

FETAL AND NEONATAL EDITION

# ARCHIVES OF DISEASE IN CHILDHOOD

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## Annotations

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### Herpes simplex virus infection in pregnancy

The incidence of neonatal herpes simplex virus (HSV) infection is about 200–500 per 100 000 live births in the USA<sup>1 2</sup> but has been estimated at two per 100 000 in the UK.<sup>3</sup> Neonatal HSV results from perinatal acquisition from the maternal genital tract in about 85% of cases. Approximately 5% of cases result from transplacental spread resulting in intrauterine HSV,<sup>4</sup> while about 10% of cases are secondary to postnatal acquisition.<sup>5</sup>

#### Intrauterine HSV infection

Nine (4.7%) of 192 infants with neonatal HSV infection enrolled in a large prospective US study had evidence of intrauterine HSV infection.<sup>4</sup> These nine babies, and four other babies selectively referred to the authors, had a combination of skin lesions and scars at birth, chorioretinitis, microcephaly or hydranencephaly, and microphthalmia. Eight mothers were asymptomatic, four had apparent primary genital HSV infection (two in the first and two in the third trimester), and one mother had recurrent genital herpes. The risk of intrauterine infection if the mother has proved primary genital herpes in pregnancy is unknown, but is probably very small.<sup>6</sup>

#### Maternal HSV infection

About 70% of babies with neonatal HSV infection are born to mothers with no history of genital lesions.<sup>5</sup> Most neonatal cases result from primary maternal HSV infection around the time of delivery, as determined by IgM production, although the maternal infection may be asymptomatic.<sup>1</sup> Of those asymptomatic women who have HSV detected in early labour, about a third have primary genital infection, and their babies are 10 times more likely to develop neonatal HSV than babies of women with asymptomatic reactivation. A distinction has been drawn between women with *primary* genital herpes, who become infected with either HSV-1 or HSV-2 in the absence of prior HSV antibodies, and those with so called *non-primary* infection, who have a first symptomatic genital infection, usually with HSV-2, in the presence of neutralising HSV IgG antibodies, usually to HSV-1. For the USA it has been estimated that the relative proportions of recurrent, primary, and non-primary HSV infections at the time of labour are 91.3%, 2.1%, and 6.6% respectively.<sup>7</sup> It was originally thought that non-primary maternal infections were less likely to lead to neonatal infection.<sup>6</sup> However, in a recent study of babies born vaginally to asymptomatic women who were found by viral culture to be shedding HSV at delivery, infection developed

in two of five babies of mothers with primary infection and four of 13 with non-primary infection,<sup>1</sup> suggesting that anti-HSV-1 antibody may not be as protective against HSV-2 infection as once thought.

Specific maternal IgG antibody against the relevant HSV serotype protects against neonatal infection, but this protection is not absolute. Prober *et al*<sup>8</sup> and Brown *et al*<sup>1</sup> studied babies born vaginally to women with recurrent HSV infection who were shedding virus at the time of delivery. In the study of Prober *et al* none of 34 exposed babies became infected, and their neutralising antibody levels to HSV type 2 were significantly higher than those of historically infected babies. In the study of Brown *et al*, one of 33 exposed babies became infected. Thus neonatal HSV infection may follow recurrent maternal HSV infection, although it is more common following primary (and non-primary) infection.

#### Neonatal infection

Neonatal HSV infection may be *localised* to skin, eye or mouth, may be *generalised* to involve the liver, adrenals, lungs, and other organs including the brain, may cause isolated *pneumonitis*, or there may be isolated *meningoencephalitis*. The prognosis of all but the first form is poor. Without antiviral treatment about 70% of babies with localised HSV infection will progress to disseminated infection.<sup>9</sup> With increasing recent recognition that neonatal vesicular skin eruptions are often herpetic, specific diagnosis by immunofluorescent staining or electron microscopy and early antiviral treatment, there has been a marked fall in the proportion of cases of neonatal HSV infection in the USA that are disseminated, and a concomitant increase in the proportion of babies with localised disease.<sup>10</sup>

The two drugs that have been shown to be effective in neonatal HSV infection are acyclovir and adenosine arabinoside (ara-A), and the two drugs are almost identical in terms of mortality and long term morbidity.<sup>11</sup> Even with these drugs, however, the mortality of disseminated disease is 50–60%.<sup>11</sup>

There is considerable concern that neonatal HSV infection may cause chronic, insidious central nervous system infection leading to progressive neurodevelopmental deterioration. Gutman *et al* described babies with neonatal HSV encephalitis who deteriorated after completing antiviral treatment or had progressive deterioration over their first year of life.<sup>12</sup> Even more alarmingly, Whitley *et al* found that four of 71 babies with neonatal HSV infection localised to the skin, eyes, or mouth had long term neurological damage.<sup>13</sup> All four babies had HSV-2 and had three or more recurrences of

## Management of HSV infection in pregnancy

Maternal infection	Risk to fetus/baby	Management of mother	Management of baby
Primary in 1st trimester	≤20% of abortion or intrauterine infection	No action	As for recurrent herpes
First ever lesions at delivery			
(a) Primary	About 50% risk of neonatal HSV <sup>6</sup>	Caesarean section	*Cultures if caesarean section performed: treat with acyclovir if positive. Prophylactic acyclovir if delivers vaginally
(b) Recurrence	Unknown	Vaginal delivery	*Cultures: treat with acyclovir if positive
(c) Unknown	About 30% chance infection is primary	Caesarean section	*Cultures: treat with acyclovir if positive
Recurrent genital herpes, no signs or symptoms	≤3% of neonatal HSV <sup>1, 8</sup>	Vaginal delivery	Observe for signs or *cultures and treat with acyclovir if positive

\*Cultures= nasopharyngeal+conjunctival viral cultures at 24-48 hours of age.

skin vesicles in the first year of life. Strong consideration should be given to long term oral acyclovir prophylaxis, perhaps for a year, for all babies with neonatal HSV encephalitis and for babies with localised HSV-2 infection who have three or more skin recurrences.

## Prevention of neonatal HSV infection

The risk to the fetus of stillbirth or intrauterine infection when the mother has primary genital herpes in the first trimester is unknown, but probably small.<sup>6</sup> Acyclovir treatment of the mother under these circumstances has not been evaluated. Acyclovir appears to cross the placenta only in small quantities,<sup>14</sup> and its safety for the fetus is unproved, so its use does not seem indicated.

The transmission rate to babies at highest risk, those whose mothers have active, primary genital herpes at delivery, is about 50% if they are delivered vaginally.<sup>6</sup> Caesarean section, particularly if performed within 24 hours of membrane rupture, reduces the risk of neonatal HSV infection,<sup>15</sup> although some babies, perhaps 15-20%, will still be infected.

In clinical practice, it is not always clear whether a woman presenting with her first episode of clinical genital herpes infection at delivery has primary or recurrent disease. About 30% of such women will have primary infection.<sup>1</sup> If there is not sufficient time to determine whether the mother has specific IgM, then it seems wise to advise caesarean section.

The risk to a baby of an asymptomatic woman with a history of recurrent genital herpes is low.<sup>1, 8</sup> The baby should be delivered vaginally. When a mother with recurrent genital herpes has active genital lesions at term, either symptomatic or on cervical examination, the risk to the baby is probably higher than if she is asymptomatic since the baby is likely to receive a greater viral load. Some authorities would advise caesarean section, although we feel that a more conservative approach is acceptable (see table). At present there are insufficient data on safety to advise giving acyclovir to pregnant women with HSV infection.

At one stage it was widely advocated that women with a history of recurrent genital herpes should have screening cervical viral cultures taken near term, but this would prevent very few cases of neonatal herpes. In the USA it would cost \$1.9 million per case averted and there would be one maternal death from complications of caesarean section for every 10 neonatal cases prevented.<sup>16</sup> Rapid antigen detection for HSV in genital specimens at delivery would identify most at-risk babies, but result in a large number of caesarean sections. Libman *et al* have analysed different strategies for prevention of neonatal HSV infection, and concluded that maternal physical examination at onset of labour would give the best results in terms of numbers of cases of neonatal HSV averted for least number of extra caesarean sections.<sup>7</sup>

There is no clear consensus as to the management of asymptomatic babies born to women with genital herpes under the different circumstances described above. The alternatives are that the baby should be treated with acyclovir from birth, should have nasopharyngeal and conjunctival viral cultures taken at 24-48 hours of age (indicating true colonisation rather than surface colonisation), and be treated with acyclovir only if positive, or should simply be observed and treated if symptomatic.<sup>17</sup> Evidently the greater the risk of neonatal HSV developing, the more reasonable it is to use aggressive intervention. Possible strategies are outlined in the table. Any at-risk baby with signs suggestive of neonatal HSV infection should be treated with acyclovir or ara-A until the baby's infection status is clarified.

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