IN THE NAME OF GOD

Kermanshah University of Medical Sciences
Medical Genetics laboratory

Genetic causes of recurrent miscarriages

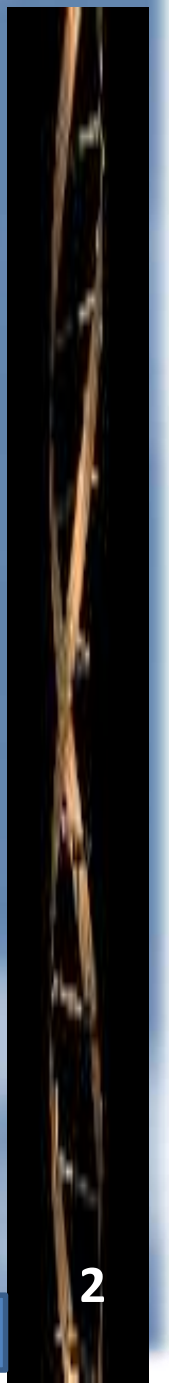
Dr. Reza Alibakhshi
Medical Geneticist (PhD)

Email: ralibakhshi@kums.ac.ir

8 December 2021

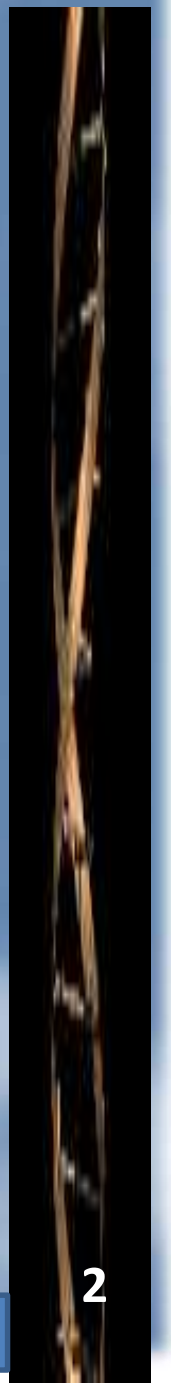
- Miscarriage is the most common complication of pregnancy. Although it is estimated to be responsible for ending 10–15% of clinically diagnosed pregnancies

- **Recurrent miscarriage is an important problem in reproductive health, which affects 1–5% of couples**

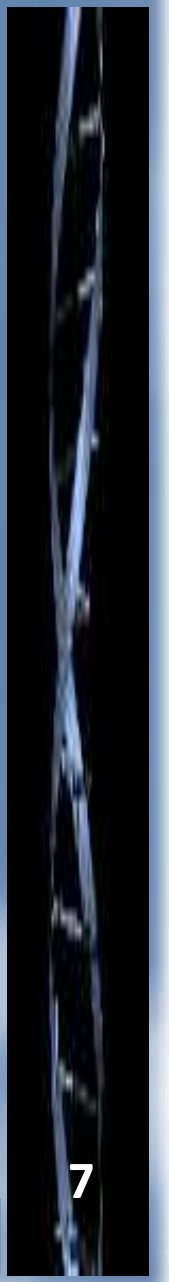


➢• A miscarriage is defined as a pregnancy loss before the 20th week of pregnancy.

➢• Recurrent pregnancy loss is when a woman has experienced two or more consecutive miscarriages with the same partner.

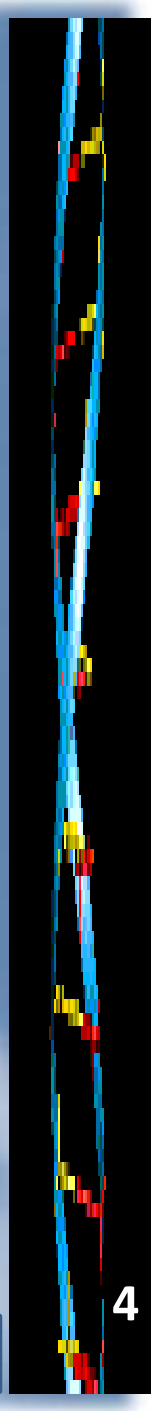


- Genetic reasons may involve changes in maternal, paternal, or fetal genetic material. Genetic tests may be performed in both parents as well as in the miscarriage material (fetus or afterbirth)



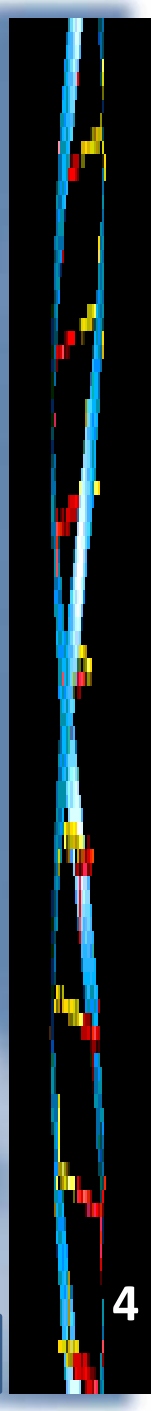
➢Chromosomal abnormalities in first trimester miscarriage

➢First trimester miscarriage without underlying medical conditions is most commonly caused by chromosomal abnormalities reported to occur in 50% or more of cases. These chromosomal changes in early losses include both numerical abnormalities and structural alterations that result in gain and/or loss of genetic information. Structural alterations are much less common than numerical changes.



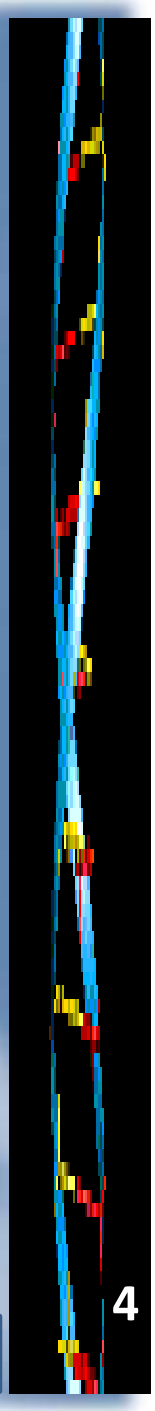
➢CHANGES IN PARENTAL GENETIC MATERIAL

➢Changes in parental (paternal and maternal) genetic material that contribute to the increased risk of miscarriage in successive pregnancies include karyotype abnormalities, recessive and dominant disease carrier status, as well as mutations in genes responsible for coagulation and the metabolism of folates.



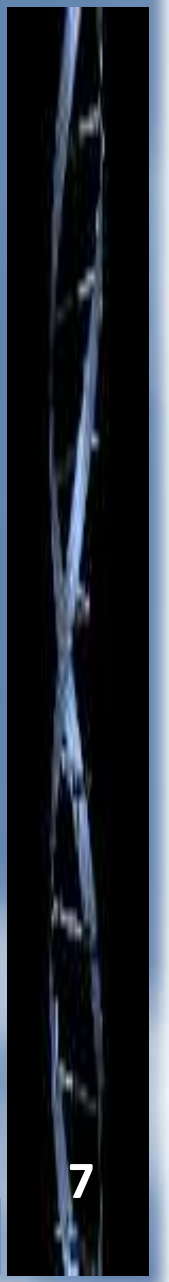
➢CHANGES IN PARENTAL GENETIC MATERIAL

➢The presence of karyotype abnormalities in one of the parents is one of the most common of the known causes of recurrent miscarriages. They are most commonly found as balanced chromosome aberrations, i.e. abnormalities that cause no clinical symptoms in carriers but possibly induce the production of abnormal reproductive cells containing abnormal amounts of genetic material.



➢CHANGES IN PARENTAL GENETIC MATERIAL

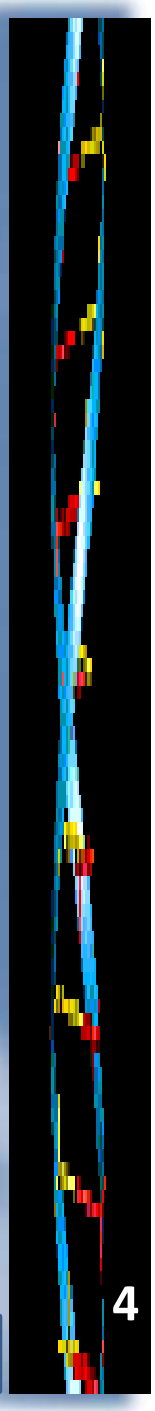
➢Among couples with recurrent miscarriages, balanced translocations are confirmed in at least one of the partners in around 3% to 5% of cases . Most commonly, these include reciprocal translocations, with inversions and Robertsonian translocations being less common. The status of a balanced chromosome aberration carrier increases the risk of miscarriage in subsequent pregnancies, as well as the risk of the child being born with an unbalanced karyotype.



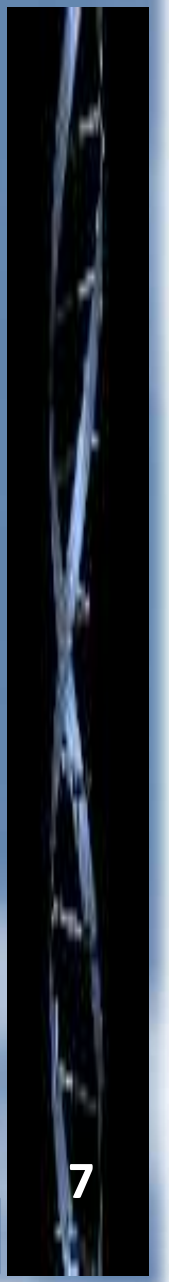
➢CHANGES IN EMBRYONIC/FETAL GENETIC MATERIAL

➢Another genomic cause of miscarriages is associated with the presence of fetal genetic abnormalities. These may include both de novo changes and changes inherited from one of the parents. The knowledge of whether a particular change is a de novo or inherited change is very important in genetic counseling.

➢ It is estimated that about 50% of first-trimester pregnancy losses are associated with chromosome aberrations in the developing embryo/fetus. In most cases, these are de novo changes, which means the risk of a similar abnormality occurring during the next pregnancy is low

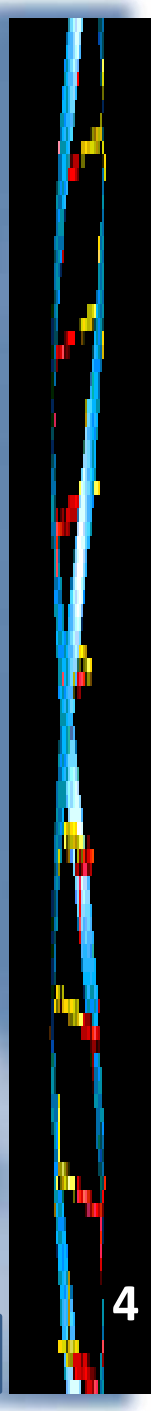


- Around 10–15% of clinically recognized pregnancies result in miscarriage, and about 50% of early pregnancy losses have chromosome abnormalities. Trisomies are the most frequently detected anomalies (61.2%), followed by triploidies (12.4%), monosomy X (10.5%), tetraploidies (9.2%), and structural chromosome anomalies (4.7%). Thus, cytogenetic analysis of spontaneous miscarriages is essential to establish the etiology of fetal losses and to assess patients with risks of recurrence in future pregnancies.



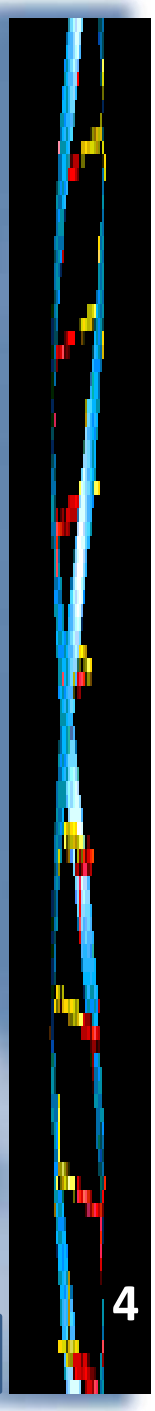
➢CHANGES IN EMBRYONIC/FETAL GENETIC MATERIAL

➢The largest group of abnormalities in embryonic/fetal genetic material consists of aberrations in the number of chromosomes (86%), mainly autosomal trisomies, monosomy X and polyploidies. The remaining group included structural aberrations (6%) and chromosomal mosaicism (8%). Fetal autosomal trisomies represent at least 50% of the chromosomal aberrations responsible for pregnancy loss. Trisomies may be generally observed in all autosomal chromosomes, although the incidence of particular trisomies varies. The most common trisomies are observed with chromosome 16 followed by chromosome 22. Also frequently encountered are the trisomies of chromosomes 13, 15, 18, and 21 . The risk of embryonic/fetal trisomies increases with maternal age

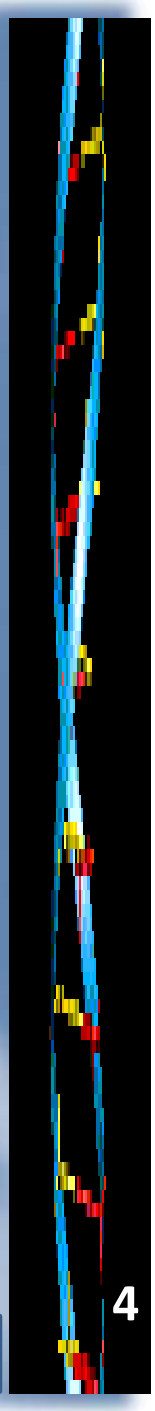


FETAL ANEUPLOIDY IN SPORADIC AND RECURRENT PREGNANCY LOSS

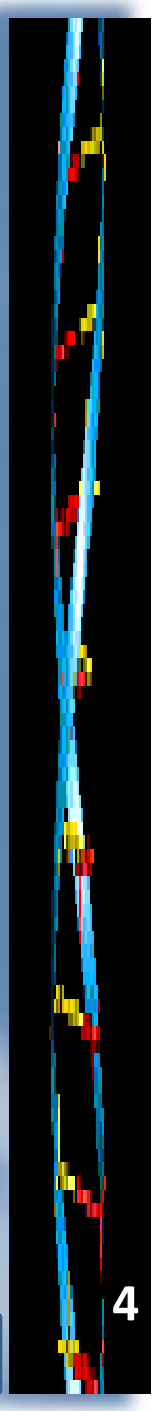
- Overall, 50%–70% of specimens from sporadic spontaneous losses show some type of cytogenetic abnormality, with the most common karyotypic defects being autosomal trisomies (60%), monosomy X (20%), and polyploidy (20%) . **Most result from random errors in germ cell development that, by definition, affect pregnancies in couples with and without a history of RPL equally**. Typically, numerical aneuploidy results from meiotic nondisjunction in the germ cells of couples with normal parental karyotypes, and the recurrence of a particular abnormality in future pregnancies is rare in patients presenting with RPL and in the general population.
- **The frequencies and specific types of chromosomal abnormalities found in tissues obtained from sporadic spontaneous pregnancy losses vary with the gestational age of the fetus at the time of demise and with maternal age.**



- Losses occurring early in pregnancy appear to display a wide range of fairly unusual aneuploidies, whereas deaths that appear later in gestation show those aneuploidies more typically detected in live births, such as trisomies 21, 18, and 13 .
- Fetal aneuploidy is present at a frequency of up to 90% in specimens obtained from losses aged 0–6 wk of gestation, ~50% in sporadic losses occurring at 8–11 wk gestation, and 30% in tissues from losses at 16–19 wk gestation. Six to 12% of miscarriage specimens obtained from demises that occur after 20 wk of gestational display chromosomal abnormalities .
- Once a fetal heart rate is evident on ultrasound, the risk of aneuploidy is <5%.

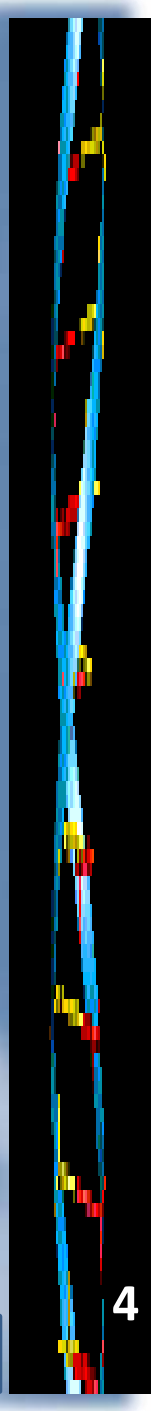


- Rates of sporadic pregnancy loss and of overall fetal chromosomal aberrations increase with maternal age, although maternal age has a preferential effect on certain aneuploidies. There are no significant associations between advanced maternal age and rates of sex chromosome monosomy or polyploidy, but strong correlations can be seen with rates of autosomal trisomy.
- The degree of the correlation differs significantly among specific types of trisomies. For example, the largest effect of advanced maternal age is seen in trisomies involving small chromosomes (8, 9, 10, 13, 14, 15, 18, 20, 21, and 22), whereas trisomy 16 is less closely correlated.

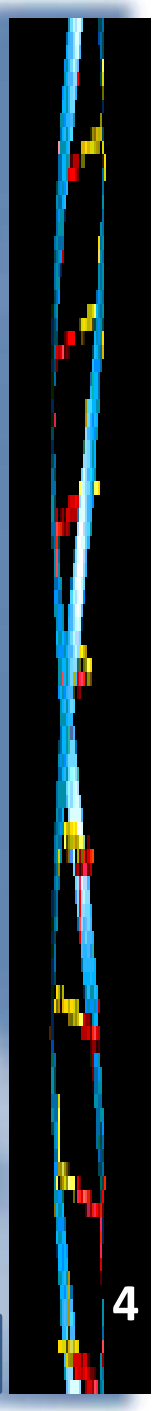


There are several lines of evidence that suggest nonrandom genetic aberrations among couples with RPL.

- First, the frequency of parental karyotypic abnormalities, including balanced translocations, is higher among couples with a history of RPL (2%–5%) than in the general population (0.2%) .
- Second, the prevalence of RPL among first degree relatives of women with RPL is increased approximately sixfold compared with controls .
- Third, preimplantation genetic screening (PGS) in age matched populations shows that embryos from women with RPL have a higher incidence of aneuploidy than those from women undergoing screening for reasons not related to pregnancy loss.
- **Although aneuploidy rates are higher in embryos from women with RPL than in controls, the frequency of cytogenetic abnormalities in miscarriage tissues obtained from women with RPL is lower than that in women experiencing sporadic loss, occurring in only 25%–50% of cases .** This suggests that noncytogenetic etiologies also occur more frequently in women experiencing RPL than in those with sporadic losses.



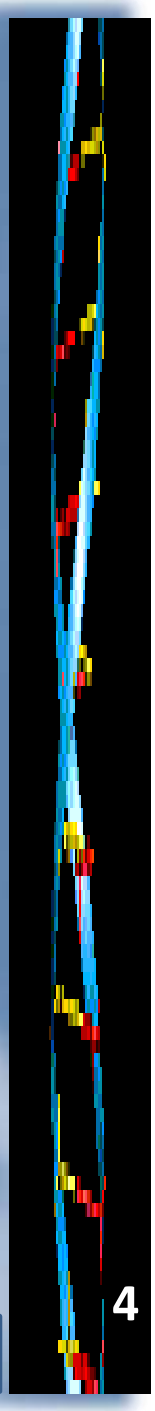
- The effects of paternal, as opposed to maternal, meiotic errors and paternal age on reproductive outcome are less clearly defined. Although errors of nondisjunction occur to a lesser extent in sperm than in oocytes, paternal errors are responsible for the majority of cases of the sex chromosome trisomies XXY and XYY .
- Sperm from couples with a history of recurrent miscarriage display an increase in sex chromosome disomy (an extra chromosome in the haploid state of the gamete) compared with control groups.
- Oligoasthenoteratozoospermic patients (patients with abnormalities in sperm number [low], motility [low], and morphology [too few normal forms]) have the highest rates of sex chromosome disomy as well as high rates of disomy of chromosomes 18 and 21 when compared with normozoospermic patients



Why Chromosomal Abnormalities Can Cause Miscarriage and Stillbirth

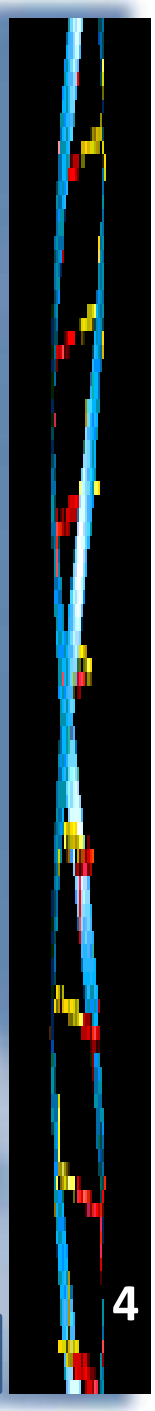
In most instances, scientists do not know the exact reason why chromosomal abnormalities lead to miscarriage.

- One theory is that the mother's immune system recognizes a problem in the developing baby's genes and thus ends the pregnancy.
- Another theory is that the developing baby ultimately reaches a point where the specific genetic problem causes the baby to stop growing. Certain genes might be missing that is necessary for continued development, or extra copies of certain genes might cause the baby or placenta to grow improperly.



Human Chromosome Nomenclature

- As the field of cytogenetics and molecular genetics evolves, a standardized nomenclature system is critical for describing karyotypes and genomic changes accurately and concisely worldwide. The International System for Human Cytogenetic Nomenclature or ISCN is the communication tool for describing human chromosomes and chromosomal aberrations associated with human disease. This reference has served cytogeneticists since 1960, and through its periodic updates, it continues to provide standardized guidelines for consistency in the descriptive and interpretive reporting of the various chromosome aberrations observed in constitutional and neoplastic disorders
- This notation includes the total number of chromosomes, the sex chromosomes, and any extra or missing autosomal chromosomes. For example, 47, **XY**, +18 indicates that the patient has 47 chromosomes, is a male, and has an extra autosomal chromosome 18.

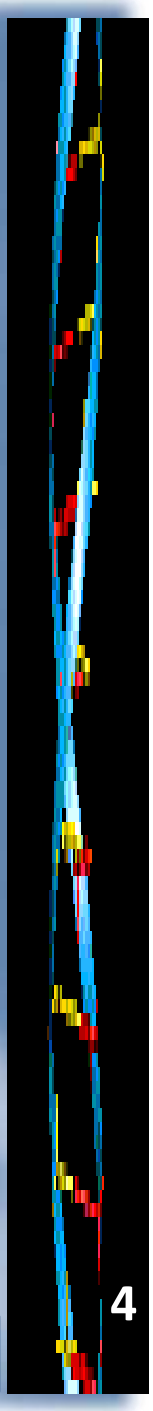


- 46,XY
- 46,XX
- 47,XXX
- 69,XXY or XXX
- 46,XX or XY, inv(9) (p11; q12)

➢ASSESSMENT OF THE MISCARRIED MATERIAL

➢The use of classic cytogenetic examination to assess fetal karyotype in the miscarried material is complicated by the sample being contaminated by maternal tissue and the associated risk of false negative results.

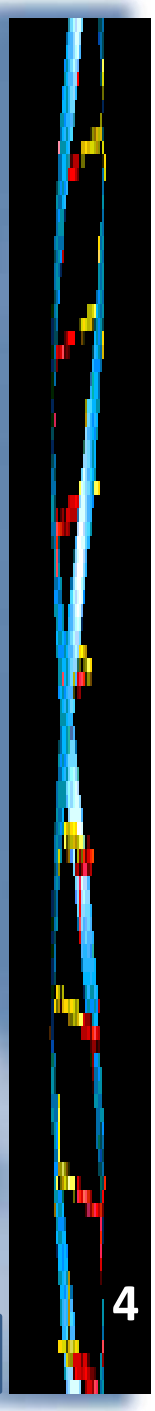
➢ The method also depends on the correct performance of cell culturing, which is not always possible in case of miscarried tissue.



➢ASSESSMENT OF THE MISCARRIED MATERIAL

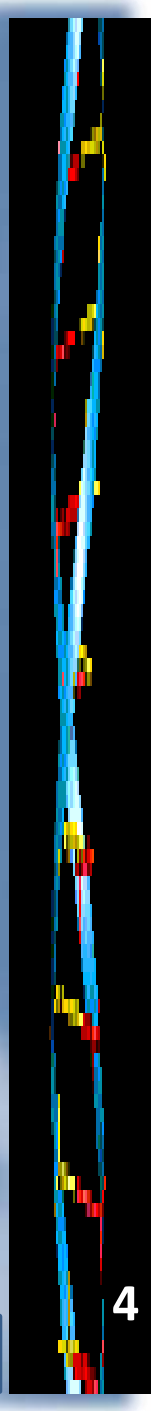
➢Genetic analyses of the miscarried material are usually based on molecular biology techniques. Proper collection of the examined sample is important to avoid contamination with maternal tissue. The miscarried material must first be dried and rinsed of blood with physiological saline, before precise isolation of chorionic villi is performed.

➢The assessment of the presence of genetic abnormalities within the miscarried material may be based on molecular diagnostic methods such as FISH, MLPA, QF-PCR, BoBs or comparative genomic hybridization (CGH), which allow not only the detection of aneuploidy in fetal tissues but also microdeletions and other unbalanced genomic changes. Some hope is offered by novel diagnostic methods such as next-generation sequencing (NGS), which facilitates the simultaneous examination of all or selected genes, allowing diagnosis and then a choice for further action.



GENETIC TESTING AS A DIAGNOSTIC TOOL IN recurrent pregnancy loss (RPL)

- Routine cytogenetic testing of POCs in couples experiencing RPL has been shown to be cost-effective and to direct management decisions , even at a time when analytical methods were based on karyotyping of cultured trophoblast cells and hindered by the occurrence of culture failure and maternal cell contamination. Genetic testing of POCs using nonculture-based techniques such as array comparative genomic hybridization with or without reflex microsatellite single nucleotide polymorphism (SNP) analysis is more precise, more detailed, and more reliable than culture-based methods and should add to cost-efficiency and overall utility. Nonculture-based techniques have been used successfully in fresh and in preserved tissues.



Parental Genetic Testing

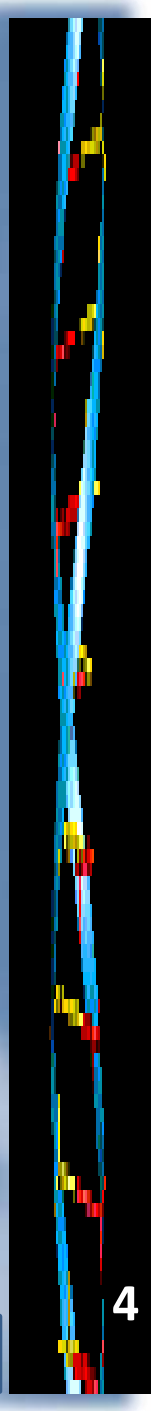
- **Peripheral Blood Karyotyping**

Parental numeric and structural cytogenetic abnormalities are perhaps the most thoroughly investigated genetic causes of RPL. Robertsonian translocations and balanced reciprocal translocations are detected in 2%–5% of couples with RPL.

- **Single Gene Defects**

Single gene defects have been significantly less studied than karyotypic causes of sporadic miscarriage and RPL. Major groups of single gene defects that have been associated with pregnancy loss encompass musculoskeletal gene mutations including trinucleotide repeat disorders, genes involved in regulation of the immune system and implantation, thrombophilic gene mutations, and mutations in specific enzymes, including angiotensin-converting enzyme, ubiquitin-specific protease, and human alkaline phosphatase.

- *Musculoskeletal gene defects:* Myotonic dystrophy, thanatoporic dysplasia, and type II osteogenesis imperfecta are among the single gene musculoskeletal disorders associated with RPL.

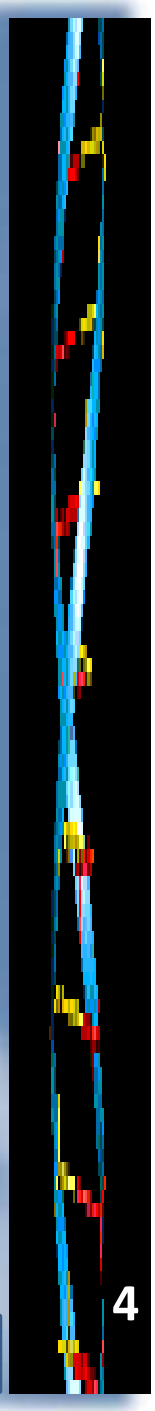


Parental Genetic Testing

Immunologic gene defects

Because of the substantial immunologic mechanisms responsible for successful reproduction, studies on the role of single gene defects in sporadic and RPL have included the role of genes involved in immune regulation. The gene encoding the human leukocyte antigen-G (HLA-G), an important component of alloimmune recognition at the maternal–fetal interface, has been extensively studied. The presence of a null allele for the most common HLA-G isoform as well as distinct polymorphisms in the HLA-G promoter region, have been associated with recurrent miscarriage, suggesting that a functional protein is necessary for reproduction .

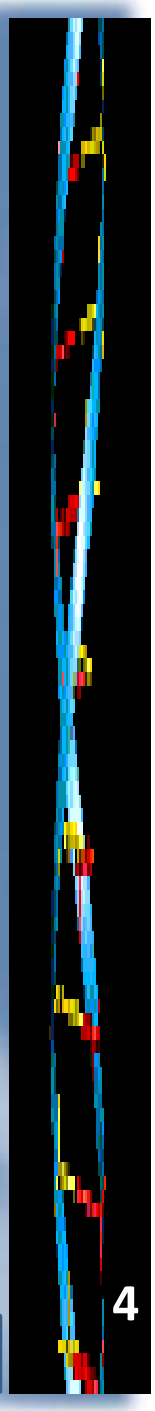
Polymorphisms in genes including p53, p72, leukemia inhibiting factor (LIF), FAS-L, and the vascular endothelial growth factor (VEGF) gene have also been linked to increased rates of implantation failure and are undergoing investigation to determine their potential roles in women with RPL



Parental Genetic Testing

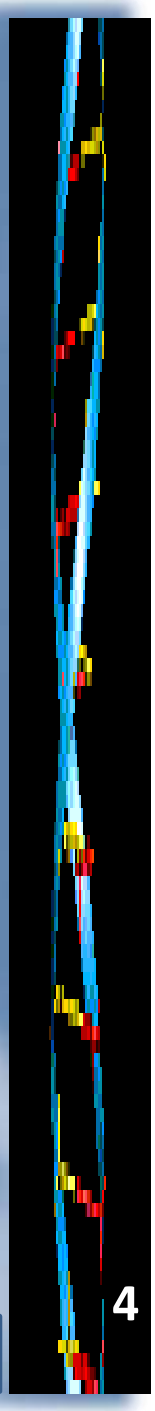
Thrombophilic gene defects

The genetic defects involved in the ever-expanding group of inherited thrombophilias are perhaps the best studied single gene mutations with reference to RPL. Among these, the majority of reports have addressed factor V Leiden, prothrombin gene promoter mutations, activated protein C resistance, and mutations in methylenetetrahydrofolate reductase, plasminogen activator inhibitor, thrombomodulin, and annexin A5 genes. Unlike trinucleotide expansion disorders and immune–related single gene mutations, the gene mutations causing several of the inherited thrombophilias are seen in relatively high prevalence in select populations. The data linking these defects to RPL, however, are conflicting. Mutations in factor V Leiden, the most common genetic cause of thrombosis, have a twofold higher prevalence in women experiencing repeated miscarriages compared with controls.
Mutations in the gene encoding Annexin A5, a protein that acts as an anticoagulant in placenta villi, have also been associated with a twofold increase in RPL ris



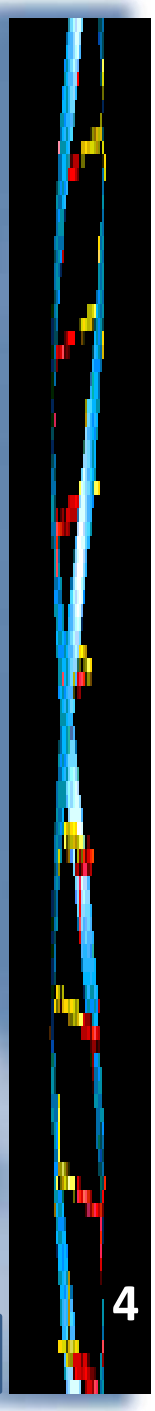
Overview of Chromosome Abnormalities in First Trimester Miscarriages: A Series of 1,011 Consecutive Chorionic Villi Sample Karyotypes (Anna Soler et al)

➢**Autosomal Trisomy:** Autosomal trisomy was the most frequent chromosome abnormality diagnosed, found in 517 cases (including the cases with a polyploidy plus an extra chromosome). Among them, 459 were single autosomal trisomies: 110 involved chromosomes 13, 18, or 21; 236 involved chromosomes 15, 16, or 22 (“common” non-viable trisomies); and 113 the remaining chromosomes (“rare” non-viable trisomies), with the exception of chromosomes 1, 3, and 19. Mosaicism with a chromosomally normal cell line was observed in 14/459 cases.

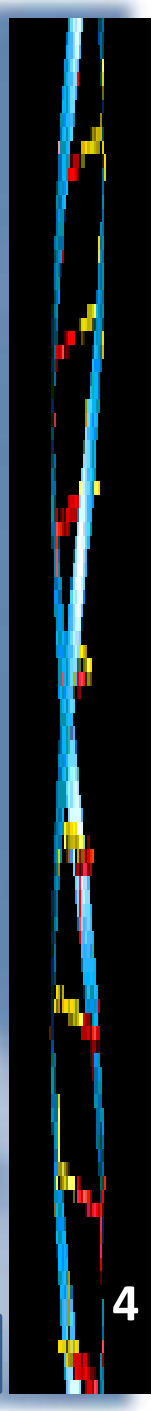


➢**Triploidy** : Triploidy was the second most frequent abnormality diagnosed (n = 93), accounting for 13.1% of the abnormal karyotypes. Eighty-four cases showed pure triploidy: 32 cases with 69,XXX, 51 cases with 69,XXY, and a single case with 69,XYY. Eight cases showed hypertriploidy with an extra autosome, and the remaining case had an extra chromosome X.

➢**Tetraploidy** : Tetraploidy was found in 1.4% of the abnormal cases (n = 10). Five cases showed a 92,XXXX karyotype, 3 cases 92,XXYY, and 1 case had an extremely rare 92,XXXY karyotype. In the remaining case, an extra chromosome was present in addition to the tetraploidy (93,XXYY,+20) **.** In 2 cases, the non-mosaic tetraploid cell line was only present in the LTC



- Sex Chromosome Trisomy:
- Only 2 sex chromosome trisomies were detected: one 47,XXX and one 47,XXY.
- Monosomy
- Monosomy was detected in 82 samples. Monosomy X accounted for 92.7% of the cases, thus representing 10.7% of the abnormal karyotypes. Sixty-nine cases showed a pure 45,X karyotype, 1 showed mosaicism (45,X/46,XX), and in 6 cases monosomy X was observed with another chromosome abnormality: autosomal trisomy (4 cases) or structural rearrangement (2 cases). The remaining monosomies involved chromosome 21 (4 cases), chromosome 8, and chromosome 13



➢Classic cytogenetics,molecular cytogenetics, and molecular biology techniques used for the examination of embryonic/fetal material

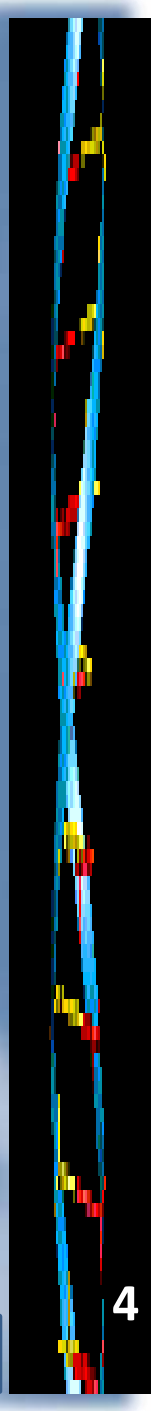
Method characteristics	Classic karyotype	a CGH	MLPA	QF-PCR	BoBs	FISH with probes	NGS
Detection	• **Changes in the number of chromosomes (aneuploidies, polyploidies)** • **Structural aberrations (such as inversions, deletions, additions,** translocations) **— balanced and unbalanced** • Marker chromosomes Standard cytogenetic examination facilitating the analysis of the entire karyotype to search for chromosome aberrations	• Changes in the number of chromosomes (aneuploidies, triploidies) • **Unbalanced structural changes** (such as duplications, deletions, and amplifications)	• Chromosomal aneuploidies (deletions and duplications) Used mainly for identification of particular subtelomeric aberrations (i.e. aberrations within the chromosomal termini) as well as known microdeletion syndromes MLPA facilitates simultaneous screening for multiple chromosome aberrations	• Aneuploidies within chromosomes 15, 16, 22 and 13, 18, 21, X and Y; • Triploidies • Determination of the origin of the additional chromosome	• Most common aneuploidies (13, 18, 21, X, Y) • Deletions and duplications of particular regions	• Chromosomal aneuploidies • Diagnostics of submicroscopic chromosomal aberrations • Identification of complex structural aberrations • Identification of marker chromosomes Used for the analysis of both metaphase chromosomes (cell culturing required) and interphase nuclei	NGS facilitates sequencing of large genomic regions, high numbers of genes, or a high number of samples within a single test
Method limitations	The requirement to culture the cells	No detection of translocations and inversions within the genome	Diagnostics of changes within the genetic material **as defined in the intended use of the kit**	Diagnostics of changes within the genetic material **as defined in the intended use of the kit**	Diagnostics of changes within the genetic material **as defined in the intended use of the kit**	Diagnostics of **specific changes** within the genetic material (depends on the probes used)	Very high sensitivity and ability to detect very minute changes within the genome, leading to excess information uninterpretable for the purposes of diagnosing the genetic causes of miscarriage
	Possibility of the sample being contaminated with maternal material must be taken into account						
Time required to obtain the result	14–21 days (previous cell culturing required)	Several days	2 days	1 day	1 day	Up to 14 days (if previous cell culturing required)	
The time required to carry out the test and obtain the result is in this case not as important as e.g. in prenatal or preimplantation diagnostics. What is important is the possibility to detect various genetic changes responsible for the miscarriage (in most cases, these are major changes rather than single point mutations which are less common)							
Cost	ca. PLN 700-900	PLN 1500–2500	PLN 700–800	PLN 600–950	PLN 1500–1600	Dependent on the number of probes — from PLN several hundred to PLN 1500)	Very high expenditures (PLN several thousand)

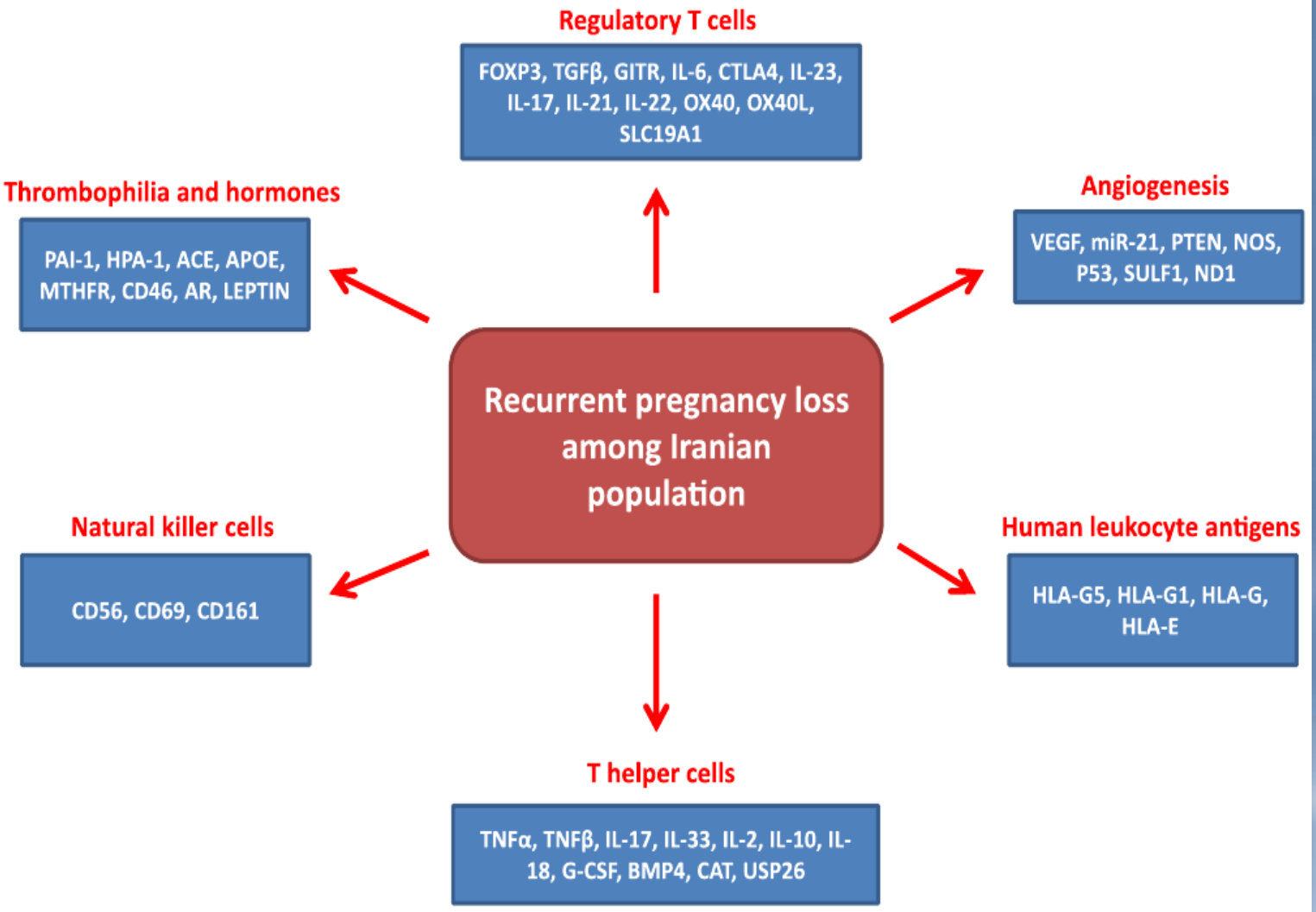
➢Genetics of recurrent pregnancy loss among Iranian population

- Various factors are associated with RPL such as immunological disorders, maternal age, obesity, alcohol, chromosomal abnormality, endocrine disorders, and uterine abnormalities. About half of the RPL cases are related with chromosomal abnormalities. Therefore, RPL genetic tests are mainly limited to karyotyping.

However, there is a significant proportion of RPL cases without any chromosomal abnormalities that can be related to the single-gene aberrations. Therefore, it is required to prepare a diagnostic panel of genetic markers besides karyotyping.

- All the significant reported genes until now which are associated with RPL among Iranian women were summarized . All the reported genes based on their cellular and molecular functions in order to determine the molecular bases of RPL in this population were categorized.
- Meysam Moghbeli, Mol Genet Genomic Med. 2019;7:e891.

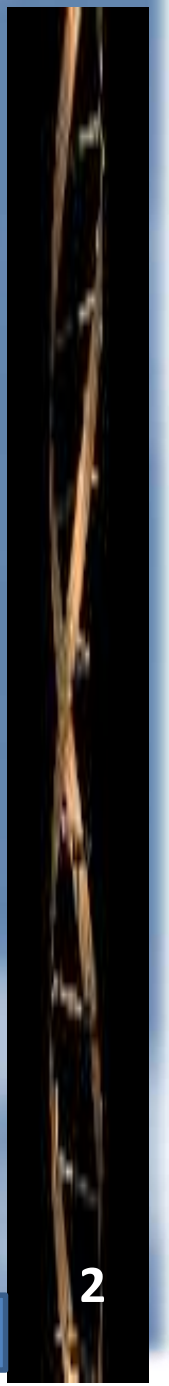



Regulatory T cells
FOXP3, TGFβ, GITR, IL-6, CTLA4, IL-23, IL-17, IL-21, IL-22, OX40, OX40L, SLC19A1
Thrombophilia and hormones
PAI-1, HPA-1, ACE, APOE, MTHFR, CD46, AR, LEPTIN
Angiogenesis
VEGF, miR-21, PTEN, NOS, P53, SULF1, ND1
Recurrent pregnancy loss among Iranian population
Natural killer cells
CD56, CD69, CD161
Human leukocyte antigens
HLA-G5, HLA-G1, HLA-G, HLA-E
T helper cells
TNFα, TNFβ, IL-17, IL-33, IL-2, IL-10, IL-18, G-CSF, BMP4, CAT, USP26

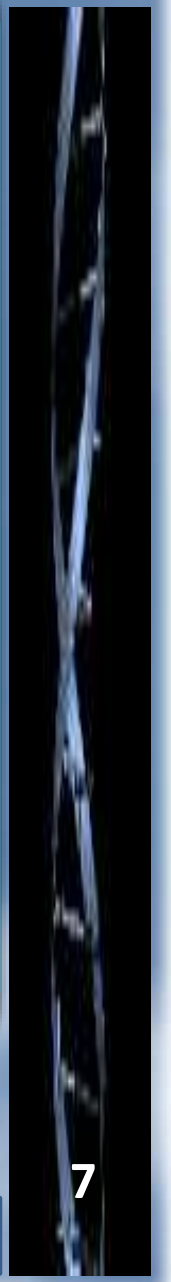
- Identifying the causes of recurrent pregnancy loss in consanguineous couples using whole exome sequencing on the products of miscarriage with no chromosomal abnormalities

Kimia Najaf 1,2, Zohreh Mehrjoo1 , FaribaArdalani1 , SiavashGhaderi-Sohi2 , Ariana Kariminejad2 , Roxana Kariminejad2 & Hossein Najmabadi1,2*

Scientifc Reports | (2021) 11:6952 | https://doi.org/10.1038/s41598-021-86309-9

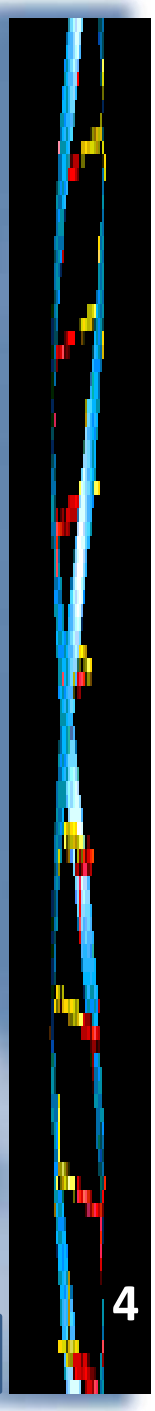


- WES on the products of miscarriage is helpful to verify lethal genes, and genes essential for embryonic development, and it expands our knowledge of prenatal phenotypes of many Mendelian disorders. The WES can assist in the diagnosis of the cause of miscarriage. Positive results and having a diagnosis can be useful in preconception genetic counselling for future successful pregnancies. Preimplantation genetic testing may be possible and the results may provide families with closure. After diagnosis, it is important to advise families on the risks of recurrence and their options for future pregnancies. Identification of the cause of miscarriage will determine the risk for future pregnancies, and enable prenatal diagnosis or preimplantation genetic diagnosis for the given family. In addition, we will be able to identify lethal genes and their role in pregnancy loss. This and other studies of this kind will provide information that can assist in the assessment of repeated pregnancy loss.
- **Conclusion : WES can be helpful in making a diagnosis of lethal disorders (especially autosomal recessive disorders) in consanguineous couples after prior genetic testing (QF-PCR and a-CGH).**



➢CHANGES IN PARENTAL GENETIC MATERIAL

➢Recessive diseases may be induced by the presence of mutations responsible for single-gene recessive diseases in both of the parents, particularly when the parents are close of kin. An example of such a disease is congenital methemoglobinemia. Other examples include the carrier status of mutations responsible for congenital arthrogryposis or Smith-Lemli-Opitz syndrome. Interestingly, the incidence of Smith-Lemli-Opitz syndrome is lower than predicted, which may be attributed to a lack of awareness of the wide spectrum of fetal defects associated with SLO syndrome among obstetricians . If the genetic problem is an autosomal recessive disease, the risk of abnormality recurring in the successive pregnancy is high, amounting to 25%.

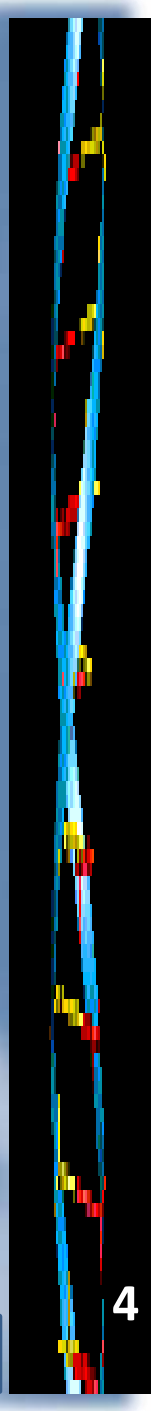


➢CHANGES IN PARENTAL GENETIC MATERIAL

➢Another group of disorders is composed of autosomal dominant diseases which are transferred to the progeny with a high probability (50%). Symptoms of these diseases may intensify in subsequent generations (anticipation), as exemplified by myotonic dystrophy, a disease affecting mainly the muscular system, and which is associated with myotonia, muscle stiffness, disturbed speech and swallowing. Myotonia may lead to obstetric complications including miscarriages, preterm birth, edemas, intrauterine fetal demise (stillbirth), prolonged labor or intrapartum hemorrhages.

➢In the case of homozygotic mutations, IUFD (intrauterine fetal death) is associated with the presence of an autosomal dominant disease in both parents, one example of which is achondroplasia. In such cases, it is feasible to use targeted diagnostics in the parents, who should be offered a thorough clinical examination and analysis of descent, followed by diagnostic molecular tests.

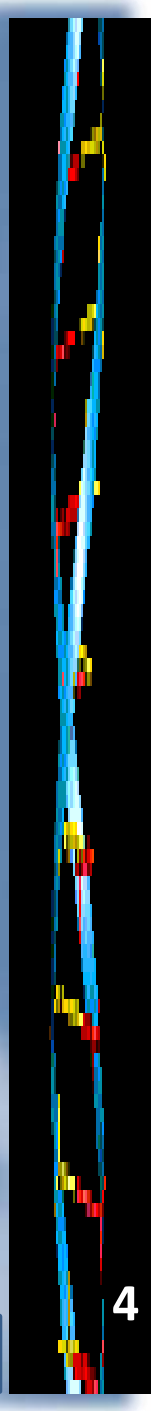
➢Diseases inherited in patterns linked to the X-chromosome may lead to the IUFD of male fetuses. These include congenital Bloch-Sulzberger disease, Goltz syndrome, Rett syndrome and Aicardi syndrome. As these syndromes are very rare, no routine diagnostic tests are currently recommended for screening.



➢CHANGES IN PARENTAL GENETIC MATERIAL

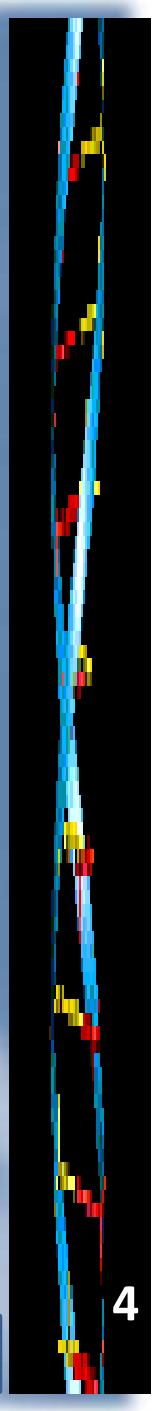
Another cause of recurrent miscarriages is congenital thrombophilia following damage to the maternal factor V gene G1691A (Leiden mutation) and prothrombin gene (G20210A mutation). These mutations are well studied and the test is part of the routine diagnostics of recurrent miscarriages. In the case of factor V, both the Leiden mutation G1691A and the T1328C mutation appear to be important in the pathogenesis of recurrent miscarriages, particularly in cases observed before the 7^{th} week of gestation . However, identification of the polymorphism within factor V gene (Leiden mutation) and prothrombin factor II gene may be an insufficient method of screening for congenital thrombophilia risk factors. Obstetric failures may also be caused by genetically-determined disturbances in the activity of, *inter alia*, factor VII, factor XIII, or beta-fibrinogen . However, no current studies report findings which unambiguously confirm the impact of these factors on recurrent miscarriage.

A relationship has been noted between recurrent miscarriage and paternal congenital thrombophilia. A six-fold greater risk of miscarriage was observed in pairs with paternal factor V Leiden mutation as compared to a control group . The mechanism of this phenomenon has not yet been appropriately studied.



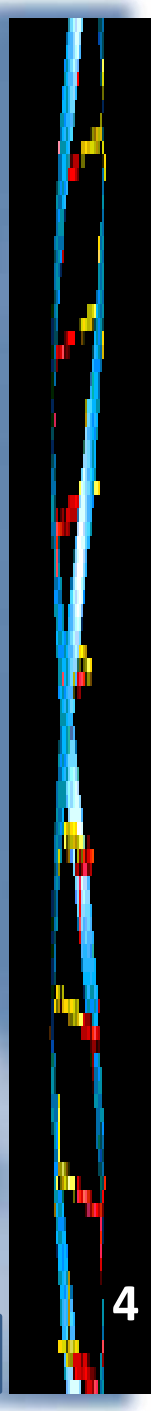
➢CHANGES IN PARENTAL GENETIC MATERIAL

- However other studies report no significant difference in the frequency of specific thrombophilia-responsible mutations in women with a history of at least two miscarriages as compared to those with no pregnancy loss. This may suggest that obstetric failures may be dependent on the total number of individual mutations rather than the presence of individual gene mutations .
- The impact of mutation within the *MTHFR* gene, a gene encoding a protein involved in the metabolism of folates, on recurrent miscarriages is currently a matter of debate. Reports suggest no relationship between hyperhomocysteinemia and reproductive failures. This may be due to folic acid supplementation, particularly during the first trimester



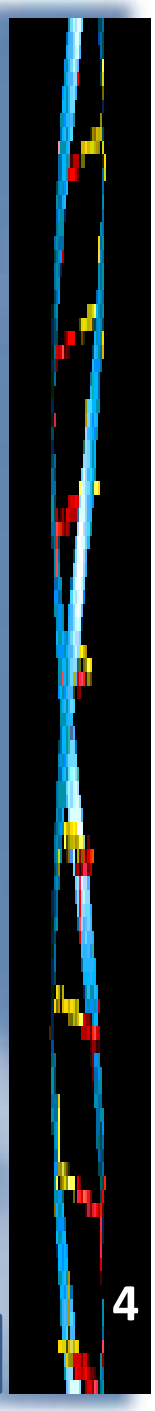
➢CHANGES IN EMBRYONIC/FETAL GENETIC MATERIAL

➢The largest group of abnormalities in embryonic/fetal genetic material consists of aberrations in the number of chromosomes (86%), mainly autosomal trisomies, monosomy X and polyploidies. The remaining group included structural aberrations (6%) and chromosomal mosaicism (8%). Fetal autosomal trisomies represent at least 50% of the chromosomal aberrations responsible for pregnancy loss. Trisomies may be generally observed in all autosomal chromosomes, although the incidence of particular trisomies varies. The most common trisomies are observed with chromosome 16 followed by chromosome 22. Also frequently encountered are the trisomies of chromosomes 13, 15, 18, and 21 . The risk of embryonic/fetal trisomies increases with maternal age



CONCLUSIONS

- Genetic variables appear to play a complex role in the efficiency of human reproduction. Classically, high rates of chromosomal errors have been among the leading etiologies for fetal loss and more recent studies have begun to highlight the important role that specific single gene defects may play in pregnancy maintenance.
- Overall, the prognosis for a patient with RPL is good and most women with a history of RPL are less likely to miscarry in subsequent pregnancy than to deliver a live–born. It is only after a large number of sequential losses that this ratio reverses. To help aid couples struggling with RPL, limited and focused genetic testing is recommended as part of the diagnostic approach.
- PGD may be indicated in a small proportion of couples with defined translocations or select single gene disorders. Although great strides have been made to increase the accuracy and practicality of PGS for couples with RPL, such investigations are not presently indicated outside of clinical studies. Still, they hold much promise for future incorporation into the treatment of couples with RPL.



با تشکر از توجه شما