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CME Article

Non-surgical interventions for threatened and recurrent miscarriages

Tien J C, Tan T Y T

ABSTRACT

Many surgical and non-surgical interventions are used in the management of threatened and recurrent miscarriages. Evidence-based management of recurrent miscarriages requires investigations into the underlying aetiology. When a specific cause is identified, directed treatment may reduce miscarriage rates. Combined aspirin and heparin for antiphospholipid syndrome, and screening and treatment of bacterial vaginosis between ten and 22 weeks of pregnancy with clindamycin, are the only interventions proven to be useful in randomised controlled trials (RCTs). The use of periconceptional metformin for polycystic ovarian (PCO) syndrome is promising, though data from RCTs are still required. The use of heparin in inherited thrombophilias, bromocriptine in hyperprolactinaemia and luteinising hormone suppression in fertile patients with PCO syndrome are more controversial. In threatened miscarriages, or when no cause is found, treatment becomes empirical. Supportive care may reduce miscarriage rates. Dydrogesterone, a progesterone derivative, may further reduce miscarriage rates. Bed rest and avoidance of sexual intercourse, though commonly advised, are of no proven benefit. Use of uterine relaxing agents, human chorionic gonadotrophin, immunotherapy and vitamins remain controversial in idiopathic recurrent miscarriages.

Keywords: human chorionic gonadotrophin, miscarriage, prospective miscarriage risk, recurrent miscarriage, threatened miscarriage

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INTRODUCTION

Miscarriage refers to the loss of a pregnancy before 24 weeks. It is a common complication of pregnancy, occurring in 12%–30% of all clinical pregnancies,[1-3] and even more if unrecognised biochemical pregnancies are included.[4] A threatened miscarriage is defined as vaginal bleeding, usually painless, that occurs in the first 24 weeks in a viable pregnancy without cervical dilatation. It is common, especially in the first trimester, occurring in 14%–21% of all pregnancies.[1,5] Recurrent miscarriages are classically defined as three or more consecutive miscarriages. It has been estimated that 0.5%–1% of women suffer from recurrent miscarriages. More recently, investigations and management similar to that for recurrent miscarriages have been started for women who suffer from two consecutive miscarriages. This latter group would include a larger percentage (2%) of women.[6]

Causes of miscarriages

Traditional thinking dictates that there is a single cause for a miscarriage or recurrent miscarriages. More recently, a multifactorial approach to the problem has been encouraged. In such an approach, all possible causes of pregnancy loss are considered, and their cumulative effects, when exceeding the threshold, contribute to a miscarriage.[7] Consideration of the timing of the miscarriage is important, as different causes of miscarriage tend to manifest at different periods of gestation. In first trimester miscarriages, important causes include chromosomal abnormalities, which occur in about 70% of the cases;[8] maternal diseases, including poorly-controlled diabetes mellitus;[9] uncontrolled thyroid disease,[10] severe systemic lupus erythematosus[11] and antiphospholipid syndrome;[12] poor maternal lifestyle habits (including alcohol consumption, smoking and use of illicit drugs); and exposure to non-steroidal anti-inflammatory drugs (NSAIDs) around the time of conception.[13] Second trimester miscarriages, on the other hand, are more commonly caused by specific types of congenital uterine anomalies;[14] cervical incompetence;[15] maternal infections;[16] maternal thrombophilic states, such as inherited thrombophilias[17] and antiphospholipid syndrome;[18] and also chromosomal abnormalities,[8] which account for up to 20% of foetal losses during this period.

Yong Loo Lin School of Medicine, National University of Singapore, 10 Medical Drive, Singapore 117597

Tien JC
Medical Student

Raffles Women's Centre, Raffles Hospital, 585 North Bridge Road, #12-00, Singapore 188770

Tan TYT, MBBS, MMed, MRCOG
Consultant and Foetal Maternal Medicine Specialist

Correspondence to:
Dr Tony Tan
Tel: (65) 6311 1230
Fax: (65) 6311 1170
Email: tan_tony@rafflesmedical.com

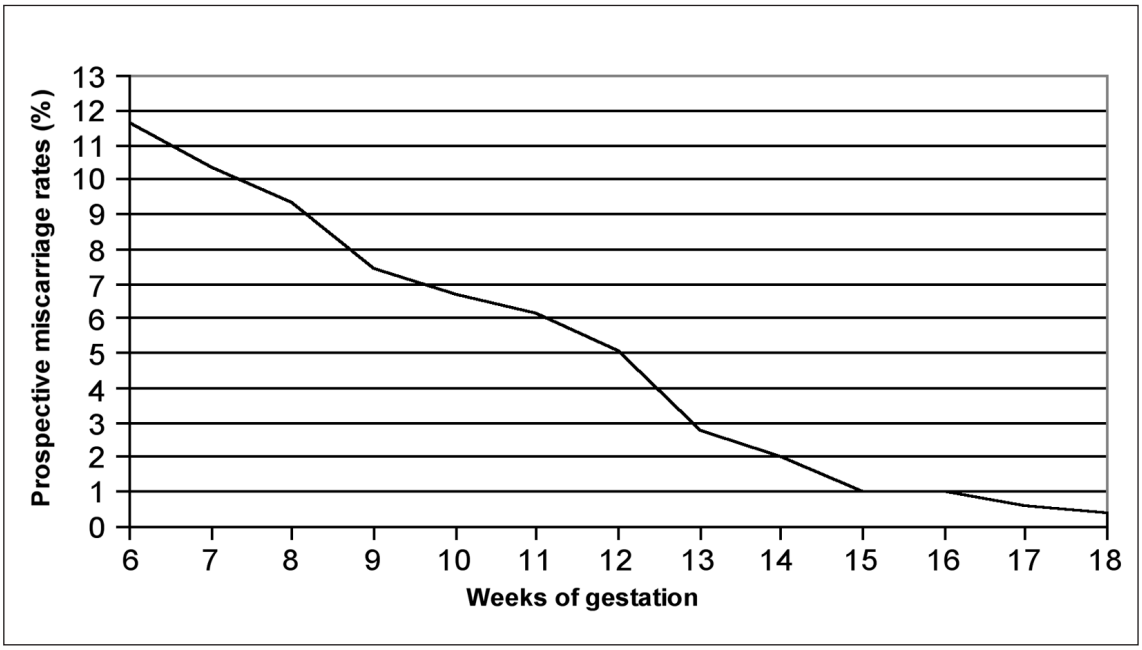

Fig. 1 Graph shows prospective risk of miscarriage according to the gestational age.

Patients with recurrent miscarriages deserve special attention, as the risk of recurrence is higher and the causes tend to be different from sporadic miscarriages. There has been no difference found in the prevalence and frequency of aetiological factors between those with two or three consecutive miscarriages.[19] This supports the initiation of investigations in women who have had only two consecutive miscarriages. The recommended investigations for recurrent miscarriages are listed in Table I. However, it remains an unfortunate fact that in half of the women suffering from recurrent miscarriages, a possible aetiological cause is never identified, even after exhaustive investigations.[19]

Risk of miscarriage

The baseline risk of miscarriage in any pregnancy is dependent on parental age, past obstetric history and gestational age.

Parental age and miscarriage risk

It is well-known that the risk of miscarriage increases with increased maternal age; a pregnancy at the maternal age of 40 years will incur double the risk of miscarriage when compared to one at a maternal age of 20 years.[20] More recently, it has also been shown that the risk of miscarriage also increases with increased paternal age; a paternal age of above 40 years incurs 1.6 times the risk of miscarriage when compared to a paternal age of 25–29 years.[21,22]

Past obstetric history and miscarriage risk

The impact of previous reproductive history on the current pregnancy is relevant because many women with previous miscarriage(s) will be anxious about how this affects them. In comparison to the baseline risk of miscarriage in the general obstetric population of between 12%–30%,[1-3] the risk of miscarriage in women who have never had a miscarriage or are primigravida, is low at 4%–5%.[23] However, in women with a history of miscarriage, the risks are significantly increased. In a woman who has experienced one, two, three and four miscarriages, the risk of a miscarriage in the next pregnancy is 19%,[23] 24%, 30% and 40%, respectively.[24,25]

Prospective miscarriage risk depends on gestational age

A useful piece of information to both clinicians and parents would be the prospective miscarriage risk for each gestational week. This concept of prospective risk has been similarly used for stillbirths.[26,27] The prospective risk is derived from the number of prospective miscarriages occurring from week N onwards, divided by the remaining pregnancies on week N (Fig. 1). We calculated this from the raw data, available from a large community prospective study, of 550 pregnancies seen by general practitioners in a health centre in the United Kingdom. A major limitation of the prospective risks of miscarriage derived from this population is that the gestational age at miscarriage is taken as the week in which the woman presented with a miscarriage. While the

Table I. Causes and recommended investigations for recurrent miscarriages.[7,19]

Causes	Diagnosis
Recurrent foetal chromosomal abnormalities, especially unbalanced chromosomal translocations	Karyotype of miscarried foetus(es), if possible, and peripheral blood karyotyping of couple.
Uterine abnormalities	Saline infusion pelvic ultrasonography / hysterosalpingography (HSG) / hysteroscopy / sonohysteroscopy.
Uncontrolled thyroid disease	fT4 and TSH (if symptomatic).
Uncontrolled diabetes mellitus	Random blood glucose / OGTT with or without HbA1c (if symptomatic).
Polycystic ovary syndrome	Clinical diagnostic criteria (2 out of 3):[62] 1. Oligo- or anovulation. 2. Clinical and/or biochemical signs of hyperandrogenism. 3. Polycystic ovaries on ultrasonography. After the exclusion of other aetiologies, such as congenital adrenal hyperplasia, androgen secreting tumours and Cushing's syndrome.
Antiphospholipid antibodies	Lupus anticoagulant (LAC). IgG and IgM anticardiolipin antibodies (ACA).
Inherited thrombophilias	Protein S assay, protein C assay, activated protein C resistance assay, antithrombin III assay, factor V leiden, total homocysteine.
Bacterial vaginosis	High vaginal swab.

absolute risks reflected in Fig. 1 cannot be used to counsel patients usefully, it is important to understand the concept of prospective risk of miscarriage and to appreciate the trend of decreasing prospective risk of miscarriage with increasing gestational age.

Prognosis of threatened miscarriage with expectant management

There are many other causes of vaginal bleeding during early viable intrauterine pregnancy, besides the more common diagnosis of threatened miscarriage. These include cervical erosions and/or polyps, decidual reaction of the cervix, implantation bleed and vaginitis.[28] The prognosis of a threatened miscarriage is further dependent on factors such as the gestational age at time of bleeding and amount of bleeding, over and above the factors that influence the baseline miscarriage risk (Table II).

Gestational age

The outcome of threatened miscarriages is linked to the gestational age at presentation of bleeding. In a small study of 182 women with threatened miscarriage, 29% of foetuses presenting at 5–6 weeks, 8.2% at 7–12 weeks and 5.6% at 13–20 weeks, miscarried.[29]

Severity of bleed

The outcome of threatened miscarriages has also been associated with the severity of the vaginal bleed. A large prospective multicentre database of 16,506 women from an unselected obstetrical population was studied, comprising 14,160 women without bleeding,

Table II. Risk of miscarriage (%) according to gestational age and amount of bleeding.

Amount of bleeding	Gestational age (weeks)		
	5–6	7–9	10–12
Light	29%[29]	No data available	1%[5]
Moderate		9.3%[30]	No data available
Severe			2%[5]

2,094 patients with light bleeding and 252 patients with heavy bleeding. The rate of foetal demise in the event of light bleeding (spotting) presenting within four weeks before ultrasonography at 10–14 weeks was associated with an actual miscarriage rate of 1%, as compared to a rate of 2% when the bleeding was severe (similar to menses).[5] In a different study where the study population of 214 women was limited to those who had active fresh bleeding (excluding spotting), and a viable foetus at presentation (average gestation period was 8 weeks), the miscarriage rate was 9.3%.[30]

Surgical and non-surgical interventions

Understandably, a couple with threatened miscarriage, or a history of recurrent miscarriages, is invariably anxious and keen to try any intervention that may improve the outcome for their unborn baby. The obstetrician, could also be keen to assist the couple in reducing the risk of miscarriage through any intervention that may work. There are a wide variety of surgical and non-surgical interventions available

that have been used to attempt the prevention of a miscarriage. Surgical interventions include cervical cerclage for a past obstetric history suggestive of cervical incompetence, and selected cases of painless cervical dilatation occurring just before 24 weeks,[31,32] and uterine surgery for selected cases of congenital uterine anomalies.[33] These surgical interventions will not be further reviewed in this paper. Non-surgical interventions include pharmacological and non-pharmacological ones, which are the focus of this review.

Diethylstilbestrol, an oestrogen derivative, was promoted in the 1940s as the contemporary view held then was that miscarriages were due to reduced placental hormone production. This was only reversed in the 1970s, when its administration before birth became strongly associated with clear cell carcinoma, and adenosis of the vagina and cervix of the child.[34] There was also no improvement in either miscarriage rates or other pregnancy outcomes. Its use has long become obsolete, and serves as a reminder that more harm than good may be done without adequate and rigorous research into the use of drugs for threatened or recurrent miscarriages.

Statistical methods

Where available, odds ratios and confidence intervals (CIs) are quoted directly from the respective studies and meta-analyses. In studies where the odds ratios and/or CIs were not reported, we derived these values from the raw data provided using standard statistical analysis with the statistical programme, Stata 8.2. (Stata Corp, College Station, TX, USA).

INTERVENTIONS

Interventions can be divided into specific interventions when an aetiological factor can be identified, and non-specific ones for idiopathic past miscarriages and threatened miscarriages.

A. Specific interventions
1. Aspirin and heparin
2. Antibiotics
3. Metformin
4. Bromocriptine
5. Luteinising hormone (LH) suppression

B. Non-specific interventions
1. Supportive care
2. Progesterone
3. Bed rest
4. Avoidance of sexual intercourse
5. Vitamins
6. Human chorionic gonadotrophin (hCG)
7. Uterine relaxing agents
8. Immunotherapy

SPECIFIC INTERVENTIONS

Aspirin and heparin

Anticoagulants, including aspirin and low molecular weight heparin (LMW heparin) or unfractionated heparin, have been used in the management of recurrent miscarriages in cases of antiphospholipid syndrome (APS). A prothrombotic state has been postulated, in these cases, to cause placental infarction and thrombotic changes in the decidual microvessels, with possible placental insufficiency and foetal death.[35] The use of anticoagulants in pregnancy also carries its own risks. Both unfractionated heparin and LMW heparin do not cross the placenta and do not have teratogenic effects, or cause bleeding in the foetus. However, there is concern over other side effects, such as heparin-induced thrombocytopenia, heparin-induced osteopenia and fractures, and also maternal bleeding. The advantages of LMW heparin over unfractionated heparin include a lower risk of heparin-induced thrombocytopenia[36,37] and heparin-induced osteoporosis,[36,37] and the once-daily dosing. Aspirin use appears to be safe in pregnancy and has not been associated with an increased risk of miscarriage in two recent meta-analyses.[38,39]

Patients with APS

APS is a type of acquired thrombophilia characterised by recurrent miscarriages and/or thromboembolism in the presence of antiphospholipid antibodies, such as lupus anticoagulant (LAC) and anticardiolipin antibodies (ACA) IgM and IgG. Controversies remain on the actual level of autoantibody level to be used as the diagnostic criteria of APS, and the variability between laboratories. The importance of antiphospholipid antibodies, other than LAC and ACA, has also yet to be resolved.[7] In general, the diagnosis of APS requires a typical clinical picture, supported by two separate samples with elevated antibody levels taken at least six weeks apart, and during the non-pregnant state, i.e. at least six weeks after pregnancy. It is reported that APS carries a 3.5 times increased risk of foetal loss.[40] However, there has been no consensus on the basis for the increased foetal loss.

It has increasingly been suggested that defective trophoblastic invasion is a strong feature of APS-associated miscarriages.[41,42] One study has shown that LMW heparin can restore *in vitro* trophoblast invasiveness and differentiation by reducing IgG binding to trophoblast cells.[43] Such findings have supported the use of heparin during pregnancy in women with APS, in addition to the usual regimen of aspirin which may improve the outcome via another pathway. A recent Cochrane review of 13 trials (849 women) studying anticoagulation in women with

APS concluded that combined unfractionated heparin and aspirin, as compared to aspirin alone, gave the greatest improvement in miscarriage rates (18/70 [25.7%] vs. 40/70 [57.1%], RR (Random) 0.46, 95% CI 0.29–0.71).[35] When LMW heparin was compared to aspirin alone, the result was statistically insignificant (11/51 [21.2%] vs. 13/47 [27.7%], RR (Random) 0.78, 95% CI 0.39–1.57). In three studies comparing aspirin to a placebo or usual care, there was also no significant reduction in miscarriage rates (10/37 [27.0%] vs. 8/34 [23.5%], RR (Random) 1.05, 95% CI 0.66–1.68). Giving prednisone or intravenous immunoglobulin together with aspirin, or unfractionated heparin, was associated with no increased benefit in reducing risk of miscarriage or premature birth when compared to heparin with aspirin.[35]

It has generally been accepted that anticoagulation therapy in women with APS improves the prognosis of the pregnancy. Although the Cochrane review reported that low dose aspirin and heparin gave the best outcome, it has to be noted that aspirin by itself did not appear to improve the outcome of the pregnancy in 71 women studied.[35] This is also in light of the individual studies that have raised doubts over the efficacy of aspirin therapy in women with APS and recurrent miscarriages.[44] Thus, the best regimen for anticoagulant therapy in women with APS and recurrent miscarriages remains to be seen, although the strongest evidence currently points towards the combined use of low dose heparin and low dose aspirin.

Patients with inherited thrombophilias

The efficacy of anticoagulant treatment for women not suffering from APS has not been as well established as that for women with APS. Inherited thrombophilias are a group of inherited coagulation disorders that include factor V Leiden mutation (failure of inactivation of activated factor V by protein C) and deficiency of physiological anticoagulants such as protein S, protein C and antithrombin III. They may present as deep vein thrombosis, Budd-Chiari syndrome and also pulmonary embolism.

Thrombophilias are more common among women suffering from recurrent miscarriages.[17,45] A cohort study has previously shown that thromboprophylaxis with LMW heparin-enoxaparin (40 mg/day), as compared to no treatment, improves the live birth rate in women with recurrent miscarriages and hereditary thromphilia.[46] However, there is a lack of randomised controlled trials (RCTs) to confirm this finding. In a RCT on 160 women who had inherited thrombophilia and one previous foetal loss after ten weeks gestation, it was shown that enoxaparin (40 mg/day) was superior to aspirin.[47] 69 out of the 80 women (86.3%) who received enoxaparin had a live birth, as compared to only 23 of the 80 women (28.8%) who received aspirin (OR 15.5, 95% CI 7–34). Another RCT involving 180 women has shown no additional advantage of using a higher dose of 80 mg/day of enoxaparin compared to 40 mg/day.[48] While there are no RCTs comparing heparin and a placebo in women with inherited thrombophilias, and hence no proof that heparin is better than no treatment at all, LMW heparin remains the current treatment of choice based on current available data.

Recommendations

The Royal College of Obstetricians and Gynaecologists (RCOG),[49] the American College of Obstetricians and Gynecologists (ACOG)[50] and the Singapore College of Obstetricians and Gynaecologists (SCOG)[51] recommended that it is mandatory for the patient to have two positive tests at least 6–8 weeks apart for either LAC or ACA of IgG and/or IgM present in medium or high titre for the diagnosis of APS to be confirmed. All recommended that combination therapy of aspirin and heparin be prescribed for patients with such a diagnosis. Even with such treatment, pregnancies associated with APS remain at high risk of complications during all three trimesters, and hence still require close monitoring even with treatment. RCOG recommended routine screening for Factor V Leiden mutation and to offer prophylaxis to those with the mutation and evidence of placental thrombosis.[49] The SCOG states that routine screening for inherited thrombophilic defects may be offered in the investigation of recurrent miscarriages and thrombophylaxis offered to those suffering from such conditions.[51]

Antibiotics

Bacterial vaginosis (BV) is a condition in which the normal vaginal flora, mainly Lactobacillus, is replaced by an overgrowth of anaerobic bacteria (*Mycoplasma hominis, Bacteroides* spp., *Mobiluncus* spp.).[52] It is a common condition among women of child-bearing age, and prevalence rates of 21.4%–32.5% have been reported in studies of pregnant women.[16,53] It is well established that BV in pregnancy predisposes to both preterm labour and second trimester miscarriages, with an increased relative risk of 3.1–3.9 times in second trimester miscarriages among women who had BV.[16,53] The association between BV and first trimester miscarriages is somewhat conflicting.[54,55] Older studies on antibiotics in bacterial vaginosis concentrated on preterm birth alone as outcomes. This is best summarised by the recent Cochrane review,[56] which stated that there was little evidence to support that

Table III. Miscarriage rates comparing metformin versus no treatment.

Study	Type of study	Treatment n (%)	Control n (%)	Odds ratio	95% CI
Jakubowicz et al, 2002[63]	RCA	6/68 (9)	13/31 (42)	0.13	0.04–0.45
Glueck et al, 2002[66]	Prospective	12/47 (26)	62/100 (62)	0.21	0.09–0.48
Thatcher and Jackson, 2006[67]	RCA	29/81 (36)	54/81 (67)	0.27	0.14–0.56

RCA: retrospective case analysis with historic controls.

screening for, and treatment of asymptomatic bacterial vaginosis, will improve preterm birth and its sequelae. However, in this subgroup of patients with bacterial vaginosis and a history of a previous preterm birth, treatment with antibiotics lowered the risk of preterm rupture of membranes and low birth weight even though the risk of preterm labour was not reduced.

More recent studies focused on second trimester miscarriages and preterm birth as a composite outcome, which is a more logical measure to assess the true impact of antibiotic treatment for BV. A RCT in 2003 screened 6,120 asymptomatic pregnant women for BV between 12 and 22 weeks, of which 740 were screened positive. Among this group, 494 were randomised into two groups, of which one group was treated with oral clindamcyin 300 mg twice daily for five days compared to placebo.[57] 5/244 (2%) in the treatment group had late miscarriages (13–24 weeks) or preterm deliveries (less than 33 weeks), as compared to 16/241 (7%) in the control group (OR 0.29, 95% CI 0.09–0.86). Another recent RCT studied the effect of vaginal clindamycin cream in 819 women, among 9,025 general asymptomatic pregnant women, who were screened positive for BV, at 10–14 weeks.[58] Treatment was given for seven days in the treatment group. Repeat smears were performed at 24 and 31 weeks. Vaginal clindamycin was repeated if a positive smear was seen at either repeat smears. 1/395 (0.3%) women who were in the treatment group, as compared to 5/390 (1.3%) women who were in the control group, delivered prior to 33 completed weeks (OR 0.20, 95% CI 0.00–1.76). While this was not statistically significant, the study showed that clindamycin vaginal cream therapy was cost effective and associated with a significantly prolonged gestation, and reduced cost of neonatal care in women with BV who delivered preterm. This may be clinically significant as preterm birth before 33 weeks is associated with greatly increased long-term morbidity and increased economic costs, as compared to deliveries between 33 and 36 weeks.[59] It is known that a significant proportion of BV resolves without treatment.[60] However, spontaneous resolution is not associated with an improvement in the rates of preterm labour.[61]

Recommendations

For women with recurrent miscarriages, the older ACOG guidelines in 2001 stated that routine vaginal evaluation for BV is not useful in evaluating otherwise asymptomatic healthy women,[50] while the more recent RCOG guideline in 2003,[49] and the SCOG guidelines in 2006,[51] stated that there is no benefit in screening and treating all pregnant women for BV. However, doing so for high risk women with a previous history of second trimester miscarriage, or spontaneous preterm labour, may reduce the risk of recurrent late misscarriage and preterm birth. None of the guidelines considered the more recent findings. In view of recent findings, screening for BV for all pregnant women between 10–22 weeks of pregnancy may be considered. Women with a positive vaginal swab for BV should be treated with a course of clindamycin to lower the risk of late miscarriage and preterm labour. Nevertheless, empirical treatment with antibiotics in the absence of documented infection is not warranted.

Metformin

Polycystic ovarian syndrome (PCOS) is a syndrome of chronic anovulation and hyperandrogenisation. Its clinical manifestations include menstrual irregularities (oligomenorrhoea), signs of androgen excess and obesity. Insulin resistance, elevated serum LH levels and polycystic ovaries in morphology are common features.[62] There is also associated comorbidity with type 2 diabetes mellitus and cardiovascular disease. PCOS is associated with infertility due to infrequent ovulation. Even after conception, affected women continue to suffer from a much higher spontaneous miscarriage rate of up to 50%.[63] About 36%–56% of women with recurrent miscarriages are reported to be suffering from PCOS.[64,65]

Metformin is an insulin-sensitising drug that is frequently prescribed for infertile women with PCOS, as it reduces the hyperinsulinaemia-mediated hyperandrogenism, and encourages the resumption of normal ovulation and menses,[66] thus improving the chances of conceiving. In the last decade, metformin has increasingly been used in PCOS patients for

ovulation induction, reduction of body weight and improvement in quality of life. As such, more PCOS patients have been getting pregnant while on metformin. The current issues being debated now are whether continuing metformin into the first trimester of pregnancy has any benefits, and if metformin use in the first trimester is associated with any congenital anomalies.

Metformin is thought to be beneficial in reducing miscarriages because of its effects on various risk factors for miscarriage, such as hyperinsulinaemic insulin resistance, hyperandrogenaemia and obesity. Pooled data from two retrospective and one prospective study[63,66-68] on the periconceptional use of metformin, with dose ranging 500–2,550 mg daily during pregnancy, showed a statistically significant reduction in miscarriage rates for all three studies (Table III), with ORs ranging 0.13–0.27. The reduction in miscarriage rates in PCOS patients were present in patients with, and without, any history of previous first trimester miscarriage.[63] Although metformin does cross the placental barrier, there has been no association of foetal abnormalities with metformin usage in pregnancy in either animals[69] or humans.[70] According to these early studies, the periconceptional use of metformin is not associated with teratogenic effects. RCTs aimed at addressing the question of the role of periconceptional metformin in PCOS patients with recurrent miscarriages are underway, and may pave the way for more widespread acceptance of this intervention.

Recommendations

The ACOG stated in 2001 that there is no known therapy for reducing the risk of pregnancy loss in women with PCOS.[50] Observational studies published after that, while small in numbers, have consistently supported the use of periconceptional metformin in PCOS, though the final answer obviously lies with well-designed RCTs with adequate sample sizes.

Bromocriptine

Hyperprolactinaemia affects the hypothalamic-pituitary-ovarian system. It is usually characterised by irregular menstruation, infertility and/or galactorrhoea. Its association with recurrent miscarriage is more controversial. Reports offer conflicting results on whether or not hyperprolactinaemia is a feature of recurrent miscarriages.[71,72] A small RCT was done on the use of bromocriptine in women who had isolated hyperprolactinaemia associated with recurrent miscarriages.[73] In this study, women were divided into those with hyperprolactinaemia (basal prolactin level > 10 ng/ml) and those with occult hyperprolactinaemia (basal prolactin level < 10 ng/ml but prolactin levels 20 min after thyrotropin-releasing hormone administration > 86 ng/ml). The study showed a significant decrease in miscarriage rate when women suffering from basal and occult hyperprolactinaemia were given bromocriptine compared to when not given (3/24 [14.3%] vs. 10/24 [47.6%], OR 0.20, 95% CI 0.03–0.99). However, there have been objections to the definition of hyperprolactinaemia in this study and many are not convinced that hyperprolactinaemia is a definite cause of miscarriages, due to both a lack of convincing evidence from studies and no strong biological basis to explain this link.[74] There is therefore no conclusive evidence that the use of bromocriptine in the first trimester is associated with congenital malformations.[69]

Recommendations

The RCOG in 2003 stated that there is insufficient evidence to assess the effect of hyperprolactinaemia as a risk factor for recurrent miscarriage.[49] Hence, the use of bromocriptine in the management of recurrent miscarriages associated with hyperprolactinaemia cannot be recommended at present.

Luteinising hormone suppression

LH is usually produced by the pituitary gland and induces theca cells within the follicle to convert cholesterol into androgens. Oversecretion of LH thus creates a hyperandrogenic state that results in follicular atresia. Endogenous LH secretion can be suppressed by an agonist analogue of LH releasing hormone, buserelin. Hypersecretion of LH has been associated with subfertility and miscarriages, and is one of the postulated mechanisms for frequent early pregnancy loss among women with PCOS. Initial studies in the general population have suggested that a high level of LH (> 10 IU/L) on day six of the menstrual cycle, was associated with an increase in miscarriage rates from 12% to 65%.[75] However, later studies have been unable to confirm these results, with no significant association seen between the levels of either LH or testosterone and the miscarriage rate.[76]

PCOS patients undergoing ovulation induction

In a small study involving 40 subfertile women with PCOS, ovulation induction was achieved in one group with buserelin, a gonadotrophin-releasing hormone (GnRH) agonist, and follicular-stimulating hormone, while the other group was administered with clomiphene citrate. It was noted that the miscarriage rate of the buserelin group was lower at 2/20 (10%) as compared to the clomiphene group at 11/20 (55%) (OR 0.09, 95% CI 0.01–0.58).[77] Thus, there was a significant

improvement in the miscarriage rates with LH suppression by GnRH agonists in women undergoing ovulation induction.

Women with polycystic ovaries (PCO) but no fertility problems

106 ovulatory women with recurrent first trimester miscarriages with hypersecretion of LH (defined as mid-follicular phase LH levels > 10 UL/L) and PCO were divided into three arms of the trial. Other than ultrasonographical evidence of PCO, it has to be noted that these women were not screened for PCOS by utilising the current diagnostic criteria. The treatment group was given LH suppression with GnRH agonist and ovulatory induction with luteal support (Cyclogest®), and two control groups were either given luteal support only, or no treatment (placebo pessaries).[78] However, the trial did not show any evidence to support the hypothesis that LH suppression improves miscarriage rates in this group. The trial was stopped after examining 106 women because there appeared to be no clinical benefit in terms of live birth rates from LH suppression (26/50 [52%] vs. 35/46 [76%], OR 0.34, 95% CI 0.13–0.89). In fact, results showed a statistically significant reduction in the live birth rate instead.

Recommendations

Both SCOG guidelines in 2006 and RCOG guidelines in 2003 stated that pregnancy suppression of high LH concentration among ovulatory women with recurrent miscarriage and polycystic ovaries, who hypersecrete LH, does not improve the live birth rate.[49,51]

NONSPECIFIC INTERVENTIONS

Supportive care and close supervision

Although there appears to be no biological mechanism for supportive care to reduce miscarriages, it has been shown that proper care and support do reduce the miscarriage rate in women suffering from unexplained recurrent miscarriages. For up to half of women suffering from recurrent miscarriages, no known cause can be identified.[15] Studies have been conducted, in which these women received specific antenatal counselling, close weekly supervision by ultrasound scan at a dedicated early pregnancy clinic until the 12th gestational week and formal emotional support.[79] No pharmacological treatment was prescribed in any of these studies. These non-randomised but controlled trials showed that additional supportive care is indeed superior to standard care in recurrent miscarriages. The studies reported that the risk for miscarriage can be reduced from over 50% to below 25% with such care[15,79,80] (Table IV). This is encouraging, although the provision of early pregnancy support is costly in terms of increased logistical requirements, such as trained staff and equipment.

Recommendations

The RCOG and SCOG stated that women with unexplained recurrent miscarriage have an excellent prognosis for future pregnancy outcome without pharmacological intervention, if offered supportive care alone in the setting of a dedicated early pregnancy assessment unit.[49,51] The ACOG guidelines stated that couples with otherwise unexplained recurrent pregnancy loss should be counselled regarding the potential for successful pregnancy without treatment.[50]

Progesterone

Progesterone and progestational agents have been used for over 50 years to treat threatened abortions, despite there being no strong evidence supporting their use. In a normal pregnancy, the corpus luteum secretes progesterone, which induces secretory changes in the endometrial lining, creating an environment conducive for implantation of the fertilised ovum. It has been postulated that some miscarriages are due to corpus luteum deficiency/luteal phase defect (LPD) where the corpus luteum produces a suboptimal amount of progesterone, resulting in retarded endometrial development.[81] LPD has been associated with recurrent miscarriages, infertility and luteal suppression in assisted reproduction. Experiments in the 1970s by Csapo et al demonstrated that seven out of 11 patients subjected to lutectomy in the early first trimester of pregnancy suffered from miscarriages, whereas another seven who underwent removal of the corpus luteum but received daily progesterone injections did not miscarry.[82] This strengthened the link between miscarriages and LPD, as it suggested that progesterone is required for the maintenance of early pregnancy.

Much controversy, however, surrounds the diagnosis of LPD since it was first described by Jones in 1949.[83] As a clinical entity, it has been poorly characterised. Much variability exists in its diagnosis; in addition, many women who do not suffer from miscarriages also fit the diagnostic criteria for LPD. Classical histological diagnosis of LPD is confirmed by endometrial biopsy, in which there is a delay in the foetal development of more than two days in at least two cycles (Noyes criteria).[84] Using this as the standard for diagnosis, studies have shown that between 17%–19% of women with recurrent miscarriages suffer from LPD.[85,86] However, up to 26.7% of normal fertile women have been reported to fit the diagnostic criterion for LPD.[87] Another diagnostic

Table IV. Miscarriage rates comparing women with, versus women without, supportive care.

Study	Type of study	Treatment n (%)	Control n (%)	Odds ratio	95% CI
Clifford et al, 1997[79]	CC	42/160 (26)	21/41 (51)	0.34	0.16–0.73
Liddell et al, 1991[80]	Prospective	6/44 (14)	6/9 (67)	0.08	0.01–0.52
Stray-Pedersen and Stray-Pedersen, 1984[15]	CC	5/32 (16)	16/24 (67)	0.09	0.02–0.38

CC: case control.

Table V. Various progestogens and their commercial preparations.

Chemical preparation	Commercial name(s)	Formulation
Medroxyprogesterone	Provera	Oral tablet / injection
17-hydroxyprogesterone caproate	Proluton	Injection
Dydrogesterone	Duphaston	Oral tablet
Natural progesterone	Progesterone biologici Utrogestan Cyclogest	Injection Oral capsule Pessary

Table VI. Miscarriage rates comparing medroxyprogesterone versus no treatment.

Study	Type of study	Treatment n (%)	Control n (%)	Odds ratio	95% CI
Moller and Fuchs, 1965a[91]	RCT	9/20 (45)	7/24 (29)	1.99	0.48–8.32
Moller and Fuchs, 1965b[91]	RCT	13/28 (46)	17/35 (49)	0.92	0.30–2.78
Moller and Fuchs, 1965c[91]	RCT	41/75 (55)	42/78 (54)	1.03	0.52–2.05

criterion is a low serum progesterone level <10 ngl/ml at the mid-luteal phase (5–9 days after ovulation). It was noted, in an observational study involving 105 women, that the rise in serum progesterone in the first four weeks was similar in women who had continuing pregnancies, and those who had miscarriages. The difference in progesterone levels was only statistically significant after six weeks. It was postulated that the decline in progesterone levels was due to placental failure, rather than LPD.[3] Other diagnostic criteria include the failure of a rise in basal body temperature after ovulation, and ultrasound examination showing a maximum mean preovulatory follicle diameter of less than 17 mm.[88] These latter criteria also show a big overlap between those who have successful pregnancies and those who miscarry.

In view of the conflicting evidence on LPD, it has been suggested that there is insufficient evidence to label LPDs as a distinct clinical entity that leads to reproductive problems, and that clinicians should refrain from costly and invasive testing to diagnose LPD.[88] Despite this controversy, exogenous progesterone supplementation remains a common intervention for both threatened and idiopathic recurrent miscarriages. Exogenous progesterone supplementation can occur in various forms such as medroxyprogesterone acetate, 17-alpha-hydroxyprogesterone caproate, progesterone and dydrogesterone (Table V). Interpretation of clinical trials on these agents is complicated by both the wide array of progestational agents and differences in drug administration and dosing. Various meta-analyses have also been done to study the effects of progestational agents in miscarriage prevention in the general population, with conflicting results.[81,89,90]

Medroxyprogesterone

Early studies on the use of medroxyprogesterone as an intervention for miscarriages did not show any improvement in the risk of miscarriages. A series of three investigations were done with low (study A), medium (study B) and high (study C) doses of medroxyprogesterone, but no improvement in outcome was seen[91] (Table VI). Medroxyprogesterone is a derivative of progesterone that has androgenic and anabolic effects. While there was an early case report that linked the first trimester use of

Table VII. Miscarriage rates comparing 17-hydroxyprogesterone caproate versus no treatment.

Study	Type of study	Treatment n (%)	Control n (%)	Odds ratio	95% CI
Shearman, 1968[95]	RCT	5/27 (19)	5/23 (22)	0.82	0.16–4.19
Yemini et al,1985[96]	RCT	8/39 (21)	3/40 (8)	3.18	0.68–19.93
Levine,1964[97]	RCT	3/15 (20)	7/15 (47)	0.29	0.04–1.81
Johnson et al, 1975[98]	RCT	3/23 (13)	0/27 (0)	NA	NA
Reijnders and Thomas, 1988[99]	RCT	2/32 (6)	1/32 (3)	2.10	0.10–125.78

Table VIII. Miscarriage rates comparing natural progesterone versus no treatment.

Study	Type of study	Progesterone formulation	Treatment n (%)	Control n (%)	Odds ratio	95% CI
Gerhard et al, 1987[107]	RCT	Suppository	3/26 (12)	5/26 (19)	0.54	0.07–3.25
Nyboe Anderson et al, 2002[108]	RCT	Pellet inserted into gluteal muscle	18/153 (12)	22/150 (15)	0.78	0.37–1.59
Swyer and Daley, 1953[109]	RCT	Suppository	11/60 (18)	13/53 (25)	0.69	0.25–1.88
Vignali and Centinalo, 2000[110]	Clinical trial	Cream	3/19 (16)	3/15 (20)	0.75	0.09–6.68
Clifford et al, 1996[78]	RCT	Suppository	4/20 (20)	7/26 (27)	0.68	0.12–3.29

Table IX. Miscarriage rates comparing bed rest versus no bed rest.

Study	Type of study	Treatment n (%)	Control n (%)	Odds ratio	95% CI
Hamilton et al, 1991[117]	RCT	2/14 (14)	1/9 (11)	1.33	0.06–88.3
Harrison, 1993[118]	RCT	15/20 (75)	10/21 (48)	3.30	0.74–15.71
Giobbe et al, 2001[119]	CC	23/146 (16)	16/80 (20)	0.75	0.35–1.63
Ben-Haroush et al, 2003[120]	CC	3/30 (10)	47/200 (24)	0.36	0.07–1.26

medroxyprogesterone with simulated congenital adrenal hyperplasia in a male neonate,[92] later and larger case control studies showed no association between teratogenicity and the use of medroxyprogesterone.[93,94] Despite this, FDA has considered it to be a category X drug, which means that it is contraindicated in women who are or may become pregnant.[69] The older studies also show no reduction in miscarriage rates with medroxyprogesterone.

17-hydroxyprogesterone caproate

A review on the use of 17-hydroxyprogesterone caproate specifically revealed that there was no effect in miscarriage prevention, even in patients who had previously suffered from recurrent miscarriages.[90] The results of individual studies are shown[95-99] in Table VII. From the review, there is no evidence that administration of 17-hydroxyprogesterone caproate reduces the risk of miscarriage, even in the context of recurrent miscarriages. On the flip side, there have been reports of incidents of foetal genital abnormalities and virilisation,[100] isolated cases of maternal transient parkinsonism[101] and retinal arteriolar obstruction[102] that are possibly associated with its use.

17-hydroxyprogesterone caproate is considered a category D drug by the FDA,[69] which means that there is positive evidence of human foetal risk, but the benefits from use in pregnant women may be acceptable despite the risk, if the drug is needed in a life-threatening situation, or for a serious disease in which safer drugs cannot be used or are ineffective. While its use in early trimester for the prevention of miscarriage is contraindicated, its use in pregnancy has been resurrected by recent evidence that it reduces the preterm labour rates in those patients at high risk of preterm labour when administered weekly from 16 gestational weeks onwards.[103]

Dydrogesterone

Recent studies have focused on the use of dydrogesterone, an orally-active progestogen with no androgenic effects. There have been no reports of foetal abnormalities other

than an isolated incident of a non-virilising abnormality of the genitourinary tract, when dydrogesterone was used together with hydroxyprogesterone caproate.[104] There is a dearth of earlier studies on this compound and a Cochrane review in 2003 on progesterone use in prevention of miscarriages did not include any trials on dydrogesterone. A small recent RCT on its use in the context of a threatened miscarriage showed that there was an improvement in outcome with more continuing pregnancies in the treatment group (71/74 [95.9%] vs. 69/80 [86.3%], OR 3.77, 95% CI 1.01–14.11).[105] The use of dydrogesterone in recurrent miscarriages has also been studied in another recent RCT, which showed a decrease in the number of miscarriages as compared to both the control group (11/82 [13.4%] vs. 14/48 [29.2%], OR 0.38, 95% CI 0.14–1.00)[106] and the group which had been given hCG.

Natural progesterone

Natural progesterone is available in various formulations: oral tablets, injections and vaginal suppositories. No meta-analysis has been done on the effect of natural progesterone on the outcome of threatened miscarriages. Thus, we have combined the results of the various studies[78,107-110] (Table VIII). From the results, natural progesterone has thus far no proven benefits on the outcome of pregnancy.

Recommendations

All three colleges stated that the benefits of progesterone supplementation for recurrent miscarriages is of unproven efficacy.[49-51] In addition, RCOG recommends that progesterone supplementation should only used in the context of a RCT.[49] In our review, individual progestational agents were evaluated separately to enable a meaningful comparison. Medroxyprogesterone is contraindicated in pregnancy. 17-hydroxyprogesterone caproate is contraindicated in early pregnancy for threatened or recurrent miscarriages, though its use for the prevention of preterm labour from 16 weeks onwards is supported by a recent trial.[103] There is recent and early evidence that dydrogesterone reduces miscarriage rates in threatened and recurrent miscarriages. Natural progesterone has thus far no proven benefits on the outcome of the pregnancy.

Bed rest

Bed rest is one of the most commonly-prescribed interventions for threatened miscarriages, with 96% of the physicians prescribing it in one study, although only 20% of the doctors felt that it was mandatory, and one third of them felt that it was of no benefit.[111] Bed rest is usually prescribed on the belief that hard work and physical activity is associated with miscarriage.[112] Bed rest can be associated with adverse effects, such as increased risk of thromboembolic phenomenon,[113] muscle atrophy and weight loss,[114] stress and financial cost to the woman. It can also induce self-blame in the event of non-compliance and subsequent misscarriage.[115] There are also increased healthcare costs if bed rest is instituted in a hospital setting. Thus it needs to be evaluated if bed rest has any value in improving the outcome in a threatened miscarriage.

Only two RCTs have been done so far on bed rest as an intervention in threatened miscarriages. These two trials have been covered in a Cochrane review and no significant improvement was seen in the eventual miscarriage rate.[116-118] No improvement was also seen a larger observational study conducted more recently[119] (Table IX). A recent retrospective study by Ben-Haroush et al[120] was done on the prescription of bed rest in 230 women who had threatened miscarriage, having presented with a subchorionic haematoma on ultrasound. Fewer miscarriages were seen in the group who were compliant with bed rest, but this was not statistically significant when we analysed the raw data.[120]

Avoidance of sexual intercourse

No study has been done on the effect of sexual intercourse on first trimester miscarriages specifically, although it is a common prescription from doctors to women who are suffering from threatened or recurrent miscarriages. This is borne out by observations that studies done to investigate other interventions have recommended avoidance of sexual intercourse to both their treatment and control groups. It has been hypothesised that there is an increased risk due to stimulation of uterine contractions[121] by both prostaglandins in the seminal fluid (use of condoms may reduce this) and release of oxytocin from nipple stimulation and orgasm. An increased number of sexual partners has also been suggested to increase the risk of pre-pregnant asymptomatic bacterial colonisation of the uterine cavity; these bacteria may then invade the foetal membranes, placenta and amniotic fluid, resulting in foetal loss.[122] More data is required to determine whether sexual intercourse has a negative impact on first trimester miscarriages. Till then, most doctors recommend that women with bleeding in pregnancy to refrain form sexual activity while permitting those without pain or bleeding in pregnancy to continue with coitus.

Vitamins

An observational study found that a diet poor in vegetables, fruit, milk and dairy products, but rich in fats, was associated with an increased risk of

miscarriage.[123] It has been suggested that since oxidative stress has been associated with spontaneous and recurrent miscarriages, antioxidants such as vitamins C and E could be beneficial in preventing miscarriages.[124] A Cochrane review of 17 trials including 35,353 pregnancies[124] analysed various types of vitamins but was unable to find any improvement in the miscarriage rates. This finding stood in both counts, when the trials were pooled and analysed together, and when they analysed the studies according to the different types of vitamin supplementation. Overdose of vitamin A, however, can result in an increased risk of miscarriages and central nervous system or cardiac defects in the foetus. Both overdose of vitamin A and D can also result in adverse effects on the mother, such as gastrointestinal symptoms. Thus, high dose vitamin supplementation to prevent miscarriage is not warranted.

Human chorionic gonadotrophin

hCG is produced by the trophoblast in pregnancy and stimulates both the corpus luteum and the foetoplacental endocrine functions, resulting in progesterone production. Exogenous hCG supplementation has been attempted, based on the assumption that some miscarriages are due to insufficient hCG, resulting in inadequate progesterone secretion. In a serial study of 105 women, the serum hCG levels of those who subsequently had a miscarriage were significantly lower than those with continuing pregnancies from six weeks onwards.[3] The use of hCG in threatened miscarriage has not been extensively studied. A recent RCT of 183 women showed that hCG supplementation did not decrease the miscarriage rate in threatened miscarriages[125] (10/83 [12%] vs. 10/91 [11%], OR 1.11, 95% CI 0.63–1.6). These results were presented despite the increase in serum levels of progesterone and oestradiol of the patients after initiating hCG supplementation. One possibility is that the trial was too small to show any detectable benefit.

In recurrent miscarriages, hCG has also not been shown to reduce miscarriage rates.[126,127] However, in a subgroup of patients with oligomenorrhoea and idiopathic recurrent miscarriages, hCG supplementation showed a reduction in the miscarriage rate from 11/13 (85%) to 4/10 (40%) in one study,[127] (OR 0.121, 95% CI 0.01–1.16). However, considering the small number of participants that fell into this group (23 out of 81 participants) and the lack of statistical significance, its use is unlikely to be widespread. Although no significant foetal abnormalities were seen in studies, hCG is a category X drug under the US FDA classification, based on literature reports of foetal forelimb and central nervous system abnormalities in mice.[69]

Recommendations

All three colleges stated that hCG supplementation has not shown any significant benefit in improving pregnancy outcome in recurrent miscarriages.[49-51] In addition, RCOG recommends the use of hCG supplementation in early pregnancy only in the context of RCTs.[49]

Uterine relaxing agents

Increased uterine activity is associated with threatened miscarriage and morphine was introduced in the 19th century in the belief that it would reduce contractions and prolong pregnancy. Morphine has now been replaced with antispasmodic drugs and myometrial relaxants (tocolytic agents). These agents are reportedly more commonly used in Latin America as compared to Europe and the US. Antispasmodic drugs (scopolamine butylbromide) are atropine-like agents commonly used to treat conditions such as intestinal, renal and hepatobiliary colic. They have anticholinergic side effects such as dry month, thirst, blurred vision, difficulty in swallowing and cardiac arrhythmias. These drugs can cross the placenta barrier.

Myometrial relaxants (fenoterol, isoxsuprine) are β2 adreno-receptor agonists, a group of drugs that are usually used to treat asthma. Their side effects include palpitations, nausea and vomiting and increase in blood glucose levels with a drop in serum potassium levels. Perhaps due to the infrequent use of uterine relaxing agents in the management of miscarriages, there has been no recent RCT conducted to study these drugs. A Cochrane review in 2005 found only one RCT done in 1986 that studied the effect of buphenine hydrochloride on threatened miscarriage in 170 women.[128] This study showed a lower risk of actual miscarriage or stillbirth when the beta agonist was used (8/85 [9%] vs. 32/85 [38%], OR 0.17, 95%CI 0.06–0.42).

Two other studies not included in the review used fenoterol hydrobromide[129] and indomethacin,[130] as an agent respectively, but no improvement was seen in the pregnancy outcome with treatment. There is thus a dearth of trials conducted to study the effects of uterine relaxing agents in the management of miscarriages. However, the results of the RCT on buphenine hydrochloride seem promising. If similar findings are found in future trials on this drug, it may then be more widely used.

Immunotherapy

The foetus contains paternal antigens that are foreign

to the mother, the reasons that the mother is able to tolerate her semi-allogenic foetus are still not fully elucidated. When the immune system first encounters a foreign antigen, the result is either sensitisation, which will activate the maternal immune system, or tolerance. For a pregnancy to survive, tolerance has to be induced instead of sensitisation. It has been postulated that some cases of recurrent pregnancy loss is thought to be due to immunological rejection of the foetus resulting from a breakdown in the mechanisms that would normally prevent sensitisation. This is based on the following clinical observations: changing partners can resolve the problem of recurrent miscarriages; these patients reject skin grafts from their partners sooner than controls, and that the outcome of recurrent miscarriages appears to be improved by immunotherapy induced by blood transfusions.[3] However, consistent results have not been obtained to confirm this hypothesis. There also appears to be no definite difference in immune system components, such as natural killer cells, cytokines and human leukocyte antigen between women who suffer from recurrent miscarriages and those who do not. Despite this lack of evidence, doctors have tried many types of immunotherapy to try inducing tolerance of the mother to the foetus. These stratedies include paternal cell immunisation, third-party donor cell immunisation, trophoblast membrane immunisation and intravenous immunoglobulin.

Paternal cell immunisation

The first successful trial of immunotherapy in women suffering from recurrent pregnancy loss was done in 1985, where women were injected with purified lymphocytes from their husband's blood.[131] A Cochrane review done in 2005 looked at 12 trials studying 641 women, and concluded that the live birth outcome between the treatment and non-treatment groups were not statistically different.[132] In the pooled data, 205/316 (65%) live births were seen in the treatment group, as opposed to 195/325 (60%) in the control group (OR [Peto] 0.70, 95% CI 0.19–2.56). Paternal blood cell immunisation is also associated with risk of being infected with blood borne pathogens, such as hepatitis B virus and the human immunodeficiency virus. Other complications include local reaction at the injection site, blood group alloimmunisation and adverse pregnancy outcomes, such as placental abruption and intrauterine growth restriction. The FDA has not approved these products for routine use and they can only be administered in the context of an approved clinical trial.[132]

Intravenous immunoglobulin (IVIG)

IVIG has been increasingly used in some centres for the prevention of recurrent miscarriages. The Cochrane review concluded, after analysis of eight trials and 305 women, that there was no significant effect of IVIG on pregnancy outcome.[132] 102/159 (64%) live births were seen in the treatment group, whereas 85/144 (59%) live births were seen in the control group (OR [Peto] 0.98, 95% CI 0.61–1.58). This result was statistically insignificant. It has been suggested if IVIG were only used for mothers with idiopathic recurrent pregnancy losses, the efficacy of treatment can be increased.[133] It must be noted that infusion of IVIG has its risks, such as life-threatening anaphylaxis and viral transmission,[134] in addition to its extremely high cost.

Third party donor cell immunisation

The Cochrane review covered three trials on third party donor cell immunisation. The live birth rates for treatment and control groups were 42/67 (63%) and 53/89 (60%) respectively (OR [Peto] 1.39, 95% CI 0.68–2.82). The results were statistically insignificant.

Trophoblast membrane immunisation

Only one trial on trophoblast membrane immunisation was covered in the Cochrane review. The live birth rates for the treatment and control groups are 8/17 (47%) and 14/20 (70%) respectively (OR [Peto] 0.40, 95% CI 0.11–1.45). The results were again statistically insignificant.

Recommendations

The RCOG and SCOG maintained that all the above-mentioned methods of immunotherapy do not improve the live birth rate.[49,51] In addition, the SCOG recommended that the above-mentioned methods of immunotherapy should not be practised.[51] The ACOG maintained that mononuclear cell (leucocyte) immunisation and IVIG are not effective in preventing recurrent pregnancy loss.[50]

CONCLUSION

All patients with recurrent or threatened miscarriages should receive supportive care and close supervision. Appropriate investigations should be carried out to elicit any treatable cause for recurrent miscarriages. For many women without any identifiable pathology, there is very good prognosis for the next pregnancy, even without treatment. Thus, there is a need for appropriate counselling and reassurance in view of this fact. Aggressive treatment without sound scientific evidence may prove more harmful than beneficial. When a specific aetiological factor can be identified, directed treatment is warranted. Women with APS should receive a course of low dose aspirin and heparin. There is some evidence supporting the

use of heparin in women with inherited thrombophilias. For women with PCOS, consideration may be given for starting metformin prior to conception, at 500–2,550 mg daily, and continued up to the first trimester in those who do get pregnant, as there is some evidence that metformin reduces the miscarriage rate.

In women upon whom bromocriptine has been started on for ovulation induction in view of hyperprolactinaemia, consideration may be given to stop the use of bromocriptine when pregnancy is diagnosed, as there is inadequate evidence to show that bromocriptine reduces the miscarriage rate. For the majority with idiopathic threatened miscarriages or recurrent miscarriages, treatment is empirical. There is early evidence that dydrogesterone reduces miscarriage rates. Consideration should be made for the screening of BV in all women between 10–22 weeks and treatment with oral or vaginal clindamycin, if the swab is positive. The role of expensive IVIG is controversial in this group, whereas more trials are required to establish the treatment role of buphenine hydrochloride, a uterine relaxing agent.

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME
Multiple Choice Questions (Code SMJ 200712A)

	True	False
Question 1. Regarding causes of miscarriages:		
(a) Antiphospholipid syndrome (APS) is associated with first trimester miscarriages.	☐	☐
(b) Chromosomal abnormalities are associated with both first and second trimester miscarriages.	☐	☐
(c) Diabetes mellitus is an important cause of miscarriages even when well controlled.	☐	☐
(d) Congenital uterine abnormalities increase the risk of second trimester miscarriages.	☐	☐
Question 2. Recommended routine investigations for patients with recurrent miscarriages include:		
(a) Karyotyping of miscarried foetus(es).	☐	☐
(b) Pelvic ultrasonography.	☐	☐
(c) Screening for TORCH infection.	☐	☐
(d) Screening for diabetes mellitus and thyroid disease, even if asymptomatic.	☐	☐
Question 3. Regarding recurrent miscarriages:		
(a) It is defined as three or more consecutive miscarriages.	☐	☐
(b) Clindamycin is useful in those with recurrent second trimester miscarriages and/or preterm labour, and who have been screened and tested positive for bacterial vaginosis.	☐	☐
(c) Immunotherapy has been shown to work in couples with HLA incompatibility.	☐	☐
(d) Combination therapy of aspirin and heparin has been shown to improve future outcome in women with antiphospholipid syndrome (APS).	☐	☐
Question 4. The following statements about risk of miscarriages are true:		
(a) The prospective risk of miscarriage at ten weeks is defined as the number of miscarriages occurring from week ten divided by the remaining pregnancies on week ten.	☐	☐
(b) The risk of miscarriage is dependent on maternal age.	☐	☐
(c) The risk of miscarriage is not dependent on paternal age.	☐	☐
(d) The risk of miscarriage is not dependent on the number of previous miscarriages.	☐	☐
Question 5. For idiopathic recurrent miscarriages, the following have been shown to be useful:		
(a) Diethylstibesterol.	☐	☐
(b) Antibiotics.	☐	☐
(c) Psychological support.	☐	☐
(d) Aspirin.	☐	☐

Doctor's particulars:

Name in full: _____

MCR number: _____ Specialty: _____

Email address: _____

SUBMISSION INSTRUCTIONS:
(1) Log on at the SMJ website: **www.sma.org.sg/cme/smj** and select the appropriate set of questions. (2) Select your answers and provide your name, email address and MCR number. Click on "Submit answers" to submit.

RESULTS:
(1) Answers will be published in the SMJ February 2008 issue. (2) The MCR numbers of successful candidates will be posted online at **www.sma.org.sg/cme/smj** by 15 February 2008. (3) All online submissions will receive an automatic email acknowledgment. (4) Passing mark is 60%. No mark will be deducted for incorrect answers. (5) The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council.

Deadline for submission: (December 2007 SMJ 3B CME programme): 12 noon, 25 January 2008