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ASSOCIATION OF CYSTITIS WITH PREGNANCY COMPLICATIONS: FROM ASYMPTOMATIC BACTERIURIA TO PREECLAMPSIA

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Abstract
Risk factors for acute cystitis include a history of ASB, anatomical abnormalities of the urinary tract, gestational diabetes mellitus, and a previous episode of pyelonephritis. Pregnant women experience a higher frequency of recurrences, often associated with the growth of multidrug-resistant strains of E. coli and impaired antibiotic susceptibility . Both asymptomatic bacteriuria and acute cystitis are considered conditions associated with an increased risk of adverse gestational outcomes. The most significant consequence of ASB is its progression to an ascending infection, whereas acute cystitis can contribute to the activation of systemic inflammation and impaired placental perfusion, especially in the absence of timely treatment.

Introduction

Urinary tract infections (UTIs), including asymptomatic bacteriuria (ASB) and acute cystitis, represent one of the most common community-acquired infectious conditions in pregnant women. Their detection rate during gestation remains high, despite advancements in prenatal care standards, and, according to various sources, ranges from 5% to 12% depending on the population and diagnostic methods [1]. For a long time, UTIs in pregnant women were primarily considered a localized pathology without systemic impact on the course of pregnancy. However, over the past decades, compelling evidence has accumulated indicating a close association between lower urinary tract infections and the development of serious obstetric complications, including preterm birth, intrauterine growth restriction (IUGR), and preeclampsia. This is particularly relevant for asymptomatic bacteriuria, which often remains undiagnosed and, in the absence of timely therapy, can contribute to the development of inflammatory and vascular disorders threatening both mother and fetus [2].

Current research indicates that the pathophysiological consequences of UTIs extend beyond the urogenital sphere, initiating a systemic inflammatory response capable of disrupting normal

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endothelial function and uteroplacental blood flow. Activation of pro-inflammatory cytokines, angiogenic imbalances, and the innate immune response create a predisposition for obstetric complications, including hypertensive disorders of pregnancy [3]. Amidst the global rise in antibiotic resistance and the high prevalence of recurrent UTIs, there is an increasing need for a substantiated, evidence-based strategy for screening and prevention. Objective risk assessment and an understanding of the pathogenetic mechanisms linking UTIs to pregnancy complications are essential for enhancing the effectiveness of perinatal care.

The aim of this paper is to conduct a systematic review of data on the incidence of urinary tract infections during pregnancy, analyze their association with major obstetric complications, and consider current pathophysiological models explaining this phenomenon. Particular attention is given to the rationale for early screening for asymptomatic bacteriuria as a clinically significant strategy for preventing gestational complications.

Urinary tract infections during pregnancy, particularly asymptomatic bacteriuria (ASB) and acute cystitis, are a significant focus of clinical attention due to their high prevalence and potential threat to both mother and fetus. In obstetric practice, they are leading bacterial complications, second only to respiratory tract infections.

ASB is defined as the presence of significant bacteriuria ($\geq 10^5$ colony-forming units [CFU]/mL) in a midstream urine sample in the absence of clinical symptoms of inflammation. According to multicenter epidemiological studies, the prevalence of asymptomatic bacteriuria in pregnant women ranges from 2% to 10%, with the highest rates observed in populations with low socio-hygienic status, anemia, and diabetes mellitus [4].The main microbiological feature is the predominance of Escherichia coli, which is detected in over 70–80% of ASB cases. Other pathogens include Klebsiella spp., Enterococcus faecalis, and Proteus mirabilis, especially in recurrent cases. The absence of clinical manifestations leads to low awareness among physicians and patients, which, in turn, results in insufficient diagnosis and therapy. It is particularly important to note that in 20–30% of pregnant women with untreated asymptomatic bacteriuria, acute cystitis develops during gestation, and in 30–40% of cases, an ascending kidney infection occurs, presenting as gestational pyelonephritis [2]. This necessitates active screening for ASB in early pregnancy, as reflected in the recommendations of most international clinical guidelines (e.g., ACOG, NICE, WHO). Acute cystitis during pregnancy is diagnosed in 1.5–3% of women, predominantly in the second and third trimesters. Unlike ASB, the clinical picture is characterized by typical dysuric symptoms—frequent and painful urination, urgency, and a sensation of incomplete bladder emptying. However, during pregnancy, these symptoms may be masked or attenuated and misinterpreted as physiological changes, often leading to delayed diagnosis.

Risk factors for acute cystitis include a history of ASB, anatomical abnormalities of the urinary tract, gestational diabetes mellitus, and a previous episode of pyelonephritis. Pregnant women experience a higher frequency of recurrences, often associated with the growth of multidrug-resistant strains of E. coli and impaired antibiotic susceptibility . Both asymptomatic bacteriuria and acute cystitis are considered conditions associated with an increased risk of adverse gestational outcomes. The most significant consequence of ASB is its progression to an ascending infection, whereas acute cystitis can contribute to the activation of systemic inflammation and impaired placental perfusion, especially in the absence of timely treatment. In this context, early detection

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and adequate antimicrobial therapy for both conditions are not only preventive but also potentially life-saving measures aimed at reducing the incidence of pregnancy complications.

Risks: Preterm Birth, IUGR, Preeclampsia Lower urinary tract infections during pregnancy, despite their relative prevalence and, at times, subclinical course, have a proven association with several serious obstetric complications. Among these, preterm birth, intrauterine growth restriction (IUGR), and preeclampsia are of the greatest clinical significance. Current epidemiological and pathophysiological studies confirm that even asymptomatic bacteriuria can serve as an independent predictor of an abnormal course of gestation, especially in the absence of timely diagnosis and therapy.

The most studied and reliably confirmed complication associated with UTIs is preterm birth, defined as delivery before the 37th week of gestation. Meta-analyses involving data from over 100,000 pregnant women have demonstrated that the presence of asymptomatic bacteriuria increases the risk of preterm birth by 42–45%, and with the development of symptomatic cystitis, the risk rises to 60–65% [5].

Pathogenetically, this effect is due to the activation of a systemic inflammatory response secondary to microbial invasion. The production of pro-inflammatory cytokines and prostaglandins in response to the infectious process can induce premature myometrial contractions and premature cervical ripening. Furthermore, bacterial toxins can directly affect the fetal membranes, contributing to their premature rupture (PROM). UTIs, especially with recurrent episodes or subclinical inflammation, are also associated with impaired fetoplacental perfusion and the development of IUGR. Infection before 24 weeks of gestation is considered most critical, as this is when active formation of the chorionic and placental vascular network occurs [6]. The mechanism involves endothelial dysfunction, microthrombosis in the chorionic villi, and reduced oxygen and nutrient supply to the fetus. Ultrasound findings in such patients more frequently include fetal size lagging behind gestational age, reduced amniotic fluid volume, and, on Doppler velocimetry, signs of placental insufficiency. Long-term neonatal consequences include low birth weight, increased risk of hypoglycemia, and neurodevelopmental disorders.

Of particular interest is the association between urinary tract infections and the development of preeclampsia—a multifactorial vascular syndrome characterized by hypertension, proteinuria, and endothelial dysfunction. Current studies demonstrate that pregnant women with UTIs, especially those with recurrent episodes of cystitis or untreated bacteriuria, have a statistically significantly higher risk of developing preeclampsia, up to 1.8–2.2 times compared to the control population [7].

It is hypothesized that a chronic infectious-inflammatory process initiates endothelial activation, disrupts the balance of angiogenic factors (e.g., VEGF, PlGF, sFlt-1), and promotes systemic vasoconstriction. The involvement of bacterial fragments and lipopolysaccharides in activating Toll-like receptors (TLRs), particularly TLR4, on endothelial cells is also plausible, triggering the chain of immune-inflammatory reactions characteristic of preeclampsia pathogenesis [4].

Thus, even in the absence of overt clinical manifestations, infectious-inflammatory conditions of the urinary tract during pregnancy can trigger systemic complications requiring hospitalization and intensive obstetric monitoring. This underscores the necessity for early diagnosis, comprehensive risk assessment, and timely etiotropic intervention.

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Pathophysiological Mechanisms: Inflammatory Cascade and Endothelial Activation

Understanding the mechanisms linking urinary tract infections to obstetric complications requires addressing the key links in the inflammatory and vascular responses of a pregnant woman. Current data indicate that even a localized infectious-inflammatory process in the lower urinary tract can trigger systemic reactions capable of disrupting endothelial function, microcirculation, and normal placentation.

The initiating step is the activation of the innate immune response to bacterial invasion. The main triggers are lipopolysaccharides (LPS) from Gram-negative bacteria, particularly Escherichia coli, which are recognized by Toll-like receptors (TLRs), predominantly TLR4, expressed on the surface of epithelial and endothelial cells [8]. This initiates a signaling cascade via the MyD88-dependent pathway, leading to the transcription of pro-inflammatory mediators—IL-6, IL-1β, TNF-α, and other cytokines.

These mediators promote systemic neutrophil activation, increased vascular permeability, enhanced expression of adhesion molecules on the endothelial surface, and activation of the coagulation cascade. During pregnancy, especially in its early stages, such activation may be incompatible with physiological vascular adaptation and the development of adequate placental perfusion.

One of the central elements in the pathogenesis of pregnancy complications related to infections is endothelial dysfunction. Under the influence of pro-inflammatory cytokines and microbial toxins, nitric oxide (NO) synthesis is impaired, vasoconstriction occurs, platelet aggregation is enhanced, and microthrombosis develops in the microcirculatory system. This leads to reduced blood flow in the uteroplacental unit and exacerbates hypoxic changes in the placenta and fetus.

Infection-induced endothelial activation also affects the pregnant woman's angiogenic profile. It has been established that chronic inflammation increases the level of anti-angiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1), and decreases the level of placental growth factor (PlGF), which is characteristic of preeclampsia pathogenesis [3].

In the early stages of gestation, inflammatory processes can disrupt trophoblast invasion and spiral artery remodeling, leading to the formation of so-called superficial placentation—a characteristic feature of many complicated pregnancies, including IUGR and preeclampsia. Furthermore, endotoxins induce apoptosis of cytotrophoblast cells, which compromises the integrity of the trophoblastic barrier and facilitates the entry of systemic inflammatory mediators into the fetoplacental circulation [4].

Thus, the inflammatory response induced even by a localized UTI can transform into a generalized pathological state involving the vasculature, immune system, and trophoblastic structures. This explains the observed link between lower urinary tract infections and systemic obstetric complications.

Rationale for Screening for Asymptomatic Bacteriuria Given the high risk of complications, international guidelines recommend mandatory screening for asymptomatic bacteriuria at the pregnant woman's first antenatal visit. Performing a urine culture allows for the detection of ASB before symptoms appear and the timely initiation of therapy with appropriate and safe antibiotics.

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Evidence shows that treatment of ASB in early pregnancy reduces the risk of pyelonephritis by 70–80% and the risk of preterm birth by 30–40% [6]. The screening approach is particularly justified in regions with high levels of antibiotic resistance and limited access to specialized care.

Conclusion Urinary tract infections during pregnancy, including asymptomatic bacteriuria and acute cystitis, should be viewed not as isolated urological conditions, but as significant predictors of systemic gestational complications. Clinical, epidemiological, and molecular biological data accumulated in recent years provide evidence of a significant association between UTIs and an increased risk of preterm birth, intrauterine growth restriction (IUGR), and preeclampsia.

The pathogenetic mechanisms of this interaction involve activation of the innate immune response, a systemic inflammatory cascade, vascular endothelial dysfunction, and angiogenic disturbances that contribute to impaired normal placentation and fetoplacental blood flow. Asymptomatic bacteriuria poses a particular danger; if not diagnosed and treated promptly, it can progress to ascending infections and become a trigger for generalized vascular dysfunction.

Amidst rising antibiotic resistance and a variety of clinical scenarios, pregnancy requires a clearly regulated program of perinatal surveillance, including mandatory screening for asymptomatic bacteriuria in the first trimester. This aligns with the recommendations of leading international organizations (e.g., ACOG, NICE, WHO) and aims to reduce the incidence of severe obstetric complications.

Therefore, incorporating UTI assessment into the pregnancy risk stratification system is a justified strategy aimed at enhancing gestational safety and improving both maternal and perinatal outcomes. Rational selection of antibacterial therapy, individualized monitoring, and targeted attention to recurrent UTI episodes can significantly reduce the burden of complications associated with cystitis and bacteriuria in pregnant women.

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