EVALUATION OF RAPID URINE SCREENING TESTS TO DETECT ASYMPTOMATIC BACTERIURIA IN PREGNANCY

Thesis

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INTRODUCTION

The presence of bacteria in the urine of an asymptomatic patient is known as asymptomatic bacteriuria (ASB) *(Nicolle et al., 2005)*. It is defined as two consecutive clean-catch midstream urine cultures showing at least 100,000cfu/mL of the same single species from an individual without any symptoms of urinary tract infection (UTI) *(Kacmaz et al., 2006)*.

Asymptomatic bacteriuria is common, it is found in 2% to 10% of pregnant women with varying prevalence by age, sexual activity, and the presence of genitourinary abnormalities *(Etherington et al., 1993).*

It is well established that asymptomatic bacteriuria has serious outcomes in pregnancy. Pregnant women with asymptomatic bacteriuria have an increased risk of pyelonephritis *(Smaill, 2004)* and there is a strong association between asymptomatic bacteriuria and preterm and low birth weight delivery *(Bookallil et al., 2005).*

Pyelonephritis will occur in 1.8%-30% of woman who have non-treated asymptomatic bacteriuria during pregnancy *(Smaill, 2004).*

Infecting organisms involved in asymptomatic bacteriuria are diverse and include *Escherichia coli, Enterobacteriaceae, Pseudomonas aeruginosa*, *Enterococcus species*, and *group B streptococcus* ***(Golgan et al., 2006).***

The diagnosis of ASB is based on urine culture, but culture results are typically not available until 24 to 48 h after the patient provides the specimen ***(Armengol et al., 2001).***

There are many urine screening tests for bacteriuria, including microscopic examination of urine sediment (a time-honored method) and dipstick analysis of nitrite (NIT) and leukocyte esterase (LE) ***(Bachman et al., 1993; Kacmaz et al., 2006)***. The benefits of these tests that they are cheap, available and rapid as the results appear at the moment of doing the test.

The performance of urine analysis tests is evaluated by calculating sensitivity, specificity and positive and negative predictive values using standard methods.

Nitrite tests are useful screening tests for detecting asymptomatic bacteriuria only if their limitations are fully understood ***(Kacmaz et al., 2006).***

A positive NIT test indicates that NIT has been produced from the reduction of nitrate by enteric bacteria, most commonly by the *Enterobacteriaceae* family ***(Semeniuk and Church, 1999)***.

False-negative results may occur with NIT when a UTI is caused by organisms that do not contain nitrate reductase, when urine has been in the bladder for insufficiently long periods for the reduction of nitrate to occur, or when dietary nitrate is absent ***(Kacmaz et al., 2006).***

The sensitivity of the NIT test has been found to be (37%- 67%) by several studies ***(Hagay et al., 1996; Millar et al., 2000).*** And its specificity is 99.2% ***(Kacmaz et al., 2006).***

The LE test for pyuria showed a sensitivity of 70% and specificity of 92.5% in previous study ***(Kacmaz et al., 2006)***. Although some investigators have reported its sensitivity to be 100% ***(Nuns et al., 1995).***

False positive result may occur with LE test with other urogenital pathogens such as Chlamydia, Neisseria gonorrhoeae or agents of vaginitis. Thus, the LE test might be considered to be a rapid, nonspecific screening test for genitourinary tract infections ***(Kacmaz et al., 2006).***

To increase the reliability of microscopy, an enhanced urine analysis (UA) method has been proposed for the diagnosis of urinary tract infections (UTIs) in the pediatric population. Under this method, uncentrifuged urine is gram-stained for bacteria, and a leukocyte count is performed using a hemocytometer *(Armengol et al., 2001)*.

Hoberman et al. (1996) report 96% sensitivity for enhanced UA in the pediatric population.

AIM OF THE WORK

The study was be performed to evaluate the performance of enhanced UA for the detection of ASB in pregnant women, and to compare reagent strip testing with enhanced UA and urine cultures in identifying significant bacteriuria.

URINARY TRACT INFECTION OVERVIEW IN PREGNANCY

Epidemiology

In the past, UTI often has been defined for research purposes as the presence of at least 10^8 colony-forming units (CFU) per liter in freshly voided urine, although symptomatic infection can occur with 10^6 CFU/L *(Neild, 2003)* and some would argue for a cutoff of 10^5 CFU/L in symptomatic patients when urine can be cultured without delay *(Stamm and Hooton, 1993).*

Urinary tract infection (UTI) is a serious health problem affecting millions of people each year. It is estimated that there are more than 10 million cases in Western Europe alone per year *(Roos et al., 2006a).* It is estimated that 40-50% of adult healthy women have experienced at least one UTI episode *(Foxman, 2002).*

Urinary tract infection (UTI) is among the most frequently encountered bacterial infections in the office setting. In addition, UTI is a major cause of hospital admissions, is responsible for significant morbidity and mortality, and has a large associated economic burden *(Fihn, 2003; Griebling, 2005).*

In a study of more than 70,000 pregnancies in a managed care organization, *Gazmararian and Colleagues, (2002)* reported that 3.5 percent of antepartum admissions were for urinary tract infections. Therefore, urinary tract infections represent the most common bacterial infection in pregnancy *(Schnarr and Smaill, 2008).*

Approximately 23% of all hospital-acquired infections are due to UTI *(Emmerson et al., 1996).* The incidence is increased in elderly men and women, particularly among those living in institutions, where it can be up to 53% and 37% in women and men, respect-tively *(Neild, 2003).*

Urinary tract infections (UTIs) are frequently encountered in the family physician's office. UTIs account for approximately 10 percent of office visits by women, and 15 percent of women will have a UTI at some time during their life. In pregnant women, the incidence of UTI can be as high as 8 percent *(Mikhail, 1995; Delzell and Lefevre, 2000).*

Infection of the lower urinary tract (asymptomatic bacteriuria and cystitis) and upper urinary tract (Pyelonephritis) is of concern. Although neither cystitis nor asymptomatic bacteriuria is more common among pregnant women compared with agematched

nonpregnant women, the risk for progression from either of these entities to pyelonephritis is significantly increased during pregnancy *(Gilstrap and Ramin, 2001).* Pyelonephritis during pregnancy threatens the mother and the fetus, making prompt diagnosis and treatment of its precursor UTI syndromes essential *(Drekonja and Johnson, 2008).*

Most uropathogens gain access to the urinary tract via an ascending route. The shorter length of the female urethra allows uropathogens easier access to the bladder. The continuous unidirectional flow of urine helps to minimize UTIs, and anything that interferes with this increases the host's susceptibility to UTI. Secretory defenses help to promote bacterial clearance and prevent adherence. Secretory immunoglobulin A (IgA) reduces attachment and invasion of bacteria in the urinary tract. Women who are nonsecretors of the ABH blood antigens appear to be at higher risk of recurrent UTIs; this may occur because of a lack of specific glycosyltransferases that modify epithelial surface glycolipids, allowing *E.coli* to bind to them better. Urine itself has several antibacterial features that suppress UTIs. Specifically, the pH, urea concentration, osmolarity, and various organic acids prevent most bacteria from surviving in the urinary tract *(Cunha et al., 2008).*

Morphological changes of urinary tract with pregnancy:

Significant changes in both structure and function take place in the urinary tract during normal pregnancy. Urinary tract dilatation is one of the most significant anatomical alterations induced by pregnancy. It involves dilatation of the renal calyces and pelvis, as well as the ureters as seen in figure (1). These changes, which are more prominent on the right side, are secondary to both hormonal and mechanical obstructive factors. The latter creates urinary stasis, and may lead to serious upper urinary infections. Another factor predisposing to infection is increased vesicoureteral reflux. Evidence for hypertrophy of renal function is apparent very soon after conception. It appears to be mediated by pregnancy-induced intrarenal vasodiltation *(Cunningham et al., 2010)*.

Glomeruli are larger, although cell numbers do not increase *(Strevens et al., 2003).* Pregnancy-induced intrarenal vasodilatation increases effective renal plasma flow and glomerular filtration. By 12 weeks' gestation, the glomerular filtration rate is already increased 20 percent above nonpregnant values *(Hladunewich et al., 2004).*

An important consequence of these physiological changes is an increased risk of upper urinary infection, and occasionally erroneous interpretation of studies done to evaluate obstruction *(Cunningham et al., 2010)*.

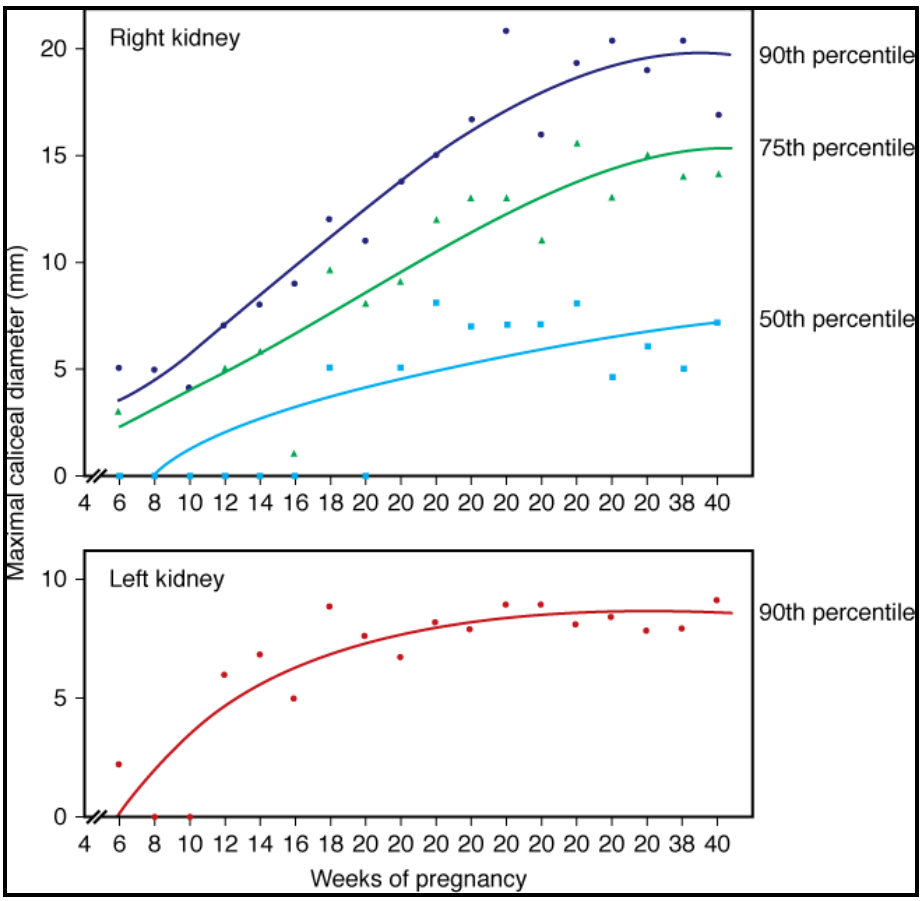

Fig. (1): The 50th, 75th, and 90th percentiles for maternal renal caliceal diameters measured using sonography in 1395 pregnant women from 4 to 42 weeks *(Cunningham et al., 2010)*.

Ultimately, RPF and GFR increase by 40 and 65 percent, respectively. Consequently, serum concentrations of creatinine and urea decrease substantively across pregnancy, and values within a nonpregnant normal range may be abnormal in pregnancy. Other alterations include those related to maintaining normal acid-base homeostasis, osmoregulation, and fluid and electrolyte retention *(Cunningham et al., 2010)*.

Table (1): Renal Changes in Normal Pregnancy *Modified by Cunningham et al. (2010)) from Lindheimer and colleagues (2000)*

Alteration		Clinical Relevance
Kidney size	Approximately 1cm longer on radiograph	Size returns to normal postpartum
Dilatation	Resembles hydronephrosis on sonogram or IVP (more marked on right)	Can be confused with obstructive uropathy; retained urine leads to collection errors; renal infections are more virulent; may be responsible for "distension syndrome"; elective pyelography should be deferred to at least 12 weeks postpartum
Renal function	Glomerular filtration rate and renal plasma flow increase ~50%	Serum creatinine decreases during normal gestation; >0.8mg/dL (>72mol/L) creatinine already borderline; protein, amino acid, and glucose excretion all increase
Maintenance of acid-base	Decreased bicarbonate threshold; progesterone stimulates respiratory center	Serum bicarbonate decreased by 4-5mEq/L; PCO_2 decreased 10mmHg; a PCO_2 of 40mmHg already represents CO_2 retention
Plasma osmolality	Osmoregulation altered: osmotic thresholds for AVP release and thirst decrease; hormonal disposal rates increase	Serum osmolality decreases 10 mOsm/L (serum Na ~5 mEq/L) during normal gestation; increased placental metabolism of AVP may cause transient diabetes insipidus during pregnancy

AVP= vasopressin; CO_2= carbon dioxide; IVP= intravenous pyelography; PCO_2 = partial pressure carbon dioxide.

There are few significant anatomical changes in the bladder before 12 weeks. From that time onward, however, increased uterine size, the hyperemia that affects all pelvic organs, and the hyperplasia of the bladder's muscle and connective tissues elevates the bladder trigone and causes thickening of its posterior, or intraureteric, margin. Continuation of this process to the end of pregnancy produces marked deepening and widening of the trigone. There are no mucosal changes other than an increase in the size and tortuosity of its blood vessels *(Cunningham et al., 2005)*.

Toward the end of pregnancy, particularly in nulliparas in whom the presenting part often engages before labor, the entire base of the bladder is pushed forward and upward, converting the normal convex surface into a concavity. As a result, difficulties in diagnostic and therapeutic procedures are greatly increased. In addition, the pressure of the presenting part impairs the drainage of blood and lymph from the bladder base, often rendering the area edematous, easily traumatized, and probably more susceptible to infection *(Cunningham et al., 2010)*.

Lower urinary tract symptoms of frequency, urgency, and nocturia are the normal during

pregnancy. There is no recommendation for their treatment, apart from ascertainment that fluid intake is not inappropriately high, and most women are willing to put up with their symptoms when they are reassured that they are likely to resolve soon after delivery *(FitzGerald and Graziano, 2007).*

Van Brummen and colleagues, (2006) reported that among 515 nulliparous pregnant women, 74% experienced urinary frequency and 63% experienced urgency by 12 weeks' gestation, increasing to a prevalence of 81% and 68% by 36 weeks.

In a prospective examination of 9734 pregnant women, 7.4% of them were diagnosed as having a urinary tract infection: 5.1% with asymptomatic bacteriuria, 1.3% with acute cystitis and 1% with acute pyelonephritis *(Harris and Gilstrap, 1981).*

Christiaens and Colleagues, (2002) stated that diagnosis is important because failure to detect a UTI can have serious consequences, particularly in certain patients such as pregnant women. However, uncomplicated UTI in nonpregnant women rarely causes severe illness or has significant long-term consequences, and in 50% of patients, the condition improves without antimicrobials within 3 days.

Determinant of urinary tract infection:

Age of gestation, low haemoglobin level, multiparty and previous history of urinary tract infection were shown to be risk factors on urinary tract infection. However, on logistic regression analysis, the following risk factors were found to be independently associated with asymptomatic bacteriuria: haemoglobin level <11gm/dl, gestational age <12 week and history of urinary tract infection *(Isabel et al., 2003).*

In healthy women, the prevalence of bacteriuria increases with age *(Nicolle, 2003).* However, *Fatima and Ishrat, (2006)* in their study stated that maternal age was not a significant risk factor. Others believe that only a slightly increasing risk of 1-2% was reported per decade of age that did not become evident probably due to small sample size. Other studies concluded that age had no detectable influence on the frequency of bacteriuria. The bacteriuric women were not older than the non-bacteriuric women *(Isabel et al., 2003).*

The prevalence of bacteriuria in pregnancy is closely related to socioeconomic status *(Schnarr and Smaill, 2008).* It has been reported that indigent women have a five fold greater incidence of