Genetic Factors in Recurrent Miscarriage

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To overcome recurrent miscarriage (RM), clinicians take tests and give the proper treatments for the etiology, but when it comes to unexplained RM, most times, they choose empirical treatment. Even though active managements are applied to RM patients, 20 to 30 percent of recurrent aborters experience repeat pregnancy loss. In these situations we feel that we have not done our best for our patients and we also feel the limit of the management of RM.

The chromosomal anomaly of the fetus results in about 50 percent of spontaneous abortion. But, this is just a result of cytogenetic studys. Even if chromosomal result is normal, molecular genetic study may be able to find another etiology that causes fetal loss.

Chromosome abnormalities are the major cause of miscarriage, with 99% of chromosomally abnormal pregnancies miscarrying[1] compared to 7% chromosomally normal.[2] However, the frequency of abnormal embryonic karyotypes has been found to be higher in sporadic abortions (63~76%) than in Recurrent miscarriage (40~60%). In addition, The frequency of abnormal embryonic karyotypes found in spontaneous abortions has been inversely correlated with the number of previous miscarriage.[3] Chromosomal aneuploidy has been reported in 60% of first trimester abortuses.[4] Aneuploidy occurs when non-disjunction during either meiotic phase I or II of gametogenesis results in the reproduction of an extra chromosome (as seen in trisomy) or the deletion of an entire chromosome (monosomy). Trisomies are the most common abnormality found in abortal tissue, with the descending order of prevalence being trisomy 16, 22, 21, 15, 18 and 13. Monosomy X (45X) is the second most common single chromosome abnormality found in abortal tissue.[5] Triploidy (68 chromosomes) is also common; while tetraploidy (92 chromosomes) occurs less frequently. The precise mechanism of loss in chromosomally abnormal embryo is unknown, but disordered timing of developmental gene regulation and hormonal regulation are speculated. Inborn chromosomal aberrations may be inherited, but more commonly arise de novo by spontaneous mutations are paternal origin during embryo development.[6] Maternal age-related problems in oocyte spindle formation and meiotic division errors lead to chromosomal abnormalities involving trisomies.[7] Monosomy X and polyploidies are not maternal age related, implying a paternal error during meiosis.[8]

Despite the high frequency of karyotypic abnormalities found in recurrent miscarriage reveal parental abnormalities in only 3~5% of couples, which is nevertheless about five times higher than in the general population.[9] The most common parental chromosomal abnormality contributing to pregnancy loss is a translocation, which involves two chromosomes in a mutual exchange of broken-off fragments. A Robertsonian translocation is a

special category of reciprocal translocation involving two acrocentric chromosomes, numbers 13, 14, 15, 21, 22; breakage occurs close to the centromere in the short arm of one chromosome and in the long arm of the other. The risk of miscarriage in couples with reciprocal translocations is approximately 25~50% and with robetsonian translocations is approximately 25%.[10] Determination of a balanced translocation would prompt the recommendation for preimplantation genetic diagnosis (PGD); While for carriers of sex chromosome anomalies, usually in mosaic form, the risk depends on the type of anomaly (XXY, XYY, XXX), degree of mosaicism. If the carrier is the female partner, it is possible to carry out an indirect diagnosis (Preconception genetic diagnosis or PCCGD) by characterization of the chromosome constitution of the 1st polar body prior to fertilization of the oocyte.[11] Use of PGD in patients with known heritable genetic disorders (e.g., cystic fibrosis, X-linked disorders) is presently in widespread use in internationally recognized ART centers. Efficancy of PGD in the treatment of patients with recurrent miscarriage is now under investigation.[12~15] Synchronization of intercourse with ovulation may benefit some patients with genetic factor recurrent miscarriage.[16,17] Robertsonian translocations involving homologous chromosomes are rare (1 in 2500) but always result in aneuploidy. In such cases, either donor oocyte or donor sperm is indicated, depend upon which partner has this abnormality. Other parental structural chromosome inversions and sex chromosome mosaicism have also been associated with recurrent miscarriage.[18] Because karyotyping detects only gross chromosomal abnormalities, the contribution of genetic factors to the etiology of recurrent miscarriage may be higher than the estimated 50~60%. Other genetic causes of abortion include multifactorial inheritance of autosomal recessive genes and X-linked disorders uncommonly may result in recurrent abortion of male but not female offspring.[19] Single gene mutations or polymorphim are possibly responsible for losses not recognized to have a genetic basis, but the scope of the problem is unknown. Skewed X-chromosome inactivation (Lethal X-linked mutations) is maternally inherited and can cause preferential activation of the paternal chromosome, leading to recurrent miscarriage.[20,21] Indeed, women with antithrombin III, protein C, and glucose-6-phosphatate dehydrogenase (G6PD) deficiency have a rate of spontaneous abortion that is double the rate in a control group.[22] Mutations predisposing to inherited thrombophilia, including factor V Leiden mutation and C677TY mutation in the MTHFR gene may be another example of a single gene associated with recurrent miscarriage.[23~25]

Immunogenetic research regarding the maternal-fetal relationship is contributing to the knowledge relating to the maintenance of normal pregnancy. Abnormalities in the structure or function of cell adhesion molecules, for example, or proteins involved in immunity may lead to recurrent miscarriage. The coordinate regulation of immunological, metabolic, vascular, and endocrine process is required for maintenance of human pregnancy. Abnormal regulation of biological process may lead to recurrent miscarriage.[26,27]

Improvements in molecular genetic techniques are revolutionizing reproductive genetics and are able to identify and characterize single-gene mutations and other specific novel genes suggesting new mechanisms of unexplained recurrent miscarriage.

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