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An observational study to assess Italian obstetrics providers' knowledge about preventive practices and diagnosis of congenital cytomegalovirus

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Abstract

Objectives: Congenital cytomegalovirus (cCMV) infection can be easily prevented by hygienic measures. Up to date the majority of the studies in literature highlighted a reduction in cCMV antenatal counseling and its prevention. Our purpose was to evaluate obstetrics providers' knowledge about cCMV infection, management and the behavioral practices to avoid it.

Methods: This is a cross-sectional survey carried out in Umberto I Hospital, "Sapienza" University of Rome between November 2019 and January 2020. We recruited 148 specialists and residents in Obstetrics and Gynecology through online anonymous multiple-choice 13-questions, 10 min-survey comparing responses between the two groups.

Results: A total of 94.6% of all participants said they always prescribe cytomegalovirus (CMV) serum screening: 73.6% of them regularly counsel about preventive practices, with specialists recording higher percentages (85.4 vs. 65.1%, $p < 0.005$). We identified a good knowledge about

the diagnostic pathway, but only 58.1% of our population knows the correct time of late amniocentesis. 12.2% of providers do not consider magnetic resonance (MRI) as a complementary exam.

Conclusions: Prevention of maternal seroconversion is crucial: even if our data show an acceptable knowledge about antenatal counseling, we encourage clinicians to firmly inform and educate women about behavioral measures.

Keywords: antenatal counseling; congenital cytomegalovirus infection; neurodevelopmental disability; preventive practices.

Introduction

Cytomegalovirus (CMV) is a worldwide prevalent double-stranded DNA virus. Congenital CMV infection (cCMV) affects 2–6/1,000 newborns, with an estimated worldwide prevalence of 0.7% and an incidence between 0.3 and 1.2% [1–3]. Around 10–15% of infected newborns are symptomatic at birth, while up to 14% of asymptomatic children develop disabilities later in life [4]. It is the leading infectious cause of sensorineural hearing loss and neurodevelopmental disability in developed countries. In literature seroprevalence for women in reproductive age ranges from 45 to 90% [5, 6]. The risk of vertical transmission following primary maternal seroconversion is estimated around 30–40%. Infection occurring in the first trimester could severely compromise fetal wellness, with a rate of neurological consequences and hearing loss of 32 and 23% respectively [2, 7]. The fetal-viral transmission rate for non-primary infection is lower, ranging around 0.2–2% [7]. The diagnostic pathway of cCMV infection consists firstly in serum maternal screening, based on the detection of IgM and IgG antibodies in a known seronegative woman. Although Italian and international guidelines recommend not to screen for cCMV infection in

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pregnancy, in good clinical practice is commonly performed at the beginning of pregnancy and repeated every month [8, 9]. Avidity determination is requested if IgG antibodies' seroconversion is detected in any trimester it occurs, in order to establish the timing of maternal infection. Secondly, serial ultrasound scans (US) are performed for fetal surveillance and magnetic resonance (MRI) could be eventually required as a complementary exam to better evaluate fetal brain damage [2, 10]. Late amniocentesis can be performed, after the 20th week of gestation and at least 6–8 weeks after maternal seroconversion, to highlight maternal-fetal transmission even if a positive result is not equivalent to symptomatic infection. According to literature, educating women about hygienic measures is the main intervention to prevent cCMV infection and is currently the best strategy to prevent cCMV disease [2, 11]. The aim of our observational cross-sectional study is to assess obstetrics providers' knowledge about cCMV infection, preventive practices and management.

Materials and methods

This cross-sectional survey was carried out in Umberto I Hospital, "Sapienza" University of Rome from November 2019 to January 2020. We recruited Italian specialists and residents in Obstetrics and Gynecology from different regions of the country through online anonymous multiple-choice 13-questions, 10 min-survey by adding a short description of the study and the informed consent to participate. We decided to use an online platform to recruit participants in order to expand the sample size; recruited participants were selected through e-mail addresses retrieved from authors' mailing lists. No compensation was offered for participation. This was an anonymous survey including non-vulnerable adults, so ethical approval was not required. This questionnaire was designed on previously published questionnaires in literature [11, 12]. In order to determinate its validity, was pilot tested with eight gynecologists with high expertise in fetal medicine at our University Hospital. Demographic information about participants, work experiences, specific knowledge regarding cCMV infection, antenatal counseling and cCMV diagnostic pathway were collected. A model of the questionnaire is illustrated in Figure 1. We investigated the work experience to differentiate residents from specialists, and among them gynecologists working in a free clinic, Hospital, University Hospital or private practice (Questions #4 – 5). Question #6 aimed to verify if providers discriminated between different levels of prevention programs. Questions ranging from #7 to #13 were designed to test participants' knowledge about CMV viral transmission, maternal serum screening and fetal surveillance (late amniocentesis, instrumental diagnostic pathway). Regarding the answers, the proposed format contained four options (one right and three false) except for Question #6, based on current literature and guidelines [2, 9, 10]. Responders were divided into two groups based on qualification experience: Group A was composed by specialists in

Obstetrics and Gynecology, Group B included resident doctors. Corrected answers were compared between the two groups.

Data analysis

Data were analyzed with SPSS statistical Software for Windows. Questionnaire's results were described by counts, frequencies and percentages. Data points, collected for this study, were analyzed using Chi-square test to compare proportions, as appropriate. Statistical significance was set at p-values lower than 0.05. All p-values presented were two sided, and associations were considered significant if the p-value was <0.05.

Results

A first e-mail was sent on November the first 2019 to 438 Gynecologists. Two remainder e-mails were sent to non-responders within 15 days. The number of participants who answered the survey was 148, for a response rate of 33.7% (148/438). All questionnaires we received were complete.

Characteristics of the study population

Group A and Group B included respectively 62 specialists (41.9%) and 86 residents (58.1%) training in University Hospital. In group A, 4.8% (3/62) of specialists worked in a free clinic, 30.6% (19/62) in Hospital, 53.2% (33/62) were private practitioners and only 11.2% (7/62) worked in a University Hospital. The majority of specialists were in the age group between 30 and 40 years (58%, 36/62), while residents ranged between 25 and 30 years (67.4%, 58/86). Among all the doctors who answered 9.5% were male (14/148) and 90.5% were female (134/148). Demographic characteristics are summarized in Table 1.

Answers to the questionnaire

Participants were interviewed about preventive program levels and cCMV screening, diagnosis and counseling. The majority of them (98%, 145/148) knew the difference between primary, secondary and tertiary prevention strategies, with no significant differences between the two groups (97 vs. 98.8%; $p=0.37$). 94.6% (140/148) of all responders said they always prescribe CMV serum screening even if our health system does not cover cost for CMV screening in pregnancy, with similar percentages in the two groups (97 vs. 93%; $p=0.31$). Only 2% (3/148) of participants rarely prescribe CMV serum screening and we found they were residents. 109/148 (73.6%) gave always

Where do you usually work?

- Free Clinic
- Public Hospital
- University hospital
- Private practitioner

What is a primary prevention of an infectious disease?

- Management of a diseases' complications and deficits-functional disabilities that could result in a pathological or dysfunctional state
- Early diagnosis of a pathology, that could allow an early intervention
- Adoption of action-behaviours able to avoid or reduce the onset and development of a disease or an unfavourable event. It aims to reduce the risk factors that could result in an increased incidence of a pathology

In your clinical practice, do you prescribe screening for early pregnancy Cytomegalovirus (CMV) infection even if it is not included in the ticket-free services?

- Yes, always
- Often
- Rarely
- No, I don't

In your clinical practice, do you give any information to the patients about how to prevent CMV infection?

- Yes, always
- Often
- Rarely
- No, I don't

How is the CMV virus transmitted?

- Through body fluids from infected subjects (saliva, urine and others)
- By sexual intercourses
- By skin contact
- I don't know

In case of positive IgM and IgG which test is useful to discriminate a recent infection from a previous one?

- Serum electrophoresis
- IgG Avidity test
- CMV DNA research
- None of the above

When is it useful to perform amniocentesis for CMV-DNA in the amniotic fluid to verify the transplacental passage?

- Always in case of previous infection
- In case of primary infection with positive IgG and IgM and low avidity, not before the 20th week of gestation
- In case of primary infection always before the 20th week of gestation
- Only in the third trimester of pregnancy

How many weeks after seroconversion is it useful to search for the virus in the amniotic fluid?

- 2
- 4–6
- 6–8
- 10

In case of congenital CMV infection which is the additional diagnostic investigation that you should perform to investigate the fetal anatomy and at what gestational age is it indicated?

- MRI scan between the 28th and 32nd week of gestation
- CT scan during the 26th week of gestation
- Only ultrasound surveillance
- None of the above

Figure 1: Model of the questionnaire proposed to investigate obstetrics providers' knowledge of congenital cytomegalovirus (cCMV). Questions ranging from #5 to #13.

information on preventive practices and hygienic measures, with a higher percentage in specialist's group (85.4 vs. 65.1%, $p < 0.005$); 25/148 (16.9%) of responders said they often did; 11/148 (7.4%) rarely counseled and 3/148 (2%) never advised women about prevention of cCMV. We identified a good knowledge about viral transmission

(99.3%, 147/148) and serum tests to evaluate a primary infection (98%, 145/148), equally partitioned between the two groups (98.4 vs. 100%; $p = 0.23$ and 98.4 vs. 97.7%; $p = 0.76$ respectively). Regarding the diagnostic pathway to confirm fetal viral infection, 8.1% (12/148) thought that CMV-DNA could be detected in the amniotic fluid before

Table 1: Demographic characteristics of our sample size.

	n, (%)	Mean age, years (%)
Residents	86/148, (58.1%)	25–30, (67.4%)
Specialists	62/148, (41.9%)	30–40, (58%)
Specialists practice location		
Free clinic	3/62, (4.8%)	
Public hospital	19/62, (30.6%)	
Private practitioner	33/62, (53.2%)	
University hospital	7/62, (11.2%)	
Sex		
Male	14/148, (9.5%)	
Female	134/148, (90.5%)	

the 20th week of gestation, 1.4% (2/148) considered amniocentesis only in the third trimester of pregnancy, 90.5% (134/148) of gynecologists correctly answered regarding the timing of late amniocentesis. Despite this, only 58.1% (86/148) exhibited knowledge of how many weeks after maternal seroconversion the test should be performed; among them, 59.3% (51/86) were residents and 40.7% (35/86) were specialists. No differences were found when comparing for these topics in cCMV diagnosis (90.3 vs. 90.7%; $p=0.93$ and 56.4 vs. 59.3%; $p=0.72$ respectively). Few participants do not consider MRI as a complementary exam in case of US suspicion in cCMV infection (12.2%, 18/148): the majority of subjects (87.8%, 130/148) correctly knew that MRI performed in the third trimester (between the 28th and the 32nd week of gestation) could better highlight central nervous system (SNC) anomalies, and we found a higher knowledge in Group B (79 vs. 94%;

Table 2: Summary of questionnaire and responses of all participants.

	Correct, n (%)
Knowledge about infection primary prevention	(145/148), 98%
Knowledge about CMV serum screening prescription	(140/148), 94.6%
Knowledge about giving information on preventive practices and hygienic measures	(109/148), 73.6%
Knowledge about viral transmission routes	(147/148), 99.3%
Knowledge about serum tests to evaluate a primary CMV infection	(145/148), 98%
Knowledge about the diagnostic pathway to assess fetal infection	(134/148), 90.5%
Knowledge about timing to perform diagnostic methods after seroconversion	(6/148), 58.1%
Knowledge about additional diagnostic investigations	(130/148), 87.8%

CMV, cytomegalovirus.

Table 3: Knowledge of cCMV infection among specialists and residents.

	Group A (n=62) n (%)	Group B (n=86) n (%)	p-Value
Knowledge about infection primary prevention	60/62 (96.7%)	85/86 (98.8%)	0.37
Gynecologists always prescribing CMV serum screening	60/62 (96.7%)	80/86 (93%)	0.31
Gynecologists always counseling about preventive practices for cCMV	53/62 (85.4%)	56/86 (65.1%)	0.005
Knowledge about viral transmission routes	61/62 (98.4%)	86/86 (100%)	0.23
Knowledge about serum tests to evaluate a primary CMV infection	61/62 (98.4%)	84/86 (97.7%)	0.76
Knowledge about the diagnostic pathway to assess fetal infection	56/62 (90.3%)	78/86 (90.7%)	0.93
Knowledge about timing to perform diagnostic methods after seroconversion	35/62 (56.4%)	51/86 (59.3%)	0.72
Knowledge about additional diagnostic investigations (MRI)	49/62 (79%)	81/86 (94%)	0.005

CMV, cytomegalovirus; MRI, magnetic resonance.

$p=0.005$). A summary of questionnaire and responses are provided in Tables 2, 3.

Discussion

To our knowledge, this is the first observational survey proposing to investigate Italian obstetrics providers' awareness about cCMV infection and how to prevent it. Some current Guidelines, including Italian ones, do not recommend universal maternal serum screening as cost-ineffective except for the risk population including pregnant women with influenza-like symptoms, seronegative women working as child-care, pregnant women with a child in a nursery or when US suspicion of CMV infection occurs [8, 9, 10–13]. Moreover, CMV screening is not covered by public health system in our country. Several Authors discussed the cost-effectiveness of universal CMV maternal serum screening, assuming that preventive practices and serum screening may reduce the long-term costs of cCMV infection [7, 14]. Despite this, our data suggest that the majority of obstetrician and gynecologists prescribe CMV serum screening in order to recognize seronegative pregnant women, in contrast with previous published studies [1, 11, 12, 15, 16]. In particular a study by Cordier et al. conducted in France showed that 64% of health

care providers do not consider CMV screening as a mandatory recommendation [16]. Shand et al. demonstrated in a survey among Australian maternity health providers a poor knowledge about cCMV prevention and serum screening: less than 8% of questionnaire responders [11]. The Centers for Disease Control and Prevention (CDC) reported a rate of only 44% of clinicians correctly conscious about cCMV in United States [12]. According to literature, preventive practices and hygienic measures are the mainstay to reduce cCMV infection rate due to primary maternal infection. Educating pregnant women is strongly recommended even if a lack of knowledge and gap of confidence about cCMV infection is reported and few obstetrics and gynecologists routinely advice on preventive practices [1, 11, 12, 17, 18]. Our data are encouraging regarding this point: we highlighted a high percentage, more than 70%, of health care providers in Italy counseling pregnant women about hygienic measures during medical examination. Despite the overall good knowledge, gaps in certain areas of cCMV screening emphasize the importance of education and training for both specialists and residents in order to continue improving. Gynecologists should also inform pregnant women about fetal surveillance (US and MRI) and the invasive procedures to ascertain fetal – viral transmission if cCMV infection occurs. Up to date late amniocentesis is necessary to highlight CMV vertical transmission especially for primary maternal infections in the first trimester. In our analysis, we found the majority of participants reported good awareness about late amniocentesis, although just over half of them know correct timing of the procedure. Our providers showed a good knowledge about the instrumental pathway to surveil the fetus as recommended by experts' reviews [7, 19]. US may be helpful to highlight suspicious findings of cCMV infection of the SNC such as ventriculomegaly, parenchymal calcification, microcephaly or septation and extra-SNC: placentitis (placenta thickness > 40 mm), hepato-splenomegaly, intra-uterine growth restriction (IUGR) [1, 10, 20]. MRI, as a complementary exam, is important to study the white matter and to diagnose anomaly of gyration and sulcation. Leruez-Ville M et al. recently underscored the main role of US and MRI in depicting brain anomalies, with a reported sensitivity of 95% [20]. Consistent with recent literature, our results show that both groups (79 and 94% respectively) extensively use MRI to better define CNS involvement in cCMV. This widespread adoption of MRI emphasizes the pivotal role of this exam despite significant difference in its utilization between specialists and residents. This study presents some limitations. First, we decided to design an online survey and data quality may be affected by Internet consultation and cross talk between participants: we were unable to avoid this bias as providers were not supervised during questionnaire collection. Second, our sample size was small with a low response

rate (33.7%) so further studies with larger samples are required to better assess cCMV knowledge among obstetrics providers. Lastly, although we sampled providers with different experience (specialists and residents) the two groups were not homogeneous. In conclusion, cCMV infection is still a challenge for health care providers. Up to date prevention of maternal seroconversion is mandatory as guidelines do not still recommend universal serum maternal screening and no proven therapies exist to prevent or to treat fetal vertical transmission [21, 22]. We suggest that clinicians must focus on primary preventive measures during pregnancy so as in periconceptional consultation, educating women on hygienic behaviors such as hand washing after body fluid contact or not sharing utensils with young children to reduce the rate of seroconversion.

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