Cytomegalovirus in pregnancy
Still as elusive as ever

Commentary by
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Careful consideration is needed when deciding on the best course of action for this woman with a suspected cytomegalovirus infection in early pregnancy.

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CASE SCENARIO

Josie is aged 23 years and was very happy to learn that she was pregnant for the first time. However, the routine antenatal blood tests revealed that she had lymphocytosis and many atypical cells. Josie felt well and was totally asymptomatic, but follow-up testing showed that she had a current infection with cytomegalovirus – both IgM and IgG were positive. A repeat check one week later showed the same result. Josie is now eight weeks pregnant.

What are the implications of this infection for her pregnancy and the future development of her baby?

COMMENTARY

This scenario is likely to create a nightmare for everyone involved. Unless Josie was tested previously for cytomegalovirus (CMV), there are no easy answers. It puts an enormous responsibility on the person who has to communicate this result, especially if Josie has never heard of CMV and seeks advice from various people close to her, if not the internet. It is easy to envisage that opinions may range from 'if it was me, I would have a termination' to 'with both IgG and IgM there is no need to worry'.

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There are no easy answers

A few years ago, one of my relatives who worked with young children had CMV IgG and IgM antibodies found on a 'routine' screening test in early pregnancy. By the time some vague prognosis could be made, she was well into the second half of her pregnancy. She and her husband opted for a termination, but could not obtain it because the pregnancy was too far advanced. Her father, a GP, went on a crusade on their behalf, including seeking help at three university hospitals, but to no avail. Having been summoned to help, I arranged a termination in another country – where it was performed with the dignity that it deserved. Viral cultures were positive, but none of us know whether the right decision was made. This young woman is now a happy mother of two, but will never forget the ordeal that she had to go through.

What to tell Josie?

Here is some information you can pass on to patients such as Josie.

'CMV is a common virus that only affects humans. It invades the body and stays there without causing problems. However, it is an opportunist. If a person's immunity is down, it can have devastating effects. Unborn babies, who have little immunity of their own, are very susceptible to attack from the virus. They depend on their mother to protect them, but mothers can only do so if their immune system already knows the virus.

So, there is a big difference in how to proceed depending on whether it is a first infection or if, like in many people, the virus has been present for years. The first thing to do is to figure out when the infection occurred. The haematology results certainly suggest that your immune system is challenged, but whether that will be good enough to protect the baby is a different matter. Given what prompted the test, a good history can be helpful. However, differentiating vague symptoms from signs of early pregnancy can be difficult and infections that occurred shortly before conception offer little reassurance.

If it is a first infection, there is about a one in three chance that the baby will be infected too. About 10 to 15% of these infected babies will be seriously affected at birth. About one in 10 of those

seriously affected will not survive and the remainder will have severe handicaps. Of the 85 to 90% of babies who are infected but apparently without symptoms, about one in 10 will experience late consequences, mainly hearing loss. However, all of these figures are just estimates.

If, on the other hand, you have had the virus for some time, there is a less than 2% chance that the baby will acquire it and even if it does the consequences are less severe. Such babies should have regular check ups, especially of their hearing, at least once a year until they reach school age because symptoms may appear late.

This is such a complex issue that we need advice from virologists and maternal-fetal specialists while we try to figure out how recent the infection was.'

Distinguishing 'primo' from 'old' infection

A CMV infection does not result in immunity, which has hampered vaccine development. Reactivations of the resident virus or reinfections with another strain do occur. Positive IgG and IgM results indicate an infection. However, they do not tell us when the infection occurred, because CMV IgM can linger for many months. There are several IgM assays and false-positive results do occur. For example, the Epstein-Barr virus of glandular fever, which also causes lymphocytosis with atypical cells but poses no threat to the fetus, is known to produce false-positive CMV IgM results. So, CMV IgM results need to be interpreted with caution.

IgG antibodies formed initially are aspecific. They acquire a specific taste (avidity) for CMV after about three months. A low IgG avidity test indicates a recent infection, whereas a high avidity indicates an old infection, a reactivation or a reinfection. However, tests can differ among laboratories.

Measuring so-named neutralising antibodies can also be helpful. These antibodies emerge about 14 weeks after a primo-infection. If present, they are believed to rule out an infection within the past three months.

Will there be transmission to the fetus?

Transmission of CMV from mother to fetus is variable. CMV initially infects the placenta, resulting in an enlarged placenta, which is a known ultrasound finding. It takes time before fetal infection becomes evident. That evidence can be obtained in three ways: from cordocentesis, amniocentesis and ultrasound. All need expert knowledge to interpret their findings.

The most reliable approach has been amniocentesis, but only after 20 weeks of gestation and at least seven weeks after an infection. This is because the interval between maternal infection and transmission of the virus to the fetus is unpredictable and because fetal kidneys need maturity to shed virus into the amniotic cavity.

In general, the choice is between viral culture and a polymerase chain reaction (PCR) of CMV DNA. PCR is more reliable than viral culture. It has a high specificity of almost 100%, but a negative PCR result offers no guarantee of there being no fetal infection. If both PCR and viral culture are 'positive' (although there is little to be positive about) fetal infection is a fact. However, if they are 'negative', they offer no guarantee. Viral loads in amniotic fluid can be measured, but they do not help to predict adverse outcomes.

Does transmission to the fetus predict outcome?

Unfortunately, nothing mentioned above predicts the outcome with any degree of certainty. When fetal infection is diagnosed, the last resort is to rely on serial ultrasounds every two to four weeks to detect early signs of poor prognosis. Unfortunately, negative findings offer no guarantee. Ultrasound detects only 25% of congenital CMV infections. Fetal magnetic resonance imaging (MRI) improves detection, but usually only in the third trimester when options are limited.

What else can be done?

Little can be done to improve outcome. Treatment with antiviral therapy and administration of hyperimmune globulin to CMV during pregnancy offer no cure, only some attenuation. In some European countries, where screening for CMV is relatively common, GPs and patients alike have often found themselves between the devil and the deep blue sea. Sometimes, repeat amniocentesis and repeat ultrasound with MRI eventually result in feticide well into the third trimester of pregnancy, but fetal euthanasia may not appeal to many mothers.

IN THE FINAL ANALYSIS

The main issue in Josie's case is to determine if this is a primo-infection or not with a CMV IgG avidity test. With a high IgG avidity the likelihood of fetal infection is small and, even then, the consequences are limited, although careful follow up of the baby is needed. If infected, about one in 10 babies will experience neurosensorial hearing loss, which is not always apparent shortly after birth.

If it is a primo-infection, Josie's options are as listed below.

- Take a chance and continue with the pregnancy with the knowledge that fewer than 50% of babies will acquire the virus and that about 85 to 90% will be asymptomatic at birth. However, these babies will need follow up, because about 10 to 20% of them may still be affected by hearing loss or other problems before reaching school age.
- Opt for termination of the pregnancy because the odds are unacceptable. If so, it is wise to wait for at least six months before conceiving again.
- Wait until at least 21 weeks of gestation and have an amniocentesis to see whether the fetus is likely to be infected before making a decision.
- Engage in a program of repeat ultrasound complemented with MRI and perhaps cordocentesis to detect abnormalities before making a decision on the options still available.

Whatever option is chosen, it is likely to cause all concerned some sleepless nights with little certainty that the right choice was made in the end. MT

COMPETING INTERESTS: None.