Chromosome abnormalities in first-trimester pregnancy loss
Goddijn, M.

Citation for published version (APA):
Genetic aspects of miscarriage

M Godijn¹ and NJ Leschot²

¹ Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Academic Medical Center, Amsterdam
² Department of Clinical Genetics, Academic Medical Center, Amsterdam.

Abstract

Fetal chromosome abnormalities account for about 50% of first trimester pregnancy losses. Most of these abnormalities are numerical abnormalities (86%) and a low percentage is caused by structural abnormalities (6%) or other genetic mechanisms, including chromosome mosaicism (8%). The recurrence risk of numerical abnormalities is low, so karyotyping of fetal material in case of a miscarriage does not seem worthwhile in daily practice. Half of the structural abnormalities may be inherited from a parent carrying a balanced chromosome translocation or inversion. Parental carriership is found in 4-6% of the couples with recurrent miscarriage. In case of parental carriership of a balanced structural chromosome abnormality, a next pregnancy may result in a child with an unbalanced structural chromosome abnormality. This child can have multiple congenital malformations and/or a mental handicap. Prenatal diagnosis is therefore recommended. Conventional laboratory techniques, such as tissue culturing and karyotyping, or (semi-)direct chromosome technique of chorionic villi, and the recently developed laboratory techniques such as fluorescence in situ hybridization (FISH) and comparative genomic hybridization (CGH) are described successively.

Until now, not enough evidence has been available about the role of other genetic mechanisms, such as single-gene abnormalities, uniparental disomy, genomic imprinting, multifactorial disorders and skewed X chromosome inactivation, in the occurrence of miscarriages.
Introduction

The prevalence of miscarriages has been estimated to be between 10 and 15% of all clinically recognized pregnancies, with the majority of these occurring in the first trimester of pregnancy. Fetal chromosome abnormalities account for about 50% of first-trimester pregnancy losses. Pregnancy loss of chromosomal origin is uncommon after 15 weeks of gestation\(^1\). Therefore, this chapter is concerned mainly with first-trimester miscarriages.

The World Health Organization's definition of miscarriage is: the expulsion or extraction from its mother of an embryo or fetus weighing 500 g or less. The weight criterion corresponds with a gestational age of roughly 20-22 weeks\(^2\). Many synonyms are used for the terms 'miscarriage' and 'recurrent miscarriage'. In this chapter we use the term 'miscarriage' to mean spontaneous abortion or first trimester miscarriage, and the term 'recurrent miscarriage' to mean repeated, recurrent, multiple or habitual abortion. It is probable that the different synonyms do not reflect different clinical entities, so that terms such as 'recurrent miscarriage' and 'habitual abortion' can be used interchangeably. More important than a semantic discussion is an accurate description of gestational age and number of miscarriages in studies concerning miscarriage or recurrent miscarriage.

In this chapter we present what is currently known about the laboratory techniques, prevalence and causes of chromosome abnormalities of miscarriages and recurrent miscarriage. The following mechanisms will be considered: cytogenetic abnormalities, i.e. numerical abnormalities, structural abnormalities and mosaicism, single-gene abnormalities and other genetic mechanisms, such as multifactorial disorders and skewed X chromosome inactivation. Furthermore, we will discuss the clinical implications of each genetic mechanism.

Cytogenetic abnormalities

Cytogenetic abnormalities can be subdivided into numerical chromosome abnormalities, structural chromosome abnormalities and other mechanisms, such as mosaicism.

Conventional cytogenetic analysis of aborted fetal material depends on tissue culturing and karyotyping or the use of a (semi-)direct chromosome technique on chorionic villi. The technique of tissue culturing is laborious and subject to problems such as external
contamination, culture failure and selective growth of maternal cells. A possible disadvantage of the (semi-)direct preparation is the discrepancy that may occur between embryonic cells and chorionic villi. Such a discrepancy might be due to the fact that mosaicism is found only in placental tissue, i.e. confined placental mosaicism. Thus, the fetal karyotype may not be represented correctly by the villous karyotype. The estimated percentage of mosaicism is 1-2% for (semi-)direct chromosome preparations in chorionic villus samplings (CVS).

Cytogenetic analysis of fetal tissue is expensive. Formerly, it was thought that histological features of miscarriages could predict karyotype, and could be a possible alternative to karyotyping. Examples of such histological features are: villus contour, hydropic villi, trophoblastic hyperplasia, trophoblastic lacunae, cisterns, inclusions, perivillous and intervillous fibrin deposits. So far, hydropic villi and trophoblastic lacunae showed a significant association with triploidy in one study, and trophoblastic hyperplasia, cisterns and inclusions with triploidy in another study. No histological features were significantly associated with other chromosome abnormalities. In general, histological features are inconvenient for predicting karyotype. The presence of a cytogenetic abnormality in miscarriages explains the reason for the loss. Some authors favour routine karyotyping of fetal material in miscarriages. We think that this is unnecessary because, in women who have had only one miscarriage, the recurrence risk of another miscarriage is not, or only slightly, elevated (16%) when compared to the initial risk of all women (10-15%).

A study which pooled data of 5318 miscarriages appeared in 1987. It combined the data of four large studies. The overall percentage of chromosome abnormalities was reported to be 51%. The chromosome abnormalities were subdivided in numerical chromosome abnormalities (96%), structural chromosome abnormalities (3%) and other chromosome abnormalities (1%). As tissue sampling, culture technique and direct preparation of chorionic villi have improved since then, we have pooled the data of more recent chromosome studies. Table 1 gives an overview of the reported frequency of chromosome abnormalities among 11 series of single miscarriages (data from 4696 spontaneous miscarriages). These data differ only slightly from the percentages found in the earlier studies. An overall percentage of 49% chromosome abnormalities was calculated, and chromosome abnormalities were subdivided into 85% numerical abnormalities, 6% structural chromosome abnormalities and 8% other chromosome abnormalities. The most remarkable finding is a higher incidence of other chromosome abnormalities, such as mosaicism, double and triple trisomies and miscellaneous chromosome abnormalities.
It is suggested that most of the chromosome abnormalities result in disordered development incompatible with prolonged intrauterine survival and live birth. The mechanism by which a chromosome abnormality could lead to regression of the conceptus is unclear.

Newer techniques which can be used in detecting chromosome abnormalities of miscarriages, and which offer a possible additional role to conventional laboratory techniques are fluorescence in situ hybridization (FISH) and comparative genomic hybridization (CGH). Until now there have been only a few published studies concerning the use of these new techniques in relation to miscarriages. One study used FISH in pre-implantation embryos in patients with unexplained recurrent miscarriages, and found that 16/39 (41%) of the pre-implantation embryos were aneuploid. The authors suggest that pre-implantation diagnosis could be a feasible method for improving the chance of a successful pregnancy. In another study, the percentage of chromosome abnormalities detected by FISH in these pre-implantation embryos proved to be higher in the group with unexplained recurrent miscarriages (35/66=53%) when compared to a control group (12/62=19%).

Comparative genomic hybridization (CGH) is a molecular-cytogenetic assay capable of detecting chromosomal gains and losses by FISH. It provides a whole-genome screen for unbalanced aberrations, and can detect the origin of extra or missing chromosomal material. CGH has been shown to detect chromosome abnormalities in 50% of the aborted fetal samples, as compared with 42% abnormality displayed by culture of chorionic villi (n=12).

New insights can be expected by the use of DNA microarrays. DNA microarrays consist of short pieces of DNA, from 20 to over 1000 nucleotides in length. By using these microarrays, every desired DNA sequence can be stained, and microdeletion syndromes or duplications can be diagnosed. No information is yet available about the use of microarrays in miscarriages.

**Numerical abnormalities**

Numerical abnormalities can be subdivided in aneuploidy (trisomies and monosomies) and polyploidy. Trisomies occur most frequently (52%), followed by polyploidy (21%) and monosomy X (13%) (see Table 1).
Table 1  Cytogenetic findings among reported series of spontaneous abortions (percentages in parentheses)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Karyotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>189</td>
<td>123</td>
<td>200</td>
<td>144</td>
<td>95</td>
<td>224</td>
<td>926</td>
<td>319</td>
<td>1607</td>
<td>74</td>
<td>119</td>
<td>4696</td>
</tr>
<tr>
<td>Abnormal</td>
<td>44</td>
<td>62</td>
<td>83</td>
<td>370</td>
<td>16</td>
<td>109</td>
<td>500</td>
<td>197</td>
<td>878</td>
<td>45</td>
<td>45</td>
<td>2377</td>
</tr>
<tr>
<td>% abnormal</td>
<td>77</td>
<td>50</td>
<td>59</td>
<td>69</td>
<td>83</td>
<td>51</td>
<td>46</td>
<td>38</td>
<td>45</td>
<td>38</td>
<td>49</td>
<td>7319</td>
</tr>
<tr>
<td>Failures</td>
<td>13</td>
<td>not</td>
<td>0</td>
<td>233</td>
<td>12</td>
<td>1</td>
<td>24</td>
<td>582</td>
<td>not</td>
<td>not</td>
<td>not</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trisomy (% of abn)</td>
<td>89 (61)</td>
<td>30 (49)</td>
<td>55 (47)</td>
<td>229 (60)</td>
<td>64 (54)</td>
<td>60 (76)</td>
<td>60 (52)</td>
<td>202 (47)</td>
<td>45 (37)</td>
<td>362 (50)</td>
<td>15 (33)</td>
<td>1216 (52)</td>
</tr>
<tr>
<td>Polyploidy</td>
<td>16 (11)</td>
<td>13 (21)</td>
<td>30 (26)</td>
<td>82 (22)</td>
<td>9 (9)</td>
<td>8 (10)</td>
<td>27 (23)</td>
<td>110 (26)</td>
<td>31 (25)</td>
<td>141 (19)</td>
<td>14 (31)</td>
<td>481 (21)</td>
</tr>
<tr>
<td>Monosomy X</td>
<td>13 (9)</td>
<td>9 (15)</td>
<td>12 (10)</td>
<td>40 (11)</td>
<td>7 (7)</td>
<td>9 (11)</td>
<td>18 (15)</td>
<td>28 (18)</td>
<td>31 (25)</td>
<td>90 (17)</td>
<td>1 (2)</td>
<td>308 (13)</td>
</tr>
<tr>
<td>Str chrom abn</td>
<td>12 (8)</td>
<td>3 (5)</td>
<td>2 (2)</td>
<td>18 (5)</td>
<td>6 (6)</td>
<td>none</td>
<td>6 (5)</td>
<td>19 (5)</td>
<td>none</td>
<td>64 (9)</td>
<td>7 (4)</td>
<td>132 (6)</td>
</tr>
<tr>
<td>Others BC</td>
<td>15 (10)</td>
<td>6 (10)</td>
<td>18 (15)</td>
<td>11 (3)</td>
<td>14 (14)</td>
<td>2 (3)</td>
<td>4 (3)</td>
<td>17 (4)</td>
<td>15 (12)c</td>
<td>67 (9)</td>
<td>13 (29)</td>
<td>182 (8)</td>
</tr>
</tbody>
</table>

Method

<table>
<thead>
<tr>
<th></th>
<th>Direct preparation</th>
<th>Culture preparation</th>
<th>Direct preparation</th>
<th>Dir prep and culture</th>
<th>Direct preparation</th>
<th>Culture preparation</th>
<th>Culture preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material</td>
<td>Chorionic villi</td>
<td>Chorionic villi</td>
<td>Chorionic villi</td>
<td>Choronic villi</td>
<td>Choronic villi</td>
<td>Embryo</td>
<td>Chorionic villi</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chorionic villi</td>
</tr>
</tbody>
</table>

a  Structural chromosome abnormalities.

b  Includes double and triple trisomies, mosaicism, huddatiform mola and triple trisomies, hydatidiform mola, autosomal monosomy and miscellaneous.

c  Includes tetraploidy.

d  Chorionic villus samplings.
Most trisomies are believed to occur as a consequence of non-disjunctio during maternal meiosis I. Trisomy 16 is the most common trisomy, accounting for 32% of all trisomies. A conceptus with trisomy 16 never survives to term. Other frequently noted trisomies include trisomy 13, 18, 21 and 22.

Monosomy X usually occurs as a result of paternal sex chromosome loss. Autosomal monosomies are seen less frequently than monosomy X in miscarriages. Of the cytogenetic results of 4696 miscarriages only 5 autosomal monosomies were reported per 2319 chromosome abnormalities (0.2%) (see Table 1). The reason why certain types of chromosome abnormalities, such as autosomal monosomies, are infrequent, or even lack in miscarriages, like trisomy 1, is unknown. It has been postulated that these chromosome abnormalities are responsible for very early pregnancy losses.

Polyploidy, triploidy (3n=69) or tetraploidy (4n=92), result from one or more extra haploid chromosome complements. The most frequent pathogenic mechanism for triploidy is dispermy. Another possible mechanism is failure of maternal meiotic cell division resulting in diploid oocytes. The parental source of the extra chromosome can be detected by DNA analysis. The pathogenetic mechanism for tetraploidy is mitotic failure after fertilization.

There are indications for a relationship between the phenotype of fetuses with triploidy and the parental origin of the extra haploid set of chromosomes. Fetuses with a relatively normal growth in association with a large cystic placenta appeared to have an extra paternal haploid set, whereas fetuses with marked intrauterine growth retardation and a disproportionately large head without trophoblastic hyperplasia appeared to have a maternal origin of the extra haploid set. Altogether, the extra chromosome complement proved to be of paternal origin in 25 fetuses, of maternal origin in eight fetuses and uninformative in two fetuses (n=35 fetuses). Although the association of the phenotypes with the parental origin of the extra haploid set of chromosomes was suggested consistently in these reports, conclusions with regard to genomic imprinting are limited by the relatively small number of fetal cases.

The risk for trisomies increases with maternal age. Monosomy X is inversely associated with maternal age, whereas the relation of polyploidies with maternal age is still unclear. A mechanism resulting in recurrent miscarriages is the recurrence of aneuploidy. Little information is available about this subject. The question whether the karyotype of one miscarriage predicts the karyotype of a subsequent pregnancy loss was addressed correctly in only one study. The authors karyotyped fetal material of at least two miscarriages in 273
women. The recurrence risk of a chromosome abnormality was not increased when there has been a trisomy, and probably slightly increased when there has been a non-trisomic abnormality (odds ratio 2.0 [95% confidence interval 1.0-4.0])\(^4\). In another study, prenatal diagnosis, amniocentesis or chorionic villus sampling was offered to women with recurrent miscarriages (without carriership) and a control group. It was reported that the rate of aneuploid conceptions was significantly higher in women with recurrent miscarriages (5/61 = 1.6%) when compared to controls (3/979 = 0.3%, \(P = 0.02\))\(^4\).

In our view, prenatal diagnosis is not justified when there has been a chromosome abnormality in fetal material, because of the low recurrence risk of chromosome abnormalities. Prenatal diagnosis is also not indicated in recurrent miscarriages without parental carriership of a balanced abnormality.

**Structural chromosome abnormalities**

Structural chromosome abnormalities can be subdivided into deletions, translocations, inversions and duplications, but only translocations and inversions play a role in miscarriage and recurrent miscarriage\(^4\).\(^5\).

Structural chromosome abnormalities occur in 6% of chromosomally abnormal abortuses (see Table 1). About half of these abnormalities may arise 'de novo' during gametogenesis, and the other half may be inherited from a parent carrying a 'balanced' translocation or an inversion\(^14\).

The latter has important implications and will be discussed here. In 1990, a review was published based on 200 cytogenetic studies in 22199 couples experiencing repeated pregnancy loss. Overall, 5% of the couples with two or more spontaneous miscarriages included a carrier individual (reciprocal and Robertsonian translocations and inversions).

Carriership of a balanced structural chromosome abnormalities was at least 10 times more frequent in couples with recurrent miscarriages when compared to the general population (0.34%). The distribution of chromosome abnormalities according to the number of miscarriages (1, 2, \(\geq 3\)) did not show any increase in the frequency of the inversions, sex chromosome aneuploidies and supernumerary chromosomes when the number of miscarriages increased, whereas there was a correlation between the incidence of Robertsonian and reciprocal translocations and the number of miscarriages (\(P<0.05\)).

Women, rather than men, appeared to be more likely carriers of a translocation (reciprocal or Robertsonian), an inversion or a supernumerary chromosome (\(P<0.05\))\(^4\).\(^5\).
Results of more recent parental chromosome studies report a comparable percentage of carriership: respectively 8% in 639 couples, 2% in 241 couples and 5% in 1743 couples\textsuperscript{45-48}. The overall percentage of the preceding three studies is 6% carriership in 2623 couples.

A high incidence of cytogenetic abnormalities was found in couples with miscarriage and a normal child (7 and 18% respectively)\textsuperscript{40,50}. The prevalence of carriership of a balanced structural chromosome abnormality in recurrent miscarriage is now well established.

The impact of carriership on fetal outcome has been studied less frequently. Only one study was found to report the outcome of prenatal diagnosis for pregnancies of reciprocal carriers with recurrent miscarriages. When the carrier was maternal 10/209 (5%) unbalanced conceptions were found, and when the carrier was paternal 2/139 (1%) unbalanced conceptions were found\textsuperscript{51}.

When one of the parents is a carrier of a balanced structural chromosome abnormality, a pregnancy can result in three types of offspring: a child with a normal chromosome pattern, a child with a balanced structural chromosome abnormality, or a conceptus with an unbalanced structural chromosome abnormality. The latter case will lead to either a spontaneous miscarriage or to a liveborn child with multiple congenital malformations and/or mental handicaps (5-10%).

The greater 'the chromosomal unbalance', the higher the chance of a miscarriage.

Standard studies (blood lymphocyte karyotyping with G and Q banding) should be used as routine screening tests when there have been recurrent miscarriages. FISH can be considered when a specific defect is suggested by routine tests\textsuperscript{52}.

Until now a genetic evaluation (parental karyotypes) is generally recommended after two or three miscarriages. A cost-effectiveness study to evaluate whether karyotyping should be carried out after two or three miscarriages is needed.

When parental karyotyping is performed, and a translocation or inversion is found, a strong indication for prenatal diagnosis in a subsequent pregnancy exists, because of the above-mentioned chance for a child with multiple congenital malformations and/or a mental handicap.

\textit{Chromosome mosaicism}

In mosaicism, two or more different genetic cell lines are present in an individual. Depending on the timing of the mutational event, i.e. prior or after the differentiation of embryonic and
chorionic compartments, the mosaicism may be found in the placenta and embryo or only in one of them. Confined placental mosaicism has been mentioned earlier as the main source of false-positive results of viable pregnancies at CVS (1-2%)\(^4\). Different types of mosaicism can play a role in fetal loss. Among them are chromosome abnormalities limited to the placenta with complete dichotomy between placenta and fetus\(^5\). This type of mosaicism was found in 2/141 abortuses (1%)\(^5\). Another type is mosaicism confined to the placenta, with both cell lines represented in the placenta. This type was found in respectively 10/54 abortuses (19%), while another pattern of mosaicism, confined to the embryo was found in 1/54 abortuses (2%)\(^5\).

The majority of mosaic miscarriages thus represent a confined placental mosaicism.

A positive correlation between placental mosaicism, diagnosed by CVS, and fetal cell death has been given in one other study\(^5\). On the other hand, mosaicism can be a survival mechanism as well. It is described in advanced trisomy 13 and 18 gestations that have a normal cell line confined to the placenta. The normality of part of the placental cells is supposed to be a mechanism for gestational survival\(^5\).

Mosaicism originating from a trisomic zygote can result in uniparental disomy. If the cells that eventually will form the fetus itself loose the extra chromosome, there is a 1:3 chance that both remaining homologue chromosomes are derived from one parent only. This is called uniparental disomy\(^5\)^8\(^5\).

For some genes, only one of the genes (maternal or paternal allele) is expressed in certain cells. This phenomenon is known as genomic imprinting. If uniparental disomy occurs in chromosomes of which parts are known to be imprinted or inactivated, abnormal phenotypic effects are to be expected. Lethal effects have been reported in mice, but an effect on fetal cell death, resulting in miscarriages in women, is still unclear\(^5\)^9.

**Single gene abnormalities**

Single gene disorders associated with recurrent miscarriage are myotonic dystrophy, lethal skeletal dysplasias, such as thanatoporic dysplasia and type II osteogenesis imperfecta\(^6\)-\(^8\). Myotonic dystrophy, an autosomal dominant disease is characterized at the molecular level, its gene localised at chromosome 19q13.3. It is one of the 'trinucleotide repeat diseases'. The phenomenon of anticipation which occurs in myotonic dystrophy is the reason why
disease symptoms become more severe and the age at onset earlier in successive generations of an affected family. More severely affected patients have more CTG repeats. Stillborns have the highest number of CTG repeats. It is conceivable that miscarriages show an even higher number of CTG repeats but there is as yet no evidence for this.

A recently discovered single-gene abnormality which possibly plays a role in some cases of recurrent miscarriages is the factor V Leiden mutation. The factor V Leiden mutation is the most common genetic predisposition to thrombosis. Its carrier frequency in the white population is 3-4%. A twofold increase in the factor V Leiden carrier frequency was found in 12 of 139 (9%) abortuses compared with 17 of 403 (4%) unselected pregnant women. Comparable results have been found in peripheral blood screening of American and European women with recurrent miscarriages. Two other studies report that the factor V Leiden mutation is not a common cause of recurrent miscarriage. In a Japanese population no association was found between the factor V Leiden mutation and recurrent miscarriages.

**Other genetic mechanisms**

Other genetic mechanisms which play a possible role in the etiology of miscarriages are multifactorial disorders, sperm chromosome abnormalities and skewed X chromosome inactivation.

In multifactorial disorders the genetic mechanism is considered to be the result of mutations or gene variants at several loci in combination with mostly unknown environmental factors. Neural tube defects are an example of multifactorial disorders which play a role in the cause of a miscarriage. In neural tube defects the environmental factor, insufficient folic acid intake, is well known. The incidence of neural tube defects is about ten times higher in miscarriages than in live births. A significantly higher miscarriage rate (48%, n=100) in the preceding pregnancy was found in the neural tube defect group compared to the group with other birth defects (20%, n=100).

Only one study has reported data about chromosome studies on spermatozoa in couples with recurrent miscarriage. All men subjected to this study had a normal karyotype. No significant differences were found for the following parameters: total rate of anomalies, rates of aneuploidy,
hypohaploid and hyperhaploid and total rate of structural anomalies. However, there was a significant difference in the occurrence of chromosome breaks (control group: n=10/413 (2%); recurrent miscarriage group: n=16/308 (6%) and acentric fragments (control group: n=10/413 (2%); recurrent miscarriage group: n=25/308 (8%)) of spermatozoa.

Another genetic mechanism, possibly related to the occurrence of miscarriages, is skewed X chromosome inactivation. X chromosome inactivation is the preferential use of either the paternal or maternal X chromosome. The inactivation is considered to be a random process during early embryonic development. As a consequence, the maternal X chromosome is inactivated approximately as often as the paternal X chromosome. Skewed X chromosome inactivation is defined as preferential use of one, maternal or paternal, X chromosome in >90% of peripheral leukocytes. Skewed X chromosome inactivation has been found more often in recurrent miscarriages when compared to controls (7/48=14.6% vs 1/68=1.5%, P<0.01) and (14/76=18% vs 6/111=5%, P<0.001). More evidence is needed to establish this genetic mechanism.

**Conclusions and recommendations**

The frequency and type of cytogenetic abnormalities in miscarriages is well established. After a single miscarriage, genetic evaluation—karyotyping of the fetal material—seems not worthwhile because of the low recurrence risk of another miscarriage with chromosome abnormalities and the high chance of a liveborn child in a next pregnancy.

Parental carrierness is found in 4-6% of the couples with recurrent miscarriages. Although this is a relatively low percentage, it is important to recognize because it can eventually result in a seriously handicapped child. In case of parental carrierness prenatal diagnosis is recommended in the next pregnancy. Whether a couple should be karyotyped after two or three miscarriages needs to be evaluated by a cost-effectiveness study. Clinical recommendations are summarized in Figure 1.
Figure 1 Clinical recommendations

<table>
<thead>
<tr>
<th>A single miscarriage</th>
<th>no genetic evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two or more miscarriages</td>
<td>parental karyotyping</td>
</tr>
<tr>
<td></td>
<td>prenatal diagnosis in the next pregnancy, in case of</td>
</tr>
<tr>
<td></td>
<td>carriergship of a balanced chromosome abnormality</td>
</tr>
</tbody>
</table>

Acknowledgment

The authors wish to thank F van der Veen, MD, PhD, head of the Center for Reproductive Medicine, Academic Medical Center, for critically reading the manuscript.
References


