CHAPTER 14

Miscarriage

1 Introduction
2 Confirmation of fetal life
3 Prevention of miscarriage
   3.1 Bed-rest and hospitalization
   3.2 Hormones
      3.2.1 Diethylstilbestrol
      3.2.2 Progestogens
      3.2.3 Human chorionic gonadotrophin
      3.2.4 Luteinizing hormone releasing hormone agonists
   3.3 Immunotherapy
   3.4 Interventions for women with autoimmune conditions
   3.5 Other medications
4 Care following spontaneous miscarriage or missed abortion
   4.1 ‘Wait and see’ versus surgical evacuation
   4.2 Medical versus surgical evacuation
   4.3 Surgical evacuation
      4.3.1 Analgesia versus general anaesthetic
      4.3.2 Suction versus conventional curettage
      4.3.3 Prophylactic antibiotics
5 Conclusions

1 Introduction

Miscarriage is the spontaneous loss of a pregnancy before the fetus is viable. Caregivers and family may sometimes not consider this to be as tragic a loss as fetal demise later in pregnancy, but it often results in a similar degree of mental suffering and anguish for the woman and her partner. Miscarriage is common. One in seven clinically recognized pregnancies will miscarry, usually during the first 14 weeks of pregnancy. Over half the babies who are miscarried during this period have a chromosomal abnormality. Other factors that influence the risk of
miscarriage include maternal age over 35 years, multiple pregnancy, polycystic ovaries, autoimmune disorders, poorly controlled diabetes, and having had two or more previous miscarriages.

Recurrent early pregnancy loss is suffered by 1–2% of couples. A number of interventions have been proposed and used in efforts to prevent miscarriage, particularly for women perceived to be at greater than average risk. Chief among these have been the prescription of bed-rest, either at home or in hospital, and the use of various hormones. For each woman, the choice of care should depend on evidence of effectiveness and on her personal preferences.

Psychological support for women who are at high risk of early pregnancy loss has not been formally evaluated in randomized trials. However, non-randomized comparisons suggest that such support alone may be associated with an improved pregnancy outcome. Proper evaluation of additional interventions is, therefore, of particular importance for the care of these women.

2 Confirmation of fetal life

Ultrasound has the ability to establish rapidly and accurately whether a fetus is alive or dead, and to predict whether a pregnancy is likely to continue when there is bleeding (threatened miscarriage). This ability has rationalized the care of women with threatened miscarriage in early pregnancy. The gestational sac can be visualized by 6 weeks menstrual age, and the fetus by 7 weeks. As soon as the fetus can be demonstrated with ultrasound, it can be measured and its viability confirmed by detection of heart movement. Fetal life is confirmed by observation of heart pulsation, and fetal death by its absence. Except in very early pregnancy, there should be no doubt about the diagnosis. Blighted ova, which constitute the largest group of early pregnancy failures, are diagnosed by the inability to detect a fetus on careful examination. When the sac is small, the pregnancy without an embryo has to be differentiated from the normal, very early pregnancy by a repeat ultrasound examination. Missed abortion can be diagnosed by absence of heart movement. The small group of pregnancies in which the embryo is alive but destined to miscarry cannot be predicted with certainty by ultrasound. These constitute less than 15% of the total number of miscarriages. Although a reduction in amniotic fluid volume, diminished fetal activity, or the presence of large intra-uterine hematomas may suggest a poor prognosis, there are no specific ultrasound features.
3 Prevention of miscarriage

3.1 Bed-rest and hospitalization
Bed-rest is often recommended for women whose pregnancies are complicated by a number of conditions, including a history of recurrent miscarriage or early bleeding in the present pregnancy. Women with these problems may be advised to rest in bed at home and in some cases may be admitted to hospital, to facilitate bed-rest and to permit closer investigation and surveillance of their pregnancy.

The extent to which women are advised to rest in bed varies considerably, but such advice is very common in some places. The intervention is not innocuous. Bed-rest and immobilization can increase the risk of thromboembolic disease. Both confinement to bed at home and hospitalization during pregnancy may result in great financial and social costs for pregnant women and their families, especially those with children. Antenatal hospitalization is often a disruptive and stressful experience involving separation of women from their families at a time of great anxiety. In addition, adoption of this policy has brought substantial costs to the health services.

The only reported attempt to undertake any form of controlled evaluation of the effectiveness of bed-rest in the management of threatened miscarriage was made over 45 years ago. The results of this study give no support to the view that a policy of recommending bed-rest reduces the risk of miscarriage after bleeding occurs in early pregnancy.

Bed-rest is sometimes advised for many days if spotting or bleeding is persistent, and this may cause considerable family disruption. Yet, in a substantial proportion of these pregnancies, the fetus is already dead. The presence of a non-viable pregnancy can now be demonstrated by ultrasound and no form of care can preserve these pregnancies.

Even with a viable embryo, there is no valid basis for advising bed-rest. The preferences of individual women should, therefore, be the deciding factor in whether or not they should rest, and this need not be in bed. Some women may feel they wish to rest. Women should be encouraged to do whatever feels best for them, although it would seem prudent to advise against prolonged immobilization.

3.2 Hormones
Over the last fifty years, various hormones have been given to pregnant women in attempts to prevent miscarriage, as well as fetal death,
preterm delivery, and other adverse outcomes of pregnancy. Studies in the mid-1930s suggested a link between abnormal hormone levels and complications of pregnancy. The conclusion that inadequate hormone secretion meant that additional hormones should be administered is a classic example of the danger of applying pathophysiological reasoning to clinical practice without appropriate evaluation.

3.2.1 Diethylstilbestrol

The synthetic hormone, diethylstilbestrol, was administered to pregnant women on a wide scale for over thirty years. Based on animal studies and uncontrolled observations in humans, it was thought that it would be effective in preventing a variety of adverse outcomes. This hypothesis appeared to be supported by studies using observational data, but studies with contemporary controls did not substantiate the postulated beneficial effects. By the mid-1950s these controlled trials, individually and collectively, indicated that diethylstilbestrol did not reduce the risk of miscarriage, pre-eclampsia, low birthweight, preterm birth, stillbirth, neonatal death, nor increase the likelihood of a woman's pregnancy resulting in a surviving infant.

Thus, strong evidence was available by the mid-1950s to challenge the claims made on behalf of diethylstilbestrol. The drug should have been abandoned at that time, or prescribed only in the context of further trials. Despite this lack of evidence of benefit, obstetricians continued to use diethylstilbestrol until the 1970s, when several cases of vaginal adenocarcinoma (a very rare form of cancer in women less than 50 years old) were reported in young women whose mothers had received diethylstilbestrol while pregnant with them.

The randomized cohorts of women and their children generated by three of the trials have been studied for between 20 and 40 years after receiving diethylstilbestrol or placebo. The data suggest that there may be an increased risk of breast cancer in the women, and they clearly demonstrate an increased incidence of psychiatric illness and urogenital abnormalities in the children of both sexes. These abnormalities include benign tumours, vaginal adenosis, vaginal/cervical ridges, abnormal cervical smears, amenorrhoea/oligomenorrhoea, and infertility among the daughters, and low sperm density and other urogenital abnormalities among the men. The long-term adverse effects of the use of diethylstilbestrol in pregnancy that later became evident could have been minimized if more attention had been paid to the results of the controlled trials showing the drug to be ineffective.
3.2.2 Progestogens
Pregnancy loss in the first 3 months is associated with low serum progesterone. One possible explanation for this is that low progesterone causes miscarriage; another is that a failing pregnancy leads to reduced progesterone levels. Several randomized trials have evaluated the use of progestogens in early pregnancy. There is no evidence to suggest that they reduce the risk of miscarriage, stillbirth, or neonatal death, in women either with bleeding (threatened miscarriage) or with a history of recurrent miscarriage. The trials, however, have not been large enough to exclude an important effect, in either direction (increase or decrease in the risk of miscarriage), and in many of the studies ultrasound examinations were not done. These could have shown the fetus to be already dead, so that there may have been few pregnancies in which the progestogens could have been effective.

One small trial evaluated combined progesterone and estrogen for women having in vitro fertilization, started at the time of embryo transfer. This study has only reported outcome during the first 3 months of pregnancy, however.

Although the progestogen follow-up studies have been largely anecdotal and uncontrolled, there have been suggestions from some studies that fetal exposure to the drugs may increase the risk of esophageal atresia, cardiac, neurological, neural tube and other major malformations, and female masculinization, or ‘tom-boyishness’ in girls. Other studies, however, have failed to detect these adverse effects, and so the safety of progestogens, like their postulated benefits, remains an open question.

3.2.3 Human chorionic gonadotrophin
Data from the several controlled trials that have examined the effects of human chorionic gonadotrophin on the risk of miscarriage in women with a past history of repeated early pregnancy loss suggest that this treatment may be effective in preventing recurrent miscarriage.

The results of these trials must be interpreted with great caution because of methodological weaknesses in the studies. They need to be replicated in good quality randomized trials before any recommendation can be made about the use of human chorionic gonadotrophin in practice.

3.2.4 Luteinizing hormone releasing hormone agonists
High levels of luteinizing hormone are associated with early miscarriage. For women who have had repeated early pregnancy loss, it is
therefore plausible that suppressing secretion of luteinizing hormone with a luteinizing hormone-releasing hormone agonist may reduce the risk of miscarriage. One trial has compared suppression of luteinizing hormone secretion, combined with low-dose ovulation induction, with spontaneous ovulation. This study was too small for any reliable conclusions about the effect on pregnancy loss.

3.3 Immunotherapy
During pregnancy, a woman’s immune system is modified to allow her body to accept the growing fetus, and not to reject it as foreign tissue. Failure of this response, for whatever reason, is one possible but unproven cause of early pregnancy loss. Immunologic laboratory tests have no predictive value for pregnancy success, and should be abandoned. Immunotherapy has been suggested as a possible treatment for some women with an unexplained history of recurrent miscarriage: those with no identifiable cause and the same partner for each pregnancy. The most commonly used form of immunotherapy is injection of the women with her partners white blood cells. White cells from a third party, trophoblast membrane, and immune globulin have also been used.

Initial uncontrolled studies of immunotherapy for recurrent miscarriage suggested a beneficial effect. To date, however, these benefits have not been confirmed in trials with proper controls. Although the use of paternal white cells may lead to a small reduction in the risk of miscarriage, this needs to be balanced against the possible serious adverse effects, which have not been adequately quantified. These potential hazards include anaphylactic shock, transfusion reactions, and hepatitis. In addition, immunotherapy is expensive and so, even if further trials do confirm a worthwhile benefit, its usefulness will be limited by the high cost.

3.4 Interventions for women with autoimmune conditions
Around 15% of women with recurrent early pregnancy loss have antibodies to some of their own cells, autoimmune factors. These include antiphospholipid antibodies, lupus anticoagulant, and anticardiolipin antibodies. In contrast, autoimmune factors are present in 2% of women with a normal obstetric history. Women with autoantibodies have a very high risk of further miscarriage, and various interventions have been tried in the hope of improving their chance of having a healthy baby.
In theory, corticosteroids might improve the chance of these women having a healthy baby. The two trials that have evaluated steroid therapy, with or without aspirin, were too small for firm conclusions about the effect on having a liveborn baby, but they do suggest an increase in the risk of preterm delivery and of complications for the mother.

Two trials have evaluated low-dose heparin, injected subcutaneously (under the skin) and aspirin for women with autoantibodies and a history of recurrent pregnancy losses. The results of these studies are promising in terms of improving the chances of having a liveborn baby, although the risk of pregnancy complications, particularly preterm birth, remained high. Confirmation in larger trials is needed before any recommendation can be made about the overall effectiveness and safety of heparin treatment for women with recurrent pregnancy loss.

3.5 Other medications
The use of indomethacin for threatened miscarriage has been tested in one small trial, and no effect on the rate of miscarriage was demonstrated. Small trials evaluating tocolytic and antispasmodic medications suggest a reduction in the rate of miscarriage, but methodological flaws in these studies mean that these results should be interpreted with caution.

4 Care following spontaneous miscarriage or missed abortion
If miscarriage occurs within the first few weeks of pregnancy, it is usually complete, with the gestational sac expelled intact, and rarely requires admission to hospital or any intervention. After 6 weeks there is an increasing risk that some products of conception will be retained within the uterus, leading to an increased risk of continued bleeding and infection. Ultrasound scanning is widely used to confirm or refute the presence of retained products. Although this has not been evaluated in trials, the overall impression is that ultrasound will help reduce the need for intervention.

For many decades women with suspected retained products of conception, including missed abortion, have routinely been admitted to hospital for surgical evacuation of the uterus. This approach has recently been challenged and there are now three options for women with retained products of conception during the first trimester: a 'wait
and see' approach; medical evacuation; or surgical curettage. Some women have strong preferences for one or other of these options.

4.1 'Wait and see' versus surgical evacuation
For women with an estimated gestational age of below 12–13 weeks and clinical evidence of retained products, the conservative 'wait and see' approach has been compared with surgical evacuation. In these trials, overall, around 20% of women managed with the expectant approach needed a surgical evacuation. There was insufficient evidence for reliable conclusions about any differential effect on pelvic infection but following the 'wait and see' approach, there did seem to be fewer complications. In the two studies reporting subsequent fertility, there was no evidence of any difference. Where women's views have been sought, they seem to prefer the 'wait and see' approach.

No trials have evaluated a 'wait and see' approach for women with a missed abortion (see Chapter 27).

4.2 Medical versus surgical evacuation
Following the successful introduction of hormonal methods for terminating pregnancy early in the first trimester, these agents are now being used for the care of women with spontaneous miscarriage. The drugs most widely used are prostaglandins and antiprogesterones, often in combination. These have been compared to surgical evacuation in a few trials. In one small study evaluating a single dose of a prostaglandin, most women with a medical evacuation went on to have a surgical evacuation, usually because of continued bleeding. This trend has not been confirmed in other studies.

One study in the UK has suggested that medical evacuation is cheaper if the theatre time freed up is put to good use. If the extra theatre time is not used, medical treatment will be more expensive than surgical evacuation. This study also suggests that about half the women with spontaneous miscarriage will have a strong preference for either medical or surgical evacuation.

Two large ongoing three-arm trials are comparing the 'wait and see' approach with medical and surgical evacuation.

4.3 Surgical evacuation
Surgical evacuation has been the standard treatment for incomplete miscarriage and first-trimester missed abortion for most of this century. It is, therefore, surprising that very few aspects of this procedure have been evaluated in adequately controlled trials.
4.3.1 Analgesia versus general anesthetic
One trial has compared systemic analgesia on the ward with a general
anesthetic in theatre. Women having a systemic analgesic were less
likely to need a blood transfusion, and had their operation more
quickly.

4.3.2 Suction versus conventional curettage
Another trial has compared suction evacuation with conventional
curettage. Women who had a suction evacuation had less blood loss.
This procedure was also faster and less painful.

4.3.3 Prophylactic antibiotics
One trial has evaluated the use of prophylactic doxycycline during
surgical evacuation in a hospital where the risk of infection following
incomplete miscarriage was low. There was no apparent effect on post-
operative pelvic infection. Another trial in Zimbabwe evaluated 1 week
of oral tetracycline postoperatively. The risk of infection was high, but
again there was no effect. However, in this study poor compliance was
thought to have been a factor.

5 Conclusions
Hospitalization during pregnancy is costly and disruptive for many
families. Discussion with individual women will make it clear that a
prescription for rest, either at home or in hospital, would sometimes
be welcome. As there is no strong evidence that this is likely to have
harmful effects, women’s views should be taken into account. By the
same token, women with bleeding in early pregnancy should not
be coerced into resting at home or in a hospital against their better
judgement.

In the present state of knowledge, hormone administration of any
type during pregnancy should be used only within randomized trials
until the ratio of benefits to hazards has been more clearly established.
Future trials should involve only those women who have had ultra-
sonography to confirm that the fetus is alive. A similar caution must
be made in regard to indomethacin, tocolytics, and antispasmodics.

The use of immunotherapy for women with an unexplained history
of recurrent miscarriage should also be restricted to those participating
in randomized trials. Maternal injection of paternal white blood
cells appears to show most promise, but it may also be associated with
serious hazards. A greater understanding of the theoretical basis for immunotherapy may help guide further research in this field.

For women with autoantibodies, combined heparin and aspirin treatment appears promising, but further evaluation of the possible hazards and the long-term effects is needed before this can be recommended for clinical use.

Following spontaneous miscarriage with retained products of conception, surgical evacuation is probably necessary if the uterine size is more than 12–13 weeks. If the uterine size is less than this and there is clinical and ultrasound evidence of retained products, the options are ‘wait and see’, medical evacuation, or surgical curettage. Women may have strong preferences, and these should be taken into account in the decision about what form of care is given. A ‘wait and see’ approach will mean that 80% of women avoid the need for surgery. The role of medical evacuation remains unclear and awaits further evidence about the optimal agents and their effects at different gestations. Prophylactic antibiotics following surgical evacuation may have a role in areas were the risk of postoperative infection is high.

Sources

Effective care in pregnancy and childbirth
Crowther, C. and Chalmers, I., Bed-rest and hospitalization during pregnancy.
Goldstein, P.A., Sachs, H. and Chalmers, T.C., Hormone administration for the maintenance of pregnancy.
Neilson, J. and Grant, A., Ultrasound in pregnancy.

Cochrane Library
Scott, J.R., Human chorionic gonadotrophin for recurrent miscarriage.
Immunotherapy for recurrent miscarriage

Pre-Cochrane reviews
Prendiville, W.J., Progestogens to prevent miscarriage and preterm birth.
Tocolytics/antispasmodics for threatened miscarriage.
17alpha-hydroxyprogesterone caproate in pregnancy.
Progestogens in pregnancy.
Progestogens for threatened miscarriage.
Indomethacin for threatened miscarriage.
Progestogen/estrogen prophylaxis in early normal pregnancy.

Other sources


