# Varicella in Pregnancy

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A 27-year-old pregnant woman at 40 weeks' gestation called the Family Medical Center eight days after onset of chickenpox in her oldest child. She stated that neither she nor her mother could recall her having had chickenpox. She had developed two lesions on her thigh and abdomen and was concerned about possible risk to her unborn child.

She was seen the following morning. The lesions, thought to not be characteristic of varicella, were unroofed and sent for culture and fluorescent antibody staining. Varicella zoster antibody titers were obtained. No further lesions had developed, and the patient was afebrile.

The patient was found to have no detectable antibodies to varicella and therefore presumed to be susceptible. After consultation with the obstetric, neonatal, and infectious disease services, she was given varicella-zoster immune globulin (VZIG), 625 units intramuscularly on the following day. Fluorescent antibody and culture results of the lesion were negative for varicella. With the information she did not have active varicella nor was she immune, the perinatal consultants recommended no intervention to start or stop labor.

Three days later she delivered a 3,852-g male infant, Apgars 8 and 9, following less than one hour of ruptured membranes. The infant received 125 units of varicella-zoster immune globulin intramuscularly in the delivery room and was observed in the neonatal intensive care unit briefly for mild respiratory distress. A chest x-ray examination was within normal limits and his breathing rapidly improved. The baby was discharged home without further treatment.

Twelve hours postpartum the mother developed a vesicular rash on her anterior chest characteristic of varicella. Simultaneous to the mother's onset of rash, the two siblings exposed at the same time as their mother to their infected sibling developed classic varicella. The mother's course was complicated by a new and more severe onset of rash and systemic symptoms one week postpartum. No effort was made to isolate the baby from the mother or siblings.

The infant was seen at 3 and 6 days of life and continued to do well. On day 20 of life he developed onset of a typical varicella rash with multiple lesions over his body and head. Liver function tests were obtained; bilirubin was 32 μmol/L (1.9 mg/dL), serum glutamic-oxaloacetic transaminase 20 U/L, serum glutamic-pyruvic transaminase 11 U/L (all within normal limits). After much discussion with the pediatric infectious disease consultants and the infant's parents, the decision was made to admit the infant for intravenous acyclovir treatment. With the exception of the diffuse varicella rash, the infant had an entirely normal physical and neurologic examination and was afebrile. The infant developed no new lesions after the acyclovir was started, a 10-mg/kg dose every eight hours. He developed no complications and was discharged home on no medications after 72 hours. His subsequent course has been entirely normal for his age.

## DISCUSSION AND LITERATURE REVIEW

### Varicella Infection

The varicella-zoster virus is a member of the herpes virus group. After primary infection, it is believed to replicate locally, probably in the nasopharynx, following which an initial viremia leads to seeding of the reticuloendothelial system. In the reticuloendothelial system, the virus is thought to undergo further replication, which is followed by a secondary viremia and dissemination to skin and other organs.[1] The replication phases and the primary viremia occur during a variable 11- to 20-day incubation period. Symptoms are probably first manifest during the dissemination phase. Persons are considered to be contagious from 24 to 48 hours prior to onset of lesions until about six days after the first lesions appear (or when all lesions are crusted and scabbed). The virus then is believed to remain quiescent in nerve ganglia for life, reactivating at times in the form of zoster.[2]

Experience with the varicella-zoster virus is ubiquitous in temperate areas. There is nearly 100 percent seropositivity by the age of 60 years.[3] The vast majority of infec-

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tions occur before the age of 9 years. Inexplicably, in tropical areas it is more common to reach adulthood without having encountered the virus.[4] In West Bengal the mean age of onset of varicella was found to be 23.7 years.[3]

While pregnancy and chickenpox are both common conditions, simultaneous occurrence is rare. Estimates of incidence range from 1.3 to 7 cases per 10,000 pregnancies in the United States.[2]

## ISSUES IN PREGNANCY

### Congenital Varicella Syndrome

Primary maternal infection with varicella-zoster virus during the first two trimesters of pregnancy has been associated with a set of stigmata that include intrauterine growth retardation, limb hypoplasia with dermal scarring, malformed digits, central nervous system manifestations including retardation, cerebellar and cortical atrophy, and seizures, and eye manifestations, specifically microphthalmia cataract and chorioretinitis.[5,6]

The risk of this syndrome occurring is low compared with syndromes associated with other congenital infections. The best estimate available is that 2.3 percent (95 percent confidence interval 0.5 to 6.5 percent)[7] of women affected by primary varicella in the first trimester will give birth to an affected child. Of note is that correlation between manifestations and stage of organ development is not precise.[7]

### Maternal Complications

Primary varicella is more severe in adults than in children. Although only 1.8 percent of cases occur after the age of 20 years in the United States, nearly 24 percent of deaths attributable to varicella occur in this population.[3] It is not clear whether pregnant women are at any greater risk of complications than the adult population in general, but there is some support for greater severity among the pregnant population.[4,8] In one study of 29 pregnant women with primary varicella, there was a 14 percent incidence of pneumonia and 3 percent mortality. Among 236 nonpregnant adults the pneumonia incidence was 11 percent and no mortality occurred.[9]

### Perinatal Complications

There is general agreement in the literature that a high-risk period for fatal outcome exists for the neonate. Generally this period is thought to correspond to prenatal exposure to varicella virus without opportunity to acquire passive maternal antibodies. Thus, when the maternal rash develops between four days before and two days following delivery, the associated neonatal mortality rate is 31 percent.[9,10] Some caution has been suggested in interpreting this estimate, as the figure is based upon case reports and not upon true prospective data.[6]

## VARICELLA ZOSTER IMMUNE GLOBULIN

### Neonate

Varicella-zoster immune globulin has been shown to prevent or attenuate the course of varicella when given within the first 96 hours following exposure.[11]

Neonates born to mothers with onset of maternal disease between five days prior to and 48 hours following delivery are a target population that should receive VZIG (125 units) according to the American Committee on Immunization Practices (ACIP) recommendations.[12,13]

One prospective study of 41 infants exposed to maternal varicella in the high-risk period and treated with VZIG reported 33 infants with no or mild subsequent symptoms, only two infants with severe disease, and no deaths.[11] The 31 percent mortality figure, if truly accurate, would represent a dramatic protective effect.

Caution in interpreting these data may be advisable; there are case reports of at least three neonates who contracted severe varicella and died despite treatment with VZIG. This finding led Great Britain to change its recommended dose of VZIG to 250 mg instead of 125 mg. The impact of this increased dose has not been evaluated.[14,15]

### Mother

At present the ACIP recommendation regarding maternal administration VZIG is to evaluate on a case-by-case basis and certainly to give VZIG to any adult who is immunocompromised. Routine administration to exposed normal adults (including pregnant women) is not recommended because there is concern about exhausting supplies.[13]

Prior to administration of VZIG to an exposed adult, susceptibility should be documented serologically. Eighty percent of adults who by history are susceptible are in fact immune by antibody studies.[13,16] Administration within 96 hours of exposure is necessary for prevention of maternal varicella.

In a prospective study of 778 women exposed to varicella during pregnancy, 724 (93.1 percent) were found to be immune. Of the 54 found to be nonimmune, 25 received VZIG within 96 hours of exposure, and only five developed symptoms of varicella. Nine women received VZIG more than 96 hours following exposure, and all subsequently developed symptoms. Of the remaining 18

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women who did not receive VZIG, 16 developed varicella; the status of two was unknown.[17] No information is available regarding fetal or neonatal outcome when mothers receive VZIG in pregnancy.

### Acyclovir Treatment

There are no prospective studies of acyclovir treatment of the neonate. There are approximately 13 case reports of infants born during the high-risk period who were treated with acyclovir as well as VZIG. Eight of these received acyclovir prophylactically, and the others were treated when symptoms developed. There were three deaths among the latter group (although acyclovir dose may have been inadequate in two of these cases). No deaths occurred in the eight infants treated prophylactically.[14,18–20]

Although some authors advocate routine acyclovir prophylaxis for the high-risk neonate,[18–20] limited experience makes it difficult to conclude definitively that prophylactic intravenous acyclovir is efficacious and safe. A larger controlled trial would be helpful.

### Varicella Vaccine

A live attenuated vaccine has been tested for 15 years in Japan and eight years in the United States, Canada, and Europe and may be available soon.[21] While the principal target group will be susceptible immunosuppressed children, a secondary group in whom this might be advisable would be healthy susceptible adults.[21] If women could be screened and vaccinated prior to pregnancy, congenital varicella syndrome and perinatal varicella should be preventable diseases.[4]

## CONCLUSIONS

Primary varicella infection in pregnancy carries risk, particularly to the fetus. In the first two trimesters the risk is mainly that of fetal malformation, although this sequela is rare. In the last trimester the risk, as for this patient, is infecting the infant at or near birth, before the mother can develop antibodies that pass transplacentally and provide passive immunity to the newborn. There is some evidence supporting administration of VZIG to pregnant women. VZIG may prevent the woman from developing clinically apparent varicella infection if given within 96 hours of exposure. There are no data to answer the question of what effect maternal VZIG has on fetal infection. Babies born to mothers exposed near term should receive VZIG at birth. Whether the 125-mg or 250-mg dose is best is not clear. Whether an infant who has known exposure during this critical time should receive prophylactic intravenous acyclovir is also not clear. No prospective data exist to help answer this question. Finally, when the varicella vaccine becomes available, checking a young woman's immune status prior to pregnancy and vaccinating the nonimmune woman could lead to primary prevention of varicella in pregnancy.

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