Management of Sub-Clinical Bacteriuria in Pregnancy: A Feasibility Trial

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Background:

Bacterial Colonization in the Urine

Assessment and treatment of bacterial colonization in the urine during pregnancy is a routine part of prenatal care.[1] A urinary tract infection (**UTI**) is defined as urine culture colonization >100,000 (**10^5**) colony forming units (**CFU**) of bacteria per ml with signs and symptoms of UTI including dysuria, frequency, urgency, suprapubic pain, and/or hematuria.[1-3] Asymptomatic bacteriuria (**ASB**) is defined as urine culture colonization > 10^5 CFU in the absence of signs and symptoms of UTI, and occurs in 2-10% of pregnancies.[3,4] Pregnant women with a UTI or ASB are routinely prescribed antimicrobial therapy based on identified organisms and sensitivities.

Sub-Clinical Bacteriuria

Sub-clinical bacteriuria **(SCB**) occurs when urine culture colonization is between 1 - 10^5 CFU**.** The frequency by which SCB occurs in pregnancy is unknown. It is also unknown the rate of progression from SCB to UTI and/or ASB, and subsequently development in to pyelonephritis. Moreover, there are no current guidelines that direct management in this particular condition in pregnancy. In current clinical practice, there is strong variation in care such that many patients are treated, despite the lack of proven benefit while other clinicians do not treat.

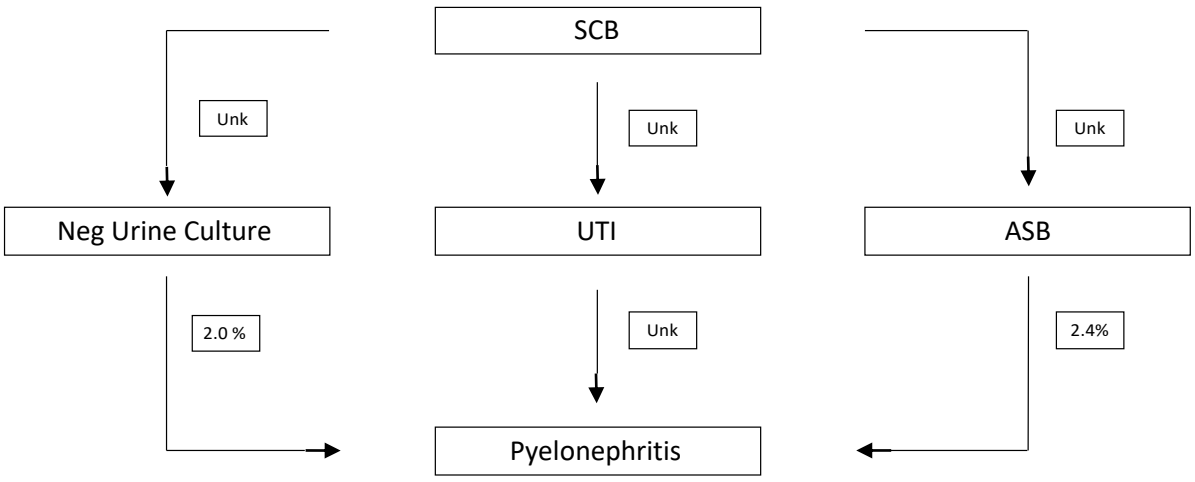

Figure 1. Schematic of potential progression of bacterial colonization in the urine.

Clinical Importance

Bacterial colonization in the urine during pregnancy can lead to adverse maternal and neonatal outcomes. Pyelonephritis is the primary concern in pregnancy due to its association with potential urosepsis, renal abscess, decline in renal function, preterm labor and preterm birth.[5] Although untreated

UTI is the greatest risk factor for developing pyelonephritis, ASB can also lead to pyelonephritis. In a recent randomized controlled trial of 4200 women in the Netherlands, they report that the incidence of pyelonephritis is only 2.4% when ASB is untreated compared to 0.6% when treated.[6] With such a low incidence, there is new debate whether to treat or expectantly manage ASB. This same debate also pertains SCB. It is unknown whether treatment or expectant management of SCB will lead to difference in the rate of progression to UTI and/or SCB, and ultimately pyelonephritis.

Risk of Antimicrobial Therapy

The two main risks of empiric antimicrobial therapy include potential for adverse drug effects and contribution to drug resistance. The use of antibiotics is not benign especially during pregnancy. Adverse drug effects include masking a diagnosis with empiric treatment of symptoms and no identification of an organism. Often times the diagnosis maybe correct, but the antibiotic that was chosen for treatment does not have sufficient coverage of the organism that is causing the infection. Common side effects to routinely used antibiotics such as nitrofurantoin, sulfa, amoxicillin and cephalexin includes rash and diarrhea.[9-10] The rise in antibiotic resistance over the past decades is evidence to the clinical consequences of unnecessary antimicrobial treatment across the disciplines in medicine. Such consequences also have been evident in the field of obstetrics. Nearly 50% of urinary isolates are resistant to routine ambulatory antibiotic therapy. Zhanel et al. looked at resistance to treatment in the NAUTICA trial. The goal of the North American Urinary Tract Infection Collaborative Alliance (NAUTICA) study was to determine antibiotic susceptibility to commonly used agents for urinary tract infections against outpatient urinary isolates obtained in various geographic regions in the USA and Canada. This study reports higher rates of antibiotic resistance in US versus Canadian outpatient urinary isolates and demonstrates the continuing evolution of resistance to antimicrobial agents.[7] Thus, if antibiotic therapy is not necessary for the management of subclinical cystitis due to low incidence of progression to pyelonephritis, it should not be prescribed.

Gap in Knowledge

The gap in knowledge is whether the risks and benefits of empiric treatment with antimicrobial therapy for treatment of SCB outweigh the risk and benefits of developing UTI, ASB or pyelonephritis from expectant management or no treatment of SCB.

Rationale for this clinical trial

The rational for this clinical trial is to determine if treatment of urine cultures with organisms of 1 – 100,000 CFU are beneficial to pregnancy outcomes when obtained at routine prenatal clinic visits. In current clinical practice, there is a strong variation in care such that many patients are treated for urine cultures with organisms of $<10^5$ CFU despite the lack of proven benefit while other clinicians do not treat.

If it is found that treatment of urine cultures with 1 - 10^5 CFU impact clinical care of a pregnant patient by decreasing adverse pregnancy outcome, guidelines will need to be modified to include treatment recommendations of urine cultures that do not currently meet criteria of a urinary tract infection. On the other hand, if there is no benefit to treatment of urine cultures 1 - 10^5 CFU, then unnecessary antibiotics could be avoided thereby potentially reducing unknown adverse effects to these drugs or resistance to antibiotics, which continues to be an alarming health challenge.

Hypothesis:

We hypothesize that treating urine cultures with organisms between 1- 10^5 CFU grown in culture media in a pregnant population leads to improvement of pregnancy outcomes.

Objectives:
To determine the rate of progression from SCB to either UTI or ASB with antimicrobial treatment of urine cultures with organisms of 1- 10^5 CFU compared to no treatment at prenatal care clinic visits.

Study Design:
For this pilot study, we propose a feasibility trial to determine if a randomized control trial for the treatment of subclinical cystitis to prevent pyelonephritis and culture proven cystitis. The trial will investigate the effects of treatment or non-treatment of urine cultures obtained during prenatal care visits prompted by a positive urinalysis or symptoms, and determine if a randomized control trial is needed to further investigate outcomes.

Patients meeting clinical indications will have a urine culture ordered due to two reasons: a) symptoms of a UTI or b) positive UA suspicious for infection/inflammation. A negative urine analysis is defined as an analysis that is negative for bacteria, leukocyte esterase, nitrites, and protein. A negative urine culture is defined as no growth or any amount of skin flora only.

Inclusion Criteria:
We will include pregnant women who seek prenatal care within the University of Texas Health System with UT Physicians.

Exclusion Criteria:
We will exclude women:

- Less than 18 years of age
- Risk factors to complicated UTI (including but not limited to: diverticula, urolithiasis, renal cysts, indwelling catheter, intermittent catheterization, stent placements, nephrostomy tubes, neurogenic bladder, cystocele, vesicoureteral reflux, ileal conduit)[8]
- Use of immunosuppressant drugs
- Abnormalities of the urinary tract (including but not limited to: known ureteric or urethral strictures, tumors of the urinary tract, pelvicalyceal obstruction, congenital anomalies, history of urological procedures)
- History of renal disease including renal failure and transplants
- Urine culture > 10^5 CFU of any organism

Those with a urine culture for bacteria but 1 - 10^5 CFU will be randomized to one of two management plans:

1. Prenatal care with treatment for any urine culture with growth of 1- 10^5 CFU of any organism
2. Prenatal care without treatment for any urine culture with growth of 1-10^5 CFU of any organism

Randomization:
Randomization will be performed based on a computer-generated list that will be created by a non-clinical member of the research team. Randomization will be stratified by clinic site. A permuted block randomization with a random fashion will be used to prevent imbalances between sites. At subsequent clinic visits, clinic staff will continue to obtain urine culture from symptomatic patients or patients where further work up of a urine culture is warranted. 'Physician to treat urine culture with 1- 100,000 (10^5) CFU" or 'Physician to NOT treat urine culture with 1-100,000 (10^5) CFU", based on the computer-

generated list, stored on the RedCap database. The research nurses and team may access the RedCap database from any clinical site.

Methods:
At the initial prenatal care clinic visit all pregnant women will have their urine screened with a UA and urine culture. Patients meeting inclusion criteria will be approached for randomization.

Those with a urine culture positive for bacteria 1- 10x5 CFU will be randomized to treatment or no treatment.

Those randomized to NO treatment will have a test of cure performed three weeks after initial negative urine culture or at next clinical visit thereafter.

Those randomized for treatment will be prescribed the most commonly used antibiotic for urinary tract infections in pregnancy. This includes: Nitrofurantoin, Cephalexin, and Amoxicillin. It is unsure which antibiotic the participant will receive but a majority of the time it will be one of the above named antibiotic. The choice will be determined by the physician, but will accommodate participants' prior medication history and adverse events.

Treatment will continue with a test of cure (urine culture performed after treatment with antibiotics) after each round of antibiotic until the urine culture shows no growth of bacteria and/or shows any amount of skin flora only.

Written, informed consent will be obtained by a member of our research team, either a physician or research assistant.

Once the patient is randomized to their designated arm, urine cultures will continue to be collected throughout prenatal care visits as clinically indicated.

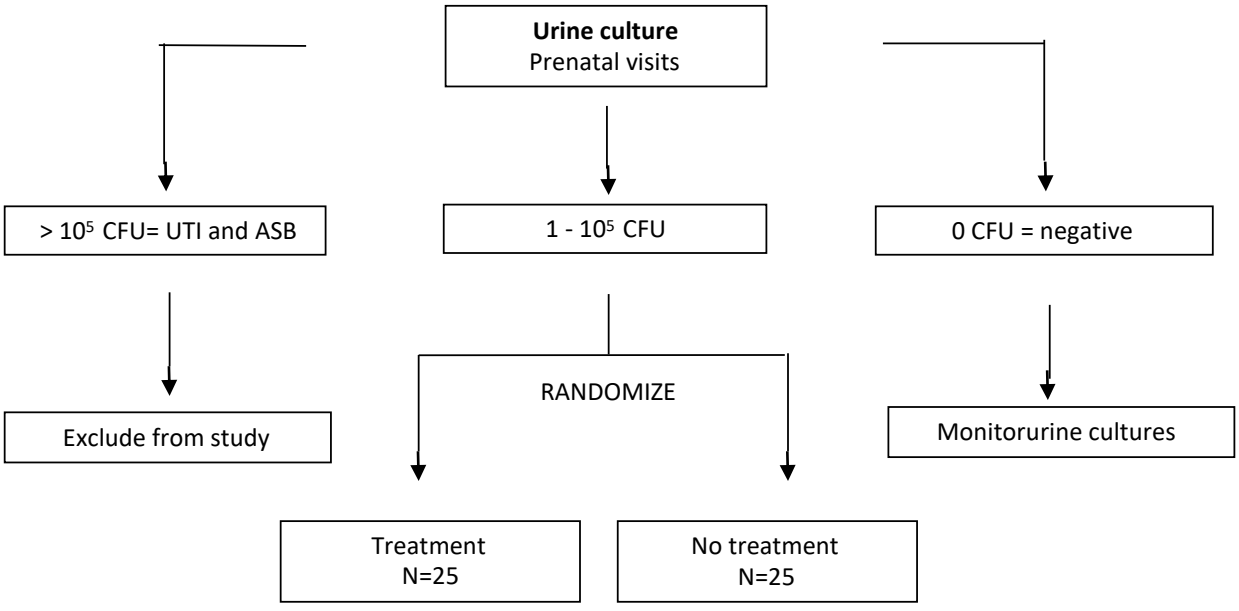

Figure 2. Flow diagram of study

Primary Outcome:
The incidence of cystitis defined as a urine culture with $>10^5$ at any point during antenatal care in this pregnancy population and the incidence of pyelonephritis.

Data Collection:
Data will be collected using standardized forms regarding maternal demographics, pregnancy characteristics, laboratory tests ordered in response to clinical signs or symptoms, medications prescribed and/or administered, and maternal/fetal adverse effects. Information for these forms will be obtained from UTPB and Bellaire clinical schedule, Care4 and AllScripts. The standardized forms that will be used during the study have been developed an approved by the Department of Obstetrics, Gynecology, and Reproductive Sciences for the purposes of uniform data collection of Internal Review Board approved studies being conducted.

Sample Size:
Because this is a feasibility trial, 50 patients will be recruited from all clinical sites. 25 patients will be randomized to prenatal care with treatment for any urine culture with growth between $1\text{-}10^5$ CFU of any organism and 25 patients will be randomized to prenatal care without treatment for any urine culture with growth between $1\text{-}10^5$ CFU of any organism. Recruitment will be stopped after recruitment of 50 randomized patients or a 10-month time period whichever is completed first.

Data Analysis
Chi-square tests will be used to compare categorical data between the two treatment groups. Student's t-test will be used to compare numerical data. The rate of progression to SCB, UTI, or pyelonephritis will be determined by clinical findings, diagnosis if admitted to the hospital and laboratory/urine culture results meeting criteria for those mentioned above.

Procedures to Maintain Confidentiality
All information and data will be kept on paper research charts that will be stored in a locked file cabinet within a locked research office of our research team/research coordinator. In addition, an electronic database of information and data will be stored on the computer of our research coordinator that is password protected, and in a locked office of the research coordinator. We will record subject information only by study code number.

Potential Benefits and Risks
There are potential risks and benefits to either treatment strategy. Since treatment or no treatment are currently both generally accepted standard of care options, providers, based on their personal preference and practice style, may choose to treat or not. Potential benefits of antibiotic treatment of those with 1- 10 5 CFU in urine culture may be decreased development of UTI, pyelonephritis, PTL, and preterm birth. Potential risks of treatment may be side effects of the medications as well as potential untoward effects of antibiotic therapy that may increase development of resistant organisms in urine and other locations (e.g. vaginal, cervix, gut) or may lead to change in flora (e.g. vaginal, cervix, gut) which may increase risk of adverse pregnancy outcomes. The benefits of no treatment may be to avoid unnecessary and unindicated antibiotic therapy. If evidence shows that treatment of this subset of

pregnant patients decreases adverse pregnancy outcome, this can leave a lasting impact on how we treat urinary tract infections in pregnancy.

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