

## Review

# Role of mycoplasma in male infertility

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**SUMMARY** We trace the evidence-based evolution of ureaplasma male infertility as an established clinical entity. We review epidemiology data, possible pathogenic mechanisms of *Ureaplasma urealyticum* in infertility, and the results of isolation studies and therapeutic trials. Future developments are outlined.

## Introduction

Throughout the world 50–80 million couples suffer from infertility. Male factors are thought to be the major cause of infertility in 30% of cases and to contribute to infertility in another 20% [1].

Acute infections in the reproductive tract of the male have long been recognized to interfere with sperm productivity, transport and longevity. Postpubertal mumps, for example, can result in testicular atrophy and fibrosis. The significance of chronic genital tract infections as causes of semen abnormalities and infertility, however, has not yet been resolved. There are still questions concerning symptoms, etiology and interpretation of positive and negative semen cultures.

Mycoplasma infections are known to cause reproductive problems in some mammals. This has led to the suspicion that chronic asymptomatic genital tract colonization with mycoplasma may contribute to human infertility. The role of genital mycoplasma, particularly *Ureaplasma urealyticum*, in the etiology of infertility has been argued for decades. This issue has been

further complicated by misleading studies which used small numbers of patients who had their infertility inadequately evaluated. Many studies have been conducted with subjects unmatched for factors that could influence ureaplasma colonization, such as age and socioeconomic status. Moreover, the majority of antibiotic therapeutic trials have not included placebo-treated controls. It has been found in some studies, for example, that men with ureaplasma in their genital tracts have an overall decline in the quality of their semen when compared with uninfected men. These observations however have not been supported by a nearly equal number of studies. Our review traces the evidence-based evolution of ureaplasma male infertility as an established clinical entity.

## Epidemiology

Surveys of a variety of human populations reveal widespread colonization of the genital tract with mycoplasma. Indeed the ubiquitous nature of this organism constitutes part of the evidence for a low-order

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pathogenicity and has complicated the problem of delineating the role of the organism in disease causation.

Genital mycoplasma can be recovered from nearly 30% of newborn infants. It has been demonstrated that infants become infected with these organisms during the passage through the birth canal [2]. Infants delivered by caesarean section are less often infected than those delivered vaginally. Isolation rates are somewhat higher for female infants than males. After puberty colonization rates increase and are directly proportional to the extent of sexual activity, rising from 0% with no sexual contact to 45% with three or more partners. This and the documentation of a "ping-pong" occurrence of infection among sexual partners indicate that transmission is primarily by venereal means.

Ureaplasma may tolerate a certain degree of desiccation, therefore other means of transmission are probably possible. It has been found that genital mycoplasma can be harboured by one partner only and that some patients acquire or lose mycoplasma spontaneously over a period of months. However, it has been shown that ureaplasma infection can be chronic, lasting several years at least, and is not necessarily the result of repeated sexual activity [3].

### Pathogenic mechanisms of *U. urealyticum* in infertility

*U. urealyticum* adsorbs to the surface of mammalian cells and replicates there. Because of its urealytic activity and subsequent release of ammonium ions, *U. urealyticum* induces cytotoxicity in a variety of established cell lines. Ammonia is capable of causing severe lesions in the ciliated epithelia of the trachea of chickens.

When grown in the presence of bovine oviductal organ culture, human genital *U. urealyticum* caused ciliary activity to cease and caused severe lesions — deciliation and desquamation — of the epithelium. Decreases in both the cilia-stopping effect and nitrogen content by boiling at high pH values indicate that ammonia is the ciliostatic factor of *U. urealyticum* [4]. *U. urealyticum* is able to hydrolyse urea to ammonia within a few seconds of contact with substrate. It is possible that such a strong local accumulation of ammonia might predict an *in vivo* pathogenic role of *U. urealyticum*.

Busolo and Zanchetta reported that preincubation of spermatozoa with the supernatant of *U. urealyticum* culture decreased the human sperm-hamster egg penetration rate. This effect could be reversed by heating the supernatant before sperm exposure [5]. Their results suggest that *U. urealyticum* produces a toxic factor that impairs sperm function. The extent to which inhibition of penetration occurred varied considerably among ureaplasma serotypes. Serotype 1 had a penetration rate similar to that of controls, whereas serotype 4 exhibited greater interference with the penetration rate.

It has been found that *U. urealyticum* can attach massively to sperm, especially at the midpiece, thus producing marked hydrodynamic drag on the infested sperm. Both scanning electron microscopy and fluorescent light microscopy have dramatically shown that these bacterial hitchhikers can cause looped tangling of tails and multi-sperm agglutinations, both of which cause loss of motility [6].

Many species of mycoplasma, including *M. fermentans* and *M. pulmonis*, act as mitogens stimulating lymphocytes to undergo

blast formation [7]. Immunological consequences of this stimulation are not known but inflammatory tissue response with resultant tissue and cellular incapacity have been suggested by some investigators. In the male genital tract colonization that induced a mitogenic reaction could produce a local immune response with the production of antisperm antibodies.

Clinically, sperm antibodies have been found in the semen of ureaplasma carriers more often than in men with negative cultures. Thus the presence of these organisms might be one of a number of nonspecific stimuli that induce a form of an autoimmune infertility [8]. However, some investigators have not been able to find a correlation between the presence of ureaplasma in semen samples and sperm antibodies [9]. Nevertheless, two possibilities exist: previous ureaplasma infection might have stimulated sperm antibodies or ureaplasma antibodies might cross-react with spermatozoa thus inducing dysfertility indirectly.

It has been reported that ureaplasma induces chromosomal damage including gaps, breaks and even tetraploidy in cultured human lymphocytes. The type of alteration seems to vary with individual ureaplasma strains. Abnormal chromosomal patterns have also been produced in human amnion cell culture. *In vivo* chromosomal damage in animal models infected with mycoplasma however has not been induced. Likewise, attempts to demonstrate similar abnormalities in human gametes have not been reported [10].

Both acute infection with residual tissue damage and reversible alterations resulting from chronic colonization have been suggested as mechanisms of ureaplasma-induced infertility. In men, there is substantial evidence documenting the ca-

capacity of *U. urealyticum* to cause acute nongonococcal urethritis, although evidence for residual disease after clearance of the acute episode is scant. To our knowledge there are no published studies that describe semen quality after acute ureaplasma infection. Chronic prostatitis might result from ureaplasma infection. Soffer et al. found that in patients with ureaplasma prostatic prostatic vasculitis, seminal zinc levels were significantly lower, indicating a malfunctioning prostate [8].

Dysfertility associated with ureaplasma might result from synergism with other bacteria that only appear infrequently. A successful antibiotic treatment, as represented by pregnancy, might result from clearance of an organism other than ureaplasma. Xu et al. conducted one of the most informative studies of ureaplasma and infertility [11]. In their study, 47 male Sprague-Dawley (SD) rats were infected artificially with *U. urealyticum* serotype 8 (T 960). Morphological changes in the seminiferous tubules were observed 3–5 weeks after inoculation in the killed animals. Dramatic impairment of spermatogenesis of both testes was found in 11 rats. Mating experiments confirmed infertility in 12 of 40 rats. Offspring of the infected rats were significantly smaller in both antenatal and birth weight than those of controls.

## Ureaplasma and male infertility

For several years it has been suspected that some unexplained human infertility might be due to ureaplasma infection. Although a considerable amount of data has been collected to support this concept, a clear answer has not been found. Studies in the field were initially hampered by the lack of an animal model, poor serologic tests and

the frequent isolation of ureaplasma from fertile control groups.

### Isolation studies

Gnarpe and Friberg isolated ureaplasma from the cervix of 85% of infertile women and from the semen of 95% of their partners but from only 23% of control females and 26% of control males [12]. The differences were statistically significant. The infertile couples were treated with doxycycline for 10 days. Within a few months of antibiotic treatment, approximately one-third of the treated women became pregnant. From their study, the hypothesis of ureaplasma-induced infertility has emerged. Nevertheless, the infertile couples and the fertile controls did not appear to be matched for sexual experience or other factors which might affect the rate of colonization in the two groups [12].

Traub et al. attempted to isolate ureaplasma from vas deferens taken at vasectomy but they were unsuccessful [13]. Taylor-Robinson found that semen specimens collected from 33 men before vasectomy contained ureaplasma but no specimen of vas deferens tissue was infected with the microorganisms [14]. Unfortunately there is no information of this kind about infertile men because of the difficulty of obtaining corresponding specimens [13,14].

In 1985, a study by Weidner et al. disclosed a significantly negative correlation between titres of ureaplasma and zinc concentration in semen and an almost identically negative correlation to the content of fructose in ejaculate. This probably indicates secretory dysfunction of the accessory glands in ureaplasma infections of the prostate [15]. Two explanations might be considered: a chronic inflammation might already exist and be followed by secondary invasion by ureaplasma since the antibacte-

rial activity of zinc is diminished by the preceding inflammation or ureaplasma infects the prostate inducing an inflammatory reaction with consequent decreases in zinc and fructose concentrations in secretions of the prostate gland and seminal vesicle. These possibilities are supported by a more recent study by Soffer et al. [8]. Upadhyaya et al., however, found that seminal zinc and fructose concentrations were not affected by the presence of ureaplasma [9]. This disagreement may reflect differences in the type of specimen cultivated. Weidner et al. [15] and Soffer et al. [8] isolated ureaplasma from prostatic massage fluid to confirm the involvement of the prostate. Upadhyaya et al. [9] isolated ureaplasma from seminal fluid only. This might not have been an optimal specimen for the diagnoses of prostatitis since the number of microorganisms in semen cannot always be correlated with the quantitative culture of prostatic massage secretions.

De-Jong et al. failed to find a significant difference between ureaplasma isolation rates from the semen of infertile and fertile men [16]. It has been proposed that a ureaplasma titre of 103 colony forming units/mL of semen is significant, whereas lower titres are due to contamination by normal urethral colonization [15].

Al-Ahwany et al. tested 39 couples with unexplained infertility and 24 fertile couples for mycoplasma in semen and cervical mucus. There were no significant differences in the rate of isolation of mycoplasma from the seminal fluid of the fertile and infertile men, i.e. no effect of mycoplasma on semen parameters was found [17]. However, this study had a number of serious shortcomings. Sample size of both patient and control groups was small. Culture media contained gentian violet which inhibits ureaplasma. To identify ureaplasma, the au-

thors depended on the appearance of typical fried-egg colonies, a very rare feature of ureaplasma colonies and unsuitable for their identification. Throughout the study the single term "mycoplasma" was used to refer both to *M. hominis* and *U. urealyticum*. Because of this, sound inferences regarding either of the organisms cannot be made.

In a number of recent studies, ureaplasma appears to be significantly associated with poor semen quality and male infertility [11,18]. Kjaergaard et al. observed, however, that semen quality was neither related to occurrence of ureaplasma nor to pyospermia [19].

### Therapeutic trials

The impetus for several therapeutic trials came from Kundsinn and Driscoll who reported conception after tetracycline therapy in a couple who were genital tract carriers of ureaplasma [20]. In another trial, a group of infertile couples were treated with doxycycline for up to 5 consecutive months; 29% of the treated women conceived within a few months of eradication of genital ureaplasma. Unfortunately the investigators did not randomize their drug trials, leaving open the possibility of fortuitous pregnancy [21].

Harrison et al. assigned 88 infertile couples to treatment (doxycycline), placebo and nontreatment groups with nearly equal numbers of culture-positive and culture-negative individuals in each group. During the 6 months that followed treatment, there was no significant difference in the rate of pregnancy (16%) among the three groups. Investigators concluded that ureaplasma was not associated with primary infertility and that although doxycycline eradicated the infection, doxycycline was of no bene-

fit in the treatment of primary infertility of unknown cause [22].

Hinto et al. conducted a randomized double-blind crossover study with 42 couples with genital ureaplasma. They found a significant increase in pregnancies after treatment but ascribed this increase to psychological effects because the pregnancies occurred in the groups which were first exposed to antibiotics and not in those exposed after the crossover [23].

Mosli et al. treated 13 infertile men for urogenital ureaplasma infection with doxycycline, tetracycline, trimethoprim or norfloxacin (singly or in combined therapy). It was observed that 8 of the 13 men (61%) had an improvement in the results of their semen analyses in response to treatment and that pregnancies of their wives then occurred [24].

Xiang and Chen isolated ureaplasma from 35.9% of 599 infertile couples. Specific treatment was given and the pregnancy rate was significantly higher among those patients who became negative than among patients who remained positive. While these observations are thought-provoking, adequate placebo-treated controls are essential to assess their significance, particularly because of the failure of others such as Harrison et al. to show consistent results [22,25].

Most studies have not identified subjects who carried tetracycline-resistant ureaplasma and thereby introduced a confounding variable into their data.

If the beneficial effect of an antibiotic was due to the eradication of ureaplasma, another microorganism or a yet unknown mechanism cannot be ruled out. The frequent isolation of ureaplasma from the urethra of healthy fertile men presents the following possibilities.

- It is possible that only certain serotypes of ureaplasma are pathogenic. Extended serotyping studies are required to assess this hypothesis.
- Disease occurs only with colonization of high counts of ureaplasma.
- Ureaplasma produces disease which subsides but the organism endures either in the primary site of infection or in another site, e.g. in the prostate or elsewhere. These do not cause disease but are detected infrequently in specimens from the genital tract.
- Disease occurs only in presence of yet unknown cofactors, such as other mi-

croorganisms, genetic factors and environmental factors.

## Prospectives

Studies that correlate histopathological findings with the recovery of ureaplasma from human testicular biopsy may further clarify the pathophysiology of ureaplasma infertility. Because polymerase chain reaction (PCR) has greater sensitivity and is quicker than culture, there is a possibility of further development of PCR for the routine diagnosis of ureaplasma infection.

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