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Impact of the Israeli Ministry of Health Cytomegalovirus Guidelines on the Local Pregnancy Outcome

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CMV · MOH guidelines · Pregnancy termination · Fetal therapy

Abstract
Objective: In 2011, the Israeli Ministry of Health (MOH) published standard guidelines for the follow-up of pregnant women infected by CMV, recommending that amniocentesis be performed in cases of maternal serum viral seroconversion or abnormal sonographic findings suggestive of CMV, in order to prove fetal infection before electing for pregnancy termination. ***Methods:*** A retrospective cohort study was performed, describing 448 pregnant women from 2006 to 2017. We collected data from all women that elected to continue their pregnancies after seroconversion and also of those who chose to undergo pregnancy termination. Subsequently, a telephone survey was then conducted to record outcomes of the newborns of women with CMV seroconversion during pregnancy. ***Results:*** 325 (73%) women chose to continue their pregnancy, while 123 (27%) opted for termination of pregnancy. We found that pregnancy termination due to CMV infection was reduced by 7%, from 72 cases (32%) to 51 cases (25%) after the implementation of the MOH guidelines in 2011. In addition, 182/305 (60%) of women responded to our telephone questionnaire regarding newborn outcomes. Of these women, 45/305 (14%) reported complications, and no correlation was found between the prenatal findings and postnatal outcome among those who have responded to our survey. ***Conclusion:*** Implementation of the new MOH guidelines has reduced the rate of pregnancy termination, without increasing the rate of neonatal complications in Israel with a similar outcome of complication rate as reported in the literature.

Introduction

CMV is one of the most common congenital viral infections. CMV infection is classified as either a primary infection or reinfection. Most cases (75–95%) are asymptomatic. However, in a minority of cases, mononucleosis-like symptoms will present. Primary infection affects ap-

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proximately 0.7–4.1% of all pregnancies. The fetal transmission rate in primary infection is around 30–60% of the fetuses, as opposed to 0.5–2% in cases of reinfection [1–4].

The spectrum of neonatal symptoms can vary from asymptomatic presentation in 90% of the cases to symptoms such as jaundice, small for gestational age, and microcephaly. Long-term complications of affected newborns include neurodevelopmental delay, motor delay, and deafness. In utero findings of CMV infection may include periventricular calcifications, echogenic fetal bowel, and intrauterine growth restriction. In the case where one of these findings is suspected on prenatal ultrasound (US), suspicion of CMV infection should arise and screening for TORCH viruses should be conducted [5].

In 2011, the Israeli Ministry of Health (MOH) released new guidelines for CMV screening and follow-up during pregnancy [6]. The guidelines state that routine serum screening tests should not be performed in low-risk pregnant women. However, CMV screening is recommended in cases of women with mononucleosis-like symptoms, sonographically suspicious findings, or in high-risk populations, such as day care and health care workers. Termination of pregnancy (TOP) is not recommended based on serology without additional imaging findings or amniocentesis confirming fetal infection, even in cases of infection during early pregnancy in which the chance for morbidity and long-term complications is known to be greater [6].

In the current study, our goal was to search for a profound effect of the new MOH guidelines on the rate of pregnancy termination versus pregnancy continuation in women prior to 2011, when the guidelines were released, and after 2011. In addition, we looked for a correlation between prenatal sonographic findings and postnatal sequelae using a telephone questionnaire after delivery.

Materials and Methods

This is a retrospective cohort study of 423 pregnant women who were managed at the Shamir Medical Center Institute between the years of 2006 and 2017. Baseline demographic data of all patients presenting with a diagnosis of CMV infection was collected. We divided the data into 2 groups, 123 cases of women who opted for pregnancy termination based on her diagnosis and 305 cases of pregnant women who chose to continue their pregnancies and undergo follow-up in our outpatient clinic. The 2 groups were further subdivided in regards to the year of MOH guidelines publication, that is, 6 years prior (2006–2001) and 6 years following (2012–2017). The goal of the subdivision was to examine the impact of the changes following the release of the guidelines in the year 2011.

In Israel, it is legal to terminate pregnancy at any given gestational age. In the cases of TOP at less than 24-week gestational age, an "institutional committee" takes place to consider termination. On the other hand, a "Supreme regional committee" is required to authorize and approve TOP for pregnancies of >24-week gestation. Such cases can only be approved after the supreme committee has reached the conclusion that there is a high probability of neonatal death or severe handicap. In Israel, each year about 240 late TOPs (at >24 weeks of gestation) are performed, of which 15% are at >32 weeks of gestation, with a majority of them (95%) being due to fetal abnormalities (www.health.gov.il) [7].

Our department is a tertiary referral center for cases to undergo both early and late TOP, mainly due to a fetal indication. We have revised our total database of the pregnancy termination between 2006 and 2017 and selected cases whom underwent TOP solely because of CMV seroconversion. Of note, we conduct a high-risk pregnancy outpatient clinic to manage and follow such complex cases.

Our primary outcome was to demonstrate the rate of termination versus continuation of pregnancy 6 years prior (2006–2011) and 6 years following (2012–2017) the MOH guidelines publication. Our secondary outcome was to examine the correlation between prenatal sonographic findings and both short- and long-term postnatal sequelae and complications using a telephone questionnaire.

The telephone questionnaire conducted aimed to reach to all women with CMV seroconversion who elected to continue their pregnancy. We inquired about short- and long-term complications, and all data were collected and recorded.

Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA, version 25). Continuous variables are presented as the mean ± standard deviation. Frequencies are presented as percentages. This study was approved by the Institutional Review Boards of the local Helsinki Committee (number 117-16-ASF). All women consented to the telephone questionnaire before the questionnaire was conducted, by giving oral consent.

Results

Our cohort included 2 study arms, one of the 305 pregnant women who elected to continue with their pregnancy after viral seroconversion, and were managed and followed in our high-risk pregnancy outpatient clinic. The second arm consisted of 123 cases of women who opted for TOP following CMV seroconversion. These data were retrieved from our total cohort of pregnancy termination cases. Baseline demographic characteristics and pregnancy information are presented in (Table 1), with a similar mean maternal age of 30.09 and 30.75 years in the continuation and termination group, respectively. The week of diagnosis of CMV seroconversion ranged from 4-week gestational age (in this, we also included preconception

Table 1. Demographic characteristics and background obstetric information of the pregnancy continued group and the pregnancy termination group

	Pregnancy continued *N* = 305	Pregnancy termination *N* = 123
Age, years	30.09±4.2	30.75±3.9
G	2.43 (range 1–9)	2.53 (range 1–11)
P	1.05 (range 0–4)	1.14 (range 0-4)
Week diagnosis of seroconversion	14.4 (range 4–37.4)	17.34 (range 5–35)

Age, age during the current pregnancy; G, gravity; P, parity. Median and IQR were used for continuous variables and frequencies for categorical variables. Age which has a normal distribution was described by mean and standard deviation. No statistical difference was found between the groups.

Table 2. Total number of pregnancy terminations and the total delivery rate at Shamir Medical Center before and after 2011, and the number of cases of pregnancy termination due to CMV versus pregnancy continuation

	Before 2011	After 2011	*p* value
Pregnancy number, *n*	46,515	54,227	ns
Pregnancy termination number, *n*	1,356	1,506	ns
CMV cases, *n*	225	203	ns
Pregnancy CMV seroconversion continuation, *n* (%)	153 (0.3)	152 (0.28)	ns
Pregnancy CMV seroconversion termination, *n* (%)	72 (5.3)	51 (3.3)	ns

seroconversion) up to 37.4 weeks of gestation. Among women who elected to continue pregnancy, the mean week of diagnosis was 14.4. Of women who elected to undergo TOP, the time of diagnosis of seroconversion ranged from 7- to 35-week gestational age, with a mean diagnosis of 17.34 weeks and TOP week occurring at a mean of 19.28 weeks.

In the cohort of patients who underwent CMV seroconversion during pregnancy, the rate of delivery and the rate of pregnancy termination have increased over recent years. In fact, 46,515 deliveries have occurred during the years 2006–2011, and 54,227 delivering occurred during the years of 2012–2017. Likewise, the rate of the total pregnancy termination due to fetal indication has increased from 1,356 cases from 2006 to 2011 to 1,506 cases from 2012 to 2017. Despite the increase in the rate of pregnancy termination, the total rate of pregnancy termination due to CMV infection has decreased from 5.3 to 3.3%. The rate of women with known viral seroconversion during pregnancy who choose to remain under follow-up has decreased from 0.32 to 0.28% (Table 2). The total number of cases of pregnancy termination versus pregnancy continuation after viral seroconversion before and after 2011 is presented in Figure 1.

We examined the postdelivery complications including positive saliva or urine PCR for CMV, findings on neonatal US of the brain, hearing, and visual disabilities, developmental delay, and complications immediately following birth. Taking the entire cohort of 305 women into account, we found that 182 out of 305 (60%) responded to the telephone questionnaire. Among these, 10 cases (3.3%) reported hearing loss, 15 cases (4.9%) reported visual complications, and 33 cases (10.8%) reported neurodevelopmental impairment. When these data were subdivided into the 2 groups before 2011 and after 2011, the rate of complications was not significantly different between the 2 groups. These data are summarized in Table 3.

Furthermore, we also examined the association between the prenatal imaging findings via US and postnatal outcomes. Significant findings on targeted fetal US scans for patients with CMV seroconversion were retrieved and recorded, including findings of the placenta and the fetal brain. Of cases in which amniocentesis was positive for CMV, MRI of the fetal brain was conducted. We then looked for an association between postnatal outcomes (positive saliva or urine PCR for CMV, US of the neonatal brain, hearing or visual disabilities, developmental de-

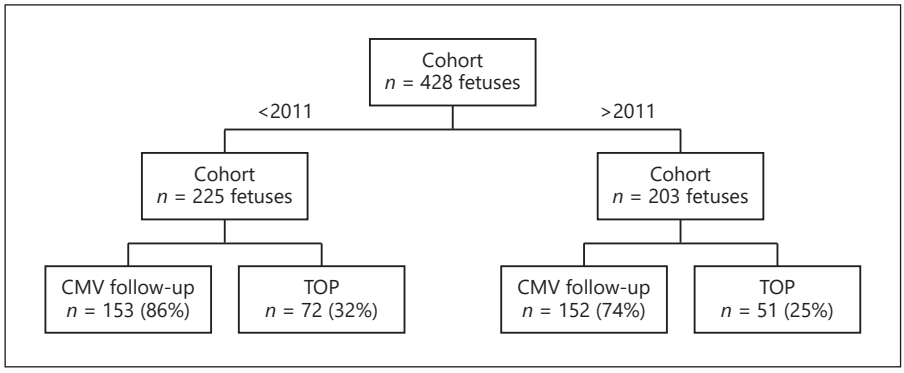

Fig. 1. The number of total pregnancy terminations and total delivery rate at Shamir Medical Center per year, and the number of cases per year of pregnancy termination due to CMV versus pregnancy continuation.

Table 3. Complications following delivery (based on a telephone questionnaire)

	Before 2011	After 2011	*p* value
Positive PCR, %	13.0	20.4	ns
Brain US findings, %	20.0	9.0	ns
Hearing disability, %	3.9	4.2	ns
Visual disability, %	6.9	8.5	ns
Developmental delay, %	17.6	16.7	ns
Birth complications, %	8.0	2.8	ns
Total, % (*n*)	19 (29)	14.8 (16)	ns

US, ultrasound. The compression was done using Fisher's exact test, with significant equals $p < 0.05$.

lay, and any complications immediately after birth) and abnormal US findings; however, no correlation was found perhaps due to small sample size.

Discussion

In this work, the impact of the new 2011 MOH standard guidelines on the rate of pregnancy termination due to CMV infection in Israel is presented. We present a decrease of 7% in the rate of pregnancy termination (Fig. 1). The common practice in the management of CMV had not been well established in Israel up until 2011. Consequently, perhaps pregnancy termination was conducted based on the presence of seroconversion alone, without amniocentesis confirmation of fetal infection. In the 2011 MOH guidelines, it is stated that after confirming seroconversion, sonographic follow-up is indicated every 2–4 weeks until birth or until abnormal sonographic findings are detected. Additionally, MRI imaging can be considered. Amniocentesis is not recommended before 21 weeks of gestation, or if 6 weeks passed from the estimated date of infection. The more recent 2011 guidelines state that amniocentesis must confirm fetal infection before pregnancy termination is executed [6].

The 2011 Israeli guidelines are similar to more recent guidelines published by the Royal College of Obstetricians and Gynecologists (RCOG) in 2018 [8]. The RCOG guidelines also recommend that after seroconversion and following amniocentesis to confirm fetal infection, sonographic follow-up should be performed every 2–4 weeks to search for fetal abnormalities or signed of congenital CMV. Fetal MRI and, in some cases, fetal blood sample are also recommended. The guidelines separated asymptomatic fetuses from mild or moderately symptomatic fetuses with isolated biological abnormalities to severely symptomatic fetuses with severe cerebral US abnormalities. They state that the severity of the US findings determines the prognosis and also the influences the consideration of in utero treatment versus pregnancy termination [8].

The Society for Maternal Fetal Medicine (SMFM) guidelines published in 2015 [9] and the Israeli guidelines (2011) alike do not recommend routine screening for CMV. It is estimated that universal CMV screening is not an effective screening test, and possibly results in premature interventions that may alter the course of the disease. There is now new published research regarding in utero therapy for infected fetuses. The rate of asymptomatic newborns born after CMV infection is 87%; among them, 6–23% will develop hearing loss [8]. Among asymptomatic cases, if routine CMV screening tests during pregnancy or immediately following birth are not performed, cases may be missed consequently these cases will not benefit from the recommended early treatment with antiviral therapy.

Recently published works regarding the treatment of women with CMV seroconversion during pregnancy show the newborn outcomes whom were treated in utero with antiviral treatment. For instance, Lervez showed that treatment with valaciclovir in utero was associated with a rate of 82% of asymptomatic newborns [10]. It was also demonstrated in this work that ganciclovir crosses the placenta and has an affect at the CSF level to reduce the viral load during brain development [11]. There are no known serious side effects of antiviral treatment to the mother, and oral treatment is sufficient to reach therapeutic levels in the fetus [12]. Although there are works presenting the benefit of universal newborn screening for congenital CMV infection, this early diagnosis and early intervention with medical and other therapies can reduce the CMV sequelae of the infected newborns [5]. Novel in utero treatment raises a question regarding the newly established guidelines of universal screening for seroconversion versus screening pregnant women with suspected CMV infection based on clinical suspicion and abnormal US findings.

We did not find a relationship between prenatal findings and postnatal sequelae, most probably due to our small sample size. In order to present a relationship between the prenatal and postnatal sequelae, we propose a need for multicenter works on this topic with a larger number of cases. The data collected in this study regarding CMV and pregnancy were of a multidisciplinary approach, involving experts in perinatology, obstetrics, infectious diseases, and neonatology. Our work is important to consider when providing consultation for women with CMV seroconversion whom are faced with serious challenges when making decision regarding further management of her pregnancy. We propose that a multidisciplinary approach should be used when making such momentous decisions.

The limitations of our study include it being a retrospective, single-center study. Larger studies are needed on this topic. Due to the extensive study period, the telephone questionnaire is prone to recall bias and drop out.

Advantages to our study include the fact that this is the first 12-year follow-up of children born after CMV infection during pregnancy, and that data were collected and analyzed using a multidisciplinary approach.

In conclusion, it has currently been shown that the implementation of the Israeli MOH guidelines in 2011 has reduced the rate of pregnancy termination due to CMV seroconversion, without increasing the rate of neonatal complications in Israel. Furthermore, while taking into consideration the encouraging data from other recent studies regarding the efficacy of in utero antiviral treatment, we propose considering amending the national guidelines calling for universal screening to all pregnant women and initiating early treatment in cases of seroconversion.

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Statement of Ethics

Our research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study was approved by the Institutional Review Boards of the local Helsinki Committee (number 117-16-ASF). Subjects of this study have given their oral informed consent prior to answering to the questionnaire, an oral consent was acquired due to the fact the questionnaire was conducted by telephone and the patient was not asked to arrive to the clinic, no physical examination was needed, and all questions were answered by the telephone.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Marina Pekar-Zlotin – data collection and writing the article. Anat Alufi Perry – data collection conduction of the telephone questionnaire. Eliassi Revivo – data collection conduction of the telephone questionnaire. Nadav Kugler – data collection and electronic retrieval of the relevant cases from the electronic database. Yaakov Melcer – data collection. Yifat Wiener – head of the high-risk clinic, patient follow-up, and writing the article. Ron Maymon – head of the department, patient follow-up, and writing the article.

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