

## Screening for Cytomegalovirus: An Analysis of Guidelines

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### Abstract

**Background:** Congenital cytomegalovirus is the most prevalent cause of infection-related neurological impairment. Screening for cytomegalovirus is in practice offered to many women in the western world. In this study we present an overview of official guidelines concerning screening/non-screening for cytomegalovirus worldwide.

**Methods:** An Internet search for guidelines concerning screening for cytomegalovirus during pregnancy worldwide.

**Results:** From the 24 guidelines we found worldwide, there were only 7 with a guideline regarding screening for cytomegalovirus during pregnancy. Six of them gave the following advice: there is insufficient evidence to support routine screening in all pregnant women for cytomegalovirus infection. Currently there is no routine screening for cytomegalovirus recommended during pregnancy. The "Federaal kenniscentrum voor de gezondheidszorg" (KCE) gave the extra advice that performing a single serological test prior to pregnancy can be useful as it may encourage (non-immune) women to take preventive measures and it can reassure (at least partially) those who are immune. They also recommend discussing primary prevention measures with pregnant women to reduce the risk of cytomegalovirus infection. The American Society for Reproductive Medicine recommends routinely screening for cytomegalovirus during the pre-conceptual screening of the female recipient of sperm donation.

**Conclusion:** No guideline recommends routine screening for cytomegalovirus during pregnancy.

**Keywords:** Congenital cytomegalovirus; Screening during pregnancy; Guidelines

**Abbreviations** ASRM: American Society of Reproductive Medicine; CMV: Cytomegalovirus; KCE (Federaal Kenniscentrum voor de Gezondheidszorg); TOP: Termination of Pregnancies

### Introduction

Congenital cytomegalovirus (CMV) is the most prevalent infection-related cause of neurological damage (impaired development, mental retardation, and neurosensory hearing deficit) since implementation of universal rubella vaccination [1].

It occurs in 0.6-0.7% of all new-borns. This equates to a birth prevalence of approximately 7/10,000 affected infants, not dissimilar to conditions for which screening is currently recommended, such as early onset groups B streptococcus infection, with a prevalence of 4.3/10,000 and Down syndrome with a birth prevalence of 11/10,000 births [2]. The probability of intrauterine transmission following primary infection is much higher than after secondary infection, with a transmission rate of respectively 30-40% and 1%. Fetal infection does not equate to an affected fetus; 10-15% of the affected fetuses will have symptoms at birth, with a neonatal mortality rate of 20%, whereas 5% to 15% of the asymptomatic infected neonates will develop sequelae later. Children with congenital CMV infection following first trimester infection are more likely to have central nervous system sequelae, whereas infection acquired in the third trimester has a high rate of

intrauterine transmission but a favourable outcome [3]. As discussed by Walker et al. [1] "Universal screening for CMV to identify seronegative women at the beginning of pregnancy could potentially reduce the burden of congenital CMV in one of three ways. The risk of acquiring the infection during pregnancy has been shown to be reduced by institution of simple hygiene measures (primary prevention). Among women who seroconvert during pregnancy, CMV hyper immune globulin (CMV HIG) shows promise in reducing the risk of perinatal transmission (secondary prevention), and CMV HIG and/or antivirals may be effective in reducing the risk of clinical sequelae among those known to be infected (tertiary prevention). The reports from these studies have reignited interest in universal screening for CMV, but against the potential benefit of these exciting therapies need to be weighed the challenges associated with the implementation of any universal screening in pregnancy.

These include: the optimal test and timing of screening, to maximize detection; an approach to the management of equivocal results, and the cost effectiveness of the proposed screening program [1]. These arguments in favour and against universal screening result in contradictory advice given to pregnant women. For example, although routinely screening in France is not recommended, 14% of the hospitals were still conducting this screening in 2012 [4]. In this study we want to present an overview of current screening/non-screening strategies worldwide.

## Materials and Methods

First, we started searching for general guidelines in Europe and the USA by entering the search terms: guideline and screening in the web search engine Google and Google scholar and in PubMed. Afterwards we started looking more specific for guidelines for gynaecology and obstetrics and for paediatrics in Europe, USA, Canada, Australia and worldwide by using the additional search terms: pregnancy and prenatal.

While browsing through the various guidelines we used the search terms: cytomegalovirus, CMV, screening, pregnancy, congenital infections and infections.

The guidelines were required to be in Dutch, English, French, German or Spanish, but no other language. We assessed the guidelines on the 4th of February 2016.

## Results

Table 1 gives an overview of the various guidelines we consulted during the search for guidelines regarding screening for CMV during pregnancy.

<b>General guidelines in Belgium</b>
KCE (Federaal kenniscentrum voor de gezondheidszorg)
<b>General guidelines in Europe and USA</b>
NICE (National Institute for Health and Care Excellence) NIH (National Institutes of Health)
<b>Specific guidelines for gynaecology and obstetrics in Europe, USA, Canada and Australia</b>
RCOG (Royal college of obstetricians and gynaecologists, UK) EAPM (European Association of perinatal medicine) EBCOG (European board and college of obstetrics and gynaecology) SGGG (Gynécologie Suisse) CNGOF (College Nationale des Gynécologues et obstétriciens français) DGGG (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe) FIGO (International Federation of Gynecology and Obstetrics) ICEA (International childbirth education association) ACOG (The American Congress of Obstetricians and gynecologists) CAOG (Central Association of Obstetricians and gynecologists, USA) ASRM (American Society for Reproductive Medicine) SRI (Society of Reproductive investigations) AHRQ (Agency for Healthcare Research and Quality, USA) Obgyn.net (Obstetrics/Gynaecology, USA) SMFM (Society for Maternal, Fetal Medicine, USA) SOGC (Society of Obstetricians and Gynaecologists of Canada) RANZCOG (The Royal Australian and New Zealand College of Obstetricians and Gynaecologists) WAPM (World Association of Perinatal Medicine)
<b>Specific guidelines for paediatrics in Europe</b>
ESPR (European Society for Pediatric Research) EFCNI (European Foundation for the Care of Newborn Infants) ESN (European Society for Neonatology)

**Table 1:** Guidelines.

Table 2 shows the search step by step. Seventeen out of 24 guidelines were excluded because one was not able to access it without being a

member and the other 16 because they hadn't a topic about screening for CMV during pregnancy.

Guideline	Search	Results
KCE	Search: Screening CMV ? Which investigations are recommended in pregnancy? Publication - KCE Reports 248A - Good Clinical Practice (GCP)-2015 ? page 16	Guideline

NICE	NICE guidance ? conditions and diseases ? fertility, pregnancy and childbirth ? pregnancy	Guideline
NIH	Health information ? publication list ? search: Screening during pregnancy ? 31 hits Search: guidelines ? clinical practice guidelines	No guideline
RCOG	Search: screening CMV ? course "an update on infections during pregnancy" Guidelines and research services ? guidelines ? by guideline types: all guidelines, by keyword: CMV ? 0 matches Guidelines and research services ? guidelines ? by guideline types: all guidelines, by keyword: screening AND pregnancy AND infections ? 3 matches Guidelines and research services ? guidelines ? by guideline types: all guidelines, by keyword: infection ? 53 matches Guidelines and research services ? guidelines ? by guideline types: all guidelines, by keyword: Cytomegaly virus ? 6 matches Guidelines and research services ? guidelines ? by guideline types: all guidelines, by keyword: screening ? 31 matches Guidelines and research services ? guidelines ? by guideline types: all guidelines, by keyword: pregnancy AND infections ? 37 matches	No guideline
EAPM	Guidelines ? guidelines by EAPM ? coming soon Guidelines ? guidelines endorsed bij EAPM	No guideline
EBCOG	Search: guideline ? standards of care for women's health in Europe ? obstetric and neonatal service 2014	No guideline
SGGG	Informations d'experts ? guidelines Informations d'experts ? avis d'expert Informations d' experts ? protocoles d'information	No guideline
CNGOF	Pratique Clinique ? guidelines	No guideline
DGGG	Publikationen ? suche: richtlinie für das screening in der Schwangerschaft	No guideline
FIGO	Search: guidelines screening during pregnancy ? 82 hits Publications and resources ? international journal of gynecology and obstetrics ? free to view Publications and resources ? figo three-year rapport ? 2012 – 2015 Publications and resources ? project publications ? FIGO committee for safe motherhood and newborn health ? review of tools and guidelines	No guideline
ICEA	No guidelines	No guideline
ACOG	Search: screening CMV ? guidelines ? 2 results ? Cytomegalovirus, Parvovirus B19, Varicella Zoster, and Toxoplasmosis in Pregnancy ? access members only	No guideline
CAOG	No guidelines	No guideline
ASRM	Site search ? cytomegalovirus ? Recommendations for gamete and embryo donation: a committee opinion	Guideline
SRI	No guidelines	No guideline
AHRQ	Guidelines ? by topic: female urogenital diseases and pregnancy complications ? pregnancy complications ? pregnancy complications infectious ? cytomegalovirus infection in pregnancy	Guideline
Obgyn.net	Pregnancy and birth ? search: cytomegalovirus: congenital cytomegalovirus infection Search: guideline	No guideline
SMFM	Publications/guidelines ? search: category: guidelines, keyword: cytomegalovirus ? no results Publications/guidelines ? search: category: guidelines, keyword: infection ? 3 hits	No guideline
SOGC	Clinical practice guidelines ? infectious disease ? cytomegalovirus infection in pregnancy	Guideline
RANZCOG	College statements and guidelines ? category obstetrics ? management of perinatal infectious ? p.5 cytomegalovirus	Guideline
WAPM	Guidelines ? recommendations and guidelines for perinatal medicine ? chapter 14. Infectious disease in pregnancy	Guideline
ESPR	Journal ? pediatric research ? advanced search: screening AND pregnancy AND cytomegalovirus AND guideline, 2005 – now	No guideline

EFCNI	Pregnancy ? infectious diseases ? cytomegalovirus	No guideline
ESN	No guidelines	No guideline

**Table 2:** Search step by step.

Worldwide there were only 7 guidelines with a guideline regarding screening for CMV during pregnancy. Of these, there was one from Belgium, one from the UK, one from Canada, two from the US, one from Australia and one global. Six of them gave the following advice: there is insufficient evidence to support routine screening in all pregnant women for cytomegalovirus infection. Currently there is no routine screening for CMV recommended during pregnancy [5-10].

The KCE gave the extra advice that performing a single serological test prior to pregnancy can be useful as it may encourage (non-

immune) women to take preventive measures and it can reassure (at least partially) those who are immune. They also recommend discussing primary prevention measures with pregnant women to reduce the risk of cytomegalovirus infection [5]. The ASRM recommends routinely screening for CMV during the preconceptional screening of the female recipient of sperm donation [11]. The detailed results of the various guidelines are listed in Table 3.

Guideline	Recommendation	Strength of recommendation	Level of evidence
KCE	<p>There is insufficient evidence to support routine screening in all pregnant women for cytomegalovirus infection. A single serological test preferably prior to pregnancy may be useful as it may encourage (non-immune) women, to take preventive measures and it can reassure (at least partially) those who are immune. [KCE 2015] In case serological tests for CMV infections are offered, pregnant women and their partners should be informed in detail about all the possible consequences and asked for their consent [KCE, 2015].</p> <p>Despite a lack of clearly proven benefit, discuss primary prevention measures with pregnant women to reduce the risk of cytomegalovirus infection, such as [new KCE 2015]: - Regularly wash your hands, especially after contact with saliva or urine of small children (e.g. changing diapers) or wear protective gloves when changing diapers or handling children's dirty laundry.</p> <p>- Clean toys, countertops, and other surfaces that come into contact with young children's bodily fluid.</p> <p>More data on the diagnostic accuracy of serological tests, value of amniocentesis and imaging, clinical evolution of infected infants and harmful effects for healthy pregnancies need to be collected in the Belgian context in order to evaluate the benefits and harms, both on the short term and on the long term, of CMV screening appropriately. [new KCE 2015]</p>	<p>Weak</p> <p>Strong</p> <p>Not Applicable</p>	<p>Very low</p> <p>Very low</p> <p>Not Applicable</p>
NICE	The available evidence does not support routine cytomegalovirus screening in pregnant women and it should not be offered.	/	/
ASRM	Evaluation of the female recipient of sperm donation: Standard preconceptional screening, testing, and counseling: Cytomegalovirus (CMV) antibody (IgG and IgM). For women who test positive for active infection (positive urine or throat culture or paired serum samples demonstrating a four-fold rise in IgG antibody and IgM antibody at least 30% of the IgG level), attempts to conceive should be postponed until they no longer exhibit active infection, owing to the risk of transmitting the infection to their fetus and the serious potential consequences of fetal CMV infection.	/	/
AHRQ	Routine screening of pregnant women for CMV by serology testing is currently not recommended.	B*	III**
SOGC	Routine screening of pregnant women for CMV by serology testing is currently not recommended.	B*	III**
RANZCOG	Routine antenatal CMV screening not generally recommended in Australia but is sometimes done. Possible indications for antenatal testing are: History suggestive of CMV illness, abnormalities on routine antenatal ultrasound (SEE ALGORITHM 2), exposure to known CMV infected individual e.g. partner with acute CMV infection.	/	/
WAPM	Screening not recommended as routine.	/	/

\*B: there is fair evidence to recommend the clinical preventive action

\*\*III: opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees

**Table 3:** Recommendations.

## Discussion

Worldwide, there are not many guidelines regarding screening for CMV during pregnancy. The ones that exist are all very short and unambiguously about their recommendation: routine screening for CMV is not recommended during pregnancy.

While no single guideline recommends routine screening for CMV during pregnancy, doctors still screen frequently for CMV infection in the blood, especially in Europe and Israel. For example, although routinely screening in France is not recommended, 14% of the hospitals were still conducting this screening in 2012. [1,2,4,12] One of the reasons is the anxiety of the clinicians to miss the diagnosis and the anxiety and the pressure of the parents. Another reason is the legal system in some countries. A women employed in a sector with young children, may not work during her pregnancy by the occupational health if she is negative for CMV, since small children are a major source of contamination. Soper showed that in a survey of 9 day-care centers in the USA and Sweden, 22-72% of the children were shedding CMV in their urine and saliva [13].

The evidence for these recommendations is low, but still strongly recommended. Systematic screening of pregnant women could lead to: anxiety, an increased number of amniocentesis and therefore of miscarriages, with possible medico-legal implications, and an unjustified number of termination of pregnancies that would be performed even in the absence of a bad prognosis such as ultrasound markers. TOP may be restricted in some countries after certain weeks of pregnancy and such policy may be difficult to undertake [2]. The KCE strongly recommends discussing primary prevention measures with pregnant women to reduce the risk of cytomegalovirus infection and reinfection. Even with a reinfection, there is a 1% transmission ratio to the fetus. Congenital CMV usually occurs in the second and third pregnancy. Especially young mothers who already have one or more children (1-6y) at home must be careful. Further research is needed into the ideal screening method, follow-on method and possible treatment for congenital CMV before universal screening can be offered.

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