Infections

Genital mycoplasmal infections: their relation to prematurity and other abnormalities of reproduction

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Mycoplasmas are a distinct group of microorganisms differing in important biological characteristics from bacteria, viruses, fungi, protozoa and chlamydia (McCormack et al, 1973a). There are eight recognized species of mycoplasmas which have been isolated from man (table I). *Mycoplasma pneumoniae*, the Eaton agent, causes cold agglutinin-positive primary atypical pneumonia. *M. salivarium, M. orale, M. buccale, and M. fauicium* are oropharyngeal commensals and have not as yet been convincingly implicated in any disease process (Freundt et al, 1974). *M. fermentans* is an unusual genital isolate which also appears to be a commensal. *M. hominis* and *Ureaplasma urealyticum*, also known as the T-mycoplasmas or T-strains, are common genital organisms (Shepard et al, 1974). Although *M. hominis* and *U. urealyticum* have been implicated in nongonococcal urethritis, pelvic inflammatory disease, and a number of other disorders, most interest in these organisms has centred around their possible involvement in disorders of reproduction. The purpose of this communication will be to review the evidence linking *M. hominis* and *U. urealyticum* to infertility, abortion, stillbirth, low birth weight, and puerperal fever.

Epidemiological Considerations

Basic to the understanding of the role of a microorganism in human disease is an understanding of the epidemiology of the organism, its mode of transmission and its prevalence among the normal population.

Genital mycoplasmas can be isolated from the genitalia and upper respiratory tract of about 30% of newborn infants. These organisms are primarily acquired during passage through the birth canal; infants who are delivered by caesarean section are colonized less often than those who are delivered vaginally (Klein et al, 1969). Colonization does not persist throughout childhood. Only about 10% of girls between 1 and 10 years of age have mycoplasmas recovered from the genitourinary tract (Lee et al, 1974).

Following puberty, sexual experience appears to be the primary determinant of colonization with both *M. hominis* and *U. urealyticum* (McCormack et al, 1972). Table II summarizes a study in which self-obtained vaginal cultures and anonymous questionnaires were obtained from a group of student and graduate nurses. Those who had not experienced genital contact had low rates of colonization, similar to those seen among young children. Among those who were sexually experienced, colonization with both *U. urealyticum* and *M. hominis* rose in relation to the number of sexual partners, reaching 75% and 16-7% among those who had had intercourse with three or more partners. It is against this background that we must view the evidence linking the genital mycoplasmas to disorders of reproduction.

Infertility

A series of reports from Sweden has suggested that...
U. urealyticum might be an important cause of unexplained involuntary infertility. These workers found that infertile couples were colonized with U. urealyticum significantly more often than couples of normal fertility. Furthermore, in an uncontrolled study, treatment of colonized infertile couples with mycoplasmicidal antibiotics was associated with conception in about 30% of cases (Gnarpe and Friberg, 1973). In similar studies, Love et al (1973) have associated M. hominis with infertility.

More recently, de Louvois et al (1974) have reported that they isolated both U. urealyticum and M. hominis as often from fertile as from infertile couples, a finding which is in agreement with unpublished observations from our laboratory. The same group of investigators has conducted a controlled therapeutic trial in which couples with infertility of unascertained cause were randomly assigned to receive doxycycline, a placebo or no treatment. Although doxycycline eradicated both M. hominis and U. urealyticum, the rate of conception was no higher in those treated with the drug than in the control group. They concluded that mycoplasmas are not associated with primary infertility (Harrison et al, 1975). It should be noted that this negative study is the only properly controlled study in which the relationship of mycoplasmas to infertility has been assessed.

Spontaneous Abortion and Stillbirth

Genital mycoplasmas have been isolated from products of conception of early abortions (Caspi et al, 1972) and mid-trimester fetal losses (Sompolinsky et al, 1975) more often than from the products of conception of induced abortions. It is not clear from these reports whether the mycoplasmas were wholly or partially responsible for fetal death. It is equally likely that these organisms were able to invade the fetus and placenta once fetal death had occurred for other reasons.

Mycoplasmas have been isolated from the viscera and lungs of spontaneously aborted fetuses and still-born infants. The isolation of mycoplasmas from fetal lungs probably represents aspiration of infected amniotic fluid whereas isolation from the viscera may be indicative of hematogenous spread, perhaps from a placitis with invasion of the fetus via the umbilical vessels (McCormack et al, 1973a).

The possible association of mycoplasmic infection with fetal loss is of considerable interest and importance since these organisms are sensitive in vitro to tetracycline and other broad-spectrum antibiotics. Thus, fetal loss, if due to these organisms, could conceivably be prevented by appropriate antimicrobial therapy. It is unfortunate in this regard that there have been no controlled studies in which pregnant women with a history of fetal loss have been randomly assigned to receive antibiotic or placebo.

In an uncontrolled study, six women with a history of a total of 29 previous unsuccessful pregnancies, most of which had ended in spontaneous abortion during the first trimester, were treated with demethyl-chlortetracycline. Treatment began before or shortly after conception and continued through the 28th week of pregnancy. Four of the six patients gave birth to viable infants (Driscoll et al, 1969). These and other instances in which women with a poor reproductive history were found to be colonized with U. urealyticum and had successful pregnancies after treatment with tetracyclines have led this group of investigators to postulate that subclinical infection with mycoplasmas is an important cause of reproductive failure (Horne et al, 1974). Their hypothesis has been strengthened by the demonstration of inflammation in endometrial biopsies from women with a poor reproductive history who were infected with U. urealyticum (Horne et al, 1973). This area, however, remains controversial and well controlled therapeutic trials are urgently needed to settle the issue.

Low Birth Weight

The chain of events linking the genital mycoplasmas to birth weight began about 15 years ago. In studies conducted before the association of prenatal tetracycline administration to staining of the primary dentition was recognized, this antibiotic was
administered to pregnant women. In each of two controlled, double-blind studies, treatment with tetracycline for six weeks was associated with a significant reduction in the prevalence of low birth weight infants (Elder et al, 1968; Elder et al, 1971). Although no microbiological examinations were performed, it was postulated that a tetracycline-responsive microorganism might be responsible for some instances of low birth weight. The mycoplasmas were among the organisms which were considered.

The first direct evidence linking the genital mycoplasmas to birth weight came when Klein et al (1969) examined newborn infants. They found that infants were colonized with mycoplasmas in inverse relation to birth weight. Their data are summarized in table III.

A prospective study was then conducted in which cultures were obtained from 484 prenatal patients at the time of their first prenatal visit (Braun et al, 1971). As shown in table IV, women who were colonized with *U. urealyticum* gave birth to infants who weighed significantly less than infants born to women who were not colonized. Colonization with *M. hominis* was also related to birth weight although the association was less striking. Another group of investigators has also noted an association between maternal colonization with *M. hominis* and low birth weight (Di Musto et al, 1973). They did not examine for *U. urealyticum*.

One mechanism by which infection might play a role in low birth weight would be to cause inflammation of the placenta and fetal membranes. In this regard, the recent study of Shurin et al (1975) suggesting that a substantial proportion of cases of chorioamnionitis may be caused by *U. urealyticum* is of considerable interest. These data are summarized in table V.

It is not possible to conclude from these data that *U. urealyticum* and *M. hominis* are a cause of low birth weight. The data, however, are highly suggestive of such a relationship, and, considering the importance of low birth weight in perinatal morbidity and mortality, would seem to warrant further investigation.

### Septic Abortions and Puerperal Infections

As is the case with most of the organisms which comprise the vaginal flora, the mycoplasmas are capable of invading the uterus and the blood stream following abortion or following delivery. *M. hominis* can be isolated from the blood of 5 to 10% of women with otherwise unexplained fever following abortion (Harwick et al, 1970) and following delivery (McCormack et al, 1973b). These patients characteristically develop low-grade fever a day or two following delivery, do not appear severely ill, and recover uneventfully even in the absence of mycoplasmacidal antibiotics. Gram-stained smears of endocervical aspirates contain many polymorphonuclear leukocytes without bacteria (Wallace et al, 1976). *U. urealyticum* has only rarely been isolated from the blood of women with postpartum fever (Sompolinsky et al, 1971).

Thus, it seems clear that *M. hominis*, and to a lesser extent *U. urealyticum*, can be isolated from the blood of a few women with fever following delivery. What remains to be established is the frequency of uterine invasion without blood stream invasion and the relative contribution of mycoplasmal endometritis to the entire spectrum of postabortal and postpartum fever.

### Summary

The genital mycoplasmas, *Mycoplasma hominis* and

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**Table III** Relationship of mycoplasmal colonization of newborn infants to birth weight

<table>
<thead>
<tr>
<th>Birth Weight (g)</th>
<th>Number of Infants Studied</th>
<th>Number Colonized(^1)</th>
<th>Percentage Colonized</th>
</tr>
</thead>
<tbody>
<tr>
<td>1500 or less</td>
<td>3</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>1501-2000</td>
<td>16</td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>2001-2500</td>
<td>49</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>2501-3000</td>
<td>47</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>3001-3500</td>
<td>69</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>over 3500</td>
<td>37</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^1\) *M. hominis* and/or *U. urealyticum* isolated from nose and/or throat

**Table IV** Birth weight and colonization with genital mycoplasmas during pregnancy

<table>
<thead>
<tr>
<th>Mycoplasma</th>
<th>Number</th>
<th>Mean Birth Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>U. urealyticum</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated(^1)</td>
<td>384</td>
<td>3099</td>
</tr>
<tr>
<td>Not isolated</td>
<td>100</td>
<td>3297</td>
</tr>
<tr>
<td>( p &lt; 0.003 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. hominis</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated</td>
<td>229</td>
<td>3084</td>
</tr>
<tr>
<td>Not isolated</td>
<td>255</td>
<td>3187</td>
</tr>
<tr>
<td>( p = 0.054 )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Isolated from cervix and/or urine at first prenatal clinic visit
Ureaplasma urealyticum (T-mycoplasmas) are common vaginal organisms. They are acquired primarily through sexual contact. There is evidence, some of it highly suggestive, linking the genital mycoplasmas to involuntary infertility, spontaneous abortion and low birth weight. Additional controlled treatment studies are needed in each of these areas to assess fully the role of the genital mycoplasmas. M. hominis has the potential to invade the blood stream and is responsible for some instances of fever following abortion and of postpartum fever.

References


