



Review Article

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Genetic Disorders in the Fetus from Diagnosis to Treatment

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Received: 24 Dec 2018

Revised: 23 May 2017

Accepted: 26 Jul 2017

ARTICLE INFO

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Keywords:
Genetic,
Pre-implantation Diagnosis,
Genetic counseling,
Congenital

ABSTRACT

Background: Today there are many diseases that genetics contributes to these, including diabetes, hypertension, cancer, heart disease, various types of cancers and even mental illness, and by the advancement of medical knowledge The number of genetic diseases is increasing now. most people think about genetic diseases as inherited diseases, which are mostly caused by gene mutations and other genetically inherited factors. Most of the genetic disorders currently do not have 100% treatment, and the only way is to preventing the prevalence of them before marriage.

Methods: Eligible articles were identified by search of databases including NCBI, PubMed, ISI Web of Knowledge and Google scholar up to July 2017.

Results: In the field of prevention of disability and genetic disorders, many members who are at risk of genetic disease should have genetic counseling to get useful information about it. Without genetic counseling, genetic testing is meaningless, as people do not go to the laboratory without a doctor's visit; Genetic counselors won't be able to stop people from getting married, but they provide solutions to prevent them from possible disorders.

Conclusions: This study provides information on genetic diseases and prevents them in newborns and suggests new solutions for the treatment of these diseases.

Introduction

Whenever any of genes is defective and cannot transfer its information properly, function of the body is impaired and a genetic disorder is created. Genetic diseases are often transmitted from parents to their offspring and over generations.

Genetic disease or genetic disorder is caused by one or more defects in one or more genes. This defect is in the genetic code of DNA and can lead to malfunctioning of vital body systems and organs activities such as the immune system or the endocrine system, or prevent the growth of a normal organ such as

bones or skin.¹

A genetic disorder appears through the creation of abnormalities in the factors and elements including DNA molecules or genomes (sequences of genes), that determine the traits and features of individual, and these abnormalities are divided into four groups: single-gene mutations, multi gene mutations, Chromosomal and mitochondrial changes.²

It is clear to researchers that some races are susceptible to certain types of genetic disorder. For example, European Mediterranean inhabitants are more susceptible to a type of genetic anemia, and some types of genetic disorders such as sickle cell anemia which is the result of the body's response to environmental stimuli.³ In fact, in patients with sickle cell anemia, a genetic mutation that transforms red blood cells helps to minimize the risk of malaria. With advances made in molecular genetics, today, it is possible to detect all genetic diseases that have been identified as pathogenic before birth.⁴

Genetic Principles

Males share 23 chromosomes (sperm) and women shares 23 chromosomes (oocytes) which are combined in fertilization and form the first cell that forms the baby (46 chromosomes total). A collection of sperm and ovum chromosomes are called sex chromosomes. The oocyte always has a chromosome of the substance (x), whereas the sperm can have a male (y) or a (x) chromosome. Chromosomes consist of a large number of genes. These genes are either dominant or recessive. The dominant genes are alone effective in determining the characteristics of the child.^{2,5}

Congenital defect

Congenital defects are disorders seen in the appearance and function of the child. Congenital defects can be diagnosed at the same time in the delivery room, later identified in the child's life, or even during pregnancy. Regardless of the time of diagnosis of congenital defects, all of them

are called congenital or genetic disorder. In most countries, large investments and serious measures are being taken to upgrade the future generation, so both couples consult with geneticists before they get married and go to childbearing.⁶

Genetic counseling can be a branch of medical genetics that examines the likelihood of developing genetic diseases in people. Genetic counseling is in fact an educational process that helps people who are at risk to understand the nature of the genetic disorder (hereditary disease) and how it is transmitted and better understand the issues associated with the treatment of these diseases and family planning.⁷ Generally referring to a geneticist, before marriage and pregnancy, or in the early stages of pregnancy, can prevent the birth of newborn babies with genetically diseases and give a healthy generation to the community. Because, according to geneticists, congenital genetic diseases account for 20% of infant deaths, of which at least 50% can be detected and prevented.⁸

Prenatal Diagnosis is the most reliable way of preventing genetic diseases that has been raised in our country so far and has prevented the birth of newborns with different hereditary, congenital and genetic diseases in the past few years. Prenatal diagnosis is actually the application of various diagnostic methods to examine the condition of the fetus during pregnancy, since postnatal genetic disorders are generally not treatable.⁹

In fact, many of the genetic diseases and birth syndromes that occur at birth in the fetus (congenital) such as Down syndrome or after birth, such as thalassemia and hemophilia, are easily identifiable before birth. These types of diseases can lead to infant deaths or illness for many years, depending on their type and severity, As a result, in addition to the patient who sustains his lifetime, they causes huge costs to the patient's family and community.¹⁰

Embryonic genetic disorders

Chromosomal abnormalities account for 6%

of abnormalities. Heredity only causes genetic abnormalities in 20% of cases. Teratogens (toxins and drugs) make congenital malformations in 4 to 5% of cases.¹¹

Types of Genetic Disorders in the Neonatal

1. Teratogenic problems in the baby:

Sometimes, teratogens can cause disorders in children. Children who are exposed to alcohol, lead, high levels of radiation, and some drugs in the first trimester of pregnancy are more likely to develop teratogenic disorders and are born with these disorders.¹²

2. Infant and single-gene defect: Gene defect in each parent and abnormal growth of the baby is a sign of this type of disorder. Now, if both parents have a history of a type of disorder, they will raise fifty percent chance of inheriting child's disease. Such disorders are known as Mendelian abnormalities inherited in the child.¹³ Examples of these disorders include:

- Cystic Fibrosis: The mucus hormone secretes a lot in your baby's lungs and causes other problems related to body parts that are involved in the absorption of food. Also, disturbances in the proper function of the child's glands may also occur.

- Tayssax disease in the baby: This disease causes progressive degeneration in central nervous systems.

- Marfan syndrome in the baby: This disease causes defects in the heart and other organs of your baby's body and is known as a disorder in connective tissues.

- Acondroplasia in the baby: This will shorten the height due to abnormal growth of the bones in your baby.¹⁴

- Hemophilia: The lack of protein that is necessary for blood clotting will cause the disease in children. If child is suffered from this disorder, it usually causes excessive bleeding of the wound after it has been exhausted and the blood is not easily clotted.¹⁵

3. Newborn and its genetic disorders:

Some other problems in newborns do not follow genetic patterns. These diseases may be due to the combination of genes with

environmental factors, which cannot be linked to heredity. For example, defects in the neural tube, heart disease, mouth cracks or gaps in the lips are among these problems.¹³

4. Chromosomal abnormalities in the neonate: Disorders occur when the baby's parents have the disease. Even though if there is no family history of this disorder, the abnormalities could be observed in some babies. Examples of these disorders include Aneuploidy, that the number of chromosomes in the baby's body will be greater or less than normal. Examples of aneuploidy include Turner syndrome and Down syndrome.¹⁶

Types of genetic disorders

Albinism: Albinism is a genetic disorder that causes the baby to born with an abnormal pigmentation in skin. The body of these people cannot normally produce melanin pigmentation. Melanin is a substance that gives color to the skin and hair and eyes. People with albinism have very delicate hair, skin and eyes. Albinism has a variety of types. It is hereditary and therefore not contagious. If an individual inherited a defective gene from parents will get affected by that.⁹

Thalassemia: Thalassemia is a disease caused by the occurrence of a number of genetic disorders. This disease occurs when hemoglobin molecule containing oxygen in the blood) is not synthesized by red blood cells. Thalassemia usually causes anemia and symptoms of severe anemia, such as excessive fatigue, spleen swelling, bone pain and susceptibility to bone fractures, shortness of breath, dark urine, jaundice, and liver dysfunction.¹³

Down syndrome: Down syndrome is a common chromosomal disorder that affects 1 in 1,000 children. The disease is more likely to occur in infants whose mothers have a high age at the time of pregnancy. Down syndrome occurs when chromosome number 21 has an extra copy of the genes. Although Down syndrome can be diagnosed with pregnancy tests, children with this syndrome after birth

have low levels of facial muscles, delayed growth and learning, heart disease and digestive system disorders.¹⁷

Muscular dystrophy: Muscular dystrophy is a genetic disorder that weakens the muscles move the body. People with the disease do not have the information to produce muscle-related proteins in their genes or have false information in their genes. Because muscular dystrophy is a congenital condition, it cannot be transmitted to others, and you will not get the disease from someone with dystrophy.¹³

Genetic counseling: Genetic counseling is an effective step in reducing disabilities. Prevention of genetic and congenital disorders involves a variety of aspects that "genetic counseling" is the core and an essential part of these services. It has an effective role in preventing the occurrence of genetic and congenital disorders by raising the level of information and awareness of people.⁷

Who needs genetic counseling?

1. Concerned about the risk of a family history of repeated illness
2. Family marriage
3. A history of mental retardation in the family or close relatives
4. Congenital multiple defects
5. Dysplasia and growth impairment
6. History of metabolic disorders in family members, such as phenylketonuria
7. Abnormal shape and appearance
8. Deafness
9. Sexual ambiguity, impairment in puberty
10. Infertility, repeated abortions, impotence
11. Pregnancy at ages over 35 years
12. Confronting environmental factors of abnormalities during pregnancy, such as radiation, drugs, chemicals and infectious agents.
13. Neuromuscular disorders and chronic and progressive neurological diseases
14. Cancer, diabetes, heart disease
15. ensuring about not be carrier of common genetic disorder in the population
16. Pregnant women that pre-natal test or screening results show an increased risk of defects or complications.

The best time to do genetic counseling is before marriage, but before pregnancy, during pregnancy and after birth of abnormal child can also refer for genetic counseling.¹⁸

What is screening?

Screening is one of the ways in which healthy people who are at increased risk for a particular disease can be identified by healthy people. It should be noted that for those who are considered to be at risk, further testing should be done to diagnose definitively. Screening programs are done in two ways: screening for embryo fertilization and embryo formation, and second screening for infant screening using a few simple tests.¹⁹

Neonatal Screening History

The first neonatal screening program began in the United States about half a century ago, and today, in at least 70 countries of the world, neonates must be tested for at least febrile neutropenia and phenylketonuria in accordance with the law.²⁰ In Iran in 2002, all infants were screened for three hypothyroidism, phenylketonuria and deficiency of the enzyme (G6PD) in Fars province. Gradually, from 2006, two other diseases, the increase of galactose and Maple syrup urine disease (MSUD) were added to screen.^{20, 21}

Diagnostic techniques

Amniosynthesis for genetic diseases is usually done between 15-20 weeks of pregnancy. This is to avoid collisions with the placenta through ultrasound. Complications are rare and include: Temporary vaginal bleeding and in 1-2% rupture of fetal membranes.²² Another method is sampling of placenta at 10-13 weeks of gestation.²³ It is done through the abdomen or cavity of the womb. All the tests performed by amniocentesis are also possible in this method. if there is a defect in the fetus, the doctor can take appropriate action as soon as possible.²² Genetic tests are performed on small blood samples or tissue samples. Genetic testing has progressed so that physicians can identify genes that are incomplete. The type of

genetic testing that is required for a specific diagnosis depends on the type of disease that the physician will guess. Various types of liquids and body tissues can be used in genetic testing. To test deoxyribonucleic acid (DNA), just a small fraction of blood, skin, bone or other body tissues is enough.²⁴ Chronic villus sampling (CVS) is usually done between 10-12 weeks of pregnancy. The doctor takes a small fraction of the fetus to examine the genetic problems of the fetus. Since Corion sampling is invasive, it may be associated with the risk of abortion.²²

If the alpha protein is high in the blood of the mother, special ultrasound and amniocentesis should be performed. The symptoms of any of these diseases can be traced back to their own symptoms. For example, in the openness of the spinal nervous system (spinobifida), it can be detected by the bony form of the head. Amniocentesis is performed as a supplementary test. The amount of alpha feto protein is measured by the test, if it is high, other tests are also done. Finally, if this is positive, the probability of fetal involvement is high.²⁵ The rate of the syndrome (Down syndrome) and other chromosomal aberrant syndromes are related to the mother's age and risk of them increase over age 35. Formerly, women aged over 35 were examined for this syndrome. Ultrasonography and laboratory tests are performed in the first and second trimesters. It is noteworthy that these percentage of diagnostic tests may be mistakenly positive. Signs of Down syndrome in ultrasound include excessive thickness of the skin behind the neck of the embryo, absence of the nose bone or smallness of the nose, short ears, heart defects, and etc.¹⁷

Existence of these methods is very useful for the discovery of fetal diseases. Even if it is not possible to treat the fetus within the uterus, it will make the baby ready for birth, and if there is a possibility of postnatal treatment, counseling is needed and the surgery team is ready. Therefore, in order to control the prevalence of genetic diseases in the

community, it is necessary to identify genetic diseases in pre-natal diagnosis. Diagnosis of genetic diseases before pregnancy is possible through the use of pre-implantation genetic diagnosis (PGD) using advanced molecular technology in the country. Pre-Birth Diagnosis gives couples the opportunity to get informed about their condition and decide on the continuation of pregnancy.²⁶ It also provides the possibility of having a healthy child for couples who carry the pathogenic genes. This method may have been considered as a method of determining the sex of the fetus, but more important than the diagnosis of sex, it is possible to detect some genetic diseases.²⁷ The aim of this study is to provide information on genetic diseases and prevent them in newborns and provide new solutions for the treatment of these diseases.

Methods and Materials

Literature Search Strategy: To identify studies investigating genetic disorders in fetus, we conducted a search in PubMed, Google scholar, Web of Science, and SID databases using the following keywords: "genetic disorders", "congenital disease", "PGD", "Fetus", "embryonic disorders". The last updated search was performed on 2017. Language restriction was set to English, Chinese and Persian. Additionally, the reference list of each retrieved article was thoroughly reviewed for more original papers.

Inclusion and Exclusion Criteria: The studies were further filtered to fit in the inclusion criteria that: full-text published studies; case-control or cohort studies; and written in English or Persian. Studies without usable data were all excluded. For more than two studies with overlapping data, the study with the most subjects or newest published data was selected. The exclusion criteria were as follows: abstract only, short communications or case reports, letter to editor, and studies with only case subjects (no healthy controls).

Results

Based on our search strategy, the primary

screening produced 53 potentially relevant articles. twelve articles were excluded because they clearly did not meet the inclusion criteria or overlapping references.

Pre-Implantation Genetic diagnosis (PGD)

PGD is a new technology for genetic testing and diagnosis of possibility to embryo disturbances before implantation to uterus, which allows individuals with special hereditary conditions to prevent transmission of these genes to their children. PGD includes all methods for testing the cells of a fetus, include the examination of chromosomes and embryonic genes, before transferring to the mother's womb during an IVF / ICSI period.²⁷

The presence of genetic disorders in couples or their families, high maternal age and such factors can increase the risk of chromosomal abnormalities in the newborn. In the prenatal diagnosis (PND) or diagnosis during pregnancy, which is carried out after conception and normal pregnancy, genetic diagnosis is performed between weeks 10 to 14 of pregnancy, which, if diagnosed with chromosomal aberrations, only suggestion, is Termination of pregnancy. However, in the PGD method, because of in-vitro fertilization (IVF / ICSI),²⁸ only fetuses that have been studied in a healthy genetic manner are selected and transmitted to the mother's womb; therefore, the physical and emotional trauma of abortion is not sought after it And it is actually the only possible method for couples who are exposed a child with genetic diseases but cannot carry out abortion, due to legal, religious or belief, if the fetus has such problems.²⁶

In this highly advanced laboratory method that helps the birth of fetuses without genetic defects or impairment, an experiment is performed on an embryo of eight cells derived from artificial insemination (IVF or ICSI), and if it is assured that the fetus is healthy, transferred to the mother womb to maintain normal growth.²⁹

PGD testing steps

The most important action before the PGD is to

identify the genetic mutation in the parent. Couples should be advised to assess the risk of genetic abnormalities transmitted to their children, especially if couples have a high risk of transmitting structural abnormalities or single gene diseases. Usually, in two-to-three-month phase, a single-cell dedicated test is performed for each family. After the end of this step, PGD is genetically possible. PGD, begins in an artificial insemination (IVF or ICSI), includes ovarian stimulation with the drug, oviposition And fertilization in the laboratory and embryo transfer. At least 5 embryos with 6 to 8 cell must seem healthy, it takes 48 hours and if the embryo is healthy, the transfer to the uterus of Mother is done.³⁰

Generally PGD involves the following steps:

- Fetal culture until the third day, stage 6 to 8 cells (or blastocyst)
- Removal of one or two cells from the embryo (blastomer)
- Performing PGD on cells removed based on the nature of the disease through one of two molecular or cytologic methods such as:
 1. Molecule: DNA replication of a cell through a process called Polymerase Chain Reaction (PCR) for the detection of single-gene diseases
 2. Cytologic: Detection of chromosomal areas for chromosomal diseases using FISH Fluorescent in situ Hybridization
- Evaluation of the DNA sequence code, through molecular analysis, to determine the possibility of inheriting a defected gene
- Embryo transfer after a PGD test and identification of genetically engineered embryos.^{29, 30}

PGD application

Pre-implantation genetic diagnosis can be useful for any couple who are at risk of transmitting a disease or genetic disorders. People who may be candidates for the PGD test are:

- Women with 35 years of age or older : with an increase in age, the birth rate of a child with Down syndrome (having 3 chromosomes 21) is about 10 times higher, and other chromosomal

disorders are about 2-3 times higher.

- Couples who have at least one of them inherited a genetic disorder based on family history.

- Carriers of sex-linked genetic disorders: such as sex-linked hemophilia, that is in boys more than girls.

- Carriers of single gene defects: single-gene diseases such as thalassemia that may occur in the baby.

- People with chromosomal abnormalities or families with a history of a defective child born due to inheritance of that disorder by a specific gene or disorder in the number of chromosomes.

- Women who have experienced repeated abortions due to chromosomal abnormalities and there are no other causes for abortion.⁹

- Structural abnormalities such as translocating in karyotype test.

- Infertility patients who have repeatedly failed IVFs. (More than 3 times have IVF or microinjection surgery, but not pregnant).

- In couples that male are ICSI candidates (sperm injection).

- To determine the type of human leukocyte antigens (HLA) in cases where a person in the family needs a bone marrow transplant, and couples asking for another child for bone marrow transplantation or using their umbilical cord blood to treat a family member.

- For the prevention of cancer or diseases that occur at older age.

- Healthy couples who oppose the termination of pregnancy during pregnancy and want to have a healthy pregnancy from the beginning.

- For sex determination. But to do this, you need to be in an IVF course even for couples who can naturally become pregnant; it usually not recommended, only in cases have the risk of a sexually transmitted disease such as Hemophilia (which is higher in boys).²⁶

Some of the single-gene diseases that have already been diagnosed with PGD include cystic fibrosis, Huntington's disease, anemia, Marfan syndrome, spinal muscular atrophy, β -thalassemia, hereditary cancers, Myotonic

Dystrophy, Congenital Adrenal Hyperplasia, Deafness, etc.

- Sexually Transmitted Diseases recognized by PGD include hemophilia, fragile x syndrome, Duchene muscular dystrophy, mental retardation and more neuromuscular problems, Rett syndrome and bone softness due to resistance to vitamin D absorption.

- Chromosomal abnormalities that detected by PGD are divided into two groups:

A: Numerical Chromosome abnormalities (such as trisomy)

B: building Chromosome disorder (chromosome rearrangements such as displacement, reversal, removal and aneuploid).³¹

PGD problems

- In some cases, a genetically defective fertilized egg may develop without any disorder or disease. Therefore, you should consult precisely about the probability of developing a disorder.

- Although PGD reduces the risk of developing a child with a genetic disorder, it cannot completely eliminate this risk. In some cases, more tests are needed during pregnancy to determine if a genetic agent is still possible.

- Symptoms of certain diseases are only manifested when affected person reach the middle age.²⁹

NIFTY

A new and non-invasive screening method, using sequencing technology, examines free DNA of fetuses in the mother's blood that increases adequately from the 12th week of pregnancy. The half-life of this DNA is very short and less than 2 hours and immediately disappears from the mother's blood after birth, so the previous pregnancy have not interference in test result. In this method, a few liters of maternal venous blood are used without the need for placental tissue cells (CVS) or amniotic fluid sampling (amniocentesis). In addition, in a simultaneous test of trisomies 21, 18 and 13 with a sensitivity of 99.9%, respectively, the percentage of false

positive and negative cases is reduced by less than 0.1%.³²

The biggest problem in traditional screening methods is the high percentage of false positive and negative results, and in the confirmation test, is the probability of abortion due to the invasive method of sampling. Other negative aspects of the common screening methods include the multi-stage nature of the testing process, non-specific and sometimes confusing and unpredictable results, and, consequently, increasing the risk of using non-invasive methods. But with the new-generation sequencing method, virtually all Down syndrome pregnancies are identified with a very low false positive. It should be noted that this test did not eliminate the need for AFP testing for NTDs screening in the second trimester, and the pregnant woman should be referred to the lab again at the 15th to 20th weeks of pregnancy.³³

In the invasive method, in addition to the possibility of abortion (0.04%), significant maternal stress, painful sampling and the risk of intrauterine infections are also noted. In addition, the results of the confirmatory test in about 1% of non-indeterminate cases and also in 0.3% of cases, is unavailable due to unsuccessful cell culture. Basically, it is difficult to choose between traditional screening tests that have high probability of error and amniocentesis or CVS that can lead to abortion for pregnant mothers, and it is possible to do a test in the second trimester of pregnancy in which the limitations Time for decision making Legal abortion or holding a fetus. In addition, if the screening test is positive or suspected in the first 3 months, the patient will have to undergo a confirmatory test in the second 3 months and will be stressed and worried during this period until the test result is received. Experts consider the presence of fetal DNA in the mother's blood as a revolution in diagnostic sciences and hope in the near future its measurement will replace test commons.³⁴

Genetic testing during pregnancy

The doctor may recommend the genetic counseling or genetic testing for the following reasons:³⁵

1) A couple who intend to form a family and one of them or one of his close relatives suffers from hereditary illness. Some people carry genes of genetic disease, even if they do not show the disease itself. This is due to the fact that some genetic diseases are recessive. That is, only when they have inherited two copies of a problematic gene, One of each parent of neonatal who inherits a problematic gene from one of the parents inherits normal gene from another, does not show symptoms of recessive disease., but it's 50% likely to pass on disease to its offspring.

2) A child with an acute congenital defect. All children with congenital malformations do not have genetic problems. Sometimes, congenital defects and defects are due to exposure to toxins, infections, or pre-natal bodily injuries. Even if a child has a genetic problem, there is always the possibility that it was not hereditary and that it was caused by a spontaneous form in its cells, not its parent's cells.

3) A woman who has had two or more abortions. Acute chromosomal problems in the fetus can sometimes cause spontaneous abortion. Multiple abortions can be a sign of a genetic problem.

4) A woman who has been born a dead child with physical symptoms of a genetic condition. Many of the genetic diseases cause acute physical malformations, which give the child a very specific appearance.³⁶

5) A 34-year-old woman who is pregnant. When the age of the mother is higher, the probability of developing chromosomal problems (such as trisomy) increases. Older parents are also at the risk of having children with genetic variations (those with a genetic defect that was not already in the family).

6) A child with a physical problem that can be genetical. When a child has a physical disorder that affects more than one body

member, it is recommended to determine the cause of the problem of genetic testing.

7) A child with a physical problem that has been diagnosed with a specific genetic syndrome. A genetic test is done to confirm the diagnosis. In some cases, it can help determine the specific type or severity of a genetic disorder for choosing the appropriate treatment.³⁵

Treatment

Genetic diseases do not have specific treatments but they can be prevented and there are various diagnostic methods for them. The treatment of the genetic disorder depends entirely on the type of disorder and genetic disease. Some children with genetic disorders can have a normal life while they are sick. The status of each patient varies according to the type of congenital disorder.³⁷

Embryo Therapy: There are several embryonic diseases that can be treated by the mother in the uterus. In such cases, the medicine is given to the mother, and then it passes through the mother's blood to the fetus and exerts its effects.³⁸

For example, hypothyroidism - heart anomalies - fatal infections and inherited metabolic diseases in the fetus can be treated by giving the corresponding medication to the fetus's mother. Also by this way, stem cells can help to treat metabolic and blood diseases.³⁹ Today, with the advancement in technology, the gene's modification in the fetus (gene therapy) is being investigated and this is done in animals.⁴⁰

Open surgery in the fetus is possible in cases where a defect in the fetus poses a threat to survival in the uterus, or a flaw that can be caused by the birth of a baby can lead to open surgery, like the large masses of the neck and chest. In the open surgery, opening the uterus is performed on the fetus, and then the fetus can continue to live inside the uterus. The technology of it is very modern, in advanced and limited countries, and requires a very skilled team. Even laser therapy and laparoscopy have been performed in the uterus on the embryo.⁴¹

Discussion

Pre-natal Diagnosis is the most reliable way of preventing genetic diseases that has been raised in our country so far and has prevented the birth of newborns with different hereditary, congenital and genetic diseases in the past few years. Genetic diseases are not seen only in familiar marriages. Couples should know that genetic testing, such as PGD, is carried out in families with genetic problems. There is also the possibility of genetic diseases in non-familiar marriages. Therefore, PGD is recommended for all families with a history of genetic disease.

Many couples carrying these types of abnormalities may never have succeeded without using PGD. Many of these chromosomal abnormalities can now be detected in the pre-implantation diagnosis using the FISH technique.

Initially, PGD was performed for only 5 common chromosomal disorders (including chromosomes X, Y, 13, 18, 21), which in the next steps were 8 to 12 chromosomes (containing X, Y, 13, 18, 21, 16, 17, 18, 15, 22, 20, 12), which allowed detection of 70-80% of chromosomal abnormalities, and now the new PGD method can confirm the health of 24 chromosomes, that detects up to 90% of chromosomal abnormalities. With the advancement and development of technology, it is possible to use this method to detect other genetic abnormalities.²⁷

In PGD, chromosomal abnormalities are divided into two categories:

A) Chromosome numerical abnormalities:

Mother's age is over 35 years old. Studies have shown that the reasons for the low success rate of IVF in older women are the formation of chromosomal abnormalities in the ovum. Using the FISH technique, embryos can be screened for specific chromosomal abnormalities before implantation, and only embryos that have natural chromosomes are selected. In this way, the rate of implantation can be increased and spontaneous abortion is reduced.

B) Chromosome building disorder

(chromosome rearrangements such as displacement, reversal, removal and aneuploid)

Chromosomal abnormalities are different in shape; one of the most common is translocation. Naturally, the chromosomes are very fragile and break down more during cell division, but they are restored again. In the translocation, the part of the chromosome that is broken is detached and acts as a separate and different chromosome.²⁶ When the cell has split up, a person called the carrier. Carriers of these abnormalities are clinically natural because they do not have a genetic deficit, But when pregnancy is done, the total number of chromosomes that is shared, is not natural, and in fact, while the chromosomal formula of the couple is normal, the number of chromosomes in eggs that develop into a primary embryo, is more or less than normal, these carriers may face abortions many times and may even have defected children or with Mental retardation, Because the main problem for these individuals is the lack of proper separation of chromosomes in the spermatogenesis (spermatogenesis) or oogenesis. PGD in couples carrying these types of chromosomal abnormalities can be very helpful in choosing the embryos with a natural chromosome set.

Neonatal screening is used to diagnose early-stage congenital diseases. Failure to diagnose these diseases in time can cause mental retardation, slowing physical growth and even death.⁹

In the table 1, a number of Detection methods for Down syndrome have been compared.

Untreated genetic disorders can cause lifelong problems in your baby, and in most cases, with no known cure for these diseases, however, some genetic disorders can be treated with gene therapy. Some of the other abnormalities of the neonates that are not genetically related to pregnancy or use of certain medications and environmental conditions, for example some epileptic medications if used by mother that unintentionally pregnant It affects the growth system of the tissues and baby will not appear to be normal. The first way to prevent birth defects in the baby is genetic counseling before marriage and before pregnancy. Genetic counseling provides a lot of information that can be used; a genetic counselor can tell you the cause of a genetic disorder, the possibility of carrying out genetic tests, outcomes of treatment, how to control the disease, and how to treat it.³⁷

In cases such as chromosome or genes dependent genetic disorders or environmental factors such as maternal nutrition during fetal life, exposure to pathogenic and viral diseases (such as mumps and rubella), and parents will be more likely to develop fetal infections. In these cases and after the necessary tests, the termination of the pregnancy (abortion) may be occurred.⁸

If the mother is exposed to any form of physical injury, such as an accident or radiology, the condition of the fetus should be investigated a family with a child that has genetic abnormalities should not be prevented for re-pregnancy; Perhaps after performing genetic counseling and testing, this family being able to have healthy children.

Table 1. Comparison of diagnostic power and the nature of various screening methods for down syndrome¹⁷

Method	Power of diagnosis	False positive	Nature of the method
Screening using maternal chemical blood markers	70-90	5%	non-invasive
Nuchal Translucency (Ultrasound NT)	60-80	5%	non-invasive
CVS	> 99%	0	Invasive (Risk of abortion 1% - 2%)
Amino synthesis	> 99%	0	Invasive (Risk of abortion 1% - 2%)
Cell free DNA	> 99%	0/034%	non-invasive

Nowadays, with the advancement of sciences, even if a family has newborn with genetic disorders, they could still hope that healthy baby would be born, after doing genetic counseling. People born with birth abnormalities can marry and have healthy and normal children if this abnormality is not related to genetic factors and it is due to environmental factors (Teratogenic factors) or pregnancy.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

The authors thank all those who have helped in carrying out the research.

How to Cite: Rabaninia T, Amjadi N. Genetic Disorders in the Fetus from Diagnosis to Treatment. *World J Peri & Neonatol* 2018; 1(1): 36-47.

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