

Infections

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

WILLIAM M. McCORMACK¹

From the Channing Laboratory, Departments of Medical Microbiology and Medicine, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts

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. faucium* 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

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Please address reprint requests to Dr William M. McCormack, Channing Laboratory, Boston City Hospital, Boston, Massachusetts 02118.

Respiratory	Genital
<i>Mycoplasma pneumoniae</i>	<i>Mycoplasma hominis</i>
<i>Mycoplasma salivarium</i>	<i>Mycoplasma fermentans</i>
<i>Mycoplasma orale</i>	<i>Ureaplasma urealyticum</i>
<i>Mycoplasma buccale</i>	
<i>Mycoplasma faucium</i>	

Table I Human mycoplasmal species

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 caesarian 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

	Number of Women Studied	Percentage with <i>U. urealyticum</i>	Percentage with <i>M. hominis</i>
No genital contact	71	5.6	1.4
Genital contact without vaginal penetration	30	26.7	0
Sexual intercourse			
One partner	32	37.5	9.4
Two partners	11	54.5	9.1
Three of more partners	12	75.0	16.7

Table II Relationship of sexual experience to vaginal colonization with genital mycoplasmas among student and graduate nurses

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 haematogenous spread, perhaps from a placentitis with invasion of the fetus via the umbilical vessels (McCormack *et al*, 1973a).

The possible association of mycoplasmal 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 demethylchlortetracycline. 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 leucocytes 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

Birth Weight (g)	Number of Infants Studied	Number Colonized ¹	Percentage Colonized
1500 or less	3	3	100
1501-2000	16	5	31
2001-2500	49	7	14
2501-3000	47	7	15
3001-3500	69	8	12
over 3500	37	3	8

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

¹*M. hominis* and/or *U. urealyticum* isolated from nose and/or throat

	<i>U. urealyticum</i>		<i>M. hominis</i>	
	Number	Mean Birth Weight (g)	Number	Mean Birth Weight (g)
<i>U. urealyticum</i> isolated ¹	384	3099	<i>M. hominis</i> isolated	229
<i>U. urealyticum</i> not isolated	100	3297	<i>M. hominis</i> not isolated	255
	P < 0.003		P = 0.054	

Table IV Birth weight and colonization with genital mycoplasmas during pregnancy

¹Isolated from cervix and/or urine at first prenatal clinic visit

Chorioamnionitis	<i>T. mycoplasmas</i>	
	Isolated	Not Isolated
None	22 (19%)	94 (81%)
1+	14 (20.6%)	54 (79.4%)
2+ or 3+	18 (37.5%)	30 (62.5%)

Table V *Chorioamnionitis and colonization of newborn infants with genital mycoplasmas*

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.

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