

Does an Upper Respiratory Tract Infection During Pregnancy Affect Perinatal Outcomes? A Literature Review

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Abstract Upper respiratory tract infection (URTI) is a ubiquitous but often benign pathology most commonly of viral etiology. This review focuses on perinatal outcomes following URTI during pregnancy. Few data exist on the explicit topic of URTI and adverse perinatal outcomes. The entire URTI burden among pregnant women is not properly represented by the studies included in this review, because only those infections severe enough to warrant hospitalization have been studied. Most probably, the number of URTIs in pregnant women not requiring hospitalization is far larger, but this has yet to be quantified. Clearly, there are logistical barriers to obtaining such statistics. Severe URTI requiring hospitalization during pregnancy was noted to be associated with adverse perinatal complications. URTI was found to be positively correlated with preterm delivery (PTD; less than 37 weeks gestation), lower birth weight, and cesarean deliveries, without a significant effect on the rates of perinatal mortality or low Apgar scores. There appears to be a possible link between various infectious processes that occur during pregnancy and the outcome of a PTD. The inflammatory environment present during infection includes high levels of cytokines that are known to increase prostaglandins, which, in turn, can induce preterm birth. Further studies should evaluate whether URTI not requiring hospitalization has any effect on perinatal outcomes.

Keywords Upper respiratory tract infection · Pregnancy · Perinatal outcome

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Introduction

Upper respiratory tract infection (URTI) is a ubiquitous but often benign pathology most commonly of viral etiology. URTI usually presents with a prodrome known as the “common cold,” involving headache, myalgia, sneezing, nasal discharge, nasal obstruction, cough, hoarseness, sore and scratchy throat, and sometimes fever [1]. The common cold is the number one reason for doctor visits in the United States [1]. On average, healthy adults will experience between two and four URTIs every year, which last from 7 to 14 days each [1]. The most common etiologies are rhinovirus, coronavirus, and adenovirus; however, these entities are clinically indistinguishable, and a specific virologic diagnosis does not alter medical management [1, 2].

URTI in the Pregnant Population

Pregnancy affects the functioning of multiple organ systems. The alterations in pulmonary function are significant. The diaphragm is elevated an average of 4 cm [3, 4]. This leads to a decrease in the functional residual capacity and residual volume. There is a transition from abdominal to thoracic breathing and an increase in minute ventilation, resulting in a mild respiratory alkalosis, which allows for better gas exchange across the placenta [3]. When a pregnant woman experiences a respiratory infection, the fetus can be negatively impacted due to its unique sensitivity to hypoxemia and acidosis. This dangerous combination has been shown to stimulate preterm labor in the second half of pregnancy [4]. Additionally, there is an increase in oxygen requirement and critical closing volume, which, in conjunction, make respiratory disease more severe in pregnancy [4].

In pregnancy, the immune system also undergoes various physiological alterations, resulting in depressed cell-mediated immunity and a reduced Th1 response [5•]. The Th1 response

is a pathway of pathogen removal involving T-helper cells, macrophages, and B-cells. In a general sense, T cells produce a chemical called interferon-gamma, which excites macrophages, turning on their bactericidal properties. Simultaneously, B-cells are also activated, and they begin to make cell-coating antibodies. Together, the tagging of the pathogen by B-cell's antibodies and the bactericidal instincts of the macrophages lead to pathogen removal, if all goes according to plan.

If this system outlined above is not functioning adequately, as in pregnancy, there will be greater susceptibility to infection. Pregnant women have been noted to have an impaired immune response to multiple viruses; among them are many causes of URTIs, such as influenza, cytomegalovirus, and streptococcal organisms [6]. It is postulated that the proinflammatory environment of infection—specifically, the cytokines and microbial endotoxins that induce prostaglandin production and matrix-degrading enzymes—can contribute to preterm labor [7].

URTI can be complicated by pneumonia, a lower respiratory tract infection (LRTI). Pneumonia is usually caused by bacterial infection, unlike URTI. However, LRTI can follow a viral URTI (e.g., Group A streptococcal pneumonia may follow influenza) [1]. LRTI carries a much greater risk in pregnancy than does URTI. There is a much higher chance of hypoxemia and acidosis due to the severity and depth of the infection. Pregnant women with pneumonia are at risk for various medical complications, such as meningitis, pericarditis, empyema, and endocarditis. Therefore, pregnant women with pneumonia are usually hospitalized and monitored. Pneumonia has been linked to low birth weight, fetal distress, and preterm birth [8, 9].

URTI and Adverse Perinatal Outcomes

Few data exist on the explicit topic of URTI and adverse perinatal outcomes. The most recent study regarding this issue compared pregnant women who had been hospitalized for URTI with those who had not. This study was a large retrospective population-based study by Stiller-Timor et al., conducted at Soroka University Medical Center in Beer Sheva, Israel. Stiller-Timor et al. reviewed 183,373 deliveries from 1988 to 2008. From this large cohort, 0.132 % ($n=246$) of the women fit the necessary criteria of fever and symptoms of URTI that required hospitalization [7].

A variety of perinatal outcomes were analyzed from this cohort, such as cesarean delivery (CD), premature rupture of membranes (PROM), Apgar score less than 7 at 1 and 5 min, perinatal mortality, preterm delivery (PTD), low birth weight, and labor induction. URTI was found to be positively correlated with PTD and CD (see Table 1). However, no difference was found in the rates of perinatal mortality or Apgar scores between those women with URTI and those without [7].

Table 1 Perinatal outcomes of women with upper respiratory tract infection (URTI)

Outcome	Number of women with URTI ($n=246$), %	Number of women without URTI ($n=246$), %	<i>P</i> value
Gestational age at delivery <37 weeks	15.9	7.9	<.001
Birth weight <2,500 grams	11.0	7.8	.170
Premature rupture of membranes	4.9	6.9	.212
Cesarean delivery	20.3	13.2	<.001
Apgar score <7 at 1 min	5.8	4.0	.165
Apgar score <7 at 5 min	0.4	0.6	.761

Note. Adopted from Stiller-Timor A, Levy A, Holcberg G, Sheiner A. Respiratory tract infection during pregnancy: Is it associated with adverse perinatal outcomes? *Am J Perinatol.* 2010;27(8).

Increased rates of PTD in the presence of URTI were also noted in a study done recently in Norway by Morken et al. In this study, which employed the use of the Norwegian Mother and Child Cohort, a low-risk population of mothers was surveyed at two different points in their pregnancies regarding a variety of criteria. This article also investigated the relationship between spontaneous PTD (SPTD) and maternal febrile episodes resulting from urinary tract infections (UTIs), pneumonia, and ear–nose–throat infections. This investigation revealed that only those women with ear–nose–throat infections (URTIs) had an increased rate of SPTD. However, this correlation was noted only in the survey administered at week 17, which reflected any URTI that these women had incurred prior to week 17 [10]. Comparatively, in the study by Stiller-Timor et al., the time during gestation at which the infection had occurred was not included in the analysis [7].

One of the unifying factors in the literature that documents an increase in adverse perinatal outcomes is the presence of fever. In a study published by Bensal et al., peripartum fever was found to be associated with an increase in PTD and was noted as an independent risk factor for perinatal mortality [11]. Some of the more common causes of peripartum fever are UTI, pyelonephritis, and endometritis, all of which have been linked to PTD [12, 13]. Despite this association, it is important to note that in a study by Maayan-Metzger et al., which analyzed perinatal outcomes resulting from various causes of maternal fever, it was found that the fetus incurred no risk from the fever itself [14].

Numerous studies were published in the aftermath of the 2009 H1N1 influenza pandemic. One of the subgroups most affected by the H1N1 influenza epidemic was pregnant women. H1N1 influenza is a viral infection that affects the

upper respiratory tract; however, it is more virulent than the average community-acquired viruses. Pregnant women are highly affected by influenza, and even the yearly H1N1 influenza strains of less virulence have historically resulted in higher mortality and morbidity in the pregnant population [9]. The results from the United Kingdom Obstetric Surveillance System (UKOSS) published by Pierce et al. show that H1N1 infection in pregnant women requiring hospitalization was also linked to an increased rate of PTDs [15]. According to the UKOSS, the factors found to increase a woman's risk for PTD were admission to the intensive care unit and secondary pneumonia infection [15]. In regards to the relationship of fever as a contributory factor, the analysis of this study did not explicitly investigate the relationship of fever to perinatal outcomes, but fever was a commonly reported symptom with H1N1 infection.

A retrospective population-based study was performed to determine the effect of pneumonia on the outcomes of adverse pregnancies [8]. This analysis also revealed a relationship between pneumonia and PTD. In a multivariable model controlling for IUGR, placental abruption, and preeclampsia, pneumonia was found to be an independent risk factor for PTD (OR=5.4, 95 % CI 3.8–7.7, $p<.001$). However, pneumonia was not found to be an independent risk factor for perinatal mortality [8]. Using the same population (from Beer Sheva, Israel), an additional study was performed by Gershovitz et al., which investigated the population of women who had undergone splenectomy in this same time period and then become pregnant [16]. This investigation found that splenectomy was an independent risk factor for PTD (OR=2.1, 95 % CI 1.4–3.3, $p<.001$) [16]. An additional study conducted with the same cohort investigated pyelonephritis and pregnancy [17]. In this study by Farkash et al., it was found that pyelonephritis was an independent risk factor for PTD (OR=2.6; 95 % CI 1.7–3.9, $p<.001$) [17].

Discussion

URTI is the number one reason that people seek medical attention in the United States [1]. Therefore, it would be safe to assume that this trend must also be true among the pregnant population. The entire URTI burden among pregnant women is not properly represented by the studies included in this review, because only those infections severe enough to warrant hospitalization have been studied. Most probably, the number of URTIs in pregnant women not requiring hospitalization is far larger, but this has yet to be quantified. Clearly, there are logistical barriers to obtaining such statistics.

Influenza is one of the major causes of URTI, and it is responsible for a great deal of morbidity in the pregnant

population. Influenza was indicated in 2.5 hospitalizations per 1,000 women in their third trimester, outside of influenza season [18]. One potential way to lower the burden of URTI, which may, in turn, lower the incidence of PTD, is through use of the influenza vaccine. This vaccine is not currently well utilized by the pregnant population. The American College of Gynecology and Obstetrics (ACOG) and the Advisory Committee of Immunization Practices (ACIP) recommend universal vaccination for pregnant women at all gestational ages [19]. However, currently, only 13 %–34 % of pregnant women are vaccinated [20]. The vaccine has been shown to reduce morbidity and is considered cost effective due to the reduction in supportive care required by the target population [18].

There appears to be a clear link between various infectious processes that occur during pregnancy and the outcome of a PTD (Fig. 1). The inflammatory environment present during infection includes high levels of cytokines that are known to increase prostaglandins, which, in turn, can induce preterm birth. The precise immunological cascade present in each of the above-mentioned infections is not equivalent. Consequently, more data would be necessary to understand the common component present in these infections that truly triggers preterm birth.

Romero et al. have extensively studied the immunologic profiles related to preterm labor and delivery. Initially, using mice models, they noted that inflammation is crucially linked to the process of preterm labor and, specifically, the process of cervical ripening that leads to preterm labor and delivery [21]. Subsequently, they further elucidated the role of the complement system, a component of the innate immune system responsible for assisting phagocytic cells in identifying and eliminating pathogens. Complement activation occurs uniquely in preterm labor, and not in the process of normal term labor and delivery [22]. This finding suggests that the inflammatory state present in preterm labor and delivery is potentially the catalyst that triggers cervical ripening preterm and allows for preterm labor to occur.

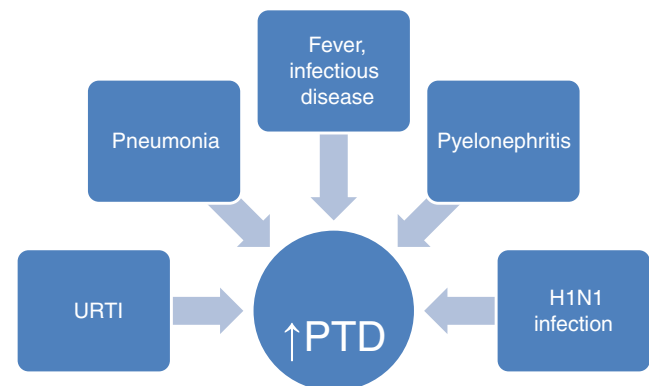


Fig. 1 A link between various infectious processes occurring during pregnancy and preterm delivery

However, it was noted that the mechanism through which preterm and term cervical remodeling occurs is identical; it is simply the trigger that was shown to be different [22, 23].

The understanding of the process of preterm labor and delivery is ever-changing. Preterm labor has been suggested to exist on a continuum with cervical changes. Primarily, it is believed that cervical shortening can progress and lead to eventual cervical funneling, which is often, but not always, followed by preterm labor itself. However, as of late, Kim et al. have brought into question whether or not cervical changes are necessary for preterm birth to occur. They have questioned the medical criteria necessary for a diagnosis of preterm labor. The suspicions are based upon the fact that when sampling amniotic fluid of women who have preterm contractions, but not cervical change, it is noted that the women who had culture-confirmed infection had elevated rates of PTD and overall morbidity [24]. This observation led to questioning the belief that cervical change is a necessary process in the early stages of preterm labor and, when quantified, can predict rates of PTD. This sparked further investigation into the inflammatory states present in pregnancies with poor outcomes.

A great deal of research has been done on the immunologic response of the mother to the fetus. One of the changes that occur in pregnancy is a reduction in the immune response, particularly in regard to cell-mediated immunity and the Th1 response [4, 6]. It is thought that this change is one of the ways in which the body prevents a graft-versus-fetus response in the mother. However, when the immune system remains robust in this regard, one of the possible results is a condition referred to as chronic chorioamnionitis. This is a condition defined by a pathology report postdelivery that shows a lymphocytic infiltration of the chorioamniotic membranes. In the research of Lee et al., chronic chorioamnionitis was found in more than one third of spontaneous PTDs [25]. This inflammatory lesion, along with vilitis of the placenta of unknown etiology, has been found to resemble allograft rejection and graft-versus-host disease of the fetus in their immunologic markers [25]. Thus, the inflammatory environment referred to as a precursor of preterm labor and delivery may be intimately related to chronic chorioamnionitis. It would be beneficial to understand the differences between the conditions leading to chronic chorioamnionitis, which causes PTD, and the infections that lead to PTD. Perhaps the changes in the immune system (or lack thereof) that lead to chronic chorioamnionitis are related to the susceptibility to certain infections, which additionally increase the likelihood of preterm labor and delivery.

PTD is the number one contributor to infant mortality worldwide [26]. In 2005, 28,382 infants died in the United States before the age of 1 year, 66 % of which were

attributed to PTD [4]. Further elucidating the processes that contribute to PTD would have massive implications in the world of obstetrics and gynecology. It is clear that the inflammatory environment present during preterm labor and delivery is unique to that of term delivery. There is a large body of data implicating infection as one of the primary causes of this inflammation; particularly important are those infections that induce fever and are severe enough to warrant hospitalization. Therefore, additional investigation into this subpopulation may contribute to decreasing this significant source of morbidity and mortality.

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