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Prevention Strategies for Congenital Cytomegalovirus Infection

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Prevention Strategies for Congenital Cytomegalovirus Infection

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Abstract

Purpose of the review

Cytomegalovirus (CMV) is the most common viral cause of congenital infection, occurring in approximately 1-2% of live births worldwide. Given our increasing knowledge of risk, advances in identification of maternal infection, and the extremely limited options for treatment of fetal infection, prevention is a promising direction for research efforts. Recently, there have been several exciting studies assessing different ways of preventing congenital infection in the fetus and one in particular has focused on the use of valaciclovir.

Recent findings

A recent study reported a 71% reduction in vertical transmission of CMV with the use of oral valaciclovir following maternal primary CMV infection early in pregnancy. The clinical impact of this study could be enormous and it has particular implications for considerations around maternal serological screening in the first trimester of pregnancy. Further research assessing behaviour modifications during early pregnancy also provide evidence for an effective primary prevention technique.

Summary

Prevention of congenital CMV infection, whether primary, secondary or tertiary, is possible, however there are barriers to its utilisation in a clinical setting. The main limitation is the requirement for early, effective and large-scale serological screening of mothers to detect asymptomatic primary infection.

Keywords

Congenital CMV, valaciclovir, prevention

Introduction

Cytomegalovirus (CMV) is the most common viral cause of congenital infection[1], representing a substantial global health burden. A prominent cause of congenital infection is maternal primary CMV infection, with 50% of mothers with primary infection transmitting the virus to their fetus[2]. Given the limited treatment options for fetal CMV infection, prevention (primary, secondary or tertiary) is a promising direction for research.

This review will provide an up to date summary of the current literature on prevention of congenital CMV infection, with a focus on new research identifying valaciclovir as a potential agent for reducing vertical transmission of CMV.

Epidemiology of congenital CMV infection

Cytomegalovirus (CMV) is the most common viral cause of congenital infection, occurring in approximately 1-2%[1] of live births worldwide. Despite the fact that many infected children are born asymptomatic[3], it represents a substantial global health burden with between 6 and 23% of infected fetuses developing hearing loss later in life[4] and 13% being born with clinical features of CMV, such as microcephaly and hepatosplenomegaly[5] (Figure 1). A prominent cause of fetal infection is maternal primary CMV infection, occurring in 0.5%-2% of pregnancies[6]. Of these, up to 50% will go on to transmit the virus to their fetus[2] (Figure 2). Women with the highest exposure risk are mothers with young children[7] as CMV is often first acquired and spread amongst pre-school aged children who excrete the virus in saliva and urine for prolonged periods of time. Transmission of CMV to the fetus also occurs in women who have previously been infected with CMV (secondary infection), either via reactivation of the same strain or infection with a different strain. The majority of congenital CMV infection is attributed to secondary infections in locations with a high CMV seroprevalence, namely countries in Asia and Africa[8].

Studies have elucidated that transmission during the first trimester is responsible for the majority of morbidity[9], emphasising the importance of prevention and of early recognition of

maternal CMV infection. Given our increasing knowledge of risk and epidemiology, advances in our ability to identify maternal infection, and the extremely limited options for treatment of fetal infection, prevention rather than therapy is a promising direction for research efforts.

Recently, there have been several exciting studies investigating promising tools for preventing congenital infection in the fetus. These can be broadly split into *primary prevention* of infection in the fetus – either by reducing the risk of infection of the mother or of preventing infection being transplacentally transferred to the fetus; *secondary prevention*, reducing the impact of the infection on the fetus via early detection of infection in the mother and pre-emptive treatment; and *tertiary prevention,* lessening the effect on the child in the long term by postnatal treatment with valganciclovir or management of the effects of CMV, such as cochlear implantation for those children with severe sensorineural hearing loss.

Primary prevention of infection of the fetus

Reducing the risk of CMV infection in the pregnant woman largely involves reducing direct mucosal contact with saliva and urine of young children, by taking simple precautions such as not sharing food, drink or cutlery with young children who may be excreting CMV, kissing on the head rather than directly on the lips and careful handwashing after touching objects that are contaminated with saliva or urine. Such measures have been found to be effective when put into practice[10] however most women have never heard of CMV or of ways to reduce the risk of acquiring CMV in pregnancy and therefore have not had the opportunity to implement them[11.] Incorporating these simple messages into routine antenatal education and thereby making these changes to behaviour might make a significant impact on the number of women acquiring CMV in pregnancy and thereby the prevalence of infants with congenital CMV infection. The required adjustments to family life might be adopted more easily now that the concept of social distancing has been established by the Covid-19 pandemic.

A recent paper[12] used a decision model to predict the efficacy of hygiene measures versus serological screening and found that hygiene promotion could be more effective in reducing mortality and morbidity related to congenital CMV infection. If applied correctly, this method could be successful, particularly given its applicability in lower resource settings. However, it is particularly reliant on implementation of behaviours prior to conception as most cases of symptomatic materno-fetal infection are attributed to peri- and post-conceptual maternal primary infection[13]. This poses challenges for those who are not immediately aware of conception. In addition, these findings were based on the assumption that there is currently no effective way to prevent vertical transmission and may no longer be applicable if an effective treatment strategy is identified.

The alternative is early identification of maternal primary infection using serological screening, and subsequent implementation of treatment to prevent transmission to the fetus. Up until recently, there has been limited exploration of this, with more research efforts focusing on early treatment. Studied options include hyperimmune immunoglobulin G (HIG), antivirals such as valaciclovir and vaccination.

A non-randomised study[14] was one of the first to suggest that HIG may be an effective option for preventing disease, however, a phase II double blind, randomised controlled trial in 2014 of the same preparation[15] found no significant difference in transmission rates between HIG and placebo, with a higher likelihood of adverse obstetric events, including pre-term birth and pre-eclampsia, in the HIG group. A further observational study published in 2019[16], corroborated these findings.

Late last year, a novel study was published, investigating the prophylactic use of valaciclovir in mothers with primary CMV infection to prevent vertical transmission. This has built upon ground-breaking work by Leruez-Ville and her research group, who investigated the use of antenatal valaciclovir for treatment of recognised fetal infection[18]. Shahar-Nissan et al. performed a randomised double-blind placebo-controlled study looking at the efficacy of

valaciclovir in the first trimester for preventing congenital CMV infection (Figure 3). This revealed a 71% reduction in infections (11% in valaciclovir group vs 30% in placebo; p=0.027). As identified in previous studies, the bioavailability and tolerability of valaciclovir in pregnancy is satisfactory, with no increase in adverse effects compared to placebo. Despite the fact that only small numbers were included in the study, the clinical impact of its findings could be huge. It has the potential to change our approach to treatment, specifically with regard to recommendations for maternal serological screening. Although more investigation needs to be done to confirm aspects of these findings, the size of the impact, the safety of the drug and the importance of the problem, suggest that it may not be ethically justifiable to undertake further, large randomised controlled trials.

The potential this study presents however, is tempered by a significant challenge in our current clinical practice. The positive impact identified was mainly seen with valaciclovir use in the first trimester. The infants who were found to be infected with CMV at birth were all born to women who started treatment later, indicating that the impact may be limited to those who receive early treatment; this implies that very early maternal screening is needed. At present, routine serological screening for CMV infection in mothers is not recommended as it does not meet the criteria for an effective screening test and most notably, until now, there has been no effective intervention to implement following identification of maternal primary infection. This study therefore questions this position. The impact that prevention of transmission would have on affected families as well as the global financial burden of congenital CMV is vast[19] [20] and makes the potential use of valaciclovir and associated screening extremely exciting.

The ultimate primary prevention strategy, vaccination, is still some way from clinical application, mostly due to the complex immunology associated with CMV infection. Recent research however is promising[21]. Modelling has provided support for the likely success of an appropriate vaccine[22] and neutralising monoclonal antibodies to CMV's glycoprotein B have been found to minimise CMV infection in developing placental cells[23]. This remains the long

term goal. The target group for a vaccine is more likely to be adolescents, or even infants, rather than pregnant women.

Secondary and Tertiary prevention of infection of the fetus

The use of HIG[24] or valaciclovir[218] in pre-emptive treatment of in utero congenital CMV infection in order to reduce the severity of clinical effects has also been investigated. Both agents appear to have some efficacy in reducing symptom burden postnatally however, further randomised-controlled trials need to be performed to confirm these findings. Tertiary prevention, using postnatal ganciclovir, has been associated with improved audiologic outcomes[25 26], and finally, a focus on rehabilitation can also reduce morbidity outcomes (Figure 4).

The future of screening and prevention of congenital CMV infection

Based on current evidence, it appears that the most promising avenue in reducing the global burden of CMV is primary prevention. Until a vaccine becomes available, this involves improving education on hygiene-based methods for preventing infection of the mother as well as the use of antivirals such as valaciclovir to prevent transmission if the mother does become infected.

However, the main limitation for the use of valaciclovir is the requirement for early, effective and large-scale serological screening of mothers for primary infection. Epidemiological studies and the evidence from a recent RCT emphasise the importance of very early recognition and treatment of maternal primary infection. The absence of a nationwide screening strategy, despite a reliable serological screening test being available, makes implementation of this challenging in a clinical setting. Secondly, to increase awareness of congenital CMV infection and how to avoid it, large public health education interventions are needed. These will require support and government funding, which may be difficult to obtain in countries with less resources. Finally, although primary maternal infection holds the highest relative risk for congenital CMV infection, in many populations, especially those with

a high seroprevalence, the predominant absolute risk for congenital infection and congenital disease is derived from reactivation or reinfection with CMV[27]. The application of these techniques in such circumstances is yet to be explored and further research is needed to establish if there would be any significant clinical benefits from the use of antiviral drugs or of behavioural modifications.

Conclusion

Prevention of congenital CMV infection, whether primary, secondary or tertiary, is possible. As the evidence accumulates, national and international bodies need to reconsider their policies on screening and healthcare professionals need to update their guidelines and management protocols. Clinical staff should be aware of these developments so that they can answer questions posed by patients. Finally, researchers should plan high quality studies aiming to address the gaps in the current literature and critically appraise existing evidence.

Figure Legends

Figure 1: A pie chart depicting the different presentations of congenital cytomegalovirus infection at birth.

Figure 2: A flowchart illustrating the epidemiology of congenital cytomegalovirus infection including the chances of both primary and secondary CMV infection of the pregnant mother resulting in vertical transmission.

Figure 3: A flowchart demonstrating the outcomes of Shahar-Nissan's Randomised controlled trial[17].

Figure 4: A diagram representing the different options for prevention of congenital cytomegalovirus infection, both current and potential.

Key Points

1. Recent evidence suggests that the use of valacyclovir to prevent vertical transmission of CMV is effective.
2. Advances in the efficacy of prophylactic treatment highlights the need to revisit screening policies.
3. A key area of focus moving forward should be increasing awareness of congenital CMV infection and how to avoid it. Large public health education schemes will likely be needed for this.

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Figure 1

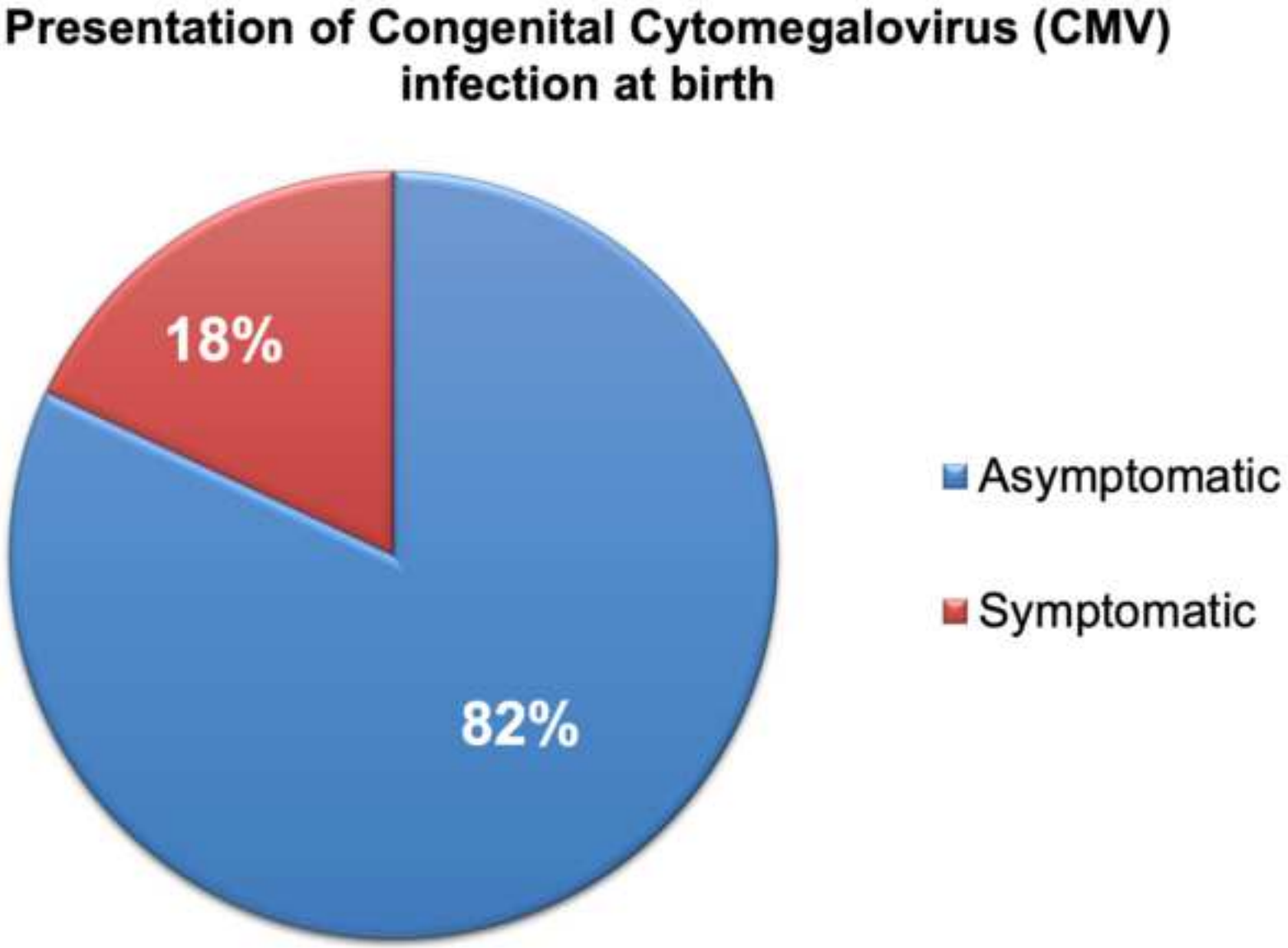

Figure 1

Figure 2

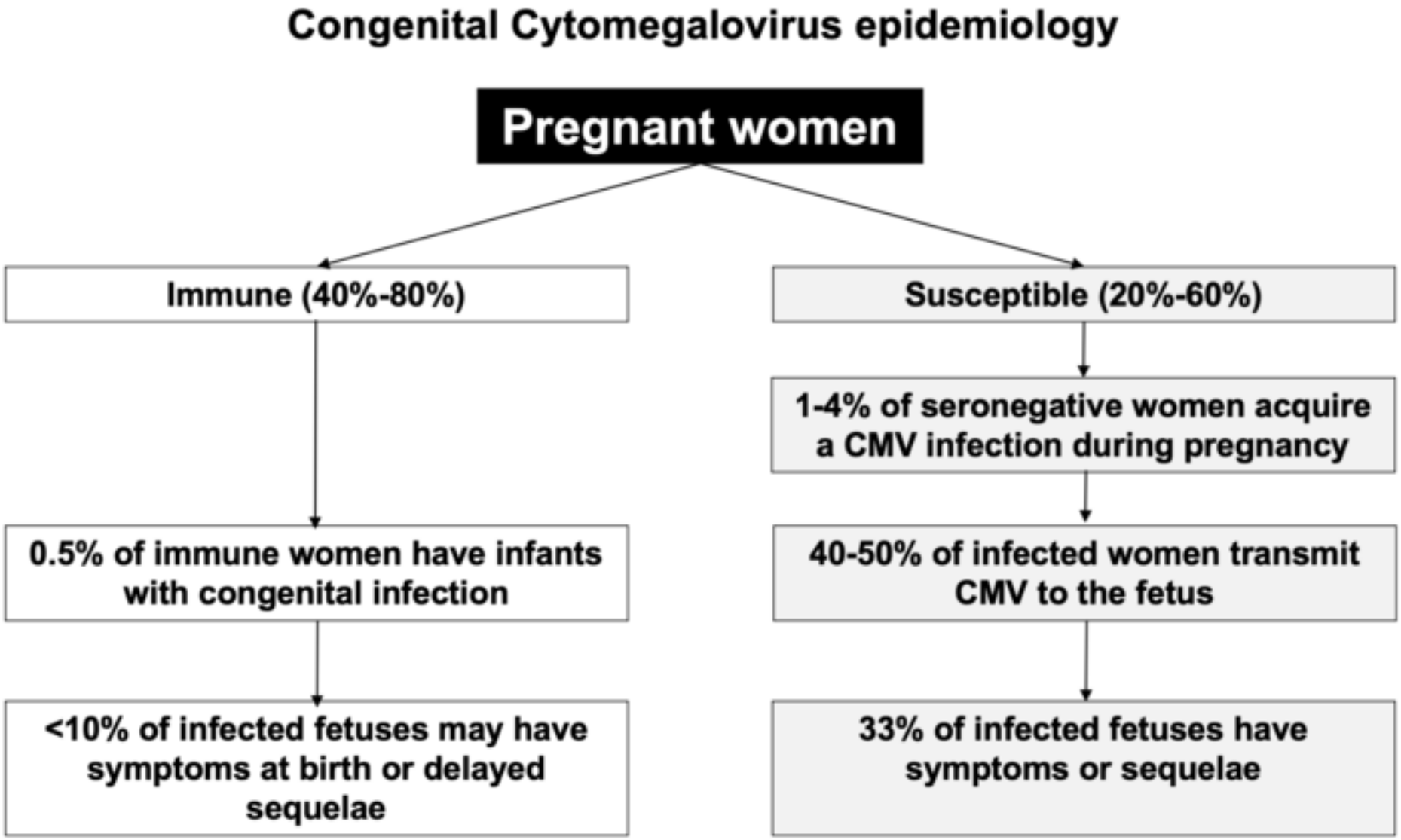

Figure 2

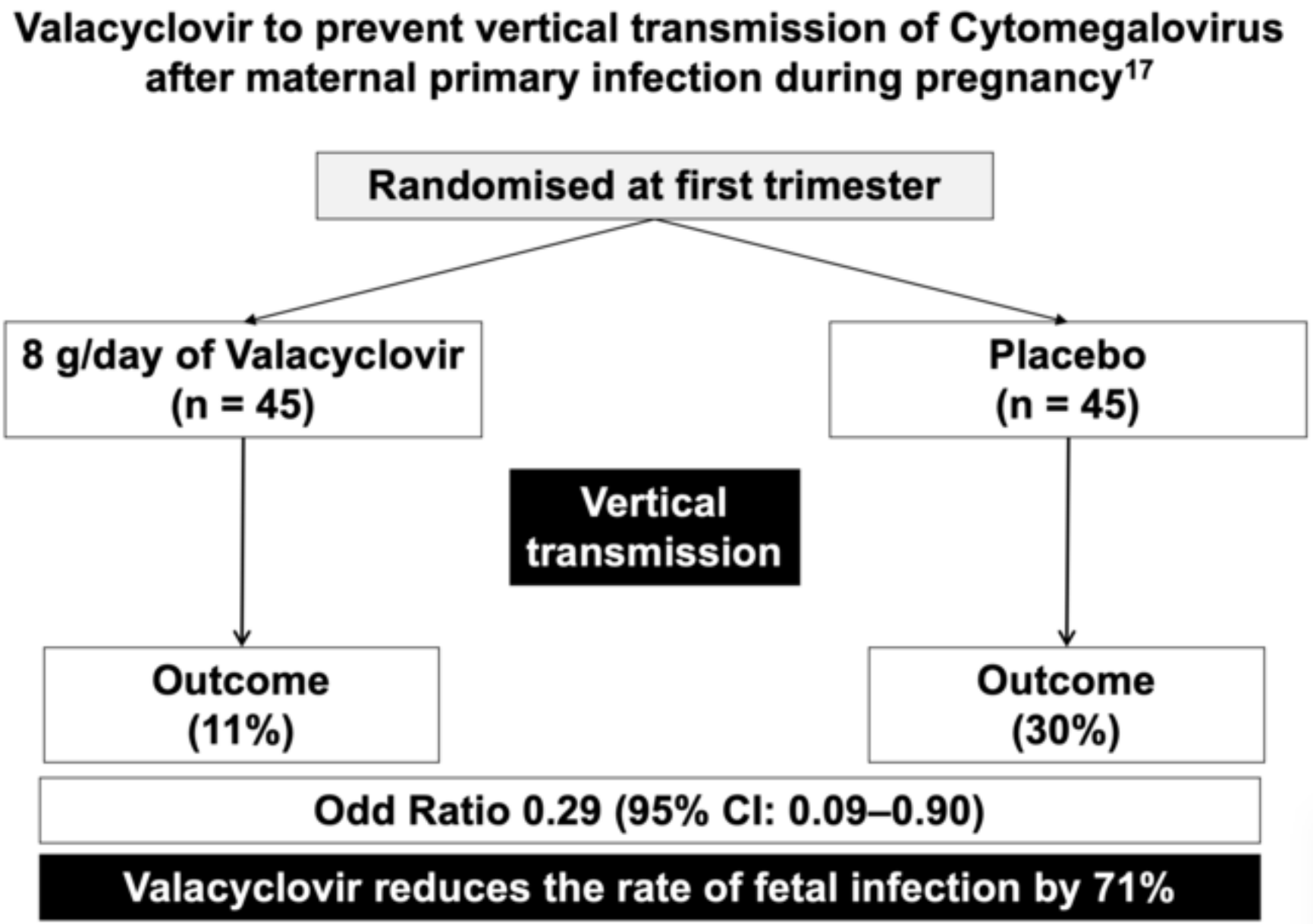
Valacyclovir to prevent vertical transmission of Cytomegalovirus after maternal primary infection during pregnancy[17]
Randomised at first trimester
8 g/day of Valacyclovir (n = 45)
Placebo (n = 45)
Vertical transmission
Outcome (11%)
Outcome (30%)
Odd Ratio 0.29 (95% CI: 0.09–0.90)
Valacyclovir reduces the rate of fetal infection by 71%

Figure 3

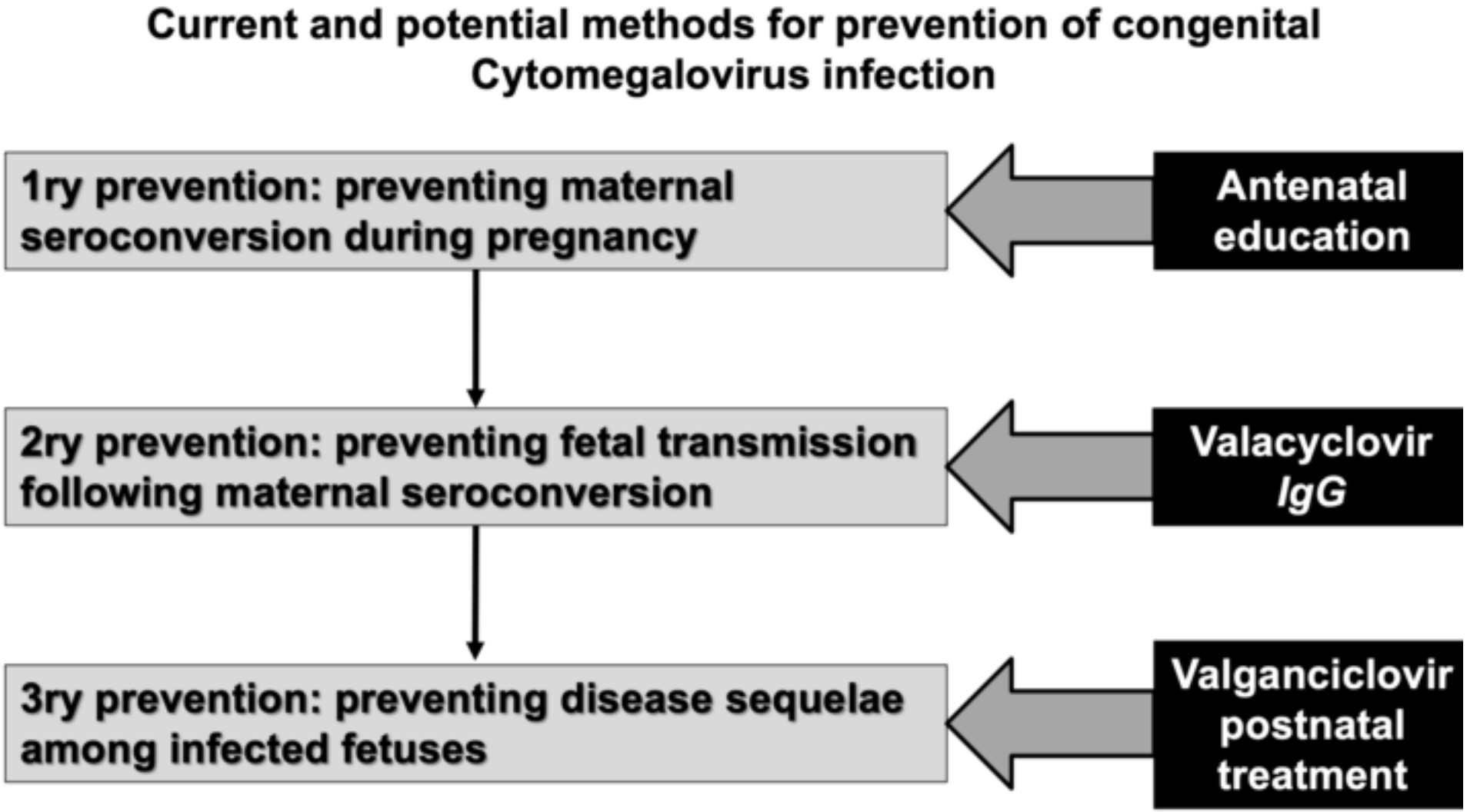
Current and potential methods for prevention of congenital Cytomegalovirus infection
1ry prevention: preventing maternal seroconversion during pregnancy
Antenatal education
2ry prevention: preventing fetal transmission following maternal seroconversion
Valacyclovir
IgG
3ry prevention: preventing disease sequelae among infected fetuses
Valganciclovir postnatal treatment

Figure 4