Guides for practitioners

Recurrent miscarriage: principles of management

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Recurrent miscarriage is a heterogeneous condition which has many possible underlying causes. Ideally, couples with the problem should be managed in a dedicated miscarriage clinic, with thorough investigations according to a protocol, with structured history and investigation sheets. Counselling is an important feature and may be provided by a specially trained counsellor, or specialized nurse appropriately trained in counselling. Counselling should include an explanation of the possible underlying causes of the condition, and of the prognosis of each of the conditions. There is no definite cause of miscarriage in approximately half of the patients. No treatment is needed in this group, apart from reassurance and tender loving care. Treatment of unproven value, for example progesterone support in early pregnancy, should not be offered. Treatment offered empirically or as part of a research project should have a sound scientific and statistical basis, and should include careful counselling with informed consent of the patient. There are many controversial issues in the management of recurrent miscarriage; consequently, there is a need for locally agreed guidelines for management. Women who conceive again should be offered regular monitoring, including serial ultrasonography in the first trimester of pregnancy. An active audit programme to review regularly the various outcome measures set against defined targets should be established in the clinic.

Key words: controversy/counselling/guideline/management/recurrent miscarriage

Introduction

A history of three or more consecutive spontaneous miscarriages occurs in ~0.5–3% of women (Daya, 1993; Tulppula et al., 1993; Katz and Kuller, 1994). This recurrent loss of pregnancy is often distressing for the patient and frustrating for the physician. In most cases, the cause is not apparent and often requires intensive and expensive clinical and laboratory investigations, despite which there is still a limited understanding of recurrent pregnancy loss. The aim of this article is to discuss the principles of management of recurrent miscarriage.

Identification of aetiological factors

Recurrent miscarriage is a heterogeneous condition. It is associated with a number of conditions:

- Parental chromosomal anomalies
- Lupus anticoagulant and antiphospholipid syndrome
- Structural uterine anomalies, including congenital anomalies (uterine septum, bicornuate uterus) and acquired anomalies (submucous fibroids, intrauterine adhesions)
- Cervical incompetence/weakness
- Polycystic ovarian disease/hypersecretion of luteinizing hormone (LH)
- Other prothrombotic states, including antithrombin III deficiency, protein C or protein S deficiency/resistance and thrombocythaemia
- More rare or less certain causes include endometrial retardation (luteal phase defect), homocysteaemia, environmental factors, maternal chronic disease, hyperprolactinaemia, bacterial vaginosis, thyroid autoantibodies, hypothyroidism, absence of antipaternal cytotoxic antibodies, and increased HLA sharing

The common causes of recurrent miscarriage are shown in Table I.

The underlying causes of mid-trimester loss are rather different to those responsible for first trimester loss. Conditions such as structural uterine anomaly, cervical incompetence, bacterial vaginosis and other vaginal infections are recognized causes of mid-trimester loss which rarely cause first trimester miscarriage. Lupus anticoagulant, on the other hand, may produce either first trimester or second trimester loss.

It follows from the above that thorough investigation is necessary to establish the underlying cause of recurrent miscarriage. Because of the heterogeneity of the condition, and the many possible underlying causes, various tests are necessary. Ideally the results of the investigations should be tabulated in a structured investigation sheet with abnormal results highlighted. The structured investigation sheets used in our clinic are shown in Table II.

A number of investigations which used to be carried out in our recurrent miscarriage clinic have now been deleted: antipaternal cytotoxin antibody, HLA typing, endometrial swab for Chlamydia, virology study including TORCH screen, random glucose, blood group, auto-antibody screen and renal function test. The change has been based on the results of our own audit and other recently published reports suggesting that they are of little importance in the management of recurrent miscarriage.

The diagnosis of cervical incompetence (weakness) poses a difficult problem (MRC/RCOG Working Party on Cervical Cerclage, 1993). It is usually based on a previous history of second trimester loss(es), occurring in the absence of recognized uterine contractions. Vaginal ultrasonography may be helpful to detect early features of cervical weakness e.g.
structured pregnancy follow-up sheets
patient information leaflets
allocation of sufficient time for consultation
specialist nurse
 counselling
ultrasound facilities

The clinic should be held weekly and should include two medical and two nursing staff in order to provide cover for leave. Based on the experience of the Jessop Hospital for Women, Sheffield, there is a need for at least one recurrent miscarriage clinic per 2 million population. In other words, there is a need for about 30 dedicated recurrent miscarriage clinics in Britain. An hour should be allocated for each initial consultation. Counselling may be provided by a specially trained counsellor, or specialist nurse appropriately trained in counselling.

Women who conceive again should be offered regular weekly follow up with ultrasonography, primarily for reassurance which is part of the ‘tender loving care’ treatment. However, miscarriage may still recur despite supportive care and treatment. It is known that expectant management of selected cases of miscarriage has a similar outcome to surgical evacuation (Nielsen and Hahlin, 1995). Expectant management does not seem to adversely affect future fertility (Blohm et al., 1997) and may instead reduce the formation of intrauterine adhesions and scarring of the endometrium. Further studies are required to establish the role of expectant management, but a dedicated miscarriage clinic or early pregnancy assessment unit provides an appropriate setting for discussion of the treatment options.

Unexplained recurrent miscarriage

There is no definite cause of miscarriage in about half of the patients, so that no specific treatment is needed in this group apart from reassurance and tender loving care. The value of tender loving care has been shown to improve pregnancy outcome in two controlled studies (Table III). The Stray Pederson study may be subject to a degree of bias, since only those patients living in close proximity to the hospital received tender loving care. However, in a recent retrospective study, Clifford et al. (1997) confirmed that supportive care in early pregnancy conferred a significant beneficial effect on pregnancy.

### Table I. The common causes of recurrent miscarriage: a comparison of data from three miscarriage clinics

<table>
<thead>
<tr>
<th></th>
<th>Stephenson (1996) (n = 197)</th>
<th>Clifford et al. (1994) (n = 500)</th>
<th>Sheffield (unpublished data) (n = 160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal paternal karyotype (%)</td>
<td>3.5</td>
<td>3.6</td>
<td>25</td>
</tr>
<tr>
<td>Antiphospholipid antibody (%)</td>
<td>17</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luteal phase deficiency (%)</td>
<td>17</td>
<td>N/A</td>
<td>28</td>
</tr>
<tr>
<td>Hypothyroidism (%)</td>
<td>3</td>
<td>N/A</td>
<td>06</td>
</tr>
<tr>
<td>Hyporesponse LH/PCO (%)</td>
<td>N/A</td>
<td>57</td>
<td>97</td>
</tr>
<tr>
<td>Uterine anomalies (%)</td>
<td>14</td>
<td>1.8</td>
<td>9</td>
</tr>
<tr>
<td>Cervical incompetence (%)</td>
<td>2</td>
<td>N/A</td>
<td>38</td>
</tr>
<tr>
<td>Unexplained (%)</td>
<td>43</td>
<td>N/A</td>
<td>45</td>
</tr>
</tbody>
</table>

N/A = not addressed.

### Table II. Investigation result summary sheet used in the Sheffield miscarriage clinic, 1997

**Investigations (use red ink for abnormal results)**

<table>
<thead>
<tr>
<th></th>
<th>Date performed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromosome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid function test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticardiolipin Ab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clotting study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D5 LH/FSH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D21 progesterone/E2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic scan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hysteroscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH-timed endometrial biopsy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Male</th>
<th>Date performed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

shortening or funnelling, but ultrasonography or radiography has not been found to be helpful in the diagnosis of cervical incompetence before pregnancy.

While it is not always feasible or necessary to carry out the complete set of investigations, one should be aware that, from time to time, dual pathology may occur. An example is that of the coexistence of uterine septum and cervical incompetence, or of LH and lupus anticoagulant syndrome. The same is true of infertility practice, in which sometimes tubal pathologies may coexist with ovulatory disorders.

**Dedicated miscarriage clinic**

Women with recurrent miscarriage require a careful history, thorough investigations, sympathetic explanation and counselling. Ideally, they should be managed in a dedicated miscarriage clinic with the following features:

- local clinic protocol
- structured history and investigation sheets

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outcome: the miscarriage rate of those who did and did not receive supportive care was 26 and 51% respectively ($P < 0.002$).

It is now accepted that tender loving care is associated with a significantly reduced miscarriage rate, compared to a control group receiving ‘ordinary’ care. Tender loving care should include the following:
- care provided in a specialized, dedicated clinic
- psychological support
- easy access to a named contact
- ample opportunity to discuss concerns
- close monitoring, including ultrasonography, during the first trimester of pregnancy
- appropriate reassurance
- staff should be caring, helpful and never dismissive

Treatment with beneficial value

Apart from tender loving care which is of value especially in women with unexplained recurrent pregnancy loss, a number of treatments have been shown to improve the pregnancy outcome. Subcutaneous heparin with or without aspirin may be useful in women with lupus anticoagulant or who tested positive for anticardiolipin antibodies (Rosove et al., 1990; Cowchock et al., 1992; Balasch et al., 1993; Rai et al., 1997). Cervical suture is of value in women with mid-trimester miscarriage associated with cervical incompetence. Hysteroscopic or conventional metroplasty improves pregnancy outcome in women with recurrent mid-trimester loss associated with septate, subseptate or bicornuate uterus (Candiani et al., 1990; Ayhan et al., 1992; Fedele et al., 1993; Pabuccu et al., 1995). However, the value of surgery in women with uterine anomaly and with a history of early first trimester losses is less certain (Ben-Rafael et al., 1991) and the value of myomectomy in women with mid-trimester loss and submucous or intramural fibroids is also uncertain, although two previous reports suggested a beneficial effect in the latter situation (Buttram and Reiter, 1981; Egwuatu, 1989). Surgical treatment should be individualized, depending on the previous history and following proper counselling.

Treatment of unproven value should not be offered

Progesterone support in early pregnancy has been shown in meta-analysis to be of no proven value, although its use is still controversial. Human chorionic gonadotrophin (HCG) support in early pregnancy has been found to be of no proven value, except in those with oligomenorrhoea prior to conception (Quenby and Farquharson, 1993). Immunotherapy involving paternal leukocyte immunization is controversial. It may be of benefit in a highly selective group of subjects (Carp et al., 1997), but is considered by many gynaecologists to be of unproven value. It is no longer offered in our unit, and many other established centres.

Research programme

Treatment offered empirically or as part of a research project should have a sound scientific and statistical basis, and should include careful counselling with informed consent from the patient.

Recent recurrent miscarriage is a relatively uncommon condition, and because it is a heterogeneous condition, each specific underlying cause is necessarily rare. Before embarking on any controlled trial, it is important to appreciate that it may be virtually impossible to conduct a study on rare causes of a rare condition. The number of patients required in a randomized, controlled trial to determine if a specific treatment would significantly increase the success rate is summarized in Table IV.

The number of patients required is dependent on the prevalence of that specific cause among women with recurrent miscarriage, and on the projected success rate in the treatment and control (i.e. not receiving treatment) groups. For example, assuming that subseptate uterus is encountered in 5% of women with recurrent miscarriage, that the success rate in the control group is 50% and the success rate in the treatment group is 80%, then the number of patients with recurrent miscarriage required in the clinical trial is 1800. One can therefore understand why there are so many unresolved issues in recurrent miscarriage. A further example is the case of endometrial factor in recurrent miscarriage. A number of studies have shown that recurrent miscarriage is associated with abnormal morphological development of the endometrium in the luteal phase (Table V).

Moreover, there is also biochemical evidence to suggest the existence of an endometrial factor in recurrent miscarriage. The levels of endometrial protein PP14 were found to be reduced in plasma of women with recurrent miscarriage (Tulpala et al., 1995) and in uterine flushings (Dalton et al., 1995). In addition, the amount of glycoprotein MUC-1 was also found to be reduced in the endometrium of women with recurrent miscarriage (Hey et al., 1995). However, there is no established treatment for recurrent miscarriage associated with endometrial factor, simply because no randomized controlled trial has ever been conducted on this condition. Assuming that the successful outcome in a given treatment group is 80%, in the control group it is 60%, and assuming that the prevalence of endometrial defect among women with recurrent miscarriage is 25%, then the number of women with recurrent miscarriage required for a clinical trial is 800. It is clearly beyond what can be achieved in a single recurrent miscarriage clinic and the only answer is a multicentre trial.

A clear understanding of the dilemma encountered in clinical trials concerning recurrent miscarriage is of fundamental importance, in order that clinical trials are not started without careful statistical considerations.
Management of recurrent miscarriage

Table IV. An analysis of how the number of patients with recurrent miscarriage required for randomized, controlled study to evaluate the result of a particular treatment for a specific condition is influenced by the prevalence of that condition among the population with recurrent miscarriage and its projected success rate without treatment (i.e. in the control group)

<table>
<thead>
<tr>
<th>Projected success rate in control group (%)</th>
<th>Prevalence of condition in recurrent miscarriage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>100  40  30  20  10  5</td>
</tr>
<tr>
<td>70</td>
<td>740  1850  2467  3700  7400  14 800</td>
</tr>
<tr>
<td>60</td>
<td>200  500  667  1000  2000  4000</td>
</tr>
<tr>
<td>50</td>
<td>90  225  300  450  900  1800</td>
</tr>
<tr>
<td>40</td>
<td>50  125  167  250  500  1000</td>
</tr>
<tr>
<td>30</td>
<td>30  74  99  148  296  592</td>
</tr>
</tbody>
</table>

Assumption: treatment success = 80%. α = 0.05, β = 0.8.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patient number</th>
<th>Number of previous miscarriages</th>
<th>% Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant et al. (1959)</td>
<td>75</td>
<td>3</td>
<td>65</td>
</tr>
<tr>
<td>Llusia (1962)</td>
<td>50</td>
<td>3</td>
<td>38</td>
</tr>
<tr>
<td>Tho et al. (1979)</td>
<td>100</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>Balasch and Vanrell (1986)</td>
<td>60</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>Davidson et al. (1987)</td>
<td>25</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>Daya et al. (1988)</td>
<td>65</td>
<td>not stated</td>
<td>40</td>
</tr>
<tr>
<td>Tulppala et al. (1991)</td>
<td>46</td>
<td>3</td>
<td>17.4</td>
</tr>
<tr>
<td>Sheffield, unpublished data</td>
<td>70</td>
<td>3</td>
<td>29</td>
</tr>
</tbody>
</table>

Comprehensive service

As recurrent miscarriage is a heterogeneous condition, and is associated with a number of possible underlying causes, a wide range of clinical skills is required for optimal care: transvaginal scan, hysteroscopy and hysteroscopic surgery for the treatment of uterine septum, submucous fibroid, intrauterine adhesions and Asherman’s syndrome, laparoscopic surgery, microsurgery, metroplasty including Strassman’s metroplasty, and open myomectomy; cervical suture, including the abdominal approach for those with badly scarred cervix.

Controversial issues

There is a need for a locally agreed protocol, to include management strategy for controversial areas. As discussed above, there are many controversial areas in the management of recurrent miscarriage. One should be willing to admit to patients that the management of certain conditions associated with recurrent miscarriage is controversial, but one should be prepared to give an opinion, including a management plan. However, one should also be able to accept alternative views and help patients to seek treatment not offered in the local clinic. An example is immunotherapy involving paternal leukocyte immunization. We explain to our patients that this is controversial (for review, see Bulletti et al. 1996; Christiansen, 1996), and that the treatment is no longer offered in our clinic, although it used to be available. The clinic and the laboratory staff do not carry out the immunization procedure, since they feel there is a lack of convincing evidence of benefit. However, the staff would be willing to refer the patient to another centre which provides the treatment, if this is requested.

Counselling

Counselling should be offered to each patient attending a recurrent miscarriage clinic. It should include an explanation of the possible underlying causes of the condition, and of the prognosis of each of the conditions. For example, after three consecutive unexplained miscarriages, the patient should be
told that there is a 60–70% chance that the next pregnancy will be successful (Edmonds, 1992; Tulppala et al., 1993). However, the probability of a live birth is reduced by 23% for each additional miscarriage beyond three (Daya, 1993). After six or more miscarriages, the chance of success is reduced to 47% (Clifford et al., 1997). Counselling is of crucial importance for those who continue to suffer further miscarriages whilst receiving treatment from the clinic. In this situation, they should be counselled by the most senior member of the medical staff. In some cases, the patient should be advised against further attempts, and other alternatives including ovum donation, surrogacy, adoption or acceptance discussed. The value of ovum donation in the management of recurrent miscarriage is controversial, although Remohi et al. (1996) reported favourable results in a small number (n = 8) of subjects. Perhaps, it may be discussed in women >40 years of age or whose serum follicle-stimulating hormone concentration is significantly elevated.

Audit
An active audit programme to regularly review the various outcome measures set against defined targets should be established in the recurrent miscarriage clinic. Outdated investigations and treatment should be discarded. Investigations and treatments of proven value published in recent reports should be incorporated into the local management protocol and the results monitored.

References

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