SVEIKATOS MOKSLAI / HEALTH SCIENCES
IN EASTERN EUROPE
ISSN 1392-6373 print / 2335-867X online
2016, 26 tomas, Nr. 3, p. 61-64
DOI: http://doi.org/10.5200/sm-hs.2016.059

GENETIC CAUSES OF RECURRENT MISCARRIAGES

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Key words: recurrent miscarriage, RSA, genetic polymorphisms.

Summary

Recurrent miscarriage is a disease distinct from infertility, defined by three or more consecutive pregnancy losses. There are a lot of causes which can be related with repetitive pregnancy losses. Miscarriages is a serious medical condition which affects about 15-20% of couples trying to get pregnant. Most of them (about 50%) are unknown and genetic factors compose 1-5% causes of repetitive miscarriages. For this reason it is important to find out genetic causes of recurrent spontaneous abortions. In this review we will analyze several cases including cytogenetic abnormalities and polymorphisms of genes.

Introduction

Recurrent spontaneous abortion (RSA) is one or more pregnancy losses before 20-24 weeks of gestation or below a fetal weight of 500 g [1, 2, 3]. There are many causes of RSA for example endocrine, autoimmune (in most cases), anatomical abnormalities, advanced maternal and paternal age, diabetes mellitus, environmental toxins and genetic factors [4, 5, 6]. There are studies which show evidence indicating genetic awareness of women is an important risk factor in occurrence of this multifactorial condition [7]. Genetic factors include *de novo* numerical abnormalities and genetic changes reflected by inherited disorders [5, 8, 9]. Lots of studies have reported that chromosomal abnormalities have a fair relationship between recurrent miscarriages and infertility [10]. The studies have been valuated that 1% of women in reproductive age are affected by RSA [4]. Genetic causes affect 1-5% human population worldwide [11; 12]. It is usually difficult to determine genetic risk factor in most spontaneous abortion patients [13].

Early studies of repetitive miscarriages was based on cytogenetic methods which showed chromosomal abnormalities. In recent years innovative methods for DNA analyses was improved and let researchers to know more about gene expression, polymorphisms and chromosomal alterations which are assosiated with reccurent spontaneous abortions.

The aim of the study. To evaluate genetic causes of recurrent miscarriages. Genetic reasons involve chromosomal aberrations such as monosomy, trisomy, translocation and other. Also we will talk about polymorphisms which have influence on gene expression.

Methods

Internet search was performed in Pub Med database for the period 1999 up to 2016. These data were obtained using combinations of the search terms “recurrent”, “repetitive”, “repeated”, “spontaneous”, “abortion”, “miscarriages” and “genetic”. In the review we selected to use only genetic alteration and genes polymorphisms causes and excluded immunological causes, anatomical abnormalities, infectious and endocrine dysfunctions. We divided selected articles into cytogenetic and molecular changes.

Results

Cytogenetic factors. Trisomies and monosomies. The frequency variation of autosomal trisomy is 43-54% by cause of cytogenetic aberrations in repetitive miscarriages [1, 14, 15]. All trisomies were identified in embryo tissues. The karyotype of abortus tissues showed that autosomal trisomy is the most common factor in repetitive miscarriages. Trisomy mostly leads to miscarriages before 10 weeks [1]. Trisomy of 9, 12, 15, 16, 21, 22 and X chromosomes is known cause of genetic anomalies in recurrent abortions [1, 15]. Trisomy of 16 chromosome mostly leads to repetitive spontaneous abortion [1, 14, 15].

Monosomy is less common than trisomy. Its frequ-

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ence is 8% of chromosomal abnormalities. In recurrent abortions autosomal monosomy is quite rare. It is mostly incongruous with life. There are some cases in repetitive miscarriages with autosomal monosomy of 13 and 15 chromosomes. Monosomy of 21 chromosome is most frequent autosomal monosomy in RSA. Monosomy linked to X chromosome is prevalent in all monosomies [14, 15].

Reciprocal or Robertsonian translocations. Reciprocal translocations are associated with parental chromosomes anomalies which may cause recurrent spontaneous miscarriages. Balanced reciprocal translocation carriers have possibility of experiencing more than one miscarriage. One or both parents with balanced reciprocal translocation are the reason of unbalanced chromosomal translocation in embryo. Unbalanced chromosomal rearrangement is correlated with embryo death. Reciprocal or Robertsonian translocation is one of the most frequent cause of RSA. Recurrent spontaneous abortion is related with Robertsonian translocation of 13, 14, 15, 21 and 22 chromosomes. There are lots of variants of reciprocal translocations which can cause repetitive miscarriages. Robertsonian translocation is rarely seen in cases than reciprocal translocation [2, 18]. Shen *et al.* made assumption that submicroscopic recombination in parental chromosomes could be the cause of RSA. By using fluorescence *in situ* hybridization (FISH) they identified few parents with submicroscopic reciprocal balanced translocations. In first place these couples had normal karyotype [14].

Other. There was found other abnormal chromosomal rearrangements in chorionic villus samples from miscarriages. Shen *et al.* reported that segmental deletion or duplication was 5,3% of chromosomal aberrations associated with RSA [14].

In Choi *et al.* studies we can see connection between repetitive miscarriages and triploidy, tetraploidy, chromosomal mosaicism, deletions, isochromosomes [1].

According to Dutta *et al.* in South of India repetitive miscarriages also were related with inversion of Y chromosome, deletion in X and 17 chromosomes, marker chromosomes and XY/XXY mosaicism. One case was associated with PAX9 gene deletion. Furthermore they suggested genomic imprinting, skewed X chromosome inactivation and chromosome instability as idiopathic causes of reproductive losses [2].

Shet*et al.* in their study again mentioned mosaicism, inversions and microdeletion on the point of causing RSA. More they mentioned small supernumerary marker chromosomes (sSMCs) which may be related in recurrent miscarriages. It was detected by FISH or array-comparative genomic hybridization (CGH) [18].

Molecular factors

Estrogen receptor alpha gene polymorphisms. Estrogen is one of the most important hormones in the entire pregnancy. Hormone controls fetal development, uteroplacental blood flow, implantation, regulation of reproduction and progesterone biosynthesis [19]. Due this reason there was made several studies to find out the potential association of repetitive miscarriages.

Estrogen receptor α (ER α) is encoded by ESR1 gene and located on chromosome 6. There was found out that ESR1 gene is extremely polymorphic, studies determined more than 2200 single nucleotide polymorphisms (SNPs) of this gene. We reviewed two studies where was investigated two ESR1 gene polymorphisms: rs2234693 (T>C: PvuII) and rs9340799 (A>G: XbaI), located in the intron 1. These SNPs was identified as the most common cause [19, 20].

These studies suggested that ESR1 as a candidate gene for spontaneous abortion, but there should be done more research to confirm the impact of single nucleotide polymorphisms on repetitive miscarriages.

Apoptosis and p53 expression in the placental villi. The p53 gene is responsible of cell growth termination, apoptosis and DNA damage repear. Apoptosis is one of the most important process in spontaneous abortion [21].

Wei *et al.* identified that there is association between higher p53 expression level and repetitive spontaneous miscarriages. They performed qPCR and imunohistochemistry to validate the variability of p53 expression in the chorionic villi of females with RSA compared with control group. p53 is an important protein in apoptosis so abnormal expresion of this protein can lead to higher chorionic villi apoptosis which can cause RSA [11].

Tumor necrosis factor-α gene polymorphisms. Tumor necrosis factor- α is a proinflammatory cytokine produced by many immunology cells such as natural killer cells (NK), mononuclear phagocytes and antigen-stimulated T cells. TNF-α is located in 6 chromosome (6p21.3) [22-23].

There was performed study to analyze how TNF-α polymorphisms are associated with spontaneous miscarriages. Lee *et al.* analyzed four polymorphisms: TNF-α - 1031T>C, TNF-α - 376G>A, TNF-α - 308G>A and TNF-α - 238G>A. Based on the data scientists hypothesized that TNF-α - 1031T>C and - 238G>A alleles may lead to increased circulating TNF-α levels which may cause spontaneous abortion. It is because increased TNF-α levels are associated with NK cells activation and may cause placental damage [22].

MTOR gene polymorphism. MTOR gene is the mammalian target of rapamycin which is very important in cell

growth, survival, proliferation and angiogenesis. It is a member of the phosphatidylinositol kinase-related kinase (PIKK) superfamily and also known as FRAP1. PIKK superfamily embraces a lipid kinase homology domain and accomplishes function of serine/threonine kinase. MTOR gene encodes mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 plays an important role in cellular growth and proliferation. There are studies which show that mTORC1 is decisive in blastocyst activation and mouse embryo implantation [8].

Histidine-rich glycoprotein gene polymorphism. Histidine-rich glycoprotein (HGR) is a multi-domain protein involved in angiogenesis, coagulation and the immune system. This protein is synthesized in liver [24]. Some studies showed that HGR acts in implantation process, embryo development and fertility [25, 26]. In their study Lindgren *et al.* were trying to find association between HRG C633T SNP and RSA [24].

Conclusion

As shown in our review not only cytogenetic factors are responsible of repetitive miscarriages. Nowadays when molecular analysis techniques progresses so fast there are identified more genetic polymorphisms which have impact to recurrent miscarriages. Detected reason for RSA can be helpful for family counselling, including prenatal diagnostics, disease monitoring and possible specific treatment.

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GENETINĖS PASIKARTOJANČIŲ PERSILEIDIMŲ PRIEŽASTYS

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Raktažodžiai: pasikartojantys persileidimai, PSA, genetinis polimorfizmas.

Santrauka

Pasikartojantis persileidimas yra liga, atskira nuo nevaisingumo, apibūdinama kaip 3 ar daugiau iš eilės pasikartojantys nėštumo nutrūkimai. Yra daug priežasčių, dėl kurių pakartotinai nutrūksta nėštumas. Persileidimai yra rimta medicininė būklė, su kuria susiduria apie 15-20% porų, kurios stengiasi susilaukti vaikų. Didžioji dalis šių priežasčių (apie 50%) yra nežinomos ir apie 1-5% visų persileidimų lemia genetiniai faktoriai. Dėl šios priežasties labai svarbu išsiaiškinti pasikartojančių spontaninių abortų genetines priežastis. Šioje publikacijoje mes analizuosime kelis atvejus, tokius kaip citogenetinės anomalijos ir genų polimorfizmas.

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Gauta 2016-06-01