Original Article

Maternal Urinary Tract Infection and Risk of Preeclampsia: A Cross Sectional Comparative Study

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Abstract

Objective: To predict the risk of pre-eclampsia in patients with urinary tract infection during pregnancy.

Methodology: Pregnant women aged >15 years (N-300) were recruited and followed up prospectively from the start of prenatal care till the end of delivery. This cross sectional comparative study was conducted at CMH Kharian and PNS shifa Karachi from July 2020 to July 2021. A structured questionnaire was filled regarding medical and obstetric history, socio-demographic details and symptoms of urinary tract infection (UTI). Maternal mid-stream urine samples were obtained at 4 visits during pregnancy and were plated on MacConkey agar, later colony count was done. Logistic regression was used to find the risk of preeclampsia.

Results: Among 300 patients, 20 (6.6%) patients were diagnosed with UTI and 40 (13.3%) with preeclampsia. A statistically significant difference ($p<0.05$) was noticed between the pregnant females with UTI and without UTI regarding age, BMI, preeclampsia, hypertension, gestational diabetes, education, and gestational age. Patients with UTI during pregnancy showed an increased risk of preeclampsia in females with BMI 25 vs 30 (OR-1.25;95%CI-3.22-39.19) and BMI>30.0 (OR-5.61;95% CI-1.92-16.42), current preeclampsia (OR-0.322;95% CI-0.116-0.896), chronic hypertension (OR 0.318; 95% CI,0.124-0.82, p-0.018), nulliparous (OR-4.058;95% CI-1.32-12.44), current gestational diabetes (OR-0.231;95% CI-0.076-0.70) and in illiterate females (OR-0.064;95% CI-0.023-0.18). UTI during pregnancy was associated with a 3–4 fold increase in the risk of developing preeclampsia during the second trimester (OR-2.11; 95% CI-0.651–6.83) and third trimester (OR-4.12; 95% CI-1.28–13.19) compared to women who did not have UTI.

Conclusion: Presence of UTI in pregnancy is strongly associated with preeclampsia

Keywords: Urinary tract infection, Pregnancy, Preeclampsia

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Introduction

Preeclampsia, a pregnancy induced vascular syndrome, is characterized by onset of blood pressure >140 mmHg systolic or >90 mmHg diastolic at two separate occasions more than four hours apart, with proteinuria after 20 weeks of gestation. [1] Its prevalence has decreased to 2%-8% but still considered the leading cause of feto-maternal morbidity and mortality worldwide. Preeclampsia is more common in old, obese, diabetics, and females with their first pregnancy or having twins.[2] In developing countries Pre eclampsia has resulted in more than 60,000 maternal and 500,000 fetal deaths per year worldwide. [3]

In spite of advanced knowledge, the exact mechanisms of PE is unclear, however, inflammation is considered its main cause resulting in vascular endothelial dysfunction. Initially placental hypo-perfusion and

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ischemia occurs due to shallow trophoblastic invasion because of adhesion molecules, and major histocompatibility complex molecules with insufficient remodeling of uterine spiral arteries in the deep myometrial tissues. Consequently, the anti-angiogenic factors of placenta, increase in $CD4^+$ T cells, decrease in regulatory T cells, oxidative stresses, release of pro-inflammatory cytokines and autoantibodies cause endothelial dysfunction. So any acute or chronic maternal infection that cause systemic inflammation and endothelial dysfunction can result in development of preeclampsia. [4] Studies have shown that maternal periodontal diseases and Urinary tract infection in pregnancy are associated with preeclampsia. [5, 6]

The UTI can be asymptomatic or symptomatic. The symptomatic UTI, mostly due to Escherichia coli, affects 40% females and 13% males once during their life and nearly half of these female have recurrent UTI. The female with diabetes mellitus, neurological diseases, on immunosuppressant drugs and multipara are associated with 66% increased risk of bacteriuria. [7] The prevalence of UTI vary by age, sexual activity, morphological and physiological changes during pregnancy especially of the genitourinary tract like dilatation of renal pelvis and ureter, decreased ureteral peristalsis with urinary stasis, vesico-ureteric reflux, decreased bladder tone, short urethra and possible contamination of urinary tract with fecal flora. Additionally, glycosuria and aminoaciduria associated with pregnancy encourages bacterial growth in the ureter due to urinary stasis. [7-9] The symptomatic bacteriuria is associated with an increased risk of intrauterine growth retardation, prematurity, and low birth weight. [8]

The asymptomatic bacteriuria is associated with anemia, increased neonatal mortality due to septicemia, cystitis (30%) and pyelonephritis. [10]

The association between UTI and preeclampsia is still inconsistent and conflicting, so we aimed to assess the association between UTI during pregnancy with risk of pre-eclampsia in these females.

Methodology

This cross sectional comparative study was conducted at CMH Kharian and later PNS Shifa Karachi, which are tertiary care hospitals, from July 2020 to July 2021 after approval from institutional ethical committee vide letter no Gyn/KHN/89/2019. A total of 300 pregnant women irrespective of age, parity, gestational age and those who gave a written informed consent were included in the study. The women who were seriously ill, had kidney disease, past history of UTI, renal transplant, diabetes, on immunosuppressive therapy, or on antibiotics since last week for any infection and those who were not willing to participate were excluded from the study.

After taking medical and obstetric history, physical and gynecological examination was performed, and a structured proforma was filled regarding demographic information (age, parity, smoking, education, past history of PE, gestational diabetes, diabetes mellitus, family history of hypertension and diabetes and symptoms of UTI (fever, dysuria and urinary frequency).

The pregnant women were asked to collect their midstream urine sample in a sterile, half-filled wide mouth bottle, about 10 ml, after washing their hands with water and cleaning their genital area with swab soaked in normal saline.

All samples were send to laboratory within 2 hrs or were stored in a refrigerator at 4^0 C till deposited to lab within 18 hrs of collection. The urine samples were placed on to the MacConkey agar by a calibrated sterile platinum wire loop using standard lab protocols. The plates were incubated at 37°C and any growth was checked after 24 hrs and 48 hrs. The growths were identified by naked eye and colonies were counted.

The urine samples were obtained on all four visits during the pregnancy and the blood pressure was recorded on lying and sitting positions. The diagnosis of UTI was made prior to the diagnosis of Pre eclampsia.

Operational definitions [11-13] Growth on urine examination - A growth on MacConkey agar visible by naked eye within 48h of incubation regardless of the colony count. Symptoms of urinary tract infection was diagnosed when a pregnant woman had increased frequency, burning and painful micturition on medical history. Asymptomatic bacteriuria was defined as colony count in a single culture is 10^5 or more and there are no symptoms of UTI. Similarly Symptomatic bacteriuria was labeled when any of the UTI symptom is present, and colony count is ≥ 105CFU/ml .Urinary tract infection is diagnosed when asymptomatic or symptomatic bacteriuria is present. Patients were diagnosed to have Preexisting chronic hypertension when a BP>140/90 mmHg before pregnancy or before 20 weeks' gestation. Gestational hypertension was diagnosed when systolic blood

pressures >140 mm Hg or diastolic >90 mm Hg at visits 2-4 with negative urinary protein test.

When gestational hypertension with positive urinary protein testing (>300 mg/24 h or protein/creatinine >0.20) were found they were diagnosed to have Preeclampsia –Mid-stream urine specimen - a specimen obtained from the middle part of urine flow.

Parity is the number of pregnancies reaching viability or beyond stage of abortion (<20 weeks/<500g). Gestational Age - is the age of the fetus estimated by computing from the first day of the last menstrual period (time that precedes conception) until the day of consultation.

History of UTI - is any history of infection pertaining to the urinary tract diagnosed by a physician. The data was entered and analyzed on SPSS version 19. Student 't' test was used for quantitative variables, while Logistic regression was used to see the risk of preeclampsia with UTI. Adjusted matched odds ratio with its corresponding 95% confidence interval was used and significance was taken at *P*-value less than 0.05. The included covariates were age, maternal body mass index, parity, current and past history of PE, pre-pregnancy diabetes mellitus, chronic hypertension, current and past gestational diabetes, educational status and parity.

Results

Table I shows clinical characteristic of the study participants with and without UTI during pregnancy. The mean age was 29.11±3.42 years, mean systolic blood pressure was 130.05±14.40, mean diastolic blood pressure was 84.79±8.72 and mean BMI was 28.98±5.13. Among 300 patients 20 (6.6%) patients were diagnosed with UTI and 280 (93.4%) did not show evidence of UTI during pregnancy. A total of 40 (13.3%) patients developed PE. A statistical significant difference (p<0.05) was noticed between the pregnant females with UTI and without UTI regarding age, BMI, current evidence of preeclampsia, chronic hypertension and current gestational diabetes. A same trend of significant difference (p<0.05) was also seen when the difference between female with and without UTI regarding illiteracy and gestational age was compared. However, the difference was found non-significant (p>0.05) when past history of gestational diabetes, past preeclampsia, pre-gestational diabetes mellitus and family history of hypertension and diabetes were compared between these females. A same trend of non-significance (p>0.05) was observed for socioeconomic condition, monthly income and employment of pregnant females and their husband.

Table II shows association between maternal UTI and pre-eclampsia. The patients with UTI during pregnancy showed an increased risk of developing PE compared to those without UTI in 25-35 years age (OR 10.8; 95% CI,1.17-100.44, p-0.035) and >35 years age (OR, 4.78; 95%CI, 1.52-14.75; p-0.007). After adjustment for potential confounders, UTI in pregnant females was significantly associated with increased odds for PE regarding body mass index (25 vs 30 - OR 1.25; 95% CI,3.22-39.19; p-0.000 and >30.0, OR 5.61; 95% CI,1.92-16.42; p-0.002), those with diagnosis of current preeclampsia (OR 0.322; 95% CI,0.116-0.896; p-0.030), and the females with chronic hypertension (OR 0.318; 95% CI,0.124-0.82, p-0.018). A same trend of statistically significant risk of developing PE was noticed in nulliparous female after diagnosis of UTI during pregnancy (OR 4.058; 95% CI,1.32-12.44; p-0.014), females with current gestational diabetes (OR 0.231; 95% CI,0.076-0.70, p-0.010) and in illiterate females compared to those without UTI (OR 0.064; 95% CI,0.023-0.18; p-0.000). The UTI during pregnancy showed 3-4 fold raised odds of developing PE during 2nd trimester (OR, 2.11; 95% CI, 0.651-6.83; p-0.047) and 3rd trimester (OR 4.12; 95% CI,1.28-13.19; p-0.017) after adjustment for confounders compared to those without UTI.

Table I. Clinical characteristic of the study participants with and without UTI during pregnancy

Variables	Total N – 300	UTI n-20	No UTI n- 280	P value
Mean Age	29.11±3.42	29.55±2.87	29.08±3.46	0.556
Mean Systolic blood pressure	130.05±14.40	134.40± 14.97	129.74± 14.34	0.163
Mean Diastolic blood pressure	84.79±8.72	87.85±9.24	84.57±8.60	0.106
BMI	28.98±5.13	29.75±4.91	28.92±5.15	0.485
Age				0.000
15-25 years	38 (12.7%)	01 (5%)	37 (13.2%)	
25-35 yrs	240 (80%)	14 (70%)	226 (80.7%)	
>35 yrs	22 (7.3%)	05 (25%)	17 (6.1%)	
BMI				0.000
Normal (18.5-24.9)	139 (46.3%)	04 (20%)	135 (48.2%)	
Overweight (25-29.9)	125 (41.7%)	07 (35%)	118 (42.2%)	
Obese (>30)	36 (12%)	09 (45%)	27 (9.6%)	
Current Preeclampsia	40 (13.3%)	06 (30%)	34 (12.1%)	0.036
Chronic Hypertension	57 (19%)	08 (40%)	49 (17.5%)	0.033

Current gestational diabetes	25 (8.3%)	05 (25%)	20 (7.1%)	0.017
Nulli-parity	145 (48.3%)	04 (20%)	141 (50.4%)	0.010
Gestational age 1st trimester 2nd trimester 3rd trimester	68 (22.7%) 129 (43%) 103 (34.3%)	04 (20%) 04 (20%) 12 (60)	64 (22.9%) 125 (44.6%) 91 (32.5%)	0.033
Education Illiterate	23 (77%)	09 (45%)	14 (5%)	0.000
Past gestational diabetes	39 (13%)	04 (20%)	35 (12.5%)	0.309
Past preeclampsia	28 (9.3%)	02 (10%)	26 (9.3%)	1.000
Pre-gestation diabetes mellitus	08 (2.7%)	01 (5%)	07 (2.5%)	0.428
F/H of hypertension	65 (21.7%)	05 (25%)	60 (21.4%)	0.779
F/H of diabetes mellitus	62 (20.7%)	03 (15%)	59 (21.1%)	0.775
Smoking	25 (8.3%)	02 (10%)	23 (8.2%)	0.677
Socio-economic Poor Middle class Rich	97 (32.3%) 144 (48%) 59 (19.7%)	08 (40%) 06 (30%) 06 (30%)	89 (31.8%) 138 (49.3%) 53 (18.9%)	0.233
Income 10,000 20,000 30,000	69 (23%) 139 (46.3%) 92 (30.7%)	07 (35%) 07 (35%) 06 (30%)	62 (22.1%) 132 (47.1) 86 (30.7%)	0.379
Wife employ	113 (37.7%)	07 (35%)	106 (37.9%)	0.884
Husband job Government Business Unemployed	82 (27.3%) 159 (53%) 59 (19.7%)	05 (25%) 13 (65%) 02 (10%)	77 (27.5%) 146 (52.1%) 57 (20.4%)	0.440

Discussion

Results of our study showed 6.6% of pregnant women with either symptomatic or asymptomatic bacteriuria. The results are in agreement with a number of studies which showed 5 -6% incidence of UTI among pregnant females,[14-16] while Subharwal et al [17] showed 25% pregnant females with UTI, the difference may be due to difference in socioeconomic status and educational level.

Our results showed significant association of UTI with the development of PE in the same pregnancy. The association was strongest when the UTI occurred in middle age groups and in second and third trimester. The results are in agreement with several studies which showed strong association between UTI and PE in older age group and pregnant females in their late trimester with a pooled OR of 1.57 (95% CI, 1.45-1.7); similarly a recent World Health Organization cohort showed an association between UTI and PE with an OR of 1.13 (95% CI, 1.03-1.24) in the developing countries. [18-19] A case-controlled study done by Caroline et al [20] showed similar results with an OR,1.22 (95% CI,1.03-1.45); while two nonrandomized clinical trials showed reduced incidence of PE (OR: 0.22, 95% CI: 0.17–0.30 and OR: 0.36, 95% CI: 0.20–0.64) after antibiotic treatment for bacteriuria in pregnant women than pregnant females with untreated bacteriuria.[20-21]

Jain V et al[22] described that asymptomatic bacteriuria in pregnant female showed 3.79 times increased risk of Preeclampsia compared to those without asymptomatic bacteriuria; however, difference regarding treatment of UTI between the two showed no significance.

The results are not consistent with a few studies which showed no relationship between UTI and PE. The difference may be due to difference in definition of UTI, the timing of the diagnoses, and the recognition of potential confounders. In our study, the definition of UTI ranged from complaints of urinary symptoms to asymptomatic bacteriuria and pyelonephritis. Some studies failed to clarify the timing of UTI diagnosis in relation to PE or they included those patients which showed UTI after PE.[23, 24]

The diagnosis of UTI before Pre eclampsia is necessary to confirm that infection is the pathway to Pre eclampsia. The patients with preexisting renal diseases limit effect of clinical variables for controlling multiple cofounders and covariates. [25]

The Pre eclampsia involves abnormal placentation and systemic inflammation. According to LaMarca et al [26] the inflammatory responses in patients with preeclampsia become exaggerated as compared to normal pregnancies. These inflammatory responses initiate and enhance atherosis of utero-placental arteries thus increasing the risk of Pre eclampsia. The same is done by infectious diseases that activate systemic inflammatory response and endothelial injury leading to placental hypoxia and utero-placental atherosis. [4, 25]

Table II: Multiple Logistic Regression showing association between maternal UTI and pre-eclampsia:							
Variables	Total N – 300	UTI n-20	No UTI n- 280	95% CI	Odds Ratio	Standard Error	p value
Age							
15-25 years	38	01	37	1.179-100.44			
25-35 yrs	240	14	226	1.528-14.755	10.882	1.134	0.035
>35 yrs	22	05	17		4.748	0.579	0.007
BMI							
Normal (18.5-24.9)	139	04	135				
Overweight (25-29.9)	125	07	118	3.22-39.19	1.250	0.637	0.000
Obese (>30)	36	09	27	1.92-16.42	5.619	0.547	0.002
Current Preeclampsia	40	06	34	0.116-0.896	0.322	0.521	0.030
Chronic Hypertension	57	08	49	0.124-0.820	0.318	0.483	0.018
Current gestational diabetes	25	05	20	0.076-0.700	0.231	0.566	0.010
Nulli-parity	145	04	141	1.323-12.44	4.058	0.572	0.014
Gestational age							
1st trimester	68	04	64				
2nd trimester	129	04	125	0.651-6.838	2.11	0.600	0.047
3rd trimester	103	12	91	1.287-13.19	4.12	0.594	0.017
Education Illiterate	23	09	14	0.023-0.181	0.064	0.527	0.000
Past gestational diabetes	39	04	35	0.631-4.054	0.571	0.587	0.341
Past preeclampsia	28	02	26	0.202-4.194	0.921	0.773	0.916
Pre-gestation diabetes mellitus	08	01	07	0.057-4.167	0.487	1.095	0.511
F/H of hypertension	65	05	60	0.286-2.342	0.818	0.537	0.708
F/H of diabetes mellitus	62	03	59	0.429-5.336	1.513	0.643	0.520
Smoking	25	02	23	0.176-3.690	0.805	0.776	0.781
Socio-economic							
Poor	97	08	89 (31.8%)				
Middle class	144	06	138 (49.3%)	0.414-3.82	1.259	0.567	0.684
Rich	59	06	53 (18.9%)	0.804-8.43	2.604	0.600	0.110
Income							
10,000	69	07	62 (22.1%)				
20,000	139	07	132 (47.1)	0.198-1.92	0.618	0.581	0.407
30,000	92	06	86 (30.7%)	0.428-4.04	0.316	0.573	0.632
Wife employ	113	07	106 (37.9%)	0.499-1.17	0.884	0.485	0.884

Our study had various characteristics, including a diverse patient population from all ages and ethnic groups. We had representatives from all of Pakistan's provinces. Additionally, the research included members of all main socioeconomic classes.

Limitations of the Study

1. Due to time and resource restrictions, the research sample was marginally on the small side.
2. We had considerable difficulties collecting samples due to the unique social fabric. In Pakistan, the legal age of marriage is more than 18 years. A few candidates may have withheld their true ages due to legal ramifications.
3. No long-term follow-up of the patients was performed, which would have strengthened our research design.

Conclusion

Presence of UTI during pregnancy is strongly associated with increased risk of preeclampsia especially in obese, illiterate pregnant female, in their third trimester, supporting that the risk of PE is increased by an increased maternal inflammatory burden. However, to find out the exact mechanism of this association and its management, further research is still required to decrease the risk of preeclampsia

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