

# The Relationship between Cleft Lip and Palate Accompanied with Tetralogy of Fallot in Children and the Mother with History of Gestational Diabetes

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## ABSTRACT

Researchers believe genetic and environmental factors cause most cases of cleft lip and palate. However, the exact cause was not found. There is an assumption that cleft lip and palate condition has something to do with Tetralogy of Fallot in children with Gestational Diabetes Mothers. Then it is also found in babies with cleft lip and palate conditions, usually accompanied by other congenital anomalies, but not always. This then led to further speculation that there is a relationship between the above variables with cleft lip and palate. Therefore, this study tries to find the relationship between these variables. Objective, Knowing the Relationship between the incidence of Cleft Lip and Palate with Tetralogy of Fallot in Children with Gestational Diabetes. Methods this research is Ssystematic Review using Preferred Reporting Items for Systematic Reviews and Meta-analyses or PRISMA. This method is carried out systematically by following the correct research steps or protocols. The source was taken from the Google Scholar website with journals published in 2017-2023 and then carried out screening results obtained from 1870 journals. The Results show that Journal clustering was carried out, and the number of Q1 indexed journals were 4 journals, 1 journal Q3, and 1 journal Q4 so 6 journals were extracted. The entire journal does not directly discuss the relationship between research variables. However, it only provides an overview of the increased risk of cleft palate in babies if the pregnant mother has gestational diabetes, the possibility of having a baby with Tetralogy of Fallot, and the baby's association with conditions cleft lip and palate and tetralogy of Fallot.



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## 1. Introduction

Cleft lip and/or cleft palate are congenital abnormalities caused by teratogenic interference in the early stages of embryonic development [25]. A cleft lip and palate is a congenital disability when a baby's lips or mouth do not form properly during pregnancy. These two congenital disabilities are commonly called "orofacial clefts." Lips form between the fourth and seventh week of pregnancy. As a baby develops during pregnancy, body tissues and specialized cells from each side of the head grow toward the center of the face and join together to form the face. The amalgamation of these tissues forms facial features, such as lips and mouth [6].

A previous study revealed that the African population has the lowest disease incidence, around 0.4/1000. In India, the mean prevalence index of this disease was 0.398/1000 from 2007 to 2011 (Which et al.,2018). In Europe, the incidence is around 1/1000, and Asia and South America have a relatively high incidence of around 2/1000 [27]. The highest cleft lip and/or palate birth rates are in Asia (especially in China and Japan) [50], and China is one of the regions with the highest incidence, around 1.663/1000 (Which et al.,2018).

Cleft lip, or cleft lip, occurs when the tissues that make up the lip do not combine thoroughly before birth. This results in a hole in the upper lip. The opening in the lips can be either a small slit or a large opening that goes through the lips to the nose. A cleft lip can be on one or both sides of the lip or in the middle, which is very rare. Children with cleft lips can also have cleft palates. The roof of the mouth (palate) forms between the sixth and ninth weeks of pregnancy. A cleft palate occurs when the tissues that make up the roof of the mouth do not fuse entirely during pregnancy. For some babies, the front and back of the palate are open, and for some, the palate is only partially open.

A cleft lip can carry an enormous health burden to patients and families, negatively affecting the mental health and quality of life of patients [44]. This disease usually accompanies various complications, mainly affecting the voice and face [41]. Children with cleft lips with or without a palate often have problems eating and speaking and may develop ear infections and difficulty eating. They may also have hearing problems and problems with their teeth.

The cause of orofacial clefts in most babies is unknown. Some children have a cleft lip or palate due to a gene change. Cleft lip and cleft palate are thought to be caused by a combination of genes and other factors, such as what the mother is exposed to in her environment, what the mother eats or drinks, or certain medications used during pregnancy. Understanding the common factors in babies with congenital disabilities will help us learn more about their causes.

Recently, a study reported essential findings from research studies on several factors that increase the chances of having a baby with orofacial clefts, including smoking. Women who smoke during pregnancy are more likely to have babies with orofacial clefts than women who do not smoke (Honeyet al.,2007, [22]. Next 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 with women who do not have diabetes [8]. Use of certain drugs: Women who take certain drugs to treat epilepsy, such as topiramate or valproic acid, during the first trimester (first 3 months) of pregnancy have an increased risk of having a baby with a cleft lip with or without a cleft palate, compared with women who do not take this drug [23], [45].

Cleft lip and palate are often associated with osteogenesis imperfecta. Osteogenesis Imperfecta (OI), also known as “brittle bone disease,” is a rare inherited disorder (prevalence of 8 per 100,000 people) characterized by recurrent fractures and, in severe cases, bone deformities [14]. Osteogenesis Imperfecta affects dentition and craniofacial development and can therefore impair oral health-related quality of life [30]. Autopsy findings reveal the typical features of type II OI, 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 asymmetry Ear. Radiological images revealed anomalies and variations such as cleft palate, mandibular dysplasia, spina bifida, costa cervicalis, and rib and vertebral fusion, which were difficult to detect during conventional autopsies [52].

Osteogenesis Imperfecta is a group of inherited connective tissue disorders characterized primarily by brittle bones, growth deficiency, and blue sclera. The pathological effects of OI on dental tissues and the oral cavity usually develop early in life and may affect oral health quality during childhood and adolescence. Orofacial manifestations are frequently associated with OI [37].

Approximately 90% of individuals diagnosed with OI have dominant mutations in the genes encoding type I collagen alpha chains (COL1A1 and COL1A2) [34]. Type II collagen (COL2A2) is an essential component of the cartilage extracellular matrix and is critical in endochondral bone formation, growth, and normal joint function. It is also necessary for the normal development and function of the eyes and inner ear. Type II collagen disorders include a diverse group of clinical phenotypes characterized by orofacial disorders (cleft lip and palate).

Then, the clinical severity of Osteogenesis Imperfecta correlates with the degree of conformational change in the triple helix (triple helices) collagen-induced by Gly substitution mutations. Osteogenesis imperfecta is a hereditary disease caused by mutations in the pro-collagen type I gene. 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 congenital disabilities. et al., 2019). Among CHD, tetralogy of Fallot (TOF) is the most common of the more severe (cyanotic) conditions. Individuals with TOF present with abnormalities (pulmonary valve stenosis, right ventricular hypertrophy, ventricular septal defect, and overriding aorta), resulting in insufficient tissue oxygenation. Genetic factors are significant contributors to the etiology of TOF. 20% of patients have a pathogenic copy number variant or more significant chromosomal anomaly [26], [29].

In this regard, the nature and severity of congenital heart disease in 78 patients with cleft lip and/or palate have been reported. The prevalence of bilateral cleft lip and palate in patients with cardiac lesions is much higher than in cleft patients with normal hearts [48]. This disease is thought to be caused by using valproic acid in mothers with catatonic schizophrenia. Valproic acid is a known teratogen, giving rise to the 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 have reported that type 2 diabetes mellitus in the mother and the use of valproic acid in the mother as a treatment for catatonic schizophrenia during pregnancy has the potential to cause congenital heart disease, which is usually dominated by Tetralogy of Fallot, in which Tetralogy of Fallot is associated with osteogenesis imperfecta due to the formation of DNA triple helix, on collagen. In addition, osteogenesis imperfecta is also associated with a COL1A2 heterozygous mutation. Osteogenesis is thought to have a relationship with cleft lip and palate occurrence. Apart from that, there is also a link between the

severity of heart disease and cleft lip and palate condition.

## 2. LITERATURE REVIEW

### Cleft Lip and Palate

#### 1. Definition

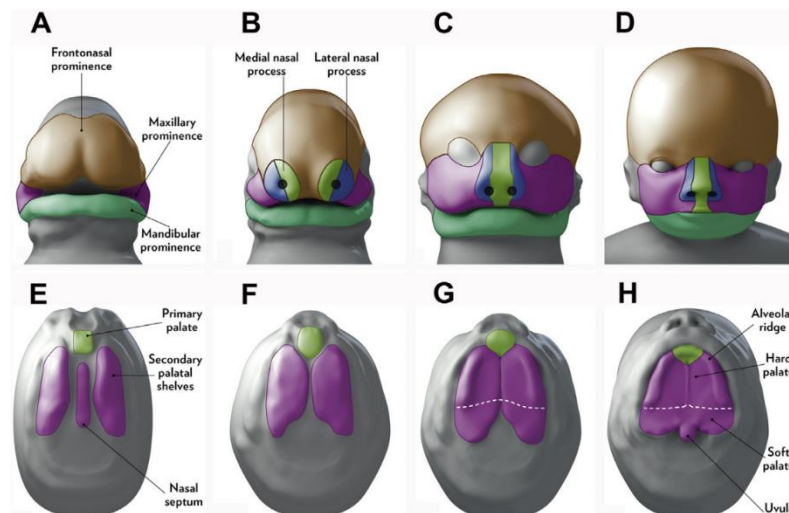
Cleft lip and/or cleft palate are congenital abnormalities caused by teratogenic interference in the early stages of embryonic development [25]. A cleft lip and palate is a congenital disability when a baby's lips or mouth do not form properly during pregnancy. These two congenital disabilities are commonly called "orofacial clefts." Although cleft lip, palate, or both may occur separately, they are often associated with additional congenital anomalies or genetic syndromes. Compared to babies with only one of the conditions, babies with both are more likely to have associated congenital abnormalities. Common anomalies that are usually seen in children with CPO include congenital heart disease (> 30%) [47].

#### 2. Epidemiology

A previous study revealed that the African population has the lowest disease incidence, around 0.4/1000. In India, the mean prevalence index of this disease was 0.398/1000 from 2007 to 2011 (Whichet al.,2018). In Europe, the incidence is around 1/1000, and Asia and South America have a relatively high incidence of around 2/1000 [27]. The highest cleft lip and/or palate birth rates are in Asia (especially in China and Japan) [50], and China is one of the regions with the highest incidence, around 1.663/1000 (Whichet al.,2018).

#### 3. Pathophysiology

Embryological development of the lips begins in the 4th week of gestation with the appearance of paired maxillary prominences and unpaired frontonasal prominences (Fig. 2.1 A–D). In the fifth week, the medial and lateral nasal processes develop from invaginations of the nasal plaques. A pair of maxillary prominences extend medially in weeks 6 to 7, fulfilling the nasal processes to form the upper lip. The primary palate develops from the fusion of a pair of medial nasal prominences in weeks 6 to 7 (Figs. 2.1 E–H). This fusion forms the intermaxillary segment, containing the 4 central incisors and the hard palate in front of the incisive foramen. At the same time, the processes or palatine shelves also extend medially from the pair of maxillary projections. Fusion of the palatal shelves to form the secondary palate begins in week 9 (fusion begins anteriorly at the incisive foramen and extends posteriorly to the uvula).



**Figure 2.1** (A–D) Sequence of development of the upper lip. (E–H) Development of soft and hard palate

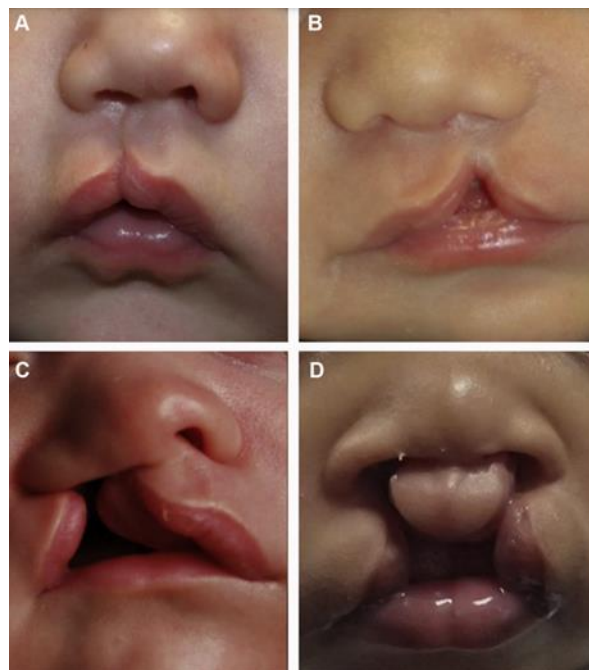
Source: [47]

Cleft lip forms at the top of the lip either as a small fissure or indentation in the lip (partial cleft) or continues into the nose (complete cleft). Cleft lip (CL) can occur on one side (unilateral) or two sides (bilateral). This is due to the failure of fusion of the maxillary and medial nasal processes (formation of the primary palate). A cleft palate is a condition in which the two skull plates that make up the hard palate (roof of the mouth) do not fit together correctly.

#### 4. Diagnosis

##### *Classification of Cleft Lips*

Cleft lip (CL) can be classified as microform, incomplete, or complete. The cleft microform describes an indentation or indentation in the soft tissue of the lip (Fig. 2.2 A). All lip tissue is formed, but there is a notch at the vermilion-cutaneous junction. In contrast, an incomplete cleft lip involves dehiscence of the orbicularis oris and can vary in that it involves skin (Fig. 2.2 B). Simonart's band refers to a thin band of soft tissue covering the superior aspect of the incomplete lip cleft at the threshold of the nose. The lip cleft extends through the lip's length and to the nose's threshold, causing an abnormal insertion of the orbicularis oris head and columella (Fig. 2.2 C). In addition, in bilateral clefts, there is anterior displacement of the intermaxillary segment in the absence of the orbicularis oris within the intermaxillary segment (Fig. 2.2 D).



**Figure 2.2** (A) Microform right CL. (B) Incomplete left CL. (C) complete the right CL. (D) Bilateral complete CL

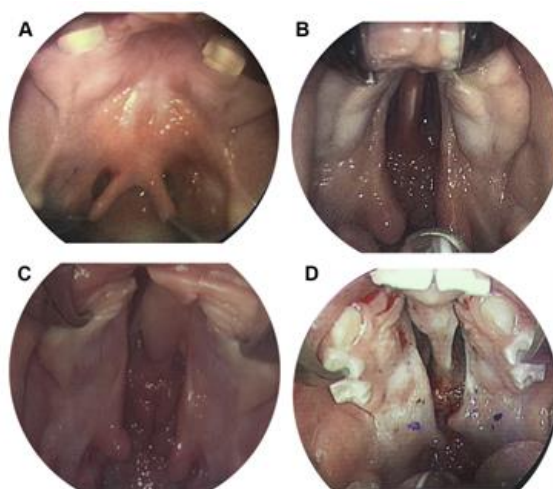
Source: [47]

##### *Cleft Palate Classification*

Cleft palate (CP) can also be classified according to the degree of anatomic involvement. The CP submucosa is characterized by dehiscence of the underlying muscle of the intact palatal mucosa. Physical examination findings associated with submucosal CP include a midline hard palate notch, a bifida uvula, and the zona pellucida (a blue line in the midline of the soft palate indicating a lack of muscle and increased transparency). The secondary cleft palate involves a defect extending posteriorly from the incisive foramen through the soft palate to the uvula. In contrast, the primary cleft palate involves the palate anterior to the



incisive foramen extending into the alveolar arches. A description of the various types of CP is shown in Figure 2.3. The terms hard and soft palate refers to the anatomical findings of the anterior bony palate and the posterior soft tissue/muscle palate, respectively.



**Figure 2. 3** (A) Submucosal CP. (B) Incomplete CP. (C) Unilateral complete CP. (D) Bilateral complete CP  
Source: [47]

*Prenatal Diagnosis of Cleft Lip and Palate*

Antenatal diagnosis of orofacial clefts is the first step that can assist families in preparing for their child's future care. Prenatal diagnosis also allows the family to consult with the prenatal craniofacial team, who can facilitate the recommended pre-postpartum evaluation for the baby [36]. The accuracy of two-dimensional (2D) ultrasonography in detecting orofacial clefts among low-risk patients varies, with a detection rate of 0–70%. Infants with CPO are less likely to be detected than infants with CL/P conditions. Compared to 2D studies, 3D ultrasonography has improved diagnostic accuracy and has demonstrated the ability to detect CP when CL has been previously detected on 2D ultrasonography.

*Medical Treatment*

Given the condition, patients with cleft lip and palate will require special care that varies according to their age level. The Treatment is summarized in the image below.

Table 1 Basic cleft care		
Age	Medical Treatments	Surgery
Prenatal to birth	<ul style="list-style-type: none"> <li>Genetic counseling</li> <li>SLP consultation for feeding</li> </ul>	—
0–5 mo	<ul style="list-style-type: none"> <li>SLP for feeding and growth</li> <li>Monitor hearing</li> <li>NAM (if indicated)</li> </ul>	<ul style="list-style-type: none"> <li>CL repair</li> <li>Ear tubes (if COM)</li> </ul>
9–12 mo	—	<ul style="list-style-type: none"> <li>Palatoplasty</li> <li>Ear tubes (if COM)</li> </ul>
1–4 y	<ul style="list-style-type: none"> <li>Introduction to pediatric dentist</li> <li>Assess language development</li> </ul>	—
4–6 y	<ul style="list-style-type: none"> <li>Assess for VPD</li> </ul>	<ul style="list-style-type: none"> <li>Corrective speech surgery</li> <li>Lip revision if needed</li> <li>Minor nasal surgery if needed</li> </ul>
6–12 y	<ul style="list-style-type: none"> <li>Orthodontics</li> <li>Assess school/psychosocial adjustment</li> </ul>	<ul style="list-style-type: none"> <li>Alveolar bone grafting</li> </ul>
12–21 y	<ul style="list-style-type: none"> <li>Orthodontics</li> </ul>	<ul style="list-style-type: none"> <li>Orthognathic surgery</li> <li>Definitive rhinoplasty</li> </ul>

## **Figure 2.4** Basic Treatment of Cleft Palate and Lips

Source: [47]

\*Abbreviations: COM, chronic otitis media; NAM, nasopalveolar print; SLP, speech language pathology; VPD, velopharyngeal dysfunction

### **Management**

#### *Preoperative Cleft Planning*

Patients with unilateral or bilateral clefts who cannot undergo the procedure of lip taping or NAM will usually use lip adhesion. This procedure is generally performed at 1 month of age in preparation for stage 2 lip repair. Definitive lip repair generally occurs within 3 months (10 weeks) to avoid the airway difficulties associated with nasal breathing in early infancy and post-apneic anesthesia. Other factors involved in the timing of surgery include body weight (ideally 4.5 kg) and hemoglobin level (ideally 10 g/dL), known as the 10's rule. Adequate NAM completion or taping may delay operation. The feeding method and associated requirements for postoperative hospitalization must be considered. Wound care after surgery usually involves gentle cleaning and the application of ointment. If permanent skin sutures were used, a second procedure to remove the sutures would be required.

#### *Operation Procedure*

The techniques used in cleft lip surgery are usually different, depending on the type of cleft. The Millard or Fisher technique is used for unilateral cleft repair, and the Millard technique is used for bilateral cleft repair [11]. Millard's technique is based on the rotation-advancement principle, whereas Fisher uses an anatomical subunit approach. At the same time, specific surgical techniques are usually used by surgeons for complete and incomplete cleft repair [39]. Nose tip surgery can be performed during unilateral and bilateral cleft repair surgery to correct the affected contour, shape, position, and nose tip. Lip repair or cheiloplasty is performed under endotracheal anesthesia, whereas the surgeon prefers local anesthesia.

For Millard's refinement, critical markings include the high and low points of Cupid's arc, the columellar base, the alar base, and the choice of the appropriate Cupid's arc high point on the lateral lip of the slit side. The basic principle of the Millard method is to rotate the non-cleft side downward and advance the lateral lip of the cleft side. Flap C is of non-medial origin and can be inserted into the columella for lengthening or nasal lintels. The M and L mucosal flaps can be rotated to bridge the alveoli and minimize the resulting fistula.

#### *Cleft Palate Preoperative Planning*

Usually, palatoplasty occurs between the ages of 9 -12 months. It is also possible to perform palate repair in two stages: early soft palate closure and hard palate closure. The effect of the procedure on the oropharyngeal airway and the potential for impaired maxillary growth caused by challenging palate dissection are factors that should be considered when deciding when to undergo surgery. Before surgery, all related parties must discuss possible risks with the patient, such as fistulas, velopharyngeal dysfunction, developmental disorders of the maxilla, and breathing disorders during sleep [7]. Bleeding, infection, tongue edema, and breathing problems are short-term consequences of surgical procedures. The meal schedule and the need for postoperative hospitalization must also be considered. Restoration of an intact levator palatini with palatal lengthening is one of the goals of palatoplasty. Ideally, the procedure should have a minimum incidence of palatal fistulas, VPD, and developmental disorders of the maxilla.

#### *Cleft Palate Surgical Procedure*

The type of palatal involvement, for example, whether only the soft palate, incomplete secondary palate,

complete secondary palate, or wide gaps between the palatal shelves, can influence the surgical procedure chosen. An axial mucoperiosteal flap based on the more significant palatine artery is used to heal the hard palate. Vomer flaps can be used to help close the nostrils. Straight-line repair, intravelar veloplasty, or double opposite Z-plasty are procedures used to repair the soft palate while placing the levator muscles into an unbroken sling. Whatever the method, all are used to minimize the occurrence of fistula formation.

## **Gestational Diabetes**

### *Definition*

One of the most common diseases of pregnant women, Gestational Diabetes, is caused by a confluence of two main factors: inappropriate insulin secretion by pancreatic beta cells and inappropriate insulin response in insulin-sensitive organs. The molecular mechanisms involved in insulin synthesis, release, and detection are carefully regulated activities as they are required to maintain glucose homeostasis. The metabolic imbalance that causes this disease can be caused by a deficiency in one of the mechanisms underlying this procedure *et al.*,2020).

### *Pathophysiology*

Regarding disease pathogenesis, unusually high blood glucose levels are caused by defective feedback between insulin action and insulin secretion [40]. As a result of decreased insulin secretion caused by cellular malfunction, the body's ability to maintain physiological glucose levels is limited. On the other hand, IR (insulin resistance) helps reduce glucose uptake in adipose tissue, muscle, and liver while increasing glucose synthesis in the liver. Even while all these processes occur early in the pathophysiology and lead to disease onset, beta-cell dysfunction is usually more severe than IR. However, hyperglycemia increased, and T2DM continued as IR and beta-cell dysfunction appeared [51].

### *Epidemiology*

The World Health Organization (WHO) describes diabetes mellitus as a chronic metabolic condition characterized by high blood glucose levels, which over time, causes damage to the heart, blood vessels, eyes, kidneys, and nerves. T2DM controls more than 90% of diabetes mellitus worldwide [40]. Statistics drawn from epidemiological data points to worrying future projections for GD. In 2019, diabetes caused 4.2 million deaths worldwide. People with diabetes are most often between the ages of 40 and 59. The prevalence and incidence of T2DM vary by geographic region, with more than 80% of patients living in low- to middle-income countries, which presents extra difficulties for efficient treatment [16].

### *Diagnosis*

Diagnosis of type 2 diabetes mellitus is usually made through tests or tests as follows:

- A1C: average blood glucose over the last 2-3 months
- Fasting blood sugar test to measure blood sugar on an empty stomach (fasting 8 hours before testing).
- Oral glucose tolerance test (OGTT). This test checks blood glucose before and 2 hours after the patient drinks something sweet to see how the patient's body handles sugar.

## **Tetralogy of Fallot**

### *Definition*

Tetralogy of Fallot (TOF) is the most common type of congenital cyanotic heart disease, accounting for 7%–10% of all congenital heart defects and occurring in 4–5 per 100,000 live births [46].

### *Epidemiology and Pathophysiology*

The prevalence of TOF in the United States is approximately 4 to 5 per 10,000 live births. This defect



accounts for about 7 to 10 percent of cases of congenital heart disease and is one of the most common congenital heart lesions requiring intervention in the first year of life. TOF occurs equally in men and women (Report of the New England Regional Infant Cardiac Program). Ventricular septal defects in tetralogy of Fallot are often described as the malalignment type because the conal septum is displaced anteriorly. This displaced septum bulges into the pulmonary outlet, often resulting in obstruction and hypoplasia of downstream structures, including the pulmonary valve, main pulmonary artery, and branches. Ventricular septal defects are usually significant; thus, the systolic pressures in the right and left ventricles (and the aorta) are equal. The pathophysiology depends on the degree of right ventricular outflow obstruction. Slight obstruction can result in a left-to-right net shunt through the ventricular septal defect (VSD), and severe obstruction causes a right-to-left shunt, resulting in low systemic arterial saturation (cyanosis) that is unresponsive to supplemental oxygen.

### *Diagnosis*

Prenatal ultrasound has been helpful in the early diagnosis of TOF and offers prompt postnatal care in pulmonary vasculature-dependent cases. Physical findings from murmur and cyanosis in neonates are not specific to TOF. The presence or absence of murmur and its quality depends on the degree of outlet obstruction and not on the presence or size of the VSD. Murmur, those absent may indicate no obstruction or the presence of severe obstruction, where there is little flow. Physical signs such as right ventricular heave, systolic thrill, or prominent pulse are not always present. However, anatomic confirmation by postnatal echocardiography is the gold standard for diagnosing TOF and associated anomalies in the current era. Echocardiography can help determine the location, extension, and number of VSDs and valve attachments concerning the VSD. In addition, the size, function, and appearance of the pulmonary valve and annulus can be assessed, along with the degree and degree of right ventricular outflow obstruction [46]. Other diagnoses can be made through chest radiograms, cardiac catheterization, and imaging studies.

## **Schizophrenia Catatonic**

### *Definition*

Schizophrenia is divided into five subtypes, including disorganized schizophrenia, paranoid schizophrenia, residual schizophrenia, undifferentiated schizophrenia, and catatonic schizophrenia. The features of catatonia have been described since the 1800s by leading physicians, who defined catatonia in the broader definition of dementia praecox [10]. Catatonic schizophrenia can be part of a more significant schizophrenic illness or even bipolar affective illness or medical illness [4].

### *Etiology*

The etiology of catatonia is multifactorial. One theory is that the neurotransmitter gamma-aminobutyric acid, which regulates emotional and cognitive functions, becomes disrupted, causing catatonic symptoms [9]. This theory postulates that extreme negative emotions can lead to "tonic immobility," leading to a lack of inhibition in the orbitofrontal cortex and hence dysregulation between the ventromedial prefrontal cortex and the dorsolateral prefrontal cortex, which can lead to catatonic symptoms. The DLPFC helps with a cognitive understanding of negative emotions.

### *Epidemiology*

The epidemiology of catatonic schizophrenia can be multivariate. It is said that about 10% of patients in inpatient psychiatric services have catatonic features [15]. On the one hand, a school of psychiatry links schizophrenia with catatonia. At the same time, more recent epidemiological studies show that 20% of patients with catatonia have schizophrenia, and about 45% have symptoms of mood disorders and medical illnesses. One prospective study showed that 7.6% of people diagnosed with schizophrenia had catatonia.

Another study showed that 10%-25% of schizophrenic patients in inpatient settings could be classified as having catatonic schizophrenia, primarily when screening tools were used.

#### *Pathophysiology*

The N-methyl D-aspartate (NMDA) receptor has been studied extensively clinically and in animal studies. NMDA encephalitis can produce catatonia-like symptoms. There have been reports of using anti-NMDA agents such as amantadine in treating catatonia. The neurotransmitter most associated with catatonia is GABA (gamma-amino-butyric acid), which has been studied extensively. Reduced GABAergic activity has been detected in the left sensorimotor cortex via positron emission tomography (PET) imaging [38].

#### **The relationship between the occurrence of cleft lip and palate and osteogenesis imperfecta with heterozygous COL1A2 mutations and the formation of DNA triple helix 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**

Cleft lip and/or cleft palate are congenital abnormalities caused by teratogenic interference in the early stages of embryonic development [25]. Cleft lip, or cleft lip, occurs when the tissues that make up the lip do not combine thoroughly before birth. This results in a hole in the upper lip. Children with cleft lips can also have cleft palates. The cause of orofacial clefts in most babies is unknown. Cleft lip and cleft palate are thought to be caused by a combination of genes and other factors, such as what the mother is exposed to in her environment, what the mother eats or drinks, or certain medications used during pregnancy.

Recently, a study reported essential findings from research studies regarding several factors that increase the chances of having a baby with orofacial clefts, one of which is diabetes. Next 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 with women who do not have diabetes [8]. The use of certain drugs, such as valproic acid, during the first trimester of pregnancy has an increased risk of having a baby with a cleft lip with or without a cleft palate compared to women who do not take these drugs [23], [45].

Cleft lip and palate are often associated with osteogenesis imperfecta. Osteogenesis Imperfecta (OI). In approximately 90% of individuals with the clinical diagnosis of OI, mutations are predominant in the genes encoding type I collagen alpha chains (COL1A1 and COL1A2). Type II collagen (COL1A2) is an essential component of the cartilage extracellular matrix and is critical in endochondral bone formation, growth, and normal joint function. Type II collagen disorders cover a diverse group of clinical phenotypes, one of which is orofacial disorders (cleft lip and palate). Then, the clinical severity of Osteogenesis Imperfecta is related to the degree of conformational change in the triple helix (triple helices) collagen-induced by Gly substitution mutations. Osteogenesis imperfecta is a hereditary disease caused by mutations in the pro-collagen type I gene. One of the manifestations of this disease is the involvement of heart disease (CHD). Among CHD, tetralogy of Fallot (TOF) is the most common..

Later, the nature and severity of congenital heart disease in patients with cleft lip and/or palate have been reported. The prevalence of bilateral cleft lip and palate in patients with cardiac lesions is much higher than in cleft patients with normal hearts [48]. This disease is thought to be caused by using valproic acid in mothers with catatonic schizophrenia. In addition, maternal diabetes mellitus is associated with an increased risk of hereditary congenital heart defects (CHD). Thus, it is widely suspected that there is type 2 diabetes mellitus in the mother. The use of valproic acid in the mother as a treatment for catatonic schizophrenia during pregnancy can cause congenital heart disease, which is usually dominated by Tetralogy of Fallot, in which Tetralogy of Fallot is associated with osteogenesis imperfecta due to the formation of DNA triple

helix on collagen. In addition, osteogenesis imperfecta is also associated with a COL1A2 heterozygous mutation. Osteogenesis is thought to have a relationship with cleft lip and palate occurrence. Apart from that, there is also a link between the severity of heart disease and cleft lip and palate condition. Therefore, the role of osteogenesis, tetralogy of Fallot, use of valproic acid, and diabetes mellitus in pregnant women concerning children with cleft lip and palate are still controversial.

### 3. METHOD

This study is a systematic study using the PRISMA method (Preferred Reporting Items for Systematic Review and Meta-analyses), which is carried out systematically by following the correct procedures in conducting research. This research draws on previous evidence-based reviews, studies, structured evaluations, classifications, and categorizations. The steps of a systematic review are highly planned and structured, differentiating it from other methods that only communicate the study literature. The steps are as follows 1) Preparing Background and Objectives 2) Research Problems 3) Finding Literature 4) Selection Standards 5) Exercise Screens 6) Quality Procedures and Checklists 6) Data Extraction Strategies, and 7) Data Synthesis Strategies.

#### Research Database Source

The data used to search the literature were selected based on the association between cleft lip and palate and osteogenesis imperfecta, which concerns medical and social health research. Next, review the literature relating to cleft lip, tetralogy of Fallot, and gestational diabetes. Articles are searched using Google Scholar as a database. The search for research articles relevant to this research is carried out using the following keywords: cleft lip and palate, tetralogy of fallot, and gestational diabetes, cleft lip and palate, and tetralogy of fallot, cleft lip and palate, and gestational diabetes.

#### Publication time

The journals taken are journals published in 2017-2023

#### Inclusion and exclusion criteria

- a. Inclusion criteria
  - 1) Research articles published in 2017-2023
  - 2) The dependent variables in the research articles are gestational diabetes and tetralogy of fallot
  - 3) The independent variables in the research articles are cleft lip and palate
  - 4) Articles indexed Q 1, 2, 3 and 4
- b. Exclusion criteria
  - 1) Research articles with incomplete text
  - 2) based articles literature review / systematic review
  - 3) Does not discuss dependent variables / articles that are not related
  - 4) Articles with incomplete content

#### Publication Search Strategy

Search for publications on Google Scholar using the selected keywords, namely cleft lip and palate, osteogenesis imperfecta, Tetralogy of Fallot, catatonic schizophrenia, and type II diabetes mellitus.

**Table 4. 1** Publication Search Strategy on the Google Scholar and PubMed databases

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Search Strategy	Publication Step	search through the database
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Step search through the database

- a. Cleft lip and palate
  - b. Tetralogy of Fallot, diabetes gestational
  - c. Cleft lip and palate, Tetralogy of Fallot
  - d. Cleft lip and palate, diabetes gestacional
- It is. Cleft lip and palate, Tetralogy of Fallot with Gestational Diabetes

**Summarize in the Bibliography Summary Table**

The journals found were selected based on the title and abstract information to see whether the article met the author's inclusion criteria to serve as an in-depth literature review; there were 6 journals analyzed. The essence taken from the research is the research title, researcher's name, and year of publication, place of research, sample, method, and research results.

**Analysis and Synthesis**

The analysis is the decomposition of a subject into its various parts and the study of the parts themselves and the relationships between the parts to obtain a proper understanding and understanding of the meaning of the whole. At the same time, synthesis is a blend (mixture) of various meanings or things so that they form a harmonious whole. The narrative is the method used in synthesizing this research. This method classifies the extracted data and analyzes the content of the research objectives and results. The analysis used is journal content analysis.

**4. RESULTS AND DISCUSSION**

This chapter will describe the results and analysis using 6 journals related to cleft lip and palate variables followed by Tetralogy of Fallot and fully accessed gestational diabetes. Journal obtained at screening and extracted into a table to make it easier to explain the journal's contents. Based on the results of journal clustering, the number of journals indexed by Scopus Q1 was 4 journals, 1 journal Q3, and 1 journal Q4.

**Data Analysis**

Data information regarding cleft lip and palate and osteogenesis imperfecta as independent variables analyzed are presented in the form of a table containing the title of the journal, year of publication, author of the purpose in the journal, sample and criteria, research instruments, between data or research methods and research results in a journal.

**Table 5. 1** Journal Analysis

<b>No</b>	<b>Journal Title and Researcher Name</b>	<b>Purpose</b>	<b>Population/ Sample</b>	<b>Instrument</b>	<b>Data Analysis / Research Methods</b>	<b>Results</b>	<b>Journal Clustering</b>
1	Oral health-related quality of life in children and adolescents with osteogenesis	Exploring the influence of OI severity on oral health-related quality of life in children	138 children and adolescents with OI type who have OHRQoL (Oral Health-	Questionnaires with paper whose results are entered into an online data retrieval system that is managed by the Study Data Management and Coordinating Center (University of South Florida).	Statistical analysis was performed by software using Stata 13.0 and a significance value of 5%	Orofacial manifestations (cleft lip and palate) are associated with Osteogenesis Imperfecta. OI affects	Q1

	s imperfecta: cross-sectional study [30]	and adolescents	Related Quality of Life) data in the two study years from 6 August 2015 to 3 August 2017			dentition and craniofacial development and may therefore impair oral health-related quality of life. Adolescents with OI have functional limitations and worse oral symptoms than those without.	
2	Pregnancy in women with osteogenesis imperfecta: pregnancy characteristics, maternal, and neonatal outcomes [33]	Pregnancy in women with osteogenesis imperfecta: pregnancy characteristics, maternal and neonatal outcomes	132 people with OI condition	Survey	cross-sectional, survey-based study.	Women with OI have an increased risk of birth defects by 3%, including orofacial defects, namely cleft lip and palate.	Q1
3	Perinatal Outcomes in a Longitudinal Birth Cohort of First Nations Mothers With Pregestational Type 2 Diabetes and Their Offspring: The Next Generation Study [32]	Knowing the level of health of children born to mothers with diabetes	112 pairs of children of mothers with mothers suffering from type 2 diabetes mellitus	The instrument used is related literature	Study of literature	Babies born to mothers with diabetes have an anomaly rate of 20.5% (4 cases of cardiac anomaly and 1 case each of polycystic kidney microcephaly, cleft palate and jejunal atresia).	Q1
4	Teratogenicity of	study of malformati	117 children	The instrument used is related literature	Retrospective study	Children are exposed to	Q3



	Antiepileptic Drugs  Guveli et al., 2017	ons in children born to mothers who took or stopped taking the drug valproic acid during their pregnancy.	born to 88 mothers with epilepsy		with statistical analysis using SPSS	valproic acid, which can cause higher rates of facial dismorphism. This means that the risk of being born with a cleft lip or palate is higher.	
5	Maternal Risk Factors Associated with the Development of Cleft Lip and Cleft Palate in Mexico: A Case-Control Study  [1]	determine maternal risk factors associated with the development of cleft lip and cleft palate.	patients who delivered babies with and without cleft lip and palate from January 2010 to December 2015 at Culiacan women's hospital, Mexico	The instrument used is related literature	case control study at the Women's Hospital in Culiacan, Mexico. Medical records were analysed, including patients who delivered babies with and without cleft lip and palate from January 2010 to December 2015. Several variables were analysed, including gestational age, birth weight, use of folic acid and multivitamins during pregnancy, smoking, alcohol abuse, drug use, history of sexually transmitted infections, marital status, socioeconomic	Faktor risiko utama yang terkait dengan perkembangan bibir sumbing dan celah langit-langit pada populasi Meksiko di Rumah Sakit Wanita di Culiacan, Sinaloa, Meksiko adalah merokok, penyalahgunaan alkohol, dan pasien yang tidak mengonsumsi asam folat dan multivitamin selama kehamilan.	Q4

					mic status, education, and nutritional status. Data were analyzed using descriptive statistical methods.		
6	The 22q11.2 Microdeletion in Pediatric Patients with Cleft Lip, Palate, or Both and Congenital Heart Disease: A Systematic Review [5]	Knowing the relationship between cleft lip and palate and congenital heart disease conditions in 22q11.2 deletion syndrome	A total of 2,391 articles were assessed. After duplicate removal and screening of studies, 1989 articles were selected. According to the inclusion and exclusion criteria, the full text of the articles was assessed for eligibility, and data from 49 articles were included	The instrument used is related literature. Searches were performed at PubMed and the National Center for Biotechnology Information (NCBI ( <a href="http://www.ncbi.nlm.nih.gov/omim/">http://www.ncbi.nlm.nih.gov/omim/</a> )) using the following descriptors: 22q11.2DS, DiGeorge syndrome, Velo-Cardio-Facial Syndrome, Takao syndrome, Opitz-GBBB, Conotruncal anomalies of facial syndrome, CL/P, CHD, cardiac defects, palatal abnormalities, and 22q11. Selected articles published between 1993 and 2018.	A systematic search of the literature was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines (PRISMA).	22q11.2 deletion syndrome (22q11.2DS) is present in approximately 5 to 8% of patients with cleft lip, palate, or both (CL/P) and in 75 to 80% of patients with cardiac disease (CHD) of which 30% is a tetralogy of fallot condition. So there is an association of pediatric patients with CL/P and CHD, in this case the tetralogy of fallot.	Q1

**Relationship between cleft lip and palate with tetralogy of fallot in children with a maternal history of gestational diabetes**

One of the extraskeletal 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 congenital disabilities. et al., 2019). Of these, tetralogy of Fallot (TOF) is the most common. Individuals with TOF present with abnormalities (pulmonary valve stenosis, right ventricular hypertrophy, ventricular septal defect, and overriding aorta), resulting in insufficient tissue oxygenation. Genetic factors are significant contributors to the etiology of TOF. 20% of patients have a pathogenic copy number variant or more significant chromosomal anomaly [26], [29]. Thus, the presence of osteogenesis imperfecta is the

trigger for the occurrence of TOF.

TOF itself is closely related to the condition of cleft lip and palate. Cleft lip, palate, or both (CL/P) is the most common congenital disability observed in newborns, with a prevalence of 1:500 to 1:2,500 live births. CL/P is syndromic in 30% of cases and nonsyndromic in the remaining 70%. CL/P syndrome is part of a constellation of different physical or cognitive disorders, while nonsyndromic CL/P occurs as an isolated finding or with a phenotype not associated with 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 microdeletion is present in 5 to 8% of cases with CL/P. Similarly, it has been reported that approximately 75 to 80% of patients with the 22q11.2 microdeletion have CHD, which is a significant cause of death.

### **Analyzing the concept description regarding the relationship between the incidence of cleft lip and palate and Tetralogy of Fallot in children with a history of gestational diabetes**

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

The fact that many babies are born with TOF to mothers who have diabetes and take valproic acid also makes it related. Then the explanation above also explains that osteogenesis imperfecta is also related to cleft lip and palate conditions. So babies born with cleft lip conditions also risk experiencing heart problems. This is justified because babies with cleft lip and palate are often born with other congenital abnormalities, although this is not always true.

## **5. RESEARCH LIMITATIONS**

The limitations experienced by researchers in compiling this report are as follows:

1. many research variables make this research complex
2. The discussion of complex topics makes it difficult to discuss material to suit the topic (not widen).
3. There are not many journals that explicitly address this topic, so finding the right journal takes a long time
4. Of the few journals found, not all of them have access to be read in their entirety

The study results showed a relationship between the incidence of Cleft Lip and Palate accompanied by Tetralogy of Fallot in Children and the Mother's History of Gestational Diabetes, from research findings. It is hoped that it can provide new knowledge for medical personnel regarding the relationship between the occurrence of Cleft Lip and Palate accompanied by Tetralogy of Fallot in Children and the Mother's History of Gestational Diabetes.

## **6. CONCLUSION**

Based on the findings from 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 cleft lip and palate in babies born to

mothers with type 2 diabetes mellitus and the use of valproate acid as a form of treatment. From schizophrenia during pregnancy and the condition of the mother with osteogenesis imperfecta in pregnant women, which can be passed on to the fetus in her womb and is also associated with cleft lip and palate conditions, in which the majority of osteogenesis occurs due to heterozygous COL1A2 mutations and the formation of DNA triple helix. Then the connection between these conditions during pregnancy also triggers the condition of the baby being born with tetralogy of Fallot. So, in general, babies born with poor osteogenic conditions tend to have more potential to experience cleft lip and palate and tetralogy of Fallot or congenital heart problems. However, no papers explicitly explain the relationship between these variables. Journal discussion only discusses the potentials that can increase the risk of these diseases with the conditions mentioned in the research variables.

## **7. SUGGESTION**

After compiling a systematic review regarding the relationship between the incidence of cleft lip and palate accompanied by tetralogy of fallot in children and a mother's history of gestational diabetes, the suggestions that the author would like to convey are as follows.

### **For Institutions**

Can contribute to students, lecturers, academics at the University of Muhammadiyah Malang, and all parties who read this article, especially regarding the relationship between the occurrence of Cleft Lip and Palate with Tetralogy of Fallot in Children and a History of Maternal Diabetes Gestational It is also hoped, writing This can be used as a reference for further research.

### **For Medical Sciences**

This can contribute to the progress of medical science regarding the relationship between the occurrence of Cleft Lip and Palate accompanied by Tetralogy of Fallot in Children and Maternal History of Gestational Diabetes. Then, as students who will later become medical staff, it is hoped that the preparation of this report can provide initial knowledge regarding cleft lip and palate conditions with Tetralogy of Fallot in children with a maternal history of gestational diabetes so that they can clearly identify related conditions later.

### **For Further Researchers**

Hopefully, this paper will be able to add a reference for further research related to the relationship between the occurrence of Cleft Lip and Palate with Tetralogy of Fallot in Children and the Maternal History of Gestational Diabetes.

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