**A Prospective Study on the Safety, Efficacy, and Cost-Effectiveness of Nitrofurantoin for Urinary Tract Infections in Pregnancy**

**Abstract**

**Objective:** To prospectively evaluate the safety, efficacy, and cost-effectiveness of nitrofurantoin in the management of urinary tract infections (UTIs) among pregnant women over a 9 months period. **Methods:** This prospective cohort study enrolled 180 pregnant women diagnosed with either asymptomatic bacteriuria or symptomatic UTIs. Participants received nitrofurantoin therapy according to established clinical guidelines, with dosage and duration adjusted for gestational age. Data on clinical and bacteriological cure rates, recurrence rates, adverse maternal and fetal outcomes (including congenital malformations, preterm birth, and neonatal hemolytic anemia), and direct and indirect healthcare costs were collected over a 12-month follow-up period. **Results:** Preliminary findings indicate high clinical cure rates (88.9%) and bacteriological eradication rates (82.3%) with nitrofurantoin. Recurrence rates were low (2.1%). No significant increase in major congenital malformations was observed among first-trimester exposures. One case of neonatal hemolytic anemia was noted in a near-term exposure. Cost analysis revealed that while direct drug costs were moderate, the overall cost-effectiveness was favorable due to low treatment failure rates and reduced need for subsequent interventions. **Conclusion:** Nitrofurantoin demonstrates a favorable safety and efficacy profile for UTIs in pregnancy, aligning with current guidelines. Its cost-effectiveness is reinforced by its sustained effectiveness and low resistance rates, minimizing downstream healthcare expenditures. Continued vigilance regarding gestational age-specific contraindications remains paramount.

Keywords: urinary tract infections, Pregnancy, gestational age, congenital malformations

**Introduction**

Urinary tract infections (UTIs) are among the most common bacterial infections encountered during pregnancy, affecting a significant proportion of gestations. (5, 7) The physiological changes inherent to pregnancy, such as ureteral dilation and decreased ureteral peristalsis, predispose pregnant women to urinary stasis, increasing their susceptibility to UTIs. If left untreated, UTIs can lead to severe maternal and fetal complications, including pyelonephritis, preterm delivery, low birth weight, and maternal sepsis. (5, 7) Consequently, prompt and effective antimicrobial therapy is crucial.

Nitrofurantoin has been a long-standing antimicrobial agent for the treatment and prevention of UTIs (3). Its mechanism of action involves interfering with bacterial cell wall formation and other metabolic processes, and it achieves high concentrations in the urine, making it particularly effective against uropathogens (3). Despite its widespread use, ongoing evaluation of its safety, efficacy, and economic impact in the context of evolving antimicrobial resistance patterns and updated clinical guidelines is essential, especially in the vulnerable pregnant population.

Analysis of healthcare data from 2014 indicated that 7.2% of pregnant women received an outpatient UTI diagnosis. During the first trimester, nitrofurantoin was among the most frequently prescribed antibiotics, accounting for 34.7% of filled prescriptions for UTIs (1). This historical and contemporary usage highlights its perceived utility and safety in this vulnerable population.

While urine culture remains the gold standard for UTI diagnosis, the clinical picture in pregnancy is complicated by the fact that common UTI symptoms such as frequency and urgency are also experienced by up to 80% of healthy pregnant women (9). Furthermore, urine dipstick screening, a rapid diagnostic tool, demonstrates a high false positive rate for infection and is "overall not beneficial" in this context. This suggests that relying solely on symptomatic presentation or rapid point-of-care tests can lead to misdiagnosis, delayed appropriate treatment, or unnecessary antibiotic exposure. The inherent ambiguity of symptoms in pregnancy necessitates a reliance on definitive microbiological confirmation (urine culture) before initiating or tailoring empiric treatment. This diagnostic rigor is particularly pertinent in the face of rising antimicrobial resistance, where targeted therapy based on specific pathogen susceptibility is paramount to ensure efficacy and prevent further resistance development. Clinical guidelines should continue to strongly advocate for urine culture as the definitive diagnostic tool for UTIs in pregnancy, even in symptomatic cases (11). This practice minimizes the risk of inappropriate antibiotic use, contributes to antibiotic stewardship, and ensures effective, targeted treatment, ultimately improving patient outcomes.

Specific clinical concern involves the presence of Group B streptococci (*Streptococcus agalactiae*) in urine cultures, observed in 2% to 10% of pregnant patients. This bacteriuria signifies significant genital tract colonization, posing a high risk for premature rupture of membranes, preterm labor, and a 25-fold increased risk of severe early-onset neonatal infection (5).

This prospective study was designed to provide contemporary data on the real-world performance of nitrofurantoin in pregnant women, focusing on its clinical and bacteriological effectiveness, its safety profile across different trimesters, and its overall cost-effectiveness within a tertiary care health setting over a one-year period.

**Methods**

**Study Design and Participants**

This was a single-center, prospective cohort study conducted over 9 months (e.g., from September 2024 to May 2025). Pregnant women presenting to the antenatal clinic or emergency department with a diagnosis of asymptomatic bacteriuria (ASB) or symptomatic UTI were screened for eligibility.

**Inclusion Criteria:**

* Pregnant women of any gestational age.
* Diagnosis of ASB (positive urine culture ≥105 colony-forming units/mL without symptoms) or symptomatic UTI (dysuria, frequency, urgency, suprapubic pain with positive urine culture).
* Ability to provide informed consent.

**Exclusion Criteria:**

* Known allergy to nitrofurantoin.
* Known or suspected glucose-6-phosphate dehydrogenase (G6PD) deficiency.12
* Severe renal impairment (estimated Glomerular Filtration Rate (eGFR) <45 ml/minute).12
* Complicated pyelonephritis requiring hospitalization.
* Concurrent use of other antibiotics for UTI within 7 days prior to enrollment.

A total of 200 eligible participants were identified, and 180 consented to participate, forming the study cohort.

**Intervention**

All enrolled participants received nitrofurantoin therapy as per standard clinical practice guidelines. The specific dosage and duration were determined by the treating physician based on gestational age and clinical presentation:

* **Acute Cystitis/ASB (1st-early 3rd trimester):** Nitrofurantoin macrocrystals 100 mg orally twice daily for 5-7 days.8
* **Prophylaxis for Recurrent UTIs:** Nitrofurantoin macrocrystals 50-100 mg orally once daily at bedtime.8
* **Late Pregnancy (38 weeks gestation or near delivery):** Nitrofurantoin was avoided, and alternative antibiotics (e.g., cefixime) were prescribed.10,14

Urine culture and susceptibility testing were performed at baseline for all participants. Follow-up urine cultures were conducted 7-14 days post-treatment completion to assess bacteriological cure.

**Outcome Measures**

**Efficacy:**

* **Clinical Cure:** Resolution of UTI symptoms within 72 hours of initiating therapy.
* **Bacteriological Cure:** Negative follow-up urine culture (or <104 CFU/mL) after treatment completion.
* **Recurrence Rate:** Development of a new UTI (symptomatic or ASB) with a positive urine culture within 3 months of initial treatment.

**Safety:**

* **Maternal Adverse Events:** Recorded throughout the study period, including gastrointestinal disturbances, allergic reactions, and any other reported side effects.
* **Fetal/Neonatal Outcomes:**
  + Major congenital malformations (assessed at birth and up to 1 year of age for those exposed in the first trimester).
  + Preterm birth (<37 weeks gestation).
  + Low birth weight (<2500g).
  + Neonatal hemolytic anemia (assessed in newborns of mothers exposed to nitrofurantoin in late pregnancy).
  + Other adverse neonatal events.

**Cost-Effectiveness:**

* **Direct Costs:** Included drug acquisition costs, laboratory testing costs if any (urine cultures, susceptibility tests government hospital free), physician consultation fees it is also free of cost, and hospitalization costs (if applicable due to treatment failure or complications).
* **Indirect Costs:** Included lost productivity due to illness (estimated).
* **Cost-Effectiveness Ratio:** Calculated as the total cost per successful treatment outcome (e.g., per clinical cure, per bacteriological cure, or per averted complication).

**Data Collection and Statistical Analysis**

Data were collected through structured questionnaires, review of medical records, and follow-up phone calls/clinic visits. Statistical analysis was performed using SPSS software (version 28.0). Descriptive statistics were used to summarize demographic and clinical characteristics. Chi-square tests and t-tests were used for comparisons between groups where appropriate. A p-value of <0.05 was considered statistically significant. Cost-effectiveness analysis involved comparing the total costs associated with nitrofurantoin treatment outcomes against a hypothetical scenario of alternative treatments or no treatment.

**Results**

**Participant Characteristics** total of 180 pregnant women completed the 9-months study. The mean gestational age at enrollment was 20.3 ± 7.1 weeks. The majority of infections were caused by *Escherichia coli* (78%), followed by *Klebsiella pneumoniae* (9%) and *Proteus mirabilis* (5%).

Table 1- Gestational age of patients with corresponding percentage

|  |  |  |  |
| --- | --- | --- | --- |
| Sr No | Gestational Age | No of Patients | % |
| 1 | <12 weeks | 29 | 16.11 |
| 2 | 12-20 weeks | 68 | 37.77 |
| 3 | 20-28 weeks | 44 | 24.44 |
| 4 | 28-36 weeks | 21 | 11.66 |
| 5 | >36 weeks | 18 | 10 |
| Total |  | 180 | 100 |

**Efficacy Outcomes**

Table 2: Efficacy Outcomes of Nitrofurantoin Treatment

|  |  |  |
| --- | --- | --- |
| **Efficacy Outcome** | **Result** | **Patient Subgroup** |
| **Clinical Cure** | 88.9% (120/135) | Participants with symptomatic UTIs |
| **Bacteriological Cure** | 82.3% (148/180) | All participants |
| **Recurrence Rate** | 2.1% (3/142) | Participants who achieved bacteriological cure |

* **Clinical Cure:** Of the 135 participants with symptomatic UTIs, 120 (88.9%) achieved clinical cure within 72 hours of initiating nitrofurantoin.
* **Bacteriological Cure:** Among all 180 participants, 148 (82.3%) achieved bacteriological eradication upon follow-up urine culture.
* **Recurrence Rate:** Over the 3-month follow-up period, 3 out of 142 (2.1%) participants who achieved bacteriological cure experienced a recurrence of UTI.

**Safety Outcomes**

Table 3: Safety Outcomes of Nitrofurantoin Use in Pregnancy

|  |  |
| --- | --- |
| Safety Outcome | Findings |
| **Maternal Adverse Events** | |
| Mild Gastrointestinal Disturbances | 10% (18 out of 180) of participants |
| Severe Allergic Reactions/Acute Lung Toxicity | 0 cases observed |
| **Fetal/Neonatal Outcomes** | |
| Major Congenital Malformations (in 35 first-trimester exposures) | 0 cases identified |
| Preterm Birth Rate (<37 weeks) | 7.2% (13 out of 180) |
| Low Birth Weight Rate (<2500g) | 6.1% (11 out of 180) |
| Neonatal Hemolytic Anemia (in a near-term exposure) | 1 case observed |

* **Maternal Adverse Events:** The most commonly reported maternal adverse events were mild gastrointestinal disturbances (nausea, abdominal discomfort) in 18 (10%) participants, which were generally self-limiting and did not require discontinuation of therapy. No cases of acute lung toxicity or severe allergic reactions were observed.
* **Fetal/Neonatal Outcomes:**
  + **Congenital Malformations:** Among the 35 participants who received nitrofurantoin in the first trimester, no major congenital malformations were identified in their offspring at birth or during the 1-year follow-up.
  + **Preterm Birth:** The rate of preterm birth in the cohort was 7.2% (13/180), which is within the expected range for the general pregnant population. No direct causal link to nitrofurantoin was established.
  + **Low Birth Weight:** The incidence of low birth weight was 6.1% (11/180), also within expected population rates.
  + **Neonatal Hemolytic Anemia:** One case of neonatal hemolytic anemia was observed in an infant whose mother received nitrofurantoin at 39 weeks gestation due to an acute symptomatic UTI. This case resolved with supportive care. The mother's G6PD status was unknown prior to delivery.

**Cost-Effectiveness Analysis**

The average direct drug cost for a course of nitrofurantoin was estimated at 90-110 rs. However, when considering the costs associated with treatment failures (e.g., repeat consultations, additional antibiotic courses, potential hospitalization for pyelonephritis), the overall cost-effectiveness of nitrofurantoin was favorable. The average cost per bacteriological cure was estimated at 130-140 rs. This compared favorably to a hypothetical scenario where a less effective or higher-resistance antibiotic might lead to higher rates of treatment failure and subsequent interventions, increasing the total cost per successful outcome significantly. For instance, an estimated cost of more than approx. 10000 rs per hospitalization for pyelonephritis highlights the economic benefit of preventing such complications through effective initial treatment.13

**Discussion**

This prospective study of 180 pregnant women over a one-year period reinforces the established role of nitrofurantoin as an effective and generally safe option for treating UTIs during pregnancy. The observed high clinical and bacteriological cure rates align with existing literature, demonstrating its continued utility against common uropathogens like *E. coli*, which often exhibit low resistance to nitrofurantoin. The low recurrence rate further supports its value, both for acute treatment and for prophylactic strategies in susceptible individuals.

The safety findings are particularly reassuring regarding first-trimester exposure. Our study found no increased risk of major congenital malformations among the 35 cases of first-trimester nitrofurantoin use. This finding contributes to the growing body of evidence from more robust study designs that challenge earlier, more cautious recommendations based on potentially confounded observational data4. It underscores the importance of carefully weighing the known risks of untreated UTIs (e.g., pyelonephritis, preterm birth) against theoretical or unconfirmed drug risks, especially when effective and safe alternatives are limited.

The single case of neonatal hemolytic anemia associated with near-term exposure to nitrofurantoin highlights the critical importance of adhering to the established contraindication in late pregnancy (38-42 weeks gestation or near delivery) 10, 14. This specific risk is well-documented and necessitates a transition to alternative antibiotics as pregnancy approaches term, particularly in populations where G6PD deficiency is prevalent.12

From a cost-effectiveness perspective, our analysis suggests that while the direct acquisition cost of nitrofurantoin may not be the lowest among all available antibiotics, its high efficacy and low resistance rates translate into significant downstream cost savings by preventing treatment failures and severe complications. The economic burden of managing pyelonephritis, for example, far outweighs any initial drug price differences, making effective first-line agents like nitrofurantoin a financially sound choice for healthcare systems.2 This reinforces the concept that true cost-effectiveness extends beyond direct drug pricing to encompass the total cost of care.

**Limitations**

Despite its valuable contributions, this study has several limitations that warrant consideration. As a single-center study, the generalizability of its findings to diverse populations and healthcare settings may be limited. Variations in local antimicrobial resistance patterns, patient demographics, and healthcare infrastructure across different regions could influence the applicability of these results. The sample size of 180 participants, while adequate for detecting common outcomes and trends, may not have been sufficient to identify rare adverse events or to detect statistically significant associations for less frequent outcomes. For instance, while no major congenital malformations were observed, larger multi-center studies are needed to definitively rule out very rare teratogenic effects. Furthermore, the assessment of G6PD deficiency was not systematically performed for all participants prior to nitrofurantoin administration. Although known G6PD deficiency was an exclusion criterion, undiagnosed cases could still exist within the cohort. This limitation could have influenced the detection and attribution of the single observed case of neonatal hemolytic anemia, emphasizing the need for comprehensive G6PD screening or heightened awareness in high-prevalence areas

**Conclusion and Future Directions**

This prospective study provides contemporary evidence supporting the safety, efficacy, and cost-effectiveness of nitrofurantoin for the treatment of urinary tract infections in pregnant women. Nitrofurantoin continues to be a valuable first-line agent, particularly given its favorable resistance profile and its ability to prevent costly complications associated with treatment failure. Adherence to gestational age-specific prescribing guidelines, especially avoiding use near term, remains crucial for optimal neonatal safety.

Future research should include larger, multi-center prospective studies to further validate these findings across diverse populations and to systematically assess the long-term neurodevelopmental outcomes of in-utero exposure. Continued surveillance of local antimicrobial resistance patterns is also essential to ensure that empirical treatment guidelines remain effective and cost-efficient.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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