10-6-2009

Utility of Repeat Screening for Asymptomatic Bacteriuria in Pregnancy

Sara Whetstone

Utility of Repeat Screening for Asymptomatic Bacteriuria in Pregnancy

A Thesis Submitted to the

Yale University School of Medicine

in Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

by

Sara Whetstone

2009

UTILITY OF REPEAT SCREENING FOR ASYMPTOMATIC BACTERIURIA IN PREGNANCY

Sara Whetstone, Stephen Thung, and Jessica Illuzzi. Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University, School of Medicine, New Haven, CT.

Asymptomatic bacteriuria (ASB) during pregnancy is associated with an increased risk of developing pyelonephritis. The objectives of our study were to determine the incidence of ASB throughout the first two trimesters of pregnancy and to compare the cost effectiveness of performing repeat screening with a single screening strategy for ASB to prevent pyelonephritis. In this prospective cohort study, 206 pregnant women at an urban academic obstetric clinic provided urine for culture at monthly prenatal visits, and the incidence of ASB was calculated at 4 weeks intervals in the first and second trimesters. Descriptive statistics were calculated and used as baseline estimates in the cost-effectiveness analysis. Decision and cost-effectiveness analyses were performed. In the decision analysis, three strategies were compared: (1) no screening; (2) screening for ASB once in the first trimester; and (3) screening for ASB once in the first trimester and once between 18 and 22 weeks gestational age (GA).

9.71% of women were positive on initial screening culture for ASB. Among women with an initial negative culture, the incidence rate of ASB was 0% at less than 14 weeks GA, 1.1% between 14-18 weeks GA, 4.2% between 18-22 weeks GA, and 1.8% at greater than 22 weeks GA. The proportion of women identified with ASB on initial culture did not differ statistically from the proportion identified on repeat culture (McNemar's test, p-value > 0.05). In the decision analysis, a policy of routine screening in the first and second trimester (2 urine culture strategy) was the dominant strategy compared to no screening and a single culture strategy. The model was robust in the sensitivity analysis.

ACKNOWLEDGEMENTS

I extend my deepest thanks to …

Doris Duke Charitable Foundation for their generous financial support of my time and my research

Dr. Thung for his teaching, humor, and support

Dr. Illuzzi for her continued patience, encouragement, guidance, and enthusiasm

The nurses, patient care associates, and physicians at the Women's Center for welcoming me into their space and for always supporting me

Mom, Dad, and Jonathan for providing endless kindness and love

Glenn for always being there and for being the wonderful person he is

TABLE OF CONTENTS

INTRODUCTION

Understanding Asymptomatic Bacteriuria

Asymptomatic bacteriuria (ASB) or asymptomatic urinary tract infection signifies bacteria in the urine in the absence of urinary tract specific symptoms. ASB occurs across populations, especially amongst women, diabetic patients, elderly individuals, and persons with spinal cord injury. The progression of ASB to more severe, symptomatic disease has not been validated in many groups of patients, and consequently screening for and treatment of ASB is not uniformly recommended. The physiologic changes of pregnancy, however, put pregnant women at increased risk for ascending infection. For this reason, the Infectious Disease Society of America (IDSA) formally advocates for ASB screening and treatment among two groups of patients: pregnant women and individuals undergoing urologic procedures.(1)

The microbiologic definition of ASB relies upon the urine culture, the threshold of greater than 100,000 CFU/mL, and a confirmatory repeat culture. This triad has been validated to distinguish true bacteriuria from contamination. The urine culture, despite its expense, is considered the gold standard in the detection of ASB as other urine screening tests perform poorly in comparison. Gram staining would be the most likely alternative to urine culture given its high sensitivity of 90% and specificity of 88%; however, it is a time consuming process and a relatively expensive method in an office setting.(2, 3) Urinalysis and urine dipstick, while more rapid to perform, are considered to be inadequate screening tools in pregnancy given their low sensitivities. Urinalysis

for pyuria detects only 25-67% of samples identified as bacteriuric by culture, and urine dipstick for leukocyte esterase or nitrite has a similar sensitivity in the range of 50-73%.(2-6) Thus, the urine culture remains the test of choice as no other currently available test has sufficiently high sensitivity and negative predictive value for ASB.

Prior to the 1950s there was no specific threshold in terms of bacterial number to differentiate contamination from true bacteriuria. Kass determined that a bacterial count of at least 100,000 CFU/mL in a voided specimen was confirmed in greater than 95% of subjects by a catherized specimen.(7, 8) Lower colony counts often were not confirmed by catherization and represented contamination of the urine specimen by vaginal and external flora during sample collection. In fact, if a sample had fewer than 100,000 CFU/mL, the probability was approximately 4% that the subsequent specimen from the same patient would culture more than 100,000 CFU/mL.(7, 9) Interestingly in practice today, many clinicians cite colony counts well below 100,000 CFU/mL as justification for the use of antibiotics in pregnancy given the risks of untreated ASB. (see Section “Asymptomatic Bacteriuria in Pregnancy”).

The definition of true ASB as defined by IDSA requires at least two consecutive voided urine specimens with greater than 100,000 CFU/mL of the same bacterial strain.(1) Kass demonstrated that bacteriuria was confirmed in only 80% of women if only one voided urine culture was used to diagnose ASB but was confirmed in greater than 95% of women if two previous specimens showed bacteriuria.(8, 10) In practice today, a single-voided midstream urine with greater than 100,000 CFU/mL is accepted as an

adequate alternative definition of ASB.(11) We suspect that practitioners find obtaining repeat specimens from their patients impractical as prenatal visits occur only once a month in early pregnancy.

Based upon the aforementioned definition of ASB, its prevalence amongst pregnant women has been reported to range from two to ten percent.(12, 13) Similar prevalence rates are reported in non-pregnant women, and accordingly pregnancy is not believed to be a risk factor for its development.(12) The microbiology of ASB in pregnancy reflects the organisms isolated from non-pregnant bacteriuric women. *Escherichia coli* is the most common pathogen with an estimated prevalence of 65 to 80%, followed by other gram-negative organisms such as *Proteus mirabilis*, *Klebsiella pneumoniae* and *Enterobacter.(11, 14)* Gram-positive bacteria like *Enterococcus, Streptococcus agalactiae*, and *Staphylococcus saprophyticus* have been identified as causing bacteriuria, particularly in the last trimester, and there is increasing recognition of fastidious organisms, such as *Ureaplasma urealyticum,* as urinary pathogens.(15-17)

Increased prevalence of ASB is associated with multiparity, multiple sexual partners, increasing age, and low socio-economic status.(18) Women with diabetes mellitus and sickle cell disease or trait have also been identified as individuals who have higher rates of bacteriuria due to alterations in genitourinary tract function. Individuals with chronic diseases that impair voiding or that involve long-term indwelling catheters have even higher rates of ASB.

Asymptomatic Bacteriuria in Pregnancy

Women are anatomically predisposed to bacterial colonization of the bladder– the external third of the urethra is colonized by vaginal flora and sexual intercourse increases the risk of urinary infection. Changes in the genitourinary tract during pregnancy predispose women to pyelonephritis; over 80% of pyelonephritis cases occur in the second and third trimesters, a period of time when physiologic adaptations of pregnancy promote greater urinary stasis and bacterial proliferation.(19) The most notable of these changes is the dilatation of the collecting system. Progesterone induces smooth muscle relaxation, leading to decreased ureteral peristalsis and tone.(20) Additionally, the enlarging uterus extends beyond the pelvis in mid-pregnancy to compress the ureters at the pelvic brim; interestingly, the right ureter, the side where pyelonephritis more frequently develops, experiences greater dilation due to dextrorotation of the uterus, while the left ureter is cushioned by the sigmoid colon.(21) The hypertrophy of Waldeyer's sheath, the longitudinal muscle at the lower ureter, may contribute to further dilatation proximally by functionally compressing the lower ureter.(20) As a result of anatomic, physiologic, and hormonal changes, the upper collecting system can accommodate 200 to 300 mL of urine and becomes a potential reservoir for infection.(20)

Other changes may also increase pregnant women's susceptibility to urinary tract infections. Like the ureters, the bladder experiences a progesterone-induced decrease in tone and subsequent increase in capacity; the expanding uterus, however, simultaneously displaces the bladder superiorly and anteriorly, causing it to flatten out

and decrease its capacity. Despite conflicting results about the bladder's capacity in pregnancy, some authors speculate an anatomic change occurs that renders the bladder more susceptible to infection; its flaccidity may also contribute to vesicoureteral reflux and increase the likelihood of ascending infection.(22, 23)

Hormonal factors of pregnancy may additionally alter susceptibility to infection. In experimental settings, rats who received diethylstilbestrol were more likely to experience renal parenchymal infection with *E coli,* and urine from women who used oral contraception had an increased rate of in vitro bacterial growth.(24, 25) In addition, the glucosuria and aminoaciduria of pregnancy, resulting from decreased fractional absorption in the kidney, facilitate bacterial proliferation in urine, an already excellent growth medium. The net effect of these changes is to increase the likelihood of a symptomatic urinary tract infection to develop during pregnancy.

Bacteriuria has been shown to be the most significant factor associated with development of acute pyelonephritis in pregnancy.(9, 10) The risk of pyelonephritis ranges from 20-40% among pregnant women with untreated ASB.(10) (12) Therefore, women with ASB detected in pregnancy have a 20-30-fold risk of developing acute pyelonephritis in comparison to pregnant women without bacteriuria.(14, 26, 27) The relationship between bacteriuria and acute pyelonephritis is substantiated by the fact that the bacterial species cultured from women with acute pyelonephritis mirror those cultured from women with bacteriuria. *E coli* is the most common pathogen amongst women with acute pyelonephritis, accounting for greater than 70% of cases.(11, 19)

Today, in the era of screening and treatment of ASB, the overall incidence of pyelonephritis in pregnancy is relatively low, at one to two percent.(21) Nonetheless, pyelonephritis continues to be the most common serious medical complication of pregnancy and genitourinary complications account for approximately 10% of antenatal admissions to the hospital.(28) Acute pyelonephritis in pregnancy also results in significant maternal and fetal morbidity. At the time of diagnosis, approximately 20% of women have concurrent bacteremia, and a similar percentage of women experience multi-organ system dysfunction.(19, 29, 30) It is believed that endothelial activation and subsequent capillary fluid extravasation lead to alterations in blood pressure, renal function, and gas exchange.(21) These vascular changes cause intravascular depletion, and hypotension is fairly common(21) Diminished renal function, albeit often transient, occurs in 5% of women, although in the past, 10-20% of women were reported to experience kidney injury.(19, 30) Twenty percent of pregnant women with pyelonephritis develop anemia during their infection, attributed to endotoxin-stimulated hemolysis.(31) Those women who unfortunately develop severe sepsis are at risk for activation of coagulation pathways. The most concerning complication is the development of acute pulmonary injury from suspected endotoxin-mediated damage to alveolar capillary membranes. The resultant respiratory insufficiency, seen in 2-8% of women, ranges in severity from an increased oxygen requirement to severe acute respiratory distress syndrome requiring intubation and mechanical ventilation.(32, 33) Urosepsis, or proliferation of the uropathogen within the bloodstream, is the leading

cause of septic shock during pregnancy, and one study reported that nearly 10% of women with pyelonephritis required admission to the obstetric intensive care unit.(19)

Prior to the 1940's and before the use of antibiotics, acute pyelonephritis was clearly associated with a 20-50% incidence of preterm birth. (27, 34, 35) The mechanisms for preterm labor resulting from pyelonephritis have not been completely elucidated but are presumed to be related to endotoxin-stimulated uterine activity or bacterial production of phospholipase A_2. A recent large cohort study (2005) found that preterm birth occurred in only 5% of women with acute pyelonephritis who received antibiotic therapy, a rate comparable to that of the general obstetric population today.(19) The association between bacteriuria and preterm birth is more controversial. Kass initially reported an increased risk of preterm birth in women with persistent bacteriuria, a risk that could be modified by the use of antibiotics throughout gestation.(9, 10) Subsequent studies of various designs showed conflicting results, with most failing to demonstrate a relationship between preterm birth and ASB. Those studies that revealed an excess rate of preterm delivery with bacteriuria were often statistically underpowered or did not show that treatment altered the rate of prematurity.(12) A meta-analysis of 17 cohort studies found a strong association between ASB and low birth weight/preterm delivery and additionally demonstrated that antibiotic treatment reduced the rate of low birth weight.(36) Critiques of the meta-analysis cite poor methodological quality of the studies included in the analysis, inability to define a mechanism in which bacteriuria causes preterm labor, and failure to control for

infections outside the urinary tract, particularly those in the cervix and vagina, that may respond to antibiotics and that have been linked to prematurity.(12, 35) If bacteriuria does contribute to preterm delivery, as Whalley stated, it accounts for a very small proportion and ASB treatment will minimally affect the rate of preterm birth.(12)

Screening and Treatment of Asymptomatic Bacteriuria in Pregnancy

There is convincing evidence that antibiotic treatment of ASB is effective in preventing the well-established adverse maternal outcomes, such as pyelonephritis, sepsis, and ARDS. A systematic review of 14 studies comparing antibiotic treatment with no treatment or placebo found that antibiotic treatment was effective in clearing ASB (OR 0.07, 95% CI 0.05-0.10) and was associated with a reduced incidence of pyelonephritis (OR 0.24, 95% CI 0.19-0.32).(35) In the literature, there is no single antibiotic that is optimal in the treatment of ASB, and no study has had the power to determine the optimal duration of therapy; therefore, current recommendations encourage empiric treatment of ASB. Even with antibiotic treatment, it should be noted that the recurrence rate of ASB is reported to be 20-30%.(12)

Based on the evidence, screening for ASB in pregnancy has been incorporated into prenatal care in most developed countries for decades. Trials have repeatedly shown that screening and treatment of ASB has substantially decreased the incidence of pyelonephritis in pregnancy.(35) Implementation of such programs in Spain resulted in a decrease in incidence of pyelonephritis from 1.8% to 0.6% and in Turkey from 2.1% to 0.5%.(37, 38) In the United States, the incidence of pyelonephritis has declined from 3-

4% in the 1970s to 1-2% with universal screening.(39, 40) When compared with a policy of no screening, screening for and treatment of ASB in pregnancy is regarded to be cost-beneficial.(41) Another study showed a single screening culture in first trimester to be cost-effective if the prevalence of bacteriuria is greater than 2% and the risk of pyelonephritis in bacteriuric women is greater than 13%.(42)

Accordingly, the United States Preventive Services Task Force (USPSTF), American College of Obstetricians and Gynecologists (ACOG), American Academy of Pediatrics (AAP), American Academy of Family Physicians (AAFP), and IDSA recommend screening for ASB in early pregnancy.(43, 44) Some of these national organizations even explicitly state that screening should occur at 12 to 16 weeks gestational age (GA) or at the first prenatal visit if after that time. The timing of screening is based on reports that the majority of bacteriuria was present by the second month of gestation.(10) Moreover, initial published studies reported that pyelonephritis occurred only amongst women identified with ASB at the initial visit and thus it followed that women should be screened when they first presented for prenatal care.(8, 10) Later studies contradicted these earlier reports and showed that approximately one to two percent of pregnant women with negative initial cultures develop pyelonephritis.(1, 14, 26, 27) This latter figure has two interesting implications, the first being that it is likely that a proportion of women develop bacteriuria later over the course of pregnancy despite an initial negative culture. This bacteriuria is most likely unrecognized and untreated leading in some cases to pyelonephritis. The second is that the absolute number of women who

initially test negative but go on to develop pyelonephritis (1-2%) is what would be expected if 2-10% subsequently developed ASB and were not treated (20-40% of 2-10% or 0.4-4%). This should raise concern that the rate of ASB may be similar in first trimester and second trimesters. An example will help to illustrate this second point (see Table 1). In a cohort of 1000 pregnant women with a 6% rate of ASB at initial culture (60 women), twelve women will develop pyelonephritis if untreated, assuming a 20% risk of pyelonephritis. Of the 940 women with initial negative cultures, approximately fourteen women will develop pyelonephritis, given a 1.5% incidence rate of pyelonephritis over the course of pregnancy. Accordingly, current screening procedures have been cited to only detect 40-70% of women who develop pyelonephritis.(45-47)

Table 1. Percentage of women predicted to develop pyelonephritis identified by current screening methods using published estimate ranges in a cohort of 1000 (12, 41, 44)

	Low Estimate	Middle Estimate	High Estimate
Prevalence of ASB at initial culture	2%	6%	10%
Risk of pyelonephritis	20%	20%	20%
Incidence of pyelonephritis among initial culture negative women	1%	1.50%	2%
Number of women with positive initial culture who develop pyelonephritis (assuming no treatment)[A]	4	12	20
Number of women with negative initial culture who develop pyelonephritis[B]	9.8	14.1	18
Percentage of women who develop pyelonephritis who are detected by screening at initial visit[C]	**29.0%**	**46.0 %**	**52.6%**

[A]Number of women with positive initial culture who develop pyelonephritis (assuming no treatment) = population of women (N) x rate of ASB x risk of pyelonephritis if no treatment

[B]Number of women with negative initial culture who develop pyelonephritis = (N - number of women with ASB at first culture) x 1%

[C]Percentage of women who develop pyelonephritis who are detected by screening at initial visit = Number of women with positive initial culture who develop pyelonephritis (assuming no treatment)/Total number of women who develop pyelonephritis

Although screening programs have been commended for their successes, there are gaps in the published literature which limit current recommendations. The IDSA and USPSTF, among others, have reported that no study has fully addressed the optimal timing for the initial urine culture.(35, 44, 48) A Swedish study reported that screening at 16 weeks would be the optimal time to maximize detection of ASB as well as the number of bacteriuria-free weeks in pregnancy.(49) In the United States, there has been no systematic effort to study the ideal time for initial ASB testing despite the fact that nearly 30 to 60% of women who develop symptomatic urinary tract infection in pregnancy are not identified by initial screening measures. The benefit from additional screening in pregnancy is unknown. In fact, Nicolle et al. write, "It has not been evaluated whether a second screening culture obtained in later pregnancy would further reduce the risk of pyelonephritis and its complications, and remain cost-effective."(44)

STATEMENT OF PURPOSE

Given the remaining questions about ASB screening, the aims of the study are to calculate the incidence rate of ASB at various times in pregnancy using a prospective cohort of women and to evaluate the cost-effectiveness of performing repeat cultures for ASB in pregnancy. The ultimate goal of the research is to inform cost-effective evidence-based guidelines for the timing of asymptomatic bacteriuria screening in order to optimally reduce the incidence of pyelonephritis and its associated maternal morbidity. It is our hypothesis that a greater proportion of women will develop ASB after an initial negative culture than previously reported in the literature, and thus repeat screening will be cost-effective given the high costs of managing acute pyelonephritis in pregnancy.

METHODS

Overview

The study design consisted of two components to determine the cost-effectiveness of repeat screening for ASB in pregnancy. As the literature lacked detailed data on the incidence of ASB throughout pregnancy, the first component involved longitudinal ASB screening of a cohort of low risk pregnant women in order to calculate the incidence rate of ASB at various gestational ages. The second component, a cost-effectiveness analysis, used the incidence rates generated as probability estimates and evaluated the strategy of repeat screening for ASB in pregnancy. In both components, the urine culture was used as the screening tool of choice for ASB.

Screening

Beginning September 2007, women with a documented pregnancy who presented for prenatal care at the Women's Center at Yale-New Haven Hospital were invited to participate in the study. The Women's Center serves as a site of care for low risk obstetric patients; women with significant co-morbidites are referred to another facility for care by maternal-fetal medicine specialists. The study protocol was approved by the Human Investigation Committee at Yale University, and informed written consent was obtained for all subject participants. Exclusion criteria were gestational age beyond 28 weeks, insulin-requiring diabetes mellitus, sickle cell disease, chronic kidney disease,

and an inability to undergo the informed consent process in either English or Spanish. Women who were unable to provide at least two urine cultures, i.e. those who presented late in the second trimester, were also excluded from the study. Study enrollment ended in April 2008, and ASB screening finished in August 2008.

As per ACOG guidelines, an initial screening urine culture was obtained at the first prenatal visit. All women were instructed how to perform a midstream clean catch. At subsequent monthly prenatal visits, study participants were asked to provide clean catch urine for culture. Screening continued until 28 weeks gestational age or until women developed true ASB, symptomatic urinary tract infection (UTI), or acute pyelonephritis; these scenarios all result in antibiotic treatment and have the potential to confound further screening cultures. It was decided not to screen in the late third trimester as the most likely time for a second screening culture would be in the second or early third trimester as the vast majority of cases of pyelonephritis develop in these trimesters. Gestational age was calculated using a woman's last menstrual period (LMP) and verified by first or second trimester dating ultrasound; if there was inaccuracy in dating by LMP, dating was changed to reflect that estimated by ultrasound.

All urine cultures were sent to the Yale-New Haven Hospital microbiology laboratory for processing and analysis. Cultures obtained for the study were handled identically as those urine cultures collected for routine patient care; results were reported to clinicians in the usual fashion. Outcome measures included the incidence of ASB in four week intervals as well as the incidence of pyelonephritis. The incidence of ASB was

calculated based on the result of one urine culture with greater than 100,000 CFU/mL of at least one identified bacterial specimen, excluding lactobacillus. The broad inclusion of many bacterial species was based on the description of microbiology of ASB by the IDSA; accordingly, bacterial species included within our definition were *Escherichia coli*, *Klebsiella pneumonia, Proteus mirabilis,* other Enterobacteriaceae, coagulative-negative staphylococci, *Enterococcus,* group B streptococci, *Staphylococcus aureus, Streptococcus viridians,* and *Garnerella vaginalis*.(1) The incidence of pyelonephritis was calculated by the number of women diagnosed with acute pyelonephritis in pregnancy amongst our study population. It should be noted that the diagnosis of pyelonephritis was determined by the participant's clinical care providers and validated based on documentation of two or more clinical findings (fever, flank pain, and costovertebral angle tenderness) in the medical record. Secondary outcome measures were the rate of pre-term birth (less than 37 weeks GA) and low birth weight (less than 2,500 grams).

Given the clear evidence that treatment for asymptomatic bacteriuria reduces the risk of pyelonephritis, all women found to have ASB were offered antibiotics and requested to provide a urine specimen for test of cure. Decisions regarding the need for repeat urine cultures, further screening for bacteriuria, and need for antibiotic suppression were delegated to the participants' clinicians. Treatment of positive urine cultures that did not meet the criteria for ASB were deemed the responsibility of the patients' clinicians; however, prior to the study's commencement, all clinicians were provided with education about evidence-based criteria for ASB and encouraged to seek repeat

cultures for women with positive cultures that did not meet the 100,000 CFU/mL threshold. Women who received antimicrobial agents during the study period were encouraged to provide urine for test of cure but they did not continue on the monthly screening regimen as antibiotics most likely altered the flora of their genitourinary tract. It should also be noted that the management of symptomatic UTI was determined by the participant's primary provider. A symptomatic UTI was defined as greater than >100,000 CFU on urine culture in the presence of common symptoms (i.e. dysuria, frequency, urgency, lower abdominal cramping). Subjects with this diagnosis were not counted as cases of ASB.

Patient characteristics such as gravidity, parity, age, history of diabetes mellitus, sickle cell trait, and history of previous urinary tract infections -- all factors known to influence the prevalence of ASB -- were extracted from medical records.

Descriptive statistics, incidence rates, and confidence intervals were calculated using SAS 9.1 and EXCEL. Likewise, women with and without ASB were compared.

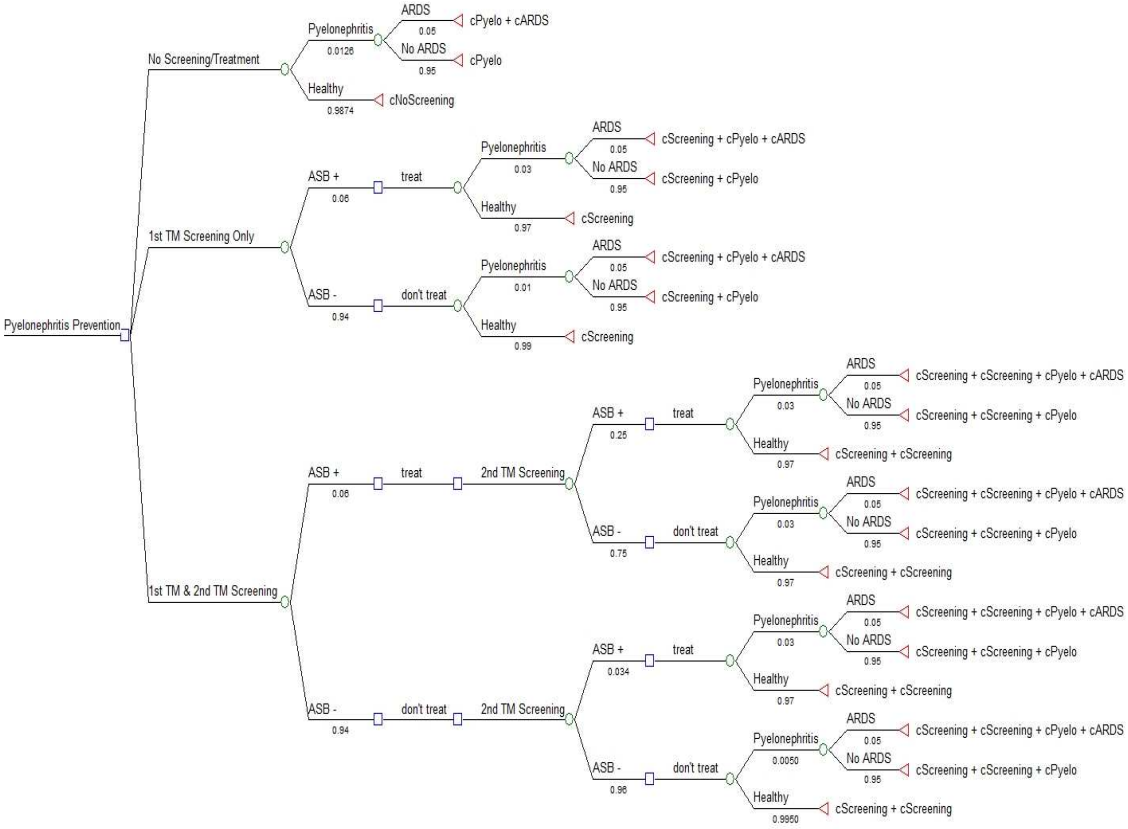
Decision Analysis

Using a decision tree model, three strategies were compared to evaluate the cost-effectiveness of ASB screening in the prevention of pyelonephritis. These strategies included (1) a policy of no screening, (2) a policy of screening for ASB once in the first trimester, and (3) a policy of screening for ASB once in the first trimester and once

between 18 and 22 weeks gestational age. In the first strategy, no routine urine cultures were performed and women who had asymptomatic bacteriuria were left untreated. For the sake of the model, there were two opportunities for ASB, once in the first trimester and once in the second trimester. Given that unscreened women were asymptomatic, we assumed they were untreated and at high risk for pyelonephritis and ARDS. In the second strategy, the current standard of care, women who entered prenatal care in the first trimester received one routine urine culture. Similar to the first strategy, there were two opportunities for ASB and progression to pyelonephritis. Asymptomatic bacteriuria in the first trimester was treated with antibiotics and a test of cure was performed. The risk of pyelonephritis due to first trimester ASB was significantly reduced by identification and treatment. A repeat screening urine culture was not performed in the 2nd trimester leaving an elevated risk of pyelonephritis similar to the first strategy. The third strategy, our test strategy, allowed for routine urine cultures in the first and second trimester. If ASB was identified in either case, it was treated and the risk of progressing to pyelonephritis was low. In all cases, women with pyelonephritis were at risk of progressing to ARDS. Furthermore, all women diagnosed with pyelonephritis received antibiotic treatment and chronic antibiotic suppression therapy for the remainder of the pregnancy.

Figure 1 displays the schematic decision tree used in this analysis. (For actual decision trees, see Appendix A-C.)

Figure 1. Schematic decision tree model comparing no screening, screening in the first trimester, and screening in the first and second trimester for asymptomatic bacteriuria in pregnancy.



Probability estimates

The baseline probabilities were obtained after a thorough review of English medical literature and are summarized in Table 2. We estimated the average prevalence of ASB among pregnant women in the first trimester to be 6%, a figure that represents the median value of previous prevalence estimates reported between 2-10%.(12, 41, 42) The risk of pyelonephritis among untreated bacteriuric women was estimated at 21%;

this risk was derived from a meta-analysis of 14 studies that involved 2302 women and reported the rate of progression from untreated ASB to pyelonephritis. The range of estimates for progression to pyelonephritis in this study was broad, from 2.5% to 36%.(35) The risk of pyelonephritis among women who were initially ASB-negative has been quoted in the literature to be 1-2%, and in the decision analysis we estimated the risk of progression to pyelonephritis among initially culture-negative women to be 1%.(12, 13)

For the purposes of this analysis, we assumed women enter prenatal care in the first trimester and that women identified with ASB are treated. Antibiotic efficacy is reported to be 80-90% in clearing bacteriuria; thus, we made an assumption that 20% of women will have a positive follow-up urine culture and require suppressive therapy.(11, 50) Women with treated ASB have been reported to have an increased risk of pyelonephritis (0-17%), and thus like Rouse et al, we estimated their risk of progression to pyelonephritis to be 3% for both women requiring and not requiring antibiotic suppression.(35, 41)

We deemed the inclusion of ARDS important as its risk of development provides, in part, the rationale for inpatient management of pregnant women with acute pyelonephritis. Approximately 2-8% of cases of acute pyelonephritis in pregnancy are complicated by respiratory insufficiency, and a recent prospective longitudinal study of women hospitalized for pyelonephritis in pregnancy reported that 7% (95% CI 5-10%) of women developed respiratory insufficiency.(19, 32, 33) We used the estimate of 5% of women

with acute antenatal pyelonephritis develop ARDS in pregnancy and require admission to ICU.(19)

For the policy of screening twice for ASB, we utilized data from our prospective cohort and estimated the prevalence of ASB at 18-22 weeks GA to be 3.4%. The calculated incidence rate of ASB at 18-22 weeks was 4.21% (see Results section); however, we assumed that 80% of our incidence rate represented true bacteriuria as only one voided urine culture was used to define ASB. Additionally, we estimated that the rate of ASB positivity on second trimester screen amongst women found to have ASB on the first trimester screen to be 25%. The recurrence rate of bacteriuria in pregnancy is reported to be between 20 and 30%, and we used the median value for our baseline estimate.(14, 46, 50) Our prospective cohort study was not powered to detect the incidence rate of pyelonephritis among women with two negative cultures. However, 3.0% of our study population developed ASB after two negative cultures, corresponding to a rate of 2.4% given the 80% probability of true bacteriuria with the use of a single culture. From this statistic, we calculated a risk of pyelonephritis among women with negative first and second trimester ASB screening. We predicted that women with two negative cultures who subsequently developed ASB would not be detected by the first and second trimester screening and thus would have a 21% risk of pyelonephritis. Therefore, we estimated that women with a negative first and second trimester screen had a 0.50% risk of progression to acute pyelonephritis.

Table 2. Baseline Estimates for Cost-Effectiveness Analysis

Variable	Baseline Estimate	Range	Reference
ASB Prevalence			
Prevalence of ASB at 1st TM (%)	6	2.0 - 10.0	12, 41, 42
Prevalence of ASB at 2nd TM (%)	3.4	0.9 – 8.6	n/a
ASB progression to pyelonephritis			
Untreated ASB (%)	21	2.5 - 36	35
Treated ASB (%)	3	0 - 17	35, 41
After one negative culture (%)	1	1.0 - 2.0	1, 12, 13, 41
After two negative cultures (%)	0.50	0 - 2	n/a
Risk of recurrence			
ASB in 2nd TM after ASB in 1st TM (%)	25	20 - 30	14, 46, 50
Risk of ASB after treatment in 1st TM			
ASB in 2nd TM after treatment (%)	20	10 - 20	11, 50
Risk of ARDS			
ARDS with acute pyelonephritis (%)	5	2 - 8	19, 32, 33

Cost Estimates

All costs are presented in 2008 US dollars. For the analysis, published non-wholesale prices from www.drugstore.com were utilized for all medication costs, and other costs were drawn from the published literature (Table 3). The cost of a 7-day course of antibiotics was derived from averaging the price of 3 different generic medication regimens (cephalexin, nitrofurantoin, and sulfamethoxazole-trimethoprim), as there is no single optimal antibiotic regimen for the treatment of ASB. The cost of an antibiotic regimen was estimated to be $9.30.(51) Approximately 10% of women treated for ASB are reported to develop vaginal candidiasis; the cost of a generic antifungal medication

for 1 week was $12.(51, 52) Thus, the cost of antibiotic treatment for ASB was estimated to be $10.50 [$9.30 + (10% x $12)]. Those women with pyelonephritis as well as women with repeatedly positive cultures were assumed to require antibiotic suppression therapy for the duration of the pregnancy. A common antibiotic regimen for suppression, 100 mg nitrofurantoin each night, was found to have a cost of $160 for a 20 week course or $8 per week.(51)

Given that the treatment for ASB is empiric, only the cost of a urine culture without antibiotic sensitivities was needed; however, with increasing antibiotic resistance, many clinicians obtain antibiotic sensitivity at time of initial culture. Urine culture cost was determined from 2008 Medicare data and encompassed the cost of urine culture, colony count, and antibiotic sensitivity.(53) As mentioned earlier, pyelonephritis in pregnancy is often treated on an inpatient basis. The costs to the patient and her family extend beyond the charges for hospitalization and treatment and include lost income and childcare; however, this analysis utilized only direct hospital costs. In analysis of costs associated with acute pyelonephritis, Brown et al used an estimate of $6580 and $4312 for the direct costs associated with inpatient treatment of pyelonephritis with and without bacteremia, respectively.(54) Taking into consideration that 20% of pregnant women with acute pyelonephritis are bacteremic at time of presentation, the cost estimate was $4698 [80% x $4312 + 20% x $6580] and was adjusted using the medical care component of the Consumer Price Index to reflect 2008 US dollars.(19, 41) Health care costs for ARDS are considerable because patients are almost exclusively

managed in an expensive ICU setting, with mean costs ranging from $48,000 to $73,000; we used the conservative estimate of $48,000 for our analysis.(55-57) We chose the lower estimate for our model as we assumed that most pregnant women are younger and healthier than many other patients admitted to the ICU with ARDS, thus most likely will require less care in comparison.

Table 3. Cost Estimates for Decision Tree Model

Variable	Baseline Estimate ($)	Range ($)	Reference
Screening			
Urine culture	11.79	10 - 55	53
Antibiotic Therapy			
7-day course	10.50	7.80 – 57.60	51
Suppression therapy	160	120-336	51
Treatment of Acute Pyelonephritis			
Inpatient hospital costs	5795	3562-8117	19, 41
Management of ARDS			
Intensive care unit costs	48,000	48,000 – 73,000	55 - 57

Analysis

A baseline decision and cost analysis was performed using TreeAge Pro 2008 (TreeAge Software, Williamstown, MA). Sensitivity analyses were subsequently done in recognition that our baseline estimates may not be applicable to all populations. The decision analysis model was used to estimate the number of cases of pyelonephritis and

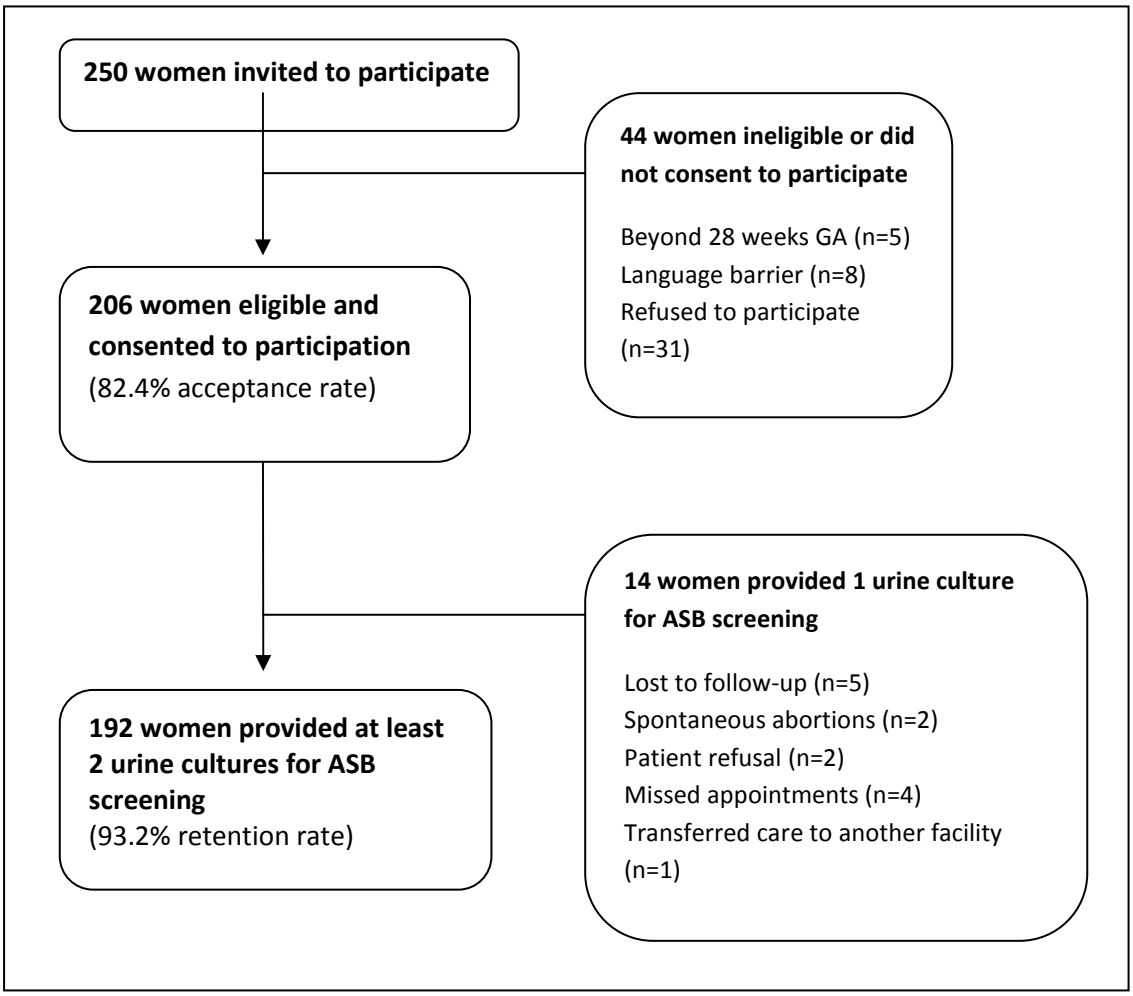
ARDS that would occur with no screening, a first trimester screening culture only, and both a first and second trimester screening. Calculated costs of each strategy encompassed ASB screening and treatment costs as well as costs of inpatient treatment of acute pyelonephritis and ARDS. Costs of the one culture strategy and two culture strategy were compared to that of the no screening strategy. Incremental savings of $1^{st}/2^{nd}$ trimester urine cultures were calculated by subtracting expected costs of the repeat culture strategy from those of the single culture strategy.

RESULTS

Prospective Cohort Study

Of the 250 women invited to participate in the study, 206 women comprised the study population, representing an acceptance rate of 82.4%. Of those, over 90% provided at least two urine cultures during the screening period, and over 70% provided at least three ASB screening cultures. Figure 2 shows detailed information on enrollment and retention.

Figure 2. Overview of Patient Enrollment and Retention



The mean age of participants was 24.3 years (SD 5.3). Forty-two percent were African-American, and 48.5 percent were Hispanic. Most women were multiparous (median gravidity and parity of 2 and 1, respectively). Only 7.8% of the study cohort possessed one or more known risk factors for ASB. (i.e. diabetes mellitus, sickle cell trait, history of pyelonephritis). The vast majority of subjects carried singleton gestations; there was one twin gestation. During the study period, there were a total of 27 cases of ASB. There were no significant differences in demographic and clinical characteristics between women with and without ASB, with the exception that women with ASB were more likely to have a documented history of urinary tract infection (Table 4).

Table 4. Selected demographic and clinical characteristics of women with ASB compared with women without ASB[D]

	Women positive for ASB (N=27)	**Women negative for ASB** (N=179)	p-value
Mean Age	22.6(5.4)	23.4(5.2)	0.587
Median Gravidity	3 (2-4)	2 (2-3)	0.205
Median Parity	1 (0-2)	1 (0-2)	0.772
Race/Ethnicity			0.596
African-American	10 (37.0)	74 (42.8)	
Caucasian	14 (51.9)	84 (48.6)	
Hispanic	2 (7.4)	13 (7.5)	
Other	1 (3.7)	2 (1.2)	
Patients with presence of at least one known risk factor of ASB	5 (18.5)	12 (6.7)	0.053
Diabetes mellitus	1 (3.7)	0 (0)	0.52
History of Pyelonephritis	1 (3.7)	5 (2.8)	0.136
Immunosuppression	1 (3.7)	0 (0)	0.52
Sickle cell trait	2 (7.4)	3 (1.7)	0.523
Documented history of UTI	7 (25.9)	17 (9.8)	0.026
Current Smoking	5 (18.5)	18 (10.4)	0.208

[D]Continuous variables expressed as mean $\pm$ SD. Comparisons made using Student t test.
Categorical variables expressed as number of patients(%). Comparisons made using Fisher's exact test.
Ordinal variables expressed as median (interquartile range). Comparisons made using Wilcoxon test.

The mean gestational age at ASB detection was 15.0 (SD 5.5) weeks. The prevalence rate of ASB was 8.93% at less than 10 weeks GA, 5.6% between 10-14 weeks GA, 4.1% between 14-18 weeks GA, 6.60% between 18-22 weeks GA, and 2.61% at greater than 21 weeks GA. Among women who developed ASB, 18.5% had one known risk factor compared to 6.7% of women who did not develop ASB during the study period, a difference that was not statistically significant (See Table 4). Moreover, women with known risk factors for ASB were not more likely to develop ASB throughout gestation in comparison to women without such risk factors (see Table 5).

Table 5. Number of women with and without known risk factors who developed ASB by gestational age[E]

Gestational age window	**Women with risk factors** (N=16)	**Women without risk factors** (N=190)	p-value
<10 wks	1	5	0.918
10-14 wks	1	5	
14-18 wks	0	5	
18-22 wks	2	6	
>22 wks	0	2	

[E]Risk factors include sickle cell trait, non-insulin requiring diabetes mellitus, immunosuppression, and history of pyelonephritis

As shown in Table 6, the predominant organism was *Escherichia coli*, accounting for 41% of all cases of ASB. The next most common uropathogen was group B *Streptococcus* and other gram positive organisms. Notably amongst all ASB bacterial isolates with documented sensitivities, 66.7% were resistant to at least one antibiotic agent, and ampicillin resistance in E coli was found to be 36.4%.

Table 6. Frequency of uropathogens in ASB-documented urine cultures[F]

Urine Culture Results	
Escherichia coli	11 (41)
Klebsiella-Enterobacter group	4 (15)
Proteus species	2 (7)
Enterococcus species	3 (11)
Group B streptococcus and other gram positive organisms	7 (26)
Total	**27 (100)**

[F]Data reported as number of patients(%).

Of note, there were additional positive cultures with colony counts below 100,000 that did not meet the study's definition of ASB. The prevalence rates of any positive urine culture are reported in Table 7; like the trend seen amongst all cases of ASB, the observed prevalence rates peak in the gestational age windows of 10-14 weeks and 18-22 weeks.

Table 7. Prevalence of ASB by gestational age for all cases of ASB and among women who were initial culture-negative and prevalence of any positive urine culture by gestational age.[G]

Gestational age window	All cases of true ASB	Any positive urine culture	True ASB among initial culture-negative women
> 10 to 14 weeks GA	5.6% (2.3- 11.5%)	10.4% (5.5- 17.8%)	0% (0 – 16.8%)
>14 weeks to 18 weeks GA	4.1% (1.3 – 9.6%)	6.6% (2.8 – 12.9%)	1.1% (0 - 6.3%)
>18 weeks to 22 weeks GA	6.6% (2.7 - 13.6%)	11.3% (5.8 - 19.8%)	4.2% (1.1 – 10.8%)
> 22 weeks GA	2.6% (0.5 - 7.6%)	2.6% (0.5 – 7.6%)	1.8% (0.2 – 6.4%)

[G]Data shown as estimates (95% Confidence Interval)

The prevalence of ASB at initial culture was 9.71%, and the mean gestational age at the time of this culture was 12 weeks (SD 3.5). Given the use of one culture to define ASB,

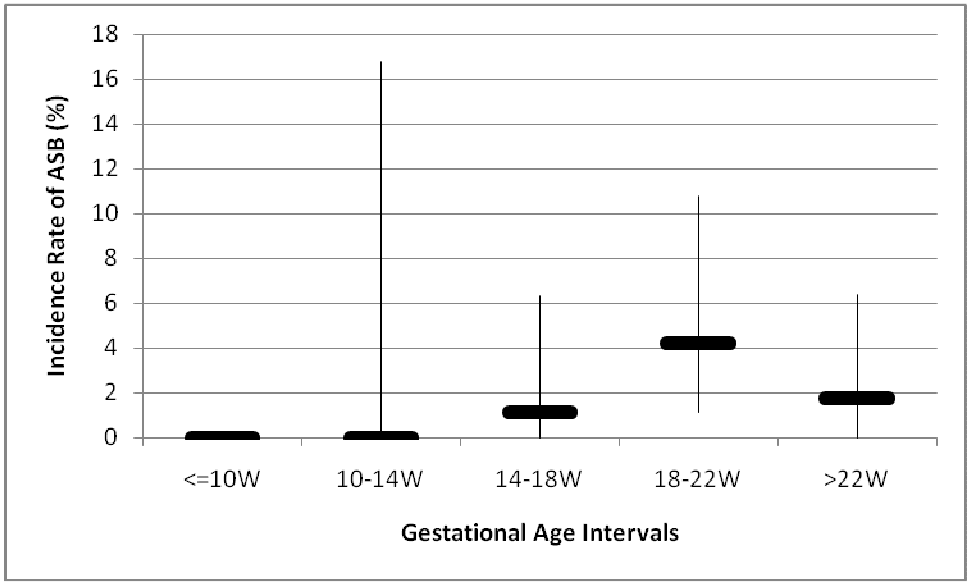
and the results of Kass et al. suggesting that 80% of cultures growing 100,000 colonies are confirmed positive upon repeat culture, we calculated an adjusted prevalence rate to be 7.77%.(8, 10)

On Initial Culture	On Repeat Culture		
	ASB -	ASB +	
ASB -	165	8	173
ASB +	15	4	19
	180	12	

Figure 3. Analysis using McNemar statistic for the number of women identified with ASB on initial culture and on subsequent culture

The proportion of women identified with ASB on initial culture did not differ statistically from the proportion identified by later cultures during gestation (McNemar's test, p-value > 0.05; Figure 3). For those women who did not have bacteriuria on initial culture, the incidence rate of ASB in the remainder of the study was 4.34% (95% CI 1.75 – 8.96%). Among women with an initial negative urine culture, the incidence rate of ASB was 0% up to 14 weeks GA (95% CI 0.0– 16.8%), 1.1% between 14 and 18 weeks GA (95% CI 0.0 – 6.3%), 4.2% between 18 and 22 weeks GA (95% CI 1.1– 10.8%), and 1.8% beyond 22 weeks GA (95% CI 0.2 – 6.4%)(Figure 4). The mean gestational age of ASB detection was 20.5 (SD 2.9) weeks for initially culture-negative women. Interestingly, among all women who had at least 2 documented negative urine cultures (N= 134), only 4 developed ASB, a rate of ASB of 3.00% (95% CI 0.81 – 7.64 %).

Figure 4. Incidence rate of ASB among women with initial negative culture



Of note, there were 11 documented symptomatic urinary tract infections, 8 of which were uncomplicated cases of cystitis. *E coli* was the most common organism responsible for symptomatic UTIs, accounting for 63.6% of such infections. Three cases of acute pyelonephritis were diagnosed amongst the study population, resulting in an incidence rate of 1.46% or 14.6 per 1000 pregnancies. All episodes of pyelonephritis occurred in the second trimester and at average gestational age of 19.8 weeks GA (SD=0.3). Diagnosis of pyelonephritis was based on clinical findings of fever (temperature>38°C) (n=2), flank pain (n=3), and costovertebral angle tenderness (n =2). Analysis of urine revealed bacteriuria with > 100,000 CFU/mL in 66.7% (n=2) of cases and pyuria (>5 leukocytes per HPF) in 100% (n=3) of cases. All women with symptomatic urinary tract infections received antibiotic therapy. No woman required admission to the intensive care unit while receiving inpatient treatment for pyelonephritis. Of note,

one of the three women diagnosed with acute pyelonephritis had previous successful treatment for uncomplicated cystitis; another woman, with known poorly controlled HIV, was diagnosed with asymptomatic bacteriuria but never received treatment, and the third woman did not have any positive urine cultures throughout gestation, including at the time of diagnosis for pyelonephritis.

Amongst our study population, there were 21 cases of preterm birth, comprising 11.4% of all documented births. Of these preterm deliveries, 42.9% resulted from spontaneously preterm birth, and the remainder resulted from obstetric intervention for maternal or fetal indications. The rate of low birth weight, infants less 2500 grams, was 4.4%; however if gestational age is considered, the rate of small for gestational age infants was only 1.65%. Amongst women with ASB, there were 4 cases of preterm delivery, of which only one was the result of spontaneous preterm labor, and there were no small-for-gestational age infants. The rate of preterm delivery or low birth weight amongst women with bacteriuria did not differ significantly from the rate amongst non-bacteriuric women. (Fisher's exact test p=0.287 and p=1.0, respectively)

Cost-Effectiveness Analysis

Table 8 shows the costs of each screening strategy, and notably total direct costs were the lowest with the 1st and 2nd trimester screening policy, while the no screening policy had the highest total costs.

Table 8. Direct costs of each screening strategy, using baseline estimates (per 100,000 patients)

	No screening	Routine 1st trimester screening	1st and 2nd trimester screening
Costs of ASB screening and treatment ($)	0	1,242,000	2,465,000
Costs of acute care (pyelonephritis and ARDS) ($)	22,303,000	13,334,000	6,777,000
Total expected costs ($)	**22,303,000**	**14,576,000**	**9,242,000**

Table 9 demonstrates the results of the base-case analysis comparing the no screening strategy to first trimester and first/second trimester urine culture screening strategies. A hypothetical cohort of 100,000 pregnant women was used to illustrate the differences in the results more clearly. With a policy of no screening, our model predicts a rate of pyelonephritis of 26.7 per 1000 pregnancies. With no screening, there are significantly more cases than predicted for the single urine culture strategy (16 per 1000 pregnancies) and the two urine culture strategy (8.1 per 1000 pregnancies). Reductions in the incidence of more significant maternal outcomes such as ARDS are also noted with a two urine culture strategy from 133 expected cases (no screening) to 41 expected cases (two culture strategy).

Although costs associated with increased screening for and treatment of asymptomatic bacteriuria result in greater initial expense with the one and two urine culture strategies compared to no-screening, these costs are small compared to the expected savings from avoiding in-patient care for pyelonephritis and acute respiratory distress syndrome.

Table 9. Results summary for baseline estimates (per 100,000 patients)

Variable	No screening	Routine 1st trimester screening	1st and 2nd trimester screening
Expected cases of pyelonephritis (#)	2,669	1,596	811
Pyelonephritis prevented (#) *(vs. no screening)*	---	1,073	1,858
Expected cases of ARDS (#)	133	80	41
ARDS prevented (#) *(vs no screening)*	---	53	92
Expected costs of strategy	$22,303,000	$14,576,000	$9,242,000
Cost savings *(vs no screening)*	---	$7,727,000	$13,061,000
Incremental cost savings *(vs 1st TM screening)*	---	---	$5,334,000

Unlike most additional screening tests which introduce increased expenses in order to improve health, an additional urine culture is predicted to not only reduce the risk of adverse maternal outcomes (by preventing pyelonephritis and ARDS), but is also expected to bring substantial cost savings. As such, there is no true cost per pyelonephritis prevented. Rather costs saved are in addition to cases of pyelonephritis prevented. This is the case when routine first trimester screening is compared to a no-

screening strategy. The improved health states and costs are magnified with a repeat urine culture in the 2nd trimester (i.e. 18-22 weeks GA).

A series of univariate sensitivity analyses were performed, changing the baseline probabilities and cost estimates across their plausible ranges. The repeat screening strategy remained the dominant strategy over both single screening and no screening strategies, except with regard to two variables. The cost-effectiveness of repeat screening was affected by the risk of progression to acute pyelonephritis among untreated bacteriuric women. When the risk of pyelonephritis was less than 4% (base case 21%), the two urine culture strategy no longer dominated the other two strategies and became more expensive than the single urine culture strategy. However, at this threshold, the two urine culture strategy continued to be the strategy that maximized maternal outcomes. In fact, when the probability of pyelonephritis in the untreated woman was reduced to 2.5% the cost to prevent one case of pyelonephritis with this strategy (compared to one urine culture strategy) would be $4,664. In addition, when the cost of a urine culture exceeded $65, screening in the first and second trimester was no longer the dominant strategy. The single screening strategy became the cheapest policy when the cost of the urine culture was between $65 and $89, while the no screening strategy had the lowest overall cost when the urine culture exceeded $89. If a urine culture costs $100, the cost to prevent one case of pyelonephritis with this 2 culture strategy (compared to one urine culture strategy) would be $4,423. Nonetheless, for any urine culture cost, the 1st and 2nd screening strategy remained the most cost-effective strategy and maximized healthy outcomes for pregnant women.

Discussion

Throughout the literature, it is reported that the incidence rate of ASB after an initial negative urine culture did not exceed 1-2%; however, the incidence of pyelonephritis amongst this same cohort of women was cited to be also between 1-2%. Closer analysis of these statistics raised the possibility that more women were becoming bacteriuric than the literature from the 1950s and 1960s suggested. Amongst our prospective cohort of women seeking prenatal care, a greater proportion of women developed ASB after a negative first urine culture in comparison to reports in the literature. The overall calculated incidence rate of ASB through 28 weeks GA amongst such women was 4.3% (95% CI 1.75 – 8.96%). This incidence rate may be underestimated as positive cultures with less than 100,000 CFU/mL were excluded from ASB calculations. Notably, women with known risk factors (i.e., diabetes mellitus, sickle cell trait, and immunosuppression) for ASB did not develop ASB at significantly increased rates in comparison to women without such risk factors – a finding that suggests that targeted screening of women with identifiable risk factors will not lead to increased detection of ASB.

Although our cohort did not have excess risk factors for ASB, its other characteristics, namely multiparity and low socio-economic status, have been associated with increased ASB prevalence. Despite the fact that the population prospectively followed was predicted to have a greater risk of ASB, the rate of ASB on initial culture was consistent with previously reported rates. The prevalence rate of ASB at initial culture, adjusted

for the use of a single diagnostic culture, was 7.7%. This prevalence falls within the range of ASB prevalence reported across various obstetric populations.

Like previous studies, we found *E coli* to be the predominant pathogen responsible for ASB. Interestingly, gram-positive organisms comprised a larger percentage of bacteriuria cases than prior studies have indicated. Hill et al, in a recent prospective longitudinal study of acute pyelonephritis, found that the frequency of gram-positive organisms doubled by the third trimester and such pathogens accounted for an increasing proportion of cases of acute pyelonephritis.(19) As a result of screening from the first prenatal visit until early in the third trimester, our data may have captured this shift in microbiology from predominantly gram-negative organisms to more gram-positive organisms. It is possible that a single screening in early pregnancy may miss the detection of gram-positive organisms that appear later in gestation.

Interestingly, the development of ASB, after a negative culture, occurred most often in the window between 18 and 22 weeks gestational age. This peak in ASB incidence, albeit not statistically significant, was seen also amongst all cases of ASB and amongst any positive culture. This increase in incidence in the 18 to 22 week GA interval has biological plausibility. It occurs as the enlarging uterus extends beyond the pelvis, compressing the ureters, and as the placenta continues its increasing production of progesterone, physiologic changes that may predispose women to greater urinary stasis and bacterial proliferation. Moreover, as women engage in sexual activity throughout

pregnancy, bacteria will be introduced in the sterile urinary tract and changes of pregnancy may contribute to enhanced bacterial growth.

As most cases of pyelonephritis occur in the second and third trimester, the goal of any screening program would be to identify cases of ASB before their progression to symptomatic infection; the mid-trimester peak in our study suggests a logical time for a second screening urine culture in pregnancy. Larger studies will be required to determine if this peak in incidence at 18-22 weeks will be replicated in other populations. In a cohort of 1050 women, McIsaac and colleagues (2005) reported that a single culture early in pregnancy failed to identify more than half of the cases of ASB, concluding that additional cultures are required; however, they made no assessment of the impact of increased ASB detection on incidence of acute pyelonephritis in pregnancy. Larger randomized controlled trials would help to resolve the question as to whether repeat screening decreases the incidence of pyelonephritis as the true objective is to prevent additional cases of pyelonephritis that would be missed by a single culture strategy.

Our study did not have sufficient power to compare the incidence of pyelonephritis between a repeat screening strategy and a single culture strategy. Nonetheless, the incidence rate of pyelonephritis in our study was 1.5%, consistent with the published incidence rate of pyelonephritis in pregnancy of 1-2%.(19, 21) Interestingly, there was only one case of acute pyelonephritis amongst all women with ASB; this woman was non-adherent to her antibiotic regimen in addition to being immunosuppressed. There

were no significant associations between bacteriuria and low birthweight or preterm birth,

Like Rouse et al, we found that use of a single urine culture for ASB screening in pregnancy was cost-saving in comparison to no screening. Furthermore, our study demonstrates that repeat ASB screening and treatment is also cost-effective in comparison to a no screening strategy and to the standard one urine culture strategy, and provides a strong case for the multiple screening strategy. It should be noted that our cost estimates most likely represented an underestimation of the total costs as we only considered direct hospital costs. The sensitivity analyses revealed the dominance of repeat screening over the alternative strategies for almost every plausible probability value and cost estimate. These results can be attributed to the relatively low cost of urine cultures in pregnancy compared to high costs of inpatient management of acute pyelonephritis in pregnancy. Some researchers have suggested that uncomplicated pyelonephritis can be treated effectively and safely on an outpatient basis; however, the relatively high rate of complications arising in pregnant women with pyelonephritis (respiratory insufficiency, need for intensive care unit admission, and septicemia) will limit the widespread implementation of outpatient management and maintain the relatively high costs of acute antepartum pyelonephritis.(58)

The variables that most affected the cost-effectiveness outcome are the cost of urine culture and the risk of progression of untreated ASB to acute pyelonephritis. Understandably when the screening tool, namely the urine culture, becomes too

expensive, then screening, and in this case repeat screening, is no longer cost-saving. Likewise when the risk of pyelonephritis among untreated bacteriuric women is lower, the benefit of ASB screening becomes less. Nonetheless, the two urine culture strategy continued to be the strategy that maximized maternal outcomes across all costs and probability estimates.

We recognize that the multiple screening strategy has its drawbacks. Obtaining urine for culture in all prenatal patients can add additional work to busy obstetric practices. Providers will be required to follow-up cultures results, prescribe appropriate antibiotics, and perform repeat cultures as tests of cure. Importantly, there is concern that inappropriate antibiotic use will lead to increasing antibiotic resistance. There are no current treatment recommendations for cultures with less that 100,000 CFU/mL as there are unclear implications of lower colony counts in pregnancy. In the absence of guidelines around lower colony counts, we found that physicians and midwives were using antimicrobial agents to treat urine cultures that did not meet the criteria for ASB due to concerns about the risks of untreated bacteriuria in pregnancy. In our study, a high rate of antibiotic resistance was observed among *E coli* and other pathogens, a finding that is consistent with reports in the literature.(35) Moreover, antibiotics have adverse effects including gastro-intestinal upset, *Clostridium difficile* infection, allergic reactions, and the development of symptomatic yeast infections. Yet despite these concerns regarding antibiotic use, our analysis strongly demonstrates that repeat screening offers the dual benefit of preventing additional cases of pyelonephritis and

decreasing overall health care costs. Any implementation of a multiple ASB screening strategy would require guidelines and provider education about appropriate antibiotic use in the care of pregnant women.

There are several limitations to our study. Our study cohort was mostly multiparous women of color with lower than average socioeconomic status, a population that may not reflect a typical obstetric practice. The estimate of ASB prevalence on repeat culture after an initial negative culture used in the cost analysis was derived from this cohort, and thus may not be universally applicable to antepartum populations. Moreover, the peak incidence of ASB after an initial negative culture was not statistically different than the other four week gestational age windows studied, and a larger sample size may be needed in order to detect differences in ASB incidence rates in four week intervals and to determine the most optimal time to perform a second urine culture. In addition, the frequent treatment of urine cultures that did not meet criteria for ASB most likely led to an underestimation of the true rate of ASB on repeat culture.

Nonetheless, this study is one of the few to evaluate repeat ASB screening and treatment in the prevention of pyelonephritis in pregnancy. The strength of the analysis lies in the persistence of the cost-benefit findings of repeat screening over a wide range of probabilities and costs. Before implementation of a repeat screening policy, larger studies will be needed to determine if screening in both first and second trimesters can indeed reduce the incidence of acute antepartum pyelonephritis. If multiple cultures are

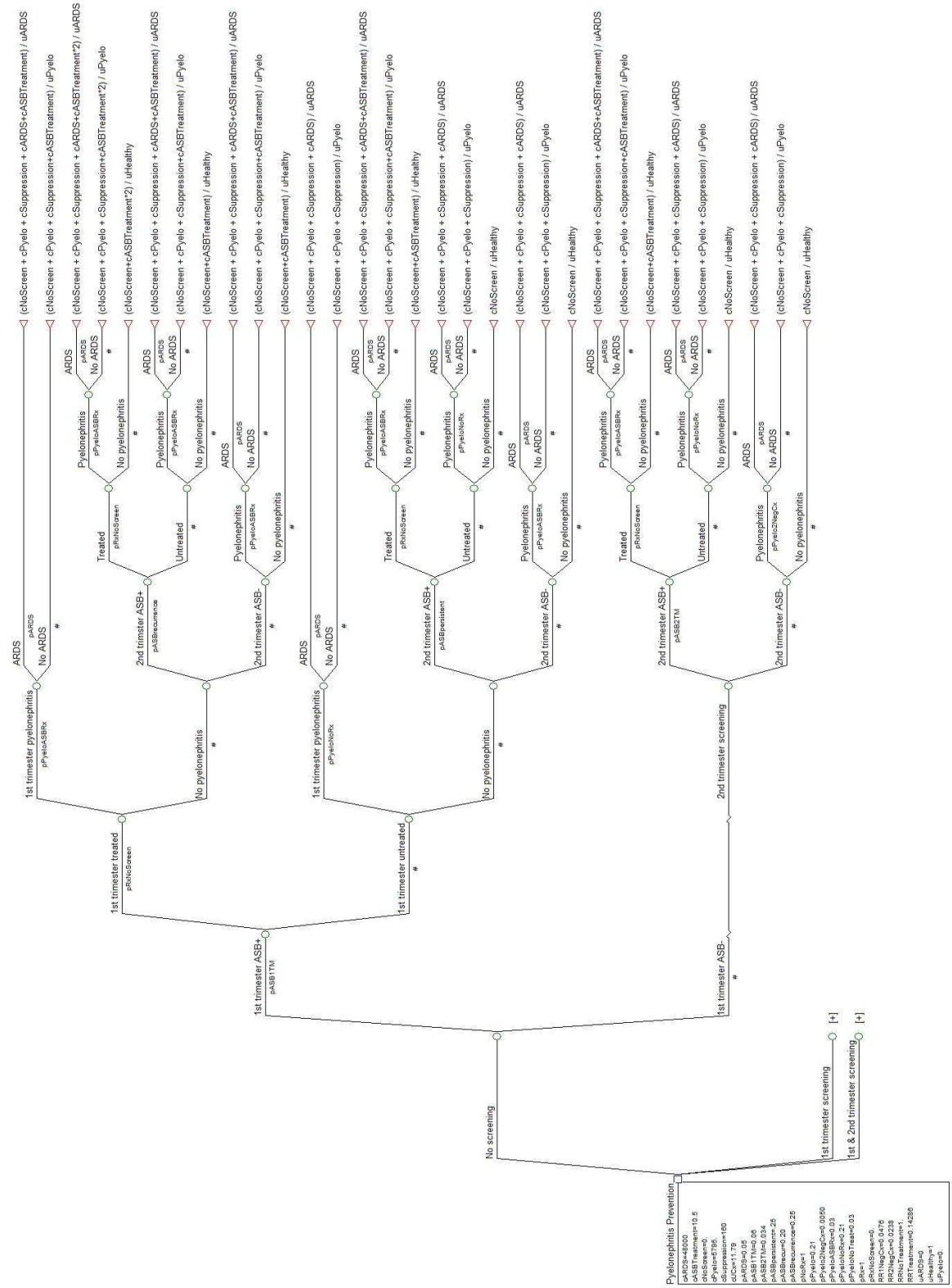
shown to decrease this incidence rate, our results offer strong evidence for the benefits of routine ASB screening in the first and second trimesters.

APPENDIX

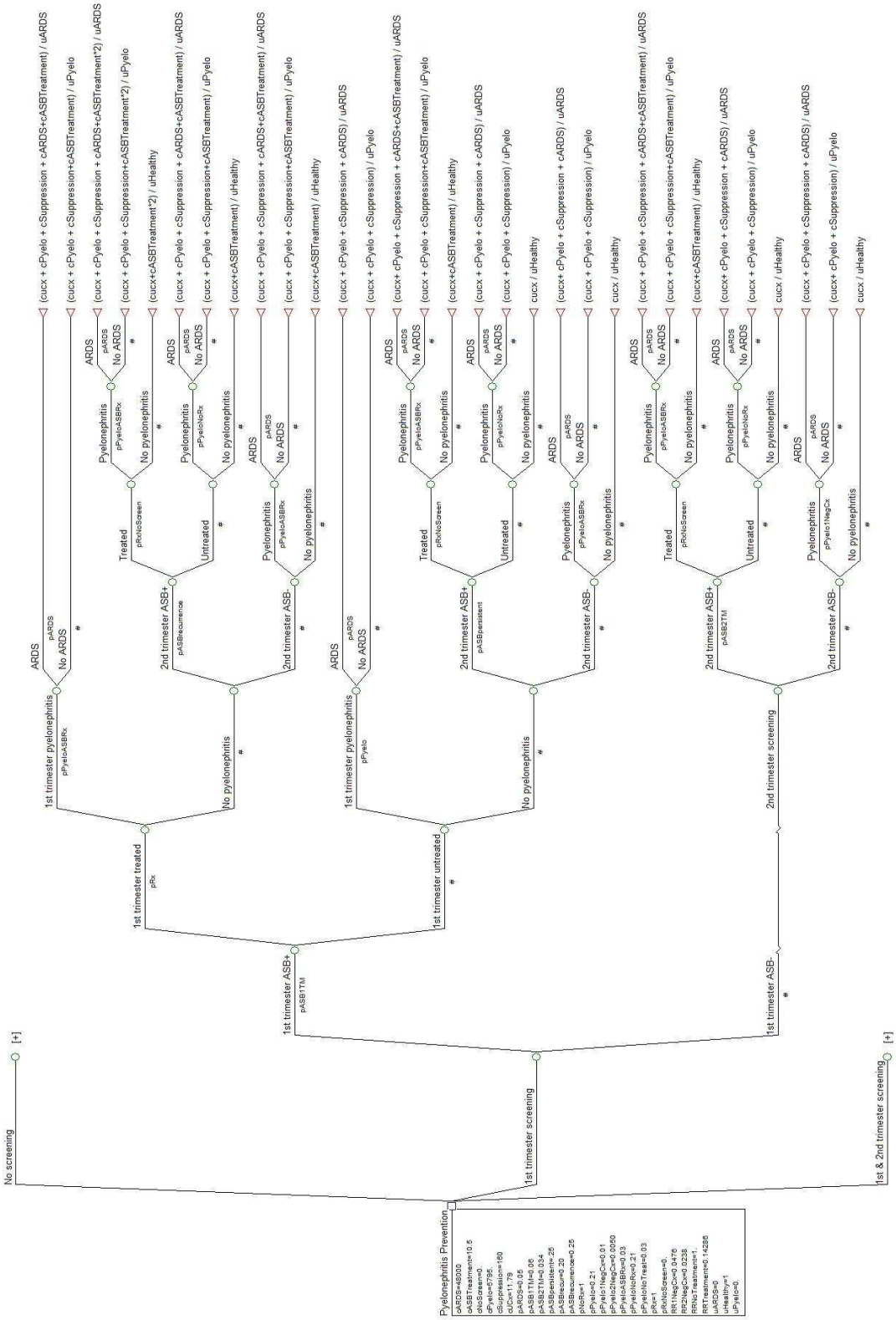
Abbreviation Key

PROBABILITIES	
pARDS	probability of ARDS
pASB1TM	probability of ASB in first trimester
pASB2TM	probability of ASB in second trimester
pASBpersistent	probability of persistent ASB
pASBrecurrence	probability of ASB recurrence after treatment
pPyelo1NegCx	probability of pyelonephritis with 1 negative screening culture
pPyelo2NegCx	probability of pyelonephritis with 2 negative screening cultures
pPyeloASBRx	probability of pyelonephritis after ASB treatment
pPyeloNoRx	probability of pyelonephritis with untreated ASB
pRx	probability of treatment
pRxNoScreen	probability of treatment with no screening
COSTS	
cARDS	cost of inpatient ARDS management
cASBTreatment	cost of ASB treatment
cNoScreen	cost of no screening
cPyelo	cost of inpatient management of acute pyelonephritis
cSuppression	cost of antibiotic suppression
cUCx	cost of urine culture
UTILITIES	
uARDS	utility of ARDS
uHealthy	utility of "healthy"
uPyelo	utility of pyelonephritis

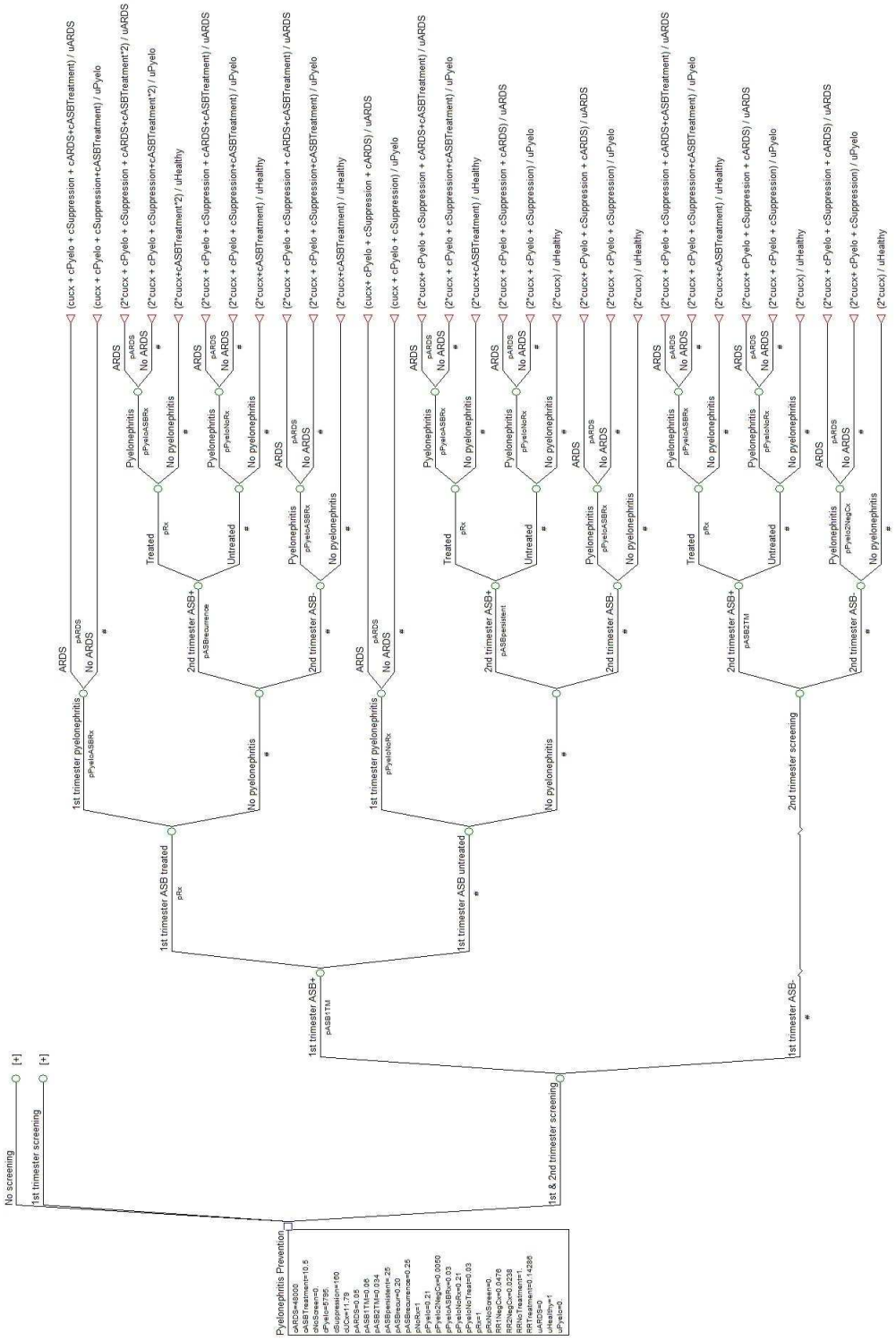
APPENDIX A. Decision analysis tree for policy of no screening



APPENDIX B. Decision analysis tree for policy of first trimester screening (1 culture strategy)



Appendix C. Decision analysis figure for policy of first and second trimester screening (2 culture strategy)



REFERENCES

1. Nicolle, L.E., Bradley, S., Colgan, R., Rice, J.C., Schaeffer A., et al. 2005. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults.[erratum appears in Clin Infect Dis. 2005 May 15;40(10):1556]. Clin Infect Dis 40:643-654.

2. Bachman, J.W., Heise, R.H., Naessens, J.M., and Timmerman, M.G. 1993. A study of various tests to detect asymptomatic urinary tract infections in an obstetric population.[see comment]. *JAMA* 270:1971-1974.

3. McNair, R.D., MacDonald, S.R., Dooley, S.L., and Peterson, L.R. 2000. Evaluation of the centrifuged and Gram-stained smear, urinalysis, and reagent strip testing to detect asymptomatic bacteriuria in obstetric patients. Am J Obstet Gynecol 182:1076-1079.

4. Lenke, R.R., and Van Dorsten, J.P. 1981. The efficacy of the nitrite test and microscopic urinalysis in predicting urine culture results. Am J Obstet Gynecol 140:427-429.

5. Tincello, D.G., and Richmond, D.H. 1998. Evaluation of reagent strips in detecting asymptomatic bacteriuria in early pregnancy: prospective case series. *BMJ* 316:435-437.

6. Etherington, I.J., and James, D.K. 1993. Reagent strip testing of antenatal urine specimens for infection. Br J Obstet Gynaecol 100:806-808.

7. Kass, E.H. 1956. Asymptomatic infections of the urinary tract. *Trans Assoc Am Physicians* 69:56-64.

8. Kass, E.H. 1962. Pyelonephritis and bacteriuria. A major problem in preventive medicine. *Ann Intern Med* 56:46-53.

9. Kass, E.H. 1960. The role of asymptomatic bacteriuria in the pathogenesis of pyelonephritis. In *Biology of Pyelonephritis*. E.L. Quinn, Kass EH, editor. Boston: Little, Brown, and Company. 399-412.

10. Kass, E.H. 1960. Bacteriuria and pyelonephritis of pregnancy. *Arch Intern Med* 105:194-198.

11. Millar, L.K., and Cox, S.M. 1997. Urinary tract infections complicating pregnancy. *Infect Dis Clin North Am* 11:13-26.

12. Whalley, P. 1967. Bacteriuria of pregnancy. Am J Obstet Gynecol 97:723-738.

13. Norden, C.W., and Kass, E.H. 1968. Bacteriuria of pregnancy--a critical appraisal. *Annu Rev Med* 19:431-470.

14. Elder, H.A., Santamarina, B.A., Smith, S., and Kass, E.H. 1971. The natural history of asymptomatic bacteriuria during pregnancy: the effect of tetracycline on the clinical course and the outcome of pregnancy. Am J Obstet Gynecol 111:441-462.

15. Barr, J.G., Ritchie, J.W., Henry, O., el Sheikh, M., and el Deeb, K. 1985. Microaerophilic/anaerobic bacteria as a cause of urinary tract infection in pregnancy. Br J Obstet Gynaecol 92:506-510.

16. Gilbert, G.L., Garland, S.M., Fairley, K.F., and McDowall, D.M. 1986. Bacteriuria due to ureaplasmas and other fastidious organisms during pregnancy: prevalence and significance. *Pediatr Infect Dis* 5:S239-243.

17. McDowall, D.R., Buchanan, J.D., Fairley, K.F., and Gilbert, G.L. 1981. Anaerobic and other fastidious microorganisms in asymptomatic bacteriuria in pregnant women. *J Infect Dis* 144:114-122.

18. Nicolle, L.E. 2003. Asymptomatic bacteriuria: when to screen and when to treat. *Infect Dis Clin North Am* 17:367-394.

19. Hill, J.B., Sheffield, J.S., McIntire, D.D., and Wendel, G.D., Jr. 2005. Acute pyelonephritis in pregnancy. *Obstet Gynecol* 105:18-23.

20. Beydoun, S.N. 1985. Morphologic changes in the renal tract in pregnancy. *Clin Obstet Gynecol* 28:249-256.

21. Sheffield, J.S., and Cunningham, F.G. 2005. Urinary tract infection in women. *Obstet Gynecol* 106:1085-1092.

22. Heidrick, W.P., Mattingly, R.F., and Amberg, J.R. 1967. Vesicoureteral reflux in pregnancy. *Obstet Gynecol* 29:571-578.

23. Mattingly, R.F., and Borkowf, H.I. 1978. Clinical implications of ureteral reflux in pregnancy. *Clin Obstet Gynecol* 21:863-873.

24. Andriole, V.T., and Cohn, G.L. 1964. The effect of diethylstilbestrol on the susceptibility of rats to hematogenous pyelonephritis. *J Clin Invest* 43:1136-1145.

25. Silk, M., and Perez-Varela, M.R. 1970. Effects of oral contraceptives on urinary bacterial growth rate. *Invest Urol* 8:239-241.

26. Leblanc, A.L., and McGanity, W.J. 1964. The impact of bacteriuria--a survey of 1300 pregnant patients. Tex Rep Biol Med 22:336-347.

27. Savage, W.E., Hajj, S.N., and Kass, E.H. 1967. Demographic and prognostic characteristics of bacteriuria in pregnancy. *Medicine (Baltimore)* 46:385-407.

28. Bacak, S.J., Callaghan, W.M., Dietz, P.M., and Crouse, C. 2005. Pregnancy-associated hospitalizations in the United States, 1999-2000. Am J Obstet Gynecol 192:592-597.

29. Cunningham, F.G., Morris, G.B., and Mickal, A. 1973. Acute pyelonephritis of pregnancy: A clinical review. *Obstet Gynecol* 42:112-117.

30. Gilstrap, L.C., 3rd, Cunningham, F.G., and Whalley, P.J. 1981. Acute pyelonephritis in pregnancy: an anterospective study. *Obstet Gynecol* 57:409-413.

31. Cox, S.M., Shelburne, P., Mason, R., Guss, S., and Cunningham, F.G. 1991. Mechanisms of hemolysis and anemia associated with acute antepartum pyelonephritis. Am J Obstet Gynecol 164:587-590.

32. Cunningham, F.G., Leveno, K.J., Hankins, G.D., and Whalley, P.J. 1984. Respiratory insufficiency associated with pyelonephritis during pregnancy. *Obstet Gynecol* 63:121-125.

33. Cunningham, F.G., Lucas, M.J., and Hankins, G.D. 1987. Pulmonary injury complicating antepartum pyelonephritis. Am J Obstet Gynecol 156:797-807.

34. Crabtree, E.G., and Prather, G.C. 1930. Clinical aspects of pyelonephritis in pregnancy. N Engl J Med 202:357-366.

35. Smaill, F., and Vazquez, J.C. 2007. Antibiotics for asymptomatic bacteriuria in pregnancy.[update of Cochrane Database Syst Rev. 2001;(2):CD000490; PMID: 11405965]. Cochrane Database Syst Rev:CD000490.

36. Romero, R., Oyarzun, E., Mazor, M., Sirtori, M., Hobbins, J.C., and Bracken, M. 1989. Meta-analysis of the relationship between asymptomatic bacteriuria and preterm delivery/low birth weight. *Obstet Gynecol* 73:576-582.

37. Gratacos, E., Torres, P.J., Vila, J., Alonso, P.L., and Cararach, V. 1994. Screening and treatment of asymptomatic bacteriuria in pregnancy prevent pyelonephritis. *J Infect Dis* 169:1390-1392.

38. Uncu, Y., Uncu, G., Esmer, A., and Bilgel, N. 2002. Should asymptomatic bacteriuria be screened in pregnancy? Clin Exp Obstet Gynecol 29:281-285.

39. Andrews, W.W., Cox SM, Gilstrap LC. 1990. Urinary tract infections in pregnancy. Int Urogynecol J 1:155-163.

40. Harris, R.E. 1979. The significance of eradication of bacteriuria during pregnancy. *Obstet Gynecol* 53:71-73.

41. Rouse, D.J., Andrews, W.W., Goldenberg, R.L., and Owen, J. 1995. Screening and treatment of asymptomatic bacteriuria of pregnancy to prevent pyelonephritis: a cost-effectiveness and cost-benefit analysis.[see comment]. *Obstet Gynecol* 86:119-123.

42. Wadland, W.C., and Plante, D.A. 1989. Screening for asymptomatic bacteriuria in pregnancy. A decision and cost analysis.[see comment]. J Fam Pract 29:372-376.

43. Force, U.S.P.S.T. 2008. Screening for asymptomatic bacteriuria in adults: U.S. Preventive Services Task Force reaffirmation recommendation statement.[summary for patients in Ann Intern Med. 2008 Jul 1;149(1):I37; PMID: 18591630]. *Ann Intern Med* 149:43-47.

44. Nicolle, L.E. 2006. Asymptomatic bacteriuria: review and discussion of the IDSA guidelines. Int J Antimicrob Agents 28 Suppl 1:S42-48.

45. Lawson, D.H., and Miller, A.W. 1973. Screening for bacteriuria in pregnancy. A critical reappraisal. Arch Intern Med 132:904-908.

46. Marchant, D.J. 1978. Urinary tract infections in pregnancy. *Clin Obstet Gynecol* 21:921-929.

47. Patterson, T.F., and Andriole, V.T. 1987. Bacteriuria in pregnancy. *Infect Dis Clin North Am* 1:807-822.

48. Lin, K., Fajardo, K., and Force, U.S.P.S.T. 2008. Screening for asymptomatic bacteriuria in adults: evidence for the U.S. Preventive Services Task Force reaffirmation recommendation statement.[see comment]. *Ann Intern Med* 149:W20-24.

49. Stenqvist, K., Dahlen-Nilsson, I., Lidin-Janson, G., Lincoln, K., Oden, A., Rignell, S., and Svanborg-Eden, C. 1989. Bacteriuria in pregnancy. Frequency and risk of acquisition. Am J Epidemiol 129:372-379.

50. Patterson, T.F., and Andriole, V.T. 1997. Detection, significance, and therapy of bacteriuria in pregnancy. Update in the managed health care era. *Infect Dis Clin North Am* 11:593-608.

51. Drugstore.com. 2008. Available at http://drugstore.com. Accessed December 1, 2008.

52. Carlson, K.J., and Mulley, A.G. 1985. Management of acute dysuria. A decision-analysis model of alternative strategies. *Ann Intern Med* 102:244-249.

53. Centers for Medicare and Medicaid Services. Washington, DC: US Department of Health and Human Services; 2008. Available at http://www.cms.hhs.gov/apps/ama/licsense.asp?file=/ClinicalLabFeeSched/downloads/08clab.zip. Accessed January 1, 2009.

54. Brown, P., Ki, M., and Foxman, B. 2005. Acute pyelonephritis among adults: cost of illness and considerations for the economic evaluation of therapy. *Pharmacoeconomics* 23:1123-1142.

55. Cheung, A.M., Tansey, C.M., Tomlinson, G., Diaz-Granados, N., Matte, A., and et al. 2006. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. Am J Respir Crit Care Med 174:538-544.

56. Hamel, M.B., Phillips, R.S., Davis, R.B., Teno, J., and Connors, A.F. 2000. Outcomes and cost-effectiveness of ventilator support and aggressive care for patients with acute respiratory failure due to pneumonia or acute respiratory distress syndrome. Am J Med 109:614-620.

57. Valta, P., Uusaro, A., Nunes, S., Ruokonen, E., and Takala, J. 1999. Acute respiratory distress syndrome: frequency, clinical course, and costs of care. Crit Care Med 27:2367-2374.

58. Millar, L.K., Wing, D.A., Paul, R.H., and Grimes, D.A. 1995. Outpatient treatment of pyelonephritis in pregnancy: a randomized controlled trial.[see comment]. *Obstet Gynecol* 86:560-564.