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Review Article

Genetic Aspects of Recurrent Miscarriages

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Abstract

Miscarriage means loss of an embryo or fetus before the 20th week of pregnancy. It is believed that a single miscarriage occurs in 10% of all pregnancies. The cause of a significant portion of the miscarriages cannot be established, with this, the most important reasons may be listed as; genetic factors, hormonal dysfunctions, anatomical anomalies, sperm & egg related complications and exposures.Genetic problems take place among the major reasons of miscarriages especially those that take place in the first trimester. The major cause of first trimester miscarriages are chromosomal aneuploidies. Incidence of chromosomal aneuploidies increase with maternal age. Aneuploidies that cause gestational loss are usually resulting from maternal meiosis. Recently, post-zygotic aneuploidies (mosaic aneuploidies) have been shown to play an important role in etiology of miscarriages. On the other hand,in about 4% of recurrent miscarriage cases, at least one of the parents were shown to carry either a Robertsonian or a reciprocal translocation.Especially in the cases of first trimester recurrent abortions, IVF with aneuploidy screening has proven itself to be a good method of treatment when the cause of the miscarriage cannot be deducted. Especially in the recent years, there have been great advances in reproductive medicine technologies, such as the 'Next Gene Sequencer' which has provided us with a very high resolution in screening of pre-implantation embryonic genome and gave rise to very pleasing results.

ABBREVIATIONS

LH: Luteinizing Hormone; PGD: Pre-implantation Genetic Diagnosis; IVF: In Vitro Fertilization; NGS: Next Generation Sequencer; ART: Assisted Reproductive Technologies; PCOS: Polycystic Ovary Syndrome

INTRODUCTION

Miscarriage is an important problem concerning a significant number of women in their reproductive ages. By definition; Miscarriage means loss of an embryo or fetus before the 20th week of pregnancy. Most miscarriages occur during thefirst 14 weeks of pregnancy. The medical term for miscarriage is spontaneous abortion.

It is believed that a single miscarriage occurs in 10% of all pregnancies, however, should a second or a third miscarriage occur, this condition is now called 'Recurrent Miscarriage' and it calls for further medical research and precautions. Reasons of spontaneous abortions show a great variety depending on which phase of the pregnancy it took place on. Especially the miscarriages that take place on the first trimester are mostly due to chromosomal abnormalities and are the main topic that will be taken at hand in this article. However, the cause of half the miscarriages cannot be established. For a woman who has suffered one or more miscarriages, the most important questions she would have is what the risk of recurrence is should she get pregnant again.A single miscarriage usually doesn't necessarily mean an increased chance of recurrence, however, if a second miscarriage occurs, the recurrence risk is considered depending on the exact reason of the abortion. For example, a miscarriage due to a balanced translocation would have a much higher assumed risk of recurrence than a miscarriage resulting from thrombophilias. Among the reasons of recurrent miscarriages, aside from the medical reasons, there are many factors such as environmental factors, diet, even life style and so on that are worth considering. Among the medical reasons, the most important ones may be listed as; genetic factors, hormonal dysfunctions, anatomical anomalies, sperm & egg related complications and exposures. Before going deep into the medical reasons, if we were to take a quick glance at the life style, we would see that the most important causes for miscarriages from this department would be smoking, alcohol consumption and obesity. Albeit open to argument, diet, environmental exposures, computers, TVs etc. may be counted among many factors that can have an affect on the continuation of pregnancy.

Among medical reasons, 'hormonal dysfunctions' are one of the most significant reasons of miscarriages. Estrogen and progesterone levels show inconsistencies in miscarriages.

Other endocrine reasons such as diabetes mellitus or glucose intolerance and thyroid hormone dysfunctions are among the important factors that may lead to miscarriages. Aside from high insulin levels, progesterone and LH level's imbalances cause the loss of especially early term pregnancies mainly by disrupting the functions of gonad cells and the endometrium.

Genetic Reasons

Genetic problems take place among the major reasons of miscarriages especially those that take place in the first trimester. When the early miscarriages are inspected, about 70% of them turn out to be due to chromosomal abnormalities (aneuploidies). Incidence of chromosomal aneuploidies increase with maternal age. The most common chromosomal anomalies are trisomies. Sex chromosome monosomies and ploidy anomalies are examples to other common chromosomal abnormalities. While trisomies show an increase in frequency with maternal age, no such relation has been reported between maternal age and sex chromosome monosomies and ploidy anomalies [1].

The correlation between a spontaneous abortion due to a trisomic pregnancy and the following pregnancy being trisomic as well has been found to be a rather weak one [2,3].Besides the maternal age, existence of other risk factors increases the occurrence of spontaneous abortions. For example, an ovarian reserve diminished with maternal age, increases the occurrence rates of trisomies [4,5].

DNA methylation or variations of proteins acting on meiotic segregation can again, increase the rates of spontaneous abortions. An example for this phenomenon is that the polymorphisms in the genes that have a role in the folic acid metabolism or irregularities in folic acid intake by the mother have been reported as a risk factor for trisomy 21 or other aneuploidies [6]. In phenotypically normal couples, recurrent trisomic pregnancies may be due to a gonadal mosaicism. Gonadal mosaicisms have been reported in recurrent trisomy 21 & trisomy18 by some authors [7-9].

The reported increase in recurrent miscarriages in women whose male partners have high levels of chromosomal abnormalities in their sperm lead us to think on the role of paternal factors on miscarriages [10,11]. On the other hand, increased sperm anomalies have been observed in the fathers of fetuses with 'Turner's Syndrome' [12]. Again in the group of increased sperm dysmorphologies, an increase in Robertsonian translocation frequencies, oligospermy and as a result, infertility has been reported to occur [13]. Aneuploidies that cause gestational loss are usually resulting from maternal meiosis I. With this, although to a lesser extend, an increase in sperm chromosome anomalies have been related to occurrence of spontaneous abortions [14]. However, it has been identified that, only at about 7% of fetal trisomies is there a paternal meiotic error [15].

In couples with a history of recurrent miscarriages, being a balanced translocation carrier has been discovered to be a major cause of it. This risk shows great variability depending on which chromosomes were involved in the translocation, the size and location of the translocated segment which decides whether the miscarriage occur early on or later in the pregnancy or even result in the birth of a child with anomalies. The recurrence risk of a miscarriage is affected by the obstetric history of the couple just as much as it is by which partner the translocation is carried by (Table 1), [16]. In the couples with spontaneous abortion history, female partner is twice as likely to have a translocation as her male partner (Table 1).

Although the positive correlation between maternal age and fetal aneuploidy is known, the underlying mechanism is not totally understood. One hypothesis suggests that the oocyte reserves in the ovaries deplete with age and the chances of finding oocytes which have an optimum level of maturation are diminished [17]. Again, it has been shown that women who had trisomic pregnancies and diminished ovarian reserve have entered menopause rather early [18,19].

Another study has shown that in couples who have undergone IVF due to recurrent miscarriages have a higher rate of embryonic aneuploidy compared to the embryos of the control group couples of the same age with no history of miscarriages [20]. In about 4% of recurrent miscarriage cases, at least one of the parents were shown to carry either a Robertsonian or a reciprocal translocation [21]. Even though couples who carry balanced translocations are phenotypically normal, as a result of meiotic segregation, end up having unbalanced gametes with a rate of 50-70%, thus have recurrent miscarriages. The miscarriage rates of such couples depend on the type of translocation, between which chromosomes the translocation took place, the location of the translocation and ultimately on which parent, male or female, the translocation is carried by [22].

When the rates of live & healthy births by two groups of couples who were translocation carriers were contrasted, the ratio favored the couples who became pregnant spontaneously over the couples who became pregnant through the aid of PGD and IVF [23]. An explanation for this unexpected outcome may be the strain that is placed on the mother's body by the procedures of ART (Assisted Reproductive Technologies).

The latest studies have shown that among the genetic causes of early term miscarriages, post-zygotic aneuploidies due to mitotic errors hold an important place. It has been shown that the rate of mitotic errors is higher than that of meiotic errors in an embryo during the cleavage phase [24]. While the meiotic aneuploidy rates increasewith maternal age [25], post-zygotic aneuploidies seem to affect the embryos regardless of maternal age [26].

On the other hand, it has been shown that mosaic aneuploid embryos in the cleavage phase, can undergo self-correction become euploid as they enter the blastocyst stage. Mechanisms such as chromosome demolition [27], anaphase-lag correction [27], non-disjunction correction [28] have been thought to take place during this self-correction process.

Table 1: Translocation rate in RecurrentAbortionCases.

Repeatedspontaneous abortionswithorwithout normallivebirth		Repeatedspontaneous Abortionswithstillbornor abnormallivebirth		Repeatedspontaneous Abortionswithout Subcategorization	
Female	Male	Female	Male	Female	Male
% 2.4	% 1.6	% 4.6	% 1.7	% 3.3	% 2.1

Table 2: Risk Factors for Recurrent miscarriages and their percentages

	Dutch Guideline Risk Factor Yes / No	Respondents Risk Factor (Yes - %)
Maternal Age (>35)	Yes	83
Number of Recurrent Miscarriage	Yes	98
Structural Chromosome Abnormalities	Yes	98
Endocrine Factors (Increased LH / PCOS)	Yes	48
Endocrine Factors (Throid Dysfunction)	No	42
Endocrine Factors (Diabetes)	Yes (unregulated)	65
Uterine Anomalies	Yes	76
Infections	No	27
Coagulation (Antiphospholipid Syndrome)	Yes	98
Coagulation (Thrombophilia)	Yes	93
Coagulation (Hyperhomocysteinaemia)	Yes	95
Lifestyle (Smoking)	Yes	64
Lifestyle (Alcohol)	Not obvious	45

Abbrevations: LH: Luteinizing Hormone; PCOS: Polycystic Ovarian Syndrome

Also, it has been determined that in an embryo at the blastocyst stage, frequency of aneuploid cells in the trophectoderm is quite high whereas the rate is very low in the inner cell mass [29,30]. Our knowledge of this situation has created a great advantage for the PGD applications aimed at the treatment of recurrent miscarriages and will be discussed in further detail in the 'Discussion' section of this article.

Thrombophilic Reasons

There is an increased tendency of coagulation by the mother during pregnancy and coagulopathies have been taking place in the medical literature for a very long time [31]. Among the thrombophilic pathologies that are involved in miscarriages, four mutations were reported to be very closely related which are; Factor V (Leiden) G1691A; factor II (prothrombin) G20210A and methylene tetrahydrofolatereductase C677T and A1298C mutations. With this, the relation between recurrent miscarriages and coagulopathies has been supported in many studies that stress the person-specific coagulation defects in addition to other mutations and variations. However, some studies have shown on the contrary that there is no significant difference between the control group and the group with coagulation defects. But beyond all this, two important meta-analyses have been published that put forth the correlation between recurrent miscarriages and Factor V Leiden & prothrombin mutations [32,33].

In a study carried out by Rai R. and his colleagues live birth rates of 19 women who had first trimester recurrent miscarriage and were carriers for Factor V Leiden mutation, was found to be 37.5% whereas in a control group of 100 women again with a history of first trimester recurrent miscarriages but this time, without Factor V Leiden mutation, live birth rates were found to be significantly higher (69.5%). Rai R. puts forward that there is a very real negative effect of thrombophilic gene pathologies in recurrent miscarriages on possible future pregnancies with this study [34]. Thrombophilic gene pathologies can cause miscarriages either by disrupting the fetal perfusion or by increasing the thrombin and fibrinogen synthesis which leads to protease activation and ultimately enabling trophoblast apoptosis [35]. On the other hand, the histological inspections carried out on first trimester miscarriage materials has shown that there was a decreased maternal blood flow into the placental intervillous space which created an oxidative stress, triggering a trophoblastic apoptosis sequence [36,37].

Countless genes having a role in the etiology of conditions such as PCOS, thrombophilias and auto-immune diseases have also been related to recurrent miscarriages. The polymorphisms of the genes that have been well studied, regarding these three conditions (Factor II, Factor V, HLA-DR3, HLA-G, MBL, INF-Gamma, IL-10, KIR2DS1) although already common in normal populations, were found to be even higher among patients suffering from recurrent miscarriages [38-41].

DISCUSSION AND CONCLUSION

The cases of recurrent miscarriages take place among the most complicated subjects of medicine and are yet to be clarified in terms of both causes and treatment. Recurrent miscarriage is defined as three or more consecutive pregnancy losses, with a gestational age up to 22 weeks. On the other hand, the previous recurrent miscarriages being consecutive or not does not cause an additional risk for the next pregnancy to result in a miscarriage [42]. The risk factors for recurrent miscarriages, have been discussed over the years, however a consensus has been reached on the fundamental factors such as parental age, genetic and immunologic conditions, anatomical and endocrine factors. The correlation between maternal age and recurrent miscarriages has been well established. For mothers between the ages of 20 – 24, the risk of miscarriage is 12% whereas when the maternal age is above 40, the risk can reach up to 50% [43,44].

Both embryonic and parental genetic conditions have an important role on the risk of recurrent miscarriages. Among the embryonic conditions that cause miscarriages, most important ones are aneuploidies arising from meiotic and mitotic (post zygotic) non-disjunction. Of these aneuploidies, monosomy

X and trisomies have been determined to have a major role in miscarriages.

The most important parental genetic reasons of miscarriages are balanced translocations. Balanced translocations are responsible for 2-5 % of recurrent miscarriages and result in one of the three possible outcomes; abortion, infertility or birth of a handicapped child [45]. Of the other risk factors for recurrent miscarriages, trombophilia, alloimmune and anatomical factors have a significant role.

Women who suffer from thrombophilias such as Factor V Leiden deficiency, activated protein C resistance, prothrombin G20210A and protein S deficiency, have been reported to have an increased incidence of recurrent miscarriages[46]. In addition to all this, women who have had recurrent miscarriages should also get tested for lupus anticoagulant (LAC) and anticardiolipin antibodies (aCL), known collectively as antiphospholipid antibodies (APA) in order to eliminate the possibility of antiphospholipid syndrome (APS) [47,48].

Guidelines have been designed both to determine the cause of recurrent miscarriages and to choose the most suitable method of treatment for that specific patient. One of these guidelines is the Dutch guideline 'Recurrent Miscarriage' was introduced in 1999 (Dutch Society of Obstetrics and Gynacology, 1999) [47]. The risk factors that were introduced by this guideline are given in table 2 with their respective frequencies. According to this, thyroid dysfunctions and infections are not considered as risk factors while elevated LH, polycystic ovary and smoking are considered mild risk factors and the remaining factors on the table such as maternal age and chromosomal abnormalities are accepted as high risk factors.

Best approach of treatment for couples suffering from recurrent miscarriages is establishing the cause of this condition and planning accordingly. For this purpose, parental karyotype analysis should be carried out and if a balanced chromosomal rearrangement is discovered; prenatal or pre-implantation genetic diagnosis protocols together with genetic counseling, evaluation of ovarian reserves, evaluation of abnormalities of the uterus via pelvic ultrasound, detection of anti-phospholipid antibodies, detection of Factor V Leiden & Prothrombin gene mutations should be carried out and corresponding precautions should be taken (such as aspirin, heparin...etc.). However, in many cases, the underlying reason of the miscarriage cannot be determined and this causes difficulties in the planning of an appropriate treatment. Especially in the cases of first trimester recurrent abortions, IVF with aneuploidy screening has proven itself to be a good method of treatment when the cause of the miscarriage cannot be established. As it is well known, aneuploidies are the most common causes of early term miscarriages. Especially in the recent years, there have been great advances in reproductive medicine technologies and embryo screening, such as the 'Next Gene Sequencer' which has paved the way for these methods and gave rise to very pleasing results. FISH technique, which has been used quite commonly in the previous years, allowed only for a limited number of chromosomes to be examined and was mostly applied to embryos on the cleavage phase which meant possible damage to the embryos and susceptibility to mosaicism and therefore wasn't a very reliable method. However, in the recent years, this method has begun to leave its place to microarray and ultimately aneuploidy screening by NGS. Since this new method allows chromosomes to be analyzed both quantitatively and qualitatively, it has led to a much more satisfying result in prevention of miscarriages compared to the FISH technique [49,50].

On the other hand, the NGS technology is a far more successful method in spotting mosaic aneuploidies, which have been recently understood to have a serious role in the etiology in recurrent miscarriages, in embryos compared to microarray and with that, it allows for detecting post-zygotic errors (mosaic aneuploidies) which are at least as common as the meiotic errors we encounter. To sum up, trophectoderm biopsy and NGS assisted aneuploidy screening in recurrent early miscarriages are truly great advances that increases the chances of the patients taking home with them, a healthy baby.

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