



Recurrent Miscarriage: Genetic Factors and Assessment of the Embryo

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In recurrent pregnancy loss, current practice often fails to make a diagnosis, as the fetal causes of pregnancy loss are usually ignored and only the maternal factors are assessed. Hence, it has been almost impossible to show that any treatment has an effect. This presentation is concerned with the fetal causes of recurrent pregnancy loss. The maternal causes are well known and include: uterine factors, antiphospholipid syndrome, possibly hereditary thrombophilias, alloimmune factors, infections, and endocrine abnormalities. However, all assessments of these factors have been confounded by the presence of abnormal embryos that may themselves be incompatible with life. The fetal causes of embryo loss include structural malformations that are incompatible with life, and chromosomal aberrations.

Structural malformations

Structural aberrations have been found in laboratory animals and may explain some pregnancy resorptions [1]. Resorption of pregnancies in laboratory animals can be considered to be the equivalent of missed abortions in humans. In human pregnancy ultrasound is the main means of diagnosing fetal structural abnormalities. However, 89% of human recurrent miscarriages occur in the first trimester [2]. At that stage the embryo is too small to be diagnosed as normal or abnormal on ultrasound. Indeed, 70% are reported to be blighted ova [2]. Philipp et al. [3] performed embryoscopy on missed abortions just prior to curettage and found developmental defects in 200/233 missed abortions (85%). These defects included anencephaly, encephalocele, spina bifida, syndactyly, pseudosyn-dactyly, polydactyly, cleft hand and cleft lip. They karyotyped 221 embryos, of which 56 (25%) were eukaryotypic. However, 20 of the eukaryotypic embryos (35.7%) were grossly disorganized. Without embryoscopy these embryos would not have been diagnosed, and the patient might have been treated empirically with hormone supplements, anticoagulants, etc., all for a presumed maternal factor. In a later series Phillip [4] showed how sonograms of first-trimester missed abortions may appear normal, but can be seen to be grossly abnormal on embryoscopy.

Once the second trimester is reached, ultrasound can pick

up structural malformations. These malformations are usually associated with a normal karyotype. However, expert ultrasound is required for diagnosis.

Chromosomal aberrations

Regarding chromosomal aberrations, our team has carried out a number of studies to determine both the incidence of chromosomal aberrations in recurrent pregnancy loss and the chance of a subsequent live birth after aborting a chromosomally normal or abnormal embryo. As patients often present in the interval between miscarriages, and karyotyping of the abortus has not always been performed, we tried to determine whether parental karyotyping is a substitute for karyotyping the abortus, the chance of subsequent live births in the presence of parental chromosomal aberration, the embryonic karyotype in the presence of parental chromosomal aberrations, and the implications for treatment.

Forty-one percent of miscarriages are aneuploid in recurrent miscarriage. The prognosis is better after an aneuploid abortion than a euploid miscarriage. However, 15% of patients will have repeat aneuploidy.

Karyotyping of the abortus

Five series have assessed the karyotype of the abortus in recurrent miscarriage [5-9]. The mean number of miscarriages was 4.12 ± 0.48 . The incidence of fetal chromosomal aberrations varied between 25% and 57% (mean $41.6\% \pm 13.9$). Ogasawara and collaborators [6] have also shown that the incidence of chromosomal aberrations decreases as the number of miscarriages

increases. Indeed, chromosomal aberrations can be found in the abortus in the presence of other causes of recurrent pregnancy loss. A 30% incidence has been reported in two small series of patients with antiphospholipid syndrome [6,10]. The author has also found chromosomal aberrations in the abortus of four patients with hereditary thrombophilias [11].

The value of parental karyotyping is limited in recurrent miscarriage, as it does not make a diagnosis of cause, offer a prognosis or indicate treatment

The karyotyping of the abortus allows the patient to be given prognostic information regarding subsequent pregnancy outcomes. Warburton and co-workers [12] summarized 273 women who had had abortuses karyotyped. They concluded that after a previous trisomic miscarriage the prognosis is favorable. Two subsequent studies [6,7] examined the outcome of the subsequent pregnancy according to the karyotype of the miscarriage. In the series of Ogasawara et al. [6], there was a statistically significant trend for a patient with an aneuploidic abortion to have a better prognosis. The same trend was apparent in the series conducted by Carp et al. [7]. In women with three miscarriages and an aneuploidic miscarriage, reassurance of a good prognosis may be sufficient and may save the patient more extensive investigations and treatment of dubious value. This may not be the case in euploidic abortions.

However, despite the better prognosis, repeat aneuploidy may occur. Fetal karyotyping has been assessed in a subsequent abortion in the study by Sullivan et al. [9]. Of 30 patients with an aneuploid abortion, only 3 (10%) had a subsequent aneuploid abortion. In the author's series (unpublished), 43 abortuses were found to be aneuploid and a subsequent abortion was karyotyped. Only 8 of the 43 abortuses were aneuploid (19%). Hence, approximately 15% of aneuploid abortions will be followed by a subsequent aneuploid abortion. Consequently, 85% of patients with an aneuploid abortion can be assured that the prognosis is good and that the aneuploid abortion may be a chance occurrence. However, the other 15% may have a recurring cause of fetal aneuploidy, and can be offered pregestational diagnosis.

Parental karyotyping

It is common practice to karyotype the parents rather than the abortus. However, parental karyotyping seeks balanced translocations and inversions rather than the more common numerical aberrations such as trisomy. Parental karyotypic aberrations have been found in 3–10% of couples with recurrent miscarriage [13–16]. Parental karyotyping does not provide a prognosis for subsequent pregnancies.

Three studies have looked at the subsequent live birth rate in patients with recurrent miscarriage and parental chromosomal rearrangements. Sugiura-Ogasawara et al. [17] reported a 32% subsequent live birth rate, whereas Carp et al. [18] reported a 44% rate and Goddijn et al. [19] a 70% rate. Taken together, the live birth rate was 47.5% for patients with a mean of 3.7 previous miscarriages. This live birth rate of 47.5% is the expected rate for patients with 3.7 abortions, according to numerous series in the literature [20]. Patients are often advised that the presence of a parental karyotypic aberration diagnoses the cause of the miscarriage, as the aberration may be transmitted to the embryo in an unbalanced form. However, our team [18] is the only group to examine the karyotype of abortuses from parents with karyotypic aberrations. Thirty-nine abortuses from recurrently miscarrying couples with parental karyotypic aberrations were karyotyped. Of the 39, 17 (26%) were euploid. Another 10 (26%) had the same balanced translocation as the parent. Hence, 69% were chromosomally normal. Only 5 (13%) abortuses had unbalanced translocations, whereas 7 (18%) of the abortuses had subsequent abortuses with numerical aberrations unrelated to the parental chromosomal disorder (five trisomies and 2 embryos with monosomy X). Hence, in parental chromosomal aberrations, the embryo should be karyotyped to reach accurate diagnosis.

The failure to take fetal abnormalities into account in recurrent miscarriage may have created a false impression of futility in the treatment of maternal causes of pregnancy loss and pregestational genetic diagnosis

Implications for treatment

Due to the failure to take embryonic karyotypic aberrations into account, various treatment modalities for maternal causes, such as resection of an intrauterine septum, suppression of high lactate dehydrogenase levels, hormone supplementation for luteal phase deficiency, thrombophylaxis and immunopotentialiation, have been said in official guidelines to have no or insufficient evidence of effect [21–23]. Similarly, if fetal therapy is used in the form of pregestational aneuploidy screening or preimplantation genetic diagnosis, there are also reports that these procedures do not produce better results than expectant management if used empirically in recurrent miscarriage, and that PGD does not improve pregnancy outcome in couples who are carriers of structural chromosome rearrangements when compared with expectant management [24]. However, in the author's view, PGD does have a place in repeat fetal aneuploidy and fetal aneuploidy

PGD = pregestational diagnosis

in the presence of parental karyotypic aberrations, and PGS may have a place in the older age groups [25].

Conclusions

In conclusion, it can be said that the structure and karyotype of the embryo determine compatibility with life. Karyotyping of the abortus is essential for diagnosis, prognosis and determining appropriate treatment. After an aneuploidic miscarriage, the odds ratio is 2.85 for a subsequent live birth. If there is a recurrent fetal cause, PGD should be considered. Parental karyotyping is a poor substitute for fetal karyotyping, as it does not provide a diagnosis, prognosis nor indicate treatment. If the previous abortion was euploidic, the patient will most likely abort again if PGS is used. However, PGD and even surrogacy have a place in selected patients.

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