Trends in Continuity of Pregnancy in Women with Positive Cytomegalovirus IgM during the First Trimester, 2008–2009

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ABSTRACT: **Background:** Cytomegalovirus (CMV) infection during pregnancy is the most common cause of intrauterine infection, and is a common cause of sensorineural hearing loss and mental retardation.

Objectives: To evaluate trends in amniocentesis and pregnancy outcome in women with suspected cytomegalovirus (CMV) infection during the first trimester.

Methods: All blood tests for CMV immunoglobulin M (IgM) done between 2008 and 2009 on pregnant women who were enrolled in the Maccabi Healthcare Services were retrieved from laboratory database. Immunoglobulin G (IgG) avidity was measured and women were classified according to the risk of acquiring CMV infection. For each patient, performance of amniocentesis and whether pregnancy came to term were recorded.

Results: Of 109,439 pregnant women evaluated during the study period, 76,712 (70.1%) were tested for CMV IgM, and 792 (1.03%) were found to be positive. Among women with positive IgM, only 205 (25.9%) underwent amniocentesis. When compared with women with negative CMV IgM, the rate of pregnancy cessation was doubled in women with positive CMV IgM (28.3% vs. 14.3%, $P < 0.05$) and mostly elevated in women with a high risk of acquiring CMV (42.3% pregnancy cessation). Among women with positive CMV IgM, those who did not undergo amniocentesis were more likely to abort than those who performed amniocentesis (35.6% vs. 7.3%, $P < 0.05$).

Conclusions: More women with suspected CMV infection during the first trimester of pregnancy aborted before all means of detection were utilized to rule out or confirm fetal infection with CMV.

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KEY WORDS: cytomegalovirus (CMV), immunoglobulin M (IgM) positive, termination of pregnancy, first-trimester pregnancy

Cytomegalovirus (CMV) infection is the most common fetal infection, affecting 0.3–2% of live born infants [1]. The risk of seroconversion during pregnancy is 1–4% and the rate of congenital infection following primary maternal infection ranges from 4.6% in the periconception period to 72% during the third trimester [2]. Ten percent of infected infants will be symptomatic at birth; approximately one-third of them will die and up to 90% of the survivors will develop long-term sequelae, such as hearing impairment or neurological abnormalities [3]. An additional 5–15% of asymptomatic newborns later develop hearing loss and neurological deficits. It is now clear that most fetal and neonatal sequelae are associated with first or second trimester infections [4,5].

Amniocentesis after 22 weeks of gestation and 7 weeks at least after maternal infection can detect those pregnancies in which the virus was transferred to the fetal compartment. This will be the case in about 40% of first or second trimester infections while in the other 60%, the virus would not be transferred to the fetus. Furthermore, solid data show that even in those 40% where fetal transmission is documented, the risk of severe sequelae is significantly reduced in the presence of normal prenatal ultrasound and magnetic resonance imaging (MRI) [6].

The aim of our study was to assess whether patients in our population with suspected periconception and first trimester CMV infection adhered to evidence-based CMV workup prior to making decisions regarding management of their pregnancy.

PATIENTS AND METHODS

We performed a retrospective computerized cohort study including all pregnant women who were referred for blood tests between January 2008 and December 2009 in Israel's second biggest health maintenance organization (Maccabi Healthcare Services). The study was approved by the institutional review board (Ref no 2010061 10.17.2010). In Israel, there are no recommendations for routine maternal–fetal screening or serial screening for CMV infection before or during the first trimester of pregnancy. The presence of pregnancy is determined either

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by a specific diagnosis note entered to the computerized medical file by the referring physician, positive beta human chorionic gonadotropin (HCG) test on the computerized laboratory database, or both. For all pregnant women, blood test results for CMV IgM were retrieved and women were placed into one of two groups accordingly (positive or negative immunoglobulin M [IgM]). For all women with an IgM positive result, immunoglobulin G (IgG) avidity was documented and women were further classified according to the risk of acquiring CMV during pregnancy, using the following definitions:

- High risk: avidity of 0–35%
- Moderate risk: avidity 36–44%
- Low risk: avidity ≥ 45%

Performance of amniocentesis was mined and documented for all patients, irrespective of CMV IgM/IgG results. For all pregnancies, we determined whether the pregnancy did not come to full term due to abortion (spontaneous or otherwise). Indications that the pregnancy did not come to full term were also determined in two additional ways:

- Computerized medical records for the relevant pregnancy were missing for the 50 gram glucose challenge test (GCT) or the 100 gram oral glucose tolerance test (OGTT, only for patients without GCT)
- Absence of birth certificate issued by the national social insurance

Both of these requirements are mandatory in pregnancy and following live birth.

Statistical analysis was performed using IBM SPSS Statistics version 22 software (IBM Corp, Armonk, New York, USA). Differences of categorical variables were analyzed using 2 × 2 chi-square or Fisher's exact tests as appropriate. Differences of continuous variables were tested using independent sample *t*-tests or Mann–Whitney *U*-tests, where appropriate. $P = -0.05$ (two-sided) indicated statistical significance.

RESULTS

During the study period 109,439 women were reported as pregnant, of whom 76,712 (70.1%) were tested for CMV IgM. Positive IgM results were documented in 792 women (1.03% of women who were tested) [Table 1]. Of those, 427 (53.9%) had low risk for transmission, 89 (11.2%) had moderate risk for transmission and 255 (32.2%) had high risk for transmission. For 21 women (2.7%), IgG avidity results were lost to follow-up [Figure 1].

Among 792 women with positive IgM, only 205 (25.9%) underwent amniocentesis. When compared with women who had negative CMV IgM results, the rate of pregnancy cessation was doubled in women with positive CMV IgM (28.3% vs. 14.3%, $P < 0.05$). Pregnancy cessation rate was mostly elevated in women with a high risk of acquiring CMV (42.3%), compared to women at moderate risk (23.6%) and low risk (19.2%).

Among 792 women with positive CMV IgM, those who did not undergo amniocentesis were more likely to have not come to full-term pregnancy compared to those who performed amniocentesis (35.6% vs. 7.3%, $P < 0.05$) [Figure 2]. This trend was consistent in all risk groups for acquiring CMV during pregnancy; however, it was more powerful in the high-risk group, where 57.5% of women who did not perform amniocentesis did not continue pregnancy to term. In the moderate-risk group 35.8% of women who did not perform amniocentesis had no evidence of continuing to full term, and in the low-risk group 23.4% of women who did not perform amniocentesis did not continue to full term.

DISCUSSION

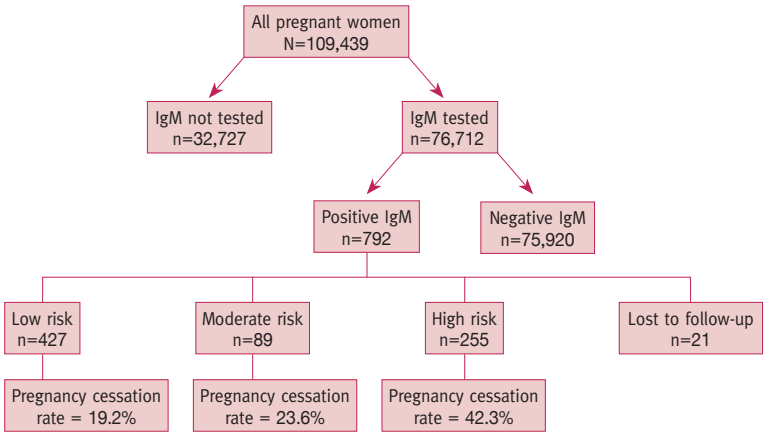
In our population with maternal CMV infection, termination of pregnancy was almost five times more common in patients

Table 1. Positive CMV IgM results, amniocentesis and termination of pregnancy rates in the study population (n=109,439)

	Positive IgM (n=792)	Performed amniocentesis*	Discontinued pregnancy		
			From those who performed amniocentesis*	From those who did not perform amniocentesis*	Total*
Low risk	427 (54%)	19%	1.2%	23.4%	19.2%
Moderate risk	89 (11.2%)	40.4%	5.5%	35.8%	23.6%
High risk	255 (32.2%)	34.5%	13.6%	57.5%	42.3%
Lost to follow-up	21 (2.6%)	–	–	–	–

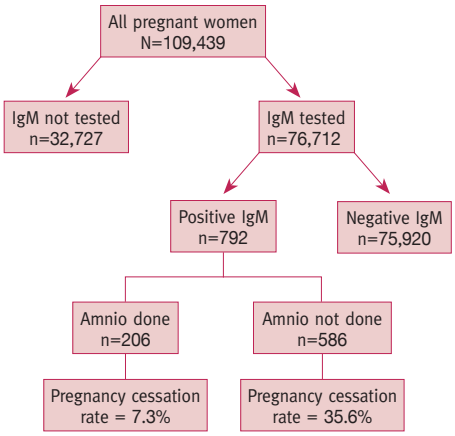
*$P < 0.05$ among the 3 groups
CMV = cytomegalovirus, IgM = immunoglobulin M

Figure 1. Avidity and rate of terminating pregnancy



Composition study population according to the risk of acquiring CMV infection and rates of termination of pregnancy in each group. CMV = cytomegalovirus, IgM = immunoglobulin M

Figure 2. Amniocentesis rate and termination of pregnancy



Composition study population, rates of amniocentesis and rates of termination of pregnancy in women who performed and did not perform amniocentesis.

IgM = immunoglobulin M, Amnio = amniocentesis

who did not undergo amniocentesis than in those who underwent amniocentesis (35.6% vs. 7.3%, $P < 0.05$). These results show that at least a third of women with CMV infection did not go through commonly available detection tests and did not continue the pregnancy to full term. As the risk for acquisition of the virus was higher (low IgG avidity), ending pregnancy prior to full workup was more common, but it existed also in women with moderate and low risk for acquiring the virus.

Counseling patients with CMV infection during pregnancy is primarily based on assessment of fetal infection by amniocentesis. When fetal infection is detected, counseling is mainly based on prenatal sonographic findings and, more recently, on prenatal MRI. Our aim was to assess whether patients with CMV infection adhere to evidence-based CMV workup prior to making decisions regarding management of the pregnancy.

Overall, the vertical transmission rate of CMV is estimated to be approximately 40% in pregnant women with primary infection and 0.2–2.2% in previously known seropositive women undergoing recurrent infection during pregnancy [1,6-8]. In our population, detection of such transmission and identification of fetal infection was conducted using polymerase chain reaction (PCR) and CMV culture. When the conditions of sampling are ideal [9], the sensitivity of prenatal diagnosis by PCR has been reported to be close to 100%. False-negative results are mainly explained in most cases by inappropriate timing of amniocentesis [10]. However, in our population, a 7–8 week interval was practiced to avoid false-negative prenatal diagnosis, and amniocentesis was well-established not before 20 weeks.

Even when timing of prenatal diagnosis is optimal, false-negative results may still occur, probably due to a late transmission of the virus. However, altogether, approximately 8% of all neonates who are born following a negative prenatal diagnosis will show viral excretion at birth. To the best of our knowledge; none of these infants so far was reported to have any symptoms [11]. But even when fetal infection is well-documented the timing acquiring the infection is critical. Lipitz and colleagues [6] examined the outcome of 71 fetuses of women with documented fetal CMV infection. Indeed, in their group, patients with first trimester infection had infants with significantly more associated complications than did patients with second-trimester infection (up to 19.7%). Aiming at correlating fetal outcome with prenatal findings, they reported that abnormal prenatal findings on ultrasound examinations were associated with increased risk of sequelae. However, when both ultrasound and MRI findings were normal, the rate of sequelae was decreased to 15.6%, and more important, partial hearing loss was the resulting disability in most cases. No patient had complete hearing loss and neuro-developmental disability was present in 3.1%. These findings are in concordance with other studies showing that in CMV-infected fetuses, normal prenatal ultrasound and MRI findings are usually associated with favorable outcome without long-term disabilities [12,13]. Sensorineural hearing loss is a common sequela of CMV infection [14-16]. There are reports however that bilateral sensorineural hearing loss, when diagnosed in early stages, can be treated with cochlear implant [6].

Preliminary results on treatment of fetal CMV infection during pregnancy were reported with valacyclovir [20] and with intravenous CMV hyperimmune globulin [18,19]. some reports on fetal outcome are promising, while others are controversial [20].

Based on the above evidence, records have shown that less than 10% of patients in the first trimester with positive CMV IgM, regardless of the avidity, will develop congenital CMV infection or sequelae after birth [21]. It is noteworthy that more than one-third of women with positive CMV IgM did not perform amniocentesis, but rather discontinued their pregnancy without further evaluation. Even if some of these pregnancy terminations were due to anomalies or signs for fetal infection detected by ultrasound, it is clear that a large portion of women with maternal CMV infection elected to terminate the pregnancy prior to full workup.

At least three studies have investigated awareness and attitudes toward congenital CMV infection among pregnant women. They assessed women in Singapore [22], France [22] and the United States [24]. Addressing the survey results of thousands of pregnant women, these studies concluded that most women were not aware of CMV and that there is a large gap between the low knowledge of CMV and the high burden of this disease. To bridge this gap, they suggested that women should receive education about congenital CMV. Lim et al. [22] also showed that women who were keen to undergo CMV testing demonstrated attitudes toward invasive testing and termination of pregnancy that were not significantly differ-

ent from those of women who refused testing. These findings are in concordance with our study demonstrating both lack of relevant knowledge regarding congenital CMV infection as well as the acceptance of termination of pregnancy option as early as maternal infection is suspected.

Coll et al. from the WAPM Perinatal Infections Working Group [25] suggested that pregnant women should not be routinely tested for CMV during pregnancy unless a primary infection is suspected or the woman is at high risk. In our study, a large percentage of women also terminated pregnancy before having amniocentesis. The magnitude of congenital CMV disease, the available reliable workup options, and the value of interventions to prevent its transmission or to decrease the sequelae need to be established before implementing public health interventions. When education and information is lacking regarding the true rates of fetal morbidity and mortality, routine screening will probably result in unnecessary termination of pregnancy. Following this route, Guerra et al. [26] showed that among 1857 consecutive pregnant women with positive screening for IgM anti-CMV, correct interpretation and communication of confirmatory test results by expert physicians may significantly reduce the rate of unnecessary abortions.

Strengths of our study are mainly in the size of the population included and in the fact that in this population, although CMV screening program is not established, over 70% of women are actually being screened. The study population represents both low- and high-income patients since the medical services during pregnancy are free and no private clinics follow pregnant patients. Our study has a few drawbacks. First, the diagnosis of pregnancy is based on a report by the primary physician. This would not take into account women who performed all the pregnancy follow-up privately. Second, for each woman we only looked at the first CMV IgM blood test. This would not include women with CMV infection later in pregnancy. Similarly, we did not separate primary from secondary infections. This separation, we believe, is less relevant as our goal was to detect trends in decision making once any (primary and secondary) maternal CMV infection is suspected. In addition, although Gindes et al. [5] reported transmission rate of 75% in women who acquired the infection after 25 weeks gestation, none of the cases had symptomatic congenital infection at birth. Accordingly, we focused on first trimester infections in which congenital infection is more severe.

Additional potential drawbacks might be in the method we used to define termination of pregnancy. Since not all terminations of pregnancy are recorded in the electronic files, if there was no record of a GCT or OGTT or if there was no birth certificate issued by the national social insurance, both of which are mandatory in pregnancy and following live birth, we assumed that in those cases the pregnancy was discontinued. Using this definition could potentially encompass pregnancies that ended for reasons other than terminations (e.g., intra-uterine fetal death) and included patients that decided to transfer to another health maintenance organization. We were not able to differentiate between spontaneous and non-spontaneous abortions. Ideally, the spontaneous abortions should be removed from both groups. We expect however that in such a large epidemiological study the cases of spontaneous abortion and other reasons for termination of pregnancy would be spread equally in both groups, including those with and without CMV infection.

CONCLUSIONS

Our data show that a large proportion of pregnancies with CMV infection do not come to term. We assume that a large proportion of these women elect to terminate the pregnancy. We believe that lack of information regarding CMV infection during pregnancy might be the cause and that correct interpretation and communication of confirmatory test results by expert physicians may significantly reduce the rate of unnecessary termination of pregnancy.

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Capsule

Marginal zone B cells control the response of follicular helper T cells in a high cholesterol diet

Splenic marginal zone B (MZB) cells, positioned at the interface between circulating blood and lymphoid tissue, detect and respond to blood-borne antigens. Nus et al. showed that MZB cells in mice activate a homeostatic program in response to a high cholesterol diet (HCD) and regulate both the differentiation and accumulation of T follicular helper (T_{FH}) cells. Feeding mice an HCD resulted in upregulated MZB cell surface expression of the immunoregulatory ligand PDL1 in an ATF3-dependent manner and increased the interaction between MZB cells and pre-T_{FH} cells, leading to PDL1-mediated suppression of T_{FH} cell motility, alteration of T_{FH} cell differentiation, reduced T_{FH} abundance and suppression of the proatherogenic T_{FH} response. Our findings reveal a previously unsuspected role for MZB cells in controlling the T_{FH}–germinal center response to a cholesterol-rich diet and uncover a PDL1-dependent mechanism through which MZB cells use their innate immune properties to limit an exaggerated adaptive immune response.

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Eitan Israeli

Capsule

Endothelial TLR4 and the microbiome drive cerebral cavernous malformations

Cerebral cavernous malformations (CCMs) are a cause of stroke and seizure for which no effective medical therapies yet exist. CCMs arise from the loss of an adaptor complex that negatively regulates MEKK3–KLF2/4 signalling in brain endothelial cells, but upstream activators of this disease pathway have yet to be identified. Tang et al. identified endothelial toll-like receptor 4 (TLR4) and the gut microbiome as critical stimulants of CCM formation. Activation of TLR4 by gram-negative bacteria or lipopolysaccharide accelerates CCM formation, and genetic or pharmacologic blockade of TLR4 signaling prevents CCM formation in mice. Polymorphisms that increase expression of the TLR4 gene or the gene encoding its co-receptor CD14 are associated with higher CCM lesion burden in humans. Germ-free mice are protected from CCM formation, and a single course of antibiotics permanently alters CCM susceptibility in mice. These studies identify unexpected roles for the microbiome and innate immune signaling in the pathogenesis of a cerebrovascular disease as well as strategies for treatment.

Nature 2017; 545: 305

Eitan Israeli

"The fool doth think he is wise, but the wise man knows himself to be a fool"

William Shakespeare (1564-1616) English poet, playwright, and actor, widely regarded as the greatest writer in the English language and the world's pre-eminent dramatist