

## Fetal-maternal Relationships in Herpes Simplex

Generalized herpes simplex infection of the newborn provides one example of an intriguing group of infections where, in the absence of maternal immunity, the inherent vulnerability of the immature tissue of the fetus and newborn infant allows a disseminated and often destructive invasion by an agent which at later ages rarely behaves in this way. Other examples of this group are toxoplasmosis, cytomegalic inclusion disease, and rubella.

Between 50 and 90% of adults have antibodies in their serum to herpes simplex virus (HSV), indicating that infection, often inapparent, has occurred at some time. The virus persists indefinitely, though often silently. In communities where most women of child-bearing age have antibodies, these will pass to the fetus and protect it from infection. When the infant's passive antibody is waning in the 4th to 6th month, he may acquire a mild or inapparent infection, usually of the buccal or gingival mucous membranes. In higher socio-economic groups, with rising standards of hygiene, the incidence of HSV infection is probably now falling, and there is a greater chance of women of child-bearing age not having antibodies to HSV (Smith, Peutherer, and MacCallum, 1967). These women may become infected during pregnancy and pass the virus to their infants. Alternatively, the infant, lacking passive antibody, is unprotected against infection from other contacts at a time when he is most vulnerable. The very severe form of generalized disease may occur up to 2 years of age if the child is malnourished (Kipps *et al.*, 1967), or has eczema.

### Routes of Infection of Fetus and Newborn

Though more than 60 neonatal cases are recorded, there is no report of HSV infection causing stillbirth or abortion, and no definite evidence of teratogenicity for the human fetus. In the few confirmed reports of fetal infection in late pregnancy the route was either transplacental (Sieber *et al.*, 1966) or ascending after rupture of the membranes (Yen, Reagan, and Rosenthal, 1965).

Probably in most cases of materno-fetal transmission, the virus is acquired during passage through the infected birth canal. After birth, infection may come from the mother, staff, or visitors. 40% of reported cases of neonatal HSV infection had a known contact, and in half of these the mother was the source. Of the remaining 60%, one-quarter were born to mothers with an unexplained febrile illness (V. A. Fulginiti, 1966, unpublished data, quoted by Sieber *et al.*, 1966).

Herpes simplex virus may occur, without symptoms of infection, in the mouth or genital tract, and this may account for the absence of any obvious source. HSV has been isolated from the vagina, in the absence of overt lesions, of a mother whose baby died of the disseminated infection (Partridge and Millis, 1968).

### Maternal and Fetal Antibody Levels

Neutralizing antibodies for HSV measured *in vitro* have shown equivalent levels in the mother and in cord blood. This antibody should protect *in vivo* if the titre is adequate, 1 in 8 or more, though it is known that the neutralizing antibodies which first appear after a primary infection are less avid than those present a year or more later. Maternal antibodies have usually been absent in cases of generalized neonatal infection, though there are insufficient data to state definitely that maternal antibodies are always protective for the infant, and they may be ineffective against a large infecting dose of the virus.

### Maternal Genital Herpes

Primary or recurrent herpetic infection of the cervix, vagina, and vulva is a potential source of infection of the baby. Yen *et al.* (1965) found 16 cases in 8 months of obstetrical and gynaecological practice in Cleveland, Ohio. Nahmias, Josey, and Naib (1967a) calculated that 1 in 2000 women in an indigent population in Atlanta, Georgia, had a herpetic genital lesion at some time during pregnancy.

Herpes should be thought of if there is a history of painless or painful genital ulcers, or, if the infection is primary, systemic upset with fever, and inguinal lymphadenopathy.

Screening all antenatal patients for the disease seems impractical, and, in a survey of 175 pregnant women by virus culture, cervical and vaginal swabs were negative in all (Nahmias *et al.*, 1967b). However, where routine Papanicolaou smears are already being undertaken, some cases may be detected, because multinucleate giant cells with intranuclear inclusions are strongly suggestive of HSV infection. Isolation of the virus will confirm the diagnosis.

The baby most at risk from infection from this source is one whose mother contracts primary genital herpes near term, and this underlines the need for obstetricians to be aware of the disease. In addition, neonatal infection may be acquired from a mother with a history of recurrent genital ulcers (MacCallum, 1959; Yen *et al.*, 1965).

The few reports of genital herpes in pregnancy make prediction of the outcome for the baby difficult. Nahmias *et al.* (1967a) report 27 pregnant women with evidence of genital herpes, whose babies were unaffected. Topical idoxuridine has been used in the treatment of genital herpes, with apparent symptomatic benefit, but has not as yet been used prophylactically as a local application before delivery in known genital herpes.

Where an apparent *primary* genital infection is discovered near term, most writers recommend caesarean section, particularly if the mother's titre is low and the membranes intact, to avoid passage through the infected birth canal. Where the mother has *recurrent* genital herpes, the baby is likely to be protected, but it would be hazardous for there to be a prolonged interval of ruptured membranes before delivery.

Herpes *labialis* in the mother may be precipitated by pregnancy and labour. There is no well-documented record of a mother with recurrent herpes labialis and complete neutralizing antibodies before conception having a severely affected baby. We have seen several cases of puerperal herpes labialis, but no transfer to babies has resulted; the mothers were isolated from other babies, but not their own.

### Diagnosis and Treatment of Neonatal Herpes

Recovery from generalized neonatal HSV infection is rare, and the survivors are usually brain-damaged. It is difficult to diagnose in a sick baby unless some clues are picked up, such as a history of

maternal infection in pregnancy, a herpetic contact, or the presence of mucocutaneous vesicles. Clinical presentation includes meningo-encephalitis, pneumonia, and hepato-adrenal failure. Fortunately the virus can be readily and speedily isolated. In the infected neonate it has been isolated from the nose, throat, conjunctiva, sputum, vesicle fluid, blood, CSF, and even faeces, and fluid from a hydrocele. If sufficient virus or virus-affected cells are present, vesicle fluid examined by electron microscopy or fluorescent microscopy may give a positive diagnosis in a few hours. Routine smears for cytology from a vesicle may show multinucleate cells with intranuclear inclusions suggestive of virus infection of the herpes group. Virus tissue culture requires only a few infecting particles, and will give a positive result in 24–48 hours. Estimation of antibody to HSV in paired sera is of value, but not, of course, for immediate diagnosis.

If a mother has an unexplained illness in the last part of pregnancy, histological examination and virus culture of the placenta may provide evidence of herpes simplex infection and thus a possible approach (Witzleben and Driscoll, 1965).

Until recently no specific treatment was available. Corticosteroids may be of value because adrenal necrosis is frequently found in the disseminated infection. Often  $\gamma$ -globulin is used, which usually has a 1 : 500 to 1 : 2000 neutralizing titre to HSV, but there is no convincing evidence of its value. Wheeler and Huffines (1965) gave 7 ml.  $\gamma$ -globulin intramuscularly to a 3.5 kg. newborn baby at risk; the titre rose from 0 at birth to 1 : 8 after 2 days. However, a further 7 ml.  $\gamma$ -globulin on the 5th and 8th days, and exchange transfusion using blood with a titre of 1 : 16, all failed to prevent the baby from dying on the 10th day. The mother had vulval herpes and had been given 15 ml.  $\gamma$ -globulin 6 days before, and 14 ml. on the day of delivery.

There have been a few recent advances in the field of virus chemotherapy, directed particularly against the DNA viruses, which include variola and vaccinia, herpes simplex, varicella, cytomegalic inclusion disease, and adenoviruses. The most effective compounds against HSV have been halogenated uridines. Topical 5-iodo-2'-deoxyuridine (IDU) has been used extensively in the treatment of acute herpetic keratitis in adults, and certain preparations, when given early, will accelerate healing of recurrent herpetic skin lesions (MacCallum and Juel-Jensen, 1966). Systemic IDU as a 0.5% solution in 5% glucose has been used for herpetic encephalitis (references in Marshall, 1967), and for neonatal systemic herpes, with possible initial improvement (Partridge and Millis, 1968).

Although this drug is cytotoxic, in a disease such as neonatal systemic herpes with an almost invariably fatal outcome, further trial is merited. It might be combined with the maximum tolerated dose of  $\gamma$ -globulin and exchange transfusion with high titre blood. Success would be more likely if these measures were used early in the disease before the general dissemination of the virus had become established. Another uridine, 5-methyl-2'-deoxyuridine, is claimed to have very low toxicity and to be more specific against HSV (Shen, McPherson, and Linn, 1966), but no clinical studies have been reported.

Topical IDU should be used for herpetic keratitis and for skin lesions in the newborn.

### Prevention of Neonatal Herpetic Infection

In the light of existing facts, the following tentative suggestions can be made.

1. Unexplained pyrexia during pregnancy should be investigated with the possibility of herpetic infection in mind.

2. In pregnant women with a history of 'cold sores', the genital tract should be examined periodically and virus culture of any ulcerative or vesicular lesion made.

3. Caesarean section, where there is proven maternal genital herpes, seems rational, though it has not always prevented the baby from being infected.

4. A mother with suspected herpes and no antibodies should be given  $\gamma$ -globulin. Suggested doses are 15 ml. at 3-day intervals for 3 doses. The baby should be given 7 ml. at birth, and at 3-day intervals for three doses.

5. All staff in maternity units should be warned of the dangers of herpes virus to the newborn. Doctors and nurses with herpetic lesions should not handle babies, and the lesions may be treated with topical idoxuridine. A similar watch should be attempted on visiting relatives. Mothers and

babies with active herpes should be isolated from other babies.

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### REFERENCES

- Kipps, A., Becker, W., Wainwright, J., and McKenzie, D. (1967). Fatal disseminated primary herpesvirus infection in children: epidemiology based on 93 non-neonatal cases. *S. Afr. med. J.*, **41**, 647.
- MacCallum, F. O. (1959). Generalised herpes simplex in the neonatal period. *Acta virol.*, **3**, Suppl., 17.
- , and Juel-Jensen, B. E. (1966). Herpes simplex virus skin infection in man treated with idoxuridine in dimethylsulphoxide. Results of a double-blind controlled trial. *Brit. med. J.*, **2**, 805.
- Marshall, W. J. S. (1967). Herpes simplex encephalitis treated with idoxuridine and external decompression. *Lancet*, **2**, 579.
- Nahmias, A. J., Josey, W. E., and Naib, Z. M. (1967a). Neonatal herpes simplex infection. Role of genital infection in mother as the source of virus in the newborn. *J. Amer. med. Ass.*, **199**, 164.
- , Naib, Z. M., Josey, W. E., and Clepper, A. C. (1967b). Genital herpes simplex infection. Virologic and cytologic studies. *Obstet. and Gynec.*, **29**, 395.
- Partridge, J. W., and Millis, R. R. (1968). Systemic herpes simplex infection in a newborn treated with intravenous idoxuridine. *Arch. Dis. Childh.*, **43**, 377.
- Shen, T. Y., McPherson, J. F., and Linn, B. O. (1966). Nucleosides. III. Studies on 5-methylamino-2'-deoxyuridine as a specific antiherpes agent. *J. med. pharm. Chem.*, **9**, 366.
- Sieber, O. F., Jr., Fulginiti, V. A., Brazie, J., and Umlauf, H. J., Jr. (1966). In utero infection of the fetus by herpes simplex virus. *J. Pediat.*, **69**, 30.
- Smith, I. W., Peutherer, J. F., and MacCallum, F. O. (1967). The incidence of *Herpesvirus hominis* antibody in the population. *J. Hyg. (Lond.)*, **65**, 395.
- Wheeler, C. E., Jr., and Huffines, W. D. (1965). Primary disseminated herpes simplex of the newborn. *J. Amer. med. Ass.*, **191**, 455.
- Witzleben, C. L., and Driscoll, S. G. (1965). Possible transplacental transmission of herpes simplex infection. *Pediatrics*, **36**, 192.
- Yen, S. S. C., Reagan, J. W., and Rosenthal, M. S. (1965). Herpes simplex infection in female genital tract. *Obstet. and Gynec.*, **25**, 479.