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Clinical and economic impact of universal screening for cytomegalovirus infection among pregnant women in Italy

S. ORNAGHI[1,2], L. ZAMMARCHI[3,4], F. FERNICOLA[1], M. TAVANTI[3], V. P. DE CHAURAND[1,2] and S. BOCCALINI[5]

[1]*Department of Obstetrics, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy;* [2]*University of Milano-Bicocca School of Medicine and Surgery, Monza, Italy;* [3]*Department of Clinical and Experimental Medicine, University of Florence, Florence, Italy;* [4]*Infectious and Tropical Diseases Unit, Careggi University Hospital, Florence, Italy;* [5]*Department of Health Sciences, University of Florence, Florence, Italy*

KEYWORDS: congenital; costs; cytomegalovirus; effectiveness; pregnancy

ABSTRACT

Objective *To evaluate the clinical and economic impact of universal screening for cytomegalovirus (CMV) in pregnant women in Italy, with valacyclovir (VCV) therapy in the case of maternal primary CMV infection, compared with no screening.*

Methods *We developed a decision-analytic model using a deterministic decision tree and compared the no-screening strategy (Scenario 1) with universal screening until 13 + 6 weeks' gestation (Scenario 2), and universal screening until 23 + 6 weeks' gestation (Scenario 3) as recommended by the Italian National Health Service. The model was applied in a hypothetical population of 400 000 pregnant women, representative of the annual number of women giving birth in Italy. Only women susceptible to primary CMV infection were considered, in whom CMV screening by serological testing (IgG/IgM testing ± IgG avidity), followed by VCV treatment (8 g/day) in the case of primary CMV infection, is recommended. Outcomes included the numbers of primary maternal CMV infections diagnosed, fetal congenital CMV (cCMV) infections, terminations of pregnancy (TOPs) and symptomatic and asymptomatic neonatal cCMV infections, and the cost per symptomatic cCMV case avoided (in Euros (€)) from the perspective of the Italian National Health Service.*

Results *Universal screening until 13 + 6 weeks' gestation would identify 910 maternal primary CMV infections. Compared with no screening, it would prevent 92% of symptomatic cCMV infections (183 vs 15 cases) and prevent 70% of TOPs (33 vs 10 cases). Extending the universal screening period to 23 + 6 weeks' gestation would result in 280 additional diagnoses of maternal primary CMV infection and a further 2% and 9% reduction in symptomatic cCMV infections and TOPs, respectively. Both screening strategies would increase costs by approximately €7 million compared with Scenario 1, with a cost per symptomatic cCMV case avoided of ∼€45 500 for Scenario 2 and ∼€44 400 for Scenario 3.*

Conclusion *Universal serological CMV screening in pregnancy until 24 weeks' gestation, with VCV treatment in the case of maternal primary infection, substantially reduces the burden of cCMV-related disabilities and appears economically justifiable in the Italian healthcare context. These findings may inform policy decisions in countries with a similar CMV seroprevalence and National Health Service.* © *2026 The Author(s). Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Congenital cytomegalovirus (cCMV), affecting approximately 0.2–1% of neonates worldwide, is the most common congenital viral infection and the leading cause of non-genetic sensorineural hearing loss (SNHL) and lifelong neurological disability[1–6].

Maternal cytomegalovirus (CMV) infection in pregnancy can be either primary or non-primary[3]. Primary CMV infection has an overall transplacental transmission rate of 35%, ranging from 21% in the periconception period to 66% in the third trimester[5]. CMV seroprevalence among women of childbearing age in Italy is 65–70%[7–11], thus leaving 30–35% of women at risk of acquiring a primary CMV infection during pregnancy. cCMV-related sequelae are predominantly

Correspondence: Prof. S. Ornaghi, Department of Obstetrics, Fondazione IRCCS San Gerardo dei Tintori, University of Milan-Bicocca School of Medicine and Surgery, Via Pergolesi 33, 20900 Monza, Italy (e-mail: sara.ornaghi@unimib.it)

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associated with infection during the first trimester of pregnancy[5,12,13]; however, maternal CMV infection during the second trimester has also been linked to SNHL and mild developmental disabilities in infants[12–14].

Recently, valacyclovir (VCV) has been proven effective in decreasing the risk of cCMV infection in pregnancies with primary maternal CMV infection[15–20]. In Italy, this led to the inclusion of VCV in the Law 648/96 list in December 2020, which allows complete reimbursement by the Italian National Health Service (NHS) for the use of VCV in pregnant women with a primary CMV infection < 24 weeks' gestation or in pregnancies with a confirmed mildly or moderately symptomatic fetal CMV infection[21,22]. Considering this, and the fact that primary CMV infection is often clinically asymptomatic but can be diagnosed through maternal serological testing, a screening strategy for CMV during pregnancy appears pivotal for timely diagnosis and VCV therapy[21,22].

In December 2023, the Italian NHS, on behalf of the Ministry of Health, published an updated national guideline on uncomplicated pregnancy, including a recommendation in favor of universal serological screening for CMV infection until 24 weeks' gestation[23]. Italy is one of few countries in which such a screening policy has been introduced on a national level[24–31]. Yet, no economic assessment of this policy has been conducted specifically.

The aim of our study was to assess the clinical and economic impact of universal maternal CMV screening in Italy, with VCV therapy in the case of primary maternal CMV infection, until 13 + 6 weeks' and until 23 + 6 weeks' gestation, and to compare these two screening strategies with a no-screening strategy.

METHODS

Study design

We built a deterministic decision-tree model to perform clinical and economic evaluation of three different screening strategies for maternal primary CMV infection in a hypothetical population of 400 000 pregnant women, which is representative of the annual number of women giving birth in Italy[32]. Only women susceptible to primary CMV infection were considered, in whom CMV screening by serological testing (IgG/IgM testing with or without IgG avidity), followed by VCV treatment (8 g/day) in the case of primary CMV infection, is recommended. The 2022 Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist was followed[33,34]. No ethical approval was required for this work as it comprised a theoretical cohort with no involvement of human participants.

The strategies evaluated were: (i) no screening (Scenario 1) (Figure 1), as suggested by international scientific societies and the National Health Institutes[24–29]; (ii) universal screening until 13 + 6 weeks' gestation (Scenario 2) (Figure 2), as recommended by the Hellenic Society of Obstetrics and Gynecology[30], the French National Authority for Health (Haute Autorité de Santé)[31,35] and the 2024 European Congenital CMV Infection Initiative (ECCI) guideline[36]; and (iii) universal screening until 23 + 6 weeks' gestation (Scenario 3) (Figure 3), as recommended by the 2023 Italian NHS guideline on uncomplicated pregnancy[23]. The three scenarios are detailed below.

In Scenario 1 (no screening), only fetuses with an abnormal ultrasound finding would be detected incidentally during routine second-trimester ultrasound examination. Hence, only pregnancies with observed fetal anomaly would be tested for maternal CMV serology (IgG and IgM) and IgG avidity and undergo amniocentesis to diagnose cCMV. Management would include possible termination of pregnancy (TOP) or, in the case of pregnancy continuation, Level-II ultrasound scans, magnetic resonance imaging (MRI) and urine polymerase chain reaction (PCR) testing to assess CMV DNA at birth.

In Scenario 2 (universal screening until 13 + 6 weeks' gestation with VCV therapy), all women would undergo a single CMV serological test within 13 + 6 weeks' gestation. In the case of positive IgG and IgM antibodies, the laboratory would automatically determine IgG avidity, and primary CMV infection would be confirmed in the case of a low or intermediate value. Women diagnosed with primary CMV infection would be counseled, treated with VCV[21] and offered amniocentesis. Management would include possible TOP or, in the case of pregnancy continuation, Level-II ultrasound scans, fetal MRI and urine PCR testing for CMV DNA at birth. This scenario also considers the possibility of primary CMV infection between 14 + 0 and 23 + 6 weeks' gestation, which would not be diagnosed via screening or treated with VCV. This possibility was included in the calculation of the total disability outcomes of Scenario 2 (Figure 2b)[12,14].

For Scenario 3 (universal screening until 23 + 6 weeks' gestation with VCV therapy), all women would undergo CMV serological testing within 23 + 6 weeks' gestation[23], for a total of four tests: one test < 13 + 6 weeks; one test between 14 + 0 and 19 + 6 weeks; and two tests between 20 + 0 and 23 + 6 weeks. Management of those diagnosed with primary maternal CMV infection would include treatment with VCV[21], possible amniocentesis, Level-II ultrasound scans, fetal MRI and urine PCR testing for CMV DNA at birth.

The data used to evaluate these strategies were drawn from previously published studies[7–10,14–16,20,37–52] and unpublished original datasets developed within a multicenter Italian study on CMV infection in pregnancy (MEGAL-ITALI study[20,21]) (Table 1). Symptomatic status after birth was defined according to European guidelines[36].

Key model assumptions

Additional assumptions were: (i) the timing of initiation and discontinuation of VCV treatment varies according to the timing of CMV infection and amniocentesis result (Table S1); (ii) once VCV treatment is initiated, blood-work follow-up, including complete blood count and liver

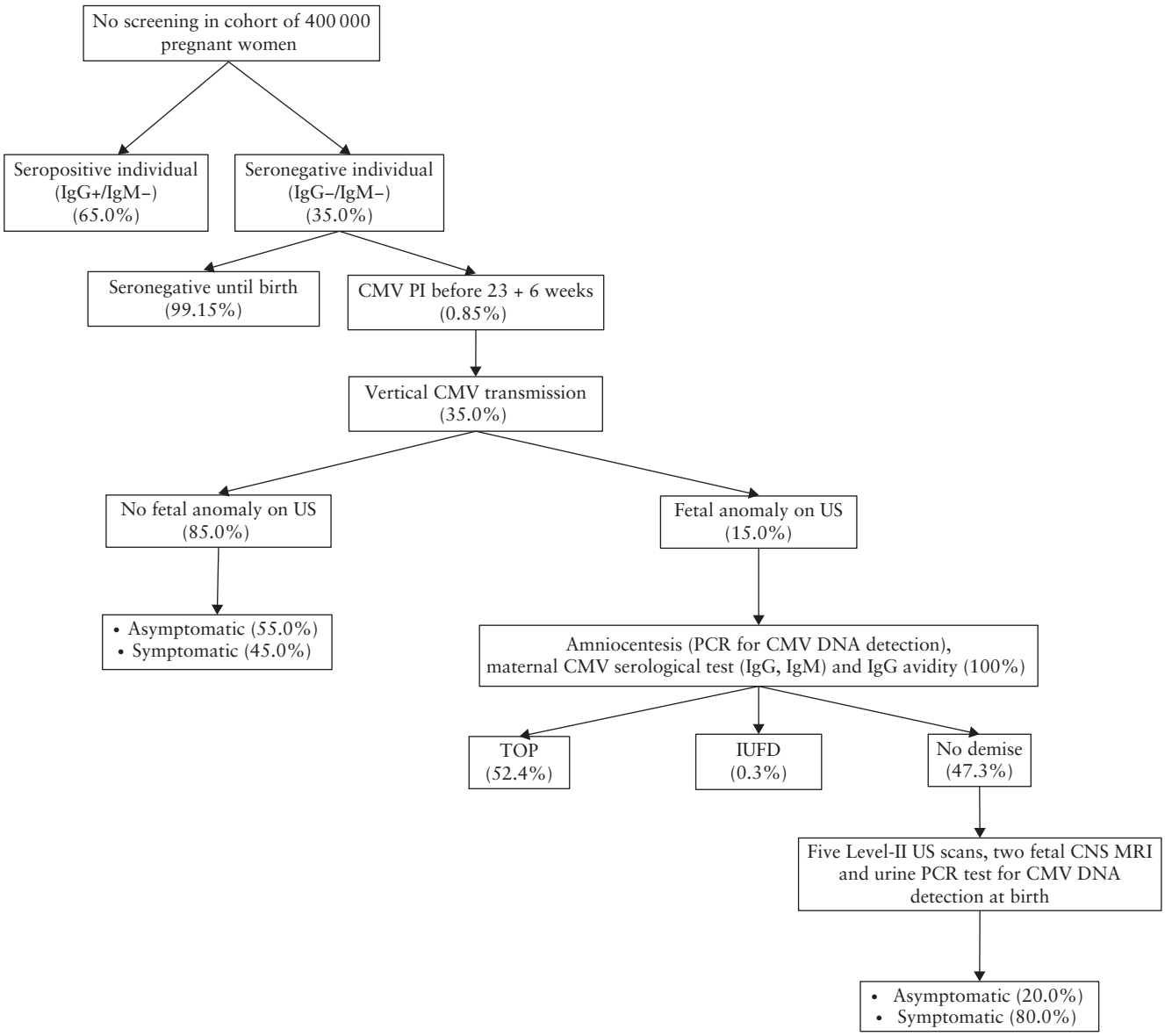

Figure 1 Flowchart showing outcomes of Scenario 1 (no serological screening for cytomegalovirus (CMV)) in hypothetical population of 400 000 pregnant women in Italy. CNS, central nervous system; IUFD, intrauterine fetal death; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PI, primary infection; TOP, termination of pregnancy; US, ultrasound.

and renal function, is undertaken in the treated woman, as described previously[21,22]; (iii) recommendations regarding hygiene counseling to decrease the risk of CMV infection are applied equally in each scenario[23]; (iv) according to Italian law, TOP can be performed $\leq$ 22 weeks' gestation if the amniocentesis result is positive for CMV DNA; and (v) if cCMV is diagnosed at birth, specific follow-up is conducted and antiviral treatment may be initiated[36]. The likelihood of TOP following a diagnosis of cCMV by amniocentesis was based on available estimates[20,39].

Costs

To determine costs for the model, we assumed that interventions were implemented in 2024, thus reflecting the healthcare and economic context of that year. Adopting the perspective of the Italian NHS, only direct medical costs were considered (Table S2). The cost analysis consisted of measuring the physical quantities of the resources consumed individually (serological testing, amniocentesis, ultrasound examination, MRI, medical consultations) in each of the strategies, combined with a monetary assessment based on the tariffs of the Italian NHS. To calculate average costs, we assessed the pricing schedules of two Italian regions with different geographic locations, Lombardy (Northern Italy) and Tuscany (Central Italy), which showed consistency.

For VCV treatment, the daily cost associated with a treatment regimen of 8 g/day VCV was calculated based on the average of the fixed drug prices applied in hospital pharmacies in Lombardy and Tuscany.

Model outcomes

The mathematical model estimated the number of asymptomatic and symptomatic cCMV cases and relative

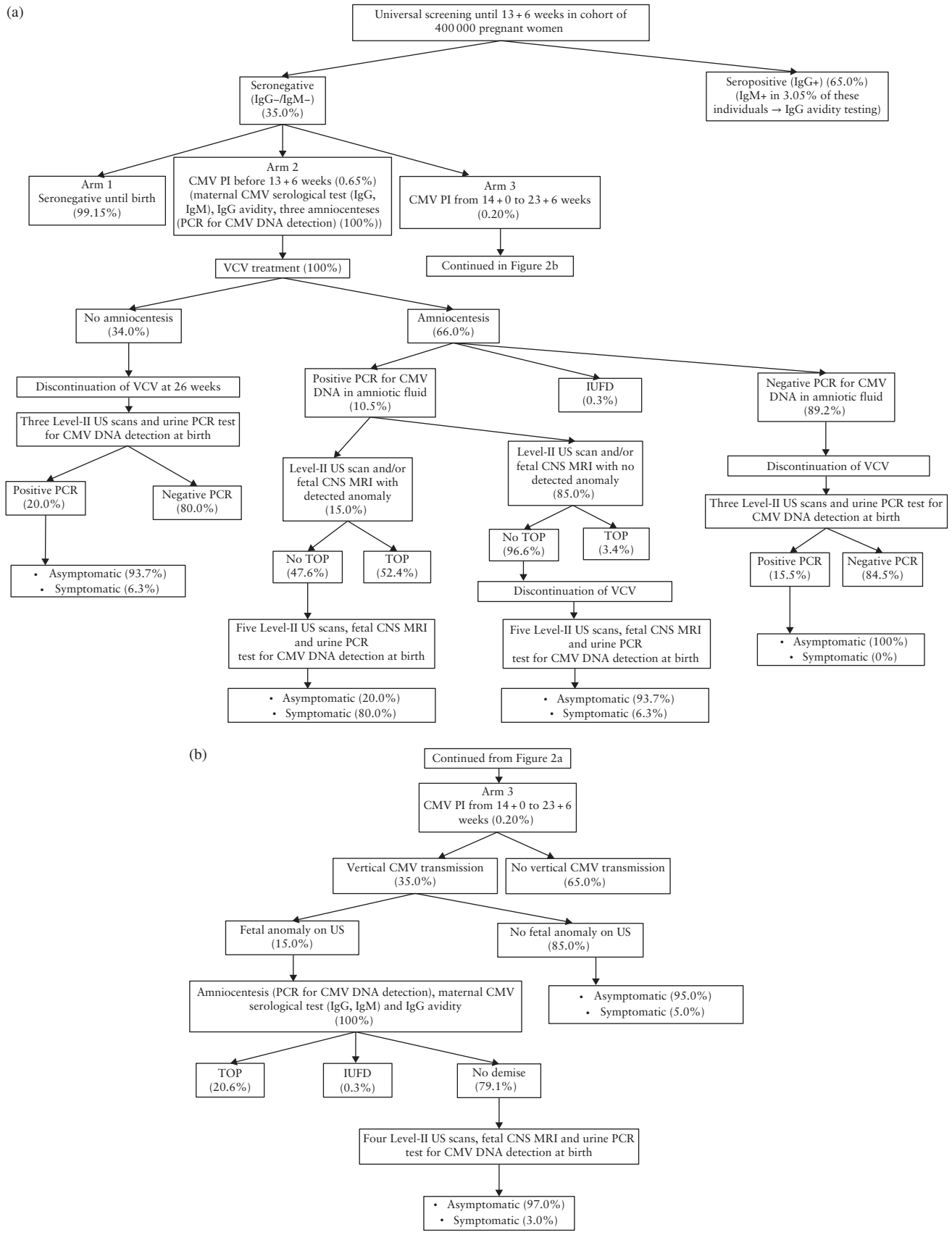

Figure 2 Flowchart showing outcomes of Scenario 2 (universal screening for cytomegalovirus (CMV) until 13 + 6 weeks' gestation) in hypothetical population of 400 000 pregnant women in Italy, considering: (a) primary CMV infection (PI) within 13 + 6 weeks' gestation, during the period of universal screening; and (b) PI following the period of universal screening, between 14 + 6 and 23 + 6 weeks' gestation. CNS, central nervous system; IUFD, intrauterine fetal death; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; TOP, termination of pregnancy; US, ultrasound; VCV, valacyclovir.

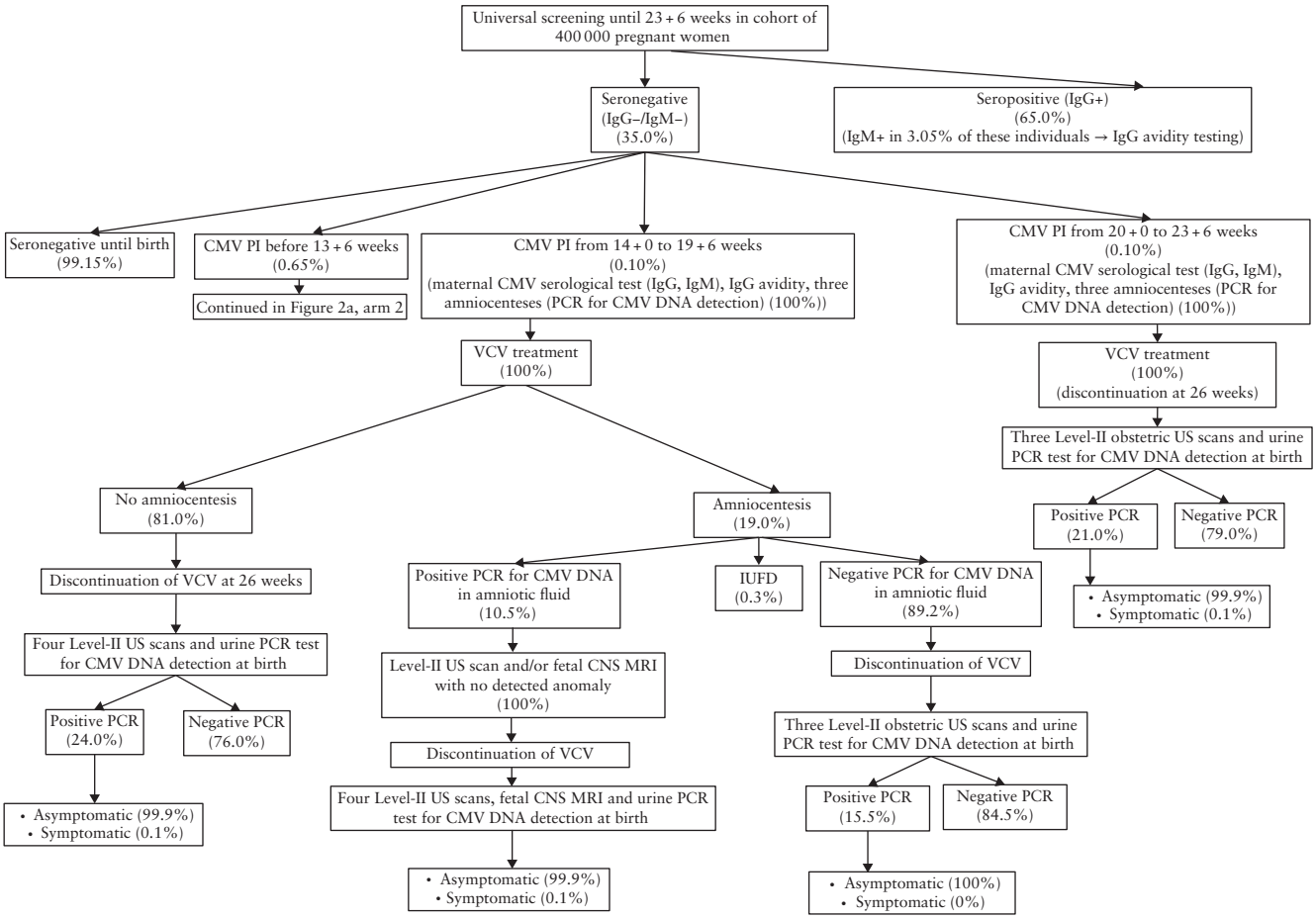

Figure 3 Flowchart showing outcomes of Scenario 3 (universal screening for cytomegalovirus (CMV) until 23 + 6 weeks' gestation) in hypothetical population of 400 000 pregnant women in Italy. CNS, central nervous system; IUFD, intrauterine fetal death; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PI, primary infection; US, ultrasound; VCV, valacyclovir.

management-related costs for each scenario. The scenarios were compared in terms of number of cases and costs. Specifically, considered outcomes included the screening detection rate (number of primary maternal CMV infections diagnosed) and the number of CMV DNA-positive amniocentesis results (fetal cCMV infections), TOPs, intrauterine fetal deaths (IUFDs) and neonatal cCMV infections with and without sequelae. For all calculations, values were computed using full-precision numbers reported by the mathematical model and rounded only at the final step.

Our analysis compared Scenario 2 and Scenario 3 with the no-screening scenario (Scenario 1) in terms of costs (in Euros (€)) per supplemental maternal, fetal and neonatal CMV infection diagnoses, and costs (in €) per symptomatic cCMV case avoided. Analysis was performed using Microsoft Excel 365 (Microsoft Corp., Redmond, WA, USA).

RESULTS

In a hypothetical population of 400 000 pregnant women who did not undergo CMV screening (Scenario 1), the routine second-trimester ultrasound examination would allow identification of only 15.0% (62/416) of cCMV-infected fetuses, 33 (52.4%) of which would undergo TOP and 24 (37.8%) of which would survive and have cCMV-related disabilities (Figure 1). The remaining 85.0% (354/416) of CMV infections would remain undetected before birth. Of these 354 neonates with prenatally undetected cCMV infection, 195 (55.0%) would also be missed after birth because of the absence of symptoms and of a universal neonatal cCMV screening program in Italy, whereas the remaining 159 (45.0%) cCMV-infected neonates would be diagnosed owing to the presence of CMV-related disabilities.

Assuming universal CMV screening until 13 + 6 weeks' gestation (Scenario 2) with a 100% sensitivity of CMV serological testing, 910 pregnant women with primary CMV infection would be identified (Figure 2a). Considering Italian data regarding amniocentesis uptake after a diagnosis of primary CMV infection at the beginning of pregnancy[20] and a 100% acceptance rate of VCV treatment[20], 63 fetuses would be diagnosed with cCMV infection at the time of amniocentesis, seven of which would be terminated. Additionally, 83 neonates would be identified to have cCMV infection only at birth, after a negative amniocentesis result and discontinuation of VCV. Among the 309 (34.0%) women not undergoing invasive prenatal testing, an additional 62 cCMV-infected

Table 1 Natural history of cytomegalovirus (CMV) and medical procedures involved in its prenatal detection, prenatal treatment and follow-up, in a hypothetical population of 400 000 pregnant women in Italy

Parameter	*Mean (%)*	*References*
Rate of seropositive women at beginning of pregnancy (IgG+/IgM−)	65.0	7–10, 43, 44
Incidence of primary maternal CMV infection (in seronegative women (35%))		8, 10, 43, 49, 50
≤ 23 + 6 weeks	0.85	
≤ 13 + 6 weeks	0.65	
14 + 0 to 19 + 6 weeks	0.10	
20 + 0 to 23 + 6 weeks	0.10	
Rate of maternal IgG avidity testing and PCR for CMV DNA detection in blood, saliva and/or urine following positive IgM	3.05	37
Rate of cCMV-infected fetuses detected by abnormal finding on routine fetal ultrasound	15.0	12, 14, 40, 51
Rate of TOP in case of symptomatic fetal CMV infection (abnormal fetal ultrasound findings)	52.4	39
Rate of TOP in case of fetal CMV infection (i.e. positive amniocentesis) with normal fetal ultrasound findings	3.4	39
Rate of amniocentesis following primary maternal CMV infection in first trimester	66.0	20
Rate of amniocentesis following primary maternal CMV infection in second trimester	19.0	MEGAL-ITALI study (Amniocentesis dataset)[20]
Rate of IUFD related to amniocentesis	0.3	52
Rate of TOP in case of symptomatic fetal CMV infection (abnormal fetal ultrasound findings) following primary maternal CMV infection in second trimester	20.6	14
Rate of vertical CMV transmission (i.e. positive amniocentesis) in women treated with VCV	10.5	15, 20
Rate of vertical CMV transmission (i.e. positive amniocentesis) in women not treated with VCV	35.0	20
Rate of abnormal fetal ultrasound and/or MRI findings in cCMV-infected fetuses (i.e. positive amniocentesis)	15.0	5, 40
Rate of positive urine PCR for CMV DNA detection at birth in neonates of women treated with VCV and with negative amniocentesis	15.5	20
Neonatal cCMV symptoms in Scenario 1		
Prevalence of symptoms among cCMV-infected neonates with normal routine fetal ultrasound findings	45.0	37
Prevalence of symptoms among cCMV-infected neonates with abnormal fetal ultrasound findings	80.0	37
Neonatal cCMV symptoms in Scenarios 2 and 3		
Prevalence of symptoms among cCMV-infected neonates following positive amniocentesis and normal fetal ultrasound/MRI findings (maternal PI ≤ 13 + 6 weeks, with VCV treatment)	6.3	41
Prevalence of symptoms among cCMV-infected neonates following positive amniocentesis and abnormal fetal ultrasound/MRI findings (maternal PI ≤ 13 + 6 weeks, with VCV treatment)	80.0	37
Prevalence of symptoms among cCMV-infected neonates following negative amniocentesis (maternal PI ≤ 13 + 6 weeks, with VCV treatment)	0	16
Prevalence of symptoms among cCMV-infected neonates of women who did not undergo amniocentesis (maternal PI ≤ 13 + 6 weeks, with VCV treatment)	6.3	41
Prevalence of symptoms among cCMV-infected neonates following positive amniocentesis and abnormal fetal ultrasound/MRI findings (maternal PI between 14 + 0 and 23 + 6 weeks, without VCV treatment)	3.0	14
Prevalence of symptoms among cCMV-infected neonates of women who did not undergo amniocentesis or with positive amniocentesis and normal fetal ultrasound/MRI findings (maternal PI between 14 + 0 and 23 + 6 weeks, without VCV treatment)	5.0	14
Prevalence of symptoms among cCMV-infected neonates of women who did not undergo amniocentesis or with positive amniocentesis and normal fetal ultrasound/MRI findings (maternal PI between 14 + 0 and 23 + 6 weeks, with VCV treatment)	0.1	41

cCMV, congenital cytomegalovirus; IUFD, intrauterine fetal death; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PI, primary CMV infection; TOP, termination of pregnancy; VCV, valacyclovir.

neonates would be diagnosed at birth. Overall, 11/201 (5.5%) neonates with cCMV infection would exhibit sequelae.

Scenario 2 must also consider the possibility of maternal CMV infection between 14 + 0 and 23 + 6 weeks' gestation, after the period of universal screening (Figure 2b). In this case, only 15 (5.4%) cCMV-infected fetuses would be identified among 280 cases of undetected maternal CMV infection due to observed cCMV-related ultrasound anomalies, with 3/15 (20.6%) ending in TOP. These terminations are most likely attributable to maternal request rather than objective findings, given the absence of severe fetal abnormality on prenatal imaging in cases of cCMV infection during the second trimester[48]. On the other hand, the lack of sonographic signs of CMV infection in the remaining 83 fetuses with cCMV would prevent prenatal diagnosis, thus leading to the birth of four (4.8%) symptomatic neonates.

Scenario 3 represents the Italian context and the real-world application of the 2023 Italian NHS recommendation[22,23], with universal screening performed until 23 + 6 weeks' gestation and VCV treatment given in the case of primary CMV infection (Figure 3). This screening model would result in 280 additional diagnoses of maternal primary CMV infection between 14 + 0 and 23 + 6 weeks' gestation compared with Scenario 2. Three fetuses would be diagnosed with cCMV infection at the time of amniocentesis, all of which would be asymptomatic at birth. TOP would not be considered or performed in these 280 additional cases of maternal CMV infection diagnosed between 14 + 0 and 23 + 6 weeks' gestation due to the Italian legislation. Four asymptomatic neonates would be identified to have cCMV infection at birth after a negative amniocentesis and discontinuation of VCV, and an additional 34 neonates with asymptomatic cCMV infection would be diagnosed at birth among the pregnancies that did not undergo amniocentesis. Assuming a 100% acceptance rate of VCV therapy in the case of primary CMV infection between 20 + 0 and 23 + 6 weeks' gestation[20], 29 neonates would be diagnosed with asymptomatic cCMV infection at birth. Overall, 0/69 neonates with cCMV infection after a primary maternal CMV infection identified between 14 + 0 and 23 + 6 weeks' gestation would display sequelae.

The numbers of total maternal primary CMV infections, TOPs, IUFDs and cCMV-infected neonates (either asymptomatic or symptomatic) according to the different screening strategies are summarized in Table 2. Considering a population of 400 000 pregnant women, 1190 primary maternal CMV infections and administration of VCV according to the Italian recommendation[21,22], Scenario 2 results in a 70% reduction in TOP (10 *vs* 33 cases) and a 92% reduction in symptomatic cCMV-infected neonates (15 *vs* 183 cases) compared with Scenario 1, as well as a 40% increase in the number of asymptomatic neonates among those with cCMV infection. Scenario 3 leads to a further 9% (three cases) reduction in TOP and a further 2% (four cases) reduction in symptomatic infected neonates in addition to the reduction achieved by Scenario 2, as well as a 30% increase in asymptomatic cases compared with Scenario 1, lower than the 40% increase observed in Scenario 2 *vs* Scenario 1. Importantly, as CMV infection occurring in the second trimester of pregnancy displays higher rates of transplacental viral transmission but does not lead to severe fetal insults compared with infection earlier in gestation[5,48], the additional reduction in TOP observed in Scenario 3 is likely representative of an enhanced maternal decision-making process regarding TOP.

Table S3 shows the base-case results of costs according to screening strategy. Implementation of a universal CMV screening program in pregnancy increases annual costs by > €7 million, regardless of the screening strategy. In addition, the cost of screening for each case of symptomatic cCMV infection prevented through universal screening within 13 + 6 weeks' gestation (Scenario 2) is approximately €45 500 per symptomatic cCMV case avoided; this cost is approximately €44 400 per symptomatic cCMV case avoided when screening is prolonged until 23 + 6 weeks' gestation (Scenario 3), and the total cost of Scenario 3 was just €22 252 more than that of Scenario 2.

DISCUSSION

Although cCMV is the most common infectious cause of non-genetic SNHL and lifelong neurological disability[1–6], and although VCV therapy has been proven effective in decreasing cCMV infections after maternal CMV infection in early pregnancy[15–20], universal screening during pregnancy has been recommended in few countries besides Italy[23–31]. Specifically, universal screening has been implemented in Greece since 2020[30], whereas the French National Authority for Health only recently agreed in June 2025 to conduct a 3-year trial[31].

In this study, we aimed to perform a clinical and economic evaluation of the CMV screening policy recommended in Italy[21,22]. This policy is particularly relevant because the Italian recommendation supports screening and treatment until 24 weeks' gestation[23], which is different from screening programs limited to the first trimester and those evaluated economically in other geographical contexts[30,31,35,37,38].

Compared with no screening, a universal CMV screening program generates an increase in annual costs of > €7 million. Yet, it allows higher detection rates of cCMV and lower rates of cCMV-related TOP and symptomatic cCMV infections at birth. Of note, a screening policy prolonged until 24 weeks' gestation (Scenario 3)[23]

Table 2 Numbers of identified cytomegalovirus (CMV) infections and outcomes according to the screening strategy applied in a hypothetical population of 400 000 pregnant women

Screening strategy	*Primary maternal CMV infection*	*TOP*	*IUFD*	*Symptomatic cCMV-infected neonates*	*Asymptomatic cCMV-infected neonates*	*cCMV-infected neonates (symptomatic and asymptomatic)*
Scenario 1 (no screening)	1190.00	32.72	0.19	182.96	200.63	383.59
Scenario 2 (universal screening until 13 + 6 weeks)	1190.00	9.81	1.85	15.28	280.85	296.13
Scenario 3 (universal screening until 23 + 6 weeks)	1190.00	6.78	1.88	10.83	259.85	270.68

All values were computed using full-precision numbers reported by the mathematical models and rounded only at the final step.
cCMV, congenital CMV; IUFD, intrauterine fetal death; TOP, termination of pregnancy.

would result in the prevention of three, four and 21 additional cases of TOP, symptomatic cCMV and asymptomatic cCMV diagnosed at birth, respectively, with only a negligible increase in total cost (€22 252) compared with a screening policy limited to the first trimester (Scenario 2). This allows for the application of the horizontal health equity principle in pregnant women with primary CMV infection, as previously noted[37,53]. Additionally, from a public health and societal point of view, an increase in costs could be considered marginal given the amelioration of all cCMV-associated outcomes[15–20]. These findings suggest that a screening strategy until 24 weeks' gestation, as the one recommended by the Italian NHS guideline on uncomplicated pregnancy[23], has a favorable clinical and economic profile when it comes to cost utility in Italy.

The economic assessment of a universal CMV screening policy in pregnancy has been performed previously in other countries, including France[37,38], the USA[54–57], Canada[58], Japan[59] and Singapore[60]. A recent cost-effectiveness analysis in France identified higher detection rates of cCMV infection, as well as increased monetary and organizational costs, of a screening policy comprising two CMV serological tests during the first trimester compared with no screening[37]. The authors state that such use of resources would favor equal access to VCV treatment, when indicated, and TOP, if permitted by national laws. Another cost-effectiveness study in France recognized a policy of universal screening consisting of two serological tests in the first trimester as cost-saving compared with a 'real-life' screening (i.e. in the absence of a national screening recommendation), in which 25–50% of women would undergo screening[38]. Of note, the number of cCMV-infected fetuses and neonates diagnosed in our model is concordant with that reported in the aforementioned studies[37,38]. Additionally, the CMV seroprevalence rate among women of childbearing age in France is comparable to that observed in Italy[5,7–11,43,44], thus lending additional support to our findings. In an American setting, Fisher *et al.*[54] showed that universal CMV screening comprising one serological test in the first trimester can be cost-effective only if VCV efficacy achieves a 75.9% reduction in the risk of vertical CMV transmission, which is approximately 5% and 10% higher than the figure identified in the setting of a randomized controlled trial[15] and in an individual patient data meta-analysis[16], respectively. Another American study[55] reported that universal CMV screening comprising one serological test in the first trimester reduces the number of cases presenting with cCMV-related sequelae, thus leading to increased effectiveness and decreased costs compared with no screening[28]. Similarly, in a Canadian cost-utility model, a universal screening policy comprising one serological test at 11–13 weeks' gestation was identified as the most cost-effective strategy compared with no screening and targeted screening (i.e. screening in women at risk)[58]. Similar findings for screening comprising one CMV serological test during the first trimester have also been reported in studies conducted in Japan[59] and Singapore[60], which display slightly higher CMV seroprevalence rates than Italy[11,61].

Screening for CMV infection is widely accepted by pregnant women once they have been informed about the risks of primary CMV infection[62,63]. Additionally, while our model assumed equal implementation of hygiene recommendations across screening and no-screening policies, it is reasonable to expect that the actual preventive effect of such recommendations would be stronger under a screening policy. Serological testing should be preceded by personalized counseling regarding CMV infection and its preventive behaviors[23,36], thus likely promoting an increase in knowledge among women and their partners[64] and, in turn, a reduction in the risk of infection acquisition[65].

Ideally, serological screening should be initiated as early as possible in pregnancy, preferably immediately after pregnancy confirmation. This approach maximizes the likelihood of identifying periconceptional or early first-trimester infections and allows timely initiation of VCV therapy, which has demonstrated the greatest efficacy when started soon after maternal CMV infection[15,66].

Our study focuses on prenatal maternal CMV screening, which allows detection of primary CMV infections among seronegative women. However, cases of cCMV following non-primary infections, which account for approximately half of the cases of cCMV in Italy[67], are not detected by such a screening program and can be identified only by universal neonatal screening, which has already been demonstrated to be cost-effective[68–70]. The value of combining prenatal and neonatal screening to reduce cCMV-related sequelae has still to be assessed.

Our study is not without limitations. First, we did not consider the total costs of cCMV infection, including medical care, rehabilitation and educational support for the affected infants, but considered only the screening costs. However, if we had considered total costs, as well as quality-adjusted life years, we would have likely identified an even more favorable economic profile for universal screening at the population level than the profile presented herein. Second, the generalizability of our results to other countries with different CMV seroprevalence rates or health systems may be limited. However, as our analysis is based on comparison of competing strategies, the clinical and economic aspects of the conclusions are likely to remain valid in broader contexts. Additionally, by providing detailed methodology, we favor adaptation to other settings with different resource utilization and monetary values. Third, we did not consider the potential benefits of VCV treatment in the case of mildly or moderately symptomatic CMV-infected fetuses[22,71], thus leading to a possible overestimation of neonatal sequelae. However, there are limited data in the literature to support a beneficial effect of VCV in such cases[71].

The strengths of our study include that it is the first to tackle the controversial topic of CMV screening in pregnancy, and its clinical and economic impact in Italy. This is particularly relevant because probabilities, utilities and costs differ among countries, especially in comparison

with the USA[54,55], Canada[58], Japan[59] and Singapore[60]. Additionally, Italy is one of the few countries where universal screening for CMV infection in pregnancy has been recommended by national guidelines[22,23,30,31,72], covering not only infection in the periconceptional period and the first trimester, during which there is the highest risk of sequelae[5,12,13], but also in the second trimester until 24 weeks' gestation, during which there could be a potential residual risk of SNHL and mild developmental disability[12–14]. Furthermore, by performing only one CMV serological test in the first trimester rather than two tests[37,38,54,55,58–60,73], our model is more representative of the real-world situation of the first prenatal care accessed by pregnant women in Italy, which occurs at approximately 9 weeks' gestation[73,74], and is particularly relevant for countries with fewer resources.

Conclusion

Our findings suggest that universal screening for CMV infection in pregnancy until 24 weeks' gestation, followed by VCV treatment in the case of maternal primary infection, has a favorable clinical and economic profile compared with a no-screening strategy and with universal screening restricted to the first trimester, when considering cost utility in Italy. We believe our results could be helpful to healthcare practitioners managing pregnant women and to policy-makers for monitoring the implementation and effectiveness over time of the CMV screening program recommended in Italy.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Timing of valacyclovir initiation and discontinuation.

Table S2 Unit medical costs of cytomegalovirus (CMV) infection diagnosis and treatment and of management of congenital CMV (cCMV)-infected newborns (in Euros).

Table S3 Cost analysis for congenital cytomegalovirus (cCMV) infection, according to screening strategy (in Euros).