Immunoligical study among pregnant and non-pregnant women with symptomatic and asymptomatic Urinary tract infection in Kirkuk city-Iraq

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الخلاصة:

أجريت هذه الدراسة كمحاوله لـ: 1- تحديد مدى انتشار ظاهرة التهابات المجاري البولية اللاعراضيه في النساء الحوامل في مدينة كركوك, والتعرف على العوامل المرضية البكتيرية المسببة لها ودراسة حساسيتها للمضادات الحياتية. 2- معرفة دور الاستجابة المناعية الخلطية لدى النساء (الحوامل وغير الحوامل) المصابات بالتهابات المجاري البولية الاعراضيه واللاعراضيه من خلال قياس مستوى الكلوبيلينات IgG, IgA, IgM ومكونات المتمم (C3, C4) في مصل المرضى باستخدام تقنية انتشار المناعي الشعاعي المنفرد Single redial immunodiffusion وتم مقارنتهم مع الأصحاء.

أظهرت النتائج ان نسبة انتشار التهابات المجاري البولية اللاعراضيه لدى النساء الحوامل قد بلغت (10%) وكانت البكتريا E. coli المسبب الرئيسي لالتهابات المجاري البولية الاعراضيه واللاعراضيه في كل من النساء الحوامل وغير الحوامل, وأظهرت هذه البكتريا حساسيتها للمضادات الحياتية Ciprofloxacin و Ceftriaxone و Gentamycin.

فيما يتعلق بنتائج الدراسة المناعية, تمكنت دراستنا من اكتشاف الأضداد ومكونات المتمم في مصل المرضى والأصحاء وكانت النتائج كالآتي:- أظهرت كلا من الحوامل وغير الحوامل المصابات بالتهابات المجاري البولية الاعراضيه ارتفاع معنوي في مستوى كل من IgG و IgA في حين لم يلاحظ وجود اختلافات معنوية في مستوى IgM في مجاميع المرضى مقارنة بالأصحاء. اختلافات معنوية بين المرضى الحوامل وغير الحوامل لوحظت فقط في مستوىIgM. نقصان معنوي في مستوى C4 ظهرت في المرضى الحوامل مقارنة بالحوامل الأصحاء, في حين لم يلاحظ وجود أي اختلافات معنوية بين المرضى الحوامل وغير الحوامل في مستوى كل من C3 و C4.

مقارنة بالحالات العرضية لالتهابات المجاري البوليه في النساء الحوامل أظهرت الحالات اللااعراضيه مستويات عاليه من كل من IgG و IgM و C3 و C4, بينما وجدت IgA عاليه في الحالات العرضية. الاستنتاج: استنتجت الدراسة الحالية ان التهابات المجاري البوليه والحمل قد تغير من مختلف مظاهر المناعة الخلطية, لذا فان تواجدهما معا ربما يؤثر احدهما على الآخر.

Abstract

In this study an attempt was carried out to: estimate the: 1- prevalence of asymptomatic bacteriuria in pregnancy, its causative agents and their sensitivity pattern in Kirkuk city.2- Role of humoral immune response in women with symptomatic and a symptomatic urinary tract infection through the measuring of IgG,IgA, IgM,C_3 and C_4 levels in urine and serum of patients and comparing them with corresponding levels of healthy control groups.

The results showed that the prevalence of asymptomatic (UTI) in pregnancy was (10%). *E.coli* was the commonest causative bacteria in both pregnant and non- pregnant with symptomatic and a symptomatic (UTI).The antibiotic ciprofloxacin, ceftriaxone and gentamicin was the most effective

Regarding the immunological study: pregnant and non-pregnant subjects with symptomatic (UTI) showed significant increase in the level of IgG and IgA and no significant differences was noticed in the level of IgM as compared with control group. Significant differences between pregnant and non-pregnant subjects with symptomatic (UTI) was observed only in the level of IgM.

Pregnant subjects with symptomatic (UTI) showed a significant decrease in the level of C_4 as compared to control group, any significant differences were not observed between pregnant and non-pregnant in the level of C_3 and C_4.

Compared to symptomatic (UTI) in pregnant subject asymptomatic (UTI) subjects recorded the highest serum levels of IgG,IgM, C_3andC_4, while the highest values of IgA was found in symptomatic UTI.

Conclusion:- Bacteriuria or pregnancy changes different aspects of humoral immunity, thus the co-existence of pregnancy and bacteriuria may influence each other.

Introduction:-

Urinary tract infection (UTIs) are the most frequently seen disease within the urinary system [1]. Acute UTI can be either symptomatic(sym) or asymptomatic (asym), sym UTI is defined as asignificant bacteria in urine with presence of a costallation of symptoms such as dysuria

(painful urination), increased urinary frequency and urgency[2]. Asym UTI is acondition characterized by the presence of bacteria in urine without classical symptoms or signs attributable to the urinary tract and the diagnosis of Asym bacteriuria is appropriate only if the same species is present in quantities of at least 10^5 cfu/ml of urine in at least two consecutive voided specimens [3],[4],[5]. UTIs account for approximately 10% of office visits by women and 15% of women will have UTI at some time during their life, and up to 40% of them will experience asym UTI and many will have recurrent episodes [5]. Asym bacteriuria in pregnancy may lead to less favorable pregnancy outcomes and complication like preterm delivery, low birth weight and anemia of pregnancy [6],[7],[8],[9], so, they must always be screend and treated [10].

UTIs are mostly of the ascending type and therefore, the first defense line to the pathogen encounters is the local immune system on the mucosa of the urinary tract, especially urinary immunoglobins (secretory IgA), it has been shown that local immunoglobins can bind to the infecting bacteria and prevent their adherence to mucosal surfaces [11], [12], [13]. Studies with *Neisseria gonorrheae* and oral *Streptococci* have demonstrated that local antibody can prevent bacterial adherence to epithelial cell surfaces [14].

The aim of the present study is to measure serum immunoglobulins and complement in pregnant women with sym UTI and compared the results with non-pregnant subjects with and without sym UTI to elucidate the humoral immunological basis of female genital tract.

Materials and Methods:-

Study population:-

The patient group consisted of 60 women (30 pregnant and 30 non pregnant) selected randomly from Kirkuk public health center during October 2009 and April 2010.The mean age of the patients was 35.6, with a range of 21 to 55 years. Thirty healthy women (15 pregnant and 15 non-pregnant) volunteers with no history of UTI, were selected as controls. The mean age of the control subjects was 36.7 with a range of 19-50 years.

Bacteriological tests:-

Clean catch mid stream urine sample from patients was collected in a sterile container and processed within one hour of collection. Samples were cultured on blood and MacConkey agar plates and incubated at 37^{o}C for 24 hours [15], [5].

Bacteriuria was defined as presence of 10^5cfu/ml of urine, suspected colonies were identified by Ap120E system [16]. The individuals who did not show symptoms of UTI but whose urine culture

yielded the growth count of > 10^5cfu/ml in two consecutive samples were considered to have Asym UTI [3]. Antibiotic susceptibility test was performed according to clinical and laboratory standards Institute recommendations [17], using the following antibiotics:- Amikacin, Vancomycin, Norfloxacin, Ampicillin, Ceftriaxone, Ciprofloxacin, Gentamycin, Cefixime, Kflene, Nalidixic acid, Tetracycline, Chloramphenicol.

Assay of immunoglobulins and complements in serum:-

Venous blood samples were collected from patients on the few days of infection. Sera were separated and stored at deep freeze until analysis. serum levels of immunoglobins (IgG, IgA, IgM) and complementes (C_3, C_4) were estimated by using commercially available immunokits of biomerieux, france, based on the principle of single radial immunodiffusion [18], [19].

After placing 5*ul* of serum samples on each well on plates (IgG, IgA, IgM) as well as C_3 and C_4, the plates were incubated for 72 hours at room temperature. At the end of this period, the diameter of precipitation was measured and converted mg/dl units using table supplied by the manufacturer.

Statisticall analysis:-

The statistical significance of the results were evaluated by student's t-test with significant results at $P<0.05$.

Results and discussion:-

Out of 30 pregnant women, 15 (50%) had UTI, 12(40%) women showed sym UTI, while 3(10%) of them showed asym UTI.In the 30 non-pregnant women, 16(53.3%) showed symUTI, while no one showed asymUTI table (1).

Table (1): prevalence of UTI among pregnant and non-pregnant women.

subject	Total number	Number of positive UTI %	Type of infection	
			Sym UTI No (%)	Asym UTI No(%)
pregnant	30	15(50)	12(40)	3(10)
Non-pregnant	30	16(53.3)	16(53.3)	0(0)

The predominant infecting organisms isolated from the urine samples of pregnant and non- pregnant women with sym and asym UTI was *Escherichia coli* except one case of non- pregnant with sym UTI showed the growth of *Klebsiella spp.*table (2). Regarding antibiotics, Ciprofloxacin, Ceftriaxone and Gentamicin were sensitive to the all

isolated organisms causing sym and asym UTI. The relationship between the incidence of UTI (sym and asym) and pregnancy has always been a subject of interest. In our study the incidence of symptomatic UTI was significantly high among both pregnant and non- pregnant women (50%) and (53.3%) respectively. This high rate may be due to the fact that the majority of the women in our study belonged to the lower and middle socioeconomic, this is supported by other studies which they found that the UTI were higher among pregnant and non-pregnant women of poor socioeconomic status [4],[8],[20].

Table(2): Organisms isolated from the urine samples of pregnant and non pregnant women with sym and Asym UTI.

Subjects	E.coli	Klebsiella
Pregnant Sym Asym	 12 3	 non non
Non-pregnant Sym Asym	 15 non	 1 Non

The results of our study detected asym bacteriuria and the prevalence of it in pregnant women was (10%). Ullah *et al* [21] conducted a similar study in Bangladesh and reported that frequency of asym UTI was (12%). The prevalence of asym bacteriuria was (28.1) (14.5%) and (29.1%) of pregnant mothers in studies from Baghdad city in Iraq [20], Rajshahi city in Bangladesh [9] and Tehran city in Iran [10]. Tadesse *et al*[22] reported (9.8%) in Ethiopia. Perera [23] demonstrated that the physiological changes, both hormonal and mechanical that occur in the urogenital tract during pregnancy increase the potential for colonization by pathogenic bacteria. So screening in pregnancy for asymptomatic UTI and treatment with antibiotics of positive cases is widely recommended, because the complication associated with AsymUTI during pregnancy not only result in increases morbidity of expectant mothers but also have detrimental effects on the fetus like preterm labour and low-birth weight [8], [24], [25].

The predominant organism isolated from urine of women with different types of UTI in this study was *E. coli* and this agreed with the results of previous reports [5], [26], [27], [28]. This result indicated that the pattern of isolated pathogens causing UTI (sym and asym) during pregnancy are the same as those found in non-pregnant patients. This is supported by other studies [21], [23]. The faecal flora serves as the source of *E.coli* which colonizes the vaginal introitus and urethra prior to infection of the bladder[29]. Like other studies [30], [31] the findings of this study also indicated that comparatively less frequently used antibiotics, like Ciprofloxacin and Gentamycin were highly effective against urinary pathogens.

Immunological study:-

The serum from patients with sym and asym UTI were tested for the presence of immunoglobulins (IgA, IgG, IgM) and complement components (C_3, C_4) by immunodiffusion plates and the results showed:-

Level of serum components (IgA,IgG,IgM,C_3 and C_4) in pregnant and non pregnant subjects with sym UTI and control subjects without sym UTI are present in (table 3) expressed as mean ± SD. Results show that the serum levels of the three immunoglobulins were higher in pregnant subjects with sym UTI than in pregnant without sym UTI and this was statistically significant with only IgA and IgG but not with IgM. The same results were observed in non-pregnant subjects with Sym UTI in comparison to those without sym UTI. The high serum values of IgG, IgM recorded in pregnant subjects with Sym UTI compared to non-pregnant subjects with sym UTI, but were only statistically significant with IgM but not with IgG, while the non-pregnant subjects with sym UTI recorded the highest values for IgA, this high serum IgA was statistically not significant when compared with those found in pregnant subjects with sym UTI.

In elements of complement system C_3 and C_4, there is a significant decrease in level of C_4 in pregnant subjects with sym UTI in comparison to subjects without sym UTI and any significant result is not observed in level of C_3 and C_4 between pregnant and non-pregnant with sym bacteriuria. The present study showed elevated levels of IgG in sym UTI subjects, both pregnant and non-pregnant women, others have documented similar observation in their studies about protective immunity against parasite [32],[33],[34] and its level has been shown to correlate with the intensity of infection [35]. The protective role of IgG against pathogens could explain the significantly high serum IgG found in symUTI subjects in the present study, since it is the immunoglobulin secreted during secondary immune response.

Raised values of serum IgM level as recorded in subjects with sym UTI, have been similarly observed by other workers [34]. The continuous release of particulate antigens from pathogenic organisms may induce a greater IgM response and this may explain the high IgM value in pregnant subjects with Sym UTI, this result was supported by [36], [34].

The mean serum IgA was raised in both pregnant and non-pregnant subjects with sym UTI, this finding was consistent with the findings of other study [37]. Some investigators have reported anon-significant changes in IgA in pregnancy [38], while others have observed low values [39]. Recent studies have suggested that normal female genital tract secretes low IgA[40].

The increase in the element of complements can be explaind by a variety of explanations, one interesting mechanism depends on the resultes of Miletic *et al*.[41], they noticed that intravenous immunoglobulins, composed principally of polyclonal IgG prevent

complement attack by inhibiting C_3 and C_4 on the target cells and tissues. Therefore, the increase in serum IgG in our patients may be the soures of the noticed increase in the complements in our patients groups.

In our studies we observed three cases of asym UTI in pregnant subjects only. Compared to sym UTI, asym UTI subjects recorded the highest serum levels of IgG and IgM, while the highest values of IgA was found in sym UTI subjects (table 4). This result agreed with other studies [17],[26]. Also asym UTI subjects recorded a high level of complement component (C_3, C_4) as compared to sym UTI subjects (table 4).

Maternal immunity is modified during pregnancy to favour implantation and development of the embryo. Research suggests that the immune response is modulated from a predominantly cell mediated response to a predominantly humoral immune response [42]. Humoral responses are less efficient as cell surface major histocompatibility receptors are not necessarily recognized during the response, therefore this may result in less efficient recognition of bacterial cell surface proteins which prevents removal of bacteria facilitating colonization and infection by bacteria [23].

Table 3: Serum immunoglobulin values and complement component (Mean±SD) in pregnant women, non-pregnant women with or without sym UTI.

Parameter (mg/dl)	Subjects	Without UTI (control)	With UTI (patients)	P-value[a] t-test
IgA	Pregnant	106.56 ± 50.54	170.78 ± 44.66	0.0032 *
	Non-pregnant	129.12 ± 73.46	203.15 ± 74.76	0.0209*
			P-value[b] = 0.195 (Ns)	
IgG	Pregnant	732.95 ± 290.28	1235.26 ± 288.41	0.00032*
	Non-pregnant	837.75 ± 414.48	1198.3 ± 279.65	0.0086*
			P-value[b] = 0.735 (Ns)	
IgM	Pregnant	56.65 ± 29.96	113.35 ± 30.77	0.247 (Ns)
	Non-pregnant	71.1 ± 38.86	84.58 ± 31.37	0.378 (Ns)
			P-value[b] = 0.033*	
C_3	Pregnant	172.2 ± 44.39	181.28 ± 46.21	0.628 (Ns)
	Non-pregnant	156.05 ± 66.46	180.88 ± 58.84	0.305 (Ns)
			P-value[b] = 0.984 (Ns)	
C_4	Pregnant	32.11 ± 9.11	19.7 ± 12.40	0.016*
	Non-pregnant	27.65 ± 7.74	29.81 ± 19.47	0.719 (Ns)
			P-value[b] = 0.128 (Ns)	

a = statistical comparison between control & patients ; *P<0.05
b = statistical comparison between pregnant and non-pregnant with Sym UTI
Ns = not significant

Table 4:- Serum values of (IgG,IgA, IgM, C_3, C_4) (Mean ± S.D) in pregnant women with sym UTI and asym UTI

Parameter (mg/dl)	Pregnant women with asym UTI	Pregnant women with sym UTI	P-value
IgA	156.066 ± 52.930	170.9 ± 44.66	0.356 (Ns)
IgG	1831.933 ± 846.296	1235.26 ± 288.41	0.1347 (Ns)
IgM	123.7 ± 62.330	113.35 ± 30.77	0.385 (Ns)
C_3	190.25 ± 55.667	181.28 ± 46.21	0.085 (Ns)
C_4	26.566 ± 10.60	19.7 ± 12.40	0.844 (Ns)

(Ns) = not significant; P>0.05

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