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Risk Factors of Chronic Kidney Disease among children in Gaza Governorates: A Case Control Study

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إهداء

أهدى هذا الجهد إلى والدى ووالدتى الغاليان على قلبي، اللذان كرسا لى ولإخوتى وقتهم وتعبهم فى الحياة، ولم يوفروا جهدا لتفوقنا ونجاحنا فى الحياة.

إلى زوجتى الحبيبة، التى صبرت ووقفت بجانبى طوال الوقت تدعمنى وتساندنى.

إلى اخوتى واخواتى الأعزاء، وأقربائى وكل من دعمنى لتقديم هذا البحث العلمى بشكل مميز.

إلى شهداء وأسرى الشعب الفلسطينى الذين ضحوا بانفسهم من أجل فلسطين والقدس.

أقدم هذا البحث المتواضع آملا ان يكون ممهدا لخدمة العلم.

محمود سعيد العبسي

Declaration

I certify that this research submitted for the degree of Master is the result of my own research, and that this thesis (or any of its parts) has not been submitted from any other previous works to any other university or institution.

Signed: ……
Date: / /

Mahmoud Said Al-Absi

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Abstract

Chronic Kidney Disease (CKD) is one of the emerging worldwide critical health problems encountered in child life. The disease in children is a fatal illness and the infants with advanced renal diseases are at higher risk of death in the first 2 years of life. This case control study aimed to determine the main risk factors of CKD among children in Gaza governorates (GGs). The sample study consisted of 400 child; 200 cases and 200 controls. The participants were selected from those medical files at Al-Ranteesy hospital while the controls were chosen from the main governmental primary health care centers in each governorate. A questionnaire was constructed and data was collected by the researcher through a face to face interview with the mothers of children. The results of the study showed that the most frequent renal cause of CKD was Nephrotic Syndrome (30%) followed by Vesico-ureteral Reflux (20%), and Focal Segmental Glomerular Sclerosis (18%). While the most congenital renal cause was kidney atrophy (23%), and born with one kidney (20%). Among socio-demographic risk factors, percentage of cases sample were (57%) male, and (43%) female. Other risk factors include lower educational level for mother, child birth weight, small gestational age, child obesity, history of HTN and anemia. The study found that there is no relation between the extensive use of antibiotics and analgesic. However, analgesic drugs use during pregnancy can lead to CKD at childhood, nevertheless it was not associated with antibiotic drugs use. Maternal obesity, and low amniotic fluid shows positive association with child CKD. Mothers with chronic health problems especially HTN and DM and maternal age during pregnancy, are not consider risk factors. A significant positive association with living area in camps and villages, living near hazards, and unsafety drinking water was confirmed. The study concluded that most of the risk factors appeared are avoidable. It is found necessary to follow up at maternal and antenatal care, encouraging child health screening for UTI and other urologic problems, controlling of environmental hazard can decrease the risks of CKD in GGs.

Key words: Chronic Kidney Disease in children, Risk factors, Gaza Governorates.

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List of Abbreviations

BMI	Body Mass Index
CDC	Center Of Disease Control
CKD	Chronic Kidney Disease
EGFR	Estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
FSGS	Focal Segmental Glomerular Sclerosis
GFR	Glomerular Filtration Rate
GGs	Gaza Governorates
MOH	Ministry Of Health
NS	Nephrotic Syndrome
NCDs	Non Communicable Diseases
NGOs	Non-Governmental Organizations
NKF	National Kidney Foundation
NSAID	Non-Steroidal Anti-Inflammatory Drug
PHIC	Palestinian Health Information Center
RRT	Renal Replacement Therapy
RSPH	EL-Ranitis Specialist Pediatric Hospital
SPSS	Statistical Package for the Social Science
UNRWA	United Nation Relief and Work Agency
USRDS	United States Renal Data System
VUR	Vesico-ureteral Reflux
WB	West Bank
WHO	World Health Organization

Chapter one: Introduction

1.1 Background

Chronic kidney disease (CKD) is one of the most critical kidney diseases which is considered according to the Center of Disease Control (CDC) an irreversible disease could lead to chronic renal failure that affect the individual health (CDC, 2014). National Kidney Foundation (NKF) defined CKD as kidney damage for more than three months and confirmed by kidney biopsy or markers of kidney damage (NKF, 2002). Recent studies acceding with the United States Renal Data System (USRDS) that they classify the severity of CKD in five stages; with stage one being the mildest and usually causing few symptoms and stage V being a severe illness with poor life expectancy if untreated (USRDS, 2010 & NKF, 2002). The mortality that is associated with end stage renal disease (ESRD) in children who receive dialysis is estimated to be at least thirty times higher than that of the general pediatric population (Furth et al., 2006).

Harvard Medical Schools (HMS) found that half of children with CKD has complained of congenital malformations in certain area of the renal system and these sites include the kidneys or the bladder, and these malformations include obstruction to kidneys that prevent access of blood to getting them, urine reflux to kidney that can cause chronic infection, dysplastic kidney that make loss of kidney functions, and the other half of them has complained of Nephrotic Syndrome (HMS, 2014). Risk factors for the increased prevalence of CKD include a positive family history, obesity, blood pressure changes, calcium/phosphorus metabolism and fluid imbalance, malnutrition, anemia, diabetes (DM), and exposure to some environmental pollutants (Amaresan, 2005). In developing countries

including Palestine, CKD is considered more serious because of the low socio- economic status and unstable political conditions and subsequently the poor health care system with lack of a data base for the epidemiology of this health problem (Boutayeb et al., 2013). So, the researcher found it necessary to conduct this study to identify the most common risk factors of CKD among children of Gaza Governorates (GGs).

1.2 Research problem

CKD is an emerging health problem in both developed and developing countries and this health problem is increasing enormously in the last few years and is now being recognized as a major public health problem that is threatening to reach epidemic proportions and there are marked variations in the incidence and prevalence of ESRD in children globally (Harambat et al.. 2012). CKD is one of epidemic trend at last two decades that considered one of the common causes of premature death and morbidity and have a major impact on health-care costs, productivity, and growth (Couser et al., 2011). Although, Harambat et al. (2012), clarify that there is a limited information about the epidemiology of this disease specially in early stages as it is often asymptomatic and therefore the incidence of the problem appear to be underreported and the prevalence stage of II-V of CKD in children aged 0-19 years across the world in 2008 was 9 per million of the age related population.

According to Harambat et al. (2012), CKD in children is a fatal illness and the infants with advanced renal diseases are at higher risk of death in the first 2 years of life, and the mortality rate for them with ESRD receiving dialysis therapy is between 30 and 150 times that of the general pediatric population. A study from the United States Renal Data System (USRDS) concluded that 70% of children with (CKD) usually develop ESRD by age of 20 years. Children with ESRD have age-specific mortality rate of about 30 times that seen in

children without ESRD (USRDS, 2013). Data from USRDS show that incidence of kidney failure is rising among CKD patients of all ages and is commonly associated with poor outcomes (USRDS, 2010). The rapid increase in the prevalence of ESRD and the enormous cost of treatment necessitate an urgent approach to the implementation of strategies to prevent the further development of ESRD, especially in developing world. Detailed chronological changes in the prevalence of ESRD may sharpen the focus on its prevention (Aghighi et al, 2009).

1.3 Justification of the study

Globally, CKD appear to be an emerging chronic disease and it is considered as one of the most critical non communicable diseases (NCDs) with a rapidly increasing prevalence in children less than twelve years (WHO, 2010). In Gaza Governorates (GGs), kidney diseases is a rapidly increasing health problem with a total registered number of cases of 1543 and 410 of them has been diagnosed with CKD. In the last three years, the number of deaths among children diagnosed with CKD was 72 child (Ranteesy hospital annual report, 2014). The life expectancy for a child 0–14 years of age and on dialysis is only 20 years (USRDS, 2010). The cost of a dialysis session is 100-150 $ for every one patient and most of patients usually need three dialysis session days per week (National Health Account, 2011).

In Palestine, the cost of kidney replacement therapy according to evidence-based resource allocation decisions for government-funded kidney disease services are limited, and some of the common modalities, such as: peritoneal dialysis (PD) and home hemodialysis (HD), are not widely available due to shortages of qualified staff, specialists, and centers to follow the patient status, provide training, make home visits, or provide educational programs for patients. The average cost of kidney transplant was US$16 277 for the first year; the

estimated average cost of HD per patient was US$16 085 per year-nearly as much as a transplant (Younis et al., 2015).

In GGs, the health care organizations providing services to children with CKD has complained of limited resources including medicines, fluids and disposals beside the lack of equipments needed for maintenance of dialysis machines which could affect the quality of services and health status of those patients (Ministry of Health (MOH) annual report, 2013).

When searching for this problem, the researcher found that many studies has been conducted globally, regionally and in Palestine to describe the magnitude of this problem in adult population but, a limited number of researchers has tried to tackle this problem in children through determining the epidemiological status, causes and the most common risk factors and the most recent advances in managing this health problem in developing countries in general and in Palestine in particular. These research trials include a study conducted by Abu Odeh to determine the risk factors for renal dialysis patients in the Gaza Strip at 2013, and a descriptive study conducted by El-Aila in December, 2013 to clarify the prevalence, etiology, and staging of CKD among children of Gaza Strip.

So, the researcher found it valuable to study this health problem to determine the most common risk factors of CKD among children and to communicate the study findings and recommendations to decision makers of the different organizations included within the health care system in GGs. This study findings and recommendations could help the stakeholders and decision makers in setting priorities and finding solutions of this health problem. This study can be considered a base for further studies to go deeply through investigating the other

aspects of the problem such as the most recent advances in term of causes, diagnoses and management of CKD in children of GGs.

1.4 Objective of the study

The overall aim of the study is to determine the major risk factors of chronic kidney disease among children less than 12 years in Gaza Governorates.

1.5 Specific objectives

1. To describe the relationship between the family's socio-economic status and the CKD in children of GGs.
2. To examine the impact of health status of mothers during pregnancy and the occurrence of CKD in their children of GGs.
3. To investigate the impact of adverse environmental conditions in increasing the prevalence of CKD in GGs.
4. To assess the relationship between hereditary and chronic diseases and congenital malformations of children and the increasing incidence of CKD in GGs.
5. To suggest recommendations for actions could be taken by the stakeholders to reduce impact of CKD among children in GGs.

1.6 Research questions

1. What are the main risk factors of CKD among children in GGs?
2. Is there a relationship between the socio-economic status and appearance of CKD in children in GGs?
3. Could intermarriage increase the incidence of CKD among children?
4. Can we consider abnormal birth weight a risk factor of CKD in children?
5. What are the most common hereditary and chronic diseases associated with CKD in children of GGs?

6. Has congenital malformations played a role in the rapid increasing incidence of CKD in children of GGs?
7. What are the most common renal diseases associate with CKD in Children in GGs?
8. Is there a relationship between blood circulation problems and CKD in children?
9. Is there a relation between maternal health status and CKD in infant and his next life?
10. What is the impact of misuse of medications on the appearance of CKD in children?
11. What are the environmental factors that could affect on the incidence of the problem?
12. What is the relationship between the child's BMI and CKD?
13. What are the recommendations to be drawn from the study in order to control of its factors?

1.7 Context of the study

1.7.1 Demography context

Palestine geographic region in Western Asia with total area 27,000 km^2 between the Jordan River and dead sea from the east, Mediterranean Sea from the west, south from Egypt and Red Sea, and north from Lebanon and Syria (Annex 1). Currently it consist of two geographically areas West Bank WB and Gaza Strip GS. Gaza strip is a narrow coastal strip consist of five governorates: North, Gaza, Mid-zone, Khan-Younis and Rafah. It consists of four cities, fourteen villages and eight refugee camps, bounded of the east and north by the occupied territories in 1948, on the west by the Mediterranean Sea, and on the south by Egypt (Annex 1). Gaza strip is very crowded place with 46 kilometers long and 5 –12 kilo-meters wide and with a total area of 365 Km^2 (Epidemiology bulletin, 2012).

GS has a population of 1.761.906 people, the Male/Female ratio in general population is 103.100. Infant Mortality Rate is 17.1 per 1000 live births. Crude Birth Rate is 38.3/1000. Crude Death Rate is 3.1/1000. Average life expectancy is 70.2 years for males and 72.9 years

for females. Fertility rate is 5.7%. , Family size Average is 5.8. (Epidemiology bulletin, 2012).

1.7.2 Socioeconomic status in Gaza strip

Gaza strip suffer from unstable economic situation, related to war on Gaza three times and affected on all daily life aspects of citizens, also siege that imposed lead to increase the unemployment's people, unsafety life and live in peace, all of these reasons lead to loss of well-being among Gaza people and increased poverty. Poverty is one determinants of poor health and scale determines the standard of living and one important indicator to read improvement or decline of economic performance, which in turn will affect the health performance, and can identify indicators of poverty through some indicators such as income level, education and living conditions and economic and social situation.

It is noteworthy that the poverty line for a family of reference, consisting of five members (two adults and three children) in the Occupied Palestinian 2,293 shekels in 2011 (about $ 637), while the extreme poverty line for the reference household 1,832 shekels. According to real consumption patterns 38% of families are poor, and extreme poverty 23%. The average daily per capita income in the Gaza Strip, 3%, where the average monthly income of $ 75 and it will be 2.5 $ per day (Determinants of health, PCBS, 2013).

1.7.3 Health care system in Palestine

Health care system in Palestine is complex, it's affected by the all health systems that applied in Palestine in the last decade. It consists of four major providers: Ministry of Health (MOH) United Nation Relief and Work Agency (UNRWA), Non-governmental Organizations (NGOs) and private sectors. MOH is the main provided source of primary, secondary, and some of tertiary cases care for all Palestinian people, while UNRWA the second major source of providing primary health care, especially for refugee people (MOH, 2011). The proportion

of beds allocated to sick children among hospitals 21.2% that reach in 2010 (637) beds, distributed between West Bank and Gaza Strip, as 36 % (228) and 64% (409) respectively (PHIC, 2011). There is one main hospital of MOH in GGs that provide services for children who complain from CKD, Abd Al-Aziz Al-Ranteesy Specialist Pediatric Hospital in Gaza city.

1.7.2.1 Setting of the study: El Ranteesy Specialist Pediatric Hospital

This hospital offers third level services for the children in Gaza Strip with chronic illnesses and need for specialized care. The hospital was created in 2003 and opened in 2006 and located at Kamal Odwan Street next to Psychiatric Hospital. The hospital provides a specialized health services to children with specific health problem such as children with blood, heart, kidney and metabolic disorders as well as children oncology and hematology disorders. In the past, these cases needed to travel abroad to be treated and receiving a specialized services. The hospital constitute of different specialized units according to the nature of the health problem such as oncology, cardiology, and neurology special care units. Nephrology and Dialysis are two specialized units provide a specialized health care services to children with renal diseases including CKDs and renal failure. The nephrology unit contain 12 beds for patients who stay and the Dialysis unit contain 10 hemodialysis machines (Abd Al-Aziz Al-Ranteesy pediatric hospital annual report, 2010).

1.7.2.2 Primary Health Care centers

Primary health care (PHC) is a major component of Palestinian health care system. PHC provides preventive, promotional, curative and rehabilitative health care to all Palestinian people especially for children and other vulnerable groups through MOH, UNRWA, non-governmental and private centers. At the end of 2014, the total number of PHC centers in GS

were 54 centers guided by MOH, 21 centers guided by UNRWA, 7 military clinics, 81 centers guided by Non- governmental organizations (MOH, 2014).

1.8 Operational definitions

1.8.1 Risk factors: Is any attribute, or exposure of an individual that raise the likelihood of developing a disease or injury. Some examples of the more important risk factors are underweight, unsafe sex, high blood pressure, tobacco and alcohol consumption, and unsafe water, sanitation and hygiene (WHO, 2014).

1.8.2 Chronic disease: A disease that persists for a long time for 3 months or more, it is cannot be cured by medication or prevented by vaccination and not transfer from person to person (WHO, 2013).

1.8.3 Kidney disease: Is any damage or disorder that affect the kidney and its function, also called renal disease (Health central, 2014).

1.8.4 Chronic Kidney Disease (CKD): Defined using NKF- Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines (GFR < 60 ml/min/1.73 m2 or proteinuria > 1+ on dipstick) (The renal association, 2014).

1.8.5 Renal failure (RF): Is a condition that kidney being inadequate to filter wastes from blood, and its progression of CKD, also called End stage renal disease (ESRD) (National Institute of Diabetes and Digestive and Kidney Diseases (National institute for health and care excellence (NIH), 2014).

1.8.6 Renal Replacement Therapy: Renal replacement therapy (RRT) replaces non-endocrine kidney function in patients with renal failure and is occasionally used for some forms of poisoning. Techniques include intermittent hemodialysis, continuous hemofiltration and hemodialysis, and peritoneal dialysis. All modalities exchange solute and remove fluid from the blood, using dialysis and filtration across permeable membranes (USRDS, 2013).

1.8.7 Child hood age: A child is a person 18 years or younger unless national law defines a person to be an adult at an earlier age (WHO, 2013). In Palestine, the MOH policy define the childhood age is a person 12 years or younger that they allowed to get the health services in pediatric hospitals.

2. Chapter two: Literature review

2.1 Conceptual framework

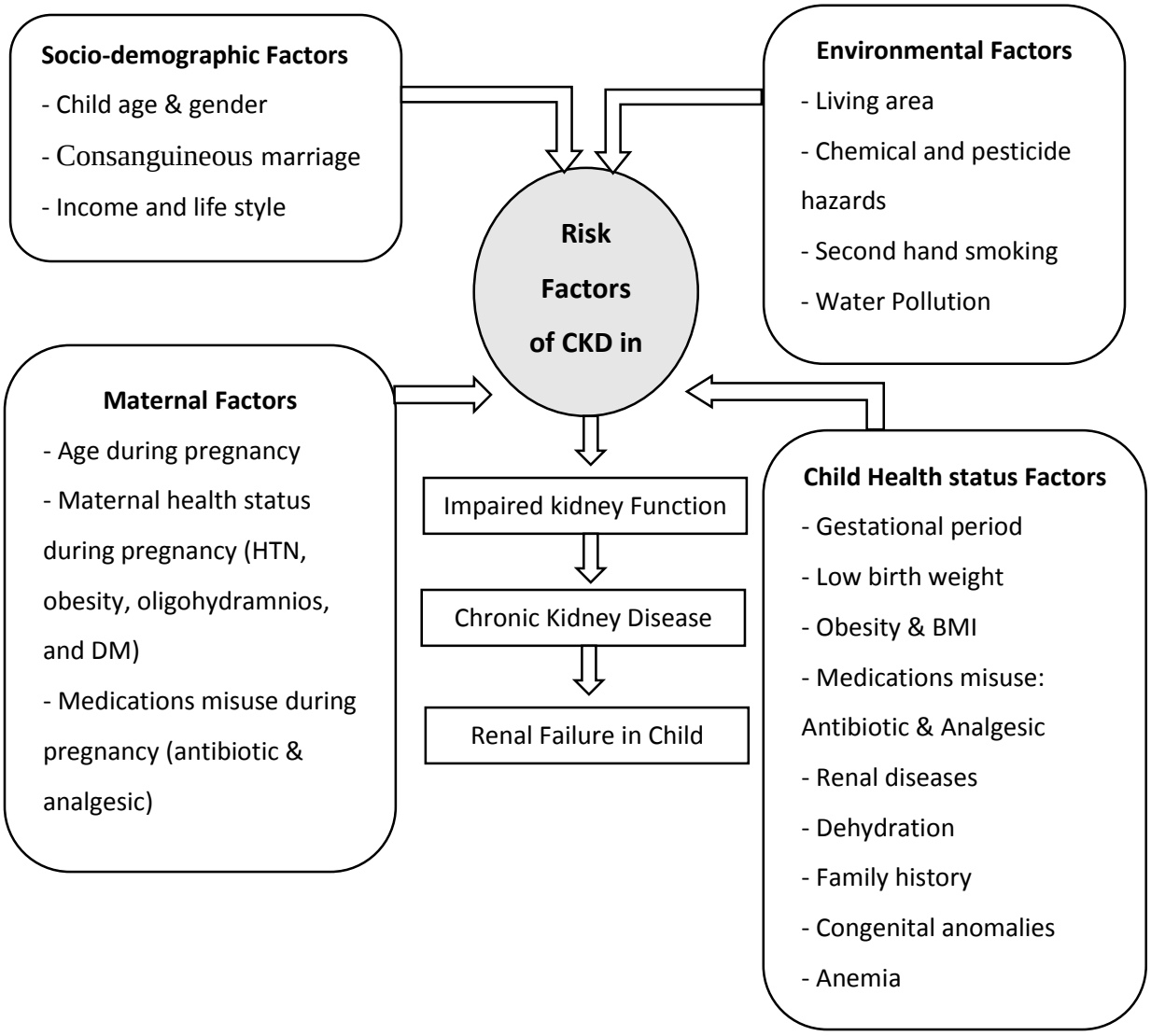

Figure (2.1) demonstrate the conceptual model of the study

Conceptual framework has been constructed by the researcher himself after reviewing literatures related to this health problem and other topics especially risk factors, and these risk factors are represented in the study in specific details in this chapter.

1- Socio-demographic factors: Are the first list which peruse the subject's notification as risk factors that include age, gender, number of family member, parent age, consanguineous marriage, and monthly income.

2- Child health status factors: Determine the health status before and during the disease including the child's height and weight, GFR level, blood pressure, body mass index (BMI), low birth weight, gestational period, congenital anomalies specially those of the renal system, renal diseases, medications misuse, blood circulation problems, other chronic diseases, and a positive family history of the problem being studied.

3- Maternal factors: The factors associated with the mother when being pregnant with the child being included in this study such as age during pregnancy, maternal health status during pregnancy; including (Hypertension (HTN), Obesity, Diabetics mellitus (DM), and oligohydramnios), place and type of delivery, and receiving a specific therapy during pregnancy.

4- Environmental factors: are the last list which the researcher explore about which include the type of living area, water supply to drink, chemical and pesticide hazards, and second hand smoking.

2.2 Epidemiological background of CKD

Recently, CKD and renal failure have been recognized as a significant and serious public health problem. Scientific and technologic improvements during the last few years provided renal replacement therapy as a life maintaining option for many patients who otherwise may have died and the impact of these medical advancements has been remarkable (USRDS, 2013).

CKD is characterized by an irreversible deterioration of renal function that gradually progresses to ESRD. Data from the USRDS show that incidence of kidney failure is rising

among adults and is commonly associated with poor outcomes and high cost. Moreover, in the past two decades, the incidence of CKD in children has steadily increased specially in poor populations (USRDS, 2010). The major health consequences of CKD include not only progression to kidney failure but also an increased risk of cardiovascular disease. Early recognition and treatment of CKD's complications is of great importance to improve growth and development (USRDS, 2010).

2.2.1 Globally

Most epidemiological information on CKD comes from data available on ESRD. There is not enough data about prevalence of early stages CKD in children. Only few reports on the epidemiology of CKD stages II to V in children are diagnosed and determined, and there is a lack of information about the disease in low-income countries (Harambat et al., 2012; Warady, 2009). Harambat et al. (2012), found that the prevalence of CKD stage II or lower in children is reported to be approximately 18.5-58.3 per million children while the renal replacement therapy among children was approximately 80% in Europe, Japan, and North America. The prevalence of patients with early stages of CKD I–IV (10.8%) is approximately 50 times greater than the prevalence of ESRD stage V (0.2%) (Warady, & Chadha, 2009).

In modern time, there is a lack of information on the prevalence of CKD among pediatric population in developing countries and data is mostly obtained from reports of major secondary and tertiary care centers, but the validity of this data is variable (Harambat et al., 2012).

2.2.2. In North America

In North America, the incidence in United States of America for all CKD stages aged 0-19 years old reached 36.5 per million population (PMP) and the prevalence approximate a 39.3 PMP, the total number of CKD in the patients has grown approximately 32% since 1990.

This is in contrast to the 126% growth experienced by the entire ESRD population over the same time period (USRDS, 2012). The mortality rate for children with ESRD receiving dialysis therapy is between 30 and 150 times that of the general pediatric population (USRDS, 2012). In Canada, the incidence rate of CKD of children aged 0-14 years old in all stages were 11.2 PMP while the prevalence in all stages around 65.1 PMP (Harambat et al., 2012).

2.2.3. In Europe

In Europe, the renal center for ESRD report that the incidence was fairly consistent, being around 11-12 PMP for CKD stages III-V, and 8 PMP for CKD stages IV-V, while an increase prevalence ranged from about 55-60 to 70-75 PMP in Spain and Italy, and the incidence of the disease increased in France since 1970s till now (Harambat, 2012). According to the Serbian Pediatric Nephrology determined that the incidence of CKD II–V stages was 14.3 PMP while those of CKD II–IV or CKD V were 9.1 and 5.7 PMP respectively in Serbia (Antic et al., 2012).

2.2.4. In Latin America

The national survey of pediatric nephrologists in Chile estimated the incidence of CKD in children which reached a 5.7 PMP and the prevalence was 42.5 PMP, while in Argentina and Uruguay the incidence of patients under age 18 years old who treated by renal replacement therapy (RRT) 18 and 7 PMP respectively, whilst the prevalence of RRT with hemodialysis in Brazil around 24 PMP (Harambat et al., 2012).

2.2.5 In Arab countries and East Mediterranean Region (EMRO)

In the Middle East and Arab countries, there is no enough data in the medical literature regarding the status of renal care registry, in Syria there is no specific data about the burden of CKD in children before or after the war, WHO website did not publish any data or statistics

in regard to renal care in Syria (Al-Makki et al., 2014). CKD rates based on referral to tertiary centers are probably underestimated and vary from 15.6 per million child population PMP in Saudi Arabia as prevalence to 35 PMP in Kuwait as incidence, in Sudan the children that had RRT were 4.5 PMP while they increase in Egypt 680 PMP and Saudi Arabia 810 PMP (Rizvi, 2013). The figures vary from less than 100 per million population PMP in sub-Saharan Africa to about 330 PMP in Jordan; 360 PMP in Iran; and 600 PMP in Saudi Arabia (Aghighi et al., 2009; Mahdavi et al., 2007; and Barsoum, 2006).

2.2.6. In Occupied Palestine, West Bank, and Gaza Strip

In Negev area, the Israeli Census Bureau recorded that the prevalence of CKD among children reached 795.4 PMP, where the age-adjusted less than 19 years old for CKD prevalence rate was 628.2 among Jewish, whereas the same age adjusted prevalence rate among Arab Bedouin was 850.2 PMP (Landau, 2013).

In West Bank, the distribution of ESRD prevalence is 240.3 PMP (adult & children), and 4.3% of them are children below 14 years of age and need dialysis therapy (Khader, 2013). In GGs, the total number of below 12 years patients who are suffering from CKD approximately is 410 cases and 26 of them are diagnosed with ESRD and treated by renal dialysis and the number increase dramatically every year (Ranteesy Hospital Annual report, 2014). In a descriptive study conducted to determine the prevalence, etiology, and staging CKD in pediatric, the researcher reviewed 260 medical record files of patients who attending nephrology department in Al-Ranteesy Hospital since 2007 to 2012. The study found that the incidence of CKDs was higher in male than female children (60% VS 40% respectively), while the incidence was 15.4% in children less than 2 years of age, 36.1% for 2-6 years, and 48.5% for 6-12 years of age. The distribution of CKD according to stage of disease was:

stage I with 58.8%, stage II 12.3%, stage III 12.3%, stage IV 6.15%, and stage V and treated by hemodialysis were 10.4% (El-Aila, 2013).

2.3 Anatomy and function of the kidney

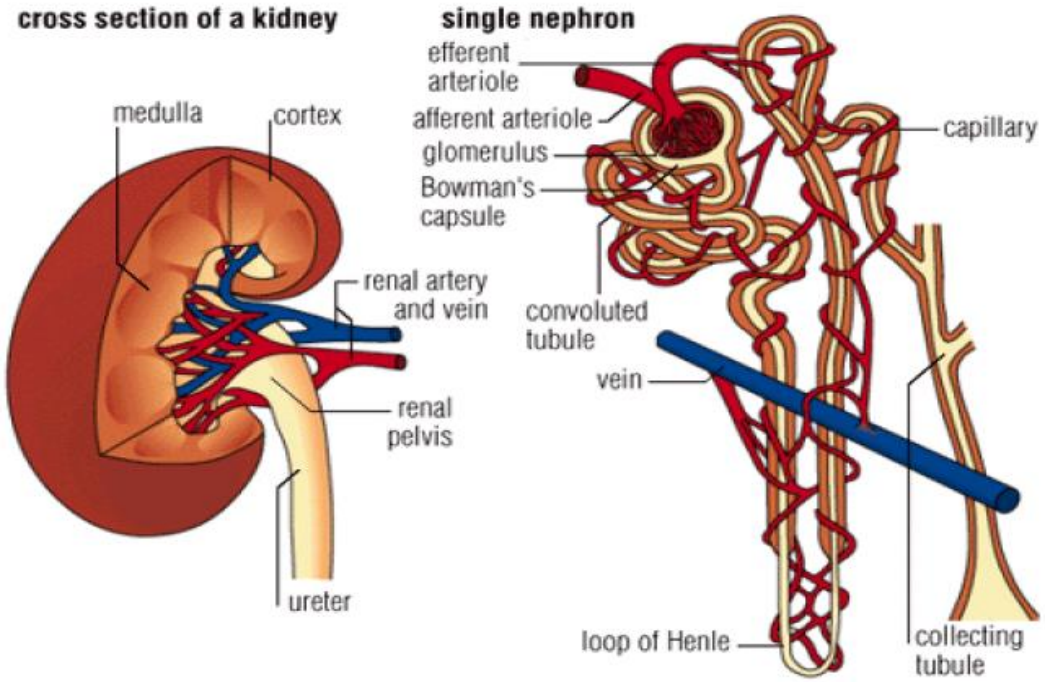

Figure (2.2) Anatomy of the Kidney and the Nephron

Kidney is a paired organ, the basic units of the kidneys are microscopically thin structures called nephrons, which filter the blood and cause wastes to be removed in the form of urine. Together with the two ureters, bladder, and the single urethra, the kidneys make up the body's urinary system. Human beings, as well as members of all other vertebrate species, typically have two kidneys. The kidneys of adult humans are about 10 to 13 cm (4 to 5 in) long and about 5 to 7.5 cm (2 to 3 in) wide (NKF, 2013). A primary function of kidneys is the removal of poisonous wastes from the blood and regulating the amount of fluid in the body. Chief among these wastes are the nitrogen containing compounds urea and uric acid, which result from the breakdown of proteins and nucleic acids. Life threatening illnesses occur when too

many of these waste products accumulate in the bloodstream. Fortunately, a healthy kidney can easily rid the body of these substances (NKF, 2013).

2.4 Pathophysiology of CKD

2.4.1 Acute renal failure

Also called "Acute Kidney Injury" is defined as “rapid decline in renal filtration function″, in this disease, the kidneys failed to remove waste and help balance of fluids and electrolytes in human body. It is usually marked by a rise in serum creatinine concentration or azotemia, the major causes include a sudden and serious drop in blood pressure related to severe blood loss in case of burns, severe diarrhea, shock; damage from some medicines, poisons such as antibiotics including aminoglycosides, analgesics such as Naproxen and Ibuprofen, some blood pressure medicines such as ACE inhibitors and the dyes used in some x-ray tests; sepsis which can reduce blood flow to the kidney; and trauma. Symptoms of the disease may include oliguria or anuria, anorexia, nausea and vomiting, confusion, anxiety, back pain, insomnia, abdominal pain, and edema (National Health Services, 2014).

2.4.2 Chronic Kidney Disease

It is a slow loss of kidney function over time. The main function of the kidney is to remove wastes and excess water from the body. This disease get worse over time. In the early grade no big symptoms appear until kidney function is less than one-tenth of normal, the final stage of chronic kidney disease is called End Stage Renal Failure (ESRD). At this stage the kidney is not able to remove enough wastes and excess fluid from the body, and the patient had only two choices which are dialysis or Kidney transplant (NIH, 2014).

2.4.2.1 Classification of CKD

Kidney function should be assessed using a combination of GFR and Albumin-Creatinine ratio (ACR) categories. Increased ACR and decreased GFR in combination multiply the risk of adverse outcomes (National institute for health and care excellence, 2014).

Stage I: normal - eGFR >90 ml/minute/1.73 m2 with other evidence of chronic kidney damage.

Stage II: mild impairment - eGFR 60-89 ml/minute/1.73 m2 with other evidence of chronic kidney damage.

Stage IIIa: moderate impairment - eGFR 45-59 ml/minute/1.73 m2.

Stage IIIb: moderate impairment - eGFR 30-44 ml/minute/1.73 m2.

Stage IV: severe impairment - eGFR 15-29 ml/minute/1.73 m2.

Stage V: established renal failure (ERF) - eGFR less than 15 ml/minute/1.73 m2 or on dialysis.

2.4.2.2 Calculating CKD level in children

Proportionality Constants: The level of GFR in the blood can be calculates by: child's GFR= patient age group* Height (cm)/ pediatric serum Creatinine in the blood (mg/dl).

Table (2.1): GFR calculator

Age Group	D
Low birth weight infants, age < 1 years	0.33
Term infants, age < 1 years	0.45
Children, ages 2-12 years	0.55
Girls, ages 13-21 years	0.55
Boys, ages 13-21 years	0.70

Table (2.1): The distribution of CKD level according GFR calculator; Source: (Medical Calculator: Pediatric Glomerular Filtration Rate, 2015).

2.5 Etiology of CKD in children (causes and risk factors)

Unfortunately, the conditions that lead to CKD in children cannot be easily fixed. Often, CKD will develop silently and goes unnoticed until the kidneys have been permanently

damaged. Causes of CKD differ in children from those in adults. Congenital anomalies of the kidneys and other parts of the renal system, blocked urine flow and reflux as well as hereditary nephropathies were the most common causes. Causes varied with age where congenital anomalies of the renal organs is the common cause in the young children, glomerulonephritis was the common cause in children older than 12 years of age (Harambat et al., 2012).

In most countries, obstructive uropathy and congenital anomalies are the predominant causes of CKD (Harambat et al., 2012), while in less developed countries, infections related glomerulopathies are the main causes of CKD in children (Kari, 2012). The other major causes leading to chronic kidney disease among children are hypertension and proteinuria which are associated with the disease; anemia, hypoalbuminemia, hyperphosphatemia, and hypocalcemia might be associated with the disease (Kari, 2012). In his study, El-Aila, (2013) clarified the causes of CKDs among Children of GGs were congenital malformation (55.4%), hereditary diseases (21.1%), Glomerulonephritis (8.5%), and miscellaneous causes (14.5%). The researcher concluded that the CKD could be one of the highest causes of death among children of GGs.

2.6.1 Renal diseases and CKD in children

Unlike adults in whom diabetes and hypertension are responsible for the majority of cases of CKD, congenital anomalies and infections of the urinary tract including acute glomerulonephritis are responsible for the greatest percentage of all cases of CKD seen in children (Warady, & Chadha, 2009). Renal causes include congenital malformations of the kidney and other organs of the urinary tract, obstructive lesions or urinary reflux appear in area of the urinary tract and infections such as glomerulonephritis (Harambat et al., 2012).

2.6.1.1 Congenital malformations and CKD

Congenital anomalies of human body usually cause many health problems related to congenital organs malformation. Kidney malformations occur during organogenesis between 4 and 12 weeks of fetal life leading to Congenital anomalies of the kidney and urinary tract (CAKUTs), which occur in 3–6 per 1000 live births, account for the most cases of pediatric end-stage renal disease and responsible for 34%-59% of CKD and 31% of ESRD among children in USA (Yosypiv, 2012). A study from Guatemala aimed to describe the prevalence of CKD among children reported that the largest proportions of CKD cases in children are caused by congenital anomalies of the kidney and urinary tract (CAKUT), 30%–60%; hereditary nephropathies 10% 35%; and asymptomatic urinary tract anomalies 5.6% (Ceron et al., 2014).

A medical team investigated the progression of birth defect with new borns at Al-Shifa Hospital, Gaza Strip, Palestine, by using a questionnaire and included 4027 infant at a cohort study found that 55 infants born with structural birth defects (14.0 per 1000 births) and the results showed that 15% of them had renal malformation (Naim et al., 2012). A cohort study in Salento, Italy of ultrasound centers screening for congenital anomalies of the kidney and urinary tract (CAKUT) in infant at 2 month of age involved 17,783 healthy infant, that they already diagnosed by abnormalities renal diseases at antenatal period, the result showed 171 of infant had CAKUT, 39 Vesicoureteral reflux, followed by ureter pelvic junction obstruction 33, kidney atrophy 26, and renal dysplasia 19 of the total infant (Caiulo et al., 2012).

A retrospective analysis of medical record data of children less than 19 years old, hospitalized for CKD at St Al-Zahra hospital, Isfahan, Iran, a total of 268 eligible records to identify the congenital malformation of kidney that cause CKD among the children, and the results

showed that the most frequent etiology of CKD was glomerular diseases (35.2%) followed by congenital anomaly of kidney and urinary tract (CAKUT) (34.5%). Nonetheless, in 21.7% of patients the etiology of CKD was unknown (Gheissari, 2012). The Behrman et al. medical text book determined the polycystic kidney disease as an autosomal disorder, occurring with incidence of 1:10,000 to 1:40,000 of CKD in children during the advanced stages of the disease. The incidence of autosomal recessive polycystic kidney disease (ARPKD) can present in infancy and young children, all cases of ARPKD, a recessive disorder of CKD, are due to a mutation in the polycystic kidney and hepatic disease 1 (PKHD1) gene (Behrman et al., 2004).

2.6.1.2 Nephrotic Syndrome (NS)

NS is a disorder of the kidneys that results from increased permeability of the glomerular filtration barrier that increase the excretion of protein in urine, and caused by damage to the clusters of small blood vessels in the kidney, which lead to edema, gradually loss of kidney function, and disability to filter blood from toxins and wastes that leading to CKD (Andolino, & Reid-Adam, 2015). NS can affect children of any age, from infancy to adolescence, and is most commonly seen among school-aged children and adolescents, and is the common factor of renal problem with underlying causes include glomerular diseases (35.2%) (Harambat et al., 2012). Corticosteroids (prednisone), cyclophosphamide, and cyclosporine are used to induce remission in NS in 4-8 weeks. When the therapy failed to achieve the remission, the problem become worse and leading to Steroidal Resistance Nephrotic Syndrome (SRNS) (Zagury et al., 2013). SRNS is associated with increased risk of ESRD due to persistent proteinuria, therapeutic drug side effects, bacterial infections, malnutrition, hyperlipidemia, and thromboembolic phenomena. The probability of occurrence of ESRD at age 10 years in children with SRNS varies between 34-64% (Harambat et al., 2012).

2.6.1.3 Focal Segmental glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is one of the most difficult and enigmatic diseases in pediatric nephrology. It can occur as a primary disorder without an identifiable cause or as an illness secondary to a variety of problems. Furthermore, the most important causes of acquired chronic kidney disease (CKD) in children and adults and there is no proven therapy for steroid-resistant cases (Kiffel et al., 2011). The main cause is often unknown, but it occurs with scar tissue in the filtering unit of the kidney called glomerulus. More than half of patients with FSGS develop chronic kidney failure within 10 years (Appel et al., 2012). In her study, Kari determined that the predominance of FSGS to be in 24% of total CKD cases in children. Additionally, the detection rate of posterior urethral valves (PUV) was only 27% in antenatal, and it is less than the international rate 70%, at Riyadh city, in Saudi Arabia (Kari, 2012).

On the other hand, FSGS accounts for 20% in children with CKD, and the second leading cause of ESRD, following congenital kidney anomalies. It has become the most common diagnosed primary glomerular disorder reported in most published kidney biopsy series (Edgar et al., 2011).

2.6.1.4 Proteinuria and CKD in childhood

Persistent proteinuria is the signal indicator of a glomerular lesion and play a central role in the progression of glomerular lesions to later stages of CKD. Chronic proteinuria glomerulopathies have in common the sustained or permanent loss of selectivity of the glomerular barrier to protein filtration. The integrity of the glomerular filtration barrier depends on its 3-layer structure. Increased intra-glomerular hydraulic pressure or damage to glomerular filtration barrier may elicit glomerular or overload proteinuria. The mechanisms underlying glomerular disease are very variable and include infiltration of inflammatory

cells, proliferation of glomerular cells, and malfunction of podocyte-associated molecules such as nephrin or podocin. (Gorriz, & Castelao, 2012).

The increase protein level in urine due to damage in the glomerular capillary wall or by decrease in tubular reabsorption of protein causes injury to renal tubular cells, and consider an independent risk factor for a progressive decline in kidney function and strong marker for advance CKD (Wong et al., 2009).

2.6.1.5 Hemolytic-uremic syndrome

Hemolytic-uremic syndrome (HUS) is characterized by the triad of non-immune microangiopathic hemolytic anemia, thrombocytopenia and renal injury related to the development of platelet thrombi and intravascular coagulation in small vessels, particularly in the renal microcirculation (Kher et al., 2007). HUS is the most common cause of renal failure in children that characterized by micro-angiographic hemolytic anemia, thrombocytopenia and uremia. HUS is most common in children younger than age 4 years but may occur in older children and adults, that event with capillary and arteriolar endothelial cell injury in the kidney leads to localized clotting, HUS occurs in approximately 9% of children with ESRD in North America (Behrman et al., 2004).

2.6.1.6 Vesicoureteral Reflux

Vesicoureteral reflux (VUR) is also called a retrograde flow of urine from the bladder into the ureter. These disorder occurs on account of abnormal defects in anatomic and functional in the urinary tract that can result in substantial morbidity. VUR may be associated with urinary tract infection (UTI), and abnormal kidney development such as renal dysplasia (Salo et al., 2010).

Approximately 1/3 of patients who have had a urinary tract infection (UTI) have VUR and 9–20% of patients with prenatal hydronephrosis have VUR when tested postnatal. The

prevalence of VUR in the general pediatric population has been estimated recently to be as high as 17.2%. Unrecognized VUR with concurrent of UTI may lead to long-term effects on renal function and overall child health status with progressive risk for pyelonephritis, hypertension, develop reflux nephropathy (RN), some patients with RN develop CKD, and a small number of patients progress to ESRD (Ristola & Hurme, 2015). The mechanisms for the development of CKD in VUR are complex. RN is usually identified as renal scarring as defined on dimercaptosuccinic acid (DMSA) scan in a patient known to have VUR. It is important to note that the causality is not completely clear as some patients have renal scarring by DMSA scan but do not have VUR. It is also clear that pyelonephritis in the presence of VUR may lead to new scarring on DMSA scans; however, some patients with VUR have RN with renal scarring by DMSA scan at the time of diagnosis whether or not they have had a urinary tract infection. One possible explanation for this is that damage to the kidney may occur embryonically due to VUR. Alternatively, some of the genes that control normal development of the ureters and ureterovesicular junction also control renal development. Thus VUR may be associated with either macroscopically abnormal renal development or subtle developmental changes that predispose the kidney to developing scarring as identified by dimercaptosuccinic acid (DMSA) scan. A portion of the patients who develop ESRD related to RN may have abnormally developed kidneys that progressively worsen over time with further decrease in renal function exacerbated by proteinuria, hypertension, and episodes of pyelonephritis (USRDS, 2013)

Ardissino et al. (2010), retrospectively evaluated the risk of progressing from CKD to ESRD in a cohort of 322 pediatric patients with VUR and creatinine clearance (CrCl) <1.25 mL/s per 1.73 m2 body surface area and found an overall risk of 56% for progressing to ESRD by the age of 20. In addition, age at diagnosis was not associated with an increased risk of

progression to ESRD with those diagnosed at age greater than 6 months having no significant difference in risk of progression to ESRD compared to those diagnosed at age ≤6 months. In this cohort, grade IV reflux was the most common grade of VUR; however, information on the grade of VUR was reported for only 51% of the patients, making it difficult to relate risk of progression to grade of reflux. 29.1% of the patients were either hypertensive or being treated with antihypertensive medication, demonstrating the association between hypertension and RN. VUR is diagnosed with an ultrasound and voiding cystourethrogram (VCUG). Children who have recurrent urinary tract infections are given this test to determine the risk of subsequent infections causing potentially damaging kidney infections.

2.6.1.7 Other renal diseases associated with CKD in children

Congenital renal anomalies such as renal dysplasia with or without Vesicoureteral reflux (VUR) with or without posterior urethral valves; were commoner among younger children. It is important to note that in 18% of all cases of CKD, the underlying primary diagnosis was not identified (15%) or was unknown (3%). A similar distribution of etiologies was also reported by the Italian registry (ItalKid project, 2003) with the leading cause being renal hypoplasia/dysplasia, which occurred with and without urinary tract anomalies in 54% and 14% of patients, respectively. Glomerular disease was common in older children, accounting for approximately 45% of cases in patients older than 12 years of age (Sinha, & Marks, 2015). Furthermore, the incidence of autosomal recessive polycystic kidney disease is about 1/10,000 to 1/20,000 births. Autosomal dominant polycystic kidney disease is much more common, occurring in about 1/500 to 1/1000 live births, which make infant born with kidneys usually greatly enlarged and contain small cysts (Rabinowitz, 2013). The UK Renal Registry data show that dysplastic/hypo-plastic kidneys together account for 40% of all children on renal replacement therapy and are six times more common than nephron phthisis, congenital

Nephrotic syndromes or metabolic diseases (Lewis et al., 2009). Using the North American Renal Trials and Cooperative Studies data base of Chronic Kidney Disease Registry, there were 4166 pediatric subjects with CKD stages II to IV, it performed a retrospective cohort study to describe progression rates and determine factors associated with CKD progression, and the result showed that the main causes were as: obstructive uropathy 837 patient, focal segmental glomerulosclerosis 478, renal dysplasia 529, reflux nephropathy 389, other 1833(Staples et al., 2010). Chronic glomerulonephritis is the main reported cause of CKD in various studies from India, Southeast Asia, Latin America, Caribbean area, and sub-Saharan Africa, with a prevalence ranging from 30% to almost 60% (Ali, 2009).

2.6.2 Child's Obesity and CKD

Epidemiological correlations and pathophysiological changes have been showed a relationship between obesity and CKD among children. The high level of BMI may be associated with low nephron mass, which could lead to CKD in later life; the elevated level of adipokines, such as leptin and adiponectin, in obesity may be factors in CKD pathogenesis and progression. Furthermore, other confounders with obesity including hypertension, increased cardiovascular morbidity, diabetes and dyslipidemia may play a significant role in increasing the incidence and pathogenesis of CKD in children (Krumar, & Barany, 2013; Guanta, & Mak, 2012). The long-term chronic disease consequences of childhood overweight or obesity are of serious complication of chronic and congenital diseases for organs including renal system (Hsu et al., 2014). Savino et al., study found a strong relationship between obesity among children and their risk to cardiovascular disease, diabetes type 2, and hypertension, that emerged strong independent risk factors for CKD and ESRD (Savino et al., 2010).

2.6.3 Birth Weight and CKD in childhood

Birth weight is a good indicator to evaluate pre and postnatal development, which also has an important short and long term implication on child health and survival (Trevino, 2015). The main causes of low birth weight (LBW) which is defined as a birth weight less than 2500 gram, include a premature birth, immature mother's uterus, or intrauterine growth retardation. In general, LBW babies has a greater risk for complications such as congenital renal malformation (Trevino, 2015). The Prematurity with LBW are the most consistent clinical surrogates for a low nephron number and are associated with increased risk of hypertension, proteinuria, and kidney failure in later life, and unfavorable prognosis of renal diseases; also is associated with reduced kidney size, which can contribute to renal hypertension. Literature studies concludes that LBW also predisposes to CKD in later life (Luyckx, 2013; Franke et al., 2010; Drougia et al., 2009; & Schmidt et al., 2005). According to Boyles study clarifies the relation between child birth weight and risk of CKD in later life, the study conclude that LBW in children had almost three times the risk of developing CKD. While High birth weight (HBW) more than 4000 gram has serious adverse impacts on health conditions, development in children, and congenital renal anomalies cause almost 60% of CKD in children with HBW (Boyles, 2014).

In an effort to determine if prenatal risk factors impact childhood CKD risk, the medical birth registry of Norway conducted a study that comprises data for 2,183,317 child that they born during 1967 to 2004 that include the development of ESRD among the children. The study results clarified that the possibility occurrence of congenital urinary malformation and hereditary renal failure might be a cause of LBW. From the same study, the HBW is significantly associated with development of ESRD among children (Vikse et al., 2008).

2.6.4 Small gestational age and CKD in childhood

Several studies have shown a reduced renal length and volume after small gestational age (SGA) and preterm birth. Gestational age is the common term used during pregnancy to describe how far along the pregnancy is. It is measured in weeks, from the first day of the woman's last menstrual cycle to the current date, and the normal pregnancy can range from 37 to 42 week (Franke et al., 2010). Several studies tried to examine the association between length of gestation and infant health status. A study aimed to determine the relationship between the length of gestation and CKD in children. The researcher classified babies according to their gestational age at birth as less than 37 weeks (294 cases 14.7% VS 1,586 control7.9%), between 37-42 (1,236 cases 62% VS 13,602 control 67.9%), and more than 42 weeks (139 cases 7% VS 1,913 control 9.6%). The results showed a strong association between SGA and congenital kidney malformation in infants (Hsu et al., 2014).

From a study included a 56 babies (premature) as cases and 10 babies (full-term) as controls. The results showed that the nephron number was highly correlated to full gestational age than in premature babies who were at greater risk for renal failure. Therefore, nephron deficit in preterm born individuals probably exists throughout life placing the patient at risk for renal function deterioration and cause CKD in later life (Keijzer-Veen; & Heijden, 2012). Also, in an observational cohort study examined children with CKD during 1,393 visits for 426 participants. The study aimed to determine the relation between period of gestation and probability occurrence congenital renal malformation in infant at later life, and the results clarifies there is positive relationship between SGA and CKD in childhood (Greenbaum, 2011).

2.6.5 Child gender and age at diagnosis

In pediatric nephrology, gender and age group are often used to determine evolution and prognosis of CKD. The diverse gender between male and female may show different impact of traditional risk factors and different response to therapies; as well as hormonal and genetic differences between both genders could influence tendency, progression, biochemical and psychological aspects of CKD (Carrero, 2010). Recently, population-based studies showed that males were associated with a worse CKD progression than females. For example, Ceron et al., (2014), concluded that age and gender play a role in the differences of the prevalence and treatment of CKD in children and the study have been reported that girls have lower rates of CKD than boys, and the incidence of the disease increased after 10 years old, and decreased at age less than 5. Additionally, Hsu et al. (2014), classified the population by age, gender, and years exposed to CKD. The study findings illustrated that male children exposed to CKD more than female, whereas the diagnostic history of CKD regarding to age among cases showed high percentage in small age less than 1 years old, while it decreased dramatically with older children. The study illustrated that the gender and age at diagnoses of CKD have had a positive association with progression of CKD in children.

A retrospective cohort study using the North American Pediatric Renal Trials and Cooperative Studies CKD database included a 4,166 children and their age more than 2 years old of CKD at stage II to IV to identify the major progression of the disease, the result showed that the incidence of CKD in male was higher than female (Staples et al., 2010).

2.6.6 Hypertension and risk to CKD

Renal hypertension disease is an uncommon but important cause of hypertension (HTN) with CKD in children (NKF, 2013). High blood pressure can damage blood vessels in the kidneys, reducing their ability to work properly. When the force of blood flow is high, blood vessels

stretch so blood flows more easily. Eventually, this stretching scars and weakens blood vessels throughout the body, including those in the kidneys. If the kidneys' blood vessels are damaged, they may stop removing wastes and extra fluid from the body. Extra fluid in the blood vessels may then raise blood pressure even more, creating a dangerous cycle and causing renal failure (NIH, 2014).

Few studies were conducted to determine the prevalence of hypertension or quantified the association between the degree of HTN and progressive kidney damage in children. The differences in creatinine clearance, systolic and diastolic blood pressure, future risk of HTN, and obesity have been extensively described as a confounders to increase risk of CKD (Flynn et al., 2008). Staples et al. study found that the HTN has been shown to be a strong clinical risk factor for renal progression to CKD and ESRD in children, almost half of the study participants had HTN disease (1,954 cases, 46.9%) of total population study and 1,928 of them use Anti-hypertensive medication (staples et al., 2010).

2.6.7 Dehydration and risk to CKD

The renal function is to filter blood from wastes, excess fluids, keeping toxins from building up in the bloodstream. Dehydration occurs when the amount of water leaving the body is greater than the amount being taken in. In case of severe dehydration, it can in turn worsen the kidney conditions. Because dehydration can disturb the normal blood circulation in the body, and the kidney is not able to remove excess fluids and waste. There will be a sharp decline of blood flow to the kidneys and cause acute renal impairments (NIH, 2014). Diarrhea and electrolyte loss-associated with HUS is the most common cause of acute renal failure among previously healthy children in the United States. Most cases are caused by antecedent infections with Shiga toxin producing Escherichia coli, which bind to a glycolipid receptor

on the endothelial cell surface, leading to diffuse vascular injury and renal failure (USRDS, 2012).

A study conducted to clarify the association between diarrhea with HUS and progression of renal failure. The sample study selected randomly a 17 clinical trial participants (6 boys and 11 girls; age between 6 months to 18 years) after 28 days of discharge from hospital. The study conclude that the patient who had acute-onset Diarrhea with HUS manifest activation of the alternative pathway of complement that is temporally related to the onset of disease and that resolves within 1 month, while the treatment could be useful to inhibit the progression of renal injury and extra renal complication (Thurman et al., 2009).

2.6.8 Hemorrhage and impaired blood circulation and CKD

The decrease blood flow to the kidney can cause critical health problems in the renal system. This condition occurs as a result of increased Azotemia level in renal system (abnormally high levels of nitrogen and creatinine in the blood). This abnormal health status is caused by systematic blood circulation problems including low blood volume, low blood pressure, and local changes to the blood vessels that supplying the kidney (Vinay et al., 2005). As hemorrhage progress, the probability of renal failure increased owing to stenosis or block in renal artery which interfere with the blood supply of the affected kidney; and can cause renal vein thrombosis, which is the formation of a blood clot in the renal vein that drains blood from the kidney. Renal ischemia can result in depression of GFR. Other causes include inadequate cardiac output and hypovolemia or vascular diseases causing reduced perfusion of both kidneys. Both kidneys need to be affected as one kidney is still more than adequate for normal kidney function and cause acute renal failure (NKF, 2013).

Anemia might begin to develop before the early stages CKD, when someone has 20 to 50 percent of normal kidney function. Anemia tends to worsen as CKD progresses (Brugnara &

Eckardt, 2011). Staples. (2009), study included 2,779 patients ages 2 year and older in the North American Pediatric Renal Trials and Collaborative Studies database with CKD stage II to V, the result showed the prevalence of anemia among children with CKD increased dramatically with progression of CKD. The study deduce that anemia is a well-known cause of CKD. A study from Guavin, France to determine the risk factors of kidney disease in children who entered pediatric intensive care unit. The study include 985 cases and the results clarified a significant risk factors for CKD following multivariate analysis with thrombocytopenia, and hemorrhage. The study conclude that the blood lose could be leads to progression of CKD in the children (Baily, 2007).

2.6.9 Maternal obesity

Maternal obesity is considered one of the most health problems that adversely increase the risk of birth defect and congenital abnormalities among newborns. At 2014, American Society of Nephrology accounted that 1% of maternal obesity during pregnancy lead to approximately 20% to 30% of perinatal abnormalities and birth defects that occurred in the kidney and urinary tract of the fetus.

Hsu et al., conducted a study in Washington, USA to measure the association between the maternal health status and prenatal risk factors and CKD in infants. The result of the study verified a strong association between maternal BMI during pregnancy and exposure to CKD in infant at later life (Hsu et al., 2014). Furthermore, a cohort study from Swedish Medical Health Registries conduct to assess the risk of maternal obesity and birth defects occurrence among infants. The study results clarified that the risk of CKD among infant at later life associated with increased mothers BMI during pregnancy. Moreover, the study found that the maternal obesity in pregnancy associated with polycystic kidney in infant, and congenital renal malfunction (Blomberg, & Kallen, 2010).

2.6.10. Maternal age at pregnancy

A number of recent studies have examined the relationship between maternal age during pregnancy and the infant outcomes including congenital malformations. Lampinen et al. (2009) clarified that the maternal age > 35 years old is considered a risk factor to have a baby with LBW and premature birth, which lead to congenital malformations including a reduction in nephron number. Also another study conducted by Baby Center Canada Medical Advisory Board, (2012) concluded that the older maternal age during pregnancy effects on the next infant at later pregnancy and cause congenital organs malformation, birth defects, and growth organs failure including renal system.

On the other hand, small maternal age less than 18 years old is associated with intrauterine growth retardation that come with reduction of nephron number (NKF, 2013). Although, the researcher found a lack in literatures try to describe the impact of young mothers and renal diseases among infants and few studies has clarified the association between small maternal age and CKD in child.

According to Hsu et al. (2014), study conducted to examine the relationship between mother's age and the child's health status. The results found a positive association between mother's age during pregnancy and the risk to deliver a baby with congenital malformation within the renal system. Additionally, another study clarified that the young maternal age with prematurity also increase the prevalence of CKD in children. That the study conclude small maternal age had a statistically significant numerically with CKD in children. Also, the result of the study found that the prevalence of children with CKD for small maternal age was higher three times than normal range acceptance at stage III-V (Franke et al., 2010).

2.6.11 Maternal Hypertension and Diabetes in pregnancy

Several investigations have suggested that the outcomes of maternal health condition during pregnancy has relatively associated with infant health status. Diabetes and Hypertension are the most maternal health problems that occurs in pregnancy. However, these diseases are associated with an increased risk of infants' birth defects including congenital malformations in the renal system. Fetal congenital renal malformations are the most common disease when maternal glucose control has been poor during the first trimester of pregnancy (Plagemann, 2008; & Barnes-Powell, 2007). However, diabetes and hypertension during pregnancy will increase the incidence of preterm labor, birth defects, infant renal disorder, and chronic renal hypertension in infant (Behrman et al., 2004).

A Hsu et al. (2014), data results showed that the gestational diabetes and gestational HTN during maternal pregnancy among the study population were associated numerically with CKD among children in later life. Concerning to a case-control study conducted for comparing the maternal health status during pregnancy and the occurrence of congenital anomalies among babies, the study include pregnant women with DM-type 1, DM-type 2, and Gestational Diabetes Mellitus. The total rate of congenital anomalies was higher only in the DM-1 group, and the most congenital rated was obstructive congenital anomalies of the urinary tract. The study clarify that the pregnant women with DM type 1, DM type 2, and gestational diabetes mellitus considered strong risk factors of structural birth defects and congenital renal malformation (Banhidy et al., 2010).

2.6.12 Small amniotic fluid volume (Oligohydramnios) and CKD

Oligohydramnios is a complication of high risk pregnancy which is associated with poor perinatal outcome. It occurs during pregnancy because of lack of amniotic fluid. However, the most severely affected neonates who had diagnosed with Potter's syndrome due to

oligohydramnios, Potter syndrome and Potter phenotype refers to a group of findings associated with a lack of amniotic fluid leads to kidney failure in an unborned infant. These children have overload fluid volume from renal failure at first year of life, and poor diaphragm function owing to enlarged kidneys and impaired renal function (Elder, 2011).

A case-control study conducted to evaluate the infant complication during pregnancy with oligohydramnios, included 456 infant with history of prenatal oligohydramnios. The result showed that the rate of renal malformations with severe oligohydramnios were significantly higher in the cases group compared with the controls. The study detected that the infants with oligohydramnios were associated with high prevalence of renal malformation compared with control at postnatal renal evaluation (Leibovitch et al., 2012). Oligohydramnios and intrauterine growth restriction during the pregnancy will increase the risk to give a baby with congenital anomalies in internal organs, and severe renal; bladder, and urethral anomalies (Behrman et al., 2004).

2.6.13 Drug abuse and risk to CKD in children

The complex nature of critical illness often necessitates to use multiple therapeutic agents, many of drugs which may prescribed lonely or by physician have the potential to cause renal injury. Also most drugs can cause nephrotoxicity, that effect on renal development and cause polycystic kidney. The drugs misuse which cause nephrotoxic has been implicated as a causative factor in up to 25% of all cases of severe acute renal failure in critically ill patients. Acute tubular necrosis is the most common form of renal injury from nephrotoxic exposure and causing CKD owing to continuously use drugs in high doses (Neesh, 2008).

2.6.13.1 Antibiotic toxicity and CKD

Many antibiotics have long been one of the commonest causes of drug-induced nephrotoxicity and effect on renal function that lead to chronic renal diseases include

Aminoglycosides that is considered the most drug group frequently cited etiology of nephrotoxic induced CKD and renal failure for all age group. Follow Cephalosporin, and Vancomycin are a common medications that could affect the kidney function (Porter, 2013). The aminoglycoside and cephalosporin are frequently prescribed for infants and children, especially newborn infants with suspected meningitis or sepsis, while in older infants used to complicated urinary tract infection and other diseases caused by gram negative enteric bacilli. The prevalence of ARF associated with use of aminoglycosides cephalosporin varies widely due to the differences in the diagnostic therapy and frequency of nephrotoxicity with these drugs which could reach to 50% (Pleviera, 2006).

Exposure to cephalosporin nephrotoxicity is becoming more prevalent as a primary cause of renal failure, comprising approximately 16% of all pediatric patient with CKD. However, both the risk of developing renal failure when any nephrotoxic medication is initiated and the additive risk of disease development with multiple nephrotoxic medications are unknown (Moffett & Goldstien, 2011).

Nephrotoxicity has been observed more frequently when high doses of the cephalosporin were used in the combination therapy which increase the ability to damage the kidney. In many cases where potentiation of drug-induced nephrotoxicity has been reported, patients were critically ill, and the underlying pathophysiological condition might have contributed to the resultant renal dysfunction (Moffett & Goldstien, 2011; & Rokushima, 2008). Renal injury can occur in a substantial number of patients whose receiving an aminoglycoside, and whether it occurs depends on the patient's clinical condition and interactions with other nephrotoxic drugs. The most usual clinical presentation for aminoglycoside-associated nephrotoxicity is acute kidney injury, which occurs following 7 to 10 days of therapy. Additionally, aminoglycoside is associated with a decrease in the glomerular filtration rate

(GFR), and impaired renal concentrating mechanisms, and cause CKD in later life (Oliveira et al., 2009).

2.6.13.2 Analgesic Drug toxicity in children

Nonsteroidal anti-inflammatory drugs (NSAIDs) are implicated in nearly 25% of all adverse drug reactions. Also, NSAIDs toxicity could be causing a decrease in renal blood flow. Additionally, subsequently decrease in glomerular filtration rate, retention of salt, water, and potassium may accumulate around the kidney cavity, and caused kidney injury (Wiegand et al., 2015). Misurac et al. (2013) conducted a study to evaluate the medical records at Riley Hospital for Children at Indiana University in Indianapolis, USA from January 1999 through June 2010 and they found that around 1,015 cases had been treated for acute kidney injury and CKD. In nearly all cases, the NSAIDs were administered before the children were admitted to the hospital. Because many of the cases involved multiple potential causes of acute kidney injury, and renal failure. The researchers conclude that several cases were used NSAIDs which that contributed to the kidney damage.

2.6.13.3 Maternal drug use during pregnancy and CKD in children

Maternal use of drugs during pregnancy may cause irreversible renal failure in the newborn. Throughout pregnancy, expectant mothers are exposed to variety medication that may produce either toxic or therapeutic side effects negatively on the fetus health status. Most studies related to fetal drug exposure are focused on the toxic effects of these agents including antibiotics and analgesics overdoses during pregnancy and cause nephrotoxicity among infant (Sahay et al., 2014, & NKF, 2013).

A cohort study conducted in the Norwegian Mother and Child center included a 69,929 medical reports of mothers that completed around 17 weeks of gestational period. The study clarified that several women were used NSAID during gestational period at weeks 0-12. The

result conclude that there is no association between use NSAIDs during pregnancy and renal diseases in the babies (Gelder et al., 2011). Otherwise, Perazella. (2009), conclude that the Nephrogenesis stops at approximately 36 weeks of pregnancy. This health problem occurred due to high dose intake of antibiotic and analgesic drugs that administered to pregnant women at gestational period. Which may effect on the kidney development and effect on the renal system. Where it ultimately may lead to a wide range of renal malformations in infants.

2.6.14 Consanguineous marriage (first cousin marriage)

Marriage between first cousins increase the chance of having a baby with potentially life threatening birth defects two times than ordinary marriage, many studies have suggested a strong association between first cousin marriages and congenital renal anomalies (Bittles, 2013).

A retrospective cohort study conducted at King Abdul-Aziz University Hospital, Jeddah, Saudi Arabia between 2006 and 2014 from medical files for 1,000 children with CKD to determine the effect of consanguinity on the progression of disease among child. The study compared children with congenital versus non-congenital causes of CKD in children. The result showed that the underlying etiology for CKD was congenital malformation that occurred in more than half of total cases, and consanguinity defined in most children (Kari, 2015). These results were consistent with the findings of a study conducted to investigate the causes of birth defect among infant in Gaza strip, Palestine. The study comprised 4027 deliveries between 4th of May to 4th October, 2011 and the results clarified that the infant delivered with congenital renal malformation were registered according to consanguinity parents (Naim et al., 2012).

A retrospective study conducted in Negev, Israel, to clarify the clinical characteristics of polycystic kidney disease (PKD) among first cousin marriage population to establish the

genetic method for prenatal diagnosis of the disease. The study concluded that the family trees in all cases were highly suggestive of a founder effect, implying that affected patient with PKD were very likely to harbor identical mutation owing to close marriage in the same family cousins.

Furthermore, inter- and intra-familial phenotypic variability was found in several families which they had consanguinity tradition factors for renal diseases (Finer et al., 2004).

2.6.15 Family history

Genetic factors across family members may play a role in developing renal failure, and is one of the most important risk factors for developing CKD in an individual is the presence of a family history of ESRD. The chance of developing chronic kidney disease in an individual is determined by interactions between genes of parents and the environment (Hildebrandt, 2010). In his case-control study, Abu-Odah. (2013), found that the prevalence of CKD was higher with a positive family history and the results showed that the majority of cases has had a positive family history of CKD and the relationship was statistically significant, and half of cases related with positive family history of ESRD. A possible contextual variable that modifies genetic predisposition is the family cultures, the family history of ESRD in a first-degree relative is reported by over 10% of randomly selected and a family history of ESRD is twice as common among black individuals as among white individuals (Patzer & McClellan, 2012). One high-risk population consists of first- or second-degree family members of patients with ESRD, who are 2 to 3 times as likely to have incident ESRD, have high rates of impaired kidney function. These individuals usually are unaware of their underlying CKD and may discount their own risk of ESRD (McClellan et al., 2009).

2.6.16 Socio-economic status

It is important to acknowledge the complexity of measuring socioeconomic status (SES) when discussing health disparities. According to many health literatures considered that low SES is a risk factor for CKD, progression to ESRD, and poor health outcomes. After adjusting for age and sex, significantly more likely among individuals with a family income below the poverty line or having less than a high-school education for parents. Individuals with a family history of ESRD also have a decreased GFR, increased albumin-to-creatinine ratio, and a substantially increased risk of progressing to ESRD. At present, the contribution of a shared genetic background to shared familial risk is not known, but the persistence of lower SES as a risk factor in multivariable models for a family history of ESRD suggests a possible gene–environment interaction that should be explored (Patzer & McClellan, 2012). Several studies have documented that increased the incidence of kidney diseases are associated with area-based measures of access to care, range of health services coverage, and the family economy status (Prakash et al., 2010).

Abu-Odah devised the SES to three parts: low income as 1700 NIS or less, moderate income as 1700-2200 NIS, and high income for more than 2200 NIS per month, the data analysis clarified that the people who live in low income are more risky to ESRD, which mean the incidence of ESRD increased with decreased the average household income (Abu-Odah, 2013). Regarding to Palestinian national accounts, clarified that low SES reflecting the poor life style, and unstable health condition, and this status include large sector of Palestinians in GG (Determinants of health, PCBS, 2013).

2.6.17 Environmental factors

Individuals are exposed to various potentially toxic agents and conditions in their natural and occupational environments. Which include water condition, pesticides, and chemicals toxins

that can enter human body through oral, inhalation, or transdermal routes, and may effect on all organ systems, including renal system at kidney with cause nephrotoxicity and kidney damage (US departments of energy, 2012; & Soderland et al., 2010).

A cross-sectional study implicated 460 patients that they diagnosed ESRD in Tabuk, Saudi Arabia to determine the prevalence of ESRD associated with environmental exposures. The study showed that there were around half of patients with ESRD living in rural areas, and many of cases were unknown main causes and it related to environmental factors (EL-Minshawy, Ghabrah, & El-Bassuoni, 2014). The elements like heavy metals, industrial chemicals toxins, and pesticides are materials that enter the body through oral, inhalation or transdermal routes and effect on all organ system include kidney. The heavy metals like lead and smelters are risk factor in industrial environmental contamination of ground water and may expose people to kidney disease without direct occupational exposure (Soderland et al., 2010).

Kamel and El-Minshawi. (2010), study in El-Minia governorate, Egypt conducted to investigate probability causes of ESRD with unknown causes, the study include 212 cases and 200 control. The result clarified that the prevalence of patient with CKD increase dramatically attributed to environmental factors such as: exposure to pesticide, and drinking unsafe water including wells, home water, and partially filtered water. Moreover, unrecognized environmental toxins or occupational exposures may lead to development and progression of CKD, in addition to the pesticide exposure which could be an environmental risk factor for the development of CKD.

2.6.18 Smoking (second hand smoking)

Second hand smoking (SHS) can be especially harmful on children's health because their lung still are developing, the long-term effect of second hand smoking may cause severe

irreversible diseases to children (CDC, 2014). SHS cause significant associated with albuminuria, increased risk for CKD in children and adulthood, increased graft loss and progression of renal insufficiency. In children, SHS has been associated with higher blood pressure variability, blood pressure load, elevated c-reactive protein and decreased cognitive function, also evidence linking tobacco exposure to proteinuria in those with and without kidney disease in children and adulthood (Omoloja et al., 2014). An observational cohort study of 366 children aged 1-16 years with CKD, the study cleared that many of the participants were exposed to SHS, the prevalence of nephrotic syndrome and proteinuria range were higher in children exposed to SHS compared to those unexposed (Omoloja et al., 2013).

2.7 Symptoms of kidney disease

The symptoms of CKD are very different in children from those in adults. At the early stage of CKD may not cause any symptoms for a while or could be very subtle, such as mild level puffiness around the eyes caused by excess fluid build-up, to the point where the child's ability to move around normally is compromised. After initial swelling, socks or a belt can leave an indentation in the skin that will persist (NKF, 2013).

Other signs, lack of or decrease in appetite, headaches resulting from high blood pressure. Flu Symptoms such as nausea, vomiting, weakness, fatigue, difficulty concentrating and poor school performance, changes in the color of the urine such as unusually dark or red, which can indicate blood, and changes in appearance of urine such as extra foam that can indicate protein, Stunted or poor growth as compared to similar age group peers (NKF, 2013).

2.8 Analysis and investigations of kidney disease

Analysis of kidney are important to all age group of human, to identify the problem, to identify early detection of kidney problem and classify the stage of kidney disease.

2.8.1 Physical imaging

The pediatric nephrologist makes general physical assessment on child's abdomen and monitor it by ultrasound imaging to determine any abnormal health problem such as: Absence of one kidney, kidney scarring, large kidney, small kidney, hydronephrosis, renal artery stenosis, and nephrocalcinosis (NKF, 2013).

2.8.2 Dimercaptosuccinic acid scan (DMSA)

DMSA stands for dimercaptosuccinic acid. A DMSA scan uses radioactive chemicals to create special pictures of the kidneys. These pictures can help doctors assess how well the kidneys are working. DMSA travels through the body joined to a radioactive chemical. It builds up in the kidneys. Pictures of the kidneys are then taken using a special camera which can detect the radioactive chemical (NKF, 2013).

2.8.3 Glomerular filtration rate

It is the best test to measure individual level of kidney function, measure the filtering capacity of the kidneys, and determine the stage of kidney disease (NKF, 2010). Since the total kidney GFR is equal to the sum of the filtration rates in each of the functioning nephrons, the total GFR can be used as an index of functioning renal mass (Harambat et al., 2012).

2.8.4 Urine analysis and urine culture

Urine analysis is needed to investigate any changes such as blood color, specific gravity, PH, proteinuria and the appearance caused by glomerular leak. According to national institute for health and clinical excellence the proteinuria is a marker for renal disease which may be as significant as GFR. Urine culture is used if there are symptoms of Urinary Tract Infection such as pain, and itching during urination to identify the specific antimicrobial therapy which kill the microorganism (Dean, 2009).

2.8.5 Blood Urea Nitrogen (BUN) test

Urea nitrogen is a normal waste product in human blood body that come from eaten food and body metabolism, in normal condition it is removed from body by kidney, but when kidney function slow down, the BUN level rises and protein level rises too (NKF, 2013).

Table (2.2) Normal glomerular filtration rate in children and adolescents (NKF, 2002).

Age	Mean GFR ±SD(ml/min/1.73 m^2)
1 week (males and females)	41±15
2-8 weeks (males and females)	66±25
≥8 weeks (males and females)	96±22
2-12 years (males and females)	133±27

2.8.6 Renal biopsy

Renal biopsy is a procedure done to determine the cause, severity, and possible treatment for kidney disease, also it is the best test to identify kidney disorder, and also it can identify the unexplained drop in kidney function as: blood and protein in urine (Salama, 2011).

2.9. Treatment of CKD

The outcome of children with severe CKD is highly dependent upon the economy and availability of health care resources, also they have a few options to get therapy, depending on the severity of their disease and financial coverage (Warady, 2009).

The treatment of CKD can slow its progression to ESRD, but the availability of all therapies is still limited. In some cases a nephrectomy for the kidney damaged is a solution that can make childhood disease easier to manage, and most children parents choose hemodialysis or peritoneal dialysis. About kidney transplant, around half of the kidney transplants in children come from a living donor, usually a parent or other closed family member according to blood match and patients body acceptance of the new kidney (Harambat et al., 2012).

The expected remaining lifetime for children 0–14 years of age and on dialysis is only 18.3 years, whereas the prevalent transplant population of the same age has an expected remaining lifetime of 50 years (USRDS, 2013).

2.10. Complications of CKD

As CKD progress to Stage III onwards, a number of complications are manifested due to impairment of the multiple functions performed by the kidneys. The complications include disorders of fluid and electrolytes, renal osteodystrophy, anemia, hypertension, dyslipidemia, endocrine abnormalities, growth impairment, and decreased clearance of toxic substances (Sinha, & Marks, 2015). Additionally, the considerable complications of chronic kidney disease are: Cardiovascular disease (CVD) that associated with non-traditional factors, protein urea, and decreased level of GFR (Levely & Coresh, 2012). Furthermore, anemia related to blood loss, and short stature with growth failure (Cassidy et al., 2007).

2.10.1. Cardiovascular and Hypertension diseases

Hypertension (HTN) is the most common complication in children with CKD, the prevalence of HTN ranging between 54%-70%. It is present in the early stages with decline of GFR level, and usually due to excess renin from damaged kidneys or iatrogenic such as use of corticosteroids or cyclosporine or tacrolimus for treatment of any underlying renal disease (Sinha, & Marks, 2015).

The increased cardiovascular risk associated with end stage renal disease has been well established, and estimated cardiovascular mortality rates are ten to one hundred fold higher among dialysis patients than in all ages- and sex-matched individuals in the general population (Harambat et al., 2012). Hypertension is a traditional cardiovascular risk factor which contributes to the cardiovascular risk associated with CKD, patients with hypertension

are at increased risk for new or recurrent cardiovascular events in individuals with stage II–III (Harambat et al., 2012).

2.10.2. Anemia

Anemia is a common characteristic of chronic kidney disease in children, the main cause owing to reduced erythropoietin enzyme during therapy as dialysis, the patient risk to loose blood and hemoglobin level and iron deficiency, and blood therapy is complex. Erythropoietin and supplemental iron are used to maintain hemoglobin levels, anemia in children with CKD has been associated with fatigue, weakness, decreased attentiveness, increased somnolence and poor exercise tolerance (Koshy & Geary, 2008).

2.10.3. Bone disease and growth failure

Child of CKD suffer from unstable of calcium level and abnormalities in the growth hormone, the bone disease of CKD, referred to as renal osteodystrophy and start with Stage II CKD disease. The pathogenesis of bone diseases is complex and its understanding is still evolving. It is believed that decreased renal clearance of phosphorus with resultant increase of serum parathyroid hormone in response to phosphate retention is a key step (Sinha, & Marks, 2015).

In addition, recent evidence also indicates an increased prevalence of generalized vitamin D deficiency in children with CKD. Subtle signs of bone disease begin to appear in patients with Stage III disease. Patients with more advanced renal osteodystrophy have bone pain, difficulty in walking, and skeletal deformities. Vitamin D deficiency, changes in parathyroid hormone which lead to increase in morbidity and mortality among them (Bacchetta et al., 2012).

2.11 summary

CKD is an irreversible deterioration of the renal function in children. The epidemiological information about CKD is not enough to determine the prevalence, only few reports determined the prevalence of CKD stage I-II around 18.5-58.3 PMP. While other reports recorded that the stage I-IV (10.8%) and stage V (0.2%). In Palestine, the results illustrated that the distribution of ESRD is 240.3 PMP at all ages, and around 4.3% for children and in GG, the total number of CKD reached 410 cases. The main predisposing factors of CKD include a positive health history of renal diseases, obesity, birth weight, small gestational age, child gender and age at diagnosis. Risk factors also include abnormal health conditions such as HTN, dehydration, and hemorrhage. Maternal health history during pregnancy including obesity, age at pregnancy, HTN and diabetes, oligohydramnios, and drug misuse for mother beside the hazardous environmental status play a role in increasing the incidence of the problem. The main symptoms of CKD include edema, headache, poor appetite, change in renal functions and urine colors. CKD can be diagnosed by many procedures such as physical image, GFR, urine analysis, BUN test, and renal biopsy. The medical therapy is expensive and outcomes is poor which include cardiovascular disease, chronic anemia, growth impairment and bone diseases. Few studies were conducted to address the problem and the researcher find it important to focus on the problem of CKD, and examining the risk factors that may lead to its occurrence will assist in taking preventive measures to decrease the incidence of CKD in children in GG.

3. Chapter Three: Methodology

This chapter presents the method of the study to answer the research questions. In this chapter different items were explained: study design, place of the study, study population, sample size, sampling process, period of the study, inclusion criteria, validity, ethical and administrative consideration, study tools, pilot study, data collection, data management, and limitation of the study.

3.1 Study Design and Method

The study is a quantitative retrospective (case-control study). This type of study was proposed because it help the researcher in exploring more than one exposure for a single outcome and it is suitable in term of time, people, small subjects, money, and it is relatively practical and manageable. Also, it was chosen because it enables the researcher to meet the study objectives in a short time.

3.2 Setting of the study

The study was carried out at Abd El-Aziz Al-Ranteesy specialized pediatric hospital (RSPH) Nephrology and Hemodialysis Departments for patients of CKD for cases, and governmental primary health care clinics for controls as it cleared in table. The researcher choose these clinics as the largest clinics in each governorate and also because it is located in the middle of the governorate (3.1) page 47.

3.3 Study population

Patients who has had renal disease and registered in the Nephrology Department of Abd El-Aziz Al-Ranteesy specialized pediatric hospital who diagnosed with CKD who reached to be 410 patients in a total and diagnosed as ESRD and got hemodialysis therapy by a nephrologist.

3.4 Study sample

A systematic random sample consisted of 200 patients (cases) diagnosed with CKD and receive care in the different settings of RSPH and 200 (controls) from children who take care in the outpatient primary health care clinics of the Ministry of Health in GGs. The control group has had no history of CKD. Control and cases participants were ≤ 12 years old and each one cases versus one control in the same age group, gender and governorate, and agree to participate in the study. The outpatient clinics chosen from ministry of health according the main health center in each governorate in GGs as appear in table (3.1).

Table 3.1: The distribution of proportional control sample for each governorate related to case sample.

Sample size case of Cases from RSPH			Distribution of control sample size among PHC centers	Sample size control from primary health clinics
1	N. Gaza	28	Shohadaa Jabalia	28
2	Gaza	114	Shohadaa EL-Remal	114
3	Mid-zone	22	Shohadaa Deer EL-Balah	22
4	Khan-younis	18	Bander Khan- Younis	18
5	Rafah	18	Shohadaa Rafah	18
Total		200		200

3.4.1 Sample size calculation

The researcher used sample size calculator (The survey system) to determine the sample size needed to help him get results that reflect the target population as precisely as needed. The sample size was calculated at 95% confidence level with confidence interval 5 and total population 410. The sample size needed was 199 case. According to this process, the researcher decided to include 200 cases from RSPH in his study.

3.5 Selections criteria

3.5.1 The inclusion criteria for cases sample

- Patients with age ≤ 12 years old and agree to participate in the study
- Diagnosed as a CKD patient.
- Attending at Al-Ranteesy hospital.

3.5.2 The inclusion criteria for control sample:

- Children less than 12 years old and agree to participate in the study.
- Attending primary health care clinics.
- Free from chronic diseases.

3.6 Period of the Study

The study was implemented immediately after the proposal being approved by the council of the university. The pilot study was conducted in February, 2015. Data collection started in middle of February 2015 and continued to mid of May 2015. Data entry, analysis and writing the final report continued till August 2015.

3.7 Data entry and statistical analysis

Data entry using SPSS (Statistical Package for Social Sciences) software package V 20 was adopted. Measurements was done by coding and entering responses into the computer. The researcher checked all data to avoid any discrepancies, data were examined for coding and entry error. Numerical Data were expressed as means, medians and standard deviations. Qualitative data were expressed as frequency and percentage. Other tests such as t test, and regression were used to examine the relationship between certain risk factors and others and with the incidence of CKD among children in GGs. Results were expressed as frequency or mean ± standard deviation. The results were statistically significant when Confidence Interval (CI) = 95% and p-value= 0.05 or less.

3.8 Data collection

Face to face interviews were used to collect data from participants using a structured questionnaire constructed by the researcher himself including: Personal and demographic data, mother and child medical history, and environmental factors. Anthropometric measures such as weight and height and blood pressure were measured using standardized tools. The researcher explained to all participants the importance, aim and purpose of the research study. The expected time for every interview was approximately 20 minute (Annex 2).

3.8.1. Anthropometric data

Standard techniques were adopted for obtaining anthropometric measurements used to measure weight and height and blood pressure. Patients were weighed in light cloths without shoes to the nearest 0.1 Kg. The height reading was taken at the nearest 1cm. Body mass index (BMI) was computed as the ratio of weight (Kg) per height squared (m^2) according CDC scale for BMI Percentile Calculator for Child and Teen. For the infant less than 2 years, the researcher used Infant Growth Percentile Calculator (annex 3).

3.8.2 The questionnaire

The questionnaire included 4 categories

1- Personal data (12 questions)

   Personal data composed of the child age and gender, place of living, parent's age and education level, citizenship, consanguinity, and monthly income.

2- Child health history (31 questions)

   It included life style, health history at gestational period, history of renal disease, health history of other diseases, history of medication therapy and family history of the CKD.

3- Maternal health status (11 questions)

   Health status during pregnancy, and history of medication therapy during pregnancy.

4- Environmental factors (9 questions)

It included living are, source of drinking water, environmental hazards, and passive smoke.

3.9 Validity & Reliability of the study

Content validity was done to identify the degree to which the used tool measure what is was supposed to measure. Tool developed by the investigator was examined by a panel of experts to determine whether the included items clearly and adequately covers the domain of content addressed. Also, a pilot study was conducted before the actual data collection to examine accuracy of data (annex 4). Since the data was collected by the researcher himself and at one time event, reliability of the questionnaire is not required.

3.10 Pilot study

A total of 20 participants were recruited for the pilot study. This was done to test the clarity, applicability of the data collection tool used and to estimate the length of time required for data collection as well as to clearly detect any barriers that might hinder the course of the study. All participants recruited to the pilot study met the criteria of the sample selection. The pilot study lasted for 2 days and it revealed that the time needed to complete the questionnaire was approximately 20 minutes. The cases were chosen from the first ten patients admitted to Nephrology department and from outpatient clinic diagnosed as CKD, while the controls were chosen from Shohdaa Al-Remal primary health care clinic. The data collection questionnaire needed a slight modification and it was done and the 20 participants in the pilot study were excluded from the study sample.

3.11 Ethical consideration

- An official letter of approval to conduct the study was obtained from the Helsinki committee (Annex 5).

- An official letter of request was obtained from MOH to conduct the study in the primary health care clinics (Annex6).
- Parents of the participants were given a full explanation about the purpose of the study, assurance about the confidentiality of the information obtained through the questionnaire and they have the right to refuse to participate or to drop out in any phase of the study.

3.13 Limitation of the study

- Scarcity of research studies investigating the problem in Palestine especially in Gaza Strip and neighbor countries.

- Lack of modern statistics about the real situation of CKD in the recent annual reports of the Palestinian ministry of health because of the current political situation in Gaza and West Bank.

- Frequent electricity cuts affected the ability to accomplish the work in a timely manner.

- Financial constraints since the study was self-funded by the researcher.

4. Chapter four: Results and discussion

In this chapter, the researcher presents the main results and findings that help the researcher in examining the objectives and answering the questions of the study. At first, this chapter conducted to identify the main risk factors that contribute to the CKD among children in GG by comparative way between cases and controls. Second, it illustrates the different risk factors including socio demographic, child, maternal, and the environmental factors.

As well as, this chapter answers the study questions by using different statistical tests including descriptive statistics such as frequency distribution for study variables such as means and percentages, in addition to, different inferential statistics including: chi square with odds ratio, independent sample t- Test, and logistic regression, to investigate the relationships between variables and compare these results with those of other related studies. The researcher adopted a statistical significant level $\alpha \leq 0.05$ to examine the relationships between variables of the study.

4.1 Descriptive analysis

4.1.1 Characteristic of the study population

Table (4.1) compares the 200 cases with the 200 controls matched with sex, age, and locality. Among the selected cases, the researcher found the distribution of CKD among study population were males (57.0%) and female (43.0%). These results were consistent with Hsu et al., (2014) study results, determined that male was represented 64.7% while female 35.3% of the cases population. Furthermore, the prevalence of CKD for males and females were 52.1% and 47.9 respectively at Ceron et al., (2014). Compared with Staples et al., (2010), the prevalence of CKD among males was higher than females with 61.5% and 38.5%

respectively. These results support the results of this study which concluded that the exposure to CKD is higher in males than females.

Table (4.1): Demographic characteristics of the study population.

Variables	Cases		Controls	
	No	%	No	%
***Sex**				
Boy	114	57.0	114	57.0
Girl	86	43.0	86	43.0
***Age group**				
< 2 years	18	9.0	18	9.0
2-5 years	60	30.0	60	30.0
> 5 years	122	61.0	122	61.0
***Locality**				
North Gaza	28	14.0	28	14.0
Gaza	114	57.0	114	57.0
Deir AL-Balah	22	11.0	22	11.0
Khan-Younis	18	9.0	18	9.0
Rafah	18	9.0	18	9.0
Home roof				
Concrete	144	72.0	155	77.5
Asbestos	38	19.0	27	13.5
Other	18	9.0	18	9.0
House hold income				
< 1700 NIS	118	59.0	125	62.5
1700-2200NIS	48	24.0	50	25.0
> 2200 NIS	34	17.0	25	12.5

*Matched variables

There were also regional differences in cases, where the highest prevalence was in Gaza city (57.0%) and the lowest percentage was in Rafah and Khan-Younis (9.0%). This distribution is corresponding to the population differences in the Governorates, where one-third of the population is living in Gaza city. The researcher supposed that the percentage of incidence in cases were high in Gaza governorates because of qualified nephrologist to diagnose and recording the new cases in database and monitor the disease and determine the stage of CKD

in pediatric hospitals. Furthermore, the prevalence of CKD disease increases continually with age with approximately 61.0% of all CKD cases have an age of more than 5 years more than younger children. The results revealed that of most of participants (72.0% of cases and 77.5% of controls) are living in concrete compared to 28.0% and 22.5% respectively are living in other types of buildings such as asbestos. The results of the study showed that the incidence of CKD is higher among children of a poor economic situation. The researcher found that 59.0% of cases has had a house hold income less than 1700 NIS, 24.0% had house hold income between 1700-2200 NIS and only 17.0% has had a house hold income more than 2200 NIS compared to 62.5%, 25.0%, and 12.5% of controls respectively.

4.2 CKD related variables among cases participants

Table (4.2): Distribution of cases according to CKD levels stage and age at diagnosis of CKD

Variable	CKD patients (n=200) No	%
Age at diagnosis		
At birth	66	33
Less than 1 year	38	19
Between (1-5) years	76	38
Between (5-12) years	20	10
Level of CKD:		
Stage I	10	5
Stage II	66	33
Stage III	62	31
Stage IV	40	20
Stage V	22	11

According to Hsu et al. (2014), the age at diagnoses of CKD among cases as followed: less than 1 years old 82.2%, between 1–5 years old 10.1%, between 6–10 years old 4.1%, and age

11–20 years old 3.6%. Compared with this study, the results as manifested by: child born with CKD 33%, less than 1 year old 19%, aged at 1-5 years old 38%, and age between 5-12 years old 10%. The study concluded that most of child exposed to CKD at birth regarding to late detection signs of the disease and insufficient medical analysis for the child. Additionally, Staples et al., (2010) cohort study determined the major number of CKD in child from stage II to stage IV were as followed: stage II 19.9%, stage III 51.9%, and stage IV 28.2% mentioned with this study the stage I 5%, stage II 33%, stage III 31%, stage IV 20%, and stage V 11% among cases. This study equal with researcher analysis with many cases of CKD between stages 2-4 with percentage 84% of total cases.

4.3 Renal diseases associated with CKD in cases children

Table (4.3): Distribution of cases according to disorders of the renal system problems

Variable	CKD patients (n=200) No	%
Renal diseases		
Nephrotic syndrome (NS)	60	30
Vesico-ureteral reflux (VUR)	40	20
Focal segmental glomerular sclerosis (FSGS)	36	18
Acute glomerular nephritis (AGN)	14	7
Posterior urethral valves (PUV)	12	6
Proteinuria	26	13
Hemolytic uremic syndrome (HUS)	4	2
Other	8	4
Congenital abnormalities:		
Polycystic kidney	16	8
Kidney atrophy	46	23
Kidney damage	16	8
Born with one kidney	40	20
Nephromegaly	12	6
Other	16	8
Did not had congenital diseases	54	27

The above table shows that 30% of cases has had NS followed by VUR 20% and FSGS 18%. The findings of this study showed that 13% of cases has had proteinuria; 6% PUV; and 2% HUS. The results were consistent with the findings of other global studies. Kari, (2012) epidemiology study found NS is a common cause of CKD in Arab and Asian children with CKD. Additionally, Harambat et al., (2012) observed that the NS is considered the major cause of CKD globally 35.2%. Furthermore, the results indicated that 20% of cases diagnosed with VUR before exposure to CKD, while FSGS were 18% of total cases. This data supported by the results of the study conducted in Saudi Arabia by Kari, (2012) which mentioned that 24% of cases with CKD complained from FSGS. At the same study, PUV constituted 27% of children where it found to be in 6% of cases of this study. Ardissino et al. (2010), verified the progression of CKD among children and the result found that more than half of the study population had history diagnose of VUR. Wong et al., (2009) clarified that the increase of proteinuria level associated with renal dysfunction could lead to CKD in children. The researcher found that 13% of total cases were diagnosed with proteinuria before being diagnosed with CKD. Ali (2009) study reported that the chronic glomerulonephritis is one of the main causes of CKD which found to be in 30% to almost 60% of children diagnose with CKD. In his study, the researcher found 7% of cases has complained from chronic glomerulonephritis. According to Behrman et al., (2004), the researcher clarified that the HUS is considered one of the main causes for CKD in children less than 4 years old (4%) compared to 2% of the participants of this study.

4.3.1 Congenital Renal Disorders

Table (4.3) indicated that the infant who born with kidney atrophy constituted the larger number of cases (23%) while a child born with one kidney was the second congenital disorder (20%). The other congenital disorders appeared less frequently in children with CKD in GG.

These results agree with the findings of a study conducted by Ceron et al., (2014) which clarified that approximately 10.7 % of children were diagnosed with asymptomatic urinary tract anomalies before exposure to CKD and congenital anomaly of kidney and urinary tract 27.7%. Gheissari, (2012) and Cailuo et al., (2012) represented the most common cause of CKD were congenital glomerular diseases, congenital anomaly of kidney and urinary tract, and kidney atrophy among the participants. According to Quirino et al., (2014) found that congenital anomalies of the kidney and other urinary tract organs constituted 6% of the causes or predisposing factors for CKD in children.

4.4 Socio-economic variables

The researcher supposed that the socio-economic variable of the participants may play a role as predisposing risk factors of CKD in children. These variable include housing hold income in month.

Table (4.4): Distribution of CKD by parent socio-demographic and economic variables

Variables	Cases		Controls		Total		OR (95% CI)	P value
	No	%	No	%	No	%		
Father education								
Primary	50	25.0	46	23.0	96	24.0	0.85 (0.50-1.44)	
Secondary	88	44.0	87	43.5	175	43.7	0.91 (0.58-1.44)	0.833
University	62	31.0	67	33.5	129	32.3	1	
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Mother education								
Primary	42	21.0	28	14.0	70	17.5	1.57 (0.99-2.49)	
Secondary	96	48.0	122	61.0	218	54.5	0.82 (0.45-1.51)	0.028
University	62	31.0	50	25.0	112	28.0	1	
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Household income (NIS)								
< 1700	118	59.0	125	62.5	243	60.7	.69(0.39-1.23)	
1700-2200	48	24.0	50	25.0	98	24.5	1.41(.69-2.86)	0.446
> 2200	34	17.0	25	12.5	59	14.8	1	
Total	**200**	**100**	**200**	**100**	**400**	**100**		

Table (4.4) cleared that maternal illiteracy show strong association with CKD (OR=1.57, 95% CI=0.99-2.49, P value= 0.028). This means that highly educated mothers had a lower risk to deliver baby had risk to CKD. Therefore, low educational level was considered as one of the risk factors that affects the chance of having a baby with CKD. From the same table shows that more than half of the participants live in unstable economic situation and under extreme poverty line for the reference with approximately 1,700 shekels per month. The results show that there is no statistically significant difference between the case and control groups in term of the socio economic status with P-value 0.446. The results of the study has led to confusion but the researcher could contribute these results to the difficult and unstable economic status, the high unemployment rate and to the large number (61%) of people who live under the poverty line in GGs (PCBS, 2013). These results were not compatible with these of other studies which indicted that poor SES has a negative effect on family health status especially children, which bind genetically with environmental factors and causes CKD in the children (Patzer & McClellan, 2012). Abu-Odah, (2013) clarified that the individuals who live in low monthly income are more likely to risk of ESRD. Also, Parkash et al., (2010) illustrated the association between low SES and the high incidence of CKD. The researcher conclude that the SES could be one of the health indicators that effects the child health status negatively at all population.

4.5 Child health status related variables (Birth weight, Gestational age, BMI)

Table (4.5): Summary table of participants by birth weight, gestational age, and BMI

Variables	Cases		Controls		Total		OR (95% CI)	P value
	No	%	No	%	No	%		
Child birth weight/kg								
Normal (2.5-4)	98	49.0	134	67.0	232	58.0	1	
Underweight (<2.5)	66	33.0	48	24.0	114	28.5	1.88 (1.19-2.96)	0.001
Overweight (>4)	36	18.0	18	9.0	54	13.5	2.73 (1.46-5.09)	
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Gestational age								
Full-term	146	73.0	172	86.0	318	79.5		
Pre term	54	27.0	28	14.0	82	20.6	2.27 (1.36-3.77)	0.001
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Child obesity (BMI)								
Healthy weight	137	68.5	155	77.5	292	73	1	
Obese	63	31.5	45	22.5	108	27	1.58(1.0-2.4)	0.042
Total	**200**	**100**	**200**	**100**	**400**	**100**		

P-value = 0.05 or less

Table (4.5) shows that 33.0% and 24% of infants in the case and control group respectively were born with a low birth weight while 18% and 13.5% of the cases and controls respectively were born with overweight and the results of this study indicated that the difference between the two groups were statistically significant at level of 0.05. Hence, the researcher can conclude that there is a relationship between birth weight and exposure to CKD later in life. The findings were consistent with these of a study conducted in Washington State, USA to assess the factor of birth weight and CKD in childhood which clarified that the high birth weight is associated numerically to occurrence CKD in child at his later life (Hsu et al., 2014). At the same condition, Boyles, (2014) matched between exposure to CKD and abnormal birth weight in children and the outcomes of his study showed that the LBW was considered a risk factor to CKD in children 9with crude odds ratio

2.41 (95% CI 2.08-2.80). On the other hand, the same study indicated that high birth weight also raise the risk of CKD with an OR of 1.17 (95% CI 1.03-1.34). Luyckx, (2013) verified the association between birth weight and probability to occurrence CKD in infants, and the result clarified that the LBW can cause decrease number of the nephron in infant, and correlated with increased risk of HTN, proteinuria, and Kidney damage in later life. Another study conducted by Vikse et al., (2008) interpreted that more than 77% of cases has had a history of LBW with an OR 1.7 (95% CI 1.4 to 2.2; P- value= 0.001).

However, the table also shows that there were a strong association between preterm (gestational age) and CKD (OR= 2.27, 95% CI= 1.36-3.77, P value= 0.001). The results indicated that CKD is more prevalent among pre-term infants and the difference between the cases and controls groups was statistically significant at level of 0.05. Some literatures agrees with the result of the study which clarified that the preterm delivery is considered a high risk factor for CKD in childhood. Hsu et al. (2014), concluded that babies born before the 37 weeks of gestation who constituted 14.7% of participants are highly susceptible to CKD at later life. Moreover, Greenbaum, (2011) explained that the premature babies were at risk to CKD more than normal birth weight and the result showed a strong statistically significant correlation between birth weight and CKD in childhood.

According to the same table, the study results indicated that 73% of the total study participants fall in the normal range of body weight. Of those, 68.5% who had been diagnosed were cases while 77.5% were controls. Contrary to that, 31.5% had more weight among cases versus 22.5% among control respectively which included infant less than 2 years old by z-score chart and the children between 2-12 years old by CDC BMI score. The association was statistically significant (P value= 0.042) and the difference between the cases and controls groups was statistically significant at level 0.05. These results were consistent with the

findings of a study conducted by Krmar and Barany, (2013), and Guanta and Mak, (2012) who indicated that the Hypertension with obesity may increase the incidence of CKD in children. These results were supported by the results of a study conducted by Savino et al., (2010) to verify the association between obesity and congenital renal malformation and the results showed that there is strong association between BMI for the child and risk to CKD.

4.6 Hypertension disease among children

Table (4.6): History of HTN among the participants

Variables	Cases		Controls		Total		OR (95% CI)	P value
	No	%	No	%	No	%		
HTN								
Yes	64	32.0	1	0.5	65	16.3		
No	136	68.0	199	99.5	335	83.7	93.6 (12.8-683.1)	0.000
Total	**200**	**100**	**200**	**100**	**400**	**100**		

Table (4.6) indicates that 16.3% of all children participating in the study has complained from HTN. The researcher observed that 32.0% of children in the cases group has complained from HTN compared to 0.5% of control and this difference was statistically significant at level of 0.05. Flynn et al., (2008) concluded that the uncontrolled blood pressure is considered a risk factor for CKD among children. Additionally, staples et al., (2010) clarified that the incidence of CKD among children with history of renal HTN before the disease were higher than whom has not had HTN before CKD. So, the researcher can conclude that HTN is a risk factor and one of the main symptoms for CKD in children before occurrence the early symptoms of the disease.

4.7 Anemia, genetic disease, and electrolyte loss at children

Table (4.7): History of Anemia, Genetic diseases, and dehydration problem among the participants

Variables	Cases		Controls		Total		OR (95% CI)	P value
	No	%	No	%	No	%		
Anemia								
Yes	128	64.0	50	25.0	178	44.5		
No	72	36.0	150	75.0	222	55.5	5.55 (3.46-8.20)	0.000
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Genetic diseases								
Yes	34	17	28	14	62	15.5		
No	166	83	172	84.2	338	84.5	1.25 (0.73-2.16)	0.407
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Dehydration problem								
Yes	68	34.0	78	39.0	146	35.5		
No	132	66.0	122	61.0	254	63.5	0.80 (0.53-1.21)	0.299
Total	**200**	**100**	**200**	**100**	**400**	**100**		

P-value = 0.05 or less

Table (4.7) shows that there were significant differences between both groups with regard to the presence of anemia. The result indicated that 44.5% of the total study populations had suffered from anemia. Of those, 64.0% who had been diagnosed were cases while 25.0% were controls. The result indicated that there is an association between anemia before CKD and the disease with P-value= 0.000. Bruganara & Eckardt (2011) reported that the kidney function correlated with blood level in the body, which increase the risk when the blood volume became low and the kidney function work around 20%-50% that raise the risk of CKD in the children.

Similarly, staples, (2009) confirmed that the prevalence of anemic children with CKD increased from stage II with average 18.5% to stage V with 68% of the total study. The study concluded that the anemia is a high risk factor of progression CKD stages. A study

conducted by Baily, (2007) that confirmed the thrombocytopenia and hemorrhage are significant risk factors of acute kidney disease in the children. This result determined that the children health program need more coverage to promote health status to decrease the percentage and the incidence of anemia among children and take in consideration the low hemoglobin level with kidney diseases that probably be symptoms of early stages of CKD. In the same table, the result indicated that 15.5% of the total study populations were diagnosed with genetic diseases. Of those, 17.0% who had been diagnosed were cases while 14% were controls. The association has not reached a statistically significant level (P value= 0.407). Furthermore, the study result clarified that 35.5% of the total study populations had suffered from diarrhea or dehydration. Of those, 34.0% who had suffered were cases while 39.0% were controls. The association has not reached a statistically significant level (P value= 0.299). After searching in the references and literatures to investigate the correlation between fluid loss from the body and CKD in children. The study result did not agree with these of the previous studies. A study clarified that the diarrheal diseases among children with HUS are the most predisposing factor that leads to CKD. However, based on plasma analysis, BUN, and peak creatinine, the result conclude that the diarrhea and dehydration among the child of HUS had chance to exposed CKD regarding to type of microorganism that causes the diarrhea (Thurman et al, 2009).

4.8 Family History and Consanguineous at the study population

Table (4.8): Distribution of Family history of CKD and Consanguineous

Variables	Cases		Controls		Total		OR (95% CI)	P value
	No	%	No	%	No	%		
Family history of CKD								
Yes	62	31.0	17	8.5	79	19.7		
No	138	69.0	183	91.5	321	80.3	4.83 (2.70-8.64)	0.000
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Relationship								
Parent	6	3.0	3	1.5	9	2.2		
Brother	24	12.0	3	1.5	27	6.7		
Sister	16	8.0	6	3.0	22	5.5		0.000
Other	16	8.0	5	2.5	21	5.3		
No relation	138	69.0	183	91.5	321	80.3		
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Consanguineous								
Yes	138	69.0	98	49.0	236	59.0		
No	62	31.0	102	51.0	164	41.0	2.31 (1.54-3.48)	0.000
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Degree of relation								
First degree	114	57.0	64	32.0	178	44.5	2.9 (1.88-4.54)	0.000
Second	24	12.0	34	17.0	58	14.5	1.16 (.63-2.13)	0.631
No relation	62	31.0	102	51.0	164	41.0	1	
Total	**200**	**100**	**200**	**100**	**400**	**100**		

P-value = 0.05 or less

The last table describes the relationship between CKD and family history of chronic diseases. The researcher observed that the prevalence of a positive family history of CKD among cases was higher than that of the controls (31.0%-8.5% respectively). However, there were a strong positive association between child family history and CKD occurrence (OR= 4.83, 95% CI= 2.70-8.64, P value= 0.000). The results indicated that CKD occurrence is more prevalent among the children with a positive family history to CKD. The highest relationships among cases were observed among brother which represent 12.0% compared with 1.5% among

controls follow sister with percentage 8% at cases, and 3% at control, while parents among cases and control were (3% and 1.5%) respectively with P-value= 0.000. This result agree with the results of previous studies conducted to clarify the relationship between the family history of CKD and the disease occurrence in children. Abu-Odah, (2013) research study illustrated that there was an association between positive family history of CKD and the degree of relation and high associated with chronic diseases including renal failure among cases and control (70.5% and 47.7%) respectively. Otherwise, Hildebrandt, (2010) clarified that the risk of CKD in child occurred by the genetic factor across family members from their medical history among parents and/or others. Moreover, the genetic preparedness related to the families cultures and traditions according to human race, which increase risk factor of CKD among black people more than white people (Patzer & McClellan, 2012). Additionally, McClellan et al., (2009) conclude that the patient with family history of CKD at first or second degree has risk 3 times to ESRD than other patients whose does not have family history.

At the same table, the relationship between consanguineous marriage and CKD, table above shows that 69.0% of consanguineous marriage was found among cases compared with 49.0 % of consanguineous marriage among controls. Further, the table also shows that CKD occurred more among cases of first-degree marriage with a percentage of 57.0% compared with 32.0% among controls. Moreover, the relationships between consanguineous marriage and CKD shows strong positive association (OR=2.31, 95% CI- 1.54-3.48, P value= 0.000), especially at the first degree with 57% in cases and 32% in control that clarify statistically significant with P-Value= 0.000. The study result was compatible with previous literatures, which verified that the consanguinity marriage between parents considered a risk factor that lead to CKD in children. A cohort study done in the King Abdualziz University Hospital,

Jeddah, Saudi Arabia to compare the causes of CKD in children, the result showed that more than half of study population who had CKD regarding to higher rates of consanguinity with 75.4% versus 47.1% of among patient whose does not have relation between parents with (P<0.0001 (Kari, 2015). Naim et al. (2012), clarified that the infant who born with birth defect found around 15% of them had kidney disease. And a 27% of the infants were registered at medical files recorded as consanguinity of parents. Finer et al., (2004) informed that the cause of the kidney diseases and other genetics health regarding to intra-familial phenotype that founded clearly among consanguinity of families. The result shows there is a clearly association between consanguinity parents and CKD in children at later life is higher than the other patients with no consanguinity among parent.

4.9 Medication therapy condition for children before diagnosed with CKD

Table (4.9): Distribution of CKD among children by drug consumption

Variables	Cases		Controls		Total		OR (95% CI)	P value
	No	%	No	%	No	%		
Analgesic drug								
Yes	140	70.0	145	72.5	285	71.25		
No	60	30.0	55	27.5	115	28.75	0.88 (0.57-1.36)	0.58
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Variables	**Cases**		**Controls**		**Total**		**OR (95% CI)**	**P value**
	No	**%**	**No**	**%**	**No**	**%**		
Antibiotic drug								
Yes	178	89.0	173	86.5	351	87.7		
No	22	11.0	27	13.5	49	12.3	1.26 (0.69-2.30)	0.446
Total	**200**	**100**	**200**	**100**	**400**	**100**		

P-value = 0.05 or less

The study results indicated that 71.25% of the total study populations were treated with analgesic drug. Of those, 70.0% out of the total cases were received analgesic treatment compared to 72.5% out of the total controls. The study indicated that there were no

associations between analgesic drugs and CKD occurrence (P value= 0.58). These results were consonant with Misurac et al. (2013), study that conducted to clarify the predisposing factor among 1,015 children who's diagnosed with acute kidney injury. And the result clarified that the NSAIDs were a causative agent among 27 children that lead to kidney damage. So, the researcher conclude that the analgesic drugs not consider a risk factor of CKD among children

At the same table shows that 87.7% of the total study populations were treated with antibiotic drug. Of those, 89.0% out of the total cases were received antibiotic treatment compared to 87.7% out of the total controls. The study indicated that there were no associations between antibiotic treatments and CKD occurrence (P value= 0.0.446). These result is not compatible with previous literatures. Such as Neesh, (2008) which concluded that the extensive use of drugs that causing nephrotoxicity among children, which consider risk factor to severe acute renal failure (Neesh, 2008). Additionally, the study result also varied with the literatures conducted by Porter, (2013). Moffet, (2011); and Rokushima, (2008) that they found the major cause of nephrotoxicity among children with CKD correlated with high dose and use antibiotics for long time, especially: aminoglycoside, vancomycin, and cephalosporin. As a result of the study is to contribute to the nephrotoxicity drugs is not associated with CKD among children in GG, the researcher found that the families take consideration to use antibiotic or analgesics a long time therapy for children, or the health services provides antibiotics and analgesics therapies with precaution.

4.10 Maternal and obstetric variables

Table (4.10.1): The association between drug consumption during pregnancy by mother and CKD among the children

Variables	Cases		Controls		Total		OR (95% CI)	P value
	No	%	No	%	No	%		
Analgesic drug								
Yes	68	44.0	64	32.0	132	33.0		
No	132	66.0	136	68.0	268	77.0	1.09 (0.72-1.66)	0.670
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Antibiotic drug								
Yes	44	22.0	69	34.5	113	28.2		
No	156	78.0	131	65.5	287	71.8	0.53 (0.34-0.83)	0.005
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Type of drug								
Cephalosporin	18	9.0	36	18.0	54	13.5		
Aminoglycosid	10	5.0	3	1.5	13	3.25		
Other	6	3.0	8	4.0	14	3.5		0.001
Don't know	10	5.0	22	11.0	32	8.0		
Not taking	156	78.0	131	65.5	287	71.8		
	200	**100**	**200**	**100**	**400**	**100**		

P-value = 0.05 or less

Table (4.10.1) shows that 44.0% out of the total cases mother had received analgesic treatment during that pregnancy compared to 32.0% out of the total controls mother. The study indicated that there were not statistically associations between analgesic treatments during that pregnancy and CKD occurrence. But for women received antibiotic medications during that pregnancy, finding shows positive association with CKD (OR=0.53, 95% CI=0.34-0.83, P value= 0.005). This result provides evidence that CKD is more prevalent among women treated with antibiotic medication. Aminoglycoside was used among 5.0% of cases women compared to 1.5% of controls women. The result agrees with a cohort study conducted in Norwegian mother and child center, to determine the correlation of

consumption of NSAIDs on infant, and found only minimum number of mothers were used analgesics during pregnancy (Gelder et al., 2011). On the other hands, Perazella, (2009) clarified that the intake of antibiotic during pregnancy consider main risk factor for infant CKD at later life, also associated with congenital renal malformation and renal development failure among neonate. Moreover, the most antibiotic drugs affects negatively on infant renal system were: Aminoglycosides, and cephalosporin more than other drugs (Sahay et al., 2014).

Table (4.10. 2): Relationship between CKD among children and: mother age during pregnancy, and amniotic fluid

Variables	Cases		Controls		Total		OR (95% CI)	P value
	No	%	No	%	No	%		
Age during pregnancy								
< 18	14	7.0	25	12.5	39	9.8	0.53 (0.26-1.08)	0.07
18 -30	116	58.0	111	55.5	227	56.8	1	
≥ 30	70	35.0	64	32.0	134	33.4	1.04 (0.68-1.65)	0.83
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Amniotic fluid during pregnancy								
Normal	104	52.0	137	68.5	241	60.3	1	
Oligohydramnios	32	16.0	23	11.5	55	13.7	1.83 (1.01-3.31)	0.04
Polyhydramnios	64	32.0	40	20.0	104	26.0		
Total	**200**	**100**	**200**	**100**	**400**	**100**		

P-value = 0.05 or less

Table (4.10.2) shows that 56.8% out of the total cases mother aged between 18-30 years when they have had the pregnancy, while the age less than 18 years was 9.8%, and age more than 30 years was 33.4%. The correlation between the mother's age and occurrence of CKD was not significant. This results not agree with previous studies that clarified the relation between mother's age and CKD in children. Hsu et al., (2014) study clarified the relation between maternal age at pregnancy and the occurrence congenital renal malformation in later life of

infant by identifying the mother's age and the results showed: the mothers less than 18 years old were (66 cases VS 723 control) and between 18 to 30 years old were (1,137 cases VS 12,058 control) and more than 30 years old were (791 cases VS 7,242 control) and p=value 0.001 that showed a confounder of infant born weight and cause congenital malformation of infant renal system. While Lampinen et al., (2009) concluded that the congenital renal system with LBW at infant occurs with maternal age more than 35 years. Also Franke et al., (2010) found an association between small maternal age and the prevalence of CKD among child in his later life. So, the researcher cannot confirmed that there is a relationship between mother's age and CKD among children in GGs.

The study results reveal that 60.3% (52% cases and 68.5% controls) of all mothers showed a normal amniotic fluid volume during that pregnancy compared to 13.7% (16% cases and 11.5% controls) complained from Oligohydramnios. However, a strong positive association between Oligohydramnios and CKD have been observed by the researcher (OR=1.83; 95% CI=1.01-3.31, P value= 0.04). The result of this study provides evidence that CKD is more prevalent among women experienced abnormal amniotic fluid level. Regarding to Elder, (2011) correlate between oligohydramnios and renal failure in the fetus who expose to renal failure.

The findings of a study conducted by Leibovitch et al., (2012) showed that the oligohydramnios was associated with increasing the prevalence of renal failure with P-value= 0.001. Also, in medical references books determined that if the amniotic fluid less than normal range (800-1000 ml), it will cause congenital renal anomalies in infant (Behrman et al., 2004). The result of this study provides evidence that CKD is more prevalent among women experienced abnormal amniotic fluid level.

Table (4.10.3): Distribution of CKD among children regarding to mother chronic diseases (HTN and DM), and obesity during pregnancy

Variables	Cases		Controls		Total		OR (95% CI)	P value
	No	%	No	%	No	%		
HTN during pregnancy								
Yes	52	26.0	40	20.0	92	23.0		
No	148	74.0	160	8.0	308	77.0	1.40 (0.87-2.24)	0.154
Total	**200**	**100**	**200**	**100**	**400**	**100**		
DM during pregnancy								
Yes	24	12.0	21	10.5	45	11.3		
No	176	88.0	179	89.5	355	88.7	1.16 (0.62-2.16)	0.635
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Obesity								
Yes	96	48.0	65	32.5	161	40.2		
No	104	52.0	135	67.5	239	59.8	1.91 (1.27-2.87)	0.002
Total	**200**	**100**	**200**	**100**	**400**	**100**		

P-value = 0.05 or less

The study indicates that 23.0% of all mothers has experienced HTN in that pregnancy. It was observed that 66 cases mother that equal 26.0% out of the total mothers has experienced HTN compared to 20.0% of control mothers. Also, the table shows that 11.3% of all mothers has experienced DM in that pregnancy. It was observed that 24 cases mother that equal 12.0% out of the total mothers has experienced DM compared to 10.5% of control mothers. Moreover, there were no statistically differences between case mothers and control mothers who experienced HTN and DM in that pregnancy at level 0.05. These results did not agree with former research and studies which indicates that the maternal health status during pregnancy with HTN or DM was a high risk to CKD in child. Hsu et al., (2014) research data showed that the gestational diabetes among population study (100 cases vs 696 control) and the crude odds ratio of maternal pre gestational DM was 1.97 (95% CI, 1.15 to 3.37, p-value 0.001), while gestational HTN among study (127 cases vs 956) and crude OR of gestational

HTN was 1.19 (95% CI, 1.02 to 1.38, p-value 0.002) were associated numerically with CKD in pediatric. Additionally, Banhidy et al., (2010) study included 22,843 and the cases were 79 (0.35%) pregnant women with DM-type 1, while 77 (0.34%) pregnant women with DM-2 and 120 (0.53%) pregnant women with GDM. Compare with control 38,151 pregnancy women that diagnosed with: DM-1 88 (0.23%), DM-2 141 (0.37%), and GDM 229 (0.60%), respectively. The total rate of cases with congenital anomalies was higher only in the DM-1 group (adjusted OR with 95% CI: 1.5, 1.1-2.0) and within obstructive congenital anomalies of the urinary tract, the study cleared that the pregnant women with diabetes mellitus type 1 (DM-1), type 2 (DM-2), and gestational diabetes mellitus are estimates with risk of structural birth defects. Meaning that, the maternal health status during pregnancy with HTN and DM cannot be considered as a risk factor for developing CKD among infant in GG. The researcher conclude that the maternal health care promote positive services and monitoring health indicators for the mothers during pregnancy in maternal health clinics.

At the same table, the result informs that 40.2% of all mothers had suffered from overweight in that pregnancy. It was observed that 96 cases mother that equal 48.0% out of the total mothers had suffered from overweight compared to 32.5% of control mothers. The study indicated a statistically positive association between obese mother and CKD in childhood (OR=1.91, 95% CI=1.27-2.87, P value= 0.002). Previous literatures is convenient with this result of the study that reported maternal overweight is considered a risk factor for CKD in children. Hsu et al. (2014), found significant correlation between maternal weight and congenital abnormalities of the kidney and renal system and the results were as follow the maternal overweight level for cases and control were (278 VS 2390) respectively and an odds ratio of 1.24 (95% CI, 1.05 to 1.48, p-value =0.001), while obesity level was (242 cases VS 1,951 control) and an odds ratio of 1.26 (95% CI, 1.05 to 1.52, p-value= 0.001). Furthermore,

Blomberg & kallen, (2010) study results clarified that the maternal obesity is associated with polycystic kidney in infant and the results determined that 10% of mothers were obese, and 0.7% very obese. So, the researcher conclude that the maternal obesity level during pregnancy could increase the risk of CKD in children.

4.11 Environmental variables

The researcher supposed that the environmental variables may play a role as predisposing risk factors for CKD in children. These variables include type of living area, home roof, use insecticide or pesticides, environmental hazards, exposed to smoking, and source of water.

Table (4.11.1): Comparison between the participants by: smoking exposure, using insecticide or pesticides at home, and type of drinking water

Variables	Cases		Controls		Total		OR (95% CI)	P value
	No	%	No	%	No	%		
Exposed to smoking								
Yes	100	50.0	88	44.0	188	47.0		
No	100	50.0	112	56.0	212	53.0	1.27 (0.85-1.88)	0.229
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Use insecticide or pesticides								
Yes	134	77.0	156	88.0	290	72.5		
No	66	33.0	44	22.0	110	27.5	0.57 (0.36-0.89)	0.013
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Type								
Insecticides	100	50.0	93	46.5	193	48.3	0.7 (0.44-1.15)	0.16
Anti-mosquito	22	11.0	42	21.0	64	16.0	0.34 (0.18-0.66)	0.001
Pesticides	12	6.0	22	11.0	43	10.7	0.36 (0.16-0.8)	0.01
Not used	66	33.0	44	22.0	110	27.5		
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Sources of water								
Municipal	22	11.0	8	4.0	30	7.5	2.93(1.26-6.76)	0.008
Well	10	5.0	13	6.5	23	5.8	0.8(0.35-1.91)	0.64
Auto mobile	168	84.0	179	89.5	347	86.7	1	
Total	**200**	**100**	**200**	**100**	**400**	**100**		

Table (4.13.1) shows that 50.0% out of the total cases has exposed to smoking compared to 47.0% out of the total controls. The study indicated that there was no a statistical association between exposure to smoking and CKD occurrence. This result of the study did not agree with the results of a study conducted by Omoloja et al., (2014) and found that the child with SHS is associated with risk factor to renal problems which that lead to CKD in children with an OR 2.64, (95 % confidence interval 1.08, 6.42).

From the same table, it shows that 77.0% out of the total cases had exposed to insecticide and pesticide at home compared to 88.0% out of the total controls. This difference was close to, but indicated that there were negative associations between using insecticide at home or local area and CKD occurrence (OR=0.57, 95% CI=0.36-0.89, P value= 0.013). Study limitations and the complexity of assessing pesticide exposure from multiple sources prevent drawing definitive conclusions.

The literature contains few studies examining the relationship between pesticide exposure and CKD in children. A study held out by Soderland et al., (2010), and by US department of energy, (2012) illustrated that the industrial chemical toxins, insecticides, and pesticide can absorbed by inhalation or the body skin and cause damage at all internal organs.

Other study from El-minia, Egypt conducted to correlate the relation between the environmental factors and ESRD among population conclude that the study participants exposed to pesticides and environmental toxins for long time in their life before the disease (Kamel & El-Minshawy, 2010). These studies are small and have limited designs, preventing any speculation regarding the significance of the researcher results.

For the relationship between CKD and sources of drinking water in the total population, the researcher observed that the municipal water as source of drinking water among cases was higher than controls (11.0% - 4.0% respectively). The association between CKD and source

of water is statistically significant level with CKD among children (P-value= 0.008). Compared with Kamel & El-Minshawi, (2010) study reported that there were a high rate of the participants whom used unsafe water such as municipal water and ground filtered water were reported by 72% and 48% respectively. Additionally, Soderland et al., (2010) study showed that the contaminated ground water with heavy toxin metals could be increase the risk factor for ESRD among people. That mean the potable water in GG is not considered a safe source for drinking water, and possible lead to health problems in renal system.

Table (4.11.2): Comparison between children with and without CKD related to living area and home roof

Variables	Cases		Controls		Total		OR (95% CI)	P value
	No	%	No	%	No	%		
Living area								
City	128	64.0	157	78.5	285	71.5	1	
Camp	58	29.0	32	16.0	90	22.0	2.22 (1.36-3.63)	0.005
Village	14	7.0	11	5.5	25	6.5	1.56 (0.68-3.55)	
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Home roof								
Concrete	144	72.0	155	77.5	299	74.7	1	
Asbestos	38	19.0	27	13.5	65	16.3	0.66 (0.38-1.13)	0.332
Other	18	9.0	18	9.0	36	9.0	0.92 (0.46-1.85)	
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Living near hazards								
Yes	122	61.0	103	51.5	225	56.3		
No	78	39.0	97	48.5	175	43.7	1.47 (0.99-2.19)	0.050
Total	**200**	**100**	**200**	**100**	**400**	**100**		
Type of hazards								
Sewage	12	6.0	22	11.0	34	8.5	0.67 (031-1.45)	0.31
Landfill	34	17.0	19	9.5	53	13.3	2.2 (1.17-4.20)	0.012
Animal farm	60	30.0	47	23.5	107	26.7	1.58 (0.97-2.58)	0.06
Others	16	8.0	15	7.5	31	7.6	1.32 (0.61-2.85)	0.46
No	78	39.0	97	48.5	175	43.7		
Total	**200**	**100**	**200**	**100**	**400**	**100**		

Concerning the relationship between living area and CKD, table above shows that 29.0% of cases were living in camp compared with 16.0% of controls were living in camp. Moreover, the relationships between living in camp and CKD shows strong positive association (OR=2.22, 95% CI- 1.36-3.63, P value= 0.005). This result agree with a study conducted in Tabuk, Saudi Arabia which demonstrates the prevalence of ESRD in children increase in rural areas than urban. The study showed that there were 55% of patients living in rural areas, and 33% of cases were unknown main causes and it related to environmental factors (EL-Minshawy, Ghabrah, and El-Bassuoni, 2014). Clearly, the researcher can conclude that the living near environmental hazards or contaminated areas can increase the risks occurrence CKD in children.

Furthermore, this table indicated that there were not statistically associations between home roof and occurrence of CKD. The study indicates that 56.3% of all study participants' were lived near environmental hazards. It was observed that 122 cases that equal 61.0% out of the CKD cases were lived near environmental hazards compared to 51.5% of controls. Living near landfills was the most environmental hazards that effect on the population with statically significant among cases and controls with p-value 0.012. The association between environmental hazards and CKD occurrence reached statistically significant level (OR= 1.47, 95% CI=0.99-2.19, P value= 0.050). The researcher found that the risk of live near landfills and municipals wastes can effect on child health status negatively and predisposing factor for CKD.

Chapter 5: Conclusion and Recommendation

5.1 Summary

The aim of this study was to determine the most common risk factors of CKD among children in Gaza governorates. This case control study was carried out at the El-Ranteesy Specialized Pediatric hospital with 200 cases, and 200 controls from five main primary health care centers in each governorate. Data was collected through a self-constructed face to face interviewed questionnaire with the participants, which included socio-demographic variables such as: age, gender, governorate which matched with control, and child health status before diagnoses with CKD, maternal health status at pregnancy with the child, and environmental variables that developed CKD in the children.

Most CKD risk factors among children are not the same risks with adults, including, maternal health status during pregnancy, child health behaviors at born and beyond, and drug toxicity. The study findings confirmed some risk factors related to different past studies in various countries. The study findings may contribute in decreasing the occurrence of CKD in children and may assist decision-makers in taking actions and implementing interventions that aid in decreasing the modifiable risk factors as possible.

The main findings of the study indicated that 57% of males were at higher risk of CKD than females with 43%. It was clear that the high exposure to CKD was at age 5 years old and later. The results clarified that there is no differences in relation to salary. For the living area, the most cases lives in Gaza governorates. Also, there was a positive association with highly statistically significant between type living area and CKD where it found to be higher in rural areas. The prevalence of CKD among children according to renal diseases showed that the Nephrotic syndrome was the main cause with 30% followed Vesico-ureteral reflux 20% because of urinary tract infection and hydronephrosis, and FSGS 18%.

Additionally, kidney atrophy 23% and child born with one kidney 20% while the other kidney is damaged or immature were the main congenital renal abnormalities causes that associate with CKD.

There was a positive association between child birth weight and the period of gestation (preterm) and the disease. Regarding history of HTN, the researcher found the prevalence among cases was 64% higher than control 0.5%. Results revealed that there was a positive association with statistically significant between the child history of HTN, anemia, and obesity or being treated with analgesics and the occurrence of CKD.

The study findings indicated that there is a positive relationship between first cousin marriage, low amniotic fluid volume during pregnancy, maternal obesity, mother's use of antibiotic during pregnancy specially aminoglycosides and the occurrence of CKD in children.

Concerning environmental related factors, the main results of the study indicated that the relationship between living near environmental hazards and the prevalence of CKD was a positive with increased risk if living near animal farms. In term of second hand smoke, the results revealed that there was no differences between cases and control with no association that increase prevalence of CKD. However, there was a negative association between exposed to insecticide or pesticide and the occurrence of CKD. The association between source of drinking water (use of municipal water) and CKD in children was positive.

5.2 Conclusion

This study examined the CKD in children for the first time in GGs, and can be implemented as a database for further studies of this subject. According to the results of this study, the researcher can conclude that different risk factors could affect the health status of the children in GG and lead to CKD. These factors include, socio-economic and

demographic, child health status factors, maternal, and environmental factors. The researcher can conclude that the reduction of these risk factors such as promote maternal health program, preterm deliveries, control of chronic diseases, management of high risk environmental hazards and enhancing mother's awareness about child health care will help in reducing the incidence and prevalence of children with CKD in GG.

5.3 Recommendations

The study finding gave the researcher a chance to highlight the problems and help him provide a number of recommendations and suggestions for controlling and decreasing morbidity and mortality of CKD among children in GGs. These recommendations include

1. Recommend the physicians in health care centers to propose protocol to monitor and demand full urine analysis for children who has symptoms of UTI and provide prophylactic antibiotic to avoid progressive of renal diseases and follow up monthly for the child with full investigation.
2. Conducting a community health campaign to aware population about the risks of early and first cousin marriage.
3. Promoting knowledge and skills of nurses providing education to mothers in the antenatal care and students within school health programs specially the use of medications during pregnancy and the screening of anemia, obesity and hypertension among students.
4. Increasing attention about environmental hazard including unsafety water especially municipal water, and living near contamination places.
5. Further studies are needed to understand the effects of multiple insecticides and pesticide exposures on kidney function in children.

6. Implementing further studies to investigate other emerging CKD factors, such nutrition factors, other maternal factors that increase the risks of CKD among child, and outcome of the disease at children and their families.
7. Developing a data base for regular reporting and documentation and accurately determining the incidence and prevalence of CKD in GGs.

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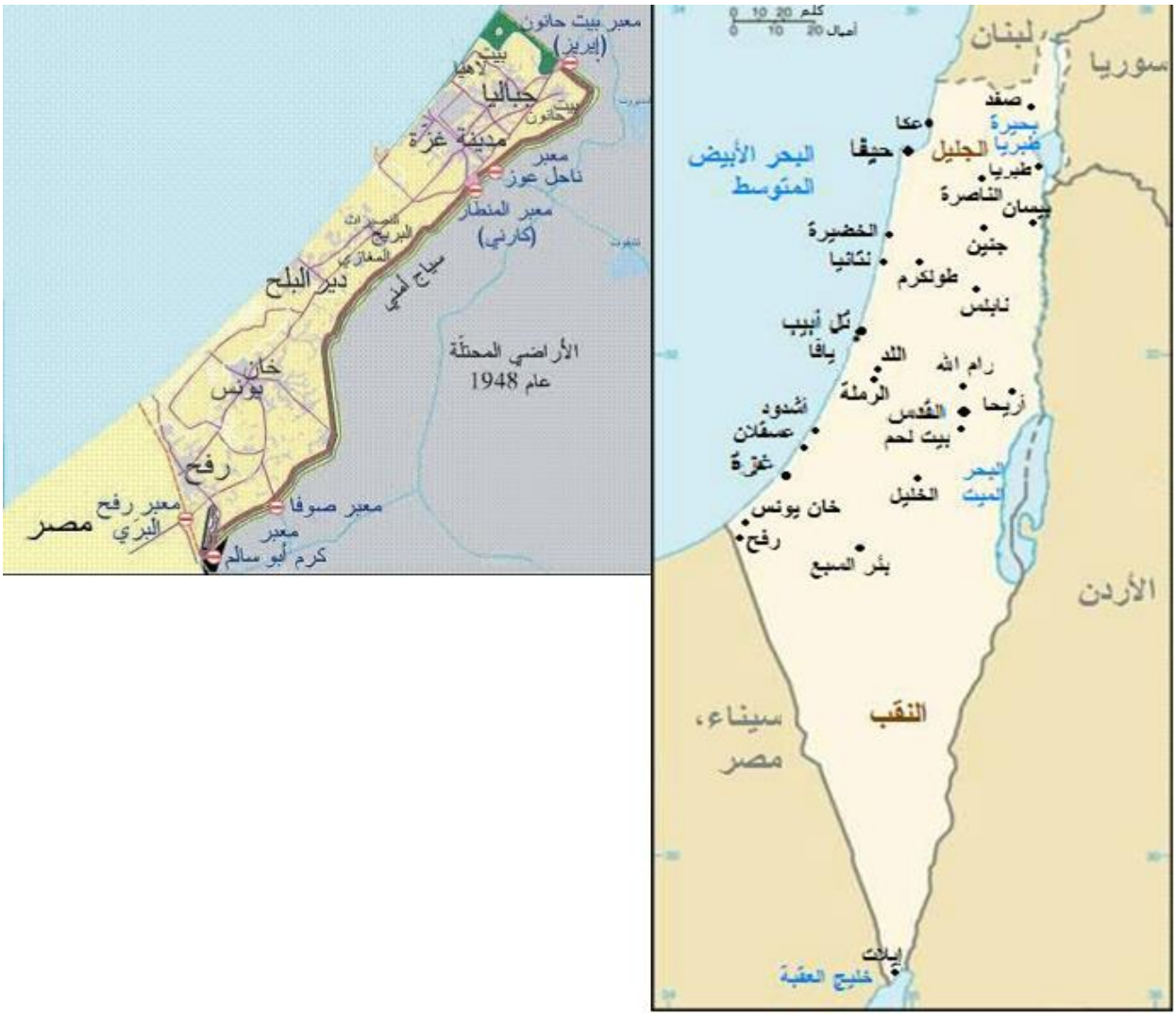
Annex (1)

Palestine & Gaza Governorates maps



Annex 2

The questionnaire

عزيزى الأب، عزيزتى الام، مرحبا

انا طالب دراسات عليا بجامعة القدس "أبو ديس" أقوم بدراسة حول ...

التعرف على أهم عوامل الخطر التى تؤدى إلى الفشل الكلوى المزمن لدى الاطفال فى محافظات غزة

ويسعدنى موافقتك على المشاركة بالاستبيان، وكما ارجو التكرم بالأجابة على جميع اسئلة الاستبانة، مع العلم أن مشاركتك فى هذه الدراسة طوعية،كما أن البيانات التى سيتم جمعها سيتم استخدامها لغرض البحث العلمى فقط، يرجى الإجابة على الأسئلة بكل امانة وصدق.

هذه الاستبانة سوف تستغرق حوالى ٢٠ دقيقة لاستكمالها. مهما كانت المعلومات التى تعطيها سوف تبقى سرية وطى الكتمان ولن يطلع عليها احد بستثناء الباحث.

فى حالة وجود مزيد من الاستفسار يمكن الاتصال على رقمى المحمول: ٠٥٩٩١٥٨٠١٤

او رقم الجامعة فرع غزة: ٢٦٤٤٢١٠

اشكرك حسن تعاونك

الباحث:

محمود سعيد العبسي

	1. Socio- demographic Information
1.1	Serial number:……. Date:…… 1- Case:…….. 2- Control:……..
1.2	Age of child in year: 1- < 2 ☐ 2- 2-5 ☐ 3- >5 -12 ☐
1.3	Gender: 1- Male ☐ 2- Female ☐
1.4	Governorate: 1- N.Gaza ☐ 2- Gaza ☐ 3- Mid Zone ☐ 4- Khan-younis ☐ 5- Rafah ☐
1.5	Citizenship: 1- Citizen ☐ 2- Refugee ☐
1.6	Mother age:……
1.7	Father age:……
1.8	Mother education level: 1-Primary ☐ 2-Secondary ☐ 3- University ☐
1.9	Father education level: 1- Primary ☐ 2- Secondary ☐ 3- University ☐
1.10	Is there relation between parents? Yes ☐ No ☐
1.11	If yes, what the degree of relation: 1- First degree ☐ 2- Second degree ☐
1.12	Monthly income(NIS): 1- <1700 ☐ 2- 1700-2200 ☐ 3- >2200 ☐
	2. Child Health Status
2.1	1- Body weight:…….KG, 2- Height:…….CM, 3- BMI:…….KG/m^2 4- Blood Pressure……MMHG, 5- GFR level:……. ml/min/1.73 m^2
2.2	Child birth weight: 1- < 2.5 KG ☐ 2- 2.5-4 KG ☐ 3- > 4 KG ☐
2.3	Gestational period (week): 1- < 37 ☐ 2- 37-42 ☐ 3- > 42 ☐

2.4	Has the child had a health problem before CKD? 1- Yes ☐ 2- No ☐ If no, please move to the question 2.42
2.5	Has the child had a congenital anomalies with the Urinary tract? 1-Yes ☐ 2-No ☐
2.6	If yes, 1- polcysytic kidney ☐ 2- Kidney atrophy ☐ 4- Kidney damage ☐ 6- Born in one kidney 7- Nephromegaly ☐ 8- Other……
2.7	Has the child had renal diseases before CKD? 1- Yes ☐ 2- No ☐
2.8	If Yes, 1- Nephrotic syndrom ☐ 2- Vesicoureteral Reflux ☐ 3- Focal segmental gloermmularsclerosis ☐ 4- Acute glomerular nefphritis ☐ 5- Posterior urethral valve ☐ 6- Proteinurea ☐ 7- Hemolytic uremic syndrom ☐ 8- other……..
2.9	What the stage of CKD in child (1-5)……
2.10	Child age at exposed the disease? 1- At born ☐ 2- At born till 2 years ☐ 3- At 2 years till 6 years ☐ 4- At 6 years till 12 years ☐
2.11	Has the child had other conginital malformation? 1- Yes ☐ 2- No ☐
2.12	If yes, 1- In Digestive system ☐ 2- in Neurogenic system ☐ 3- In Cardiac system ☐ 4- Other……
2.13	Has the child had genitic disease? 1- Yes ☐ 2- No ☐
2.14	If yes, 1- Thalasemia ☐ 2-Hemophilia ☐ 3- Sicle Cell Anemia ☐ 4- Down syndrom ☐ 5- Other…….

2.15	Has the child had Diarrhea before diagnosis with CKD? 1- Yes ☐ 2- No ☐
2.16	If yes, exposed to dehydration? 1- Yes ☐ 2- No ☐
2.17	Has the child had Hypertension before diagnosis? 1- Yes ☐ 2- No ☐
2.18	If yes, how many years? 1- less than 1 year ☐ 2- between 1-5 years ☐ 3- More than 5 years ☐
2.19	Has the child had Anemia before diagnosis with CKD? 1- Yes ☐ 2- No ☐
2.20	Has the child had hemorrhage before or during diagnosis with CKD? 1-Yes ☐ 2-No ☐
2.21	has the child had treatment with antibiotic for long time ? 1- Yes ☐ 2- No ☐
2.22	what the drug group: 1- Did not know name ☐ 2- Penicillin ☐ 3- Aminoglycoside ☐ 4- Cephalosporin ☐ 5- Other……..
2.23	Duration therapy (in days) : 1- < 5 ☐ 2- 5-10 ☐ 3- > 10 ☐
2.24	Has the child had analgesic therapy before diagnosis with CKD? 1- Yes ☐ 2- NO ☐
2.25	Drug name: 1- Did not know name ☐ 2- Aspirin ☐ 3- Paracetamol ☐ 4- Trufen ☐ 5- Other……
2.26	Duration therapy : 1- To much ☐ 2- Sometime ☐ 3- Rarely ☐
2.27	Has the child had other health problems? 1- Yes ☐ 2- No ☐
2.28	If yes, 1- Growth failure ☐ 2- Cerebrovascular accident ☐ 3- Brain atrophy ☐ 4- Cardiomegaly ☐ 5- thyroid diseases ☐

	6- paraplegia ☐ 7- Other……
2.29	Is there a family history of CKD? 1- Yes ☐ 2- No ☐
2.30	If yes, 1- Father ☐ 2- Mother ☐ 3- Brother ☐ 4- Sister ☐ 5- Other……
	3. Mother health Status
3.1	Mother age during pregnancy with the child? (in years). 1- < 18 ☐ 2- Between 18-30 ☐ 3- > 30 ☐
`3.2	Has you had Hypertension during pregnancy? 1- Yes ☐ 2- No ☐
3.3	Has you had diabetes during pregnancy? 1- Yes ☐ 2- No ☐
3.4	Amount of aminotic fluid during pregnancy? 1- Normal ☐ 2- Oligohydramnios ☐ 3- Polyhydramnios ☐
3.5	Had you exposed to obesity during pregnancy? 1- Yes ☐ 2- No ☐
3.6	Has you had medication during pregnancy? 1- Yes ☐ 2- No ☐
3.7	If yes, was it: 1- Analgesic ☐ 2- Vitamins ☐ 3- Antibiotics ☐ 4- Other……
3.8	What the antibiotic name? 1- Does not know ☐ 2- Aminoglycoside ☐ 3- Cephalosporin ☐ 4- Penecillin ☐ 5-Other…….. 6-Not used ☐
3.9	Period of drug used (Days): 1- less than 5 ☐ between 5-10 ☐ 3- More than 10 ☐
3.10	What the analgesic name? 1- Does not know ☐ 2- Paracetamol ☐

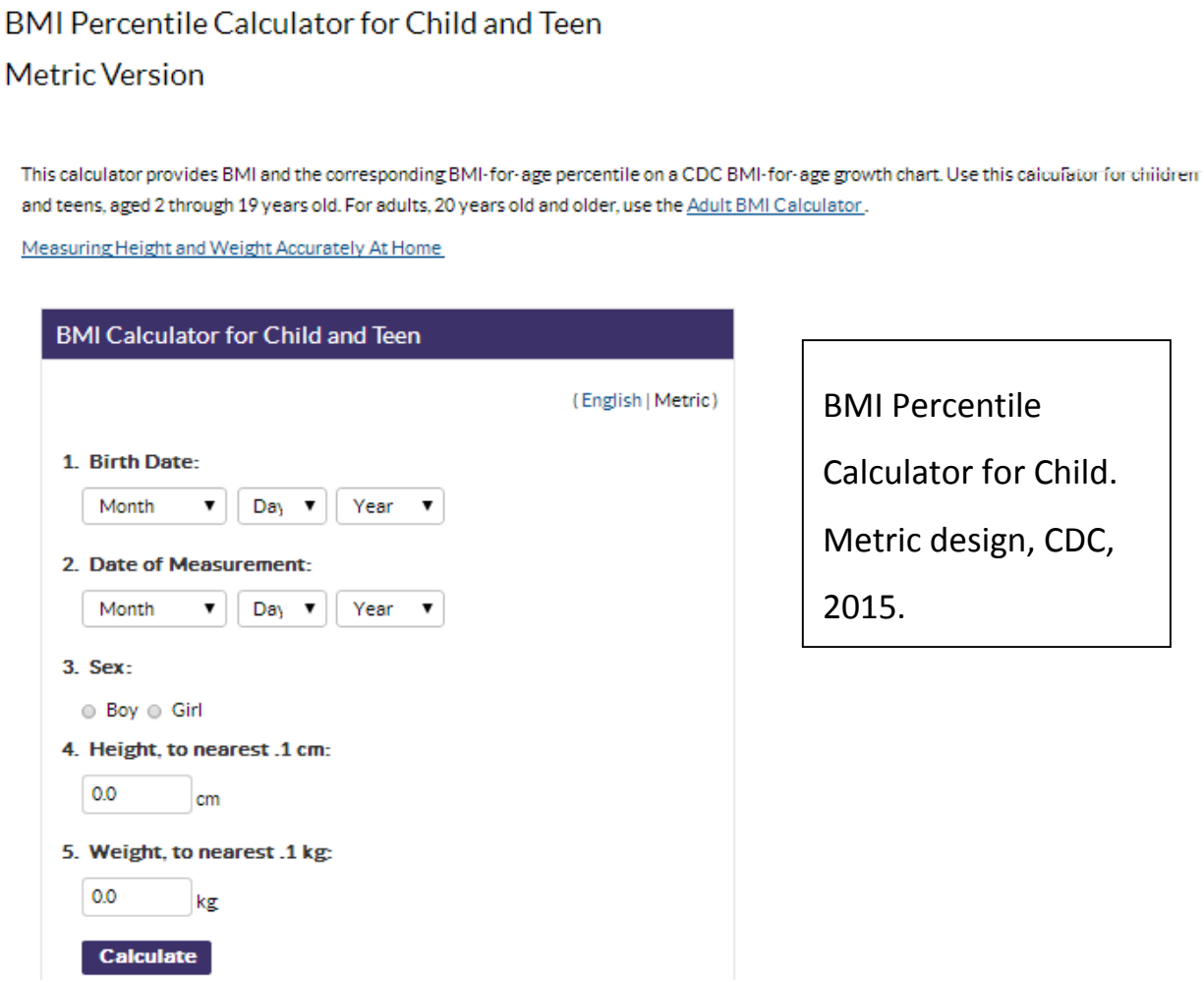
	3- Diclofen ☐ 4- Aspirin ☐ 5-Other…… 6- Not used ☐
3.11	Period of drug used (Days): 1- less than 5 ☐ between 5-10 ☐ 3- More than 10 ☐
	4. Environmental factors
4.1	Living area: 1- City ☐ 2- Camp ☐ 3- Village ☐
4.2	Type of home living: 1- Concrete ☐ 2- Asbestos ☐ 3- Other:……..
4.3	What is the source of drinking water before the disease? 1- Municipal water ☐ 2- private well ☐ 3- Filtered tanks ☐ 4- Packed mineral water ☐
4.4	Is there environmental hazards in the living are? 1-Yes ☐ 2-No ☐
4.5	If yes, is it: 1- Land fill ☐ 2- Sewage ☐ 3- Chemical factory ☐ 4- Incineration ☐ 5- pesticides ☐ 6- communication tower ☐ 7- Other:…….
4.6	Is there used the pesticide or Insecticide at home? 1- Yes ☐ 2- No ☐
4.7	If yes, how many time of used? 1- To much ☐ 2-Sometimes ☐ 3- Rarely ☐
4.8	Does the child exposed to smoking? 1- Yes ☐ 2- No ☐
4.9	how many hours in one day: 1- <1 ☐ 2- Between 1-5 ☐ 3- > 5 ☐

Annex 3

Anthropometric data

Detect 339 400lb.
Beam Weight Scale
with Height Rod

Blood pressure
Sphygmomanometers

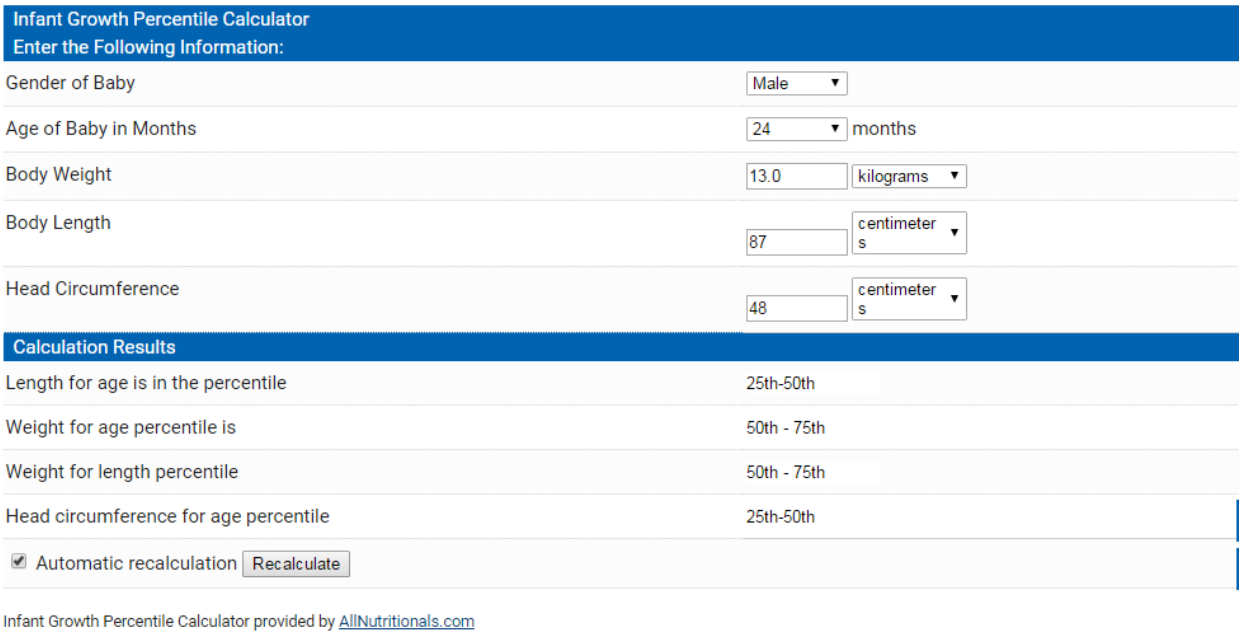


BMI Percentile Calculator for Child. Metric design, CDC, 2015.

Available on:

http://apps.nccd.cdc.gov/dnpabmi/Calculator.aspx?CalculatorType=Metric

Body mass index for infant less than two years



Infant Growth Percentile Calculator Enter the Following Information:	
Gender of Baby	Male
Age of Baby in Months	24 months
Body Weight	13.0 kilograms
Body Length	87 centimeters
Head Circumference	48 centimeters
Calculation Results	
Length for age is in the percentile	25th-50th
Weight for age percentile is	50th - 75th
Weight for length percentile	50th - 75th
Head circumference for age percentile	25th-50th
Automatic recalculation Recalculate	

Infant Growth Percentile Calculator provided by AllNutritionals.com

Available on: http://www.disabled-world.com/calculators-charts/infant-gp.php

Annex 4

Control Panel

Name	Position
Dr: Bassam Abu Hammad	Associate Professor, Al-Quds University
Dr: Yehia Abed	Associate Professor, Al-Quds University
Dr: Ibrrahim Shameya	Associate Professor, University College of Applied Science
Dr: Mohammed Al-Gergawee	Associate Professor, Palestine college of Nurse
Dr: Hamza Abed aljawwad	Associate Professor, Palestine college of Nurse
Dr: Mostafa El-Aila	General director of Al-Ranteesy pediatric hospital
Dr: Marwan Arafat	Director of Renal transplantation at Al-Shifaa Hospital

Annex 5: Approval from Helsinki committee

المجلس الفلسطيني للبحث الصحي
Palestinian Health Research Council

تعزيز النظام الصحي الفلسطيني من خلال مأسسة استخدام المعلومات البحثية في صنع القرار

Developing the Palestinian health system through institutionalizing the use of information in decision making

Helsinki Committee
For Ethical Approval

Date: 02\02\2015 **Number:** PHRC/HC/05/15

Name: Mahmoud Said Ahmed Al-Abssi **الاسم: محمود سعيد العبسي**

We would like to inform you that the committee had discussed the proposal of your study about: نفيدكم علماً بأن اللجنة قد ناقشت مقترح دراستكم حول:-

"Risk Factors of Chronic Kidney Disease among children in Gaza governorates: A Case Control Study"

The committee has decided to approve the above mentioned research. Approval number PHRC/HC/05/15 in its meeting on 02/02/2015 و قد قررت الموافقة على البحث المذكور عاليه بالرقم والتاريخ المذكوران عاليه

Signature

Member **Member**

Chairman

Genral Conditions:-

١. Valid for 2 years from the date of approval.
٢. It is necessary to notify the committee of any change in the approved study protocol.
٣. The committee appreciates receiving a copy of your final research when completed.

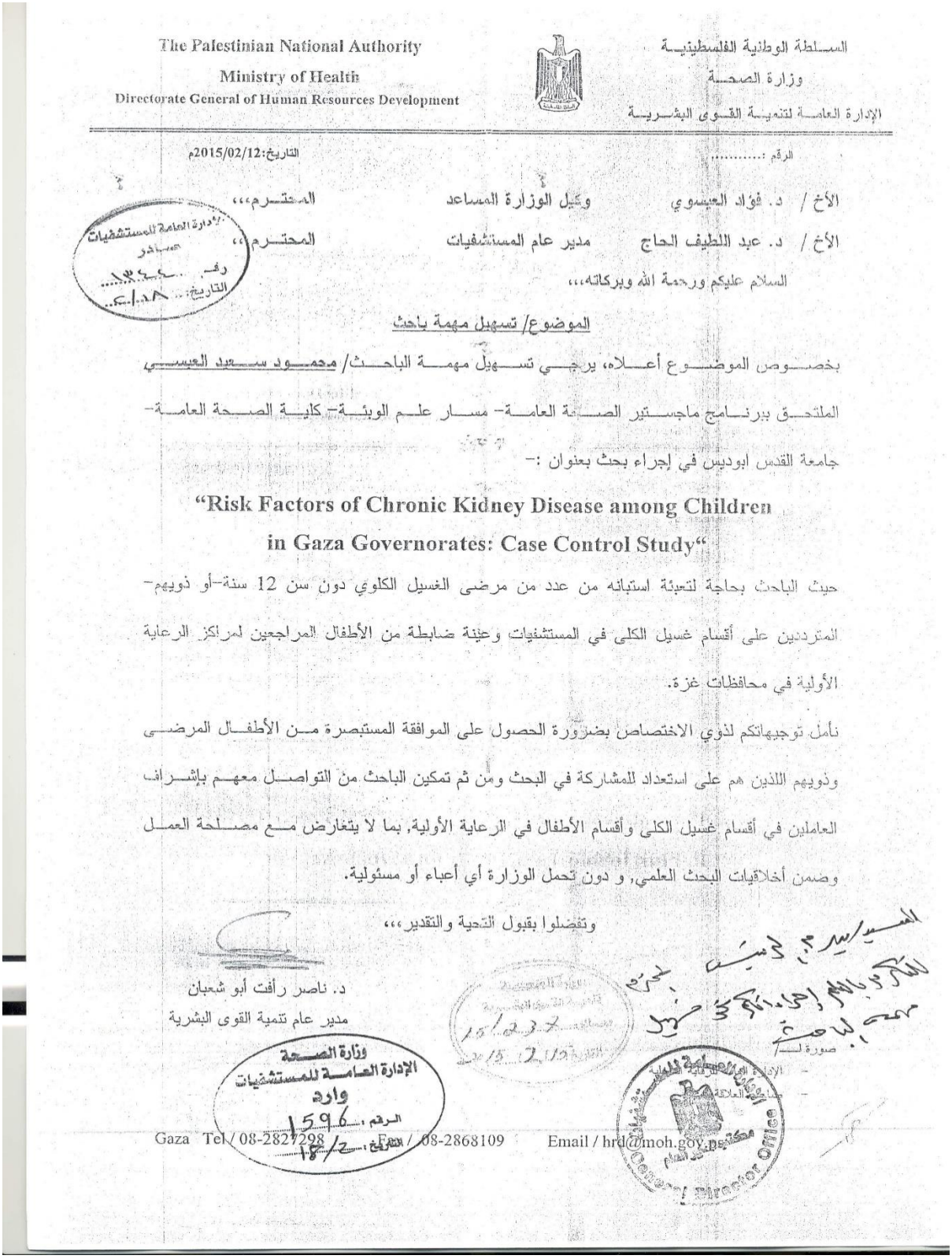
Specific Conditions:-

The subject was approved following the World Medical Association Declaration of Helsinki-Ethical principles for medical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, Korea, October 2008.

E-Mail:pal.phrc@gmail.com

Gaza - Palestine غزة - فلسطين
شارع النصر - مفترق العيون

Annex 6: Approval from MOH



The Palestinian National Authority
Ministry of Health
Directorate General of Human Resources Development

السلطة الوطنية الفلسطينية
وزارة الصحة
الإدارة العامة لتنمية القوى البشرية

الرقم :.....
التاريخ:2015/02/12م

الأخ / د. فؤاد العيسوي وكيل الوزارة المساعد المحترم،،،
الأخ / د. عبد اللطيف الحاج مدير عام المستشفيات المحترم،،،

السلام عليكم ورحمة الله وبركاته،،،

الموضوع/ تسهيل مهمة باحث

بخصوص الموضوع أعلاه، يرجى تسهيل مهمة الباحث/ محمود سعيد العيسي الملتحق ببرنامج ماجستير الصحة العامة- مسار علم الوبئة- كلية الصحة العامة- جامعة القدس ابوديس في إجراء بحث بعنوان :-

"Risk Factors of Chronic Kidney Disease among Children in Gaza Governorates: Case Control Study"

حيث الباحث بحاجة لتعبئة استبانه من عدد من مرضى الغسيل الكلوي دون سن 12 سنة-أو ذويهم- المترددين على أقسام غسيل الكلى في المستشفيات وعينة ضابطة من الأطفال المراجعين لمراكز الرعاية الأولية في محافظات غزة.

نأمل توجيهاتكم لذوي الاختصاص بضرورة الحصول على الموافقة المستبصرة من الأطفال المرضى وذويهم اللذين هم على استعداد للمشاركة في البحث ومن ثم تمكين الباحث من التواصل معهم بإشراف العاملين في أقسام غسيل الكلى وأقسام الأطفال في الرعاية الأولية, بما لا يتعارض مع مصلحة العمل وضمن أخلاقيات البحث العلمي, و دون تحمل الوزارة أي أعباء أو مسئولية.

وتفضلوا بقبول التحية والتقدير،،،

د. ناصر رأفت أبو شعبان
مدير عام تنمية القوى البشرية

وزارة الصحة
الإدارة العامة للمستشفيات
وارد
الرقم: 1596
التاريخ: 18/2

صورة لـ:

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Time table of the research

Date / Activity	Oct		Nov		Dec		Jan		Feb		March		April		May		June	
Proposal revision																		
Material preparation																		
Approval of Helsinki																		
Approval of MOH																		
Pilot study																		
Sample collection																		
Data entry & coding																		
Data analysis																		
Data interpretation																		
Research writing																		

عوامل الخطر التى تؤدى إلى الفشل الكلوى عند الأطفال فى محافظات غزة.

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مقدمة

يعتبر الفشل الكلوى المزمن من الأمراض المزمنة المستجدة فى جميع انحاء العالم التى تؤثر على حياة ونمو الطفل، حيث تظهر هذه المشكلة غالبا فى الاطفال صغار السن والرضع دون سن السنتين، كما ان معدل الوفيات بالفشل الكلوى عند الأطفال أعلى بثلاثين مرة بالنسبة لمعدلات الوفاة العادية للأطفال الذين لا يعانون من الفشل الكلوى.

أهداف الدراسة

الهدف العام للدراسة هو التعرف على أهم عوامل الخطورة التى تؤدى إلى حدوث الفشل الكلوى المزمن عند الاطفال فى محافظات غزة.

منهجية الدراسة

تكونت عينة الدراسة من ٤٠٠ طفل، وتنقسم العينة إلى مجموعتين: المجموعة الأولى تكونت من ٢٠٠ طفل من المصابين بالفشل الكلوى المزمن (مجموعة الحالات)، ويتم متابعتهم فى مستشفى عبد العزيز الرنتيسي التخصصى للأطفال، والمجموعة الأخرى (المجموعة الضابطة) وتكونت من ٢٠٠ طفل من الأطفال الأصحاء فى نفس الفئة العمرية والجنس وعنوان المحافظة، وقد تم اختيارهم بواسطة العينة عشوائية منتظمة من أكبر عيادة الرعاية الأولية الحكومية لكل محافظة وهم (عيادة شهداء جباليا، عيادة شهداء الرمال، عيادة شهداء دير البلح، بندر خانيونس، عيادة شهداء رفح) حيث تم استخدام استبانة من إعداد الباحث وتم جمع البيانات بطريقة المقابلة الشخصية مع ولى أمر الطفل.

أهم النتائج

- أظهرت النتائج ان الفشل الكلوى يصيب الذكور اكثر من الأناث بنسبة (٥٧%) مقابل (٤٣%) على التوالى.
- أظهرت النتائج ان احتمالية الأصابة فى الفشل الكلوى تزداد فى سن سنة الى خمس سنوات بنسبة (٣٨%) يليه فترة الحمل الاخير والولادة بنسبة (٣٣%). كما ان أكثر المراحل انتشارا بين الأطفال هو المرحلة الثانية بنسبة (٣٣%)، يليه المرحلة الثالثة (٣١%)، ثم الرابعة (٢٠%).
- وضحت النتائج ان اكثر الأمراض الكلوية المسببة للفشل الكلوى عند الأطفال كانت Nephrotic syndrome (٣٠%)، يليه Vesico-ureteral reflux (٢٠%)، يليه Focal segmental

glomerular sclerosis (١٨%). كما وضحت ان اكثر المشاكل الخلقية التى تسبب الفشل الكلوى كانت ضمور الكلى بنسبة (٢٣%)، يليه ولادة الطفل بكلية واحدة سليمة (٢٠%).

- ❖ بينت الدراسة وجود علاقة بين مستوى تعليم الأم المتدنى وظهور الفشل الكلوى عند الأطفال بنسبة (٥٤,٣%)، بينما بينت النتائج عدم وجود علاقة ذات دلالة إحصائية بين مستوى تعليم الأب بنسبة (٤٣,٧%)، مستوى الدخل الشهرى للأسرة.
- ❖ تم إيجاد علاقة إيجابية بين حدوث الفشل الكلوي وبين: عدم الولادة بوزن طبيعى (٥٨%)، الولادة قبل أكتمال فترة الحمل (٢٠%)، ودرجة البدانة عند الطفل (٢٣%)، والإصابة بمرض الضغط الدموى(١٦,٣%) ،وفقر الدم قبل الإصابة بالفشل الكلوى(٤٤,٥%).
- ❖ أظهرت الدراسة عدم وجود فرق ذات دلالة إحصائية بين الفشل الكلوى وبين كل من: وجود أمراض جينية بالطفل، و الإصابة بالجفاف أو الأسهال المتكرر.
- ❖ بالنسبة للتاريخ المرضى فى العائلة بنسبة (١٩,٧%)، وزواج الأقارب بين الوالدين (٥٩%)، وجد علاقة قوية بين هذه العوامل وبين الأصابة بالفشل الكلوى عند الطفل .
- ❖ بالنسبة للعوامل المتعلقة بأستعمال الأدوية للطفل وللأم أثناء الحمل، فقد وجد علاقة ذات دلالة احصائية بين الفشل الكلوى و استخدام الأم للمضادات الحيوية بكثرة خلال الحمل بنسبة (٢٨,٢%) خصوصا مجموعة السيفالوسبورين (١٣,٥%) والأمينوجليكوسيد. بينما لم توضح الدراسة علاقية بين الفشل الكلوى وكل من: اعطاء الطفل مضادات حيوية او أدوية مسكنة، و استخدام الأم للمسكنات أثناء الحمل.
- ❖ بالنسبة للعوامل المتعلقة بالحالة الصحية للأم أثناء الحمل، فقد بينت النتائج أن كل من العوامل التالية قد مثلت عوامل خطر ذات دلالة إحصائية وهى: نقص سائل الأمنيوسي حول الجنين (١٣,٧)، البدانة أثناء الحمل (٤٠,٢). بينما لم تظهر علاقة مع عمر الأم عند الولادة، مرض السكرى ومرض ضغط الدم المرتفع.
- ❖ بالنسبة للعوامل البيئية التى تسبب فى ظهور الفشل الكلوى عند الطفل، فقد وجدت علاقة بين المرض وبين كل من: استخدام المبيدات الحشرية بعلاقة عكسية مع حدوث المرض، مصدر مياه الشرب، طبيعة مكان السكن، العيش بالقرب من الأماكن المكروهة صحيا. بينما لم تظهر علاقة مع كل من: نوع البناء للمنزل، التعرض للتدخين.

أهم التوصيات

خرجت الدراسة بعدة توصيات التى من الممكن ان تساعد فى تقليل نسبة الأصابة بالفشل الكلوى بين الأطفال، منها:

- تنظيم حملات تتعلق بصحة المجتمع لتوعية السكان حول مخاطر الزواج المبكر وزواج الأقارب.
- تعزيز خبرات ومهارات الممرضات لتوفير التعليم للأمهات في الرعاية الأولية ما قبل للولادة وكذلك للطلاب ضمن برامج الصحة المدرسية وخصوصا استخدام الأدوية أثناء الحمل وفحص فقر الدم بشكل دورى، و السمنة وارتفاع ضغط الدم بين الطلاب.
- توصيات للمسؤولين بعمل بروتوكول يحتذى به الاطباء العاملين فى مراكز الرعاية الصحية لعمل تحاليل ومزارع بولية للأطفال الذين لديهم اعراض التهاب المسالك البولية بشكل مستمر، وكذلك عمل فحوصات مثل الموجات فوق الصوتية و صورة المثانة والحالب اثناء التخلص من البول (voiding cystourethrogram)، وصورة (dimercaptosuccinic acid) وتوفير المضادات الحيوية الوقائية لتجنب المضاعفات لأمراض الجهاز البول مع متابعة شهرية للطفل.
- زيادة الوعى والرقابة الحكومية على المخاطر والمكاره البيئية تشمل الأفات واستعمال المبيدات الحشرية وتربية الحيوانات بالقرب من السكان، وتحسين جودة المياه المستخدمة آدميا.
- الحاجة واستقصاء مزيدا من الدراسات والفحوصات المخبرية عن العوامل البيئية المؤثرة لدراسة اثارها على الجهاز الكلوى عند الأطفال وخاصة المبيدات الحشرية
- تحقيق مزيد من الدراسات لاستقصاء مزيد العوامل الأخرى المسببة للفشل الكلوى عندى الأطفال، هذه العوامل مثل مشاكل التغذية، والعوامل الأخرى التي تتعلق فى صحة الأم اثناء الحمل التى من المحتمل ان تزيد من مخاطر ظهور الفشل الكلوى بين الأطفال.
- تطوير قاعدة بيانات للتقارير بشكل منتظم وتوثيق وتحديد دقيق لحدوث وانتشار الفشل الكلوى بين السكان لكل الأعمار في كافة محافظات غزة.