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Efficacy and Safety of Hyperimmunoglobulin Cytomegalovirus Therapy Against CMV Congenital Infections: A Systematic Review

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ABSTRACT

Background: Cytomegalovirus infection in pregnancy can cause congenital CMV. CMV hyperimmunoglobulin therapy aims to prevent vertical infection to the fetus causing congenital CMV, therefore, the authors conducted a systematic literature review to determine the efficacy of hyperimmunoglobulin by reviewing outcome parameters. Methods: Systematic literature review following the Preferred Reporting Items for Systematic Reviews and Meta- Analysis (PRISMA) guidelines.
Results: Through data search in PubMed, ScienceDirect, and Cochrane using the keywords 'Therapy' 'Pregnancy' 'Pregnant' 'Cytomegalovirus' and 'Treatment', 230 articles were obtained. Then the selection was carried out, 52 articles were excluded, 43 review articles, 30 case-control studies, 35 cohort studies, and 71 observational studies, so that 2 journals were obtained that met the inclusion criteria.
Conclusion: as much as 30% and 35.6% of CMV congenital events in the group of mothers given HIG, compared to the control group which was 44%.

Keywords: hyperimmunoglobulin, cytomegalovirus, pregnancy, therapy

INTRODUCTION

Human cytomegalovirus (CMV) is the most common congenital infection in developing countries, accounting for up to 0.7% of all live births.1 Approximately 11% of infected neonates are born with clinical disease and a 30-40% risk of long-term neurological sequelae [1–3], while asymptomatic neonates have a 6–23% risk of hearing loss later in life [4]. In Europe, primary CMV infection occurs in 1–8% of pregnant women, with a maternal CMV transmission rate of 32%. It is estimated that 25% of newborn babies will contract the infection if their mother is infected in the first trimester and this figure doubles in subsequent trimesters [3]

However, recently, Shara-Nissan et al. reported the first randomized, placebo-controlled trial to show that treatment with oral valacyclovir can reduce the rate of vertical transmission in first-trimester primary CMV infection. 5 More extensive research experience is available for CMV-specific hyper immunoglobulin (CMV-HyperIg), nonrandomized studies have supported the potential benefit in clinical outcomes of infected neonates. 6– 8 Evidence from prospective trials regarding the ability of CMV-HyperIg to prevent congenital CMV infection remains equivocal. Meanwhile, based on the research results of Nigro et al. found a significant 24%

reduction in vertical transmission rates in a non-randomized study, in 2 subsequent randomized placebo-controlled trials, Revello et al and Hughes et al found a 14% reduction and a 3% increase, and in each study, the results which are not statistically significant [8,9,10]

Until now, research regarding therapy to treat cytomegalovirus infection in pregnant women is still very small and limited, therefore the main aim of the research is to describe the efficacy and safety of therapy using hyperimmunoglobulin in pregnant women infected with cytomegalovirus.

LITERATURE REVIEW

Prenatal and perinatal infections cause the majority of cases of maternal and fetal morbidity and mortality. One of the prenatal and perinatal infections that can occur is TORCH infection (Toxoplasma gondii, Rubella virus, Cytomegalovirus, Herpes simplex virus). TORCH infection is the most common cause of poor obstetric history in mothers and also causes many congenital abnormalities in babies [15.16]

Infection due to Cytomegalovirus (CMV) is the most common congenital infection and causes quite high morbidity in newborn babies. CMV transmission can occur horizontally (from one person to another) or vertically (from mother to fetus). Most children born with congenital CMV infection show no symptoms (asymptomatic) at birth.

Infection due to Cytomegalovirus (CMV) is the most common congenital infection and causes quite high morbidity in newborn babies. CMV infection is widespread throughout the world, both in developed and developing countries. CMV infection occurs in 0.2-2.4% of all live births in the world and occurs in 0.6-0.7% of all live births in developed countries. CMV infection causes disturbances in the development of organs in the fetus. CMV is also the most common cause of hearing loss, neurodevelopmental disorders, and mental retardation in children [17,18,19]. CMV infection can be symptomatic or asymptomatic. A CMV immunoserology study in Indonesia in 2004 involving 395 people who did not have any complaints showed that 344 people showed seropositive anti-CMV IgG results with 7 of them also showing seropositive IgM anti-CMV and 3 people showing only seropositive anti-CMV IgM. The results of this study show that many people have been infected with CMV without any complaints as evidenced by IgG and IgM anti-CMV seropositivity [20].

Cytomegalovirus (CMV) CMV that infects humans is called human Cytomegalovirus. CMV is a DNA virus that belongs to the herpesviridae family. This virus is called cytomegalovirus because infected cells will enlarge up to twice the size of uninfected cells. CMV invades host cells and then reproduces (replication). The structure of CMV consists of the tegument, capsid and envelope which are rich in lipids. CMV infects cells by binding to receptors on the surface of the host cell, then penetrates the cell membrane and enters the vacuole in the cytoplasm, then the viral envelope is released and the nucleocapsid quickly travels to the host cell nucleus [21].

CMV transmission can occur horizontally (from one person to another) or vertically (from mother to fetus). CMV is transmitted horizontally through body fluids and requires close contact with body fluids that have been contaminated with CMV. CMV can be found in blood, urine, semen, cervical secretions, saliva, breast milk, and transplanted organs. CMV transmission occurs vertically in the following ways:[3]: 1. In utero: via the transplacental route with CMV viremia in the maternal circulation. 2. Intrapartum: exposure of the fetus to cervical and vaginal secretions containing CMV during the birth process. 3. Postnatal: ingestion of breast milk containing CMV or through blood transfusion contaminated with CMV.

Infection due to CMV is the most common congenital infection and causes quite high morbidity in newborn babies. CMV infection is widespread worldwide, both in developed and developing countries. CMV infection occurs in 0.2-2.4% of all live births worldwide and in 0.6-0.7% of all live births

in developed countries. CMV infection also causes problems with the development of organs in the fetus. CMV is also the most common cause of hearing loss, neurodevelopmental disorders, and mental retardation in children.[3-5]

Most children born with congenital CMV infection show no symptoms (asymptomatic) at birth. Asymptomatic in this case is defined as the detection of CMV in any body fluid in a child in the first 3 weeks of life, but does not show abnormalities in clinical, laboratory results and radiological examination results. Only 7-10% of children show symptoms of congenital CMV infection at birth. Jaundice (62%), petechiae (58%), and hepatosplenomegaly (50%) are three clinical manifestations that are often found, so it is also called the triad of congenital CMV infection.[8,9]

The gold standard for diagnosing congenital CMV infection is isolation or culture of the virus in children within the first three weeks of age. Samples taken for virus isolation can include urine, saliva, cervicovaginal secretions, amniotic fluid, blood and cerebrospinal fluid (CSS). Other supporting examinations that can be carried out are polymerase chain reaction (PCR) examinations from urine or saliva samples with a sensitivity of 89% and a specificity of 96% [3,10]

MATERIALS & METHODS

The systematic review was conducted based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement rules. Randomized controlled trials were reviewed through medical databases, with the Boolean Operator rule Cytomegalovirus, OR CMV AND Pregnancy, OR Pregnant AND hyperimmunoglobulin. The search results are downloaded and next, duplicate removal is performed using the Zotero application. Studies were then filtered, extracted, analyzed, and synthesized for qualitative and quantitative data. Study titles and abstracts were screened according to inclusion criteria by one independent reviewer Any disagreements were discussed to reach consensus.

This study was screened using inclusion and exclusion criteria. The inclusion criteria are (1) P = Population. Pregnant patient. (2) I = intervention. Studies eligible for inclusion in the meta-analysis used only CMV hyperimmunoglobulin therapy without restrictions on dose or route of administration. (3) C = Comparison. Studies comparing the use of CMV hyperimmunoglobulin with placebo or other biomaterials were eligible for systematic review. (4) O = Outcome. The main outcome variable of eligible studies was represented by the occurrence of congenital CMV in infants. (5) S = Settings. Only RCT studies were included.

Exclusion criteria were case reports, observational studies, animal studies, technical studies (protocols), and reviews. The search results are downloaded and further, duplicate removal is also carried out using the Zotero application. Studies were screened based on title and abstract and then followed up with inclusion criteria by one independent reviewer.

Data collection in this study followed the PRISMA flow diagram, including identification of studies in the database; duplication, title, and abstract screening; assessing full eligibility texts; and extraction and analysis of included studies. We extracted studies manually in the extraction tabulation. The data extracted are (1) Author and year of publication, (2) Country, (3) Study design, (4) Characteristics and sample size, (5) Age of participants, (6) The incidence of congenital CMV, (7) Type of intervention, (8) Dosage, and (9) Control group.

Final inclusion studies were evaluated for risk of bias using the Revised Tool for Risk of Bias in Randomized Trials (RoB 2.0) consisting of five domains. The author will assess the risk of bias according to the algorithm created by Cochrane. The results will then be input into a bias domain file (.xlsx). The file will then be entered into the

ROBVIS website so that the resulting data can be visualized properly.

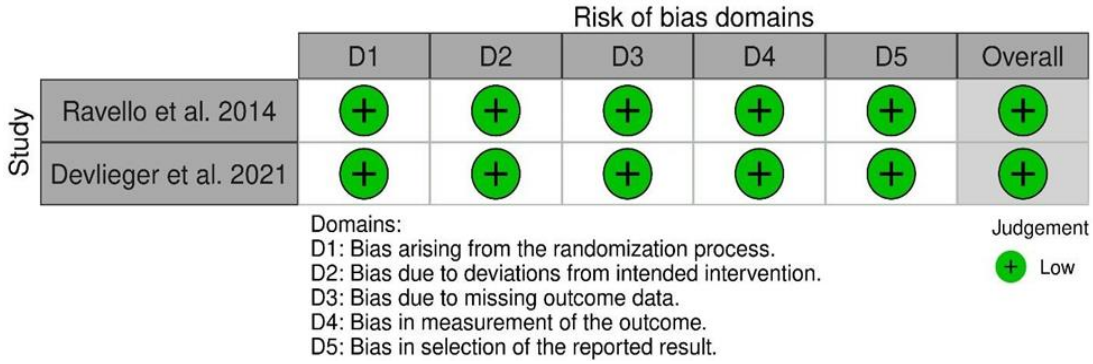
RESULT

Study Characteristics

Study	Study Design	Sample		Type of Intervention	Mean Age	Treatment Dose	Follow-up (bulan)	Control	Congenital Events CMV
		Characteristic	Amount						
Ravello et al, 2014	RCT	Pregnant mother who is affected infection CMV primer on age pregnancy 5-26 weeks	123	Injection Intravenous	30	100 U/KgBB	1	Placebo	45 neonates
Devlieger	RCT	Pregnant mother aged 18-45 years old Which screened CMV on age < 14 weeks	304	Injection Intravenous	29,9	200 U/KgBB	1	Placebo	31 neonates

All studies were published from 2014 to 2021. The sample size in the studies ranged from 123 to 304 and the follow-up duration was 30 days. The average age of patients in this study was intervention vs. control (30 years vs. 29.9 years). All patients were found to meet the requirements, namely showing the presence of congenital CMV

Risk of Bias Assessment



Overall, the included studies had a low risk of bias as individuals.

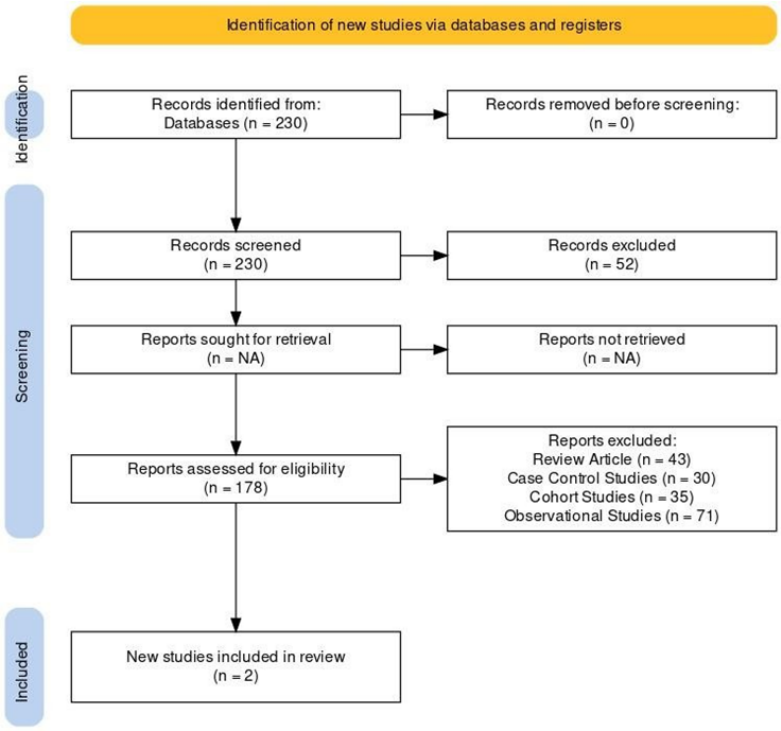
Congenital CMV Incidence Rate

Based on the results of Ravello et al's study, it was found that there was a 30% incidence of congenital CMV in the group of mothers given HIG, while the results of Devlieger et al's study found a 35.6% incidence of congenital CMV in the group of mothers given HIG, as presented in table 2 below:

Table 2. Congenital CMV Incidence Rate

Study	Intervention Group	Control Group
Ravello et al, 2014[11]	18 Congenital CMV in 61 Births (30%)	27 congenital CMV of 62 births (44%)
Devlieger et al, 2021[12]	16 Congenital CMV in 45 Births (35.6%)	15 Congenital CMV in 34 Births (44%)

Collection of Studies Based on the PRISMA Algorithm can be seen from diagram 1 below:



DISCUSSION

Based on the results of a systematic review, it was found that the results of Ravello et al's study showed that there was a 30% incidence of congenital CMV in the group of mothers given HIG, while the results of Devlieger et al's study found a 35.6% incidence of congenital CMV in the group of mothers given HIG. compared to the control group, which was 44% in both studies. In Ravello et al's study, results were not significant between the group of mothers given HIG and placebo, likewise based on the results of Devlieger et al's study, results were not significant in the group of mothers given HIG therapy compared to the placebo group [11,12]

Similarly, hyperimmune globulin did not significantly change maternal DNA levels in the blood or the time to clear DNA from the blood, nor did it significantly change DNA levels in the placenta. No significant differences in DNA levels in the blood were noted in either study group between women who were shedding the virus and those who were not shedding the virus in a finding that is consistent with the results of previous studies. 11 In one study, 27 of 67 newborns (40%) born to mothers who had been treated with intravenous immune globulin were found to be infected at birth. However, it is unclear whether the lower preventive efficacy of standard immune globulin compared with hyperimmune globulin is due to differences between study protocols or immune globulin preparations [11,13]

Congenital CMV infection is one of the main causes of birth defects in babies. Transmission of CMV through the placenta results in sequelae of adverse outcomes, including severe fetal growth restriction, hydrocephalus, microcephaly, and fetal death [14,15]. CMV infection is more associated with central nervous system or organ damage such as sensorineural hearing loss, bilateral hearing loss, underdevelopment mental illness, and chorioretinitis rather than recurrent infections. The presence of maternal antibodies in secondary infections, which act as a defensive barrier, reduces adverse birth outcomes but does not prevent the transplacental passage of the virus [14]

The main treatments recommended are ganciclovir and valganciclovir. Valganciclovir is safer in terms of neutropenia. Neonates receiving 6 mg/kg ganciclovir intravenously twice per day

showed improved hearing outcomes. The significant percentage of neutropenic adverse reactions among treated patients discourages patients from using ganciclovir. Valganciclovir did not show significant improvement in outcomes compared with controls despite its good safety profile [14,16,17]

The absence of a vaccine to protect against CMV infection encourages the need to develop other strategies for the prevention and treatment of pregnant women and newborns. However, the purpose of administering hyper immunoglobulin to the infected mother appears to be a significant predictor of congenital CMV levels [14].

CONCLUSION

There were 30% and 35.6% incidences of congenital CMV in the group of mothers given HIG, compared to the control group, which was 44%. Giving hyperimmunoglobulin therapy to pregnant women in research to date, especially in randomized clinical trials, still provides insignificant results compared to the placebo group, but has been proven to reduce the incidence of congenital CMV. Therefore, there is still a need for randomized clinical trials to see and determine the efficacy of using hyperimmunoglobulin, especially in pregnant women, to prevent congenital CMV.

Declaration by Authors

Ethical Approval: Not Applicable

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Conflict of Interest: The authors declare no conflict of interest.

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