VARICELLA ZOSTER VIRUS INFECTION IN PREGNANCY

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ABSTRACT
Varicella and herpes zoster during pregnancy has been associated with birth defects, neonatal varicella, herpes zoster in newborns and infants. The aim of the present study was to determine the consequences for the neonates, whose mothers were closely exposed to varicella zoster virus (VZV) during pregnancy. Fifty six pregnant women with uncertain histories of prior VZV infection, after a close exposure to varicella, were enrolled for examination of specific anti VZV antibodies. CFT and ELISA were performed. Eleven (20%) pregnancies were complicated with varicella and 4 (7%) with herpes zoster. Intrauterine varicella infection was identified on the basis of clinical evidences (anomalies characteristic for the congenital varicella syndrome, acute varicella at birth or herpes zoster in infancy) by history of delivery. Four infants with neonatal varicella and their mothers were examined serologically. After a close exposure to varicella, seronegative by CFT were 19 (34%) pregnant women and 9 (16%) by ELISA. Birth defects or herpes zoster in infancy were not found. None of the 4 infants whose mothers had herpes zoster were with physical anomalies. One infant whose mother was with first trimester varicella showed intrauterine retardation. Three babies with neonatal varicella were born by mothers with third trimester varicella and low levels of antibodies to VZV. One infant whose mother lacked antibody to VZV died of neonatal varicella. Varicella during pregnancy was associated with fetal or neonatal infections and diseases, but herpes zoster wasn’t.

Introduction
Varicella zoster virus (VZV) causes varicella mostly in infancy. After recovery the virus remains latent in the organism and is capable to cause herpes zoster later in life when reactivated (5). Specific anti VZV antibodies can be detected in sera of these humans. Seroepidemiological investigations and analyses of incidence rate of varicella during the last years in our country and worldwide, show increase in number of seronegative persons over 15-18 years old (2,4,8). This can be dangerous for severe disease of pregnant women, lacking immunity against VZV (12). The implications of primary VZV infection in pregnancy for the mother and for the fetus vary with the period of gestation. For the mother, the risk of adverse effects is greatest in the third trimester, whereas for the fetus the risk is greatest in the first and second trimester (7). VZV can pass comparatively common through the placental barrier and contracts the fetus (1,10), with transmissive frequency according to data 24% - 60% (9,12). Most severe consequences result when the infection is in the first trimester of pregnancy. Congenital varicella syndrome (limb hypoplasia, cutaneous scars, microcephaly, cortical atrophy, chorioretinitis, cataracts and other anomalies) is seen in 3% - 9% (3,5,12). Varicella during the third trimester may be asymptomatic for the baby, but in perinatal period, neonatal varicella is very likely to develop in more than 60% of the cases (9).

The aim of the present study was to detect the consequences for the newborn in-
Sero logical anti VZV IgG status of pregnant women after close exposure to varicella

<table>
<thead>
<tr>
<th>Titer</th>
<th>First trimester</th>
<th>Second trimester</th>
<th>Third trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CFT ELISA</td>
<td>CFT ELISA</td>
<td>CFT ELISA</td>
</tr>
<tr>
<td></td>
<td>Negative Positive</td>
<td>Negative Positive</td>
<td>Negative Positive</td>
</tr>
<tr>
<td>&lt; 4</td>
<td>7 5 15</td>
<td>7 15</td>
<td>5 16</td>
</tr>
<tr>
<td>4</td>
<td>5 2</td>
<td>3 5</td>
<td>2 16</td>
</tr>
<tr>
<td>8</td>
<td>3 1</td>
<td>2 5</td>
<td>3 15</td>
</tr>
<tr>
<td>16</td>
<td>1 3</td>
<td>1 2</td>
<td>1 1</td>
</tr>
<tr>
<td>Total</td>
<td>20 20</td>
<td>18 18</td>
<td>18 18</td>
</tr>
<tr>
<td>%</td>
<td>35% Negative</td>
<td>25% Negative</td>
<td>38% Negative</td>
</tr>
<tr>
<td></td>
<td>17% Negative</td>
<td>28% Negative</td>
<td>11% Negative</td>
</tr>
</tbody>
</table>

Infants, whose mothers were closely exposed to varicella during pregnancy.

Materials and Methods

Study population: Fifty six pregnant women with uncertain history of prior VZV infection, who have had a close exposure to varicella, were enrolled for detection of specific anti VZV antibodies by CFT and ELISA. Seronegative pregnant women (by CFT) were tested again after 3 – 4 weeks to prove seroconversion. Eleven (20%) of the pregnant women developed varicella and 4 (7%) – herpes zoster. The referring obstetricians made the clinical diagnosis of maternal varicella or herpes zoster. Fifty six live births infants were studied using the data from history of delivery. Intrauterine varicella infection was identified on the basis of clinical signs (anomalies typical for congenital varicella syndrome, acute varicella at birth or herpes zoster in infancy) (12). Four babies with clinical symptoms of neonatal varicella were tested for the presence of specific anti VZV antibodies after informed consent and in comparison with the mothers.

Laboratory methods: CFT (complement-fixation test) by micromethod (according to S. Bradstreet and S. Taylor), modification of I. Dobrev (8) was performed. Antigens, produced by the National Center of Infectious and Parasitic Diseases - Sofia, Herpesvirus Laboratory and Behring (Germany) were used. Titers of anti VZV < 1:4 were assessed as negative. Titers >= 1:4 were determined as evidence of immune response to experienced infection.

ELISA (enzyme linked immunosorbent assay) for detection of specific IgG anti VZV antibodies in dilution of serum samples 1:44 (Behring Diagnostics, Germany) and 1:101 (EUROIMMUN Medizinische Labordiagnostika GmbH, Germany, VIROTECH VZV ELISA IgG Testkit, Germany) was performed, according to the manufacturer’s recommendations. The results were calculated according the detection limit and cut off value.

Results and Discussion

The results from the study of pregnant women after close exposure to varicella sick children are shown on the Table 1. Among 20 pregnant women who were exposed during the first trimester of pregnancy, 7 (35%) were seronegative by CFT and 5 (25%) – by ELISA. Three (15%) pregnant women experienced varicella and 1 (5%) – herpes zoster. Seroconversion by CFT was detected in 2 pregnant women with varicella and 1 showed a positive result in the acute phase serum sample. Congenital varicella syndrome was not registered in the newborns. One of the babies had signs of intrauterine retardation. Asymptomatic seroconversion by CFT without clinical consequences for the in-
TABLE 2

Outcome in 4 infants whose mothers had chickenpox in the last 20 days before delivery

<table>
<thead>
<tr>
<th>Infants (№)</th>
<th>Onset of mother's rash (days before delivery)</th>
<th>Clinical evidence of intrauterine infection (days after delivery)</th>
<th>Anti VZV Ig assessment mothers</th>
<th>Anti VZV Ig assessment infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 / 1715</td>
<td>9</td>
<td>skin lesions at 7 d</td>
<td>1:4 (CFT) ; + (ELISA)</td>
<td>1:16 (CFT) ; + (ELISA)</td>
</tr>
<tr>
<td>2 / 3595</td>
<td>20</td>
<td>skin lesions at birth</td>
<td>1:4 (CFT) ; + (ELISA)</td>
<td>1:16 (CFT) ; + (ELISA)</td>
</tr>
<tr>
<td>3 / 3604</td>
<td>9</td>
<td>skin lesions at 5 d</td>
<td>1:8 (CFT) ; + (ELISA)</td>
<td>1:32 (CFT) ; + (ELISA)</td>
</tr>
<tr>
<td>4 / 3852</td>
<td>contraction last 2 days before delivery</td>
<td>skin lesions at 7 d</td>
<td>&lt; 1:4 (CFT) ; - (ELISA)</td>
<td>&lt; 1:4 (CFT) ; - (ELISA)</td>
</tr>
</tbody>
</table>

Among 18 pregnant women exposed to varicella in second trimester of pregnancy, 7 (39%) were seronegative by CFT and 3 (17%) – by ELISA (Table 1). One woman (6%) experienced varicella, proved by seroconversion and 3 (17%) underwent asymptomatic seroconversion by CFT. We registered no congenital varicella syndrome in the newborns.

Among 18 pregnant women, exposed to varicella during the third trimester of pregnancy, 5 (28%) were seronegative by CFT and 2 (11%) – by ELISA (Table 1). Seven (39%) experienced varicella and 3 (17%) – herpes zoster. The onset of varicella in the 3 of them occurred more than 30 days before delivery. Clinical symptoms of congenital or neonatal varicella in the newborns were not registered. The onset of varicella in other 3 occurred within the last 20 days before delivery. The mothers showed low levels of antibody titers by CFT (Table 2). The infants, born by these mothers developed neonatal varicella. One woman had a close exposure to varicella in last two days before delivery, but was seronegative by CFT and ELISA. The infants of this mother died with clinical signs of neonatal varicella.

Our findings in the present study showed relative high number VZV seronegative pregnant women with uncertain history of previous varicella infection. Of the exposed to VZV, 34% were seronegative by CFT and 16% - by ELISA. According to the results, ELISA was a more sensitive method to detect previous contraction with the virus in a single serum sample. Congenital varicella syndrome was not registered although 4 women underwent varicella in first half of pregnancy, including the period of organogenesis of the fetus. Only one of the newborns had signs of intrauterine retardation, but we are not sure that this is a result of VZV infection. Many authors report (3, 5, 7, 12), that congenital varicella syndrome is detected in 3% - 9% of the infants, whose mothers experienced first or second trimester varicella. We studied only 4 pregnant women with first and second trimester varicella, and that’s why it is difficult to compare our results with statistical data from the literature. Varicella in the third trimester of pregnancy might remain asymptomatic for the baby, but in some cases may result in neonatal varicella. In our study 7 women had varicella during the third trimester and 1 was contracted in the last 2 days before delivery. Clinical and laboratory data for neonatal varicella were registered in 4 (57%) neonates born by these women. According to other authors (9), 64% of the neonates, exposed to VZV during the last 28 days before delivery or 4 weeks after that were infected, and 57% showed clinical symptoms. Neonatal varicella is a disease of newborns within the first two weeks after delivery. When the infant is contracted in utero this is a consequence of primary or secondary viremia of...
the mother, when the virus is able to pass through placental barrier (5). Intrauterine infection in 3 infants in this study was a result of secondary viremia of mothers with low titers of specific antibody by CFT, and in 1 – a result of primary viremia and lack of maternal antibody by CFT and ELISA (Table 2). Maternal varicella in the peripartum period poses a risk of severe neonatal varicella with mortality rate up to 30% (7). Infection of the mother with onset of the rash 7 – 5 days or less before delivery and 1 – 2 days after delivery, puts the infant at risk of severe neonatal varicella, due to lack or low level of transplacental passage of specific anti VZV antibody to protect the infant (9). Hence, neonatal varicella 5 – 10 days postpartum hints greater danger for exitus letalis, as it was shown in our study for one of the infants. The other 3 live infants with neonatal varicella showed anti VZV IgG by CFT with titers, higher than those of their mothers (Table 2). The explanation of this, may be is the fact, that tested serum samples were taken 5 or more days after the onset of children’s rash and after application of gammaglobulins and administration of transfusions of blood products, that probably contains anti VZV antibody, or because of own synthesis. The presence of specific anti VZV antibodies helped favorable outcome for the neonates. Maternal varicella with onset more than 7 days before delivery usually ensures adequate transplacental passage of specific anti VZV antibody to protect the infant. The asymptomatic seroconversion in part of the seronegative pregnant women remained without evidence of fatal consequences for the infants at birth. In our study asymptomatic intrauterine infection was not follow up. Asymptomatic intrauterine varicella infection could be demonstrated only by proving herpes zoster 1 – 2 years after delivery or by detection of specific anti VZV IgM in the neonatal period, or persistent anti VZV IgG at one to two years of age (12). Our findings confirmed literature (9, 12, 13), that herpes zoster during pregnancy was not associated with serious maternal morbidity or with any evidence of intrauterine varicella infection, because absence of evidence for transplacental transmission of VZV and because preexisting maternal immunity to VZV, that protect the fetus (14).

Pregnant women with uncertain history of previous VZV infection, after close exposure to varicella, must be tested to define the immune status by detection of specific anti VZV IgG antibodies. According to our results, ELISA was more appropriate method in single serum sample. When the result of IgG testing is negative, IgM specific anti VZV antibody can be evaluated. It is recommended also, to test second serum sample after 3 – 4 weeks, to detect seroconversion or rise of titers of anti VZV IgG. At present, there is no reliable marker to predict the development of congenital varicella syndrome. Therefore, close ultrasound monitoring for fetal abnormalities after maternal first trimester varicella is recommended (7). All babies of mothers with third trimester varicella, especially in the peripartum period, should be examined for immunological data of infection, even they were asymptomatic. Presence of anti VZV IgM antibodies at birth and persisting anti VZV IgG 1 – 2 years after delivery were markers for expected development of herpes zoster in early childhood. Some authors report (7, 11), that intravenous (IV-VZVIG) or intramuscular (IM-VZVIG) varicella zoster immunoglobulin, given within 72 - 96 hours after significant exposure to varicella of pregnant women who are seronegative, or with no history of varicella, may prevent or modify the course of disease. But it may not abolish the risk of fetal infection. VZIG is indicated for the baby as early, as possible, if maternal varicella develops up to 7 days before delivery or up to 28 days after delivery (7, 12). VZIG cannot we obtained in some
countries, including Bulgaria. Intravenous Acyclovir treatment should be administered to babies presenting with varicella, which are unwell including those, who are premature. (7). Oral Acyclovir prophylactic (40 mg/kg daily) administration (6) may prevent the development of varicella in preterm infants possibly exposed to VZV.

In conclusion, according to our data varicella during pregnancy, as a primary VZV infection, was associated with maternal morbidity and evidence of fetal and neonatal infection. The infants, whose mothers were with varicella peripartum and with missing or low-level specific anti VZV antibodies, developed neonatal varicella. Herpes zoster during pregnancy was not associated with serious maternal morbidity or with any evidence of intrauterine varicella infection

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REFERENCES