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Review Article

Congenital Cytomegalovirus Infections: (no) Focus on Africa: A Review

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ABSTRACT

Cytomegalovirus (CMV) infection during pregnancy is a major cause of congenital infection worldwide. Congenital CMV (cCMV) infection can result in significant morbidity, mortality, or long-term sequelae, including sensorineural hearing loss. Although the increase of awareness and international guidelines on the management of cCMV is observed across the developed country, data in Africa on rates of congenital and maternal CMV infection are rather scarce and scattered. Published data are compiled in this review indicating a high pooled prevalence of CMV IgG among pregnant women in Africa (87.4%, range of 72%-100%) as well as pooled reported cCMV prevalence in the newborn (3.3%, range of 1.3%-6.3%). As a continent with a high Human Immunodeficiency Virus (HIV) burden as well as other medical (eg. sexually transmitted diseases, lack of optimal/structured ante- and postnatal care, lack of adequate equipment and funding for laboratory facilities) and socioeconomic (eg. poverty, low awareness, and literacy, teenager pregnancies) challenges, Africa can benefit from the more concentrated worldwide efforts regarding the management of cCMV in pregnancy and infancy.

Keywords: Maternal; Congenital cytomegalovirus; Africa

INTRODUCTION

CMV infection during pregnancy is a major cause of congenital infection in developing countries [1]. The high maternal seroprevalence of CMV IgG does not exclude the threat of cCMV infection and clinically apparent disease in the newborn as cCMV is also common among pregnant women with pre-existing CMV IgG antibodies due to risk of reactivation or reinfection with a different viral strain [2]. Yet a pregnant woman with primary CMV infection is more likely to transmit infection compared to the mother with reactivation or recurrent (secondary) infection [3].

cCMV infection can result in significant morbidity, mortality, or long-term sequelae, including sensorineural hearing loss in an affected newborn. Despite being a leading cause of congenital infections worldwide, currently, there are no global programs that offer maternal or neonatal screening to identify infected mothers and infants, no vaccines as well as no efficacious and safe therapies in pregnant or newborns are available [4].

Depending on the characteristics of a specific maternal population such as age, economic status, and co-existing sexually transmitted infections including Human Immunodeficiency Virus (HIV), the prevalence of cCMV varies across the world. Low prevalence of cCMV infections is reported in developed countries, while the highest prevalence is recorded in Africa, Southern Asia, and South America [5]. Studies have also indicated the likelihood of being CMV seropositive before conception correlates negatively with socioeconomic status and is 92%, 47%, and 34% in expectant mothers with low, middle, and high socioeconomic status, respectively [6].

The challenge in the management of cCMV in de developing countries lays mainly in insufficient focus on cCMV worldwide and this can be due to the following: the absence of knowledge of cCMV infection apart from the wrong assumption that congenitally infected children who are born to women with pre-existing antibodies have normal outcomes, the lack of laboratory facilities resulting in lack of attention for serodiagnosis, not the least because most infected pregnant women and newborn at birth are asymptomatic. Also, sequelae as a result of cCMV infection in babies are frequently delayed in onset requiring more challenging retrospective diagnosis. All these factors contribute to the neglection of cCMV in developing countries [1].

For Africa, as one of the low-income continent, even though scarcely studied and lack compiled data, the rate of congenital and maternal CMV infection thought to be higher than reports from the rest of the world. The intention of the current review

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is to compile data published on congenital and maternal CMV infection in Africa.

APPROACH

This review summarizes congenital CMV and seroprevalence of CMV infection among African pregnant women. A PubMed and Google scholar search of the English-language literature was done using the following search term: (prevalence of CMV among pregnant women and congenital CMV infection in Africa [title]) AND (CMV among pregnant women* OR maternal CMV* OR maternal and congenital CMV OR *Cytomegalovirus* *OR "In Africa" [Mesh] OR Africa OR Current availability of national and international guidelines on cCMV in Africa OR Currently available and used diagnostic tools in Africa for cCMV [title]). The references of included studies were also searched for candidate articles. We included studies that applied validated CMV tests to patients. All studies on a specific population (pregnant women and newborns) were included. All available articles published up to June 2020 was included and exported to Endnote version 7.1.

MATERNAL CMV SEROPREVALENCE IN AFRICA

Studies from northern Africa have indicated the large burden of maternal CMV in the region. As to the study from Egypt, a 100% CMV IgG positivity among tested 546 pregnant women and 40/546 (7.3%) positive or equivocal IgM antibodies were reported [7]. Similarly study in Tunisian also has reported a high (96.3%) CMV seroprevalence among pregnant women [8].

Maternal CMV seroprevalence in East Africa varied from 72%-97.5%. One Kenyan study [9] found a relatively lower prevalence, 77.3%, of IgG and 8.1% of IgM while the other Kenyan study reported a higher prevalence 93.1% of CMV IgG among 1066 pregnant women [10]. Likewise in Tanzania, 73.9% of pregnant women had IgG antibodies while IgM antibodies were present only in 0.4% [11]. Additionally, the other Tanzanian study which was conducted on 368 pregnant women attending Sexually Transmitted Diseases (STDs) and antenatal clinics had reported a prevalence of 94% IgG and 8.5% IgM. According to the study CMV IgM was detected in higher numbers of patients with STDs than in those without STDs [12]. Again in a similar manner out of 231 Sudanese pregnant women, 72.2% and 2.5% were seropositive for CMV IgG and 2.5% CMV-IgM, respectively [13], whereas, in another Sudanese study, out of the 200 pregnant women tested: 195 (97.5%) IgG and 12 (6.0%) CMV IgM was reported [14].

A study conducted at St. Paul's Millennium Medical College Hospital, Addis Ababa, Ethiopia, reported a 95.5% CMV IgG and 5.5% CMV IgM positivity among pregnant women [15]. On the same site, among 200 pregnant women, the seroprevalence of 88.5% (IgG) and rather a high percentage of 15.5% for IgM were reported [16].

In West Africa, seroprevalence is reported in the range from 60%-100%. A study at Kano State of Nigerian disclosed 91.1% CMV IgG seropositivityamong 180 pregnant women [17]. The other Nigerian study found 11.1% CMV IgM positive while 93.9% were positive for CMV IgG among HIV seropositive pregnant women [18]. A study in Nigeria at Lagos State University Teaching Hospital has reported 97.2% of pregnant women being positive for CMV IgG [19].

The other West African countries also reported a high prevalence of CMV antibodies among pregnant women. A study on 169 Gambian pregnant women found a 100% CMV IgG positivity [20]. A similar finding was also reported in Ghana, a 100% prevalence of CMV IgG among tested 172 pregnant women [21]. In Benin, among 211 pregnant women 97.2% were positive for CMV IgG and 6% positive for CMV IgM [22].

On the other hand, according to the molecular assay of 200 samples from pregnant women in Burkina Faso, 13 (6.5%) were positive for CMV [23].

Reports from Southern Africa have shown almost 100% seroprevalence of maternal CMV. In Namibia 100% prevalence of CMV IgG and a 3.2% CMV IgM was documented [24]. In Zimbabwe, 99.6% IgG and 4.6% IgM positivity were reported. The study also documented that CMV seroprevalence was not associated with the HIV status of the women, perhaps due to the ubiquitous exposure of the population to CMV [25]. A study in Mozambique also reported 100% IgG prevalence among 118 pregnant women [26].

In South Africa, among 2,250 asymptomatic pregnant women who were investigated for active CMV infection, 132 (5.9%) were positive for active CMV infection. Among the 132 patients with active CMV, only 5 primary infections (3.8%) were diagnosed; the vast majority 127 (96%) had reactivation or reinfection resulting in the transplacental transmission rate of 6.4% [27].

The cited studies on CMV seroprevalence in pregnant women in Africa are presented in Table 1.

To summarize the pooled reported prevalence of CMV IgG among pregnant women in Africa was 87.4% (4864/5563) with a range of 72%-100%.

NEONATAL PREVALENCE OF CONGENITAL CMV IN AFRICA

Compared to the world investigations cCMV in newborns are scarce in Africa. When we tabulate the published data on congenital infections in Africa (Table 2), the number of neonates tested for cCMV infection varied from 115 to 2685, and all clinical specimens were collected within 2 weeks of birth. In 9 studies PCR techniques were used for the detection of CMV, urine culture in 2, and antibody detection with ELISA in a single study. Most of the studies have used urine or saliva samples while only one study has used umbilical cord and nasopharyngeal aspirates.

In Egypt a study by Salwa et al. identified cCMV in 1.3% of 178 newborns using PCR technique on saliva sample [28] whereas the other Egyptian study found a higher prevalence of cCMV infection, 5.7% using urine culture [29]. In a study in Kenya using saliva swab and PCR on Dried Blood Spot (DBS), out of 1078 newborn 39 (3.6%) were positive for cCMV infection. According to this study maternal HIV infection may increase the risk of cCMV infection, but the role of maternal malaria on the intrauterine transmission of CMV remains unclear [10].

A study from Ethiopia conducted using a serological test found a 1.3% prevalence of cCMV in newborns [15]. But in this study, a CMV IgM based assay known for low sensitivity and specificity was used [1]. In a case series report of four children with acute CMV infections diagnosed clinically and serologically the author emphasizes the need for advanced diagnostic tools for congenital and acquired childhood CMV infections in Ethiopia [30].

The reported rates of cCMV from West Africa range between 1.4-

Table 1: Studies on CMV seroprevalence of pregnant women in Africa.

First author and year of publication	Country	Number of patient tested	Positive for CMV n(%)	
			IgG	IgM
North Africa				
Kamel et al. [7]	Egypt	546	546 (100%)	40 (7.0%)
Hannachi et al. [8]	Tunisia	404	392 (96.3%)	
East Africa				
Maingi et al. [9]	Kenya	260	201 (77.3%)	21 (8.1)
Otieno et al. [10]	Kenya	1066	93.10%	Not done
Chibwe et al. [11]	Tanzania	261	193 (73.9%)	1 (0.4%)
Ray et al. [12]	Tanzania	368	193 (94%)	8.50%
Hamdan et al. [13]	Sudan	231	167 (72.2%)	6 (2.5%)
Khairi et al. [14]	Sudan	200	195 (97.5%)	12 (6%)
Mamuye et al. [15]	Ethiopia	156	149 (95.5%)	8 (5.5%)
Mamuye et al. [16]	Ethiopia	200	177 (88.5%)	31 (15.5%)
West Africa				
Hamid et al. [17]	Nigeria	180	164 (91.1%)	No done
Fowotade et al. [18]	Nigeria	180	169 (93.9%)	20 (11.1%)
Akinbami et al. [19]	Nigeria	179	174 (97.2%)	Not done
Rodier et al. [22]	Benin	211	205 (97.2%)	12 (6%)
Völker et al. [21]	Ghana	172	172 (100%)	0
Kaye et al. [20]	Gambia	169	169 (100%)	not done
Ouedraogo et al. [23]	Burkina Faso	200	Molecular PCR method; 13 (6.5%)	
Southern Africa				
Van der Colf et al. [24]	Namibia	344	344 (100%)	11 (3.2%)
Mhandire et al. [25]	Zimbabwe	524	522 (99.6%)	39 (7.4%)
Madrid et al. [26]	Mozambique	118	118 (100%)	Not done
Schoub et al. [27]	South Africa	2,250	Molecular PCR method; 132 (5.9%)	

5.4% among newborns. In a Study from Lagos, Nigeria, CMV was reported in 10 of 263 births (3.8%) based on an RT-PCR assay on dried saliva specimens [31]. In Ivory Coast, 28 of 2032 (1.4%) newborn infants had cCMV infection based on investigations on urine culture [32].

In a cohort study of Gambian term infants, cCMV infection was detected in 40 (5.4%) of 741 tested infants using PCR techniques from urine samples at birth [33]. In another Gambian study, cCMV infection was detected in 11 (3.9%) of 281 infants on urine samples obtained within the first 2 weeks of birth using the PCR method [20].

In Southern Africa, a higher rate of cCMV compared to the rest African region was reported. In a Mozambican district hospital, 3 newborns out of 115 (2.6%) were positive for cCMV using a PCR assay from an umbilical cord sample. This study also used nasopharyngeal aspirate samples from part of these neonates. Accordingly, in 6 of 96 (6.3%) cCMV were detected. The authors indicate the significant incident of vertical transmission of CMV in southern Mozambique [26].

In Zambia from 395 neonate samples tested on urine and saliva by PCR, 3.8% (15/395) were diagnosed with cCMV [34]. The study reported a higher prevalence of cCMV among neonates born to HIV-infected mothers; 11.4%, compared to only 2.1% among neonates born to uninfected mothers.

In accordance, in Johannesburg, South Africa, significantly higher cCMV prevalence was reported in HIV-exposed neonates, (5.2%, 95% CI 3.8-6.9) than HIV unexposed neonates (1.4%, 95% CI 0.9-2.0). The risk of in utero HIV infection was 20-fold greater (odds ratio 20.1, 95% CI 6.09-66.46) among cCMV infected neonates [35].

In contrast, in another Southern Africa study in one of the rural central hospitals in South Africa, a 5.96% prevalence of cCMV was reported using a PCR assay on a saliva swab. But prevalence was equal in HIV exposed and HIV unexposed neonates {Prevalence Ratio (PR)=1.00; 95% CI 0.94-1.06; p=0.869}, and hence there was no association between maternal HIV status and cCMV. The study also assessed other factors associated with cCMV. Accordingly, newborns with a birth weight of <2400 g were either 5% or 7% more likely to have cCMV than those with higher birth weight of between 2400 and 3500 g (PR=1.05; 95% CI 0.97-1.14; p=0.249) and >3500 g (PR=1.07; 95% CI 0.97-1.18; p=0.182) respectively; but the difference is not statistically significant. Congenital CMV infection was also not significantly associated with the economic status or other maternal demographic characteristics in this particular report [36].

According to our review, the pooled reported prevalence of cCMV among newborns in Africa was 3.3% (278/8401) with a range of 1.3%-06.3%.

NEONATAL PREVALENCE OF CONGENITAL CMV IN AFRICA

Also, routine testing for CMV in pregnant women has several benefits mainly to identify fetuses at risk of developing sequelae [4],

which most current international guidelines do not recommend. In African countries, the lack of routine testing for CMV in pregnant women is not only the result of the absence of broadly available recommendations but is also mainly due to the un-affordability of test kits.

The diagnosis of CMV infection can be made by detecting virus-specific IgG and IgM antibodies in the serum of a pregnant woman. The presence of IgG antibodies indicates a past infection from 2 weeks to several years duration while IgM assays have been assessed in pregnant women as an indicator of acute or recent infection. However, IgM can be produced in pregnant women with non-primary CMV infections [37]. As a result serologic assessment of CMV IgG along with CMV IgM and IgG avidity of a pregnant woman can identify pregnancies at risk of transmitting CMV to the fetus.

The CMV IgG avidity assay is considered a primary tool to date the timing of an infection. Finding CMV IgM antibodies with low CMV IgG avidity indicates primary infection within the preceding 3-4 months with an increased risk of intrauterine transmission to the fetus. Whereas with high avidity, the risk of transmission is lower. Therefore, if avidity testing is available, the presence of IgM antibody and low-avidity IgG antibody provides strong evidence of recent primary infection [38].

Table 2: Studies on congenital CMV in Africa.

First author and year of publication	Country	Number of patient tested	Positive for CMV number (%)	Samples used and laboratory methods
North Africa				
Morgan et al. [29]	Egypt	175	10 (5.7%)	Urine PCR
Salwa et al. [28]	Egypt	178	2 (1.3%)	Urine culture
East Africa				
Otieno et al. [10]	Kenya	1078	39 (3.6%)	Saliva swabs and DBS PCR
Mamuyeet al. [15]	Ethiopia	156	2 (1.3%)	Cord blood ELISA
West Africa				
Olusanya et al. [31]	Nigeria	263	10 (3.8)	Dried saliva PCR
Schopfer et al. [32]	Ivory Coast	2032	28 (1.4%)	Urine culture
Van der sande et al. [33]	Gambia	741	40 (5.4%)	Urine PCR
Kaye et al. [20]	Gambia	281	11 (3.9%)	Urine PCR
Southern Africa				
Madrid et al. [26]	Mozam-bique	115	3/115 (2.6)	Umbilical cord PCR
			6/96 (6.3%)	Nasopharyngeal aspirates
Mwaanza et al. [34]	Zambia	395	15 (3.8)	Urine and saliva PCR
Pathirana et al. [35]	South Africa	2685	67 (2.5%)	Saliva swab PCR
Tshabalala et al. 2018 [36]	South Africa	302	18 (5.96%)	Saliva swab PCR

CURRENTLY AVAILABLE DIAGNOSTIC TOOLS FOR CONGENITAL CMV IN NEWBORNS IN AFRICA

Viral culture of the urine and saliva obtained within the first two weeks of life continue to be the gold standard for diagnosis of congenitally infected infants. But saliva PCR assays are currently being assessed as a useful method for cCMV infection as congenitally infected newborns persistently shed very high levels of CMV in the saliva and urine [4]. Practically newborns need to be diagnosed if there is clinical suspicion of cCMV infection or the mother having a previous history of CMV infection. However, in Africa diagnosis of cCMV for the clinically suspected newborn is practically non-existing due to the lack of awareness, laboratory capacities, and guidelines. Yet a very little number of reports witness the significance of cCMV in Africa [1].

Obtaining the saliva sample at least 1 hour after breastfeeding to avoid potential contamination with CMV from breast milk is essential to reduce the risk of contamination from mother breast milk. Studies already revealed that PCR assay of saliva showed high sensitivity and specificity and PCR appears to identify more congenitally infected newborns that would be missed by rapid culture [4]. However, the cost of a comprehensive diagnosis of CMV infection is unaffordable in Africa.

Yet, serologic CMV IgG and IgM assay are not suggested for the diagnosis of cCMV infection because only 20%-70% of infected babies will have a positive CMV IgM antibody titer and many newborn will have a positive CMV IgG antibody titer from blood passed to them from their mother [39].

CONCLUSION

Despite the high reported pooled prevalence of CMV IgG among pregnant women (87.4%, range of 72%-100%) as well as high pooled reported cCMV prevalence in newborns in Africa (3.3%, range of 1.3%-6.3%), there are barely efforts in African countries for diagnosis of maternal CMV infections and cCMV in newborns. Most studies performed reflect very necessary epidemiological assessments rather than on-going routine diagnostic practices and there are currently no internationally or nationally adopted guidelines in the region regarding cCMV management. Lack of management and diagnostic policies on cCMV unbearably results in underreporting what in turn signals that cCMV awareness in the region can be seen as a neglected disease in Africa. As a continent with a high HIV burden as well as other medical (eg. STDs, lack of optimal/structured ante and postnatal care, lack of adequate equipment and funding for laboratory facilities) and socioeconomic (eg. poverty, low awareness, and literacy, teenage pregnancies) challenges, Africa can benefit from the more concentrated worldwide efforts regarding the management of cCMV in pregnancy and infancy.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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