Routine Screening for CMV in Pregnancy: Opening the Pandora Box?

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> For in much wisdom is much grief: and he that increases the knowledge increases the sorrow
>
> Ecclesiastes 1:18

The problem of cytomegalovirus infection in pregnancy has become a major issue in Israel in recent years, creating an enormous amount of public anxiety, which in turn has resulted in repeated blood tests, many amniocentesis procedures and, ultimately, unnecessary terminations of pregnancies. A major contribution to the current chaotic situation is the increasing tendency of many obstetricians to perform routine serologic screening for CMV immunoglobulin G and M antibodies in women in the first trimester of pregnancy. A woman with CMV IgM antibodies, regardless of her current or previous IgG status, is then summoned for evaluation. Repeated tests are performed, including a repeat IgM test (typically by several methods such as enzyme-linked immunosorbent assay and fluorescent antibody staining), and IgG avidity assay. The usual scenario is that more uncertainties are created, and at that point the couple is utterly confused by the various medical opinions and layman input and is flooded with semi- and non-professional information on the internet. Therefore, it is very difficult for an expert to reassure the couple, and either termination of pregnancy or at least amniocentesis is performed. The "CMV screening program" is not based on formal recommendations of any professional organization. In fact the opposite is the case: the Ministry of Health has issued a clear statement, as have other professional organizations, that such a routine screening should not be performed. Nevertheless, for various reasons mostly related to medico-legal issues, it is very often done. This "routine" self-motivated screening program is not practiced in the rest of the world. Yet, there are repeated initiatives by experts from several disciplines such as obstetrics, infectious diseases and others, to establish such a routine screening program for CMV infection in women of childbearing age, both pre- and post-conception. In this paper I will discuss the pros and cons of initiating such a screening program in Israel.

CMV has become the major cause of congenital infection in the developed world, leading in some cases to significant neurological sequelae. Since blood testing for CMV antibodies is a minor and safe procedure, one might argue that all pregnant women would benefit from this additional information. However, in evaluating this matter, it is crucial to first understand the natural history of CMV infection in pregnancy and its consequences for the newborn. Also, one should be familiar with the various tests performed during pregnancy and their yield in predicting both maternal and fetal infection, and even more importantly – fetal outcome. In addition, one should adhere to the common principles of routine screening programs.

Natural history

Figure 1, adapted from Stagno [1], illustrates the natural history of CMV infection in pregnancy and its consequences for the newborn, along with numerical equivalence when applied to the 135,000 annual deliveries in Israel. These numbers are based on the 80%–85% IgG seroprevalence rate [2]. It is very clear from this algorithm that only a small fraction of all newborns exposed *in utero* to maternal primary CMV infection (around 8% of all infected mothers) will be clinically affected to some degree. As seen on the right-hand side of this algorithm, 14–68 children per year are expected to suffer significant effects. In addition, as seen on the left-hand side of this figure, an unknown number of children exposed to maternal CMV reactivation during pregnancy should also be included. Hence, the diagnosis of CMV infection in pregnancy, which at times is very difficult to make, is far from proving fetal damage.

Laboratory studies

Tests that are commonly performed during pregnancy include:

- *Antibodies screening for* CMV I*g*G *and* I*g*M, at any point during pregnancy. It is very important to realize, however, that CMV IgM antibodies are neither specific nor sensitive in detecting acute CMV infection. These antibodies may remain in the circulation for years and do not necessarily indicate acute infection.
- I*g*G *avidity assay*, that would indicate the time of primary infection. This assay, although helpful, is also limited in the pertinent information that can be derived from it. Both avidity testing and antibody screening can be performed at any stage in pregnancy and will potentially lead to intervention.

CMV = cytomegalovirus
Ig = immunoglobulin

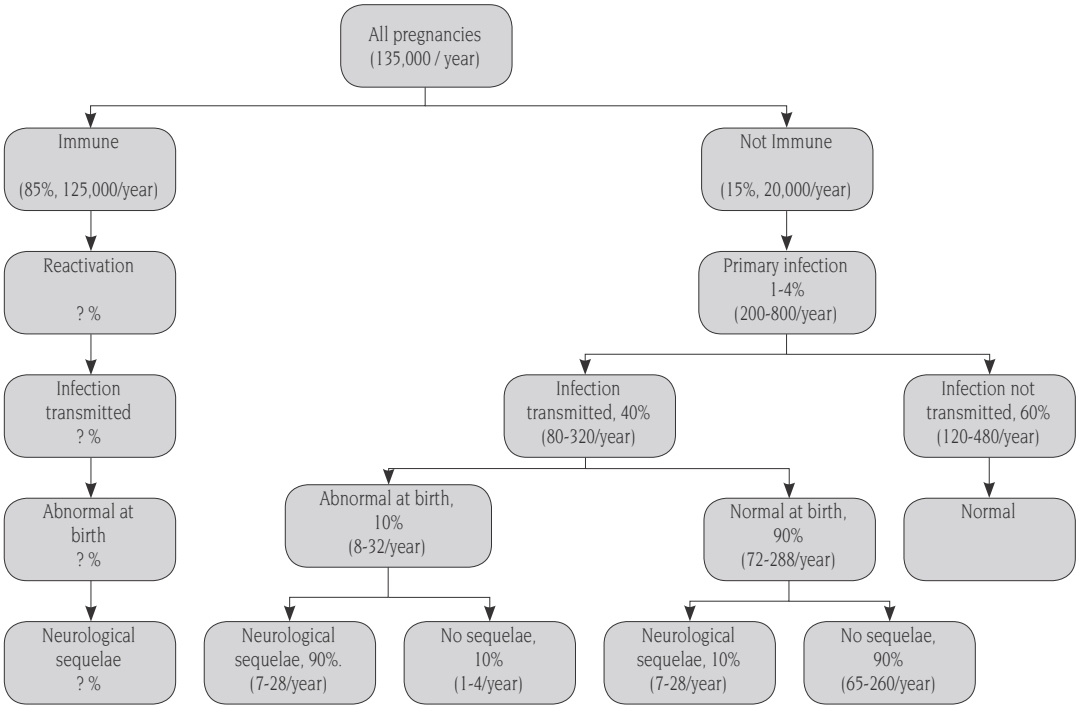

Figure 1. Consequences of CMV in pregnancy (annual impact in Israel)

- A*mniocentesis*, to detect CMV in amniotic fluid (by both polymerase chain reaction and viral culture), indicating fetal infection. The test is reliable for this purpose only after the 21st week of pregnancy. Of note, as seen in Figure 1, most infected infants (around 80%) will not be affected.

Principles of routine screening programs

The article by Wilson and Jungner [3], entitled "Principles of Early Disease Detection," is probably the most cited source of criteria for screening. In 1974, the criteria were revised by Frankenburg [4], who stated that screening carried out without knowledge and due consideration might do more harm than good. Briefly, the criteria are: a) the disease should be a serious health problem and early detection should have a positive impact on morbidity and mortality, b) the condition should be relatively common (prevalence of ≥ 1:15,000), c) the screening test must distinguish normal from affected subjects, d) patients must be identified before diagnosis is clinically suspected, e) diagnostic tests and treatment must be available, and f) the costs of finding affected individuals should be economically balanced with the benefits.

Application of these criteria can be evaluated by the following parameters. It is evident that many of them are not met.

- S*everity of disease*: Clearly, congenital CMV may indeed be a severe disease, leading in some cases to significant morbidity and mortality. It can be argued that early detection of this condition is warranted because further tests or even termination of pregnancy can then be performed.
- P*revalence*: It is also true that congenital CMV is a common condition; it is estimated that combined primary infection and reactivation of previous infection occurs in around 1% of newborns. To date only one study on screening newborns for congenital CMV in Israel has been published [5,6]. Of the 2000 newborns in two medical centers, 14 (0.7%) were found to have congenital CMV, and only one was symptomatic. It is likely that many of those infants were exposed to reactivation than to primary infection. If applied to the 135,000 annual deliveries in Israel, an estimated 900–1000 cases per year from both primary infection and reactivation are expected.
- T*est discrimination power*: IgM screening is very poor in differentiating between current primary infection, reactivation of previous infection, long-lasting IgM antibodies from past infection, and even a false-positive result, not uncommonly seen in pregnancy. A full panel of tests, including IgG, IgM and igG avidity assay may be more informative, but this will be prohibitively expensive to perform and interpret as a screening method, and even this much information will not avoid uncertainty.
- D*iagnostic timing*: The serologic test result, prior to the appearance of clinical symptoms, has the power to detect the disease that in many cases may not exist at all.
- I*ntervention*: Currently there is no established modality for treating a pregnant woman with CMV infection. A recent article by Nigro et al. [7] suggests that the infusion of anti-CMV monoclonal antibodies into a pregnant woman with CMV infection may ameliorate fetal damage. This method, as attractive as it is, is far from being proven, and a prospective control trial should be performed prior to the adoption of this recommendation [8]. Other options

will then be amniocentesis or termination of pregnancy. However, amniocentesis is by no means the end of the road because it can only detect neonatal infection, not disease. If it is a reactivation, it will be very hard to justify any intervention, and even with primary infection only 20% of infected newborns have some degree of damage.

- *Cost-effectiveness*: It is beyond the scope of this paper to evaluate the cost-benefit ratio of a universal CMV screening program.

Taken together, the multiple points of uncertainty along the decision-making tree regarding CMV in pregnancy preclude a systematic and rational approach toward routine screening during pregnancy.

Another approach that might then be considered is preconception screening for CMV IgG antibodies only. A seropositive woman will be reassured and will not be tested again, and a seronegative woman will be re-screened periodically. Of note, many experts in Israel recommend that immune mothers be screened as well, because they are concerned about reactivation. Indeed, a recent report by Ross and colleagues [9] showed that there was no significant difference in infants' hearing deterioration between those whose mothers had primary or secondary infection. Nevertheless, the significance of this finding is still not clear and one should refrain from jumping to conclusions based on this exceptional report. I support the recommendation of the most recent scholarly textbook [1], namely: "Because the risk of transmission is very low and the risk of fetal disease even lower, women known to be seropositive before conception do not need to be virilogically or serologically tested, nor do they need to be unduly worried about the very low risk of adverse effects on the fetus." According to this plan, a seronegative mother who becomes pregnant should take measures to minimize exposure to CMV during pregnancy [10], and may consider undergoing repeated screening that will allow intervention in a case of primary infection. This approach, albeit more rational than the previous one, suffers also from several inherent flaws, Firstly, the logistics and expenses of such a mega-screening program are extremely high and are not feasible in Israel. Secondly, it is estimated that about 50% of pregnancies in Israel are not preplanned, and there is no pre-pregnancy doctor visit. Hence, this "pre-pregnancy" screening program will very often lead to screening in the first trimester of pregnancy, with the numerous difficulties outlined above. Thirdly, even seropositive women may not be fully reassured. As already mentioned, many experts in Israel, whether right or wrong, recommend that immune mothers also be screened because of their fear of reactivation. Finally, unlike the case with rubella, no CMV vaccine is available. Hence, this screening program will expose all seronegative women (~20,000/year) [Figure 1] to information that will cause them a great deal of anxiety during pregnancy, with little recourse to act upon this information.

A third, completely different approach to the problem of congenital CMV is universal newborn screening. This approach has recently gained attention [5,6,10,11], but is beyond the scope of this paper. It is sufficient to say that it will avoid many of the false alarms expected in a pre-labor screening program, but it is likely to require resources that are not available to Israel's health system.

In summary, it is my strong opinion that neither of these two screening programs is justified. Future studies are needed to elucidate mechanisms of maternal-fetal transmission and fetal damage by maternal infection. Only when these are available will it be possible to focus on the subgroup of pregnancies at the highest risk for congenital CMV disease, and consider screening for those.

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Never advise anyone to go to war or to marry

Spanish proverb