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Fact Sheet 40

Recurrent Miscarriage

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Miscarriage is a common problem that can affect any woman who has conceived. Overall one in six pregnancies reaching six weeks of amenorrhoea (absence of periods) will miscarry. By 12 weeks this rate has dropped to one in a hundred. By far the majority of these losses are due to random abnormalities of the chromosomal makeup of the embryo.

Approximately one in two hundred women who conceive, will lose three consecutive pregnancies in the first 12 weeks of pregnancy. This is the gynaecological definition of recurrent miscarriage. It is usually at this stage that a series of investigations is undertaken to look for causes.

Causes

Random chromosome abnormalities

Studies looking at the genetic makeup of embryos lost in the first trimester show abnormalities in 60 – 70 per cent. The majority of these aberrations are due to the presence of an extra chromosome (trisomy e.g. Down syndrome) or one less chromosome (monosomy e.g. Turner's syndrome). These are not reflected in the mother's or father's chromosomes but occur when the sperm and egg genetic material get together just after fertilisation. These abnormalities arise as chance events. The possibility of this happening in the next pregnancy is no greater than in the previous pregnancies. i.e. one in six.

However as eggs get older (i.e. women older than 40 years) chromosomal abnormalities occur more frequently and account for the increased risk of Down syndrome and a higher chance of miscarriage in older women. In addition, more subtle chromosomal abnormalities are probably responsible for many of the remaining 30 - 40 per cent of miscarriages. However there are a number of rarer conditions that also cause miscarriage.

Parental carriage of a lethal chromosome abnormality

Either parent can carry an abnormality that is balanced in their own chromosomal pairs, (so is compatible with life). However when the pair split to form the chromosomes of the sperm or egg and then link with the other partner's chromosomes, it can become unbalanced and therefore lethal. The incidence of such events is rare i.e. less than one in a hundred even in women with three previous miscarriages. However by three losses, such abnormalities are worth excluding by analysis of both parents' chromosomes (karyotype).

Autoimmune disease

The human immune system can produce proteins which attack the body's own cells (auto antibodies). It has been shown that if a woman makes some varieties of these proteins, miscarriage is much more likely. Other pregnancy complications are also more common. One group is particularly implicated. The anticardiolipin antibodies (ACA) or lupus anticoagulant are found in 15 per cent of women who have recurrent miscarriages. The chance of pregnancy continuing in the presence of one or other

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of these is around only 30 per cent, if no treatment is given. Treatment with aspirin and heparin increases the chances to better than 70 per cent. It is therefore important to look for these antibodies circulating in the blood.

Chronic infection of the uterus

While it has been traditional to look for evidence of chronic infections that might affect the uterus e.g. chronic toxoplasmosis or cytomegalovirus, the evidence is that these are not significant factors in recurrent miscarriage.

Medical Conditions

Diabetes and thyroid disease have been associated with miscarriage. If they are well controlled, the chance of a miscarriage is no greater than in fit and healthy women. However it is important to exclude these conditions in women suffering from recurrent miscarriage.

Uterine abnormalities

Abnormalities in the shape of the uterus can lead to miscarriage. These usually occur after 12 weeks of pregnancy and are due either to a weakness of the neck of the womb (cervical incompetence) or implantation on a fibrous band (septum) found within the uterus. This fibrous area within the uterus is unable to provide appropriate blood supply to the growing foetus and thus miscarriage can occur. Hysteroscopy or hysterosalpingogram (HSG) can be performed to assess the shape of the womb.

Hormone deficiency

In the past there has been a vogue to give hormones to prolong pregnancies in women with recurrent miscarriage.

There is no evidence that hormone deficiency is a cause of miscarriage.

Sadly the giving of some of these hormones, e.g. stilbestrol, has led to abnormalities in the children after they are born. It is therefore a practice that has almost ceased. Measuring hormones once pregnancy has commenced can be reassuring if they are rising, but if they are low or falling the pregnancy is already doomed. Giving hormones makes no difference.

Investigations

- Parental chromosomes
- ACA, lupus anticoagulant
- Exclude diabetes and/or thyroid disease
- HSG or hysteroscopy if the loss is occurring after 12 weeks

Frustratingly, positive results will be found in less than 20 per cent of cases even after three miscarriages.

Treatment

The first step is to realise the chance for a subsequent ongoing pregnancy is in excess of 70 per cent even after three miscarriages (provided the above investigations are negative).

The next step is to have the pregnancy monitored regularly from the time a positive BhCG has been confirmed. This involves weekly (or twice weekly) hCG estimations to demonstrate rising levels until a transvaginal ultrasound can show a sac, foetal parts and a heart beat. This should be visible by around six weeks. The scan can be repeated every ten to fourteen days to demonstrate growth and continued heart action. The aim of this approach is to assure, and to find a problem at the earliest opportunity. A Swedish study has shown such a programme increases the chances of a successful pregnancy by some ten to fifteen per cent.

For those with an ACA positive result, half an adult daily dose of aspirin can be started from ovulation in any planned conception cycle and heparin injections introduced from the time of a positive pregnancy test. It is debatable as to how long these injections should continue. The risks of heparin include bruising and a reduction in bone thickness during pregnancy. This latter problem has been reported to cause vertebral collapse in the spine – a serious event.

If parental chromosome problems are found the degree of risk determines the management, e.g. if one chromosome is affected the chances of repeat miscarriages may be as high as 50:50. The couple then have to decide if they are prepared to take this one in two chance of a miscarriage. One option available is to use donor eggs or sperm to bypass the problem. The other option with modern technology is to have IVF, create embryos and have one cell from the embryos tested to see if they are affected, then any unaffected embryos can be transferred to the uterus.

If a uterine abnormality is found, surgery can be performed to correct it.

Summary

The vast majority of miscarriages are due to random chromosome abnormalities. After three miscarriages there are a series of investigations which are worthwhile to exclude various rare problems. If any of these are positive, specific treatment can be undertaken. However, for most, the chance of a normal pregnancy in the future is still greater than 70 per cent without any form of treatment.

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Recurrent Implantation Failure with IVF

Women undergoing IVF where embryos are replaced but no implantation occurs, are the dilemma of every IVF Unit. We do not understand the reasons for this failure. Extrapolating from the data about miscarriage as outlined above, it is highly likely that many of the embryos that are replaced carry lethal chromosome abnormalities despite looking normal at the time of embryo transfer. There is nothing that can be done to prevent these losses. Spare embryos have been analysed for chromosomes and an increased rate of such abnormalities has been shown. Whether any of the other causes of miscarriage play a part in implantation failure is still debatable. There is currently much interest relating to the immunological problems of auto antibodies and implantation failure, although there is no definitive evidence that this is a specific cause.

Professor Michael Chapman