TURKISH REPUBLIC OF NORTH CYPRUS
NEAR EAST UNIVERSITY
HEALTH SCIENCE INSTITUTE

PREVALENCE, ANTIMICROBIAL SUSCEPTIBILITY PATTERN OF *E. COLI* ISOLATES, AND ASSOCIATED RISK FACTORS OF URINARY TRACT INFECTIONS AMONG PREGNANT WOMEN IN ZAKHO CITY, KURDISTAN REGION, IRAQ.

Prepared by:
ILAF JASIM MOHAMMED MOHAMMED

MASTER OF SCIENCE THESIS

MEDICAL MICROBIOLOGY AND CLINICAL MICROBIOLOGY PROGRAM

SUPERVISOR: Prof. Dr. Kaya Süer

CO-ADVISOR: Asst Prof. Dr. Ibrahim A. Naqid

NICOSIA
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DEDICATION

To the greatest prophet Mohammed (Pace be upon him), to the department of Medical and Clinical Microbiology to Prof. Dr.Kaya Süer. To Asst. prof. Dr.Ibrahim A. Naqid, to my father's pure soul to the biggest supporter to me my Mother, Grandfather and Grandmother the greatest example of love faithfulness, and patience, to my life partner and the endless love Sihad to my brothers and sisters and to my relative’s uncle and aunts with love and respect and love to all friends…………......

Who gave me a hand to complete this project and finally, to all those who share even a word Thanks to all of you.

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APPROVAL

This thesis was submitted to the Institute of Health Sciences at Near East University in partial fulfillment of the requirement for the dissertation of Master of Science in Medical Biology and Genetics.

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ABSTRACT

Background: *Escherichia coli (E. coli)* is a major cause of both community-acquired and nosocomial infections. As a result, this bacterium is clinically important and may be isolated from a variety of clinical specimens. Pregnancy causes anatomical, functional, and physiological changes in the urinary system, which frequently results in bacteria climbing into the urinary bladder and causing urinary tract infections (UTIs). Pregnant women's UTIs, especially *E. coli*, continue to be a clinical concern and a major issue for doctors. Pregnant women have a greater rate of UTIs than other healthy women in the general community. UTIs, both symptomatic and asymptomatic, are common in pregnant women and are linked to negative outcomes for the mother, fetus, and newborn. The incidence of bacteriuria increases through pregnancy stages due to major changes in the urinary tract and immune system, posing risk factors to both the mother and the fetus. The risk of urinary tract infection in pregnant women is increased by parity, increasing age, sickle cell anemia, diabetes, urinary tract infection, and a history of UTI. In most situations, Bacterial infections such as *E.coli* are the most common cause of UTIs, particularly gastrointestinal pathogens, that infect the urethral meatus by contaminating the region around the rectum and spreading to the bladder, are the most prevalent cause of UTIs in most cases.

Approximately the common pathogenic causes of urinary tract infection are "*Escherichia coli*, *Staphylococcus spp.*, *Streptococcus spp.*, *Proteus spp.*, *Klebsiella spp. Corynebacterium*, *Neisseria*, *and Pseudomonas. spp*. The severity of a urinary tract infection is determined by the bacteria's virulence and the host's susceptibility. The most effective antibiotics for treating the majority of urinary tract infections include penicillin, amoxicillin, norfloxacin, and cefoxitin.

The Aims of the Study: The identification and isolation of *E. coli* causing UTIs among pregnant women in Zakho city, Kurdistan, Region, Iraq. Secondly, to evaluate the risk factors associated with UTI and pattern of urinary complaints during pregnancy and finally the investigation of the antibiotic susceptibility profile of *E. coli* isolates obtained from urine samples and determine the antibiotic resistance pattern.

Material and Method: Pregnant women were the participants of this study, who attended Maternity Hospital determined by treating physicians in Zakho City, Kurdistan Region, Iraq. From October 2020 to January 2021, In this study, 196 patients were enrolled, Antimicrobial Susceptibility Pattern of *E. coli* Isolates, and Associated Risk Factors of Urinary Tract Infections in Pregnant Women were studied to determine the prevalence of *E. coli* in pregnant women., After sample collection urine analysis is done , followed by culturing the sample on MacConkey agar the media incubated for the whole night ,In the next day the growing bacteria undergo several biochemical test to insuring that the growing bacteria is *E.coli* , Such as indole test, simmon citrate test , methyl red and Voges Proskauer in addition to the using of Eosin methylene blue (EMB) media as a differential media.

Result: 196 urine samples, 34 (17.34%) was culture positive for *E. coli* infection in pregnant women, On the other hand the prevalence of *E. coli* infection in non-pregnant women was 17 (34.69%). The highest prevalence rate of infection was recorded in non-pregnant when compared to pregnant women with statistically significant differences ($P<0.032$) using Chi-Square (Fisher exact test). All of the196 sample examined for several risk factors associated with the UTIs the result showed that diabetes mellitus ($p<0.28$), history of UTI infection ($p<0.05$) and present of symptoms during infection ($p<0.001$) showed statistically significant association with *E. coli* UTI. The antibiotics sensitivity pattern in urine samples of pregnant women showed that *E. coli* isolates were highly sensitive to Nitrofurantoin (82.4%), Meropenem (79.4%) and around 67.6% for both Amikacin and Ciprofloxacin. On the other hand, in non-pregnant women *E. coli* isolates from urine samples were highly sensitive to Amikacin (100%), followed by Meropenem (94.1%) and Gentamicin (82.4%).

Conclusion: *E.coli* is the most common causes of UTIs infection among pregnant women followed by *Klebsiella spp*., The infection among non-pregnant women is higher than pregnant women may be due to pregnant women take care of themselves and eat healthy food during their pregnancy, also the prevalence of *E.coli* during pregnancy in our study is lower than in previous studies conducted in the same region, which might be attributed to differences in the environment, social behaviors, personal cleanliness standards, or the research subjects' low economic status. There is many risks factor that increase the rate of infection within UTIs, in the current study diabetes mellitus, past history of UTI infection, abortion and present of symptoms during infection were significantly related to UTI in pregnant women. Antibiotics that are most effective against E.coli isolates from urine samples among pregnant women were found to be Nitrofurantoin, Meropenem, and Amikacin, as well as Ciprofloxacin. Cefixime, ceftriaxone, and doxycycline sensitivity was lower in *E.coli* isolates. As a result, it is recommended that a physician conduct an antibiotic susceptibility test to ensure that the most effective antibiotic is prescribed and used.

Keywords: *E.coli*, pregnancy, urinary tract infection.

ÖZ

Giriş: *Escherichia coli (E. coli*), hem toplum kökenli hem de hastane enfeksiyonlarının önemli bir nedenidir. Sonuç olarak, bu bakteri klinik olarak önemlidir ve çeşitli klinik örneklerden izole edilebilir. Hamilelik, üriner sistemde anatomik, fonksiyonel ve fizyolojik değişikliklere neden olur ve bu da sıklıkla bakterilerin mesaneye tırmanmasına ve idrar yolu enfeksiyonlarına (İYE) neden olur. Hamile kadınların İYE'leri, özellikle *E. coli*, doktorlar için klinik bir endişe ve önemli bir sorun olmaya devam ediyor. Gebe kadınlar, genel toplumdaki diğer sağlıklı kadınlardan daha yüksek bir İYE oranına sahiptir. Hem semptomatik hem de asemptomatik olan İYE'ler hamile kadınlarda yaygındır ve anne, fetüs ve yenidoğan için olumsuz sonuçlarla bağlantılıdır. Bakteriüri insidansı, idrar yolu ve bağışıklık sistemindeki büyük değişiklikler nedeniyle hamilelik evrelerinde artar ve hem anne hem de fetus için risk faktörleri oluşturur. Gebe kadınlarda idrar yolu enfeksiyonu riski, parite, artan yaş, orak hücreli anemi, diyabet, idrar yolu enfeksiyonu ve İYE öyküsü ile artar. Çoğu durumda, *E.coli* gibi bakteriyel enfeksiyonlar, İYE'lerin en yaygın nedenidir, özellikle gastrointestinal patojenler, rektum etrafındaki bölgeyi kontamine ederek ve mesaneye yayılarak üretral meatusu enfekte eden, çoğu durumda İYE'lerin en yaygın nedenidir. vakalar.

İdrar yolu enfeksiyonunun yaklaşık olarak yaygın patojenik nedenleri "*Escherichia coli, Staphylococcus spp., Streptococcus spp., Proteus spp., Klebsiella spp. Corynebacterium, Neisseria* ve *Pseudomonas. spp.* Bir idrar yolu enfeksiyonunun şiddeti, bakterinin virülansı ve konağın duyarlılığı ile belirlenir. İdrar yolu enfeksiyonlarının çoğunu tedavi etmek için en etkili antibiyotikler arasında penisilin, amoksisilin, norfloksasin ve sefoksitin bulunur

Çalışmanın Amacı: Irak, Kürdistan Bölgesi, Zakho şehrinde gebe kadınlarda İYE'ye neden olan E. coli'nin tanımlanması ve izolasyonu. İkinci olarak, gebelikte idrar yolu şikayetleri ve İYE ile ilişkili risk faktörlerinin değerlendirilmesi ve son olarak idrar örneklerinden elde edilen *E. coli* izolatlarının antibiyotik duyarlılık profilinin araştırılması ve antibiyotik direnç paterninin belirlenmesidir.

Gereç ve Yöntem: Bu çalışmanın katılımcıları, Irak Kürdistan Bölgesi, Zakho Şehrinde tedavi gören doktorlar tarafından belirlenen Doğumevine başvuran gebelerdir. Ekim 2020'den Ocak 2021'e kadar, Bu çalışmaya 196 hasta alındı, *E. coli* İzolatlarının Antimikrobiyal Duyarlılık Modeli ve Gebe Kadınlarda İdrar Yolu Enfeksiyonlarının İlişkili Risk Faktörleri, hamile kadınlarda *E. coli* prevalansını belirlemek için incelendi. Numune toplama idrar analizi yapıldıktan sonra, numunenin MacConkey agar üzerinde kültürlenmesi ardından, ortam bütün gece inkübe edilir, Ertesi gün büyüyen bakteriler, büyüyen bakterilerin *E.coli* olduğundan emin olmak için indol gibi birkaç biyokimyasal teste tabi tutulur. diferansiyel ortam olarak Eosin metilen mavisi (EMB) ortamının kullanımına ek olarak test, simmon sitrat testi, metil kırmızısı ve Voges Proskauer.

Sonuç: 196 idrar örneğinde 34'ü (%17.34) gebelerde *E. coli* enfeksiyonu için kültür pozitifti, Öte yandan gebe olmayan kadınlarda *E. coli* enfeksiyonu prevalansı 17 (%34.69) idi. En yüksek enfeksiyon prevalansı, Ki-Kare (Fisher kesin testi) kullanılarak istatistiksel olarak anlamlı farklarla ($P<0.032$) hamile kadınlarla karşılaştırıldığında hamile olmayanlarda kaydedilmiştir. İYE ile ilişkili çeşitli risk faktörleri için incelenen 196 numunenin tümü, sonuç, diabetes mellitusun ($p<0.28$), İYE enfeksiyonu öyküsünün ($p<0.05$) ve enfeksiyon sırasında semptomların varlığının ($p<0.001$) istatistiksel olarak anlamlı ilişki gösterdiğini gösterdi. *E. coli* İYE. Gebe kadınların idrar örneklerindeki antibiyotik duyarlılık paterni, *E. coli* izolatlarının Nitrofurantoin'e (%82.4), Meropenem'e (%79.4) ve hem Amikasin hem de Siprofloksasin için yaklaşık %67.6'ya duyarlı olduğunu göstermiştir. Öte yandan, hamile olmayan kadınlarda idrar örneklerinden elde edilen *E. coli* izolatları Amikasin'e (%100) oldukça duyarlıydı, bunu Meropenem (%94.1) ve Gentamisin (%82.4) izledi.

Sonuçlar: *E.coli*, hamilelerde İYE enfeksiyonunun en sık nedenidir ve bunu *Klebsiella spp*. takip eder, Gebe olmayan kadınlarda enfeksiyonun hamilelere göre daha yüksek olması hamilelerin kendilerine bakmaları ve sağlıklı beslenmeleri nedeniyle olabilir. Ayrıca çalışmamızda gebelik sırasında *E.coli* prevalansı aynı bölgede yapılan önceki çalışmalardan daha düşüktür, bu durum çevre, sosyal davranışlar, kişisel temizlik standartları veya araştırmadaki farklılıklara bağlanabilir. deneklerin düşük ekonomik durumu. İYE'lerde enfeksiyon oranını artıran birçok risk faktörü vardır, mevcut çalışmada diyabetes mellitus, geçmiş İYE enfeksiyonu öyküsü, düşük ve enfeksiyon sırasında semptomların varlığı, gebe kadınlarda İYE ile anlamlı olarak ilişkiliydi. Gebe kadınlarda idrar örneklerinden *E.coli* izolatlarına karşı en etkili antibiyotiklerin Nitrofurantoin, Meropenem ve Amikasin ile Siprofloksasin olduğu bulundu. *E.coli* izolatlarında sefiksim, seftriakson ve doksisiklin duyarlılığı daha düşüktü. Sonuç olarak, en etkili antibiyotiğin reçete edildiğinden ve kullanıldığından emin olmak için bir doktorun antibiyotik duyarlılık testi yapması önerilir.

Anahtar Kelimeler: *E.coli*, gebelik, idrar yolu enfeksiyonu.

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LIST OF ABBREVIATION

UTI: Urinary tract infection

E.coli: *Escherichia coli*

UPEC: Uropathogenic *Escherichia coli*

ABU: Asymptomatic bacteriuria

LAP: lower abdominal pain

EPEC: Enteropathogenic *E. coli*

EHEC: Enterohemorrhagic *E. coli*

EIEC: Enteroinvasive *E. coli*

DAEC: Diffusely adherent E. coli

GBS: Group B Streptococcus

LPS: Lipopolysaccharide

OMPs: Outer-membrane proteins

NTD: N-terminal domain

HlyA: The lipoprotein-haemolysin

iNOS: Inducible nitric-oxide-synthase

SAT: Secreted autotransporter toxin

CDT: Cytolethal distending toxin

TIR: Toll/interleukin receptor

AR: Antibiotic resistance

NA: Nalidixic acid

CRO: Ceftriaxone

AK: Amikacin

CN: Gentamycin

F: Nitrofurantoin

CIP: Ciprofloxacin

DO: Doxycycline

CTX: Cefotaxime

CFM: Cefixime

MEM: Meropenem

EMB: Eosin Methylene Blue

VP: Voges Proskauer

CHAPTER ONE

1. INTRODUCTION

1.1. General Information of Urinary Tract Infection

The inflammatory conditions of the urinary system induced by abnormal pathogen growth are known as urinary tract infections (UTIs). UTIs are a common infection among males and females, but the occurrence among females is very high because of their Psychology. In simple terms, it's an infection that all women will suffer at some point during their lives, especially during pregnancy. UTIs are considered as a major source of severe bacterial infections especially in children and women. The upper UTIs which involve (kidney) and lower which involve (bladder, urethra, prostate) of the urinary system. The infection termed for the part of the body that is diseased as (phylonephritis) in the case of kidney infection, (urethritis) when urethra infected, and (cystitis) when bladder infected (Demili et al., 2012; Parveen et al., 2011). The presence of UTIs caused by a virus or fungus is considered to be a rare occurrence, the infection looks to be benign at first, but the patient develops a number of symptoms as the stage develops, and in extreme circumstances, the infection can lead to death. According to surveys, UTI is a common form of bacterial infection (Parveen et al., 2011; Demili et al., 2012;). The infection is typically caused by the invasion (colonization) of the urinary system by bacteria, including the upper urinary tract and lower urinary tract. Under certain conditions, microorganisms can enter the bloodstream. The entire urinary system, composed of the urinary tract sections it is at the risk when any portion of the urinary tract may be affected by bacteria. Bacterial pathogens must attach to host cells, colonize tissues, and in certain circumstances enter cells in order to initiate infection which is followed by intracellular growth, propagation to additional tissues or resistance (Khandelwal et al., 2009). The infection involves a wide range of clinical syndromes and disorders, each with its own epidemiology, etiology, and severity. In addition to the above causes, it differs of expressing local signs, frequency of recurrence, degree of harm produced, prevalence of complicating conditions, and risk of recurrence in addition to the preceding reasons the most common hospital-acquired infection is urinary tract infection which can be caused by a misdiagnosis (Smaill & Vazquez, 2015).

UTIs are identified scientifically as complicated and uncomplicated UTIs (Hooton et al., 2012) Usually, Uncomplicated UTIs are caused by bacterial infection that affect females more than males. Infections affecting the lower and upper urinary tracts such as cystitis and phylonephritis , result in bladder and kidney infections , affect individuals who are generally healthy and have no anatomical or neurological problems with their urinary tract These differentiated into lower UTIs (cystitis) and upper UTIs (pyelonephritis) (Hannan et al., 2012 ; Hooton et al., 2012). Cystitis is associated with many risk factors, including prior UTI, vaginal infection, sexual activity, ethnicity, genetic susceptibility, and diabetes (Hannan et al., 2012; Foxman, 2014). Uncomplicated UTIs rarely cause significant harm and can be removed spontaneously by the host immune system without the use of antibiotics. Men and women can have complicated UTIs at any time in their lives, and they have a high tendency for catastrophic results, which can lead to death in extreme cases. Also Urinary tract infections (UTIs) are defined as infections caused by conditions that harm the urinary system or compromise the host's defense such as urine obstruction, neurological disease-induced urinary retention, immunosuppression, renal failure, renal transplantation, breastfeeding, and the presence of invasive species such as calculi, indoor catheters, or other drainage equipment (Foxman, 2014). The risk of chronic and/or recurring infections is higher with this form of UTI, complicated UTIs require long-term therapy.

Asymptomatic bacteriuria is described as bacterial contamination of the urine in the absence of clinical sings (ABU). The majority of ABU patients do not need care, Urinary tract infections can cause short-term morbidity including dysuria, fever, and lower abdominal pain (LAP) as well as irreversible kidney scarring (Vasudevan, 2014). Approximately around 150 million people suffering from UTI worldwide each year, culminating in greater than 6 UTIs billions $ in direct health insurance (Stamm et al., 2001). UTI is historically viewed as an illness of women, 50%of whom will be affected during their lifetime. Within 6 months of a first bacterial cystitis episode over 25% of women tend to have chronic UTIs with some having 6 or more infections in the year after the original episode (McLellan & Hunstad, 2016). UTI is one of the most prevalent causes of morbidity in the common populace. Although bacteria are the most common cause of human infection, the significance of fungi and viruses should not be disregarded.

Gram-negative and Gram-positive bacteria, as well as fungi and viruses, can all cause UTIs. Uropathogenic *Escherichia coli* (UPEC) is the most prevalent cause of both uncomplicated and complicated UTIs. *E.coli* is a genus of bacteria present in the intestines of all mammals and many other animals. It is gram negative, facultative anaerobic, rod shaped bacteria. *E. coli* contributes for up to 80-85% of the infections, also known as the primary pathogen responsible for UTI and is followed by Staphylococcus saprophyticus, which accounts for 5-10 % (Flores- Mireles et al., 2015).

Klebsiella, Proteus, Enterobacter, and *Pseudomonas* are among the bacteria connected to UTIs in addition to the ones described above. Bacteria invade the bladder via the urethra, and blood and lymph may also induce the infection. Pathogens such as *E. coli* and *Staphylococcus saprophyticus* are linked to an uncomplicated acute infection obtained by the population, while *Klebsiella, Proteus* species, *Enterococcus, Enterobacte*r are known to be related with uncomplicated cystitis and phylonephritis that are sporadic (Flores-Mireles et al., 2015).

After anemia, UTIs are the second most prevalent problem among pregnant women and if not adequately treated they may have a detrimental effect on the health of the child or the pregnant woman (Franklin et al., 2000; Mittal et al., 2005). There are two types of UTI in pregnancy: symptomatic and asymptomatic. The most common cause of UTI during pregnancy is lower urinary tract involvement which leads to asymptomatic bacteriuria. Upper urinary tract involvement can result in symptomatic bacteriuria and is distinguished by acute pyelonephritis. According to reports, 17.9% of pregnant women have a symptomatic UTIs, while 13% suffer from asymptomatic type. The risk of infection with in UTI in pregnant women can be raised by increased age, number of pregnancies, asthma, previous history of UTI, recessive sickle cell anemia, number of intercourses a week, immunodeficiency and urinary tract anomalies (Alemu et al., 2012; Jido et al., 2014; Atacag et al.,2014). By the 6th week of pregnancy, there's a good possibility to get a UTI during pregnancy this chance peaks between 22 and 24 weeks Based on previous studies. Anatomical and physiological changes during pregnancy affect the course of bacteriuria, and increasing the susceptibility of pregnant women to UTI issues (Amiri et al., 2015).

Pregnancy and sexual intercourse are two other key factors that raise the incidence of UTI in women., glycosuria is occasioned by a physiological rise in plasma levels and a decrease in urine concentration in up to 70% of pregnant women which contributes to bacteria development in urine (Riziv et al., 2011). Intra - uterine restriction, pre-eclampsia, caesarean sections, and preterm deliveries are all linked to urinary tract infections during pregnancy (Mazor-Dray et al., 2009). Pregnant women with bacteriuria are more likely to deliver infants with low birth weight, increasing neonatal mortality and morbidity (Rahman et al., 2014). In non-pregnant women the uterus is also above the bladder, while the enlarged uterus affects the urinary tract in the pregnant women (Warren et al., 1999). UTIs are commonly caused by sexual activity because germs can be driven into the urethra during sexual contact and then rubbed up the urethra into the bladder after delivery (Ebie et al., 2001). When a diaphragm presses against the urethra, preventing it from completely emptying the bladder it might cause UTI. The tiny amount of urine left in the bladder allows germs to develop resulting in urinary infection (UTI) (Okonko et al., 2009). Up to 30% of pregnant women with ABU will acquire a symptomatic urinary tract infection (cystitis and pyelonephritis) during their pregnancy if they are not treated (Smaill & Vazquez, 2007; Fournié et al., 2008). Pr-eclampsia, sepsis, Anemia, and chronic kidney failure have also been related to acute pyelonephritis (Wing et al., 2014; Easter et al., 2016). In studies performed in developed countries, this prevalence can reach up to 30% (Assefa et al., 2008). Acute cystitis affects 1 to 2% of pregnant women (Alemu et al., 2002; Assefa et al., 2008; Hamdan et al., 2011; Marzieh et al., 2014). And acute pyelonephritis affects 0.5 to 2% of women during pregnancy (Wing et al., 2014; Société, 2015). One of the risk factors for bacteriuria is age. Bacteriuria is increasingly common in healthy women as they become older, rising from roughly 1% in girls aged 5 to 14 years to more than 20% in women over the age of 80. Another risk factor for bacteriuria or UTI was the presence of genitourinary defects (ureteral and bladder stones, kidney, tumors, vesico-ureteric reflux and, urethral strictures) (Société, 2015). Anemia, physical behavior, lower social backgrounds, and a history of UTI were all risk factors for UTI in pregnant women (Emiru et al., 2013; Société de, 2015). In some recent research, Ethnicity, gestational age, and multiparity were not established as risk factors for UTI during pregnancy (Awolude et al., 2010; Emiru et al., 2013).

1.2. History

Theodor Escherich, a German microbiologist and doctor, began researching the relevance of infant gut microorganisms in the digestive system and sickness in 1884.During this investigation, he found the fast-growing bacteria Bacterium coli commune, which is today known as Escherichia coli, the biological rock star (Escherich,1988 ;Shulman et al., 2007; Zimmer, 2008). He studied the development of intestinal flora in neonate meconium and breast-fed baby feces. The meconium and feces of five-day-old neonates contained bacterial strains with a wide phylogeny, which were strongly represented in adults. Under the microscope, he found "slender short rods" of 0.3-0.4 m in width and 1-5 m in length in the preparations of meconium and stool samples. These bacteria matured as white, non-liquidating col0onies on agar and blood serum plates, where he cultivated them. He also demonstrated that these bacteria cause milk to clotted over time as a result of acid formation, and that they have fermentative capacity. He also used the Gram staining technique, which demonstrated that all aniline dyes produce the same results. These bacteria take color rapidly, but lose it after being exposed to potassium iodide and alcohol. The motility and shape of Bacterium coli led to its classification as a genus. Classification of prokaryotes in their early stages. Ernst Haeckel's bacterial classification was later revised. Bacteria have been assigned to the Monera kingdom (Olusegun et al., 2012; Adamczyk & Reed, 2017). Later in 1895 Migula reclassified bacteria in the genus *Escherichia* and in 1919, the bacterium was renamed by Castellani and Chalmers after its discoverer and became Escherichia coli (Olusegun et al., 2012; Méric et al., 2016; Adamczyk & Reed, 2017). Formally, this genus belongs to the bacterial group. The “coliforms,” which are classified as “the enteric” are named after them. Family Enterobacteriaceae (Brenner et al., 2010; Adamczyk & Reed, 2017). In 1976, it was discovered that *E. coli* collected from the urine of individuals with acute symptomatic pyelonephritis attached to exfoliated uroepithelial cells in larger numbers than *E. coli* collected from the blood. Asymptomatic bacteriuria individual have had bacteria isolated from their urine. The flexibility with which *E. coli* can be found and worked with accounts for its elevated status and meteoric rise and in biology. Isolating hardy, non-pathogenic and adaptable strains that grow quickly on a range of nutrients can be done with almost any human. *E. coli* became a standard in microbiology lab collections as a result of these characteristics. As a result, when early twentieth century microbiologists were looking for a model organism, Bordet and Ciuca were chosen (1921), Werkman (1927), Wollman (1925), Wollman and Wollman (1937), and Bronfenbrenner and Korb (1925), Bronfenbrenner (1932) were among those who opted to work with *E. coli*. They published groundbreaking research on viruses, microbes, and genetics (Daegelen et al., 2009). When the molecular biology revolution began in the 1950s, *E.coli* had already established itself as the preferred bacterial model organism. As a result, it was the organism in which the most fundamental components of life, such as translation, genetic coding, replication, and translation, were discovered (Crick et al., 1961; Nirenberg et al., 1965; Judson, 1996) for a good explanation of early molecular biology and E. coli's importance in it.

1.3. Major Causes of Urinary Tract Infections

The entering of bacteria to the urinary tract from the nearby vagina and perineum is the main causes of UTI. Those areas hold a large number of bacteria that colonized it the urethral opening is situated here and the urinary tract is susceptible to infection. The pathogens that cause UTIs are mostly found in the enteric or vaginal flora in healthy women, the most prevalent cause of UTIs is *E. coli*. accounting for about 80% of infections (Stamm,2002; Gaspari et al., 2005), Enteric/diarrheal illness is caused by one subset of *E. coli*, while another subset causes extraintestinal illness, such as urinary tract infection (UTI). There are six distinct *E. coli* "pathotypes" that cause enteric/diarrheal illness. enteroaggregative *E. coli* (EAEC), Enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), enterohemorrhagic *E. coli* (EHEC), enteroinvasive *E. coli* (EIEC), and diffusely adherent *E. coli* (DAEC) have all helped us learn more about them. Each pathotypes infects humans and produces disease by utilizing various virulence factors with several different molecular pathways, resulting in distinct disease symptoms. (Kaber et al., 2004). *E coli* and other Enterobacteriaceae are the most common causes of UTIs. The remaining percentages are related to Gram-positive bacteria such as *Staphylococcus saprophyticus*, *Streptococcus agalactiae* (*group B Streptococcus*, GBS), *Enterococcus faecalis*, and other isolated species. The most common gram-positive uropahogenic bacteria include *Enterococcus facecalis* and *Staphylococcus saprophyticus (*Edwards et al., 2005).

1.4. Clinical Presentation

E. coli is the major cause of UTIs, evidence from earlier studies show that the frequency of *E.coli* varies by time and location. As a result, each region must obtain a single result regarding the prevalence of *E. coli* as a cause of urinary tract infections (Nesheret al., 2007). The symptoms of UTIs depends on host response, age, the type of the bacteria causing the infection and stage of the infection. In adults more specific sings such as increased frequency are present in lower UTI and pain during voiding. On the other hand, upper UTIs is associated with fever and wing pain (Foxman, 2002). UTIs with severe clinical manifestations (acute pyelonephritis, acute exacerbation of chronic pyelonephritis, urosepsis, acute prostatitis, and chronic prostatitis) necessitate hospitalization and immediate scientific antimicrobial therapy because there isn't enough time to wait for causative agents to be detected by urine culture Since it is the same risk factor for more acute clinical manifestations of disease it is particularly relevant in patients with diabetes mellitus and urosepsis. This approach to UTI care in the hospital is critical for avoiding advanced renal injury, extended treatment, accidents, recurrences, and chronicity (Nesheret al., 2007). In pregnant women 20% to 30% of them that suffering from (ABU) develop acute pyelonephritis. In modern countries screening ABU throughout pregnancy to reduce the risk of acute pyelonephritis is suggested (Smaill, 2001).

1.5. Uropathogenic E. Coli and Virulence Factors

UPEC known as the main causes of UTI in community (around 80–90%) (Foxman, 2014; Flores-Mireles et al., 2015).The method by which *E. coli* gained entrance to the urinary tract demonstrates a unique capacity to adapt to a different environment than the gut, they must alter their metabolism (Smith et al.,2008). *E. coli* that successfully invade the urinary system have unique characteristics that allow them to survive in the UTI environment. They rise against the flow of urine and then attach to the epithelial cell. These *E. coli* strains are known as uropathogenic *E.coli* (UPEC) is a subgroup of extra-intestinal pathogenic bacteria linked to (UTIs). (Dale and Woodford, 2015). UPEC identified four primary phylogroups based on the presence of genomic Pathogenicity Islands (PAI) (A, B1, B2, and D) (Bien et al., 2012). A large number of UPEC are members of group B2 and some areas of group D, while other commensal isolated belong to group B1 and A (Ewers et al., 2007). The strains that belongs to group B2 have very high virulence factor when compared to those of phylogenetic groups A and B1 (Moreno et al., 2008).

Virulence factor and apart from phylogenetic group result, there are pathogen and host factors that affect the ability of a given strain to cause UTIs (Moreno et al., 2008). UPEC hold flagella that simplify payment against urine flow, then the bacteria attach and invade the epithelial cell by using adhesive organ (fimbria) the bacteria have the ability to form intracellular bacterial communities by multiplying and quiescent intracellular reservoirs alternately, then distributing cellular function by secreting toxins, UPEC can use their virulence factor for protection against host defenses and this is a form of adaptations of UPEC. UPEC do not have unique collection of virulence factors, but they express genes that mediate adhesion, invasion, immune evasion, iron acquisition, and toxin releasing (Kaper et al., 2004).During UPEC colonization of the bladder they use a number of virulence factor that have the main role in the pathogenicity of UTI such as the cell surface component like lipopolysaccharide (LPS),pili , flagella, TonB-dependent iron uptake receptors, polysaccharide capsule, including siderophore receptors ,outer membrane vesicles, outer-membrane proteins (OMPs), non-pilus adhesins, as well as poisons secreted, secretion systems, All of these structures are intriguing potential for new medication and vaccine development (Klemm et al., 2000; Werneburg et al., 2015; O'Brien et al., 2016). Specific virulence genes in the bacterial genome are essential for UPEC's virulence as compared to non-pathogenic *E. coli.* There are substantial differences across isolates and no single gene has been linked solely in uropathogenesis (Wiles et al., 2008). There are two types of *E. coli* virulence factors associated with the development of UTIs.

1-virulence factors linked to the cell wall of the bacterium, and 2virulence factors released and delivered to the site of action (Emody, 2003).

1.5.1. Surface Virulence Factors

First type the surface virulence factor consist of different number of adhesive organelles (fimbriae) which aid bacteria's adhesion to host tissue in the urinary tract. The most significant determinant of pathogenicity is UPEC's adhesins. Fimbriae also called as pili, are long hair-like structures located on the surface of bacteria that identify certain substances from the target host cells, most typically carbohydrates. Fimbriae is a short form of pili, and the two names are interchangeable. Oligomeric pilin proteins make up fimbriae. These proteins are thinner and smaller than flagellum and are arranged in a helical cylindrical form. These proteinaceous features are thought to be virulence factors in uropathogenic *E. coli* strains (Winberg, 1984). Carbohydrate receptors make up the bulk of these fimbriae receptors P fimbriae, type 1 fimbriae, and thin aggregative fimbriae are among them (Collinson et al., 1992). Several bacterial pathogens can generate variety of adhesins, and the inhibition of only one of them can cause a bacterium to lose its virulence. The activities of pili or fimbriae are not restricted to attachment; they may also aid the bacteria in surviving and evading the host's immune system in a variety of ways. Different forms of adhesins have evolved over time and play a role in tissue evolution. In gram-negative bacteria like UPEC, a chaperone-usher-assisted route reveals adhesins. This pathway is made up of two proteins: a protein named usher and a periplasmic chaperone. Usher found as the structure's foundation, while chaperone's function is to fold and recruit subunits (Klemm & Schembri, 2000). Pili proteins are degraded and misfolded in the absence of the chaperone, and thus cannot be assembled into a mature pilus. Usher, moreover, aids in the maturation of the fimbriae and their transport via the outer membrane, ensuring the integrity of the outer membrane. Usher proteins are composed of an N-terminal domain (NTD), a 24-stranded beta-barrel channel, a plug domain, and two C-termina. In the case of the lake of the chaperone, pilus proteins are degraded and misfolded, and hence cannot be organized into a mature pilus. Usher proteins are made up of an N-terminal domain (NTD), a plug domain, a 24-stranded beta-barrel channel, and two C-termina, fimbriae of the Chaperone-usher family are more frequent in uropathogenic E. coli strains (Volkan et al., 2015).

UPEC adhesins can help with virulence in a variety of ways including (I) stimulating host and bacterial cell signaling pathways directly (ii) promoting bacterial invasion. (iii)Increasing the transport of other infectious agents to host tissues (Mulvey, 2002). Form 1 fimbriae genes can be found in 99 percent of *E. coli* strains (Vigil et al., 2011). Type-1 fimbriae are adhesion factors that have been extensively studied and are essential for UPEC invasion and adhesion into bladder cells (Connell et al., 1996; Mulvey, 2002). Type 1 fimbriae are UPEC's surprisingly flexible virulence factors, capable of stabilizing the bacteria's attachment to various types of cells in the urinary tract. While their binding sites in Bowman's capsules and glomeruli were unknown, type 1 fimbriae were found to have a strong affinity in proximal tubules and vessel walls. They form a strong connection with the bladder's muscular layers and the vessel's walls. Mannose sensitive pili, also known as type 1 pili, are found in both nonpathogenic and pathogenic strains of *E. coli*. Because the haemagglutination of erythrocytes is hindered in the presence of mannose, they are known as mannose sensitive (Reid & Sobel, 1987). Type 1 fimbriae receptors have also been identified in the distal tubules and accumulation ducts, they may also cause macrophages to attach to their surfaces (Vizcarra et al., 2006).They have a protein named FimH on their tip along with FimG, FimF ,and FimH that is responsible for interacting with the host cell. (Jones et al., 1995). FimA proteins are abundant, they are not required for virulence. Allelic variations of FimH, among other components of type 1 fimbriae, assess sugar specificity, and loss of fimH leads in reduced colonization in mice models of ascending UTI, which may be restored by plasmid expression containing the fimH gene (Connell et al., 1996). FimH can induce toll-like receptor 4 (TLR4) alone or in combination with LPS, Activating the humoral immune response by activating a signaling cascade. Many experiments have shown that type 1 fimbriae expression leads to virulence and that absence of expression leads to loss of expression, but their presence cannot be linked to UTI since normal fecal bacteria express type 1 fimbriae in the same way (Nielubowics & Mobely, 2010). The attachment of type 1 fimbriae is a critical step in cystitis. These fimbriae's adhesins are sensitive to mannose. It binds to a wide range of proteins. Uroplakin IA, which covers the bladder's facet cells, is the most significant structure on uroepithelial cells. (Zhou & Mo, 2001). They also attach to β-integrin resulting in cytoskeleton reorganization and bacterial internalization (Eto & Jones, 2007). Complement factor 3 is released by epithelial cells during infection and can attach to type 1 fimbriae in renal epithelial cells forming a complex with CD46 to aid internalization (Springall & Sheerin, 2001).

1.5.2. Secreted Virulence Factors

Toxins play a crucial role in the pathogenicity of *E. coli*-based infections. Toxin generation by colonizing *E. coli* can induce an inflammatory reaction, which can lead to symptoms of a urinary tract infection. The most major secreted virulence component of uropathogenic *E. coli* is lipoprotein-haemolysin (HlyA) which is connected to higher UTIs such pyelonephritis (Johnson, 1991). The HlyA toxin is a pore-forming toxin found in Gram-negative bacteria that belongs to the RTX (re-peats in toxin) class of toxins (Eberspacher et al., 1989). Extraintestinal pathogens like UPEC can use HlyA to lyse erythrocytes and nucleated host cells at high concentrations, allowing them to effectively traverse mucosal barriers, destroy functional immune cells, and obtain access to host nutrition and iron stores (Keane et al., 1987). At low doses HlyA may cause apoptosis in target host cells such as neutrophils, T lymphocytes, and renal cells, as well as assist bladder epithelial cell exfoliation (Chen et al., 2006). HlyA has also been shown to generate Ca2+ oscillations in renal epithelial cells, which results in higher amounts of IL-6 and IL-8 (Uhlén et al., 2000). HlyA is in-volved for about half of all occurrences of pyelonephritis a kidney disease. Endothelial injury and renal vascular constriction can be caused by the intrarenal production of endothelin by *E. coli*-ex-pressed -hemolysin, for example, by the intrarenal production of endothelin (Kohan, 1994). HlyA as well as other *E. coli* toxins have been shown to cause cell membrane damage and apoptosis via the inducible nitric-oxide-synthase (iNOS) route, which is mediated by extracellular signal-regulated kinase (ERK) and is independent of the p53 pathway (Chen et al ., 2003). One-third of the pyelonephritis strains contain cytotoxic necrotizing factor 1 (CNF1), which may be implicated in kidney invasion.

In vitro, *E. coli* secretes this enzyme, which induces the development of actin stress fibers and membrane ruffles in a Rho GTPase-dependent fashion, allowing *E. coli* to get inside the cells. The precise involvement of CNF1 in invasion mechanisms during pyelonephritis is unknown and controversial (Bower et al., 2005). CNF1 inhibits polymorphonuclear phagocytosis and apoptosis in urinary epithelial cells in vitro and in vivo it can promote bladder cell exfoliation and increased bacterial access to underlying tissue (Mills et al., 2000). The virulence factor secreted autotransporter toxin (SAT) is identified in *E. coli* strains that induce pyelonephritis. (SAT) is toxic to bladder and kidney cell lines, suggesting that it may have a role in the etiology of UTIs (Guyer et al., 2002). The cytolethal distending toxin (CDT) might be a virulence factor in UTIs caused by *E. coli (*Féria et al., 2000). Tcp stands for toll/interleukin (IL-1) receptor (TIR) domain-containing protein, which is a new family of virulence factors that can subvert TLR signaling to gain a survival advantage during UTIs. Importantly, in vivo, Tcp encoded by UPEC facilitates bacterial survival and kidney pathology (Girl et al., 2008).

1.6. Pathogenesis

UTI pathogenesis is a complicated mechanism mediated by a variety of biological and behavioral influences in the host, as well as pathogen properties, including virulence factors (As mentioned above). First step of the UTI pathogenesis is kicked off by adhesion. The method by which *E. coli* enter to the urinary tract demonstrates a unique capacity to adapt to a different environment than the gut. They must alter their metabolism. The *E. coli* that successfully infest the urinary tract have specialized factors that allow them to survive in the UTI environment (Khandelwal & Abraham, 2009). The effects of complicated host–pathogen interactions in the bladder eventually decide whether uropathogens colonize or are eliminated. The receptors on bladder epithelium can be recognized by several bacterial adhesins and mediate colonization. UPEC and other uropathogens get iron via invading the bladder epithelium, creating toxins and proteases to extract nutrients from host cells, and manufacturing siderophores. The uropathogens will then ascend to the kidneys, colonizing the renal epithelium through adhesins or pili, and producing tissue-damaging toxins after replicating and overcoming host immune surveillance. As a result, uropathogens are able to penetrate the tubular epithelial membrane and reach the bloodstream, causing bacteremia. UPEC can use their virulence factor for protection against host defenses and this is a form of adaptations of UPEC (Lee et al., 2011). While UPEC primarily colonizes the bladder and produces cystitis in the urinary system, it may also ascend through the ureters and produce pyelonephritis in the kidneys (Flores-Mireles et al., 2015).

1.7. Risk Factors Associated With *E. coli* Infection

A risk factor increases the chances of developing an illness or disorder. UTIs may occur with or without all of the symptoms, many studies have considered UTI to be the most frequent bacterial infection experienced by humans, and have attempted to examine the pathogen infection leading to bacteremia antimicrobial sequence, They looked into the importance of related risk factors and their role in affecting thousands of people per year as a result of Gram negative pathogen infection contributing to bacteremia. Several researchers have investigated and validated the role of risk factors such a previous UTI, anemia, and sexual abuse in causing UTI in pregnant women (Emiru et al., 2013). Women have a greater risk of UTI than men due to their reproductive physiology the short urethra in female's increases the scope of pathogenic penetration of the urinary system, and sexual intercourse encourages pathogen entrance, resulting in UTI (Feitosa et al., 2009). Also pregnancy increases the risk of infection. When breastfeeding is taken into account, there are a number of factors that may cause the disease. It is common knowledge that the infection begins in the sixth week of pregnancy and occurs in the twentieth week. Factors such as gravidity and parity have acritical role in the transmission of infection during breastfeeding. The number of births is known as gravidity, and the number of safe deliveries is defined as parity. Multiple pregnancies have been identified as a risk factor in scientific studies, but this is debatable (Creinin et al., 2009). UTI risk is linked to factors such as age, parity, and gestational age (Gilstrap et al., 2001; Dimetry et al., 2007). In addition, factors such as the use of immunosuppressants, the individual's financial situation, and geographic location all have a role in infection pathogenesis. Although UTI is considered to be the result of bacterial infection, on the other hand, there are many other factors that indicate infection. Due to hormonal and physiological improvements, pregnancy is considered a critical time that increases the risk of infection. When compared to non-diabetic people, diabetes patients are much more likely to get the infection (Lentz, 2009).

1.8. Diagnosis of *E. coli*

Urinalysis performed to identify bacteria in urine samples, the urine samples analysed under the microscope to see whether bacteria are present. Gram staining of uncentrifuged urine samples, or close examination of bacteria in urine samples, can be used to detect bacteria microscopically. Gram staining of uncentrifuged urine specimens is a simple method. A small amount of urine is placed on a glass microscope slide, which is then allowed to air dry before being stained with Gram stain and analyzed under a microscope. Since various parameters have been used to determine a positive test outcome (Carroll et al., 1994). The urine Gram stain test has the essential advantage of allowing the practitioner to choose empiric antibiotic treatment based on the kind of infecting bacteria or yeast (rarely pathogenic microorganisms like microsporidia). The Gram stain test has three limitations that make it unsuitable for use in the majority of clinical situations. For example, it's a sensitive test that can only detect infections with a bacterial concentration of 10^5 cfu/mL. Infections with bacterial concentrations of 10^2–10^3 cfu/mL can go undiagnosed. Second, due to its time-consuming nature, most diagnostic laboratories are unable to perform the technique on a more than sporadic basis. Finally, because it cannot identify bacteria at concentrations of 10^2–10^3cfu/mL, it cannot be employed in the outpatient setting for patients with uncomplicated UTIs. or other patients with whom it is important to know the essence of the pathogen infecting them (Pappas, 1991).

Outpatients with simple UTIs might use the culture approach as part of their therapy. A urine culture may not be needed. Urine cultures are used for outpatients with chronic urinary tract infections, treatment deficiencies, or complicated UTIs (Stamm et al., 1993; Wing et al., 2000). Urine cultures are also important for inpatients who acquire infections (UTIs). Bacterial cultures are thought to be a good way to diagnose a urinary tract infection, not just because it helps in the documentation of infection, Antimicrobial susceptibility testing and determining the identity of the infecting microorganisms are also needed. This is especially important in view of the rising frequency of antibiotic resistance. The occurrence of $\geqslant 10^5$ cfu per milliliter of urine is the most widely used criteria for determining severe bacteriuria (Warren et al., 1999; Hemal et al., 2000). This criteria was designed for women who have acute pyelonephritis or who have been asymptomatic but have had several urine cultures with this quantity of bacteria; nevertheless, it is commonly used to a variety of different patient categories (Clarridge et al., 1998). Most of the patients with UTIs, on the other hand, do not fall into either categories and 30%–50% of patients with acute urethral syndrome have colony counts of $\geqslant 10^5$ colony-forming units per milliliter. As a result, several laboratories have chosen to view and record findings using lower colony counts as a criterion. A colony count of 10^4 cfu/mL is one typical requirement, which will be required to improve the test's sensitivity without making it impractical for clinicians and laboratories to use (Clarridge et al., 1998). In catheterized patients (who could have low amounts of bacteria that can progress to higher amounts) and several patients with infections of the lower urinary tract, colony counts are much lower than 10^5cfu/mL if specimens are collected by suprapubic aspirate or catheterization. As a result, a bacterial concentration of $\geqslant 10^2$ cfu/mL is the most suitable diagnostic criteria for urinary culture specimens obtained by suprapubic aspirate or catheterization (Van et al., 2000). Patients with asymptomatic bacteriuria, acute uncomplicated cystitis, or acute uncomplicated pyelonephritis do not require frequent follow-up cultures for cure testing. And for which evidence of a positive therapeutic response to treatment exists. patients with chronic UTIs, patients with anatomic or functional anomalies in the urinary tract, or patients with unexplained pathological urinalysis results may have follow-up cultures performed (Stamm,2002).

1.9. Resistance of E. coli to Antimicrobials

Antimicrobial resistance is a significant and growing problem in the world of medicine. With the discovery of penicillin, a large number of bacteria have evolved and transmitted antimicrobial resistance to other organisms in response to antibiotic usage (Von et al., 2005). Antibacterial resistance has developed in *E. coli* and other bacteria for a number of causes, but it has been linked to the addition of these medications to the human and veterinary medicine therapeutic arsenal. According to research, *E.coli* has the highest rates of antibiotic resistance among bacteria that have been in use for the longest time (Tadesse et al., 2012). As shown by the high levels of sulfonamide tolerance around the world (Ny et al., 2019). The first E. coli-resistant clones were found in 1950, and their usage in humans goes back to the 1930s (Tadesse et al., 2012). Although antibiotic resistance is usually considered to be primarily the result of human intervention and antibiotic treatment, many resistance factors have been discovered in the genomes of human bacterial commensals and environmental bacteria, according to genetic analysis (Sommer et al., 2009). That were not acquired by horizontal transmission and existed before the widespread use of antibiotics in clinical practice intrinsic resistance is a type of AR that gives emerging strains a selection advantage by blocking or killing microorganisms that compete for resources. In contrast to recently evolved extrinsic antibiotic resistance, intrinsic antibiotic resistance remains unaffected (Cox & Wright, 2013). Studying intrinsic resistance as a potential new strategy to combat bacterial resistance has become increasingly intriguing in this era of growing AR and a shortage of new antibacterial drugs, as suppression of components that make up the intrinsic resistome makes bacteria highly susceptible to antibiotics (Liu et al., 2010). The outer membrane, which is impermeable to some chemicals, and the production of different efflux pumps, which effectively lower the intracellular concentration of particular antibiotics, are two major factors to Gram-negative bacteria's innate resistance, such as *E. coli* (Sommer et al., 2009).

In 2017, *E. coli* bacteria expressing extended spectrum -lactamases (ESBL) accounted for 15.7% of all isolates in the United States, while levofloxacin and trimethoprim-sulfamethoxazole resistant *E. coli* strains accounted for 24 % of all isolates (Critchly et al., 2017). According to national surveillance data from Mexico, China, and Turkey, where *E. coli* is present, the situation in developed countries is deteriorating. Resistance to antibiotics including cephalosporins, quinolones, and trimethoprim/sulfamethoxazole (TSX), which are commonly used to treat bacterial infections empirically, is on the rise. has been found to be >40 %, Alexander Fleming issued a warning to the world about antibiotic overuse in 1945, just a few years after the first *S. aureus* strain was discovered to be resistant to penicillin. Just a few years later, his prediction came true when the first *S. aureus* strain was confirmed to be resistant to penicillin (Read & Woodes, 2014).

`1.10. The Aims from the Study

1. The identification and isolation of *E. coli* causing UTIs among pregnant women compared to non-pregnant women using culture and biochemical tests in Zakho city, Kurdistan, Region, Iraq.

2. To evaluate the potential risk factors associated with UTI and pattern of urinary complaints during pregnancy.

3. To evaluate the chemical and microscopical examination of urine from infected people

4. The investigation of the antibiotic susceptibility profile of *E. coli* isolates from urine samples and determine the antibiotic resistance patterns.

CHAPTER TWO

2. METHODOLOGY

2.1 Reagents and Media

This section describes the preparation of general reagents, buffers, culture media and biochemical tests used in this thesis.

2.1.1. Preparation of Macconkey Medium (Neogen, USA):

12.87 gr of agar were added to 250 ml of purified water then heated until boiling to completely dissolve the agar, after that sterilized by the autoclave on 15 lbs pressure 121°C for about 15 min, and cooled until temperature reaches 45-50 °C and at the final step mix well then poured into clean and sterilized Petri dishes.

2.1.2. Preparation of Eosin Methylene Blue (EMB) Medium

(NEOGEN, USA): 37.5 gr of agar was added to 250ml of purified water heated until boiling to completely dissolve the agar, after that sterilized by the autoclave on 15 lbs pressure 121°C about 15 min, and cooled until the Temperature reach 45-50 °C and at the final step mix well then poured into clean and sterilized petri dishes.

2.1.3. Preparation of Mueller Hinton Medium (Neogen, USA):

38 gr of agar added to 1L of purified water heated to boiling to completely dissolve the agar, then sterilized by the autoclave on 15 lbs pressure 121°C about 15 min , after that waited until cooled then poured into clean and sterilized petri dishes

2.1.4. Preparation of Peptone Water Medium (Neogen, USA):

15 gr of agar was added to I litter of purified water heated until boiling to completely dissolve the medium after that sterilized by the autoclave on 15 lbs pressure 121°C about 15 min, and cooled until the Temperature reach 45-50 °C after that the medium kept in a closed bottle in the refrigerator until use, when needed poured into the special tubes and then placed in the incubator to warm.

2.1.5. Preparation of Simmons Citrate Medium (Neogen, USA):

24gr of Simmons citrate agar was added to 1 litter of purified water heated until boiling to completely dissolve the medium, after that sterilized by the autoclave on 15 lbs pressure 121°C for

15 min, then the medium poured in clean tube in slanted position, the tubes kept in the refrigerator until use.

2.1.6. Preparation of Methyl Red, Voges-Proskauer Medium (HIMEDIA):

17 gr of agar added to 1 L of purified water heated until boiling to completely dissolve the medium, after that sterilized by the autoclave on 15 lbs pressure 121°C for 15 min, then waited until cooled then kept in the refrigerator until use, pour into two tubes, one for voges-proskauer test and the other for the methyl red test, as needed.

2.2 Design of Study

From October 2020 to January 2021, At Zakho Maternal Hospital, a hospital-based cross sectional research was done to evaluate the prevalence, associated risk factors, and antibiotic sensitivity test of urinary tract infection (UTI) among pregnant women. Out of these periods, 196 patients and 50 patients of non-pregnant women used as a control were enrolled in this study. The patients' ages ranged from 16 to 45, with a mean of (25.65 years±5.4 SD).

2.2.1. Data Collection Instrument

Data were collected using structured questionaries. Patients were interviewed face to face and asked them many questions before the sample collections. The questionaries included age, gestational age, number of children, miscarriages, and a prior history of urinary tract infection. The patients who were enrolled in this study gave their written consent. Pregnant women and consent to participate in the study were among the research's inclusion criteria. Patients who refused to participate in the study were excluded. Pregnant women who had taken antibiotics within the previous seven days and were unwilling to participate were also excluded from the study.

2.2.1.1. Inclusion Criteria:

This study included only pregnant women who attended Maternity Zakho Hospital and who agree to participants of this study.

2.2.1.2. Exclusion Criteria:

Pregnant women who had taken antibiotics during the previous seven days and who refused to participate were excluded from the research.

3.2.1.3. Ethical approval:

The procedure and protocol of this study was approved by the Ethics and Research Committee of the College of Medicine, University of Zakho, Kurdistan Region of Iraq (Approval No.02.05.2019/4/154/NW). The Committee followed the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained from all participants before sample collection.

2.3. Sample Collection and Processing

Midstream urine (4-5ml) was taken from participants in a sterile disposable container to avoid contamination, the specimens were labelled with names and transported to the clinical laboratory and analyzed For the isolation of bacterial pathogens from urine samples, a loopful of urine was plated on MacConkey agar (NEOGEN, USA) using a calibrated loop technique, and the inoculated plates were incubated at 37 °C overnight and evaluated for the presence of bacterial growth. Plates that did not have a colony at the end of the 24-hour incubation period were kept for another 48 hours. On microscopic examination of the urine, a specimen was ruled positive if an organism grown at a concentration of $\geq 10^5$ cfu/mL or an organism grown at a concentration of $\geq 10^4$ cfu/mL and >5 pus cells per high-power field. On the next day, bacteria isolates were identified based on their cultural and biochemical properties. The standard biochemical test was used to identify Gram negative bacteria (*E. coli*).

2.4. Urine Analysis

The urine sample obtained in a clear midstream tube, before centrifuging the urine cultured on MacConkey agar. For the bacterial growth, then the urine tube centrifuged for about 10 min after that microscopic examination done for searching several elements such as pus cell, red blood cell, mucus, epithelia, and bacteria.

2.5. Identification of *E. coli* by Culture

E. coli isolates were first recognized by their morphological features on MacConkey agar based on standard microbiological cultures and biochemical characteristic reactions (as shown in section 2.5) based on the Clinical and Laboratory Standards Institute (CLSI) guidelines (1, 2).

2.6. Biochemical Tests for Identification of *E. coli*

2.6.1. Indole Test (Cheesbrough, 1985)

Tryptophan is an amino acid that may be deaminated and hydrolyzed by bacteria that produce the enzyme Tryptophanase. With the aid of the intermediate molecule indole pyruvic acid, indole is produced through reductive deamination of tryptophan. The deamination process, which removes the amine ($-NH_2$) group from the tryptophan molecule, is catalyzed by Tryptophanase. Indole, pyruvic acid, ammonium (NH_4^+), and energy are the reaction's end products. Pyridoxal phosphate is required as a coenzyme. The solution turns from yellow to cherry red when indole and Kovac's Reagent are combined (which comprises hydrochloric acid and p-dimethyl amino benzaldehyde in amyl alcohol). Because amyl alcohol isn't water soluble, the red color will show up as an oily layer on top of the broth.

2.6.2. Methyl Red (MR)

In MR-VP medium, *E. coli* may undergo mixed acid fermentation of glucose. During mixed-acid fermentation, a complex mixture of acids, particularly lactate, acetate, succinate, and format, as well as ethanol and equal amounts of H_2 and CO_2, is produced. As a result, the medium's pH becomes acidic. When the pH is less than 4.4, the pH indicator Methyl Red becomes red.

2.6.3. Voges Proskauer (VP)

The Voges-Proskauer (VP) test is used to determine if an organism produces acetyl methyl carbinol from glucose fermentation. Acetyl methyl carbinol is converted to diacetyl in the presence of - naphthol, strong alkali (40 % KOH), and atmospheric oxygen. The - naphthol was not originally included in the procedure, but Barritt found that it functions as a color intensifier and must be added first. The peptones in the broth include diacetyl and quinidine containing compounds, which condense form a pinkish red polymer.

2.6.4. Simmons Citrate

Because organisms need citrate as a source of energy, this test is used to determine their capacity to utilize it. The only source of nitrogen is ammonium dihydrogen phosphate. Buffering is provided by dipotassium phosphate. Sodium Chloride maintains the osmotic balance of the medium. Sodium Citrate is the only carbon source in this medium. Magnesium sulfate serves as a cofactor in a number of metabolic processes. On this medium, organisms that can use ammonium dihydrogen phosphate and citrate will grow unrestrictedly. If citrate is used, alkaline/basic byproducts will be accumulated by the microorganism. Citrate-permease, an enzyme that converts citrate to pyruvate, is produced by bacteria that survive in this environment. Pyruvate is then utilized to create energy in the metabolic cycle of the organism. Citrate utilization, an intermediate molecule in the Krebs cycle, is suggestive of growth.

2.7. Antimicrobial Susceptibility Test

Kirby Bauer's disc diffusion technique was used to test the isolated bacteria for antibiotic susceptibility. Standard inoculums calibrated to 0.5 McFarland were swabbed on Mueller Hinton agar (NEOGEN, USA) and left to soak for 2 to 5 minutes. After that antibiotic disks (as described in section 3.4) were gently pressed over the surface of the media and left to stand at room temperature for 10 minutes. Mueller Hinton agar using the disk diffusion (Kirby Bauer's) were inverted and then incubated at 37°C for 24 hrs. After incubation, without opening the palate, the zone diameter with complete inhibition, including the diameter of the disk, is measured with a ruler and recorded in millimeters on the underside of the plate. The inhibition zones were measured and interpreted according to the clinical and laboratory standards (NCCLS) guidelines (NCCLS 2003) (Table 1)

Table 1: Standard antimicrobial inhibition zone according to the Clinical Laboratory Institute

Antibiotics	**Resistance**	**Sensitive**
Nalidixic acid (NA)	≤13	≥19
Ceftriaxone (CRO)	≤13	≥18
Amikacin (AK)	≤14	≥17
Gentamycin (CN)	≤12	≥15
Nitrofurantoin(F)	≤14	≥17
Ciprofloxacin (CIP)	≤15	≥21
Doxycycline (DO)	≤10	≥14
Cefotaxime (CTX)	≤14	≥18
Cefixime (CFM)	≤15	≥19
Meropenem (MEM)	≤17	≥22

2.7.1. The Standard Antibiotic Discs

The antibiotics with their concentration were used in this study described in details in the (Table 2).

Table 2: Antibiotics used in this study

Antibiotics	**Concentration**	**Company**
Nalidixic acid (NA)	30mg	Bioanalyse (TURKEY)
Ceftriaxone (CRO)	10mg	Bioanalyse (TURKEY)
Amikacin (AK)	10mg	Bioanalyse (TURKEY)
Gentamycin (CN)	10mg	Bioanalyse (TURKEY)
Nitrofurantoin(F)	100mg	Bioanalyse (TURKEY)
Ciprofloxacin (CIP)	10mg	Bioanalyse (TURKEY)
Doxycycline (DO)	10mg	Bioanalyse (TURKEY)
Cefotaxime (CTX)	30mg	Bioanalyse (TURKEY)
Cefixime (CFM)	5mg	Bioanalyse (TURKEY)
Meropenem (MEM)	10mg	Bioanalyse (TURKEY)

2.8. Statistical Analysis

This study's findings were analyzed using the GraphPad Prism software package, version 8. The results were expressed as simple percentages, frequency and ranges or mean ± standard deviation accordingly. Comparisons between variables and pregnant and non-pregnant women were made using the Chi-Square and Fisher Exact Test. If P value ≤ 0.05 the results were considered significant.

CHAPTER THREE

3. RESULT

3.1. Isolation and Identification of E. coli

3.1.1 Culture

E. coli infection were primarily identified on MacConkey agar according their morphological characteristics on agar plate and based on standard microbiological cultures and biochemical characteristic reactions. *E coli* isolates showed bright pink colonies MacConkey agar (Figure 1) and on the Eosin Methylene Blue medium appear large, blue-lack colonies usually metallic sheen colonies. (Figure 2)

Figure 1: Morphological characteristics of E. coli on MacConkey Agar.

The morphology of the colony on the selective media MacConkey agar was used to make a pre-sumptive identification of *E. coli*. Rapid lactose fermenting *E .coli* colonies were dry and dark pink in appearance, with a dark pink region of accumulated bile salts surrounding them.

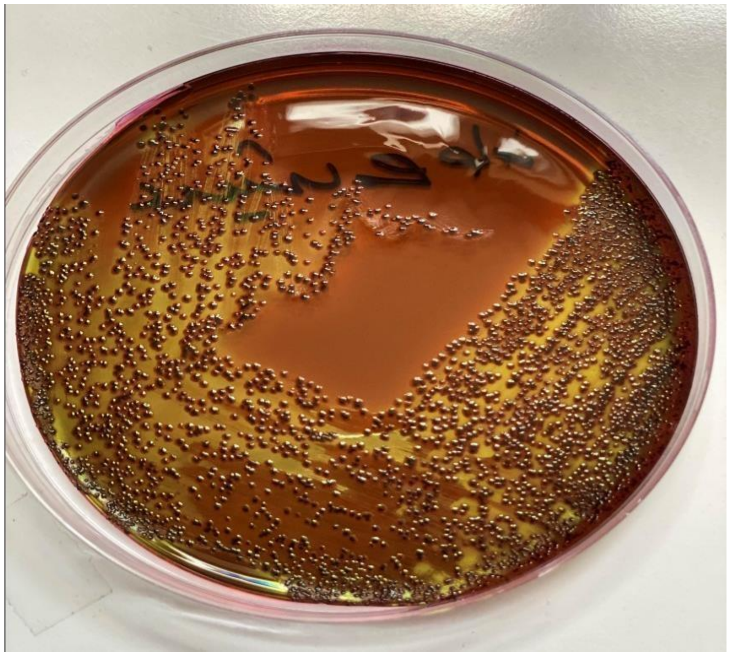
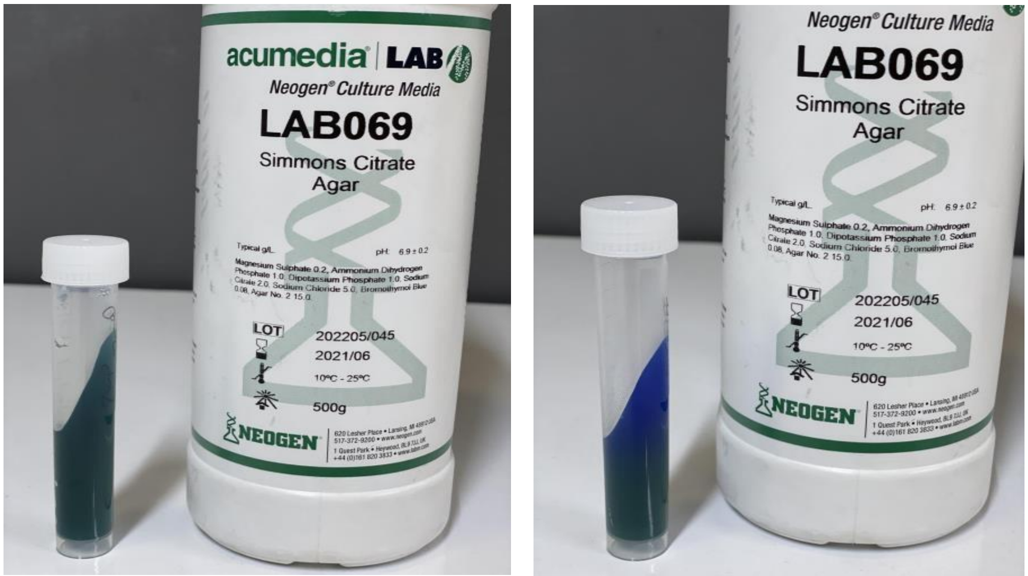


Figure 2: Growth of E. coli on EMB medium

3.1.2. Biochemical Test

The *E. coli* were also confirmed by using several biochemical tests. The indole test was positive for *E. coli* and appeared in the form of a red ring on the medium's surface, and the negative results indicate no change. (Figure 3). The growth of *E. coli* on Simmons Citrate Agar appeared blue in color and negative one appears green color (no change) (Figure 4). Methyl red and Voges-Proskauer test was also positive for *E. coli* (Figure 5).

Figure 3: Indole test; positive result with the red ring, negative result showed no ring



(A) (B)

Figure 4: Simmon citrate test; (A) negative result (no change), (B) positive result showed blue color.

(A) (B)

Figure 5: A: Methyl red test positive result, B: VP test negative result.

Briefly, methyl red indicator (1 to 2) drops added to methyl red tube, positive result makes change in the color of the tube and convert it to red, negative result found with no change. In the case of VP test 10 drops from each of the two indicators added to the VP test tube, positive result shows changing of the color of the medium to dark red, negative result shows no change in color.

3.1.3. Antibiotic Sensitivity Test:

The isolated *E. coli* were tested for antimicrobial Susceptibility test using Mueller Hinton agar. The zone of inhibition was measured as resistance and sensitive (Figure 6 and Table 1).

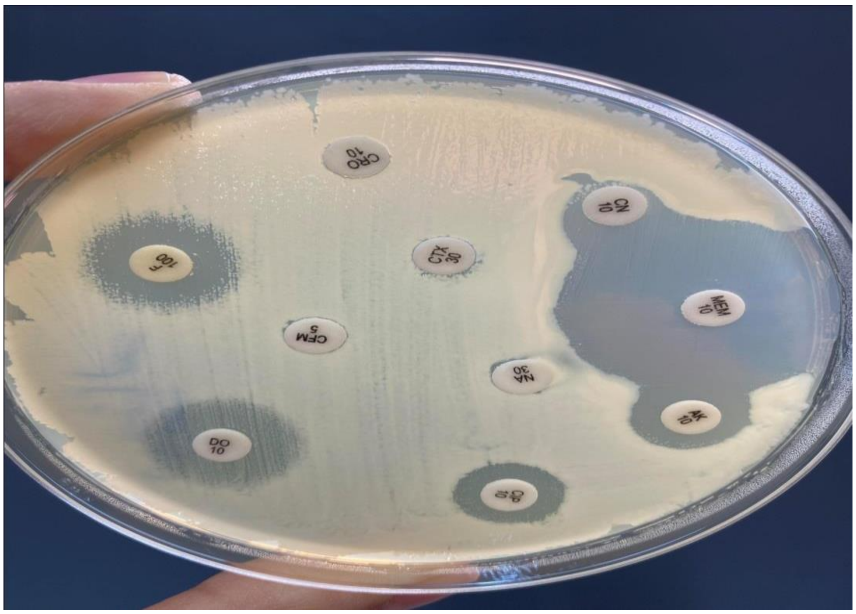


Figure 6: Antimicrobial susceptibility test

3.2. Results

3.2.1. Sociodemographic Characteristic of Study Participants

Sociodemographic characteristics linked with the *E. coli* UTI infection in pregnant women are presented in **Table 1**. A total of 196 study participants were enrolled during the study period. Pregnant women age ranged from 16-45 years, with mean of (25.65 years±5.4 SD). Group of 25-34 years were the majority of the participants (56.6%) and 15-24 years (38.3%). Educational status of participants ranged from illiterate to postgraduate studies. 15.8% of the participants were unable to read and write while 34.7% of the participants had their higher educational level **(Table 1).** Around 94.4% of the study participants were house wives, while the rest were government workers. Of total study population, 87.8% lived in urban areas and 80.1% were intermediate levels of family income **(Table 1).**

3.2.2. Prevalence Rate of *E. coli* among Sociodemographic Variables

The rate of infection among different demographic variables are presented in **table 1.** In the present study, there were no significant differences between the studied sociodemographic variables and *E. coli* prevalence rate **(Table 1).** However, the high infection rate was found in age group between 25-34 years (21.6%). The highest rate of *E. coli* infection was reported in illiterate people 19.4% followed by higher education (18.9%). Additionally, around 18% of *E. coli* infection was found for both worker and house wife. Th people lived in rural area was reported the highest rate of infection (20.8%). The highest prevalence rate was found among people with higher family income categories (33.3%) followed by lower income (24.2%)

Table 3: Socio-demographic characteristics of pregnant women visiting Maternity General Hospital in Zakho City (n=196)

		Culture results for *E. coli* infection		
Variables	**Total No. (%)**	**No. (%) of positive**	**No. (%) of negative**	**P value**
Age group (Year)				
16-24	75 (38.3)	8 (10.7)	67 (89.3)	0.51
25-34	111 (56.6)	24 (21.6)	87 (78.4)	
35-45	10 (5.1)	2 (20)	8 (80)	
Education status				
Illiterate	31 (15.8)	6 (19.4)	25 (80.6)	0.91
Primary school	60 (30.6)	11 (18.3)	49 (81.7)	
High school	68 (34.7)	10 (14.7)	58 (85.3)	
Higher education	37 (18.9)	7 (18.9)	30 (81.1)	
Occupation				
Worker	11 (5.6)	2 (18.2)	9 (81.8)	0.6
House wife	185 (94.4)	32 (17.3)	153 (82.7)	
Residence				
Urban	172 (87.8)	29 (16.9)	143 (83.1)	0.41
Rural	24 (12.2)	5 (20.8)	19 (79.2)	
Family income				
Low	33 (16.8)	8 (24.2)	25 (75.8)	0.27
Intermediate	157 (80.1)	24 (15.3)	133 (84.7)	
High	6 (3.1)	2 (33.3)	4 (66.7)	

3.2.3. Risk Factors Associated With UTI

The presence of risk factors linked to *E. coli* UTIs was examined in a total of 196 pregnant women. Diabetes mellitus was found to be a risk factor for UTI in a study evaluating related risk factors. (p<0.28), history of UTI infection (p<0.05) and present of symptoms during infection (p<0.001) showed statistically significant association with *E. coli* UTI. On the other hand, gestational age (P<0.44), number of pregnancy (p<0.99) and abortion (p<0.08) revealed not statistically significant differences with UTI.

Table 4: Associated risk factors of UTI with E. coli among pregnant women visiting Maternity General Hospital in Zakho City (n=196)

Risk Factors	Total No. (%)	Culture results for *E. coli* infection		P value
		No. (%) of positive	**No. (%) of negative**	
Gestational age				
First Trimester	52 (26.5)	12 (23.1)	40 (76.9)	0.44
Second Trimester	71 (36.2)	11 (15.5)	60 (84.5)	
Third Trimester	73 (37.3)	11 (15.1)	62 (84.9)	
Number of pregnancies				
1 to 2	100 (51)	17 (17)	83 (83)	0.99
3 to 4	73 (37.3)	13 (17.8)	60 (82.2)	
> 5	23 (11.7)	4 (17.4)	19 (82.6)	
Diabetes mellitus				
Yes	9 (4.6)	4 (44.4)	5 (55.6)	**0.028**
No	187 (95.4)	30 16.1)	157 (83.9)	
Abortion				
Yes	50 (25.5)	5 (10)	45 (90)	0.08
No	146 (74.5)	29 (19.9)	117 (80.1)	
Past history of UTI				
Yes	151 (77.1)	30 (19.9)	121 (8.1)	**0.05**
No	45 (22.9)	4 (8.9)	41 (91.1)	
Presence of symptoms				
Yes	31 (15.8)	20 (64.5)	11 (35.5)	**0.001**
No	165 (84.2)	14 (8.5)	151 (91.5)	

3.2.4. Prevalence of *E. coli* between Pregnant and Nonpregnant Women

Out of 196 urine samples, 34 (17.34%) was culture positive for *E. coli* infection in pregnant women (Table 3). And the prevalence of *E. coli* infection in non-pregnant women was 17 (34.69%).

Surprisingly, the highest prevalence rate of infection was recorded in non-pregnant when compared to pregnant women with statistically significant differences (P<0.032) using Chi-Square (Fisher exact test) (Table 3; Figure 1). Overall, 49/245 (20%) urine samples were culture positive for *E. coli* infection.

Table 5: Prevalence of E. coli infection between pregnant and non-pregnant women in Zakho City, Iraq

	No. of sample	**Frequency**	**Percentage (%)**	***P value**
Pregnant women	196	34	17.34	0.032
Non-pregnant	49	17	34.69	
Total	**245**	**49**	**20**	

P value were determined using Chi-Square (Fisher exact test)

P value<0.05 is considered statistically significant differences

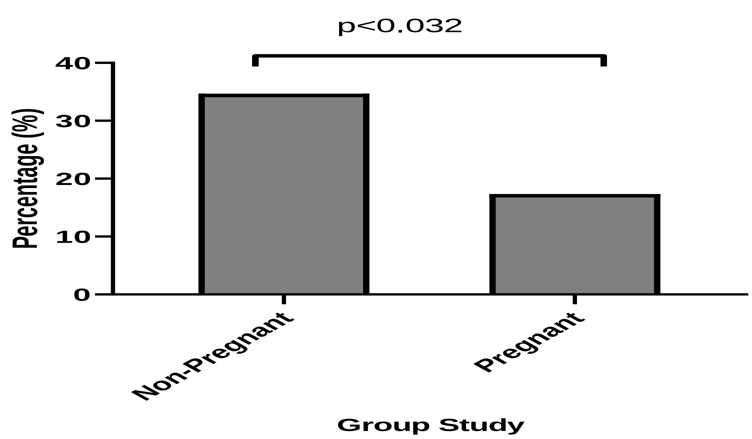


Figure 7: Comparison between prevalence rate of E. coli infection between pregnant and non-pregnant women

3.2.5. Antibiotic Susceptibility Test to *E. coli*

According to antibiotic sensitivity patterns in urine samples of pregnant women the result showed that isolated *E.coli* were very sensitive to Nitrofurantoin (82.4%), Meropenem (79.4%) and around 67.6% for both Amikacin and Ciprofloxacin **(Table 6).** On the other hand, in non-pregnant women isolated *E.coli* from urine samples were very sensitive to Amikacin (100%), followed by Meropenem (94.1%) and Gentamicin (82.4%) **(Table 6).** The results of the other tested antibiotics to *E. coli* isolates are found in **Table 6.**

Table 6: Antibiotics Susceptibility Patterns of E. coli between pregnant and non-pregnant women

Antibiotics	Number of Isolates Recovered from Urine (% of Sensitive)	
	Pregnant (n=34)	**Non-Pregnant (n=17)**
Amikacin (AK10)	23 (67.6)	17 (100)
Cefixime (CFM5)	10 (29.4)	8 (47.1)
Cefotaxime (CTX30)	12 (35.3)	11 (64.7)
Ceftriaxone (CRO10)	10 (29.4)	11 (64.7)
Ciprofloxacin (CIP 10)	23 (67.6)	10 (58.8)
Gentamicin (CN 10)	15 (44.1)	14 (82.4)
Nalidixic acid (NA 30)	16 (47.1)	12 (70.6)
Doxycycline (DO 10)	7 (20.6)	9 (52.9)
Meropenem (MEM10)	27 (79.4)	16 (94.1)
Nitrofurantoin (F100)	28 (82.4)	11 (64.7)

3.2.6. Urine Analysis Results

The microscopic examination of urine samples of patients positive with *E. coli* infection between Women who are pregnant and non-pregnant was shown in table 5. There was no noticeable difference between non-pregnant and pregnant women, according to the findings in terms of pus cell (p<0.25), RBC (p<0.48), epithelial cell (p<0.95) and Specific gravity (p<0.28). More importantly, in the current study, In terms of the quantity of germs discovered in urine samples, there was a significant difference between non-pregnant and pregnant women. (p<0.001) using unpaired t test. Additionally, the chemical analysis of urine including sugar, albumin, urobilinogen, bilirubin and ketone bodies of urine samples was also investigated in the present study and found that all these components were we not existed or normal in positive samples (Data not shown).

Table 7: Urine analysis results of patients positive with E. coli urinary tract infection

	Mean + Standard Deviation (SD)		
	Pregnant women (n=34)	**Non-pregnant women (n=17)**	***P value**
Pus cell/HPF	11.3±10.6	15.4±12.9	0.25
RBC/HPF	3.5±3.5	4.7±9.1	0.48
Epithelial cell	11.2±8.7	11.6±8.5	0.95
Bacteria	9.56±5.9	22.27±11.3	0.001
Specific Gravity	1.018±0.007	1.021±0.006	0.28

*P value were determined unpaired *t* test

*P value <0.05 is considered statistically significant differences

CHAPTER FOUR

4. DISCUSSION, CONCLUSION AND RECOMMENDATION

4.1. Discussion

UTIs are a serious public health issue that affects millions of individuals each year. (Hooton, 2001). Due to the shorter urethra, which allows pathogens to enter the bladder more readily, and sexual activity, which increases the risk of uropathogens, UTIs are more common in women than in males. (Magliano et al., 2012). UTI affects up to 60% of women at some point during their lives (Olds et al., 2004). The risk of UTI rises during birth, partly as a result of the gravid uterus's pressure on the ureters, which causes a blockage of urinary flow, and partly as a result of the hormone progesterone (WHO, 2005; Zeighmi et al., 2008). UTI affects between of (5% to 10%) people (Todar et al., 2008). And in pregnancy it can be seen in three different forms: asymptomatic bacteriuria, acute pyelonephritis and/or acute cystitis. (Hooton, 2001; Tutuncu et al., 2005). Asymptomatic bacteriuria has been confirmed to occur in 2-13 percent of pregnant women around the world, and if left untreated, it can raise the risk of premature birth and low birth weight neonates, as well as induce acute pyelonephritis in 15-30 percent of cases (Alan, 2007; Benshushan.et al.2007). Several researches conducted over the last 30 years have shown an association between UTI during pregnancy and adverse outcomes (Ramazan et al., 2004). Approximately 90% of all community-acquired UTIs are caused by pathogenic *E. coli*. (Foxman, 2002; Marrs et al., 2005), while in hospital-acquired complicated UTIs, *Klebsiella*, *Pseudomonas*, *Proteus*, and other species are more prevalent. (Kodner and Gupton, 2010). Antimicrobial resistance to *E. coli* remains a major threat to public health globally especially in developing countries including Kurdistan Region Iraq and causes serious health problems such as treatment failure and prolonged hospitalization (Okeke et al., 2005, Moges et al., 2014). It's also one of the main reason of failure in the treatment of infectious diseases like *E. coli*, which leads to higher, mortality, morbidity, and health-care costs (Bouza and Cercenado, 2002). Antibiotic resistance in *E. coli* is becoming a major problem across the world. (El Kholy et al., 2003). Present study is focused on isolation and antibiotic susceptibility pattern of *E. coli* isolated from pregnant women, so that overall pattern of antibiotic sensitivity towards *E. coli* could be used for future treatments during pregnancy in the region. In addition, during their antenatal follow-up, women should be tested for predisposing risk factors and the causal organism of UTI. The urine examination for the detection of pathogens and the appropriate antibiotic course should be provided for maternal and fetal health safety. In our study, 196 urine samples were collected from pregnant women who visited the maternity hospital in Zakho city, Kurdistan Region, Iraq. Out of these, the prevalence of *E. coli* isolates was 17.34% among pregnant women when compared to non-pregnant women (34.7%). The prevalence rate of *E. coli* among non-pregnant and pregnant women was statistically significantly differences (P<0.032) using Chi-Square (Fisher exact test). The low prevalence on infection among pregnant women in the present study attributed to that the pregnancy is the stage in which the vaginal microbiota conditioned by very high estrogen levels has a blood supply of glycogen and a high concentration of lactobacilli flora which significantly reduce the development of pathogenic bacteria, more because of the production of defense factors by bacilli. The rate of the prevalence of *E. coli* in our study is higher than a study conducted in Kirkuk City, Iraq, who mentioned that the prevalence of *E. coli* was 11.7% **(**Almukhtar, 2018). On other hand, in the present study, the prevalence of *E.coli* infection is lower than other findings of similar research conducted in in Zakho city, 35.25% (Ibrahim et al., 2020), and in Duhok City, Kurdistan Region, Iraq 74.32% (Assafi et al., 2015). Furthermore, a study conducted in other countries like Iran showed that the prevalence of *E.coli* among pregnant women was 61.6% which is higher when compared to our study (Azami et al., 2019). The rate of prevalence was comparable to a previous research done in Tanzania, which found that the prevalence of infection in pregnant women was about the same as it was in the current research (16.4 %) (Olsen et al., 2000). These findings were virtually identical to those of researchers in other countries, with slight variations that may be attributed to variations in the environment, community social habits, low economic status of the study subjects and personal hygiene and education standards (Al-Haddad, 2005). Comparisons of prevalence in various research may be hindered by variances in methodologies and research populations. Regular health education provided at health facilities and public knowledge among pregnant women on antenatal care and follow-up throughout pregnancy in the studied region may be attributable to the lower prevalence of UTI infection identified in this study compared to previous studies. Different factors have been documented to contribute to UTIs including *E. coli* among pregnant women. These include, gestation age, age, and level of education (Gilstrap et al., 2001; Dimetry et al., 2007). In this study, pregnant women in their first trimester had the highest rate of *E. coli* (37.3 %), followed by those in their second trimester (36.2 %) and then those in their third trimester (26.5%) with no statistically significant differences (p<0.44). These findings were disagreement to previous study conducted in Mosul city, Iraq, who reported the highest rate of *E. coli* was among pregnant women in the third trimester 53% flowed by those in the second trimester 44% and then those in the first trimester 30% (Al-Jawadi , 2012).On the other hand, these findings are in the line with research's conducted in Bangladesh ,Iran, Ethiopia, Yemen, and India (Kawser et al., 2011; Ferede et al., 2012 ; Sibi et al., 2014). Urethral dilation and urinary stasis are caused by both structural and hormonal modifications in pregnant women, which contribute to an increased risk of UTI (Le et al., 2004). This study showed that, the highest proportion of *E. coli* was detected among women aged 25-34 years (21.6%) with high parity and the least was in 16-24 years, and this nearly in agreement with other studies done in Babylon, Iraq (Almamoryi and alsalman, 2019) .This is also consistent with the study conducted by (Krcmery et al., 2001), followed by the age group 35-45 years 20% and 10.7% for the age group 16-24 years , The prevalence of UTI was found to be higher in the age group of 25-34 years This might be due to the fact that women between the ages of 25-34 are sexually active. (Bandyopadhyay et al., 2005). The highest rate of infection was reported among pregnant women who lived in rural area (20.8%) than in urban area (16.9%).. This may be due to the nature of rural sanitation as well as a lack of concern with personal hygiene. Similar finding reported in Iraq (Al-Gasha'a et al., 2020), and in Egypt (Shaheen et al., 2016). Current study showed that the higher rate of *E. coli* was found among worker (18.2%) than house wife women (17.3%) but there are no statistically significant differences between them ($P<0.6$). Similar findings noted in Mosul city, Iraq (Al-Jawadi, 2012), and in Tanzania (Olsen et al., 2000), may be due to that house wife can visit the health unit regularly for antenatal car and also could be due to women who worked more exposed to different risk factors. According to the educational level of participants, the higher rate of *E. coli* infection was found in illiterate women (19.4%) followed by higher education level (18.9%). This might be due to pregnant women's lack of information regarding the transmission and prevention of uropathogens such *E. coli*. Furthermore, physician-confirmed kidney diseases such as glomerulonephritis, genetic abnormalities of the kidneys, kidney stones, adrenal gland disorders, and renal malformations are all substantial risk factors for UTI in pregnant women (Sobotová, 2011). Our result is consistent with the studies conducted in Egypt, and Iraq, they found that the highest infection rate was recorded among women who were low level of education or illiterate (Dimetry et al., 2007; Al-Jawadi, 2012). Another study conducted in Ethiopia found that significant UTI was linked with low educational status ($p = 0.002$). Furthermore, A study conducted in Turkey found that UTI was significantly high among women who had secondary level education in their study ($P < 0.05$) (Gunes et *al., 2005).* Another study performed in Pakistan found that there was no significant effect of education on the prevalence of UTI among pregnant women (Sheikh *et al.,* 2000). Furthermore, In the present study, the highest infection was found among pregnant women who had history of UTIs (19.9%) than those without history of infection (8.9%) with statistically significant differences ($P<0.05$). The prevalence of pathogen resistant strains in persons with a history of UTI might be the reason for this. (Johnson et al., 2016). Furthermore, during pregnancy, a variety of hormonal, mechanical and physiologic alterations causes major changes in the urinary system, which has a considerable impact on the acquisition and natural history of bacteriuria (Al-Kuwari et al., 2009). This study in the line with other studies done in Kirkuk city, Iraq (Chateen et al., 2007). Other studies conducted in Iraq and Pakistan found that there was a significant association between people who had history of UTI than those without (Sheikh *et al.,* 2000*;* Haider et al., 2009; Al-Jawadi, 2012*).* On the other hand, several studies conducted in Sudan and Thailand reported that there is no association between past history of infection and UTI infection (*Kovavisarach et al., 2009;* Hamdan et al., 2011). In the current study, there was highly significant differences between asymptomatic and symptomatic patients ($P<0.001$). The percentage of prevalence of symptomatic pregnant women with UTI in this `study is in the line with previous study conducted from Ethiopia (Rohini et al., 2017), and the Sudan (Hamdan et al., 2011), but higher than a study done in Pakistan, the difference between the two studies might be attributable to the lower number of symptomatic pregnant women (Haider et al., 2010). Diabetes is a metabolic disorder that affects the body's function and affects blood sugar levels, and having a higher sugar level than necessary may have serious effects. In the present study, there was also significantly associated between diabetic and non-diabetic pregnant women with UTI caused by *E. coli* Infection ($P<0.028$). This is contrast to the study conducted in Ethiopia, who reported that there was no significant association between diabetic and non-diabetic patients (Taye et al., 2018). These variances might be attributable to culture, practice, living standards, and the research population's categorization, as well as the research time and urine screening procedures used (Getachew et al., 2012, Fantahun et al., 2009).

Diabetes' importance in connection to UTI has been established in research studies, there is sufficient evidence in the form of statistics to suggest that diabetes has a role in UTI (Wild et al., 2004). Diabetic women are more likely to get a urinary tract infection than non-diabetic women. It is well known that the infection starts with asymptomatic bacteriuria and evolves to symptomatic bacteriuria as the illness develops. Studies have highlighted the implications of asymptomatic bacteriuria, and its function in causing renal defect in untreated cases has been identified. The presence of type I and type II diabetes increases the risk factors for UTI (Harjutsalo et al., 2008). The antioxidant system, which is active in bactericidal action, is compromised in diabetic patients. Various tests have found that poor glycemic function is a risk factor for a variety of infections (Shah et al., 2003; Thomosen et al., 2011). Similar finding noted by Yadav et al (Yadav et al., 2015) and (Hamdan et al., 2015). Bacterial adherence to uroepithelial cells is increased in diabetic patients, especially in *E. coli* that expresses Type-1 fimbriae, possibly indicating increased pathogenesis and prevalence of bacteriuria in diabetic patients (Chen et al., 2009).In this study there is no significant difference in the prevalence of UTI when it comes to abortion as risk factor ($P< 0.08$) this disagree with another finding noted by Yaris et al (Yaris et al., 2004) he found that there is significant difference in the prevalence of UTI and abortion. UTIs is one of the most prevalent pregnancy problems. In the time of administering antibiotics for urinary tract infections in women of reproductive age, the risk of pregnancy should be considered. Routine monitoring of antibiotic resistance in urine samples to UTI provides data for the current use of antibiotic therapy and resistance control. In Kurdistan Region, Iraq, Several research have been conducted on the incidence and antibiotic resistance profiles of E. coli, which were mostly isolated from male and female urine specimens (Assafi et al., 2015, Abdulrahman, 2018, Hussein et al., 2018). In the present study, *E. coli* isolated from urine samples of pregnant women showed difference in antibiotic sensitivity pattern. The antibiotic sensitivity pattern showed that *E. coli* isolates were very sensitive to Nitrofurantoin (82.4%), and imipenem (96.4%) and around 88% of the isolates were resistance to ampicillin. This result was in the line with other previous studies showing that *E. coli* isolates in urine samples were found to be highly resistance to ampicillin (78%), Meropenem (79.4%), Amikacin (67.6%) %, Ciprofloxacin (67.6%), Followed by the less sensitive Nalidixic acid (47.1%), Gentamicin (44.1%), Cefotaxime (35.3%), Cefixime (29.4%) , Ceftriaxone (29.4%) and the more resistant antibiotic was Doxycycline (20.6%).

In our study, the highest rate of sensitivity to Gentamicin, Meropenem, Nalidixic acid, Amikacin agree with finding of another study conducted in Duhok city, Kurdistan region, Iraq (As-safi.et al.2015). Most of the isolated bacteria were susceptible to Nitrofurantoin this finding agrees with a previous study conducted in Tikrit city, Iraq (Mohemid, et al., 2013) and in Kenya (Mitema and Kikuvi., 2004). Nitrofurantoin is a urinary antiseptic that blocks multiple enzymes and damages bacterial DNA and it is used to treat urinary tract infections. In this study 82.4 % of all isolated bacteria were sensitive to nitrofurantoin comparing the findings to those of Nashtar's 2016 report at

Al-Kindy Teaching Hospital, which observed 80% were sensitive to nitrofurantoin (Nashtar.2018). Alhamdany (2015) observed a higher prevalence of antibiotic resistance at 41.3 %. This was attributed to the fact that his study consisted of diabetic patients who had chronic UTIs (Alhamdany, 2018).

In the current study, the isolated *E. coli* were less sensitive Nalidixic acid, Gentamicin, Cefotaxime, Cefixime Ceftriaxone and Doxycycline. These findings represent alarming increased rates in resistance *E. coli* to several antibiotic especially Gentamycin this could be due to increases overuse and misuse of this antibiotic among general population. Therefore, an urgent measure to stop this threatening development antibacterial resistance is necessary in the region. This result is in line with other previous studies found that *E. coli* isolates were less sensitive to ampicillin (78%) (Khan et al., 2002). In another study in Iraq around 25% of the isolated *E. coli* from urine samples were sensitive to clavulanic acid\ amoxicillin (Hussein et al., 2018). Same authors have showed that around 98%% of isolated *E. coli were* sensitive to amikacin and imipenem (Hussein et al., 2018). Al-Awwad and Mohsen (2018) also found that 1.8 % of people in Karbala were amikacin resistant and 38.2 % were gentamicin resistant (Al-Awwad.et al.2018). Carbapenems, macrolides, tetracyclines, quinolones, cephalosporins, aminoglycosides, and nitrofurans were found to be resistant against uropathogens isolated from various studies (Al Sweih, et al., 2005; Akram, et al., 2007; Kanj and Shigemura et al., 2009; Ahmed, et al., 2014). Antibiotic resistance can be caused by a variety of conditions, but one of the most common causes is incorrect antibiotic usage. (Larsson et al., 2000). This alarmingly high rate of resistance to widely used antibiotics necessitates decisive and aggressive action to counteract certain patterns of resistance.

4.2. Conclusion:

One of the most common causal agents of bacterial diseases that cause UTI in women is *E. coli*. Multidrug resistance is on the increase. *E. coli* is inevitable and poses a significant public health threat globally, especially in developing countries like Iraq's Kurdistan Region, where infectious illnesses, malnutrition, and poverty are all common. (Okeke et al., 2005, Planta, 2007, Moges et al., 2014) . The prevalence and susceptibility profile of *E. coli* showed significant changes in different populations, types of samples, and settings, as well as substantial variances in geographical areas. In the present study, the prevalence rate of infection is quite lower among pregnant women compared to other studies reported in Kurdistan Region, Iraq. This variation could be linked to differences in the environment, standard of personal hygiene, social habits. or maybe low economic status of the study subjects. Design and methodologies may also affect the differences in comparison of prevalence in different studies in the region. The high prevalence rate of infection rate was found in age group between 25-34 years. Additionally, the highest rate of *E. coli* was found in illiterate people followed by higher education. Furthermore, the highest percentage rate of infection was reported among women who lived in rural area. The highest prevalence rate of *E. coli* was also found among people with higher family income categories followed by lower income. In this study, In the presence of associated risk factors, the risk of *E. coli* infection was higher among pregnant women. Such as diabetes mellitus, past history of UTI infection, abortion and present of symptoms during infection were significantly associated with UTI among pregnant women. Therefore, during their routine follow-up, pregnant women should be examined for related risk factors. As a result, routine screening of antenatal women through all trimesters should be considered in order to minimize problems and bad fetal outcomes, especially in the presence of established risk factors such as growing age, multiparity, and a history of UTI. In the present study, Nitrofurantoin, Meropenem and Amikacin and Ciprofloxacin found to be the most efficient antibiotics against *E. coli* isolates from urine samples among pregnant women. However, *E. coli* isolates exhibited less sensitive to Cefixime, ceftriaxone, and doxycycline. Therefore, Antibiotic susceptibility testing should be performed by a physician to guarantee that the most effective antibiotics are prescribed and used, as well as to prevent treatment costs.

4.3. Recommendation

The results obtained in the present study could help physician to identify and know the factors that lead to urinary tract infections in pregnant women. Therefore, during regular follow-up, pregnant women should be examined for associated risk factors. It's also a smart option for practitioners to do antibiotic susceptibility tests based on clinical samples to ensure that the most effective antibiotics are prescribed and used, as well as to prevent treatment costs. More studies are required among pregnant women using more advance techniques including polymerase chain reaction (PCR) to identify the major causative agents

1. Further study is required among large number of populations in Duhok province, Kurdistan Region, Iraq to confirm our results.

2. It is also recommended to perform molecular characterization of different virulence factors associated with *E. coli* isolated from pregnant women.

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