
Asymptomatic trichomonas and candida colonization and pregnancy outcome

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Trichomonas vaginalis is a sexually transmitted surface pathogen of the lower urogenital tract, and may be associated with asymptomatic vaginal colonization or intensely symptomatic vaginitis. In pregnancy it is associated with an increased risk of preterm delivery. However, a randomized trial of treatment of asymptomatic trichomonas colonization in pregnancy showed an increase in the risk of preterm delivery in treated women. The reasons for this paradox are yet to be fully elucidated. *Candida* species, on the other hand, may be present – usually in the yeast form – in the vaginal flora of up to 40% of healthy pregnant women. Although candidiasis is not usually associated with chorioamnionitis or preterm delivery, there is some emerging evidence to suggest that screening for and eradication of candida during pregnancy may reduce the risk of preterm delivery. This chapter reviews the impact of these common vaginal infections on pregnancy outcome and appraises the recent evidence on the role of treatment during pregnancy.

Key words: *Trichomonas vaginalis*; metronidazole; *Candida albicans*; pregnancy; preterm delivery.

Trichomonas vaginalis causes an intensely irritant vaginitis and a profuse, purulent discharge when symptomatic. Before metronidazole was developed in the 1960s, treatment was often lengthy and unsuccessful. Keighley summarized this well: 'since the introduction of 'Flagyl' a whole generation has no knowledge of the sufferings of women with trichomoniasis; the indignities and discomfort of the perpetual local treatments, douches, paintings, insufflations and insertions of pessaries etc. All these things

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women suffered for months and sometimes years on end, only to relapse when the treatment was discontinued.^{1,2}

Trichomonas vaginalis is one of the most common sexually transmitted infections. In 1994 the WHO estimated that 120 million women worldwide acquire trichomoniasis every year.³ In the UK trichomoniasis has become less common over the last 40 years; the number of cases reported from genitourinary medicine (GUM) clinics in England and Wales dropped from over 20,000/year in 1982 to below 6000/year in the early 1990s, and has continued to decrease with an estimated population prevalence of 34.6/100,000 women.⁴ Published series from the mid 1970s gave a prevalence of 5% in women attending a family planning clinic and 7–32% among women attending a GUM clinic.⁵ Currently, fewer than 1% of women attending our clinic at St George's Hospital are diagnosed as having trichomoniasis. There are few data on the prevalence in men, as infection is frequently asymptomatic and the organism is detected rarely unless there has been recent intercourse with an infected woman. In some developing countries the prevalence of *Trichomonas vaginalis* is much higher. For instance in Rakai, Uganda, a prevalence of 23.8% was found.⁶ Although it is standard practice to perform partner notification and treatment for *T. vaginalis*, only one trial investigated the treatment of male partners.⁷ All the women with trichomoniasis received standard treatment with tinidazole 2 g. The male partners were randomized to treatment with tinidazole 2 g single dose or placebo. Although there was no difference in parasitological results at the first follow-up after 1 month, significantly more women (3/59 versus 14/59) whose partners received placebo were *Trichomonas*-positive by the second follow-up at around 2 months compared with women whose partners were treated.

Vertical transmission occurs in about 5% of pregnancies. The infection usually remits in the neonate as the influence of maternal sex hormones diminishes, but treatment is appropriate if infection lasts more than 1 month. The organism can survive in moist places, and many patients suggest they might have acquired it from swimming pools or sharing a towel, but there is no documented evidence of non-venereal transmission. The organism only colonizes the urogenital tract in women, preferring the squamous epithelium of the vagina, although it has been isolated from aspirated bladder urine, the rectum, and Fallopian tubes. Asymptomatic carriage occurs, but it is estimated that one third of women will develop symptoms within 6 months, and ultimately between 50 and 90% will become symptomatic if not treated.

DIAGNOSIS

The vaginal pH is usually raised to a level between 4.5 and 7.0 in women with trichomoniasis. Wet mount examination has a sensitivity of 40–80% compared to culture. Experienced observers can recognize non-motile organisms, but it is usually the movement of the flagellae which leads to identification of the organism. In addition, there is usually a high concentration of polymorphs in the vaginal fluid. *T. vaginalis* grows in normal saline at room temperature, but grows optimally in specialized media such as Fineberg–Whittington or Bushby. *T. vaginalis* is not detected easily on a Gram-stained smear of vaginal fluid. Usually there is a high concentration of polymorphs and bacterial vaginosis or an intermediate vaginal flora. Cervical cytology using a Papanicolaou stain has a sensitivity of 60–70% compared to culture. DNA detection methods are being developed but are not yet commercially available. Their sensitivity is likely to be higher than that of culture.

TREATMENT

Most strains of *Trichomonas vaginalis* are sensitive to metronidazole and other imidazole antibiotics. More than 90% of women are cured by a single 2-g stat dose of metronidazole or a 5-day course of 400 mg twice daily. Tinidazole, 2 g, can be used as an alternative. Many physicians have been reluctant to prescribe metronidazole during the first trimester of pregnancy because high doses were associated with mutagenesis in animal studies. There is, however, no evidence of such complications following its use in pregnancy in humans.^{8–10} Sexual partners of women with trichomoniasis should be examined and screened for sexually transmitted pathogens, including *T. vaginalis*. Even if the organism is not detected, contacts should receive treatment with metronidazole 2 g stat dose or 400 mg twice daily for 5 days.

TRICHOMONAS IN PREGNANCY

Several studies published between 1974 and 1995 suggested that *Trichomonas vaginalis* is associated with adverse pregnancy outcome. In five cohort studies, *T. vaginalis* was associated with premature membrane rupture¹¹, preterm delivery^{12–14}, low birth weight among women with spontaneous membrane rupture¹², and low birth weight and preterm delivery.¹⁵ In two other studies, data from treatment trials support a positive but not statistically significant association between *T. vaginalis* infection and preterm delivery.^{16,17}

The largest prospective study specifically designed to investigate the role of infections in preterm birth screened 13,816 women in a multicentre study in the USA.¹⁸ The overall prevalence of *T. vaginalis* was 12.6%, whilst in black women, who have twice the incidence of preterm birth as white women, it was 22.8%. The multivariate analysis controlled for factors including race, demographic variables, smoking during pregnancy, gravidity, previous adverse pregnancy outcome, other co-flora including *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, bacterial vaginosis, and intercurrent metronidazole use. It found that *T. vaginalis* detected at mid-gestation was significantly associated with low birth weight (OR 1.3; 95% CI 1.1–1.5), preterm delivery (odds ratio 1.3; 95% CI 1.1–1.4), and preterm delivery of a low-birth-weight infant (odds ratio 1.4; 95% CI 1.1–1.6). Because of the higher prevalence the attributable risk of *T. vaginalis* infection for low birth weight in Blacks was 11% compared to 1.6% in Hispanics and 1.5% in Whites.

A 2006 Cochrane review of treatment for *Trichomonas vaginalis* in pregnancy identified only two RCTs in which metronidazole treatment was tested as a means of reducing the incidence of preterm birth in pregnant women.¹⁹ In both studies women diagnosed with *T. vaginalis* were given metronidazole to pass on to their partners. Cure rates were reported as approximately 90% in both studies. In 1983 Ross and colleagues in South Africa screened 376 women, 225 (60%) of whom tested positive for *T. vaginalis* on wet mount examination.²⁰ Assignment to groups was by alternate allocation rather than by randomization. Treatment was prescribed relatively late in pregnancy: women were classified as diagnosed at <34 weeks' gestation, or initially negative but diagnosed at 38 weeks' gestation. There was no difference between the groups in mean birth weight, gestational age, or the incidence of low birth weight (12% in treated versus 11% in control).²⁰

The US study was designed to test whether treatment of asymptomatic trichomoniasis could prevent preterm birth. Women were enrolled at 16–23 weeks. Double-blind treatment was allocated in a randomized fashion in the form of metronidazole

2 g stat, repeated after 2 days, and both doses again administered 2 weeks later. In this study metronidazole treatment was associated with an increased risk of preterm birth (relative risk (RR): 1.8; 95% CI: 1.2–2.7) and low birth weight (RR: 1.4; 95% CI: 0.9–2.1).²¹ The trial was stopped prematurely because it was highly unlikely that the treatment would be effective if all women had been recruited. However, the question of whether the drug actually increases the preterm birth rate remains unanswered. Recruitment was stopped after 617 women were randomized (32% of total planned sample size). The authors discuss the possible reasons for an increase in preterm birth rate, including the possibility of toxic substances being released from destroyed trichomonas and an unpredicted change in the vaginal flora triggered by the high-dose metronidazole treatment. Most of the excess of preterm birth was in the 34–36-week period, which is not associated with a high risk of adverse neonatal outcome. There are further limitations to the study. Of women assigned to the placebo group, 22% received treatment for *Trichomonas vaginalis* outside of the study protocol. Only 615 of 2377 who screened positive for *Trichomonas vaginalis* were randomized. The Cochrane review reports that 90% of the women in the metronidazole arm were cured, but the paper does not state this. It is possible that adverse pregnancy outcome is associated with reinfection from an untreated partner, and neither study gives data to assess this. Whether inclusion of symptomatic women would have changed the result is unknown.

One further study was dismissed from the Cochrane review because it was a sub-study of a larger mass-treatment study. The Rakai study investigated whether mass treatment for sexually transmitted infections administered at 10-monthly intervals would reduce the incidence of HIV in rural Uganda. Treatment include metronidazole 2 g single dose for men and women.²² The prevalence of trichomoniasis decreased with repeated treatments. Since some of the women were pregnant, a sub-study reported on the effects of treatment in pregnancy. Kigozi and colleagues reported that approximately 950 women from each treatment arm were screened for trichomoniasis in pregnancy.²³ The children of 94 women with trichomonas who were treated had increased low birth weight (RR, 2.49; 95% CI, 1.12–5.50), preterm birth rate (RR, 1.28; 95% CI, 0.81–2.02), and 2-year mortality rate (RR, 1.58; 95% CI, 0.99–2.52), compared with children of 112 women with trichomonas who were not treated. There was also an increased risk of infant death up to 2 years (RR 1.6). There was more HIV in the treatment group (28.9% versus 22.3%), so the RR decreased to 1.4 when controlled for HIV.²³ Additional confounding factors include the lower prevalence of *Trichomonas vaginalis* in the treatment arm due to previous treatment earlier in the study, and that women who received treatment also received ceftriaxone and benzathine penicillin. In the candida section of the RCT of screening and treating vaginal infections in pregnancy by Kiss and colleagues, there were only two women in the intervention group and four on the control group diagnosed with trichomonas, so no conclusions can be drawn on the effect of treatment on preterm birth.²⁴ Diagnosis was by Gram stain, which has a poor sensitivity and specificity for trichomonas.

The Cochrane review concluded that two research questions remain unanswered:

(1) whether the treatment of pregnant women with symptoms (trichomonas vaginitis) is effective in reducing preterm birth; and (2) whether the adverse effect of increased preterm birth in treated asymptomatic women with trichomonas observed in one prematurely stopped trial is real. Since absolutely clear conclusions cannot be drawn, we should continue to treat symptomatic women in pregnancy to relieve their symptoms, and design further studies.

VAGINAL CANDIDIASIS IN PREGNANCY

Up to 40% of pregnant women may have vaginal colonization by *Candida* species, a two-fold increase from the prevalence rate in non-pregnant women. This is believed to be driven by increased levels of circulating oestrogens and deposition of glycogen and other substrates in the vagina during pregnancy. Unlike trichomonas and bacterial vaginosis, candida colonization in pregnancy is not usually associated with increased risk of preterm delivery. However, there is some emerging evidence that eradication of candida in pregnancy may reduce the risk of preterm birth and late miscarriage.

In a large Austrian RCT of antenatal screening for bacterial vaginosis, candida and trichomonas, Kiss and colleagues reported that screening and treatment for infections between 15 and 20 weeks' gestation in 4429 asymptomatic women produced a preterm birth rate of 3% compared to 5.3% in the control group.²⁴ There was a non-significant excess of medically induced preterm births in the intervention group (1.2% versus 0.7%), and a non-significant reduction in late miscarriage (0.4% versus 0.7%); 21% of women had a vaginal infection diagnosed on Gram-stained vaginal smears. Those with candida hyphae and/or spores received treatment with clotrimazole intravaginally 100 mg daily for 6 days. Trichomonas was treated with intravaginal metronidazole 500 mg daily for 7 days, with partner treatment. Bacterial vaginosis was treated with intravaginal clindamycin 2% cream for 6 days. Of the 177 women treated for bacterial vaginosis with 2% clindamycin vaginal cream, 59 (29%) required retreatment with oral clindamycin for persistent bacterial vaginosis at 24–28 weeks' gestation. Numerically, most of the benefit appeared to be in women treated for candidal infection. In the intervention group, 6/175 women treated for bacterial vaginosis had a spontaneous preterm birth compared to 10/176 in the control group (OR 0.59, 95% CI 0.17–1.54, $P > 0.05$). Spontaneous preterm birth occurred in 8/289 women treated for candidiasis versus 22/291 women with candidiasis in the control group (OR 0.35, 95% CI 0.14–0.84 $P = 0.009$). Only two women in the treatment group and four in the control group had trichomonas diagnosed. This is an intriguing study, as the improved outcome associated with treatment for candidiasis was unexpected.

Czeizel and colleagues did a series of retrospective analyses of the prevalence of preterm births in the population-based data set of the Hungarian Case–Control Surveillance of Congenital Abnormalities.^{25,26} The authors found an association between topical and vaginal clotrimazole treatment of candidiasis during pregnancy and a significant reduction in the rates of preterm birth and low-birth-weight infants, and speculated that the protective effect of clotrimazole for preterm birth may be attributable to the restoration of the abnormal colonization of the female genital tract and its known antibacterial and/or antiprotozoal effect.^{25,26} Whilst these Hungarian studies involved large numbers of subjects, and also support a benefit from treating candida, they are observational rather than randomized data. Future studies should attempt to replicate these results, but also to investigate putative mechanisms. The largest observational study of candida in pregnancy found no association with preterm birth, although it did not include women with low-level colonization.²⁷ However, screening was performed later in pregnancy at 24–28 weeks' gestation. Why then should treatment for candida improve pregnancy outcome? In a sub-study at one participating centre (in the study of Cotch and colleagues) it was found that whilst 9.4% of cultures were heavy or moderate for candida, a further 12.9%

exhibited low growth. This implies that fewer than half the women colonized with candida were included in the analysis. Candida itself is seldom identified as a cause of chorioamnionitis. Possibly it has an effect on the vaginal bacterial flora, maybe by supporting the development of bacterial vaginosis or colonization by pathogenic bacteria.

Practice points

- symptomatic trichomoniasis or candidiasis in pregnancy should be treated adequately
- although trichomoniasis is associated with preterm delivery, the role of treatment in reducing this risk is not yet established and may even be harmful
- routine screening for and treatment of vaginal colonization by trichomonas or candidal species is not recommended

Research agenda

- further studies on the role of treatment of trichomoniasis and the risk of preterm delivery and other adverse pregnancy outcomes
- the precise mechanisms through which the treatment of trichomoniasis leads to an increased risk of preterm delivery
- the magnitude and spectrum of the risk of vaginal colonization by candida in pregnancy
- the interaction between candida and other microbes that inhabit the vagina, and the risk of adverse pregnancy outcome

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