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Relationship Between Cleft Lip and Palate Followed by Osteogenesis Imperfecta Accompanied by Tetralogy of Fallot in Children with a Maternal History of Catatonic Schizophrenia with Valproic Acid Therapy and Diabetes Mellitus

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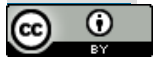
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ABSTRACT

Researchers believe that most cases of cleft lip and cleft palate are caused by genetic and environmental factors. Nevertheless, the exact cause was not found. Nevertheless there are allegations that the condition of the cleft lip and palate has something to do with osteogenesis imperfecta with the heterozygous mutation COL1A2 and the formation of triple helix DNA accompanied by Tetralogy of Fallot in children with a maternal history of catatonic schizophrenia followed by the use of valproic acid and type II diabetes mellitus. Then, it is also found in babies with cleft lip and sky conditions usually accompanied by other congenital anomaly, but not always. This then further gives rise to speculation that there are links between the above variables and the cleft lip and palate. Therefore. Knowing the Relationship Between Cleft Lip and Palate Events with osteogenesis imperfecta with heterozygous mutation COL1A2 and triple helix DNA formation accompanied by Tetralogy of Fallot in children with a maternal history of catatonic schizophrenia followed by the use of valproic acid and type II diabetes mellitus. This research is a Systematic Review using the Preferred Reporting Items for Systematic Reviews and Meta-analyses method or commonly called PRISMA, this method is carried out systematically by following the correct research stages or protocols. The source was taken from the Google Scholar site with journals published in 2017-2023 and then screened the results of 1,870 journals. Journal clustering was carried out and the number of Q1 indexed journals was obtained in 4 journals, Q3 in 1 journal, and Q4 in 1 journal so that there were 6 journals extracted. The entire journal does not directly discuss the relationship between the research variables, but only provides an overview of the increased risk of celestial cleft conditions in babies if the expectant mother has type 2 diabetes mellitus conditions, osteogenesis imperfect, and the relationship of the two health conditions to the possibility of birth of the baby with the Tetralogy of Fallot condition, as well as the relationship of the baby to the condition of the cleft lip and palate and tetralogy of fallot

INTRODUCTION

Cleft lip and/or cleft palate are congenital from birth abnormalities, caused by teratogenic threat disorders in the early stages of embryonic development (McLeod et al., 2004). Cleft lip and palate are birth defects that occur when the baby's lips or mouth are poorly formed during pregnancy. These two birth defects are commonly called "orofacial fissures". Lips are formed between the fourth and seventh week of pregnancy. As the baby develops during pregnancy, body tissues and special cells from each side of the head grow towards the middle of the face and merge together to form a face. The incorporation of these tissues forms facial features, such as lips and mouth (CDC, 2020).

A previous study revealed that the African population has the lowest incidence of the disease, which is about 0.4/1000, in India, the average prevalence index of this disease was 0.398/1000 from 2007 to 2011 (Yang et al., 2018), in Europe the incidence was about 1/1000, Asia and South America had a relatively high incidence of about 2/1000 (Michael et al., 2011). The birth rate with the highest cleft lip and/or palate is found in Asia (especially in China and Japan), (Yu et al., 2017) and China is one of the regions with the highest incidence of around 1,663/1000 (Yang et al., 2018).

Cleft lip, or cleft lip occurs if the tissues that make up the lips do not merge completely before birth. This results in a hole in the upper lip. The opening in the lips can be small slits or large openings that pass through the lips to the nose. Cleft lip can be on one or both sides of the lip or in the middle of the lip, which is very rare. Children with cleft lip may also experience cleft palate. The roof of the mouth (palate) is formed between the sixth and ninth weeks of pregnancy. Cleft palate occurs if the tissues that make up the palate do not coalesce completely during pregnancy. For some babies, the front and back of the palate are open and some are only part of the palate open.

Cleft lip can carry a huge health burden on patients and families, and has a negative impact on mental health and the quality of life of patients (Wehby and Cassel, 2010). The disease is usually accompanied by various complications, which mainly affect the voice and face (Suleiman et al., 2005). Children with cleft lips with or without a palate often have problems with eating and speaking clearly, may have ear infections, difficulty when

eating. They may also have hearing problems and problems with their teeth.

The causes of orofacial fissures in most babies are unknown. Some children have a cleft lip or cleft palate due to gene changes. Cleft lip and cleft palate are thought to be caused by a combination of genes and other factors, such as things related to the mother in her environment, or what the mother eats or drinks, or certain medications she uses during pregnancy. Understanding the more common factors that occur in babies with birth defects will help us learn more about their causes.

Recently, a study reported important findings from a research study on several factors that increase the likelihood of having a baby with an orofacial slit, among which is smoking, women who smoke during pregnancy are more likely to have a baby with an orofacial slit than women who do not smoke (Honein et al., 2007, Little et al., 2004). Next up is diabetes, women with diabetes diagnosed before pregnancy have an increased risk of having a child with a cleft lip with or without a cleft palate, compared to women who do not have diabetes (Correa et al., 2008). The use of certain medications, women who use certain medications to treat epilepsy, such as topiramate or valproic acid, during the first trimester (first 3 months) of pregnancy have an increased risk of giving birth to a baby with a cleft lip with or without a cleft palate, compared to women who do not take this drug (Margulis et al., 2012, Werler et al., 2011).

Cleft lip and palate are often associated with osteogenesis imperfecta. Osteogenesis Imperfecta (OI), also known as "fragile bone disease," is a rare congenital disorder (prevalence of 8 per 100,000 people) characterized by recurrence of fractures and, in severe cases, bone deformities (Forlino and Marlini, 2016). Osteogenesis Imperfecta affects dental and craniofacial development and therefore can interfere with oral health-related quality of life (Najirad et al., 2018). Autopsy findings showed typical OI type II features, including soft calvarium, deformed extremities, hip flexion and abduction, and uncommon features, such as white sclera, coxa vara, absence of some bones and organs, cleft lip, and asymmetrical ear. Radiological images reveal anomalies and variations such as cleft palate, mandibular dysplasia, spina bifida, costa cervicalis, and rib and spinal fusion, which are difficult to detect during conventional autopsies (Zhou et al., 2016).

Osteogenesis Imperfecta is a group of inherited connective tissue abnormalities characterized mainly by bone fragility, growth deficiency, and blue sclera. The pathological effects of OI on dental tissue and oral cavity usually develop early in life and may therefore affect the quality of oral health during childhood and adolescence. Orofacial manifestations are often associated with OI (Rizkallah et al., 2013).

Within approximately 90% of individuals with a clinical diagnosis of OI, a dominant mutation occurs in genes encoding type I alpha collagen chains (COL1A1 and COL1A2) (Rauch et al., 2016). Type II collagen (COL1A2) is an important component of the extracellular matrix of cartilage, and is essential in endochondral bone formation, growth, and normal joint function. It is also necessary for the normal development and functioning of the eyes and inner ear. Type II collagen disorders include a diverse group of clinical phenotypes characterized by one of which is orofacial abnormalities (cleft lip and palate).

Then, the clinical severity of Osteogenesis Imperfecta, is related to the degree of conformational changes in the triple helix of collagen induced by the Gly substitution mutation. Osteogenesis imperfecta is a hereditary disease caused by mutations in the procollagen gene type I. One of the extra skeletal manifestations of this disease is the involvement of heart disease. Congenital heart defects occur in 8 out of 1000 live births and are the leading cause of death from birth defects (Glidewell et al., 2019). Among CHDs, the Fallot tetralogy (TOF) is the most common of the more severe conditions (cyanotics). Individuals with TOF present with a combination of abnormalities (pulmonary valve stenosis, right ventricular hypertrophy, ventricular septal defects, and aortic overriding) that together lead to insufficient tissue oxygenation. Genetic factors are a major contributor to the etiology of TOF, 20% of patients have pathogenic copy number variants or larger chromosomal anomalies (Mercer-Rosa et al., 2015, Morgenthau and Frishman, 2018).

In this regard, the nature and severity of congenital heart disease in 78 patients experiencing cleft lip and/or palate have been reported. The prevalence of bilateral cleft lip and palate in patients with heart lesions is much higher than in cleft patients with a normal heart (Wyse et al., 1990). This disease is caused by the use of valproic acid in

mothers suffering from catatonic schizophrenia. Valproic acid is known as teratogen, giving rise to a characteristic craniofacial picture, fetal valproic syndrome. Fetal valproate syndrome can also cause congenital heart malformations. In addition, maternal diabetes mellitus is associated with an increased risk of hereditary congenital heart defects (CHD).

Several studies report that type 2 diabetes mellitus in mothers and the use of valproate acid in mothers as a treatment for catatonic schizophrenia during pregnancy have the potential to cause congenital heart disease which is usually dominated by the Tetralogy of Fallot, where the Tetralogy of Fallot is associated with osteogenesis imperfect due to the formation of triple helix DNA on collagen. In addition, imperfect osteogenesis is also associated due to the presence of the heterozygous mutation COL1A2. Where osteogenesis is thought to have a relationship with the occurrence of cleft lip and palate, in addition, there is also a link in the severity of heart disease with the condition of the cleft lip and palate. Therefore, the role of osteogenesis, tetralogy of fallot, the use of asan valproate and diabetes mellitus in pregnant women in relation to children with cleft lip and palate conditions is controversial. To answer this question, the relationship between the incidence of cleft lip and palate with osteogenesis imperfecta with heterozygous mutation COL1A2 and triple helix DNA formation accompanied by Tetralogy of Fallot in children with a maternal history of catatonic schizophrenia followed by the use of valproic acid and type II diabetes mellitus

METHODS

This study is a systematic study using the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analyses) method, which is carried out systematically by following the correct procedures in conducting research. This study utilizes previous evidence-based reviews, studies, structures, classifications, and categorizations. The steps of a systematic review are very planned and structured, which distinguishes them from other methods that communicate only the study literature. The steps are as follows 1) Preparing for Background and Objectives 2) Research Problems 3) Finding Literature 4) Selection Standards 5) Exercise Screen 6) Quality Procedures and Checklists 6) Data

Extraction Strategies, and 7) Data Synthesis Strategies.

RESULTS AND DISCUSSION

1. The Relationship of the Cleft Lip and Palate With Osteogenesis Imperfecta

OI can be detected in fetuses at different gestational ages, depending on whether clinical questions are asked regarding family history or routine ultrasound examinations. The fetus is usually at 50% risk for OI when its parents suffer from OI (Byers et al., 2006). That is, the mother with the OI condition is most likely to pass it on to the baby she is carrying. OI itself is often associated with cleft lips and palate. Cleft lip and palate are birth defects that occur when the baby's lips or mouth are poorly formed during pregnancy. These two birth defects are commonly called "orofacial fissures". The causes of orofacial fissures in most babies are unknown. Some children have a cleft lip or cleft palate due to gene changes. Cleft lip and cleft palate are thought to be caused by a combination of genes and other factors, such as things related to the mother in her environment, or what the mother eats or drinks, or certain medications she uses during pregnancy. Understanding the more common factors that occur in babies with birth defects will help us learn more about their causes.

Osteogenesis Imperfecta affects dental and craniofacial development and therefore can interfere with oral health-related quality of life (Najirad et al., 2018). Autopsy findings showed typical OI type II features, including soft calvarium, deformed extremities, hip flexion and abduction, and uncommon features, such as white sclera, coxa vara, absence of some bones and organs, cleft lip, and asymmetrical ear. Radiological images reveal anomalies and variations such as cleft palate, mandibular dysplasia, spina bifida, costa cervicalis, and rib and spinal fusion, which are difficult to detect during conventional autopsies (Zhou et al., 2016). The explanation gives an idea of the relationship between the cleft lip and palate to osteogenesis

imperfecta. That is, mothers with OI conditions are likely to give birth to babies with cleft lip or palate conditions.

2. Association of Osteogenesis Imperfecta with Heterozygous Mutation COL1A2 and Triple Helix DNA Formation

Within approximately 90% of individuals with a clinical diagnosis of OI, a dominant mutation occurs in genes encoding type 1 alpha collagen chains (COL1A1 and COL1A2) (Rauch et al., 2016). That is, such mutase is the most frequent in cases of osteogenesis imperfect. Type II collagen (COL1A2) is an important component of the extracellular matrix of cartilage, and is essential in endochondral bone formation, growth, and normal joint function. It is also necessary for the normal development and functioning of the eyes and inner ear. Type II collagen disorders include a diverse group of clinical phenotypes characterized by one of which is orofacial abnormalities (cleft lip and palate).

Type I OI is usually due to mutations in the COL1A1 gene, resulting in a synthesis of roughly half the normal number of functional pro- α 1 chains, since one allele is zero. Only a small percentage of individuals with type 1 OI were found to have substitutions for glycine by small amino acids (cysteine, alanine, and serine) near the amino terminal end of the triple-helical domain of the COL1A1 or COL1A21 genes. Therefore, mutations in the COL1A2 gene, are a rarer cause of type 1 OI. Then, the clinical severity of Osteogenesis Imperfecta, is related to the degree of conformational changes in the triple helix of collagen induced by the Gly substitution mutation. Osteogenesis imperfekta is a hereditary disease caused by mutations in the procollagen gene type I.

3. Association of Osteogenesis Imperfecta with Tetralogy of Fallot in Children with a Maternal History of Catatonic Schizophrenia Followed by the Use of Valproic Acid and Type II Diabetes Mellitus

One of the extra skeletal manifestations of osteogenesis imperfecta is the involvement of heart disease. Congenital heart defects occur in 8 out of 1000 live births and are the leading cause of death from birth defects (Glidewell et al., 2019). Among them the tetralogy of Fallot (TOF) is the most common. Individuals with TOF present with a combination of abnormalities (pulmonary valve stenosis, right ventricular hypertrophy, ventricular septal defects, and aortic overriding) that together lead to insufficient tissue oxygenation. Genetic factors are a major contributor to the etiology of TOF, 20% of patients have pathogenic copy number variants or larger chromosomal anomalies (Mercer-Rosa et al., 2015, Morgenthau and Frishman, 2018). Thus, the presence of osteogenesis imperfecta can be said to be a trigger for the presence of TOF conditions.

TOF itself is closely related to the condition of the cleft lip and palate. The cleft lip, palate, or both (CL/P) are the most common birth defects observed in newborns, with a prevalence of 1:500 to 1:2,500 live births. CL/P is a syndrome in 30% of cases and nonsyndromic in the remaining 70%. CL/P syndrome is part of a physical supplemental constellation or cognitive abnormality, while nonsyndromic CL/P occurs as an isolated finding or occurs with phenotypes unrelated to CL/P. CL/P syndrome is associated with 400 to 500 genetic syndromes, 275 of which are caused by mutations in a single gene, chromosomal abnormalities, or teratogens.

CL/P and CHD (congenital heart disease) with 30% of cases being Tetralogy of Fallot are some of the most heterogeneous congenital conditions, with complex etiologies influenced by genetic and environmental risk factors. 22q11.2 microdeletions are present in 5 to 8% of cases with CL/P. Similarly, it has been reported that approximately 75 to 80% of patients with 22q11.2 microdeletion have CHD, which is the leading cause of death

4. Analyzing The Conceptual Picture Of The Relationship Between The Incidence Of Cleft Lip And Palate With Osteogenesis Imperfecta With Heterozygous Mutation COL1A2 And Triple Helix DNA Formation Accompanied By Tetralogy Of Fallot In Children With A Maternal History Of Catatonic Schizophrenia Followed By The Use Of Valproic Acid And Type II Diabetes Mellitus

The condition of the mother during pregnancy, including what she consumes will affect the fetus she contains. It is known that the condition of type 2 diabetes mellitus in mothers and the use of valproate acid in mothers as a treatment for catatonic schizophrenia during pregnancy has the potential to cause congenital heart disease. And as diata has explained, that the frequent heart disease is usually dominated by the Tetralogy of Fallot. The explanation above also explains that the Tetralogy of Fallot is associated with osteogenesis imperfecta due to the formation of triple helix DNA on collagen.

The fact that many babies are born with TOF conditions to mothers who suffer from diabetes and consume valproate acid also makes them interconnected. Then, the explanation above also explains that osteogenesis imperfecta is also related to the condition of the cleft lip and palate. So it is argued that babies born with cleft lip conditions are at risk of heart problems as well. This is justified by the fact that babies with cleft lip and palate conditions are often born with other congenital abnormalities, although this is not always the case

CONCLUSION

Based on the findings of related journals that have been indexed Q1-Q4 through a systematic review process, it is known that there is a relationship between the condition of the cleft lip and palate in babies born to mothers with type 2 diabetes mellitus conditions and the use of valproate acid drugs as a form of treatment of schizophrenia during pregnancy, and the condition of mothers with osteogenesis imperfecta in pregnant women which can decrease in the fetus in the womb which is also related to the condition cleft lip and palate, where osteogenesis mostly occurs due to heterozygous mutation COL1A2 and triple helix DNA formation. Then the association of these conditions during pregnancy also triggers the condition of the baby born with the tetralogy of fallot. So in general it can be said that babies born with osteogenesis imperfecta conditions tend to be more likely to experience cleft lips and palate and tetralogy of fallots or congenital heart disorders. Nevertheless, there is no journal that explicitly explains the relationship of variables. Journal discussions only discuss the potentials that can increase the risk of these diseases with the conditions mentioned in the research variables.

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