# A practical approach to the prevention of miscarriage Part 4 - role of infection

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**Summary**

*Purpose:* To evaluate the role of infection as a cause of pregnancy loss. *Methods:* Studies concerning the risk factor of certain microorganisms for first trimester miscarriage and premature rupture of membranes are reviewed. The microorganisms especially considered were *ureaplasma/mycoplasma*, the potpourri of organisms causing bacterial vaginosis and *chlamydia trachomatis*. *Results:* The consensus is that all these microorganisms can on occasion lead to first trimester spontaneous abortion and second trimester loss especially related to premature rupture of membranes. *Conclusions:* Reactivation during pregnancy is possible so the best strategies involve giving a course of appropriate antibiotics prior to pregnancy but giving antibiotics at least intermittently during the first trimester. Similar antibiotic therapy could be considered for unexplained recurrent miscarriage where negative cultures exist.

*Key words:* Spontaneous abortion; Bacteria; Premature rupture of membrane; Antibiotics.

## Introduction

In our large population of women who have conceived following in vitro fertilization-embryo transfer (IVF-ET) aged 39.9 and under, irrespective of their previous infertility or miscarriage history or their status of ovarian oocyte reserve, there is approximately a 10% chance that a woman showing ultrasound evidence of pregnancy at 6-8 weeks will have a miscarriage. Accidental aneuploidy is the most common cause of a given miscarriage [1]. It is debatable if a predisposition to aneuploidy exists or not but if it does it is uncommon [2-4].

Nevertheless by chance alone a younger woman could have had two consecutive first trimester spontaneous abortions or miscarried in two of three pregnancies related to two accidental aneuploidal fetuses. Theoretically one in 100 women could lose two in a row from a factor that can not be controlled or prevented.

Prior editorials have discussed certain causes of spontaneous abortion that are remediable, e.g., progesterone deficiency. A woman presenting with frequent miscarriages could have been unlucky and have had several different etiologies to the various first trimester pregnancy losses. The frantic primary, secondary, or tertiary aborter wants to not only eradicate any of the causes of miscarriage that she may be prone to have, e.g., need of extra progesterone, but would like to prevent another loss from any new etiology, especially if it is remediable.

Recurrent miscarriage is defined as three or more consecutive miscarriages. It has been estimated to occur in 0.5% to 3% of women [5]. There is little evidence that pelvic infections are a cause of recurrent miscarriages. However, there are data suggesting that a first trimester miscarriage or a loss later in the pregnancy can be related to an infectious etiology. This editorial will present some of the data suggesting that certain infections could result in a loss of a pregnancy. As in most areas of medicine there will be studies not finding an association. Nevertheless after weighing the evidence I hope to present a strategy to cover the possibility of an infection leading to a miscarriage.

### *Microorganisms considered as possible causes of some miscarriages or pregnancy loss*

There are studies suggesting that the following microorganisms may on some occasions lead to fetal loss: *ureaplasma urealyticum, mycoplasma hominis, chlamydia trachomatis*, a group of microorganisms responsible for causing bacterial vaginosis, streptococcus, several bacteria in the *clostridiales* order, genital tuberculosis, *trichomonas vaginalis, neisseria gonorrhoeae, listeria monocytogenes*, cytomegalovirus (CMV), herpes simplex virus and toxoplasmosis [6].

Any one of these could cause a miscarriage but some are more likely candidates in any given miscarriage. The more likely microorganisms will be discussed because they are the ones that lead to my final suggested strategy. I will emphasize that infection and miscarriage is a highly controversial area and there is no one strategy that can be said to be the correct one. I will provide the studies that have led me to my particular strategy but it should be emphasized that it is personal. Perhaps after presenting the data and evidence the reader will decide on their own strategy different than mine.

### *Evaluation for infections*

In all women coming to our practice for either infertility or history of miscarriage we culture the cervix for

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*mycoplasma, ureaplasma, gonorrhea*, and *chlamydia*. Moreover vaginal cytology for bacterial vaginosis is evaluated. For the subgroup of women who have a history of miscarriages, we also do a deep vaginal culture for Group B streptococcus.

*Culture positive for mycoplasma or ureaplasma*

Not only do we culture the cervical fluid but we also culture the semen specimen. If either the female or male partner tests positive we generally treat both partners with doxycycline 100 mg twice daily for two weeks.

We do not repeat the culture but instead with a positive pregnancy test begin treatment with either erythromycin 500 mg four times a day or azithromycin 250 mg a day for a week then skip a week then resume on an alternate week basis throughout the first trimester. I do not reculture after the initial two-week course of doxycycline because it is hard to eradicate, thus giving a more prolonged antibiotic course of therapy could lead to complications, e.g., toxic bacterial enterocolitis or thrush.

I do not reculture necessarily when pregnancy occurs because based on one positive culture I will nonetheless add a macrolide drug to keep the infection in check. If the repeat culture of the cervix was negative I could not be sure that it was still not present at the endometrial level. Also even if the cultures were negative at the moment in the pregnancy they were obtained one can never tell when the concentration will become high enough again to do damage. It is not practical to keep getting cultures on a weekly basis plus it may take ten days to grow *mycoplasma/ureaplasma*. The male partner is only treated once but is advised to use condoms during the first trimester.

One study found that in pregnant women with a vaginal discharge 49% cultured positive for *U. urealyticum* and an additional 14% were positive for M. hominis [7]. It is unlikely that all or even most women that culture positive for these organisms will lose a pregnancy. However there are data suggesting that women with enough concentration of these microorganisms to demonstrate a positive culture will have a greater pregnancy loss rate than those who are negative. Cervical colonization ureaplasma was found in 43% of normal pregnant women (n = 310), 42% of women undergoing voluntary termination (n = 89), 41.5% of normal fertile women (n = 65), 53% of women with spontaneous abortion (n = 122), and 69.5% of women with recurrent miscarriage (n = 76) [8]. Another study found *U. urealyticum* and *M. hominis* in 74.1% and 27.6% of 58 women with spontaneous abortion vs 48% and 10% of 50 women who had live deliveries [9].

Thus studies by Naessens *et al*. would suggest that treating women with antibiotics who culture positive for mycoplasma could reduce the risk of miscarriage [8].

One study did find an extremely high percentage (90%) of pregnancy loss in women whose cervical cultures were positive for mycoplasma [10]. Using doxycycline only prior to conception reduced the miscarriage rate to 48% whereas using erythromycin in addition during pregnancy reduced the miscarriage rate to 15% and pretreating with doxycycline then using erythromycin during pregnancy resulted in a loss rate of 16% [10]. This was a prospective study though it is hard to believe that untreated controls could have a 90% loss rate. Nevertheless, it is this study that has guided my decision to give only a two-week course of doxycycline rather than a prolonged course prior to pregnancy and not to re-culture for the microorganisms but always treat with a macrolide, eg., erythromycin or azithromycin at least during the time that our practice is responsible for patient care, i.e., the first trimester.

*Bacterial vaginosis (BV)*

Bacterial vaginosis is an interesting condition in which the normal predominant type of bacteria that populates the vagina, i.e., *lactobacilli*, which reduces the vaginal pH by metabolizing squamous cell glycogen to lactic acid, is replaced by predominantly anerobic bacteria. Bacterial vaginosis is probably the most common cause of vaginal discharge; for some reason colonization with these microorganisms does not cause an inflammatory reaction so that is why it is given the name vaginosis rather than vaginitis. Actually sometimes mycoplasma and ureaplasma can be the cause of BV but other common bacteria include Gardnerella vaginales, various mobiluncus species, prevotella, porphyromonas, *bacteroides* and *peptostreptococcus*.

Most commonly I identify BV by observing a fishy vaginal odor and confirm it by a wet smear of cells taken from the lateral vaginal wall demonstrating the adherence of bacteria by a phase contrast microscope showing "shaggy" epithelial cells (so called clue-cells). Occasionally for borderline cases the diagnosis will be confirmed by the demonstration of a vaginal pH > 4.5 or eliciting a fishy odor from the vaginal fluid by adding potassium hydroxide.

Interesting, though the actual cause of BV is unknown, one study of infertile women undergoing IVF-ET found that BV was three times more likely to be present in women with tubal factor than women having IVF-ET for endometriosis, unexplained infertility or male factor [11]. When lactobacilli are the predominant vaginal microorganism of the vagina the acidic pH helps provide protection against infection. By replacing the flora with organisms associated with BV and raising the pH, the woman is at greater risk of infection whether BV vaginal microorganisms ascend and now inhabit the endometrial cavity (but since not evoking a host inflammatory response so-called endometriosis) and directly in some manner creates an adverse mileu leading to pregnancy complications, or merely allows a more serious pathogen to cause the problem, remains to be determined [12, 13]. For example women may have colonization with *chlamydia* from previous exposure but host defenses are keeping it in check. The presence of BV could activate the *chlamydia* which in turn leads to pregnancy loss. One study found that women with endometrial cultures that

grow out *chlamydia* had a 59% miscarriage rate whereas treatment with antibiotics reduced the miscarriage rate to zero [14, 15]. Normally the uterine cavity is considered relatively sterile. However, studies performing endometrial cultures have demonstrated the presence of pathogenic bacteria even in the presence of normal cervical cultures [16].

Intravaginal or oral clindamycin treatment will help to eradicate BV [17, 18]. Metronidazole therapy was found to be about as effective as clindamycin [19]. Metronidazole therapy vs placebo showed marked reduction in preterm labor and preterm births and also premature rupture of membranes [19, 20]. Not all studies concur that treating BV prevents pre-term deliveries. A Cochrane meta-analysis concluded that antibiotic treatment (better with oral than intravaginal) resulted in a trend for fewer births before 37 weeks gestation especially in those women with a previous history of preterm births [21].

As far as miscarriages related to BV a large study of 867 consecutive women undergoing IVF-ET found that there was no difference in the conception rate of the 25% demonstrating BV vs the 75% without BV [22]. However, the group with BV had a significantly higher miscarriage rate (32% vs 18.5%) with no obvious confounding variables. Another study found that the presence of BV significantly increased the risk of first trimester bleeding [23].

### *Chlamydiae*

One study reported a 60% miscarriage rate with *chlamydiae* cultured during pregnancy yet antibiotic treatment resulted in 100% full-term deliveries [14]. In that same study 42% of 163 women with recurrent miscarriages cultured positive for *chlamydiae* [14]. Of course this prevalence will depend on the study population. We predominantly see private patients in our practice and we culture all women for *chlamydia* and rarely obtain a positive culture.

The relationship of high titer IgG antibodies to *C. trachomatis* and miscarriage is controversial. One study found a three to four fold increased miscarriage rate in women with three or four previous miscarriages compared to controls with no history of miscarriage [24]. The author suggested that the pregnancy could reactivate dormant chlamydial infection, thus causing the miscarriage [24]. However other studies found no correlation [25-27].

### *History of miscarriage with negative cervical cultures*

Supposing a woman presents with three consecutive miscarriages with the karyotype of two of the abortuses finding normal males. Suppose these last two miscarriages occurred despite aggressive progesterone support started in the luteal phase and continued throughout the first trimester. The women seeks your help to try to prevent another one. Furthermore, her uterine cavity was demonstrated to be normal by sonohysterogram and hysteroscopy. Coagulation studies are normal.

Theoretically, the reason for the losses could be immunological in nature or infectious. Immune issues are very controversial. Nevertheless even if one does believe that immune therapy can be effective (I am one of those reproductive endocrinologists who think some cases will benefit from such therapy), the treatment is problematic. In the United States the Food and Drug Administration requires that investigational new drug approval (IND) be obtained prior to using lymphocyte immunotherapy (LIT) and the cost for this IND is about one million dollars. Thus no or few American centers perform this procedure and couples must go to Mexico for therapy. Intravenous immunoglobulin is extremely expensive and for most women cost-prohibitive.

If culture of the sperm or cervix demonstrates ureaplasma/mycoplasma or clue-cells are seen in the wet smear then one can hope that the pregnancy losses were related to an infectious etiology and the woman can be treated both before conception and during her first trimester.

However, what should the treating physician suggest if all cervical and vaginal cultures are negative? Can a physician and patient be sure that the endometrial cavity was not overgrown with these microorganisms? The answer is no. Some of these microorganisms are fastidious and may be present in the cervix but not grow out on culture explaining a negative culture. There is also the possibility that they have colonized the endometrial cavity but are not present in the cervix. As mentioned, molecular genetics has allowed the detection of many other types of bacteria in the vaginal flora and with cervical cultures for which there has not been developed as yet growth media [6].

Under these circumstances I will frequently empirically prescribe erythromycin or azithromycin intermittently during the first trimester. Since some studies have found ureaplasma and mycoplasma in about three-fourths of women with miscarriages and it can develop at any time I use the macrolides because they will cover the *mycoplasma* and Group B *streptococcus* and they are safe in pregnancy and generally well tolerated [9].

We previously found that when performing a fetal ultrasound during the first trimester there was a high miscarriage rate if the sac size was found to be more than one week earlier for gestational age than the crown-rump length [28]. We considered the possibility that this phenomenon could be related to leakage of amniotic fluid by an infection. Our policy is to add a macrolide when we see this occurrence even if repeat cultures for ureaplasma and mycoplasma are negative. The exception would be if we find clue-cells on vaginal cytology when metronidazole or tinidazole would be used instead. These agents would be given intermittently. Since instituting this policy we have found a marked reduction in miscarriages when a crown-rump length/sac size discrepancy is found. These data are unpublished because our ethics committee rejected a proposal for a placebo control or no-treatment control.

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