Is antenatal screening for rubella and cytomegalovirus justified?

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Abstract **Altogether 2 250 asymptomatic pregnant women attending an antenatal clinic were investigated for serological evidence of past exposure to rubella and cytomegalovirus (CMV) as well as for active primary infection or reinfection/reactivation. Only 7 (0,3%) active rubella infections were diagnosed, none of them primary. Similarly, out of 132 patients with active CMV, only 5 primary infections (3,8%) were diagnosed; the vast majority — 127 (96%) — had reactivation infections. No congenital rubella infections were detected, while the transplacental transmission rate for CMV was 6,4%. None of the infants followed up was clinically affected at birth or at 6 months. No racial differences in seroprevalences for CMV or rubella immunoglobulin were observed, but immunoglobulin antibody prevalence to CMV was significantly lower in the white group. From this study there appeared to be no indication for routine antenatal screening for CMV in asymptomatic mothers.**

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Routine screening tests for rubella and cytomegalovirus (CMV) infections in pregnancy are carried out with some regularity in many obstetric practices in this country. Concern about congenital infection with fetal damage or loss as a result of antenatal infections with either of these viruses is not unjustified. In the USA, despite excellent vaccine coverage, the incidence of rubella and congenital rubella syndrome increased twofold in 1989 and an additional threefold in 1990,[1] after having been virtually eliminated up to 1985.[2] In South Africa outbreaks of rubella still occur regularly in spring and early summer and may be extensive.[3] From 13% to 23% of women of childbearing age of all population groups lack antibodies and are susceptible to infection[4,5] and, even in the presence of pre-existing antibodies, reinfection may cause fetal infection and damage.[6,7] CMV is the commonest of all congenital viral infections in man, occurring in about 1% of all newborn infants throughout the world.[8] Longitudinal follow-up of infected infants has demonstrated that some 5% of them have typical cytomegalic inclusion disease and a further 5% have atypical involvement which may manifest later in developmental, sensory or intellectual deficiencies.[9]

In this study a cohort of asymptomatic pregnant women attending the antenatal clinic at Johannesburg Hospital were screened for rubella and CMV, and infants born to immunoglobulin M (IgM)-positive mothers were examined at birth and at 6 months for clinical and laboratory evidence of infection with either virus. The objective of this investigation was twofold: (*i*) to determine the prevalence of exposure to these agents and to assess serological evidence of active infection (primary/reinfection/reactivation) and transmission of infection to the infant; and (*ii*) to assess the potential benefit of routine antenatal screening of asymptomatic women for rubella and CMV.

Subjects and methods

A total of 2 250 asymptomatic pregnant women attending the antenatal clinic at Johannesburg Hospital were tested serologically for rubella and CMV. Blood specimens were subsequently taken from infants born to rubella and CMV IgM-positive mothers. These infants were also examined clinically at birth and CMV IgM-positive infants were booked for a repeat examination at 6 months of age when an audiological examination was also carried out. Informed consent was obtained from all the mothers taking part in the study, which was also approved by the University Senate Committee for Research on Human Subjects. There were no refusals to participate.

Blood specimens were centrifuged and sera separated at the National Institute for Virology. Sera were tested for IgM and IgG antibodies to both rubella and CMV using commercial enzyme-linked immunosorbent assay (ELISA) kits (M A Bioproducts, Virginia) according to the manufacturers' instructions. Sera found to be positive for IgM, either for rubella or CMV, were then fur-

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ther tested for avidity of their IgG antibodies. Commercial IgG ELISA kits were used for both viruses but an 8M urea wash step was incorporated, as described in an earlier study.[10] Briefly, the wells of the ELISA plate were rinsed twice with an 8M urea solution after the initial incubation of patients' sera with antigen; they were then left to soak in the solution for 3 minutes to remove low-affinity antibodies. The wells were then washed with standard rinse buffer and the test continued as per manufacturers' instructions. An avidity index (AI) was calculated as follows:

$$AI = \frac{\text{absorbance reading after urea wash}}{\text{absorbance reading without urea wash}} \times 100.$$

AI values of less than 30% were interpreted as indicating primary infection and those of over 50% as reactivation infection (for CMV) or reinfection (for rubella). Indeterminate results between 30% and 50% were retested. Statistical analysis was by means of the χ^2 test.

TABLE I.
Distribution of rubella IgM antibodies by race group

	No. positive	%	95% CI*
Black	2/761	0,3	0,1 - 0,7
White	4/1058	0,4	0 - 0,8
Mixed descent	1/172	0,6	0,5 - 1,1
Asian	0/169	0	
	$P = 0,7805$		

* CI = confidence intervals.

Results

Rubella IgG antibodies were detected in 2 780 of 2 992 specimens tested (92,9%) (additional specimens above and beyond the original 2 250 were tested for rubella IgG up to 20 September 1991). Active infection, as indicated by IgM positivity, was found in 7 of 2 250 specimens (0,3%), none of which had AI values consistent with primary rubella infection. The distribution of IgM positivity with regard to race among the 2 160 specimens for which race details were provided is shown in Table I. No significant difference in IgM prevalence was noted between the four race groups. Blood specimens were obtained from 4 of the 7 infants born to IgM-positive mothers; all were IgM-negative but IgG-positive. All infants were clinically healthy at birth.

Of the 2 250 specimens tested for CMV infection, 1 952 (86,8%) were positive for IgG antibodies and 132 (5,9%) for IgM. Of the 132 IgM-positive sera, 5 (3,8%) had low IgG antibody avidity indicative of primary infection. Thus primary infection was diagnosed in only 5 of the 2 250 (0,2%) specimens. Two of the primary infections were in white and 3 in black subjects. The distribution of IgG and IgM positivity among the race groups is shown in Table II. No significant differences in prevalence were observed between the races for CMV IgM although seroprevalence for CMV IgG was significantly lower in white women ($P < 0,0001$). Blood specimens were obtained from 47 infants (all from mothers with IgM-positive blood and high-avidity IgG antibodies suggesting reactivation infection). Of these sera 6 were IgM- and IgG-negative, and 38 IgM-negative and IgG-positive; 2 were both IgM- and IgG-positive and 1 was IgM-positive and IgG-negative. Thus serological evidence of intra-uterine infection was found in 3 of the 47 sera examined (6,4%). All the babies, however, were clinically normal at birth and 3 babies examined at 6 months were clinically and audiologically normal.

Administrative and logistical difficulties, as well as deliveries occurring elsewhere, were reasons why only 3 of the 7 babies from rubella IgM-positive mothers, only 47 of the 127 reactivation IgM-positive mothers and none of the primary IgM-positive mothers were available for clinical examination and the taking of blood specimens at birth.

Discussion

The susceptibility to rubella in only 7% of women tested was considerably lower in this antenatal study than in previous South African studies. Those studies showed seronegativity in 18% of male and 12% of female university students,[5] 18,4% of laboratory specimens from women of childbearing age,[6] and 11,1 - 15,4% of rural black pubertal schoolgirls in the northern Transvaal.[11] Active infection was very uncommon in this cohort — only 7 cases were detected by IgM serology from the total of 2 250 tested (0,3%) and all of these were the result of reactivation infection according to avidity testing. All the mothers were asymptomatic and none of the infants tested had clinical or serological evidence of congenital infection. This relatively extensive rubella survey, while providing useful prevalence data, did not detect any cases of congenital rubella syndrome. As in an earlier study of university students, where no significant difference in distribution of rubella seropositivity was found between the races,[5] in this antenatal study no significant difference in distribution of active IgM-positive rubella infections was observed between the races.

The findings for CMV were similar to those for rubella. Thus, IgG seropositivity was detected in 87% of all mothers tested. Acute IgM-positive primary infection was found in only 5 out of 132 mothers who tested positive for CMV (3,8%); the great majority 127 (96%) had reactivation infection where fetal damage as a result of congenital infection is far less likely to occur.[8,12] In the final analyis, only 5 cases of primary CMV infection in pregnancy were detected after screening 2 250 mothers, but none of these infants was available for evaluation at birth. The rate of transmission of infection, 6,4%, is considerably lower than the 30 - 40% reported from the UK,[13] although the number of infants examined in our study was small and not all susceptible babies were tested. Stagno *et al.*[12] found that women from lower socioeconomic groups have significantly higher prevalences of CMV antibodies. In our study, seroprevalence for CMV IgG was significantly lower in white women although there was no significant difference in active infection as indicated by IgM positivity.

TABLE II.
Distribution of CMV antibodies by race group

	IgG			IgM		
	No. positive	%	95% CI*	No. positive	%	95% CI*
Black	757/761	99,5	99 - 100	58/761	7,6	5,7 - 9,5
White	775/1058	73,7	70,6 - 76,0	57/1058	5,4	4,0 - 6,8
Mixed descent	171/172	99,4	98,3 - 100,5	10/172	5,8	2,3 - 9,3
Asian	163/169	96,4	93,6 - 99,2	7/169	4,1	1,1 - 7,1
	$P = < 0,0001$			$P = 0,1605$		

* CI = confidence intervals.

Conclusion

It is apparent from this study that routine screening of asymptomatic pregnant mothers is unlikely to detect active primary rubella or CMV infection, and was rarely of benefit in preventing fetal damage caused by congenital infection. Routine CMV screening of asymptomatic women in pregnancy is therefore not recommended, although there may still be a place for routine rubella screening. On the other hand, when indicated, laboratory tests for rubella or CMV should, of course, be carried out to confirm or exclude infections in pregnant mothers who come into contact with either virus or develop clinical symptoms consistent with rubella or CMV infections. However, serological evidence of primary or reactivation CMV is not an indication for termination of pregnancy[13] but may be of value in alerting the paediatrician to the possibility of early or delayed symptomatic infection of the infant.

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