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Genetic Etiology of Stillbirths

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Abstract: ***Stillbirths remain a significant global public health challenge, with an estimated 2 million babies worldwide being stillborn in 2019 alone. Understanding the genetic factors is important for improving prevention and diagnosis. This review will summarize various genetic syndromes, mutations associated with stillbirths, and placental abnormalities and give an overview of its prevalence and some diagnostic techniques. Genetic reasons for stillbirths consist of many unknown factors which could be chromosomal abnormalities, alterations in mitochondrial and nuclear DNA. Early detection of these roots will reduce the chances of stillbirths. Research indicates that up to 25% of cases may have a genetic origin.6 - 13% of stillbirths are because of an abnormal karyotype. Some common chromosomal aberrations are trisomy 21, trisomy 18 and 13, and monosomy X. Standard karyotypic analysis and chromosomal microarray analysis are the techniques that are implemented to identify genetic abnormalities in stillborn babies. Genetic abnormality can occur by single gene mutations and cause disorders like sickle cell anemia cystic fibrosis, and long QT syndrome. Specific alterations in genes like Factor V Leiden, Prothrombin, and TRPM7 are explored in detail. Mitochondrial disorders are also examined as a significant contributor to stillbirths, with mutations in DNA (mtDNA) linked to conditions such as lactic acidosis, myoclonic epilepsy with ragged red fibers (MERRF), and Leber's hereditary optic neuropathy (LHON) and mitochondrial encephalomyopathy, and stroke - like episodes (MELAS). Mutations in mtDNA can result in mitochondrial disorder, which can affect various cellular processes and potentially cause mitochondrial diseases. Nuclear DNA (nDNA) mutations are implicated in stillbirths, including defects in genes involved in mitochondrial function, assembly, and maintenance. Coenzyme Q10 deficiency is highlighted as an example, emphasizing the importance of understanding the root (molecular) cause of mitochondrial disorders.***

Keywords: Stillbirths, Alterations, Genes, Placenta, Mitochondrial DNA

1. Introduction

A stillbirth is when the loss of a baby occurs at the time of delivery or in the third trimester of pregnancy [1]. The possible causes according to the research are pregnancy and labor complications, problems with the placenta such as insufficient blood flow, fetal genetic problems, and birth defects, high blood pressure disorders, some genetic causes can be pre - diagnosed and prevent stillbirths [2]. Stillbirths can occur due to fetal growth restrictions because of deficiency in the placenta, disease from the mother's side, genetic disease in the fetus, or an amalgamation of these factors [3]. Genetic causes are considered a crucial contributor to fetal death. Different methods are there to detect genetic aberrations like cytogenetic techniques (karyotyping) and molecular genetic techniques (chromosomal microarray and next - generation sequencing) [4]. A normal estimate shows that genetic factors contribute to a considerable proportion of stillbirths, according to some studies up to 20 - 25 percent of dead born babies may have a genetic cause [5].

In 2019, 2 million babies globally were stillborn, with significant regional variations. Rates ranged from 22.8 per 1000 births in some parts of Africa to 2.9 in the west side of Europe [6]. Progress in reducing stillbirths has been milder than neonatal and child mortality, with a global annual reduction rate of 2.3% from 2000 to 2019. While 114 countries saw decreases, 81 showed no improvement, notably in sub - Saharan Africa, east Asia and the Pacific, and Latin America and the Caribbean [7]. Quick response is needed to address disparities and accelerate efforts to prevent stillbirths, ensuring equitable access to maternal and newborn care worldwide [8].

2. Different genetic syndromes that cause stillbirths

2.1 Chromosomal abnormalities

It is estimated that approximately 6 - 13% of stillbirths are caused by an abnormal karyotype [5]. The estimate of karyotypic abnormalities is higher, at over 20%, in fetuses that have anatomic abnormalities or growth restriction [9]. However, in normally formed fetuses, the estimate of chromosomal mutations is 5.4% on the basis to a large study. If an abnormal chromosomal makeup is present in association with stillbirth, trisomy 21, monosomy X, trisomy 18, and trisomy 13 are the most frequent abnormalities [10].

2.1.1. Methods for identifying genetic abnormalities

(a) Standard karyotyping

The karyotypic analysis is a technique in which the number, size, and makeup of chromosomes get analyzed in a sample of cells and can be implemented to detect genetic abnormalities in stillborn babies. However, this method is not always successful. In around half of attempts, cell culture fails. To increase the success rate of cell culture, it is recommended to perform invasive testing, such as chorionic

villi sampling or amniocentesis, before delivery [11]. A study in Western Europe (Netherlands) showed that intrusive testing had a much higher tissue culture rate than fetal tissue sampling after birth. In cases where invasive testing is declined, it is possible to analyze a section of the placenta, an umbilical cord slice, or internal fetal tissue for genetic abnormalities [12].

Stillbirths are due to different factors including genetic abnormalities. One of these is confined placental mosaicism, which refers to a condition where there's an abnormal cell line linked to the placenta but the fetus has a normal karyotype. This condition has been linked to a risky extent of stillbirth. However, it's not yet part of standard testing [13].

(b) Chromosomal microarray analysis

It is a more advanced technique that not only identifies aneuploidy but also recognizes copy number variants (smaller deletions and duplications) that can't be detectable by karyotyping. Compared to karyotype analysis, microarray analysis increased the pre - detection of a genetic cause in all stillborn babies, 34.5% in stillborn babies before delivery, and 53.8% in stillborn babies with anomalies [7]. Microarray analysis is more presumable than karyotype study to provide a genetic pre - detection, mainly due to its effectiveness with tissue that cannot survive [14]. Microarray analysis has been incredibly helpful in studying stillborn infants with genetic issues or cases where karyotype testing isn't possible. This method, now a crucial part of stillbirth investigations, boosts the chances of identifying genetic problems compared to traditional karyotyping. It's the go - to choice for these reasons [15].

However, because of expenses and practical issues, some patients might only have access to karyotype testing. Although in the future, whole exome sequencing or whole genome sequencing could become part of the standard stillbirth examination, it's not the norm yet. There are also inherited disorders that can lead to stillbirth, adding another layer of complexity to the diagnosis [16], [9].

These disorders can be happened by spontaneous mutations or inherited parental mutations that lead to long QT syndrome (heart disorder) [17]. However, it's improbable that any point mutation can lead to this high rate of stillbirths. Therefore, time - to - time evaluation for single gene defects and microdeletions is currently limited. Decisions regarding genetic assessment should be based on the clinical background and any abnormalities observed in the fetus [7].
It's worth noting that about 20% of stillborn babies have distorted features or skeletal abnormalities, and 15 - 20% have a significant malformation [18].

2.2. Single gene mutations

Single - gene mutations can contribute to stillbirths. These mutations can occur in genes that are prone to cause genetic disorders such as cystic fibrosis or sickle cell anemia. However, they can also involve genes not typically associated with stillbirthsc [19], [20]. Due to this mutation, the amino acid sequence of factor V changes, making it resistant to inactivation by activated protein C (APC). Normally, APC helps regulate the clotting process by inactivating factor V, thereby preventing excessive blood clot formation. However, in individuals with Factor V Leiden, APC does not effectively inactivate the mutated factor V, leading to a prothrombotic state. Individuals who inherit double copies of the mutated gene (homozygous) may have an even higher risk of thrombosis [21].

2.2.1. TRPM7: Mutations in this gene have also been linked with an elevated risk of unexplained stillbirth. Studies have indicated that alterations in genes related to ion channel function, such as those associated with Long QT Syndrome (i. e. it is a heart signaling disorder that can cause fast, chaotic heartbeats), can also contribute to stillbirths [17]. Genetic studies have also highlighted the role of specific genes in causing recurrent stillbirths [22].

2.2.2. NLRP7: Alterations in the gene have been recognized as a cause of familial biparental hydatidiform mole which is a gestational trophoblastic disease that originates from the placenta and can metastasize, which can result in recurrent spontaneous abortions, stillbirths, and intrauterine growth retardation [23].

2.2.3. DHCR7: 7 - dehydrocholesterol reductase, provides instructions for producing an enzyme that plays a role in the synthesis of cholesterol. Mutation in this gene can cause a rare genetic disorder known as Smith - Lemli - Opitz syndrome (SLOS) which will result in low levels of cholesterol in the body and an accumulation of 7 - DHC [24]. This will lead to symptoms including developmental delays, intellectual disability, distinctive facial features, growth abnormalities, and organ defects. This mutation can be one of the causes of stillbirths [25].

Identifying these mutations can be challenging as they may not present with the typical clinical features of the associated disorder. However, advancements in genetic testing and analysis have improved the detection capacity to identify these mutations. As a result, families can receive more accurate risk assessments and counseling [26].

2.3. Thrombophilia's

A healthy pregnancy requires the healthy invasion of trophoblasts into the maternal uterine spiral arteries, which helps in turning them into larger and more dilated vessels. Microthrombi are commonly discovered in the blood vessels of placentas from women who have undergone pregnancy loss [27]. Placental restriction has been observed in the placentas pregnancy loss experienced women and has a condition known as thrombophilia. According to published meta - analyses, a high risk of recurrent failed pregnancy in the early stage and non - recurrent late pregnancy loss is associated with factor V Leiden, prothrombin, protein S deficiency, and pre - eclampsia [28].

Several studies suggest that adverse pregnancy outcomes might be associated with heritable thrombophilia and homozygosity for methylene tetrahydrofolate reductase (MTHFR) 's thermolabile mutation, which can lead to homocysteinemia [29] [30]. The evidence is weak, but it is postulated that thrombophilia might cause placental

deficiency due to placental vascular thrombosis. However, some studies do not support this association [31].

2.3.1 - MTHFR - Methylenetetrahydrofolate reductase (MTHFR) is a crucial enzyme that regulates folate and homocysteine metabolism. Deficiencies in MTHFR can result into hyperhomocysteinemia with homocystinuria, or mild hyperhomocysteinemia. The latter is more common and results in a minute increase in total homocysteine levels in the blood, which is a problematic factor for cardiovascular disease [32]. The frequent cause of elevated homocysteine levels is a polymorphism in the MTHFR gene, known as the C677T MTHFR polymorphism. This leads to the exchange of cytosine with thymine at position 677, resulting in an amino acid change from alanine to valine in the enzyme. This common gene mutation affects homocysteine levels and is thought to contribute to hyperhomocysteinemia, reduced folate levels, and several cardiovascular diseases [33].

2.4. Mitochondrial disorders

These alterations were linked with a disease that is inherited from the mother's side. While the father and mother both contribute to the nuclear segment of the zygote, the mother's ovum is the chief source of the zygote's cytoplasmic contents, which contain several hundred intracytoplasmic mitochondria [34]. This means that the genome of the mitochondria is transmitted from the mother to all her children, with no paternal mtDNA contribution, which is known as "maternal inheritance". Mitochondria produce the energy necessary for normal cellular function and maintenance. Thus, cells in tissues that rely heavily on mitochondrial energy production, such as the CNS (central nervous system), including the optic nerve, retinal pigment epithelium, and extraocular muscles, will contain more mitochondria [35].

There are three mitochondrial DNA mutations:

2.4.1 - Leber's hereditary optic neuropathy (LHON)
Leber's hereditary optic neuropathy (LHON) is a type of vision loss that is inherited from the mother's side and caused by the destruction of retinal ganglion cells (RGCs) and their axons. This results in a sudden loss of central vision. LHON is usually caused by one of the specific mutations in the three in the mitochondrial DNA (mtDNA) [36]. These mutations occur at nucleotide positions 11778 G to A, 3460 G to A, and 14484 T to C, respectively in the ND4, ND1, and ND6 subunit genes of complex I of the oxidative phosphorylation chain in mitochondria. Alterations in the MT - ND1, MT - ND4, MT - ND4L, and MT - ND6 genes cause LHON [37]. These genes are responsible for coding the NADH dehydrogenase protein, which plays an important role in the normal mitochondrial function of oxidative phosphorylation. This process converts oxygen and simple sugars into energy through a series of four large multienzyme complexes sink in the inner mitochondrial membrane [38]. Mutations in any of these genes can disrupt this process and cause different syndromes, based on mutation and other factors. While it is still unknown how these genetic changes lead to the death of cells in the optic nerve and cause the specific features of Leber hereditary optic neuropathy, researchers are working to uncover the underlying mechanisms [39].

(a) GENES: MT - ND1, MT - ND4, MT - ND6 genes encrypt for subunits of NADH dehydrogenase, also known as complex - 1, which is a chief constituent of the mitochondrial respiratory chain that is further in charge of generating ATP [40]. Mutations in these genes can result in mitochondrial disorder, impairing ATP production and potentially resulting in mitochondrial diseases. ND1 and ND4's function is to catalyze the exchange of electrons from NADH to ubiquinone during oxidative phosphorylation [38].

2.4.2 - Myoclonic epilepsy with ragged red fibers (MERRF)
MERRF disorder is a genetic condition that happens due to mutations in the mitochondrial genome. This means that it is a variant in the DNA (mtDNA) and is inherited from the mother. The primary cause is a point mutation that affects the mitochondrial gene for tRNA - Lys, which disrupts the synthesis of proteins. The remaining mutations account for only 10% of cases. Moreover, in 10% of patients with MERRF, no identifiable mutation is present in their mitochondrial DNA [41].

(a) GENES: MT - TK - This gene is accountable for encoding the molecule tRNA lysine, which carries the amino acid lysine to the ribosome during protein synthesis. Lysine is an amino acid that generates protein in cells [42]. If any mutations in the MT - TK gene are found, they can disturb the structure or function of the tRNA lysine molecule, which can result in a reduced ability to deliver lysine to the ribosome accurately and efficiently during protein synthesis. Such mutations can result in mitochondrial malfunction, which can affect various cellular processes and potentially cause mitochondrial diseases [43].

2.4.3 - MELAS
MELAS is a disorder that is mainly caused due to a nucleotide substitution in transfer RNA (tRNA) [44]. It is characterized by the developing distortion of the nervous system, which eventually leads to neurological impairment and dementia during adolescence or early adulthood. This means that the disease affects the brain and nervous system, causing a decrease in cognitive and motor functions [45].

(a) GENES: MT - TL1 - MT - TL1, also mentioned as MT - TL or tRNALeu (UUR), is an RNA (tRNA) gene that is present in the mitochondrial DNA (mtDNA) [46]. The function of this gene is to encode a specific tRNA molecule that is behind for carrying the amino acid leucine during mitochondrial protein synthesis. Alterations in the MT - TL1 gene can affect the structure or function of the tRNALeu (UUR) molecule, hampering its ability to accurately recognize and deliver leucine during protein synthesis [47]. Such mutations can cause mitochondrial dysfunction and may result in various mitochondrial diseases, including mitochondrial encephalopathy, lactic acidosis, and stroke - like episodes (MELAS), as well as other disorders [45].

2.5 Nuclear DNA (nDNA) mutation

Issues in the nuclear DNA (nDNA) can result in complications like alterations in the structure of respiratory chain complexes, affecting how cells produce energy. Nuclear DNA mutations can contribute to mitochondrial disorders by affecting genes responsible for mitochondrial function,

including assembly, maintenance, and regulation of mitochondrial components [48].

2.5.1 - Coenzyme Q10 Deficiency - Coenzyme Q10 (CoQ10) is a crucial constituent of cellular pathways, including the mitochondrial respiratory chain and beta - oxidation. The biosynthesis of CoQ10 remains an incompletely characterized pathway that involves at least fifteen genes (COQ genes). Sometimes severe lactic acidosis also gets detected in neonatal cases but improper Q10 deficiency [49].

3. Conclusion

The review has highlighted various genetic factors and syndromes associated with stillbirths, emphasizing the importance of genetic testing and pre - diagnosis to prevent such occurrences. The prevalence of genetic causes and regional disparities in stillbirth rates underscore the urgent need for equitable access to maternal and newborn care worldwide. Moreover, the review has discussed the significance of genetic abnormalities, including chromosomal anomalies, single gene mutations, thrombophilias, and mitochondrial disorders in contributing to stillbirths. The advancements in genetic testing and analysis have improved the ability to detect alterations, enabling more accurate risk assessments and counseling for families. It is imperative for future research and clinical practice to consider emerging techniques such as chromosomal microarray analysis and the potential inclusion of whole exome sequencing or whole genome sequencing in the evaluation for stillbirth workup. These developments hold promise in enhancing our perception of the molecular pathways behind mitochondrial disorders and other genetic factors contributing to stillbirths.

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Author Profile

Sunidhi Vaish is an aspiring researcher, currently pursuing her Master of Science in Biotechnology at Amity University. Her academic background includes a Bachelor's degree in Biotechnology, where she gained foundational knowledge in Biotechnological techniques. Her current project focuses on Genetic causes of stillbirths. With her dedication and enthusiasm, Sunidhi is composed to make significant contributions to the field of Biotechnology and emerge as a promising young scholar in the scientific community.