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CONGENITAL VARICELLA SYNDROME: A SYSTEMATIC REVIEW

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Abstract
Herpes viruses are extremely infectious, and the varicella-zoster virus (VZV) is one of the most contagious. Because the varicella vaccination was made available to all children in the United States (US) and Europe in 1995, the vast majority of adults in these regions are immune. It is believed that more than 90 percent of the prenatal population have VZV IgG antibodies, and as a result, is resistant to illness caused by the virus. The woman had a history of varicella before to the beginning of her pregnancy, which lasted the first three months of her pregnancy. Manifestations in newborns can start as early as a few weeks before delivery and can continue for up to a month after birth. Manifestations can begin as early as a few weeks before delivery. A centripetal rash, which begins on the trunk and spreads to the face and limbs, is one of the clinical signs that can be seen on the skin. This rash begins with erythematous macules, then progresses to vesicles, and finally ruptures to form crusts. In order to establish a diagnosis of varicella, medical professionals look to the clinical signs of the disease on the skin. On the other hand, there is always the opportunity to carry out more research. If a pregnant woman contracts varicella at any point throughout her pregnancy, at term, or in the immediate postpartum period, it has the potential to cause substantial morbidity in the newborn offspring of that woman. Varicella congenital syndrome can result in serious birth malformations such as hypoplasia of an extremity, microcephaly, abnormalities of the skin and eyes, intellectual impairment, and low birth weight.

Keyword: *Eye; Glaucoma; Oxidative Stress; Superoxide Dismutase*

INTRODUCTION

Varicella-zoster virus (VZV) is a highly contagious herpes virus. With the introduction of universal childhood varicella vaccine in 1995, most adults in the United States (US) and Europe are immune. It is estimated that more than 90% of the prenatal population has VZV IgG antibodies and hence is immune to infection. Seronegative people are at risk of contracting VZV during pregnancy, which is linked to a greater fatality rate owing to varicella pneumonitis.[1,2] Varicella may also have prenatal repercussions, such as fetal death or signs of congenital varicella syndrome (embryopathy) or newborn varicella in the first 10 days of life, all of which are associated with severe morbidity and mortality.[3,4]

Because of extensive protection in women of childbearing age following chickenpox or varicella vaccine, which was introduced in 1995, varicella infection during pregnancy is uncommon. Varicella infection in a seronegative pregnant female develops when she comes into touch with varicella-zoster lesions or respiratory droplets disseminated by an infected person with chickenpox. The clinical presentation and severity of the neonate will be determined by when the mother became infected with the virus throughout her pregnancy.[4,5]

When a mother is infected with the VZV during the early half of her pregnancy, she develops congenital varicella syndrome (CVS).[5] The biggest risk (2%) occurs between 13 and 20 weeks of gestation in the second trimester. CVS has been recorded as late as 28 weeks of gestation in rare circumstances. Since the first instances were published in 1947, the overall number of neonates with congenital varicella syndrome has been reported to be roughly 41 cases per year in the United States, 4 cases per year in Canada, and 7 cases per year in the United Kingdom.[4,6]

When a pregnant woman contracts varicella around the time of delivery, neonatal varicella infection can occur. Transplacental viremia, direct contact with skin lesions or blood during birth, and post-natal contact by respiratory droplets or skin contact with infected vesicles are all possible routes of transmission from mother to kid. Infants are most vulnerable to severe varicella infection when maternal illness occurs 5 days before and 2 days after birth. During that time, the baby will be exposed to high levels of viremia but will not have enough time to develop maternal protective antibodies.[6,7] This article review about congenital varicella syndrome.

METHODS

Protocol

This review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 criteria. These components served as the foundation for the regulations that were put in place.

Eligibility Criteria

This is a survey of the literature on congenital varicella syndrome. This is the main argument presented in the research being evaluated. The requirements for research to be included in this article include: 1) Articles must be written in English and emphasize the benefits of tranexamic acid for primary postpartum hemorrhage in order to be accepted for publication. (2) Articles published after 2018 but before this systematic evaluation was conducted, were evaluated. The following types of entries will not be considered for publication in an anthology: Original research does not include editorials, submissions without a DOI, review papers that have already been published, or submissions that are significantly identical to those already published in the journal.

Search Strategy

The search for studies to be included in the systematic review was carried out from January, 7nd 2023 using the PubMed and SagePub databases by inputting the words: “congenital varicella syndrome”. Where *"varicella zoster virus infection"[MeSH Terms] OR ("varicella"[All Fields] AND "zoster"[All Fields] AND "virus"[All Fields] AND "infection"[All Fields]) OR "varicella zoster virus infection"[All Fields] OR ("congenital"[All Fields] AND "varicella"[All Fields] AND "syndrome"[All Fields]) OR "congenital varicella syndrome"[All Fields]* is used as search keyword.

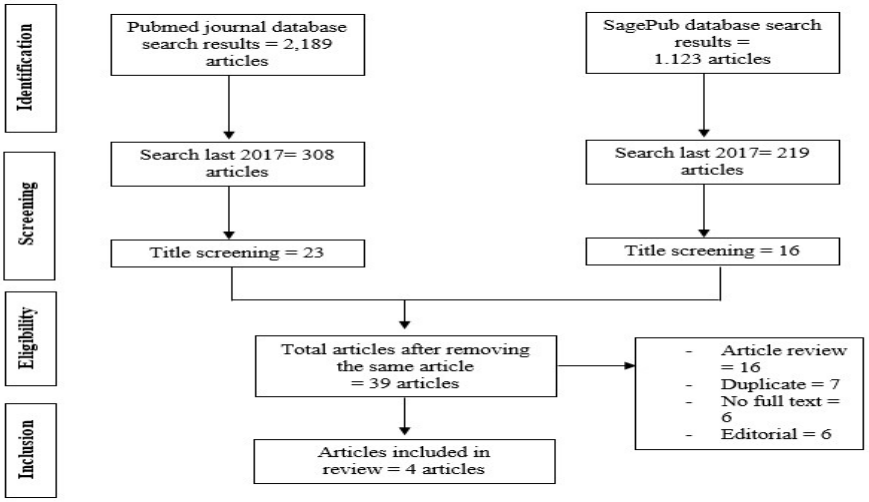

Figure 1. Article search flowchart

Data retrieval

The study's author changed the criteria for what was included and what wasn't after conducting a literature review and reading the titles and abstracts of previously published studies. The updated criteria can be found in the study's additional materials. This was done to narrow the scope of the problem and determine which areas required additional research. The author arrived at this conclusion after reviewing other studies that had been conducted and published with similar results. During the systematic review's preparation, it was decided that only studies that met all of the inclusion criteria should be included.

As a result, we could only consider research proposals that met all of the criteria. This was done to ensure that the evaluation was as thorough as possible. This project's goal was to collect information about each study, such as its title, author, publication date, location of the study, research study design, and research parameters. It is possible to learn more about these subjects. The following are some examples of information sources that could be used: Depending on the type of presentation you prefer, you can obtain this information in a variety of ways.

Quality Assessment and Data Synthesis

Some of the research described in the titles and abstracts of the papers was evaluated by the authors on their own, so they could decide which papers should be evaluated. Then, the full texts of the papers that meet the criteria for the systematic review will be looked at to decide which papers will be included in the review. This will be done so that the review can decide which publications to include. This is done to answer the question, "Which studies are good enough to be considered for the review?"

RESULT

Case report by Patokar showed right foot patient's appeared to have congenital talipes equinovarus based on the clinical presentation of the condition. During the first trimester of the mother's pregnancy, the mother had a previous history of varicella. During the ocular examination, it was discovered that the right eye had subretinal hypopigmented exudation along with sparse vitreous hemorrhage and tunica vasculosa lentis, which could be detected by indirect ophthalmoscopy. A microphthalmia was suspected after an ultrasonic A/B scan was performed on the right eye. We determined that the patient had FVS based on the patient's history, clinical manifestations, and the fact that they tested positive for varicella-zoster IgG antibodies.[8] Other study showed skin, limbs, eyes, and the central and autonomic nervous systems are all affected by Congenital Varicella Syndrome abnormalities.[9]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Main Topic	Result
Patokar, 2022[8]	India	Case report	-	History and clinical presentation	Her right foot's clinical appearance resembled congenital talipes equinovarus. Mother had a history of varicella throughout her first pregnancy. On indirect ophthalmoscopy, the right eye showed subretinal hypopigmented exudation, scanty vitreous hemorrhage, and tunica vasculosa lentis. An ultrasonic A/B scan of the right eye revealed microphthalmia. We validated the diagnosis of FVS based on the patient's history, clinical characteristics, and the presence of varicella-zoster IgG antibodies.
Cherukuri, 2019[9]	India	Case report		Clinical presenattion	Skin, limbs, eyes, and the central and autonomic nervous systems are all affected by Congenital Varicella Syndrome abnormalities.
Earlia, 2022[10]	Indonesia	Case report		Diagnosis and management	Physical examination revealed macules, papules, pustules, and vesicles that were numerous, distinct, miliary to guttate in size, and universally distributed in the face, thoracic, and upper extremities area et inferior bilaterally. Tzank testing revealed multinucleated large cells. A skin biopsy revealed stratum spinosum edema, as well as powdered lymphocyte inflammatory cells (typical for varicella). After 5 days, intravenous acyclovir treatment showed improvement.
Sile, 2022[11]	United Kingdom	Prospective study	186	Prevention	Even after adjusting for maternal age, gestational stage, type of exposure, and IgG titre, the researchers were unable to find a statistically significant difference between the oral aciclovir and VZIG groups (adjusted OR:0.83; 95%CI:0.26–2.65; p = 0.75).

Other case report with 14 days old baby and had a rash that covered her entire body was brought to the Department of Pediatrics. A fever for four days was present in the patient prior to the formation of the rash. The rash appears first on the face and then spreads to the rest of the body. The patient's mother was infected with varicella while she was in her third trimester of pregnancy. The patient gave birth vaginally to a baby that weighed 3,400 grams and was delivered at full term by the midwife.[10]

Upon conducting a physical examination, the patient was found to have macules, papules, pustules, and vesicles that were numerous in number, distinct, miliary to guttate in size, and universally distributed. These lesions were found in the facial, thoracic, and upper extremities region and inferior bilaterally. The Tzank test revealed the presence of large cells with

many nuclei. A biopsy of the patient's skin revealed edema in the stratum spinosum along with powdered lymphocyte inflammatory cells (typical for varicella). After 5 days of treatment with intravenous acyclovir, patients exhibited signs of improvement.[10]

Sile, et al (2022)[11] identify and monitor 186 pregnant women who had been exposed to chickenpox and then compare the results of their pregnancies. The findings demonstrated that 171 out of 186 (91.9%) of these women were treated with either VZIG or oral aciclovir. Among the 145 women who were given VZIG, 53 of them, or 36.6%, went on to acquire chickenpox. In comparison, just 8 of the 26 women who were given oral aciclovir, or 30.8%, did so (p = 0.32). Even after adjusting for maternal age, gestational stage, type of exposure, and IgG titre, the researchers were unable to find a statistically significant difference between the oral aciclovir and VZIG groups (adjusted OR:0.83; 95%CI:0.26–2.65; p = 0.75).

DISCUSSION

The infection with the varicella zoster virus that pregnant women get in their final three weeks of pregnancy or in the days before delivery can cause a condition known as neonatal varicella. Manifestations in babies can begin as early as a few weeks before delivery and can last for up to a month after birth. Clinical manifestations on the skin include a centripetal rash (beginning on the trunk and extending to the face and limbs), beginning with erythematous macules, advancing to vesicles, and eventually rupturing to create crusts. The clinical manifestations of varicella on the skin are used to establish a diagnosis of varicella. On the other hand, there is the possibility of conducting more studies. Varicella, if contracted by pregnant women either throughout their pregnancies, at term, or soon after delivery, can cause serious morbidity in their newborn children.[6,12]

Direct contact exposure is defined as having personal contact with an infected individual that lasts for an hour or longer when the interaction takes place inside. When it comes to hospital contacts, substantial exposure can be defined as either sharing the same hospital room as an infected patient or having lengthy, direct, face-to-face contact with an infectious individual (e.g., health care workers). Contact with an infectious individual for a shorter amount of time, such as that which occurs during an X-ray or cleaning shift, is associated with a lower risk of VZV transmission than contact with that person for a longer period of time.[7,13]

Skin, limbs, eyes, and the central and autonomic nervous systems are all affected by Congenital Varicella Syndrome abnormalities. Cicatrix, or scarring skin lesions, occur in a dermatomal distribution over the body. Hypoplasia, atrophy, and deformed digits are examples of limb abnormalities. Chorioretinitis, cataracts, and nystagmus are common eye abnormalities.[12] Microcephaly, cortical atrophy, seizures, and mental retardation are all examples of central nervous system disorders.[12]

Neurogenic bladder, hydronephrosis, esophageal dilatation, and gastrointestinal reflux can all result from autonomic nervous system malfunction. Infants born to varicella-infected moms during the high-risk period for neonatal varicella infection appear to be healthy at first. They usually show with classic vesicular skin lesions if they become symptomatic. Disseminated illness can cause pneumonia, hepatitis, meningoencephalitis, and severe coagulopathy due to liver failure and thrombocytopenia.[6,14]

Samples of fetal blood or amniotic fluid do not accurately identify instances of congenital varicella syndrome. Prenatal ultrasounds may be utilized to detect severe signs of intrauterine VZV infection. These findings include asymmetric limb shortening or deformities, intestinal and hepatic echogenic foci, intrauterine growth restriction, brain defects such as hydrocephalus and microcephaly, and fetal hydrops or fetal mortality. It is advisable to confirm the virus in the mother in the case of neonatal varicella infection.[6,14,15]

The traditional clinical appearance of a diffuse vesicular rash in various phases of development may often be used to diagnose varicella in pregnant women. If the diagnosis is in doubt, the base of a vesicular skin lesion can be scraped for direct fluorescent antibody testing or PCR. Viral cultures can also be acquired, although these can take up to a week to provide findings. These diagnostic tests should also be done on worrisome lesions on the infant's body.[6,14,15]

The pathogenesis of birth abnormalities in FVS can be linked to a disruption of the developing nervous system. This disturbance may involve diffuse VZV infection and/or herpes zoster that occurs in utero. This provides support for the hypothesis that the lesions are caused by herpes zoster in utero. The hypothesis is based on the observation that skin lesions follow the dermatomal pattern distribution associated with herpes zoster, and that lesions of the musculoskeletal system and the nervous system are also segmental.[16,17]

This provides evidence for the hypothesis. Because the VZV virus is neurotropic, it has the potential to halt the development of the central, peripheral, or autonomic nervous systems. Denervation of the limb bud, which can progress to hypoplasia if the spinal cord and ganglia are infected, can be caused by infection of the spinal cord and ganglia. Infection of the optic tract can lead to conditions such as optic atrophy and chorioretinitis, and infection of the brain of the developing fetus can result in a condition known as microcephaly. It is believed that brain lesions are caused by intrauterine encephalitis during VZV reactivation. This occurs when the virus causes destructive and inflammatory lesions in the brain.[16,17]

Sile, et al (2022)[11] locate and track 186 pregnant women who have had chickenpox and then compare the outcomes of their pregnancies. The data revealed that 171 of the 186 women (91.9%) were given either VZIG or oral aciclovir. Among the 145 women who were administered VZIG, 53 (or 36.6%) developed chickenpox. In comparison, only 8 of the 26 women (or 30.8%) who were administered oral aciclovir did so (p = 0.32). Even after controlling for maternal age, gestational stage, type of exposure, and IgG titre, the researchers found no statistically significant difference between the oral aciclovir and VZIG groups (adjusted OR:0.83; 95%CI:0.26-2.65; p = 0.75).

Congenital varicella syndrome, a very uncommon illness that occurs in 0.39% of maternal cases of varicella during the first 20 weeks of infection, is one of the complications that might affect the foetus and the newborn baby. Newborns who are afflicted with this condition may have a low birth weight (a condition known as intrauterine growth retardation), skin scar tissue on the arms and legs, and abnormalities in brain function.[18]

The breadth of symptoms and the intensity of each one are strongly affected by the stage of foetal development that the mother was in when she became infected. It is believed that between one and two percent of maternal varicella infections that occur within the first 20 weeks of a pregnant woman's pregnancy result in congenital varicella syndrome. In the United States, it is estimated that more than forty people are born each year with congenital varicella syndrome, which has a death rate of roughly thirty percent in the first few months of life.[18,19]

CONCLUSION

Congenital varicella syndrome can result in serious birth malformations such as extremities hypoplasia, microcephaly, skin and eye abnormalities, intellectual impairment, and low birth weight.

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