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Role of infections in miscarriage

Elena B. Kostova, Ph.D.,[a,b,c] Jelmer R. Prins, M.D., Ph.D.,[d] and Madelon van Wely, Ph.D.[a,b,c]

[a] Center for Reproductive Medicine, Location Academic Medical Center, Amsterdam UMC, Amsterdam, the Netherlands; [b] Cochrane Gynaecology and Fertility Satellite and Sexually Transmitted Infections Group, Amsterdam, the Netherlands; [c] Amsterdam Reproduction and Development Research Institute, Amsterdam, the Netherlands; and [d] Department of Obstetrics and Gynecology, University Medical Center Groningen, University of Groningen, the Netherlands.

Infections with certain pathogens can lead to perinatal complications. Several infections have been also associated with an increased likelihood of miscarriage. This manuscript discusses these infections, their modes of transmission, the evidence linking them to an increased risk of miscarriage, and whether prevention or treatment strategies are available. (Fertil Steril® 2023;120:948–50. ©2023 by American Society for Reproductive Medicine.)

Key Words: Pathogens, infectious diseases, early pregnancy, pregnancy loss

Miscarriage is defined as the spontaneous loss of pregnancy before 20–22 weeks of gestation, although some countries definitions include pregnancy loss up to 24 weeks. Miscarriage affects approximately one in ten pregnancies, with the majority occurring in early miscarriage, i.e., before 12 weeks of gestation, and has an enormous psychological impact (1–3). The causes of miscarriage are often unknown, although experts agree that approximately half of the miscarriages are because of chromosomal abnormalities (4). Risk factors include uncontrolled diabetes, uterine anomalies, woman's age, number of previous pregnancy losses, woman's body mass index, smoking, alcohol, and drug use, and man's age (1).

In addition, infections have been linked to an increased risk of miscarriage and other pregnancy complications. It has been described that infections may account for up to 15% of early miscarriages and up to 66% of late miscarriages (4–6). The changes in the immune system that need to occur to accommodate the fetus are likely to make a pregnant woman more vulnerable to some infections (4, 5). Consequently, some infections may result in an increased severity of the disease in pregnant women compared with nonpregnant women. Indeed, increased disease severity in pregnant women has been described for influenza, hepatitis E virus, herpes simplex virus (HSV), malaria, measles, smallpox, varicella, coccidioidomycosis, and more recently also for severe acute respiratory syndrome coronavirus 2 (5–8). There is generally a lack of evidence for an increased susceptibility to most infections, except for malaria and listeriosis, for which there is evidence for a higher prevalence in pregnant women compared with nonpregnant women (6).

In addition to the higher risk for miscarriage, some pathogens can cross the placenta, particularly TORCH infections, which are well known. These pathogens can cause severe pregnancy complications such as fetal growth restriction, preterm birth, and sepsis as well as major congenital defects and fetal and neonatal deaths. TORCH pathogens include *Toxoplasma gondii* and other agents (varicella-zoster virus, parvovirus B19, human immunodeficiency virus, rubella virus, cytomegalovirus [CMV], and HSV). In addition, Zika virus infection is known to lead to similar negative sequelae with serious congenital defects, such as microcephaly. But many more pathogens have been associated with perinatal complications. Pathogens that cause perinatal complications may also increase the chance for a miscarriage to occur. In this manuscript, we focus on those infections that most likely increase the chance of a miscarriage.

ASSOCIATION BETWEEN MISCARRIAGE AND INFECTIONS

For this overview, we evaluated data on infections in pregnancy as presented on the websites of WHO.org, the United Kingdom National Health System (https://www.nhs.uk), the National Institute of Health (https://www.nichd.nih.gov/health/topics/pregnancy/conditioninfo/infection), the Center for Disease Control (https://www.cdc.gov/std/pregnancy/), the European Center for Disease Prevention and Control (https://www.ecdc.europa.eu/), and reviews that investigated the association between infections and miscarriage (4, 7, 9, 10). On the basis of this information, we selected 25 pathogens for which information on associations with miscarriage has been described.

We report on their (main) transmission, evidence that infection results in

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Reprint requests: Madelon van Wely, Ph.D., Centre for Reproductive Medicine, Amsterdam University Medical Centers, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands (E-mail: m.vanwely@amsterdamumc.nl).

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an increased risk of miscarriage, and whether the infectious disease could be prevented or treated by an infectious agent (bacteria, viruses, or protozoa) (Table 1).

Bacteria

For syphilis, there is strong evidence that infection may result in miscarriage. Syphilis is on the rise in the USA but can easily be treated; without treatment, >40% of syphilis-infected pregnancies may result in miscarriage, stillbirth, or neonatal death.

Gonorrhea, bacterial vaginosis, brucellosis, and listeriosis have been shown to consistently increase the chance of miscarriage. Another bacterial infection that has clear associations with miscarriage, although seemingly of lesser strength, is salmonella infection. The impact seems to differ largely between studies, such that no estimates of their miscarriage chance are presented. For Q-fever, there is a lack of evidence for an association with miscarriage. All these infections need to be treated with antibiotics, but they can largely be prevented. Sexually transmitted infections can be prevented by abstinence from sex or at least good use of condoms. For prevention, access to medical care and education remains important (https://www.cdc.gov/std/prevention/default.htm). In cases of sexually transmitted infections, all sexual partners need to be treated to prevent reinfection. Food-borne infections like brucellosis, listeriosis, salmonella, and toxoplasmosis can be prevented by hygienic measures such as not eating raw meat, fish, or milk products and cooking them well.

Viruses

For rubella virus, there is strong evidence that infection may result in miscarriage. Rubella virus infection can be prevented by vaccination; a 20% miscarriage rate has been estimated in nonvaccinated pregnant women with rubella virus infection.

Human immunodeficiency virus and CMV infections have been shown to increase the chance of miscarriage consistently. Other virus infections that have clear associations with miscarriage, although seemingly of lesser strength, are HSV, hepatitis B virus, Zika virus, dengue virus, and influenza virus. The impact, however, seems to differ largely between studies, such that no estimates of their miscarriage chance are presented here. For most of these infectious diseases, prevention is available through vaccination. This is not the case for CMV infection, which is globally highly prevalent with usually mild symptoms but can be dangerous in

TABLE 1

Transmission, evidence for increased miscarriage risk, and presence of prevention or intervention for 25 infectious agents that have been associated with miscarriage.

Infectious agent	Transmission	Evidence increased miscarriage risk	Prevention/intervention
Bacteria			
Chlamydia	STD, blood	↑	Antibiotics
Gonorrhea	STD, blood	↑↑	Antibiotics
Syphilis	STD, blood	↑↑↑	Antibiotics
Bacterial vaginosis	Probably sexually	↑↑	Antibiotics
Brucellosis	Food	↑↑	Antibiotics
Listeriosis	Food	↑↑	Antibiotics
Salmonella	Food	↑	Antibiotics
Q-fever	Airborne	?	Antibiotics
Virus			
HSV	Mouth, droplets, and blood	↑	Antiviral medication
HPV	HPV1 oral HPV2 STD, and skin-skin	↑	Vaccination
Hepatitis B	STD, blood	↑	Vaccination
HIV	STD, blood	↑↑	HIV medication
Zika	Mosquitos (rare STD)	↑	No[a]
Dengue	Mosquitos	↑	Vaccination in endemic areas
Rubella	Airborne	↑↑↑	Vaccination
CMV	Body fluids	↑↑	Antiviral medication
Parvovirus B19	Airborne and blood	↑	No, immunoglobulins
Varicella-zoster	Airborne	Probably no	Vaccination, antiviral medication
Polyoma virus	Airborne, water, or food	?	No
SARS	Airborne	?	No
MERS	Airborne—zoonotic[b]	?	No
H1N1 flu virus	Airborne	↑	Vaccination
SARS-CoV-2	Airborne	?	Vaccination
Protozoa			
Toxoplasmosis	Food, cat litter	↑	Antibiotics
Malaria	Mosquitos	↑↑	Prophylaxis, vaccination in endemic areas

CMV = cytomegalovirus; HIV = human immunodeficiency virus; HPV = human papilloma virus; HSV = herpes simplex virus; MERS = middle east respiratory syndrome; SARS = severe acute respiratory syndrome; STD = sexually transmittable disease.

[a] Vaccines are being tested in clinical trials.

[b] Zoonotic—transmitted between animals (here, infected dromedary camels) and humans.

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pregnancy at reactivation or primary infection. It is the only untreatable common infection that has no effective vaccine yet.

Varicella-zoster virus infection seems not to be related to miscarriage, but this virus infection can result in severe maternal and congenital infections. For the other infections, there is a lack of evidence or evidence that is incomplete. For human polyomaviruses infection such as severe acute respiratory syndrome and Middle East respiratory syndrome, there are small studies that point to an increased miscarriage chance, but the available evidence is scarce. For severe acute respiratory syndrome coronavirus 2, there is low-quality evidence that miscarriage is not increased in the first and second trimesters (10). However, because very large population studies have shown that influenza virus infection results in higher miscarriage rates, particularly in women with severely illnesses, such a relationship in coronavirus diseases 2019 cannot be excluded at this moment.

Protozoa

Malaria has been shown to increase consistently the chance of miscarriage, and toxoplasmosis is likely also associated with a higher miscarriage risk. For malaria, vaccination is available in endemic areas, and prophylaxis is provided to people traveling to areas where malaria is endemic. For toxoplasmosis, there is no effective vaccine; it can be treated with antibiotics. Because *Toxoplasmosis gondii* is prevalent in cats, pregnant women are advised not to clean the cat litter box and wear gloves when working in the garden, besides some other preventative hygienic measures (https://www.cdc.gov/parasites/toxoplasmosis/prevent.html). Irrespective of the relationship with miscarriage, all the described pathogens have been reported to increase perinatal complications like higher preterm births, still births, and/or neonatal deaths and congenital malformations. Pregnant women and their developing fetus are more susceptible to infections, and these infections can have a devastating effect on the mother, the pregnancy, and the neonate.

Most of the evidence on the relationship between infections and miscarriage concerns sporadic miscarriages. For the majority of the infections, it seems less likely that they are associated with recurrent miscarriage unless the infection was not treated and is ongoing. There may be a different case for bacterial vaginosis in view of the high recurrence rate, which could be because of reinfection by their own partner.

DISCUSSION

A significant number of miscarriages may be because of infections during pregnancy. For many infectious agents, there is evidence that these increase miscarriage risk, particularly for syphilis, gonorrhea, bacterial vaginosis, brucellosis, listeriosis, human immunodeficiency virus infection, rubella virus infection, CMV infection, and malaria. More information is needed on the exact impact of the infection on miscarriage or stillbirth at a later gestational age. Furthermore, there is a lack of complete knowledge on the mechanisms by which infectious diseases cause adverse pregnancy outcomes, specifically pregnancy loss (9).

Because pregnant women are particularly vulnerable to infections, prevention and early management are important (4–6). In theory, the majority of these infections are preventable, but this is feasible only in the presence of adequate knowledge, education, and access to care. Studies have indicated that vaccinations are effective in preventing complications in pregnant women (6). Awareness, furthermore, is particularly important for the very common viral CMV and varicella-zoster infections and for the sexually transmitted infections that are on the rise. Large national prevention programs seem advisable.

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