment such as D&C, referral to a specialist center for the above-mentioned investigations might be well accepted by the patients and be more cost-effective. *Investigations for recurrent miscarriage should be performed when the patient is not pregnant*.

Basic investigations

Vaginal ultrasound for uterine abnormalities A two-dimensional pelvic ultrasound scan should be performed to assess uterine anatomy. When available, a transvaginal probe gives a higher resolution and better diagnostic accuracy. In cases of suspected uterine anomalies, further investigations like saline infusion sonogram (see Chapter 1), hysteroscopy or laparoscopy could be performed where available.

Particular attention should be paid to identifying various types of Müllerian anomalies (see Figure 2) and the presence of cavity-distorting lesions, e.g. submucosal fibroid and/or endometrial polyp.

Advanced investigations

In most low-resource settings, screening for antiphospholipid antibodies, chromosomal abnormalities and thrombophilia are not available. Referral to specialist center may be required when appropriate and feasible.

Screening for APS At least two positive test results ≥6 weeks apart with either lupus anticoagulant or anticardiolipin IgG and/or IgM class present in a medium or high titer over 40 g/l or ml/l would be required to make the diagnosis.

Karyotyping Karyotyping of the products of conception allows an informed prognosis for the future pregnancy. In cases where an unbalanced chromosomal abnormality is found in the products of gestation, parental karyotype studies could be performed to identify carrier(s) of balanced translocations.

Thrombophilia (for second-trimester miscarriage) Women with second-trimester miscarriage could be screened for inherited thrombophilias including factor V Leiden, prothrombin gene mutation and protein S deficiency. Thromboprophylaxis should also be considered during antenatal and/or postnatal period in case of positive results.

MANAGEMENT OF RECURRENT MISCARRIAGE

Of the many treatment options for couples with recurrent miscarriage, only treatment in women with the APS (aspirin plus heparin) has proven benefit. Cervical cerclage may improve pregnancy outcomes in well-selected cases but the evidence is conflicting.

Antiphospholipid syndrome

Low-dose heparin, either unfractionated or low-molecular-weight heparin (LMWH) such as fraxiparine (where available) combined with aspirin should be the treatment of choice.

A recent systematic review[60] confirmed the combination of unfractionated heparin and aspirin reduced pregnancy loss by 54% in couples with recurrent pregnancy loss associated with antiphospholipid antibodies compared to the use of aspirin alone [relative risk (RR) 0.46, 95% CI 0.29–0.71]. Aspirin alone should not be used for women with APS. Unfortunately, the diagnosis of APS and the treatment with LMWH may not be available in most low-resource settings.

Pregnancies associated with APS treated with aspirin and heparin remain at high risk of complications during all three trimesters, including repeated miscarriage, pre-eclampsia, fetal growth restriction and preterm birth[61,62]. Close antenatal surveillance is required to optimize pregnancy outcomes.

Anatomic factors

Congenital uterine anomalies

There are no published randomized trials assessing the benefit of surgical correction of uterine abnormalities on pregnancy outcome and the surgical technique of choice. Open uterine surgery has been shown to be associated with postoperative infertility and carries a significant risk of uterine scar rupture during pregnancy[63]. Transcervical hysteroscopic resection of uterine septae is less likely to have these complications and results from case series appear promising. A *transcervical hysteroscopic* approach should be the preferred technique when available.

Endometrial polyps and submucosal fibroids

While definitive evidence is lacking, it is generally believed that removal of endometrial polyps and/or submucosal fibroids could improve fertility and reduce miscarriage by rendering the cavity normal. Hysteroscopic resection would be the treatment of choice.

Cervical incompetence

See section on cervical cerclage.

Endocrine factors

Progesterone supplementation

Whether supplementing early pregnancy with exogenous progestogens reduces the risk of miscarriage is still controversial[64,65]. A large multicenter study (PROMISE trial, http://www.medscinet.net/promise) is currently under way to assess the benefit of first-trimester progesterone supplementation in women with unexplained recurrent miscarriage. Before further information from well-designed trials, routine progesterone supplementation cannot be routinely suggested.

Human chorionic gonadotropin and metformin

There is insufficient evidence to evaluate the effect of human chorionic gonadotropin[66,67] or metformin[68,69] supplementation to prevent miscarriage in women with recurrent miscarriage and their use cannot yet be justified.

Inherited thrombophilia

LMWH may be beneficial for the treatment of women with a history of a single late miscarriage after 10 weeks of gestation who carry factor V Leiden or prothrombin gene mutation or have protein S

deficiency. An improved live birth rate from 29% in women taking aspirin alone to 86% in women taking LMWH and aspirin has been shown[70–72].

Taking into account the increased risk of venous thromboembolism (VTE) in women with heritable thrombophilia during pregnancy, the use of heparin in women with inherited thrombophilia can probably be justified to reduce the risk of VTE[70] and further pregnancy loss. Unfortunately both the tests for thrombophilia and LMWH are not readily available in most low-resource settings but patients' previous history or family history of VTE may suggest the condition(s). Use of heparin to lower the risk of recurrent miscarriage and VTE during pregnancy should be considered after balancing the risk/benefit ratio in individual cases.

Unexplained recurrent miscarriage

Despite detailed investigations, the cause of recurrent miscarriage in roughly 50% of couples will remain unexplained, and this will be higher if some of the investigations are not available locally.

Aspirin alone or in combination with heparin has been prescribed for women with unexplained recurrent miscarriage in an attempt to improve pregnancy outcome. However, two recent randomized controlled trials (RCTs) did not prove this empirical treatment as neither of these options improved the live birth rate[73,74] and such practice should be discouraged.

The common practice of using D&C to clear the womb will not lead to improved pregnancy outcomes. Indeed, vigorous D&C causes intrauterine scarring and adhesions and further compromises the chance of successful pregnancy.

The prognosis worsens with increasing maternal age and number of previous miscarriages. However, the couple should be reassured that the prognosis for a successful future pregnancy with supportive care alone is in the region of 75%[11,17]. Continued care and support by family and dedicated staff during early pregnancy has been shown to be beneficial[11,17,42].

FURTHER PREGNANCY MANAGEMENT

Pregnancies in women with a history of recurrent miscarriage remain at high risk in all three trimesters even when treated. Close monitoring of these pregnancies is required to optimize the outcome. During the third trimester, close monitoring of fetal size and amniotic fluid volume are advisable. Clinical assessments could be supplemented by serial growth scans aiming at detecting signs of intrauterine growth restriction (IUGR) in these women, particularly those with APS or inherited thrombophilia.

Women with transvaginal cervical suture *in situ* should be admitted (in a maternal waiting home) in the third trimester and the cerclage should be removed between 36 and 37 weeks of gestation or when contractions start. Elective cesarean section should be arranged at 37–38 weeks for women with transabdominal cerclage.

DELIVERY AND PUERPERIUM

If the pregnancy is progressing well, a history of recurrent miscarriage is not an indication for any specific interventions.

There are no prospective data on the risk of systemic thrombosis to determine the optimal management of asymptomatic women with inherited thrombophilia. Current guidelines of the Royal College of Obstetricians and Gynaecologists (RCOG) recommend that postnatal thromboprophylaxis is indicated for women with known inherited thrombophilias (e.g. factor V Leiden and prothrombin gene mutations), but individual assessment will be guided by the type of thrombophilia and the presence of other thrombotic risk factors. There is no evidence to justify routine postnatal thromboprophylaxis women with APS.

CERVICAL CERCLAGE

Incidence of mid-trimester loss has commonly been quoted as ~2%. Many cases are multifactorial and components of cervical weakness, APS or thrombophilia may co-exist.

Cervical cerclage has been performed in women considered to be at high risk of mid-trimester loss and spontaneous preterm birth with cervical 'incompetence', with the aim of preventing recurrent loss. Insertion of cerclage may reduce the risk of further late pregnancy loss by providing a degree of structural support to a 'weak' cervix, as well as maintaining the cervical length and the endocervical mucus plug as a mechanical barrier to ascending infection.

It is imperative to exclude other co-existing causes before planning a cerclage because the treatment is invasive and carries a significant risk of an adverse outcome.

Diagnosis of cervical incompetence

There is no specific and accurate method to diagnose cervical incompetence and there is insufficient evidence to recommend the use of pre-pregnancy diagnostic techniques, e.g. cervical resistance index, hysterography or insertion of cervical dilators.

Diagnosis is mainly based on the history of mid-trimester loss following painless cervical dilatation without uterine contractions. Risk factors include previous major cervical surgery (e.g. conization, large loop excision), documented trauma to the cervix in previous birth, *in utero* exposure to diethylstilbestrol and previous prelabor premature rupture of membranes. Other causes of preterm delivery such as uterine anomaly, fibroids or infection should be excluded.

Indications

History-indicated cerclage

Insertion of cerclage may be based on the risk factors in a woman's obstetric or gynecological history which increase the risk of spontaneous second-trimester loss or preterm delivery. It is performed as a prophylactic measure in asymptomatic women and should be inserted at 12–14 weeks of gestation as an elective procedure.

The largest randomized trial which was co-ordinated by the Medical Research Council (MRC)/RCOG comparing history-indicated cerclage with conservative treatment yielded a small reduction in births under 33 weeks of gestation (13% vs 17%; RR 0.75, 95% CI 0.58–0.98)[75]. However, similar benefit has not been proven in a meta-analysis of four randomized trials which included the above mentioned. Subgroup analysis showed only women with a history of three or more pregnancies ending before 37 weeks of gestation would be likely to benefit. Based on the current available data, history-indicated cerclage should only be offered to women with three or more previous preterm births and/or second-trimester losses.

Ultrasound-indicated cerclage

Cervical cerclage is inserted as a therapeutic measure in asymptomatic women where cervical length shortening is observed on transvaginal ultrasound. Cervical assessment by ultrasound is usually performed at 14 and 24 weeks of gestation and a short cervix of <25 mm is the best independent predictor of spontaneous preterm birth before 34 weeks' gestation[76].

It has been shown from a RCT that when compared with expectant management, cervical cerclage significantly reduced pre-viable birth <24 weeks from 14% to 6.1% and perinatal death from 16% to 8.8%. However, it did not prevent birth at >35 weeks of gestation unless the cervical length was <15 mm[77].

It is recommended that women with a history of one or more spontaneous mid-trimester losses or preterm births should be offered sonographic surveillance of cervical length (preferably transvaginal when available) and should be offered ultrasound-indicated cerclage before 24 weeks of gestation if the cervix is ≤25 mm. *Insertion of cerclage in women without such history who have an incidentally identified short cervix is not recommended*.

Types of cerclage

*McDonald suture (transvaginal)*This is the commonest technique used. It involves the placement of a simple purse-string suture around the cervico-vaginal junction just below the reflection of the vaginal skin onto the cervix without bladder mobilization[78]. Mersilene tape or nylon can be used and a knot is tied anteriorly to facilitate removal at 36–37 weeks of gestation.

Shirodkar suture (high transvaginal) This is usually performed in women with a short cervix, which makes insertion of a McDonald suture difficult. An incision in the skin is made over the anterior cervix and the bladder is dissected and mobilized to allow access to the upper part of cervix. A purse-string suture is placed above the level of cardinal ligaments[79].

Transabdominal cerclage This is indicated when there has been a previous failed vaginal suture, traumatic or surgical damage making a vaginal approach difficult, or severe scarring or chronic cervicitis or the presence of a cervico-vaginal fistula. This type of cerclage should only be performed by an experienced doctor and should ideally be performed at 12 weeks' gestation via laparotomy or laparoscopy with placement of a suture at the cervico-isthmic junction[80].

Contraindications

Cerclage is potentially a dangerous treatment as it needs to be removed before labor starts (in cases of

vaginal cerclage) or the woman needs a primary cesarean section (in cases of abdominal cerclage). If a woman is potentially not compliant with early admission in a maternal waiting home or hospital, she should not undergo a cerclage procedure. Contraindications include:

- Doubt about patient compliance for early admission (see above).
- Active preterm labor.
- Clinical evidence of chorioamnionitis.
- Ongoing vaginal bleeding.
- Preterm prelabor rupture of membranes (PPROM).
- Evidence of fetal compromise.
- Lethal fetal defect.

Potential risks with cervical cerclage

- Intraoperative bladder damage, cervical trauma, membrane rupture or bleeding, miscarriage.
- Maternal pyrexia.
- Cervical laceration/trauma/uterine rupture if there is spontaneous labor with suture in place.

Cervical cerclage has not been shown to be associated with an increased risk of PPROM, chorioamnionitis, induction of labor or cesarean section, risk of preterm delivery or secondary-trimester loss in experienced hands.

Preoperative management

Patients should be properly counseled on the potential benefits and risks of the procedure and written information should be given. It is recommended that an ultrasound scan is performed before insertion of cerclage to confirm the viability and to rule out any lethal/major fetal abnormality. In cases of clinical vaginal infection, a wet mount and culture should be done and cervical cerclage should be performed after treating with broad-spectrum antibiotics.

Routine maternal white cell count to detect subclinical chorioamnionitis is not necessary and should not be the reason to delay clinically indicated rescue cerclage.

Perioperative care

Tocolysis There is no evidence to support the routine use of perioperative tocolysis (e.g. with salbutamol or nifedipine) in women undergoing insertion of cerclage[81].

Prophylactic antibiotics There are no studies on perioperative antibiotic use in women undergoing cervical cerclage and the decision should be at the discretion of the operating team. In cases of presence of positive culture from a genital swab, a complete course of antimicrobial eradication therapy is recommended before the insertion.

Bed rest Bed rest after insertion of cerclage is not routinely recommended[82] but the decision should be individualized.

Serial sonographic surveillance of cervical length Routine serial sonographic measurement of cervix is not recommended.

Removal of cerclage

Transvaginal cerclage

Transvaginal cerclage (McDonald suture or Shirodkar suture) should be removed before labor, usually between 36 and 37 weeks of gestation unless delivery is by elective cesarean section where the suture can be removed at the same setting. In women presenting with established preterm labor, the cerclage should be removed to avoid potential trauma to the cervix with progressive dilatation. Anesthesia may be required in the removal of Shirodkar suture as the technique involves the burial of the suture and manipulation of the cervix is required during removal.

Transabdominal cerclage

All women with transabdominal cerclage require delivery by cesarean section and the abdominal suture may be left in place following delivery. There are no published data on the long-term outcome comparing removing the abdominal cerclage or leaving it in place after delivery. In women planning for further pregnancies, it is reasonable to leave the abdominal suture in place.

SUMMARY

Recurrent miscarriage is a devastating event and affects 1% of couples. The healthcare of couples should ideally be managed by someone with a special interest in the area in a sensitive and systematic manner.

Parental karyotype abnormalities, cervical incompetence, APS and APCR are established causes of recurrent miscarriage. Investigations of couples should be targeted and include a pelvic scan (preferably transvaginal) to screen for uterine abnormalities. The importance of careful history taking should not be overlooked, especially in establishing the diagnosis of cervical incompetence.

Low-dose aspirin and heparin are the first-line therapy for women with APS and are associated with a live birth rate of over 70%, and low-dose heparin may be beneficial for women with recurrent miscarriage associated with factor V Leiden and APCR but is not readily available in many low-resource settings. Elective cervical cerclage may confer benefits for women with one or more mid-trimester losses as a result of cervical incompetence. Cervical length ultrasound screening during pregnancy may be useful in equivocal cases, but insertion of cerclage in low-risk women with a short cervix on ultrasound alone (without a history of mid-trimester pregnancy loss) is not recommended.

Despite standard screening, >50% of cases have no underlying systematic causes for the recurrent pregnancy loss. Couples should be reassured that the chance of a successful pregnancy outcome after three consecutive miscarriages is good, and supportive care in couples with unexplained miscarriage is associated with an excellent prognosis. Empirical treatments should be avoided, not only because they are not proven to be effective and usually incur a cost, but also because adverse outcomes have been reported (as with diethylstilbestrol many years ago!).

When resources and treatment are not available locally, onward referral to a specialist center (if available) may confer benefits in selected couples when resources allow.

REFERENCES

1. Kline J. *Conception to Birth: Epidemiology of Prenatal Development (Monographs in Epidemiology and Biostatistics*, vol. 14). Oxford: Oxford University Press, 1989
2. Stephenson M, Awartani K, Robinson W. Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: a case–control study. *Hum Reprod* 2002;17: 446–51
3. Greenwold N, Jauniaux E. Collection of villous tissue under ultrasound guidance to improve the cytogenetic study of early pregnancy failure. *Hum Reprod* 2002;17: 452–6
4. Hogge WA, Byrnes AL, Lanasa MC, Surti U. The clinical use of karyotyping spontaneous abortions. *Am J Obstet Gynecol* 2003;189:397–400
5. Drakeley AJ, Quenby S, Farquharson RG. Mid-trimester loss: appraisal of screening protocol. *Hum Reprod* 1998;13:1975–80
6. Rai R, Regan L. Recurrent miscarriage. *Lancet* 2006; 368:601–11
7. Regan L, Braude PR, Trembath PL. Influence of past reproductive performance on risk of spontaneous abortion. *Br Med J* 1989;299:541–5
8. Knudsen UB, Hansen V, Juul S, Secher NJ. Prognosis of a new pregnancy following previous spontaneous abortions. *Eur J Obstet Gynecol Reprod Biol* 1991;39:31–6
9. Andersen AMN, Wohlfahrt J, Christens P *et al*. Maternal age and fetal loss: population based register linkage study. *BMJ* 2000;320:1708–12
10. Risch HA, Weiss NS, Clarke EA, Miller AB. Risk factors for spontaneous abortion and its recurrence. *Am J Epidemiol* 1988;128:420–30
11. Brigham S, Conlon C, Farquharson R. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. *Hum Reprod* 1999;14:2868–71
12. Strobino B, Fox H, Kline J, *et al*. Characteristics of women with recurrent spontaneous abortions and women with favorable reproductive histories. *Am J Public Health* 1986;76:986–91
13. Clifford K, Rai R, Watson H, Regan L. Pregnancy: an informative protocol for the investigation of recurrent miscarriage: preliminary experience of 500 consecutive cases. *Hum Reprod* 1994;9:1328–32
14. Sullivan AE, Silver RM, LaCoursiere D, *et al*. Recurrent fetal aneuploidy and recurrent miscarriage. *Obstet Gynecol* 2004;104:784
15. Hassold T, Chiu D. Maternal age-specific rates of numerical chromosome abnormalities with special reference to trisomy. *Human Genet* 1985;70:11–17
16. de La Rochebrochard E, Thonneau P. Paternal age and maternal age are risk factors for miscarriage: results of a multicentre European study. *Hum Reprod* 2002;17: 1649–56
17. Clifford K, Rai R, Regan L. Future pregnancy outcome in unexplained recurrent first trimester miscarriage. *Hum Reprod* 1997;12:387–9
18. Lindbohm ML, Sallmén M, Taskinen H. Effects of exposure to environmental tobacco smoke on reproductive health. *Scand J Work Environ Health* 2002;28:84
19. Rasch V. Cigarette, alcohol, and caffeine consumption: risk factors for spontaneous abortion. *Acta Obstet Gynecol Scand* 2003;82:182–8
20. Kesmodel U, Wisborg K, Olsen SF, *et al*. Moderate alcohol intake during pregnancy and the risk of stillbirth and death in the first year of life. *Am J Epidemiol* 2002;155:305–12
21. Leviton A, Cowan L. A review of the literature relating caffeine consumption by women to their risk of reproductive hazards. *Food Chem Toxicol* 2002;40:1271–310
22. Lashen H, Fear K, Sturdee D. Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case–control study. *Hum Reprod* 2004;19:1644–6
23. Stewart FM, Ramsay JE, Greer IA. Obesity: impact on obstetric practice and outcome. *Obstetrician Gynaecologist* 2009;11:25–31

24. Metwally M, Saravelos SH, Ledger WL, Li TC. Body mass index and risk of miscarriage in women with recurrent miscarriage. *Fertil Steril* 2010;94:290–5
25. Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. *Fertil Steril* 2008;90:714–26
26. Wilson WA, Gharavi AE, Koike T, *et al*. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome. *Arthritis Rheum* 1999;42:1309–11
27. Miyakis S, Lockshin M, Atsumi T, *et al*. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295–306
28. Lyden TW, Vogt E, Ng AK, *et al*. Monoclonal antiphospholipid antibody reactivity against human placental trophoblast. *J Reprod Immunol* 1992;22:1–14
29. Di Simone N, De Carolis S, Lanzone A, *et al*. *In vitro* effect of antiphospholipid antibody-containing sera on basal and gonadotrophin releasing hormone-dependent human chorionic gonadotrophin release by cultured trophoblast cells. *Placenta* 1995;16:75–83
30. Sthoeger ZM, Mozes E, Tartakovsky B. Anti-cardiolipin antibodies induce pregnancy failure by impairing embryonic implantation. *Proc Natl Acad Sci* 1993;90:6464–7
31. Katsuragawa H, Kanzaki H, Inoue T, *et al*. Monoclonal antibody against phosphatidylserine inhibits *in vitro* human trophoblastic hormone production and invasion. *Biol Reprod* 1997;56:50–8
32. Bose P, Black S, Kadyrov M, *et al*. Heparin and aspirin attenuate placental apoptosis in vitro: implications for early pregnancy failure. *Am J Obstet Gynecol* 2005;192: 23–30
33. Salmon J, Girardi G, Holers V. Activation of complement mediates antiphospholipid antibody-induced pregnancy loss. *Lupus* 2003;12:535–8
34. De Wolf F, Carreras L, Moerman P, *et al*. Decidual vasculopathy and extensive placental infarction in a patient with repeated thromboembolic accidents, recurrent fetal loss, and a lupus anticoagulant. *Am J Obstet Gynecol* 1982;142:829
35. Out HJ, Kooijman CD, Bruinse HW, Derksen RHWM. Histopathological findings in placentae from patients with intra-uterine fetal death and anti-phospholipid antibodies. *Eur J Obstet Gynecol Reprod Biol* 1991;41: 179–86
36. Peaceman AM, Rehnberg KA. The effect of immunoglobulin G fractions from patients with lupus anticoagulant on placental prostacyclin and thromboxane production. *Am J Obstet Gynecol* 1993;169:1403–6
37. Rai R, Clifford K, Cohen H, Regan L. High prospective fetal loss rate in untreated pregnancies of women with recurrent miscarriage and antiphospholipid antibodies. *Hum Reprod* 1995;10:3301–4
38. De Braekeleer M, Dao TN. Cytogenetic studies in couples experiencing repeated pregnancy losses. *Hum Reprod* 1990;5:519–28
39. Stephenson MD, Sierra S. Reproductive outcomes in recurrent pregnancy loss associated with a parental carrier of a structural chromosome rearrangement. *Hum Reprod* 2006;21:1076–82
40. Carp H, Toder V, Aviram A, *et al*. Karyotype of the abortus in recurrent miscarriage. *Fertil Steril* 2001;75: 678–82
41. Saravelos SH, Cocksedge KA, Li TC. Prevalence and diagnosis of congenital uterine anomalies in women with reproductive failure: a critical appraisal. *Hum Reprod Update* 2008;14:415–29
42. Grimbizis GF, Camus M, Tarlatzis BC, *et al*. Clinical implications of uterine malformations and hysteroscopic treatment results. *Human Reprod Update* 2001;7: 161–74
43. Lidegaard Ø. Cervical incompetence and cerclage in Denmark 1980–1990. A register based epidemiological survey. *Acta Obstet Gynecol Scand* 1994;73:35–8
44. Romero R, Gonzalez R, Sepulveda W, *et al*. Infection and labor: VIII. Microbial invasion of the amniotic cavity in patients with suspected cervical incompetence: prevalence and clinical significance. *Am J Obstet Gynecol* 1992;167:1086–91
45. Richards P, Richards P, Tiltman A. The ultrastructure of fibromyomatous myometrium and its relationship to infertility. *Hum Reprod Update* 1998;4:520–5
46. Pritts EA. Fibroids and infertility: a systematic review of the evidence. *Obstet Gynecol Survey* 2001;56:483–91
47. Donnez J, Jadoul P. What are the implications of myomas on fertility? *Hum Reprod* 2002;17:1424–30
48. Sunkara SK, Khairy M, El-Toukhy T, *et al*. The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. *Hum Reprod* 2010;25:418–29
49. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. *Fertil Steril* 2009;91:1215–23
50. Somigliana E, Vercellini P, Daguati R, *et al*. Fibroids and female reproduction: a critical analysis of the evidence. *Hum Reprod Update* 2007;13:465–76
51. Benecke C, Kruger T, Siebert T, *et al*. Effect of fibroids on fertility in patients undergoing assisted reproduction. *Gynecol Obstet Invest* 2005;59:225–30
52. Mills JL, Simpson JL, Driscoll SG, *et al*. Incidence of spontaneous abortion among normal women and insulin-dependent diabetic women whose pregnancies were identified within 21 days of conception. *N Engl J Med* 1988;319:1617–23
53. Abalovich M, Gutierrez S, Alcaraz G, *et al*. Overt and subclinical hypothyroidism complicating pregnancy. *Thyroid* 2002;12:63–8
54. Bussen S, Sütterlin M, Steck T. Endocrine abnormalities during the follicular phase in women with recurrent spontaneous abortion. *Hum Reprod* 1999;14:18–20
55. Li T, Spuijbroek MDEH, Tuckerman E, *et al*. Endocrinological and endometrial factors in recurrent miscarriage. *BJOG* 2000;107:1471–9
56. Coutifaris C, Myers ER, Guzick DS, *et al*. Histological dating of timed endometrial biopsy tissue is not related to fertility status. *Fertil Steril* 2004;82:1264–72
57. Regan L, Jivraj S. Infection and pregnancy loss. In: MacLean A, Regan L, Taylor-Robinson DEA, eds.

Infection and Pregnancy. London: RCOG Press, 2001: 291–304
58. Kenyon S, Pike K, Jones D, *et al*. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. *Lancet* 2008;372:1319–27
59. Lund M, Kamper-Jørgensen M, Nielsen HS, *et al*. Prognosis for live birth in women with recurrent miscarriage: what is the best measure of success? *Obstet Gynecol* 2012;119:37–43
60. Empson MB, Lassere M, Craig JC, Scott JR. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. *Cochrane Database Syst Rev* 2012; in press
61. Backos M, Rai R, Baxter N, *et al*. Pregnancy complications in women with recurrent miscarriage associated with antiphospholipid antibodies treated with low dose aspirin and heparin. *BJOG* 1999;106:102–7
62. Branch DW, Silver RM, Blackwell JL, *et al*. Outcome of treated pregnancies in women with antiphospholipid syndrome: an update of the Utah experience. *Obstet Gynecol* 1992;80:614–20
63. Jacobsen L, DeCherney A. Results of conventional and hysteroscopic surgery. *Hum Reprod* 1997;12:1376–81
64. Daya S. Efficacy of progesterone support for pregnancy in women with recurrent miscarriage. A meta-analysis of controlled trials. *BJOG* 1989;96:275–80
65. Karamardian LM, Grimes DA. Luteal phase deficiency: effect of treatment on pregnancy rates. *Am J Obstet Gynecol* 1992;167:1391–8
66. Harrison RF. Human chorionic gonadotrophin (hCG) in the management of recurrent abortion; results of a multi-centre placebo-controlled study. *Eur J Obstet Gynecol Reprod Biol* 1992;47:175–9
67. Quenby S, Farquharson R. Human chorionic gonadotropin supplementation in recurring pregnancy loss: a controlled trial. *Fertil Steril* 1994;62:708–10
68. Palomba S, Falbo A, Zullo F, Orio F Jr. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. *Endocr Rev* 2009;30:1–50
69. Jakubowicz DJ, Iuorno MJ, Jakubowicz S, *et al*. Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2002;87:524–9
70. Carp H, Dolitzky M, Inbal A. Thromboprophylaxis improves the live birth rate in women with consecutive recurrent miscarriages and hereditary thrombophilia. *J Thromb Haemost* 2003;1:433–8
71. Brenner B, Hoffman R, Carp H, *et al*. Efficacy and safety of two doses of enoxaparin in women with thrombophilia and recurrent pregnancy loss: the LIVE-ENOX study. *J Thromb Haemost* 2005;3:227–9
72. Ogueh O, Chen M, Spurll G, Benjamin A. Outcome of pregnancy in women with hereditary thrombophilia. *Int J Gynecol Obstet* 2001;74:247–53
73. Kaandorp SP, Goddijn M, van der Post JAM, *et al*. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. *N Engl J Med* 2010;362:1586–96
74. Clark P, Walker ID, Langhorne P, *et al*. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. *Blood* 2010;115:4162–7
75. MacNaughton M, Chalmers I, Dubowitz V, *et al*. Final report of the Medical Research Council/Royal College of Obstetricians and Gynaecologists multicentre randomised trial of cervical cerclage. *BJOG* 1993;100: 516–23
76. Goldenberg RL, Iams JD, Mercer BM, *et al*. The preterm prediction study: the value of new vs standard risk factors in predicting early and all spontaneous preterm births. NICHD MFMU Network. *Am J Public Health* 1998;88:233–8
77. Owen J, Hankins G, Iams JD, Berghella V, *et al*. Multicenter randomized trial of cerclage for preterm birth prevention in high-risk women with shortened midtrimester cervical length. *Am J Obstet Gynecol* 2009;201: 375.e1–8
78. McDonald IA. Suture of the cervix for inevitable miscarriage. *BJOG* 1957;64:346–50
79. Shirodkar V. A new method of operative treatment for habitual abortions in the second trimester of pregnancy. *Antiseptic* 1955;52:33
80. Benson RC, Durfee RB. Transabdominal cervicouterine cerclage during pregnancy for the treatment of cervical incompetency. *Obstet Gynecol* 1965;25:145–55
81. Visintine J, Airoldi J, Berghella V. Indomethacin administration at the time of ultrasound-indicated cerclage: is there an association with a reduction in spontaneous preterm birth? *Am J Obstet Gynecol* 2008;198:643.e1–3
82. Sosa C, Althabe F, Belizan J, Bergel E. Bed rest in singleton pregnancies for preventing preterm birth. *Cochrane Database Syst Rev* 2004;1:CD003581.