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Risk Factors of Hyperbilirubinemia among Admitted Neonates in Gaza Governorates: Case Control Study

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Dedication

I dedicate this work to my dear mother and father

To my brothers, and all my relatives who encouraged and inspired me

To my friends for their support and endless help

To everyone wants to be better and appreciates this work

Declaration

I certify that this thesis submitted for the degree of Master is the result of my own research, except where otherwise acknowledged, and that this thesis or any of its parts has not been submitted for higher degree to any other university or institution.

Signed: ……

Safaa' Awaad Abu Mostafa

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Abstract

Neonatal hyperbilirubinemia is a widespread and significant clinical condition amongst neonates worldwide that about 60% of term neonates and 80% of preterm neonates develop jaundice in the first week of life. The study aimed to identify the main risk factors either socio-demographic, maternal, or neonatal factors that contribute to neonatal hyperbilirubinemia among hospitalized neonates in Gaza governorates. The design of this study is case-control study. The study sample consisted of 180 neonates (90 cases and 90 controls). Cases were selected from Al- Nassir pediatric hospital and Naser Medical Complex while controls were selected from Martyrs Khanyounis clinic and Martyrs Al-Remal clinic. The researcher used an interview structured questionnaire; face and content validity were done. The collected data analyzed by SPSS version 20 and different statistical tests were used for data analysis including descriptive statistics, bivariate analysis using Chi-square and multiple logestic regression using Odds Ratio and confidence interval 95%.Socio-demographic factors were studied by bivariate test using by person's chi-square, the results revealed that there was a significant association between family income andneonatal hyperbilirubinemia (P value < 0.05), other factors were statistically insignificant risk factors including mother age, mother education and mother occupation (P value > 0.05). Among maternal factors; bivariate test by by person's chi-square revealed that there were significant associations between hyperbilirubinemia andmother's blood group, maternal anemia and pregnancy disorders (P value < 0.05). On the other hand; there were no significant association between hyperbilirubinemia and parity, mother's Rh type, Premature RuptureOf the Membranes, oxytocin use, delivery type, gestational diabetes, pregnancy induced hypertension, urinary tract infection, vaginal infection, perinatal hemorrhage, and discharge from postnatal department (P value > 0.05).Concerning neonatal factors; bivariate analysis using by person's chi-square showed that birth weight, and feeding practices that include; feeding method, feeding initiation time, feeding difficulty, feeding frequency, and number of wet diapers/24hourswere statistically significant risk factors for developing hyperbilirubinemia (P value < 0.05). Others factors including newborn order, cephalhemama and bruising, and history of previous sibling with jaundice showed statistically insignificant risk factors for developing hyperbilirubinemia (P value > 0.05). Multiple logistic regression analysis was used to detect the independent factors associated with neonatal hyperbilirubinemia. The results showed that there were statistically significant association between hyperbilirubinemia and family income groups; < 1800NIS (AOR: 23.345, 95% CI: 2.083-261.688) and > 2300 NIS (reference group), maternal anemia groups; yes (AOR: 5.383, 95% CI: 1.035-27.998)and no(reference group), and birth weight groups; 2500 - 3000gram (AOR: 0.117, 95% CI: 0.028-0.498) and > 3000gram (reference group). All feeding practices showed statistically significant association with hyperbilirubinemia occurrence except number of wet diapers / 24 hours as following: feeding method groups; exclusive (AOR: 0.017, 95% CI: 0.003-0.093), bottle (AOR: 0.006, 95% CI: 0.000-0.141), and mixed (reference group), feeding initiation time groups; 1st hour (reference group) and more than 4 hours (AOR: 0.046, 95% CI: 0.004-0.586), feeding difficulty groups; yes (AOR: 0.079, 95% CI: 0.019-0.328), and no(reference group), lastly feeding frequency groups; on demand (reference group), every 2-3 hours (AOR: 0.108, 95% CI: 0.026-0.448)], and more than 3 hours(AOR: 0.003, 95% CI: 0.000-0.045).In conclusion, our study implies the need for paying attention on ongoing screening and close monitoring for neonates at high risk. In addition, emphasize on health education regarding an effective feeding practices to reduce rates of hospitals readmissions and morbidities of neonatal hyperbilirubinemia.

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List of abbreviations

AAP	American Academy of Pediatrics
AOR	Adjusted Odds Ratio
BW	Birth Weight
C/S	Cesarean Section
CI	Confidence Interval
GA	Gestational Age
GS	Gaza Strip
Km2	Kilometers
MOH	Ministry of Health
NICU	Neonatal Intensive Care Unit
NMR	Neonatal Mortality Rate
NNH	Neonatal Hyperbilirubinemia
NNJ	Neonatal Jaundice
NVD	Normal Vaginal Delivery
OR	Odds Ratio
PCBS	Palestinian Central Bureau of Statistics
PROM	Premature Rupture of the Membranes
Rh	Rhesus
SD	Standard Deviation
TcB	Transcutaneous Bilirubin
TSB	Total Serum Bilirubin
UNICEF	United Nations Children's fund
WB	West Bank
WHO	World Health Organization

Chapter1

1.1 Introduction

Neonatal Jaundice (NNJ) is the most common morbidity problem in neonates in the first week of life, occurring in about (60%) of term neonates, and (80%) of preterm neonates, 10% of breastfed babies have jaundice during the first month of age. It is the most common health condition requires medical attention in newborn babies (National Collaborating Centre for Women's and Children's Health, 2010).

The pattern of neonatal jaundice includes yellowish discoloration of the skin, sclera and mucous membranes results from accumulation of bilirubin in the skin and mucous membranes. This is associated with rising in the level of bilirubin in the blood circulation, a condition known as hyperbilirubinaemia (National Collaborating Centre for Women's and Children's Health, 2010).

World widely, neonatal jaundice is very common in healthy newborn with peaks in severity between 3 and 5 days after birth and then recovers within 7 to 10 days (Cabra and Whitfield, 2005). In most babies with jaundice, there is no actual disease and this termed "physiological jaundice" which generally harmless and self-limited. Rarely there are pathological causes of jaundice in the newborn such as serious liver disease, which need to be detected by health care professionals (National Collaborating Centre for Women's and Children's Health, 2010).

A complication of neonatal hyperbilirubinemia (NNH) may occur when bilirubin rises to toxic levels, which referred as bilirubin encephalopathy or kernicterus. Recently, there is an increase in the number of infants with kernicterus in United States which has made prevention of severe hyperbilirubinemia a national priority (Cabra and Whitfield, 2005). In rural Kenya, a retrospective study founded that neonatal jaundice cases had significantly more neurological, motor and developmental difficulties with (43%) of the neonatal jaundice cases unable to sit and/or stand independently and(18%) died after discharge (Gordon et al., 2005).

Globally, Newborns whorequire phototherapy were accounted 14.1 million babiesand approximately 100,000 reach extreme hyperbilirubinemia of Total Serum Bilirubin (TSB)

≥ 30 mg/dL, a threshold associated with brain damage. The largest percentage was in low income countries as in South Asia and Africa (Cline et al., 2011)

In Arab countries, it was estimated that the prevalence/incidence of neonatal jaundice in Egypt, (33%) of total admission cases to Cairo University Children‘s Hospital in 2006 were diagnosed by severe NNH (Iskander et al., 2012). Also, Yahya and Alajeely (2013) study in Mosul revealed that the incidence of neonates with hyperbilirubinemia reached (35%).

American Academy of Pediatrics (AAP) stated that jaundice has many possible risk factors, including blood group incompatibility, maternal age ≥ 25 years, gestational diabetic mother, previous sibling with jaundice, cephalohematoma or significant bruising, exclusive breastfeeding, newborn male gender, prematurity, and discharge from hospital before 72 hour. Understanding the major potential contributing factors of early NNHmay help health care professionals to identify closely before discharge to home which can reduce both morbidity and readmission rates (AAP, 2004a).

However, data on incidence, potential risk factors, neonatal management and outcome ofNNHhave been word widely studied, till now there are no research studies have been established to investigate risk factors of NNHin Gaza Strip (GS). Therefore, our study adds to explore the risk factors by which this perceived common problem as explained.

1.2 Research problem

NNHis one of the most common pediatric problems globally associated with high morbidity and mortality in neonatal period (Taheri et al., 2014) that affect up to approximately 85% of newborns (Watchko and Tiribelli, 2013). It is the most common reason for hospital readmission and medical consultation in newborn babies (National Collaborating Centre for Women’s and Children’s Health, 2010; Hansen, 2014). The most common reason for re-hospitalization in Escobar et al. (2005) study was jaundice, with 253/738 (34.3%). Olusanya et al. (2009) study showed that NNJ was reported for351 (6.7%) infants, out of which 291 (82.9%) received phototherapy while 98 (27.9%) further had blood exchange.

Worldwide, the global prevalence of Rh hemolytic disease was estimated at 276/100,000 live births, reaching to 373,300 babies in 2010. In addition to Europe/Central Asia, South

Asia and Sub-Saharan Africa were found to have the highest prevalence, estimated at roughly 386/100,000 live births. This is incontrast to an estimated prevalence of 2.5/100,000 live births in high-income countries with well-established health-care systems that offer sophisticated perinatal and neonatal care for mothers and their infants (Bhutani et al., 2013).

Each year approximately 60% of 4 million neonates in the United States are reported to have clinical jaundice (AAP, 1994). In a prospective study to investigate severe NNH in the United Kingdom, the incidence of severe hyperbilirubinemia was 7.1/100 000 live births and the incidence of bilirubin encephalopathy was 0.9 case per 100,000 live births (Manning et al., 2007).

Low and middle income countries represent the higher incidence\prevalence rate of severe NNH in comparison to high-income countries characterized by high rates of morbidity, mortality and neurodevelopmental consequences (Olusanya et al., 2015). Bhutani et al. (2013) study explained that kernicterus with Rh disease ranged from 38, 28, 28, and 25/100,000 live births for Eastern Europe/Central Asian, sub-Saharan African, South Asian, and Latin American regions, respectively.

In spite of high incidence and serious consequences of NNHglobally, there is limited availability of epidemiological researches to accurately estimate the exact magnitude as well as the intensity of this problem in GS. Therefore, this clinical study will investigate the risk factors of NNHwhich will be a necessary tool in formulating measures of prevention, early detection and management of severe NNHthereby reducing newborn deaths.

1.3 Justification

NNHoccurs in high incidence rates and considers as the most common health problem leads to hospital readmission that cause a huge cost for management affected and disabled newborns from the complication ofNNHespecially in fragment health care systems where lack of resources, add the over- burden of affected handicapped babies on their families and the community. Despite what previously mentioned,NNHand kernicterus still aren't reportable diseases, and there are no reliable sources of information providing national annual estimates as stated by AAP (Ip et al., 2004).

Worldwide, annually estimate at least 14.1 million babies (10.5% of live births) require phototherapy. Of these, more than 6 million infants of those requiring treatment (~45%) do

not receive effective treatment, and approximately 100,000 reach extreme hyperbilirubinemia of TSB≥30 mg/dL, a threshold associated with brain damage. The largest percentage is in South Asia and Africa, particularly because of a high number of births and pre-term births, fragment health systems, and non-modifiablerisk factors (Cline et al., 2011).

NJ accounted for (17%) of all pediatric admissions and (34%) of deaths over 1000 admissions during the first 7 days of life in a study carried out in a hospital in rural Kenya (English et al., 2003). Based on a summary of multiple case reports that extended to more than 30 years which produced by the Tufts-New England Medical Center's Evidence-Based Practice Center under contract to the Agency for Healthcare Research and Quality, concluded that kernicterus has at least 10% mortality and at least (70%) long-term morbidity (Ip et al., 2004).

Although risk factor for NNHhave been commonly studied worldwide, there are limited well-formed studies or systemic surveys have been established to evaluate either risk factors of NNHin Gaza Strip or the short and long term sequences of hyperbilirubinemia. Moreover, there is no systematic, adequate and accurate information about NNH in GS hospitals. Currently,an available data only in West Bank (WB) that the percentage of infant deaths due to unspecified neonatal jaundice reached 5 (1%) infants, (3) male and (2) female in 2014 (MOH, 2015).

This study could be the first one to be conducted in GSwhere the researcher is going to investigate the main suspected risk factors that may contribute to NNH in GS either socio-demographic, maternal, or neonatal factors. The results of the study will highlight the need for implementing some strategies to alleviate the modifiable factors which will reduce risk for future babies to develop jaundice, enhance early management and reduce mortality rate.

1.4 Research objectives

1.4.1 General objective

To identify the main possible risk factors that contributing to neonatal hyperbilirubinemia among admitted neonates in Gaza governorates.

1.4.2 Specific objectives

1. To investigate an association between socio-demographic factors and NNHamong newborns in Gaza governorates.

2. To determine an association between maternal factors and NNHamong case and control group.

3. To explore neonatal factors that in association to occurrence ofNNH.

4. To suggest recommendations for stockholder and policy makers in Ministry of Health (MOH), health care providers, and mothers to improve infant health and reduce the occurrence of neonatal hyperbilirubinemia.

1.5 Research questions

This study addresses the following research questions:-

- What are the main possible risk factors contributing to NNHin Gaza governorates?
- Are there significant associations between the socio-demographic factors such as (mother age, mother education, mother occupation, and family income) and occurrence of NNH?
- Do maternal related factors contribute to NNH development?
- Are there significant associations between mothers' pregnancy disorders and NNHoccurrence?
- Is there a significant association between the mother blood group and Rh type and occurrence of NNH?
- Is there a significant association between maternal oxytocin drug use and developing of NNH?
- What is an association between type of delivery and occurrence of NNH?
- What are the main neonatal health factors that may lead to NNH?
- Is there a significant association between family history of previous sibling with jaundice and occurrence of NNH?
- Are there significant associations between birth weight, feeding practices, and presence of cephalhematoma or bruising and occurrence of NNH?

1.6 Context of the study

1.6.1 Geographical context

Palestine is known in ancient history as the land of Canan, with the entire area of about 27,000 kilometers (km2) which occupied by Israeli in two stages; the first one in 1948 and the second in 1967 (MOH, 2011)**.** Palestine has an important strategic geographic location (Annex1.1). It constitutes the southwestern part of Belad El-Sham that is bordered by Lebanon, Syria and Jordan, in addition to Egypt. Palestinian area stretches from Ras Al-Nakoura in the north to Rafah in the south (MOH, 2006)**.** The land controlled by the Palestinian Authority is called the Palestinian territory with total area reach to 6,020 Km2. It is consisting of two geographically separated areas: WB and GS (MOH, 2011).

GS is a narrow zone of land lying on the coast of the Mediterranean Sea. It is very crowded place with area 365 sq. Km and constitutes (6.1%) of total area of Palestinian territory land with population density reached 3,808 inhabitants/km2 The last occupation was Israel who occupied GS from Egyptians in 1967. It is administratively divided into five governorates: North, Gaza, Mid-zone, Khanyounis and Rafah (MOH, 2006)**.**

WB is located west of the river Jordan with area of 5,655 sq Km with population density reached 420 inhabitants/ km2. It has been under Israeli Military Occupation, together with East Jerusalem and GS since June 1967. WB is divided into four geographical regions. The North of WB includes the districts of Jenin, Tulkarem, Qalqylia, Salfit and Tubas districts. The Center includes the districts of Ramallah and albireh, and Jerusalem. The South includes the Bethlehem and Al-Khaliel districts, and the sparsely populated Jordan valley including Jericho (MOH, 2006)**.**

1.6.2 Demographic context

The total number of Palestinian population in State of Palestine at the end of 2014 was 4.62 million: 2.83 million in WB (61.2%) and 1.79 million (38.8%) in GS. There were 2.35 million males in state of Palestine compared to 2.27 females; 1.44 million males and 1.39 million females in WB, and 909 thousand males and 881 thousand females in GS (PCBS, 2014a).

The population density in State of Palestine at the end of 2014 was 767 individuals/km^2; 500 individuals/ km^2 in WB and 4,904 individuals/ km^2 in GS (PCBS, 2014b). It has been

estimated by MOH in 2014 that the rate of natural increase in the population of Palestine was (2.9%) in the WB (2.6%) and in the GS (3.4%). The reported crude birth rate in Palestine was 26.7\ 1,000 population in 2014; 23.6\1,000 in WB and 31.6 \ 1,000 in GS. The crude death rate for Palestine reached 3.1 per 1,000 of population in 2014; 3.8 / 1,000 of population in GS and 2.56/ 1,000 of population in WB. Moreover, total fertility rate in Palestine was 4.1; 3.7 in WB and 4.5 in GS (MOH, 2015).

The total number of live births in hospital were 104168, 42167 births in GS and 62001 in WB (MOH, 2010). According to the Palestinian Central Bureau of Statistics(PCBS) (2013), infant and under-child mortality rates continued to decline, but started to rise again during 2006-2010 due to the high rates of neonatal mortality that affected infant mortality rates in general and reflected higher risks during pregnancy. The under-five mortality rate was 23.4 per 1000 live births between 2006 and 2010. The GS had the highest rates at 26.8 per 1000 live births compared to the WB at 21.0 per 1000 live births (PCBS, 2013).

1.6.3 Socioeconomic context

The Palestinian population continues to live under unstable economic circumstances Unemployment and poverty rates are still high. The unemployment rate for those 15 years of age or older remained alarming rise reaching (23%)(MOH,2014). In regards to the health economic indicators, the National Health Accounts data indicates an increase in total expenditure on health at current prices increased during 2011-2012 to 261.9 million United States Dollar in 2012 compared to 201.0 million United States Dollar in 2011(PCBS, 2014a).

1.6.4 Palestine health care system

The Palestinian health system is composed of three major components, primary health care, secondary health care and tertiary health care. Five major service providers share the responsibility in health care service provision: governmental health sector, United Nations Relief and Works Agency, Non- governmental organizations, Palestinian Military Medical Services, and the private sector(MOH, 2014).

Primary health care services are the backbone of the Palestinian health care system. Primary health care centers throughout Palestinian governorates have expanded from 454 centers in 1994 to 750 centers in 2012,(65.2%) increase. The Ministry of Health (MOH)is

the main primary health care center operating (61.3%) of the total primary health care centers (MOH, 2014).The primary health care centers distributed in Palestinian governorates as 163 primary health care centers in GS and 604 primary health centers in WB(MOH, 2015).

S**econdary health care services** are provided mainly byMOH. It owns and operates 2,979 hospital beds distributed over 25 hospitals throughout the various Palestinian governorates. The overall number of hospital beds in Palestine is 5,414 beds distributed over 79 hospitals; 49 are in WB with 3,163 beds, making up (57.6%) of total hospital beds, the remainder is in GS (MOH, 2014).

Tertiary health care services are covered also mainly by MOH which participate in provision of some limited services in its facilities, and through purchasing these services from other service providers inside (private sector and nongovernmental organizations specifically East Jerusalem Hospitals) and outside Palestine (MOH, 2014). Tertiary health service centers increased from 80 centers in 2010 to 94 centers in 2011; mainly due to expanding secondary centers to provide various tertiary care services (MOH, 2014).

1.6.4.1 Governmental hospital services

In Palestine, there are 80 hospitals; 50 in WB and 30 in GS, with total number of 5,939 beds in governmental and non-governmental hospitals; (59%) in WB and (41%)in GS. Seventy three percent of them are general beds, (18.6%) specialized beds, 3% rehabilitation beds and (15.3%) maternity beds. There are 13.1 beds per 10,000 of populations; 12.6 beds in WB and 13.8 beds in GS (MOH, 2015).

1.6.4.1.1 Al-Nassir Pediatric Hospital

Al-Nassir Pediatric Hospital is the main pediatric referral center in Gaza. Every year, it provides health care to approximately 90,000 girls and boys below 12 years of age in its emergency ward and inpatient units. The total beds 122 beds (MOH, 2015). Approximately 1800 critically ill infants receive care in the hospital’s 22-bed Neonatal Intensive Care Unit (NICU) (MOH, 2015). It is located in the western part of GS, which the hospital is providing several medical services for children. The hospital consists of several different sections; the NICU has been established by 1973 started with 7 incubators. In the year

2011 the NICU department was rehabilitated and renewal by UNICEF funded. Now the department become fully equipped and contains 33 incubators (MOH, 2009).

AL-Nassir pediatric hospital offers pediatric services, and clinical capacity with 151 beds, located in Al-Nassir district in Gaza city which was built in 1962 on an area 4400 m2, and serves the area coverage of the province of Gaza from Wadi Gaza, south, until the neighborhood of Sheikh Radwan north, and with a population of 496,411 inhabitants (MOH, 2009).

1.6.4.1.2 Naser Medical Complex

Naser Medical Complex is the second largest governmental medical institution in the Gaza Strip. It is located in the western area of Khanyounis governorate, general hospital, which was built in 1958 on an area of 50000 m2, and serves the area of Khanyounis, with a population of 269,601 inhabitants (MOH,2006). The total beds 260(MOH, 2015), the NICU has been established at 1989 started with 8 incubators, now has 17 incubators. This hospital provides secondary health services that include medical and surgical services as well as obstetric and maternity care. The hospital includes two main buildings; Al-Tahreer and Naser buildings. Al-Tahreer building includes obstetric and gynecology words, pediatric department, NICU in addition to administrative offices. Naser building includes medical, surgical, orthopedic, physiotherapy, coronary care unit and general intensive care unit (MOH, 2014).

1.7 Theoretical and operational definitions

1.7.1 Risk: Risk is defined as the probability that an event will occur. In epidemiology, it is most often used to express the probability that particular outcome will occur following a particular exposure (Last, 2001).

1.7.2 Risk factors: In (2015), World Health Organization (WHO) defined a risk factor as any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury, but is not necessarily causal factor. Some examples of the more important risk factors are underweight, gender, high blood pressure, tobacco and alcohol consumption, and unsafe water, sanitation and hygiene.

The researcher defined risk factors operationally as those factors that may lead to incidence of NNH, these factors include; socio-demographic, maternal, and neonatal factors.

1.7.3 Maternal factors: The researcher defined maternal factors operationally as mother related conditions during pregnancy which have shown impact on increased risk of NNH.

1.7.4 Neonatal factors: The researcher defined neonatal factors operationally asneonate related conditions which have an established effect on increased risk of NNH.

1.7.5 Socio-demographic factors: The researcher defined scio-demographicfactors operationally asfamily andsocial status related conditions which have shown impact on increased risk of NNH.

1.7.6 Birth weight: Birth weight is the first weight of the newborn obtained after birth. For live births, birth weight should preferably be measured within the first hour of life, before significant postnatal weight loss has occurred (UNICEF, 2004).

1.8 Lay out of the study

This study consists as a general from five chapters: introduction, conceptual framework and literature review, methodology, results and discussion, finally; conclusion and recommendation.

The first chapter presents a general introduction on the study, in which a brief background about the study participants is given, the research problem, justification for study, the general and specific objectives, the context of study, and definition of terms.

The second chapter includes two parts: the first part is conceptual framework where the researcher provides a representation diagram of the main study variables. The second part is the literature review of previous studies related to the study topic and variables.

The third chapter offers the methodology including study design, study setting, study population, sample size and sampling process, period of the study, eligibility criteria, data collection instruments, validity and reliability, pilot study, data collection, data management and statistical analysis, ethical and administrative considerations and finally the study limitations.

The forth chapter describes the results and discussion where the researcher displays the study results in form of tables and graphs and combines with clarifying comments. Then, these results are discussed in relation with previous published studies in respect to the study topic and its objectives.

The fifth chapter, the researcher demonstrates conclusion and recommendations in the light of the study results.

Chapter 2

Literature Review and Conceptual Framework

In this chapter, the researcher presents the conceptual framework and literature review of the study themes and variables. In depth information regarding the main concepts and variables, besides previous studies were mentioned.

2.1 Conceptual framework

Conceptual frameworkrepresents way of thinking about a problem or a study, or way of representing how complex things work. Researcher constantly uses conceptual framework to guide his work. Conceptual framework illuminates individual's work and illustrates several variables and outcomes, and their interrelation (Bordage, 2009).

In this chapter, the researcher reviews the critical points of the study variables that are related to developing NNH. As well as, the researcher reviews relevant previous studies and experiences of other researchers in this field. After that, the researcher was able to sketch map showing lines of the interdependence of the factors which contribute in the development of NNH.

There are several factors related and affecting the occurrence of NNH. Time restriction and the nature of the study did not allow studying all these variables and therefore a researcher focused on part of these variables and developed new brief model (Figure 2.1).

The following conceptual framework consists of three dimensions as shown; each dimension represents multi-variables to measure the associated factors as elucidated below:

2.1.1 Socio-demographic factors:

The first domain was the socio-demographic factors which include mother age, mother education, mother occupation, and family income.

2.1.2 Maternal factors:

The second domain was the maternal factors which include: mother blood group and Rh type, parity, pregnancy disorders, delivery type, premature rupture of membranes, oxytocin drug use, and length of stay in postnatal department.

2.1.3 Neonatal factors

The last domain was the neonatal factors which contain neonate order, birth weight, cephalhematoma and bruising, previous sibling with jaundice and feeding practices.

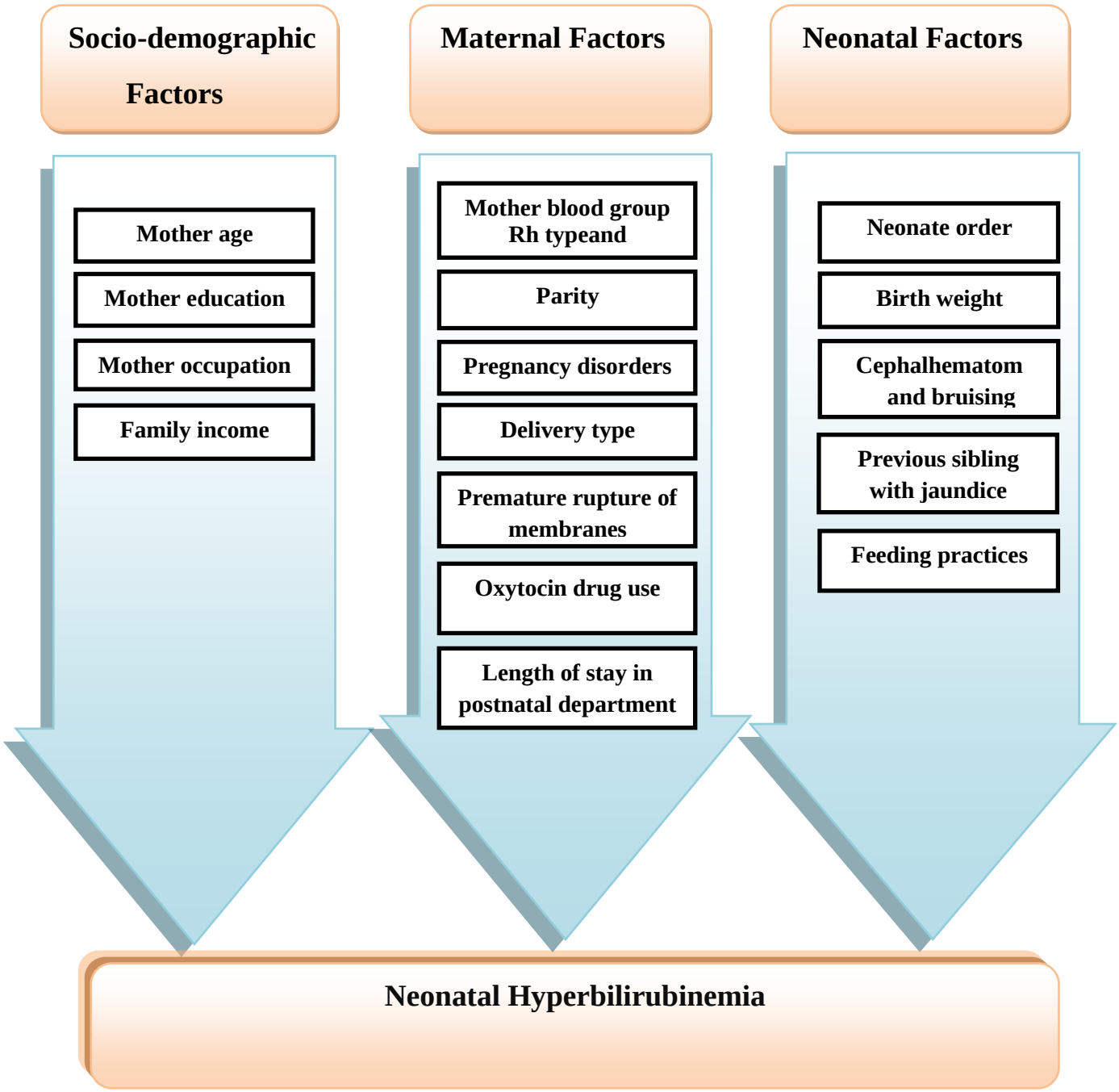

Figure 2:1 Conceptual framework diagram "self-developed"

2.2 Literature Review

2.2.1 Background

NNHmay have been noticed by heath care providers through the centuries, but the scientific description and study of this disease have started in the 18th and 19th centuries. In 1785, Baumes who first scientifically described the clinical course of NNJ in 10 neonates, and as a result, he was awarded a prize from the University of Paris. Hervieux**,** in 1847 first portrayed brain jaundice staining in 31 of 44 autopsied cases. After that, Orth in 1875, first described yellow staining of the brain. Thereafter, Schmorl in 1903 presented the results of his autopsies of 120 jaundiced infants to the German Society for Pathology. All of these infants' brains were jaundiced, but only 6 cases demonstrated a staining phenomenon similar to that previously described by Orth. Schmorl coined the term kernicterus (jaundice of the basal ganglia) for this staining pattern (Hansen, 2000).

In October 1994, the Provisional Committee for Quality Improvement and Subcommittee on hyperbilirubinemia of the American Academy of Pediatrics (AAP) produced a practice parameter for the management and treatment of hyperbilirubinemiain (AAP, 2004a).

The current guideline represents a consensus of the committee charged by the AAP with reviewing and updating the pre-existing guideline and is based on a careful review of comprehensive literature review evidence by the New England Medical Center Evidence-Based Practice Center (AAP, 2004a).

2.2.2. Epidemiological background

NNHis a frequently common phenomenon in newborns around the world because almost every newborn develops high level of an unconjugated serum bilirubin level related to immature liver function. Through the literature review in numerous researches studies, were noted high incidence rate of NNHdue ABO and Rh hemolytic diseases and the new trend towards earlier hospital discharge and higher survival rate of preterm infants. It is mentioned that every year, ~24 million pregnancies and their babies are at risk worldwide (Bhutani et al., 2013). For this reason, NNHstill roughly threat for newborn infants.

Global prevalence of extreme hyperbilirubinemia (bilirubin encephalopathy;TSB >428 μmol/l in full-term babies) and Rh disease was estimated in systematic review and meta-

analysis study to reach 373,300 live births in 2010 were affected by Rh disease (277/100,000 live births; and 107,400 live births by bilirubin encephalopathy; due to other cause. The majority of the total bilirubin encephalopathy; and Rh disease (80%) occurred in those born in countries with neonatal mortality rate (NMR)>15 that account for (60%) of the global live births (Bhutani et al., 2013).

Available evidence suggests that low and middle income countries represent the greatest burden of severe NNHcharacterized by high rates of morbidity, mortality and neurodevelopmental disorders compared to high-income countries(Olusanya et al., 2015). In sub-Saharan Africa, jaundice occurs in a high proportion of neonatal hospital admission (Gordon et al., 2005). Olusanya et al., (2015) study illustrated that three-quarters of mortality occurred in sub-Saharan Africa and South Asia.

The global burden of hyperbilirubinemia is disproportionately heavy, Cline et al. (2011) study states that annually, at least 14.1 million babies worldwide (10.5% of live births) require phototherapy and approximately 100,000 reach extreme hyperbilirubinemia of TSB≥30 mg/dL, a threshold associated with brain damage (see Table 2.1). Of those, more than 6 million (~45%) infants do not receive effective treatment mainly be in South Asia and Africa where high number of births and pre-term births, weak health systems, and hereditary risk factors.

Table (2.1): The incidence rate of Sever neonatal hyperbilirubinemia by region

	Sub-Saharan Africa	**Middle East and North Africa**	**South and central Asia**	**Eastern Asia**	**Latin America and the Caribbean**	**Europe**	**North America**	**Oceania**	**World**
Annual incidence of TSB.≥25mg\dl	670,000	110,000	480,000	90,000	27,000	*	*	*	1,380,000*
Annual incidence of TSB.≥30mg\dl	48,000	8,000	34,000	6,000	2,000	*	*	*	98,000*
Annual need for phototherapy	5,880,000	1,090,000	3,770,000	2,101,000	658,000	237,000	309,000	24,000	14,100,000
Annual unmet need for phototherapy	3,290,000	530,000	2,360,000	440,000	130,000	*	*	*	6,750,000*

Cline et al. (2011)

United States are reported clinically jaundiced in (60%) of newborns annually (AAP, 1994). Manning et al. (2007) study reported the incidence of severe hyperbilirubinemia to be 7.1/100 000 live births in United Kingdom. Furthermore, in Denmark, Ebbesen et al.

study (2005) explained that twenty-five per 100 000 infants born at term or near-term developed extreme hyperbilirubinemia. Also, in Sgro et al. (2006) study, an estimated incidence of NNHin Canada was 1 in 2480 live births.

In low and middle income countries, NNHobserved more significantly, the prevalence of 314,700 surviving neonates with extreme hyperbilirubinemia and Rh disease, (75,400 cases; 24%) who developed kernicterus were 56/100,000 live births. More than (83%) of survivors with kernicterus had one or more impairments (Bhutani et al., 2013).A study was done in Federal Medical Centre Abakaliki, South East Nigeria revealed that neonatal jaundice accounted for (35%) of all NICU admissions (Onyearugha et al., 2011).Furthermore, Henny-Harry and Trotman (2012) study conducted to describe the epidemiology of neonatal jaundice at the University Hospital of the West Indies; the incidence of clinically significant neonatal jaundice was (4.6%) for the study period from January 1, 2006 to June 30, 2007. Kavehmanesh et al. (2008) study explained that the prevalence of readmission for hyperbilirubinemia in infant with birth weight of≥2500 gram in Najmieh Hospital, Tehran, from 2004-2005 was (12.6%).

In Arab countries, it is estimated that the prevalence/incidence of neonatal jaundice in Egypt, (33%) of total admission cases to Cairo University Children‘s HospitalNICU at age ≥ 6 days over an 18-month period in 2006 were diagnosed by severe NNH (Iskander et al., 2012). Yahya and Alajeely (2013) descriptive study was conducted on 440 neonates attending the Al-Khansaa Teaching Hospital and Ibin-Sena Teaching Hospital in Mosul revealed that the incidence of neonates with hyperbilirubinemia reached (35%).

Global estimate indicated that there were 114,000 neonatal deaths associated with Rh disease and bilirubin encephalopathy due to other causes in 2010 (for 85/100,000 live births, 22% or 25,000 deaths with bilirubin encephalopathy). Eastern Europe/ Central Asia, Latin America, sub-Saharan Africa, and South Asia account for 6, 7, 35, and 39% of the deaths, respectively, with a combined prevalence of 119/100,000 live births compared with (0.1%) (n = 94; prevalence 1/100,000 live births) in high income countries (Bhutani et al., 2013).

Although neonatal hyperbilirubinemia have been commonly studied worldwide as mentioned in the previous studies, till now there are limited research studies have been established to investigate risk factors of NNHin GS.

2.2.3. Definition of neonatal hyperbilirubinemia

Hyperbilirubinemia is defined as an excess of bilirubin in the blood (National Collaborating Centre for Women's and Children's Health, 2010). In specific term, NNHis defined as a total serum bilirubin level above 5 mg per dL (86 µmol per L (AAP, 1994). In 2004a, American Academy of Pediatrics stated that hyperbilirubinemia in infants ≥35 weeks gestational age (GA) is defined as total bilirubin >95th percentile on the hour-specific Bhutani nomogram.

2.2.4. Pathophysiology of bilirubin metabolism

Bilirubin is produced in the macrophages of the reticuloendothelial system. These macophages contain two essential enzymes: hemeoxygenase and biliverdinreductase. Hemeoxygenase converts heme; the source of bilirubin - One gram of hemoglobin produces 35 mg of bilirubin - into biliverdin. Biliverdinreductase then converts biliverdin into unconjugated bilirubin (or 'indirect') (Marcdante and Kliegman, 2013) which is the bilirubin that has been processed by the liver (National Collaborating Centre for Women's and Children's Health, 2010). Due to its hydrophobic nature, unconjugated bilirubin is transported in the plasma tightly bound to albumin (National Collaborating Centre for Women's and Children's Health, 2010).Consequently, unconjugated bilirubin is conjugated in the liver in presence of uridinediphosphoglucuronyltransferase to produce conjugated (or "direct") bilirubin, which then passes through the intestine and is excreted in the stool. In addition, bacteria in the neonatal intestine convert bilirubin to urobilinogen and stercobilinogen, which are excreted in urine and stool and usually limit bilirubin reabsorption (Marcdante and Kliegman, 2013).

Physiologic jaundice

Bilirubin formation in newborns is 2 to 3 times greater than in adults because newborn babies' red blood cells have a shorter life span than those of adults; 70 to 90 days in newborns compared with 120 day in adults (Marcdante and Kliegman, 2013). Add that metabolism, circulation and excretion of bilirubin in newborn is slower than in adults (National Collaborating Centre for Women's and Children's Health, 2010).

The previously mentioned circumstances lead to physiologic jaundice; term used to describe common, generally harmless, jaundice seen in neonates in the first 2 weeks of life (National Collaborating Centre for Women's and Children's Health, 2010).

Pathological jaundice

It is non-physiological type to be said when jaundice appear within 24 hours, TSB concentration exceeds 5 mg/dl on first day of life in term neonate, 10 mg/dL on second day, or 12-13 subsequently. Any jaundice present in the first 24 hours with TSB reach to17 mg/dL, or appear beyond 3 weeks and conjugated bilirubin (dark urine staining the clothes and light colored stool) should be presumed pathologic and warrants investigation for a cause and possible intervention, (Mishra et al., 2007).

2.2.5. Types of hyperbilirubinemia

❖ **Conjugated hyperbilirubinaemia:**

Conjugated hyperbilirubinemia can results from impaired flow of bile into the intestine, as in patients with biliary obstruction or from reduced secretion of conjugated bilirubin into the bile, such as in patients with hepatitis (Weisiger, 2014).

❖ **Unconjugated hyperbilirubinemia:**

Unconjugated hyperbilirubinemia can result from increased the rate of bilirubin formation, reduced the rate of bilirubin conjugation or impaired hepatic uptake of bilirubin (Nazer and Roy**,** 2014).

2.2.6 Causes of unconjugated hyperbilirubinemia:

1. Increased hemolysis of RBCs

- **Hemolytic jaundice**

- ABO incompatibility: It is most often seen when the mother has blood group O and the newborn has blood group A or B (Beeby, 2005). Hemolytic disease develops from maternal anti-A or anti-B immunoglobulin G antibodies that cross the placenta and attach to the appropriate antigens on the neonatal red cells (Kaplan et al., 2009).

- Rhesus (Rh) hemolytic disease: This condition primarily occurs when Rh-negative mothers who have become sensitized to the D-antigen in an Rh-positive fetus develop anti-D antibodies which can cross the placenta and attack the blood of Rh-positive babies in

subsequent pregnancies. It is involves hemolysis of red blood cells before and after birth (Beeby, 2005).

2. Decreased hepatic uptake and conjugation of bilirubin

- **Breast milk jaundice**

Breast milk jaundice occurs infrequently, peaks in the 2nd or 3rd week, and may extend at moderately high levels for 3-4 weeks before declining. If feeding with breast milk is stopped, the serum bilirubin usually falls, however this would uncommonly be indicated. The potential harms of stopping breast feeding would outweigh any risks of a mild or moderate hyperbilirubinaemia. The etiology is unknown, but there is some support for both a hormonal factor in the milk acting on the infant's hepatic metabolism, and an enzyme (lipase) facilitating intestinal absorption of bilirubin (Beeby, 2005).

3. Increased enterohepatic reabsorption

- **Breastfeeding jaundice**

Jaundice in breast-fed babies usually appears in 24 hours of age. In case of healthy breast fed newborns, a certain degree of yellow skin coloration appears approximately 2-4 days after birth. Jaundice disappears or its intensity decreases spontaneously in one or two weeks, with no needed treatment (AAP, 2004a). In Schneider's meta-analysis (1986) of 25 studies has shown that (13%) of breast-fed babies had peak TSB levels of 12 mg/dL or higher as compared to (4%) of artificially fed babies.

Early neonatal jaundice

Jaundice is that onset on the first day of life, is always pathologic and immediate attention is needed todetect the cause. Early onset often is a result of hemolysis, internal hemorrhage (cephalhematoma), or infection (Marcdante and Kliegman, 2013).

Prolonged jaundice

Jaundice which occurs in babies with a gestational age of 37 weeks or more lasting for more than 14 days, and in babies with a gestational age of less than 37 weeks with jaundice lasting for more than 21 days (National Institute for Health and Care Excellence, 2010).

2.2.7 Risk factors for hyperbilirubinemia in newborns

American Academy of Pediatrics (2004a) listed the risk factors that are clinically significant and most frequently associated with an increase the risk of severe hyperbilirubinemia. In this study, the researcher selected most of these risk factors and classified as: socio-demographic, maternal, and neonatal factors. After in-depth review of the previous literature, the researcher made a summary for the selected risk factors of NNH.

2.2.7.1 Socio-demographic factors

The selected socio-demographic factors in our study which may influence the incidence of NNHinclude: mother age, mother education, mother occupation and family income.

Mother age

There was considerable controversy regarding association between mother age and neonatal hyperbilirubinemia. Najib et al. (2013) study illustrated that the mother's age of (52.6%) of patients was more than 25 years old. Furthermore, Henny-Harry and Trotman (2012) study founded that maternal age ranged from 16 to 46 years with a mean of 29.4 ± 6.3 compared with mean age of mothers was 28.0 ± 5.18 years that (88%) of mothers age were between 20 – 35 years old. Additionally, more than half (59.1%) of the mothers were aged between 25 to 34 years old with mean ages of mothers were 29.1 ± 5.6 years (Ng and Chong, 2014).

Yahya and Alajeely (2013) mentioned that there were a significant differences between mother age (25-35 years) and neonates with hyperbilirubinemia, P value = (0.008). Moreover, Grupp-Phelan (1999) study showed that mothers who younger than 18 years old had higher risk for hospital readmission with hyperbilirubinemia than older mothers (Odds Ratio (OR): 2.50, 95% Confidence Interval (CI): 1.00- 6.41); (OR: 1.32, 95% CI: 1.11-1.58) respectively.

On the other hand, Srivastav et al. (1999) study showed that slightly higher serum bilirubin levels were obtained in the neonates of older age group mothers on day one, which were statistically insignificant, thus the maternal age did not affect the blood serum bilirubin level. On observing serum bilirubin levels again on day 3 and day 5, the researcher

founded statistically significant higher serum bilirubin levels in younger age group mother on day 3 (peak) whereas there was no significant difference observed on day 5, however slightly higher in older age group mothers. Furthermore, Wood et al. (1979) study mentioned that no effect of maternal age on NNH. Also, Kavehmanesh et al. study in 2008 explained that maternal mean (standard deviation) age was 27.71 (5.4) years and didn't differ between the jaundiced and non- jaundiced babies [28.1 (5.6%) in jaundiced and 27.6 (5.4%) in non- jaundiced, P=0.45]. Finally, Israel-Aina and Omoigberale (2012) study showed that mean maternal age of mothers was 30.44 ± 5.63 years, (P value = 0.62).

Mother education

Low maternal education level had a significant relationship with delayed health care-seeking and the use of home remedies for newborn jaundice so;their offspring may be more affected by hyperbilirubinemia than high education (Ogunlesiand Ogunlesi, 2012)**.** In Yahya and Alajeely (2013) study, the results showed a significant relationship between educational level and hyperbilirubinemia that the high proportion of the sample is not read and write was (67) of 224, (36) of 105 were primary school, (21) of 41 were secondary school, (14) of 44 were intermediate school, and (16) of 36 were institutes and university. Furthermore, Boo et al. (2011) study illustrated that the mean duration of education was 11, standard deviation (SD) =2.7years. Additionally, Ng and Chong (2014) study showed that most mothers were educated with at least secondary school education (85.3%) with (14.6%) having tertiary school education.

Few conflicting results were observed, Iskander et al. (2012) study showed that (75.4%) of the mothers' cases were literate and (24.6%) were illiterate. Similarly, in Najib et al. (2013) study in which there were (55%) of cases' mothers were high graduates.

Mother occupation

There is consistency in the literature that mother work may influence the occurrence of NNH. Olusanya et al. (2009) study showed that infants of mothers without full-time employment were significantly less likely to have severe NNHthan those with fully employed mothers. Similarly, Boo et al. (2011) study which illustrated that (47.7%) of the babies mothers were housewives, (5.8%) were professionals, (20.3%) were skilled workers, and (25.0%) were semi-skilled workers. Elhissi (2012) study showed that

neonatal jaundice appeared in (28.1%) of newborns; (31%) of working pregnant women gave birth to jaundiced infants while (27.9%) housewives gave birth to jaundiced infants.

On the other hand, Iskander et al. (2012) study explained that (42.3%) of cases mothers were working and (57.7%) of them non-working. Moreover, Ng and Chong (2014) study which revealed that approximately half of the mothers were housewives (53.0%) while (40.4%) were working with more than two thirds of those mothers working being in the private sector.

Family income

The role of family income was studied in many epidemiological studies aspredisposing factor for NNHthat thought to be interfering in mother's dietary regimes and life style. Olusanya et al. (2015) meta-analysis study examined the influence of social class on severe hyperbilirubinemia that the results did not show any significant association (P value = 0.090), this mean that low social class was not associated with an increased risk of severe hyperbilirubinemia.Additionally, Ng and Chong (2014) study verified that the family income was not statistically associated with NNH(P value = 0. 682).

2.2.7.2 Maternal factors

There were numerous of maternal risks may influence the NNHincidence. Several previous studies showed a difference in maternal risk contribution. In our study, the included maternal factors were: mother blood group and Rh type, parity, pregnancy disorders (including: gestational diabetes, pregnancy induced hypertension, urinary tract infection, vaginal infection, anemia, and perinatal hemorrhage), delivery type, premature rupture of membranes, oxytocin drug use, and length of stay in postnatal department by hours.

Maternal blood group and Rh type

Maternal O negative blood groupis thought to be considered a risk for developing NNH.Despite thefact that the prevalence of Rh-negative type is significantly lower among Africans thanCaucasians, Rh alloimmunization remains a major factor responsible for perinatal morbidity inSub-Saharan Africa and may result in the compromise of the woman’s obstetric care due to theunaffordability of anti-D immunoglobulin (Osaro and Charles, 2010).

There is a controversy in the literature about the influence of this risk. Henny-Harry and Trotman (2012) study founded that the majority of mothers had blood group O (66%) and 20 (12%) of mothers had Rhesus negative. Furthermore, Kavehmanesh et al. (2008) study explained that the Rh-negative mothers had more jaundiced infants (17.9%) compared with Rh-positive mothers (12%) (P value = 0.01). In a logistic regression analysis adjusted mother's Rh type, the results showed a significant effect of Rh type on neonatal admission for jaundice (OR: 1.30, CI: 0.67-2.52). Furthermore, Kalakheti et al.(2009) study conducted to estimate the incidence of hyperbilirubinemia in babies born to O positive mothers, the results showed that 37 (18.5%) babies had developed hyperbilirubinemia and among them 14 (38%) were from group of babies having O positive blood group and 23 (62%) were from group of babies having other than O positive blood group. In addition, Sgro et al. (2006) study stated that 32 cases (66.7%) involved infants born to mothers with type O blood. Moreover, Najib et al. (2013) study showed that the percentage of infants born to mothers with type O blood was (66.7 %).

On the other hand, in Kavehmanesh et al. (2008) study, the results showed that there were no differences between maternal blood groups of jaundiced and non-jaundiced babies (P value = 0.3), no significant effect of maternal blood groups; O, A, B, and AB on jaundice as [(OR: 1.14, CI: 0.53-2.45), (OR: 1.06,CI: 0.67-1.66), and (OR: 1.17, CI: 0.69-1.98)] respectively. Also, in a retrospective analysis of 166 cases with ABO hemolytic disease of the newborn, risk factors for the severity of jaundice were compared in infants with blood group A or B. The results explained that there were no statistically significant differences in hematological parameters including initial and final indirect bilirubin levels and hemolytic findings between the both groups (Akgül et al., 2013). Additionally, Bhat and Kumar (2012) study showed that there was no significant difference in the incidence and severity of haemolysis between the O-A and O-B-incompatible neonates. Finally, Wood et al. (1979) study which mentioned that no effect of ABO blood group on NNH**.**

Parity

The reviewed studies have incongruent results showed that multipara had a significant relationship with reduce risk for newborn hyperbilirubinemia.

Dubal and Joshi (2012) study conducted to analyze maternal factors affecting neonatal jaundice in Gujara. The results showed that primi mothers were having higher chances of neonates with neonatal jaundice (44% of cases) and also TSB level was higher in

neonates who were first born (20.4 ± 5.6) compare to neonates of multipara mothers. Furthermore, in Henny-Harry and Trotman (2012) study, (54%) of mothers was primiparous, (39%) were Para 1–2, and (7%) were Para 3–6. Similarly, Iskander et al. (2012) study showed that (67.7%) of patients mother were primipara and (32.3%) were multipara. In addition, Olusanya et al. (2015) study, which includes a total of 13 studies with 1,951 subjects and 32,208 controls from India, Nigeria, Pakistan, Nepal and Egypt, the results showed that primiparity with OR: 1.59 (95% CI: 1.26-2.00).

On the other hand, Ng and Chong (2014) study revealed that a large proportion of the mothers were multiparous with (61.6%) having 2 to 5 children and (8.1%) having more than 5 children.

Pregnancy disorders

Several maternal disorders could play a role in influencing the NNH that reported in the literature review. These disorders include: gestational diabetes, pregnancy induced hypertension, vaginal infection, urinary tract infection, anemia, and perinatal hemorrhage. The previous literatures mentioned that commonest pregnancy complication could lead to NNHwas gestationaldiabetes that the frequency of polycythemia results in an elevated and uncontrolled red blood cell production is 10-20% in infants of diabetic mothers. This abnormal red blood cell production leads to accumulation of bilirubin (Emedicine, 2015). Boskabadi and Zakerihamid (2012) study explained that (21%) of newborns with jaundice, their mothers had a history of pregnancy problems and (79%) had a history of normal pregnancy. The most frequent problems in the history of pregnancy were hypertension (4.7%), vaginal bleeding (3.3%), diabetes (2.78%), and urinary tract infection (0.8%). In Al-Hakeem(2006)study which revealed that the commonest complication in neonates of gestational diabetic mothers and the leading cause for NICU admission was hyperbilirubinemia, (41.2%) compared to (6.4%) for neonates of non-diabetic mother. Also, Titi and El Sharif(2013) study mentioned that infants born to mothers with gestational hypertension or gestational diabetes were (34%); (P value =0.002). Furthermore, Henny-Harry and Trotman (2012) study showed that there were 23 (14%) of jaundiced newborn mothers documented diabetic disorders. An etiology of clinically significant hyperbilirubinaemia in 10(6%) infants was mother diabetes.

Nonetheless, those results were incongruent with Al-Khalifah et al. (2012)study which showed that newborns of gestational diabetic mothers wasn’t significantly different in

comparison with normal mothers (OR= 1.02, 95% CI: 0.95-1.10; P value = 0.55). Also the results of the data analysis in Bertini et al. (2001) study showed that there was no statistically significant correlation between jaundice onset and maternal diabetes (6.6%); (P value= 0 .59). In addition, Mesic et al. (2014) study showed that (8 of 34) jaundiced newborn; their mothers reported diabetes mellitus or gestational diabetes with P value > 0.05.

Other studies investigated the effect of maternal hypertension during pregnancy on NNHas a risk factor. Bertini et al. (2001) study explained that there was no statistically significant correlation between jaundice onset (TSB .12.9) and maternal hypertension (5.4%), (P value = 0.75). Furthermore, Mesicet al. (2014) study showed that there was no statistically association between jaundice and preeclampsia (P value >0.05).Aboutmaternal infection, Mesic et al. (2014) study showed that a statistically significant difference between jaundice onset; (25 of 72) jaundiced babies and maternal infection (P value < 0.05).

Delivery type

The method of delivery may be normal vaginal delivery (NVD), cesarean section(C/S), or instrumental method. Many studies in the literature demonstrated that normal vaginal method increases the risk for neonatal jaundice. Najib et al. (2013) study illustrated that (73.5%) were delivered with NVD and (26.5%) with C/S. Furthermore, in Iskander et al. (2012) study, (72.3) % of cases were delivered with NVD and (27.7%) with cesarean section method. Moreover, Friedman et al. (1978) study showed that (21.3%) of neonates with jaundice delivered by ventouse extraction (P value<0.001). In addition, Henny-Harry and Trotman (2012) study explained that (66%) of cases were NVD and (34%) were delivered by C/S. Also, Heydarian and Majdi (2010) study showed that (63.6%) of patients' mothers were NVD and (36.4%) were C/S. In addition, Olusanya et al. (2009) study showed that the percentage of cases delivered vaginally were (94.7%) and to those delivered by C/S were (5.3%). Bertini et al. (2001) study results showed a positive, statistically significant correlation between TSB .12.9 and delivery by vacuum extractor (17.5%) (P value = 0.001).

On the other hand, Wood et al. (1979) study mentioned that no effect of type of delivery on NNH. Moreover, Bilgin et al. (2013) demonstrated that mode of delivery had no effect on bilirubin levels during first 48 hours in healthy neonates**.** Also, Bertini et al. (2001) study

results showed no statistically significant correlation between TSB .12.9 and delivery by neither vaginal delivery (4.8%),(P value= 0 .67)nor cesarean section (4.7%), (P value= 0 .79). Moreover, Dubal and a Joshi (2012) study which showed that there strong association (P value <0.05) was founded between cases with TSB<15 mg and cases with TSB ≥ 15 mg in relation to mode of delivery indicating higher chances of neonatal jaundice with high TSB in neonates born by lower segment cesarean section (20.5 ± 5.6) as compared to those delivered by normal vaginal delivery (14.5 ± 4.0). Add to that, Mesic et al. (2014) study which revealed a statistically significant difference between the onset of jaundice and mode of delivery: jaundice was more common in newborns that were born by stimulating or inducing labor than in those born spontaneously (P value <0.05).

Premature rupture of the membranes (PROM)

There were variations in the role of rupture of membranes surrounded the fetus and development of NNH. Henny-Harry and Trotman (2012) study explained that 16 (9%) of admitted neonates with jaundice, their mothers were with prolonged rupture of membranes. Additionally, Boskabadi and Zakerihamid (2012) study explained that (2.7%)newborns with jaundice, their mothers had a history of premature rupture of membrane. Furthermore, Mesic et al. (2014) study confirmed the association between the onset of jaundice in newborns and premature rupture of membrane that (27 of 71) jaundiced newborn, their mothers with PROM (P value <0.05).

Unlike previous studies, Kavehmanesh et al. (2008) study revealed that premature rupture of membranes was in (11.4%)of the cases which not reached to the statistically significant level; (P value =0.7).

Oxytocin drug use

The association between oxytocin-induced labor and NNHis documented. The literature suggested that oxytocin use causes to include hepatic glucuronyltransferase immaturity, anoxic liver damage, enhanced placenta-fetal transfusion, increased erythrocyte fragility, and mechanical trauma to erythrocytes (Buchan, 1979).

Literature review explained incongruent evidence in the relation between oxytocin administration and NNH. Najib et al. (2013) study showed that 66 neonates (32.4%) of neonates with indirect hyperbilirubinemia, their mothers were given oxytocin during labor.

Moreover, Buchan (1979) study illustrated that infant born after oxytocin-induced labor had an increased plasma bilirubin concentration (P value < 0.001) than others. In addition, Chalmers et al. (1975) study which revealed that (12.4%) infants born after oxytocin administration became jaundiced with relative risk (RR): 1.61, (P value< 0.000001), while (8.1%) infants born after spontaneous laborbecame jaundiced. Additionally, Davies et al. (1973) study mentioned that the infants of mothers whose delivered artificially induced with oxytocin had a mean total bilirubin level which was significantly higher (P value < 0.05) than that in the infants whose mothers delivered spontaneously and did not require oxytocin during labor.

Nevertheless, literature review explained incongruent evidence to show that there was no increase in mean plasma bilirubin levels when the oxytocin was given (Wood et al., 1979).In addition, Kavehmanesh et al. (2008) study revealed that oxytocin used in (34.5%) of the cases which not reached to the statistically significant level; (P value =0.4). Also, Davies et al. (1973) study stated that infants of mothers whose labor was of spontaneous onset but required oxytocin to accelerate progress did not did not differ significantly from mothers whose mothers had had a spontaneous onset of labor and did not require oxytocin.

Length of stay in postnatal department

American academy of pediatrics defines early and very earlyhospital discharge as 48 and 24 hours, respectively, after uncomplicated vaginal delivery and less 96 hours after birth by cesarean section (AAP, 2004b). The American Academy of Pediatrics (1995) defined early discharge from well-baby nurseries defined as less than 48 hours after birth.

Routine hospital stay for newborns and their mothers has decreased clearly over the recent years intended largely by cost containment strategies and financial reimbursement(Grupp-Phelan et al., 1999). In the past, newborns remained in the hospital for many days; jaundiced babies subsequently could be identified before discharge so would be treated appropriately. Today, because of exaggerated rates of delivers, limited hospital's capacity and the shortage in bed numbers; almost all infants delivered by vaginal method leave the hospital before they are 24 hours old, therefore the bilirubin concentration peaks after discharge. This practice in combination with other risk factors leads to difficulty in recognition, follow-up, and early treatment of neonatal jaundice (Kavehmanesh et al., 2008). For this reason, AAP (2004a) recommended guidelines for timing of the assessment

and follow up of all newborns discharged before 72 hours of age. The guidelines explained that infant who discharged before age 24 hours, should be seen by age of 72 hours and infant, who discharged between 24 and 47.9 hours, should be seen by age of 96 hours while infant who discharged between 48 and 72 hours, should be seen by age of 120 hours.

There was controversy in the results of reviewed studies. Escobar et al. (2005)study showed that newborns whose stay was less than 72 hours, were at a significantly greater risk for readmission than those who had longer stays. Iskander et al. (2012) study showed that (79.2%) of mothers discharged in ≤ 24 hours, (14.4%) of babies mothers discharged within 25–48 hours and (6.4%) of them discharged in > 48hours. This was consistent with Grupp-Phelan et al. (1999) study which stated that healthy infants leave hospital to home at younger than 30 hours were between (10%) and (64%) more likely to be readmitted for jaundice than similar infants with longer neonatal stay. As a comparison, infants staying ≤2 days: (OR: 1.35, 95% CI: 1.12-1.63) and infants staying >2 days: (OR, 1.43, 95% CI, 1.01-2.04) for infants staying >2. Najib et al. (2013) study showed that 137 (73.5%) neonates developed jaundice after early discharging from hospital early discharge (P value = 0.035). Also, Maisels and Kring (1998) study explained that discharge at any time < 72 hours significantly increases the risk for readmission to hospital and the risk for readmission with hyperbilirubinemia when compared with discharge after 72 hours. Finally, Gupta et al. (2006) revealed that neonatal jaundice was the most frequent problem seen in 105 (54.4%) children on follow-up. Only 16 (8.3%) newborns needed re-hospitalization; the most common indication being neonatal jaundice (n=9).

On the other hand, there were other studies showed that infants whose length of stay was <48 hours were at no greater risk for readmission for jaundice or other causes than those whose length of stay was ≥48 hours to <72 hours; [length of stay <48 hours (OR: 2.40, 95% CI: 1.09- 5.30) and 48 to <72 hours (OR, 3.15, 95%CI: 1.40 to 7.09) versus ≥72 hours]. Also, Kavehmanesh et al. (2008) study mentioned that mean (SD) length of primary nursery stay was 30.2 (23.9) hours. Mean neonatal stay in jaundiced babies was 30.6 (2.5) hours, but in non-jaundiced babies was 27.7 (9.8) hours, that is significantly longer in non-jaundiced infants (Pvalue< 0.001).

2.2.7.3 Neonatal factors

Numerous neonatal factors were suspected and investigated as possible risk factors for neonatal jaundice. We classified them as follows: neonate order, birth weight (BW), cephalhematoma and bruising, previous sibling with jaundice, and feeding practices.

Neonate order

There are incongruences in the literature about the risk of neonate order and developing of NNH. Dubal and Joshi (2012) study revealed that birth order was found to be associated (P value <0.05) with level of total serum bilirubin in neonatal jaundice. In contrast, Mesic et al. (2014) study showed that jaundice was most common in first-born infants; (98 of 341) jaundiced neonate were first-born infants, but the association not reached to statistically significant level (P value >0.05). In addition, Kavehmanesh et al. (2008) study reported that there were 1547 (57.3%) first offspring, (12.9%) of them were jaundiced neonates and (87.1%) were non-jaundiced neonates, no significant increase of readmission because of jaundice was found among those infants compared with subsequent babies (OR: 0.74; 95% CI: 0.50-1.09; P value = 0.55).

Birth weight

There is debate in the literature about the effect of birth weight on occurrence of NNH. Narang et al.(1997) study carried out to assess the incidence, severity, causes and therapeutic interventions for jaundice in neonates, founded that there was significant neonatal jaundice occurred in (14.56%) of all births with an incidence nearly three times higher in low birth weightbabies(< 1500gram) compared to babies above 2500 gram; (34.5%) of low birth weight babies (< 2500 gram) developed significant NNJ and among the very low birth weight (<1500gram), (65.6%) developed significant jaundice. Furthermore, Omekwe et al. (2014) study illustrated that the low birth weights (52.8%).Also, Olusanya et al. (2015) study, in which a total of 13 studies with 1,951 participants and 32,208 controls from India, Nigeria, Pakistan, Nepal and Egypt were studied, the results showed that underweight/weight loss was with (OR: 6.26, 95% CI: 1.23-31.86). Moreover, Friedman et al. (1978) study reported that there was significantly association between neonatal jaundice and birth weight (P value<0.001). Finally, Henny-Harry and Trotman (2012) study reported thatbirth weight ranged from 670 gram to 4830 gram with a mean of 2696 ± 799.

On the other hand, Henny-Harry and Trotman (2012) study determined that (65.3%) of patients their birth weight was above 2500gramand (34.7%) their birth weight was 2000-2500 grams. Furthermore, Kavehmanesh et al. (2008) study revealed that mean (SD) neonatal birth weight was 3301.1 (395) gram totally [3284.6 (393.0) in jaundiced babies and 3303.5 (385.9) in non- jaundiced babies], which did not differ between the two groups (Pvalue =0.41). Also, Heydarian and Majdi (2010) study showed that the birth weight in 77 (65.3%) of cases was above 2500 gram (P value= 0.001) while there were 41(34.7%) of cases, their birth weight was 2000-2500gram.

Cephalhematoma and bruising

Cephalohaematoma is a collection of blood that develops beneath the outer layer of periosteum of a neonate's skull. Clinically, it appears as a firm, tense mass at birth and resolves in a few weeks to months (National Collaborating Centre for Women's and Children's Health, 2010).

There were variations about the risk role of cephalhematoma or bruising and occurrence of neonatal hyperbilirubinemia. In Najib et al.(2013) study, (4.7%) of the cases had cephalhematoma and (7.7%) of cases had bruising similar to Henny-Harry and Trotman (2012) study, in which there were 4 (2%) of jaundiced newborn documented cephalohaematoma and 10(6%) were excessive bruising. An etiology of clinically significant hyperbilirubinaemia in 3(1%) infants was cephalohaematoma and excessive bruises in 7(4%). Kuzniewicz et al. (2008) study demonstrated that bruising on examination doubled this risk of severe hyperbilirubinemia Adjusted Odds Ratio (AOR) = 2.36, 95% CI: 1.17 - 4.77). Bertini et al. (2001) study also demonstrated statistically significant positive correlation was found between hyperbilirubinemia and cephalohematoma; (P value <001).

On the other hand, Hung (2004) study showed that cephalhematoma wasn't statistically significant risk factor identified with the univariate logistic regression models [AOR: 7.39. 95% CI: 0.84–64.66; (P value = 0.071)]. Additionally, Kuzniewicz et al. (2008) study demonstrated that cephalohematoma wasn't a risk factor in this study (P value =0.5).

Previous sibling with jaundice

There is consensus in the literature review that the incidence of NNHis higher in infants with siblings who had neonatal jaundice or treated for neonatal jaundice. Kuzniewicz et al. (2008) study revealed that a family history of jaundice appeared to increase the risk of severe hyperbilirubinemia by almost 4-fold (AOR: 3.83, 95% CI: 0.93 - 15.7). In Najib et al. (2013) study, (27.9%) neonates had history of jaundice in their siblings (12.4%) of need phototherapy and 5.3% of them need exchange phototherapy). Moreover, Henny-Harry and Trotman (2012) study which demonstrated that (4%) of newborns with neonatal hyperbilirubinemia had previous sibling treated for hyperbilirubinaemia. Also Khoury et al. (1988) study illustrated that the risk of hyperbilirubinemia in newborns who had one or more prior siblings with NNHwas 3.1 times higher than that of newborns that hadn't prior siblings'NNH (10.3% vs. 3.6%). Finally, Yahya and Alajeely (2013) study demonstrated that (68%) of cases had positive history (32%) had negative history of jaundice in sibling.

Feeding practices

It is meanable prediction that improper feeding practices may lead to development of NNH.For accurate assessment of this risk, that involves: feeding method, feeding frequency, feeding difficulty, feeding initiation time and number of wet diapers /24hours.Many epidemiologic studies examined the effect of feeding practices on occurrence of NNH.In relation to feeding method, Iskander et al. (2012) study explained that (66.9%) of the cases were breast fed, while (8.5%) were bottle fed, (4.6%) were fed both methods, and (20%) were fed by breast milk and others. Moreover, Ng and Chong (2014) study revealed that an admirable proportion of mothers surveyed were breast feeding exclusively (81.8%) with 3 mothers (1.5%) bottle feeding only while the rest (16.7%) mothers gave breast feeding and bottle feeding to their babies. Furthermore, the percentages of feeding method among 154 neonates with hyperbilirubinemia in Iraq were (88%) breast feeding,(6%) artificial feeding, and (6%) mixed feeding. Also, the results showed that the breast feeding had highly significant risk for hyperbilirubinemia, (P value = 0.000) (Yahya and Alajeely, 2013). Additionally, Henny-Harry and Trotman (2012) study which showed thatinfants who were exclusively breastfed had a significantly higher mean admission 350.7 ± 77.2 μmol/L and peak bilirubin 370.7 ± 66.7 μmol/L level than infants who were getting supplementation 233.4 ± 113.1 μmol/L and 316.73 ± 47.6 μmol/L respectively, (P value< 0.01). Furthermore, Bilgin et al. (2013) study founded that

vaginally delivered mothers initiated breastfeeding earlier and needed less nutritional support for their babies than mothers delivered with c/s. Infants born with cesarean section were fed later and more often had mixed feeding. Moreover, Saigal et al. (1982) study showed that mean TSB were significantly higher in the breast-fed infants than formula-fed infants on each postnatal day (P value< 0.001). The proportion of babies with peak bilirubin levels at or above 12 mg/dl was higher in the breast-fed group (26% v. 7%, P value < 0.001). Furthermore, Hung (2004) study showed that breast feeding was statistically significant risk factor related to neonatal jaundice identified with the univariate logistic regression models [AOR:4.60, 95% CI:2.40–8.81; (P value< 0.001)] and similarly, multivariate logistic regression models adjusted for the breast feeding confirmed the statistical significance of these factors [AOR:4.64. 95% CI: 2.25–9.57; (P < value 0.001)]. A similar trend was seen inKuzniewicz et al. (2008) study which illustrated that exclusive breastfeeding was highly statistically significant (AOR: 2.09, 95% (CI) =1.05 to 4.03) and had twice the risk of developing TSB≥25 mg/dL. Also, Maisels and Kring, (1998) study revealed that breastfeeding showed a significant risk factor for hospitalized infants for jaundice(OR: 4.21, 95% CI: 1.80 to 9.87). Add to that, Wood et al. (1979) study presented a higher incidence of neonatal jaundice in breast fed mother.

Unlike previous studies, Bilgin et al. (2013) study demonstrated that feeding route had no effect on bilirubin levels during first 48 hours in healthy neonates**.** Furthermore, Bertini et al. (2001) study demonstrated a statistically significant positive correlation between patients with a total serum bilirubin concentration >12.9 mg/dL and supplementary feeding [refers to infants who were breastfed and received additional formula supplements.] (13.1%), (P value <0.001); oppositely, negative correlation had been showed between breastfeeding and patients with a total serum bilirubin concentration >12.9 mg/dL (2.7%), (Pvalue < 0.001). In Heydarian and Majdi (2010) descriptive cross sectional study performed among 118 neonates weighting 2 kilogram and more who had exchange transfusion. This study explained that the majority of neonates fed breast milk exclusively (57.6%), (26.3%) fed breast milk and formula,(11%) took formula alone and (5.1%) had not oral feeding and only got intravenous fluid therapy (P value = 0.000).

2.2.8 Complications

2.2.8.1 Kernicterus (Acute or chronic bilirubin encephalopathy)

In young infants, unconjugated bilirubin can penetrate the blood–brain barrier to be toxic to brain and spinal cord and can cause both short-term and long-term neurological dysfunction. Acute clinical manifestations include lethargy, irritability, abnormal muscle tone and posture (hypotonia), temporary apnea and convulsions. This presentation is known as **acute bilirubin encephalopathy**. Yellow staining is produced in brain as a result of bilirubin deposition; this is referred to as **kernicterus**. The term kernicterus is also used to denote the clinical features of acute or chronic bilirubin encephalopathy (National Collaborating center for Women'sand Child's Health, 2010). Untreated infants progressively develop hypertonia, backward arching of the neck (retrocollis) and trunk (opisthotonus), and high-pitched cry. The latter features is referred as **chronic bilirubin encephalopathy** that may occur if no treatment adding long-term neurological problems; cerebral palsy, hearing loss, visual and dental problems, and occasionally intellectual disabilities (AAP, 2001).

In developing countries, kernicterus ranks as the fifth leading cause of mortality in newborns (Bhutani and Johnson, 2003). In the United States, it has been estimated that between 35–105 cases per year would develop kernicterus with 3.5 million term deliveries if untreated (Wennberg et al., 2006).

2.2.9 Diagnosis

2.2.9.1 Clinical assessment

All babies need to be monitored for jaundice development by ongoing assessment whenever vital signs are measured or at least every 8 to 12 hours. Jaundice assessment is applied in a well-lit room or in daylight at a window, by blanching the baby’s skin with digital pressure by a finger and observing the underlying color of the skin and subcutaneous tissues. Jaundice appears first in the face and progresses caudally to the trunk and extremities.Kramer’s rule (see Annex 2.1) has been used traditionally in visual assessment of the severity of jaundice that explains the cephalocaudal progression of jaundice as TSB increase. It divided the baby into 5 zones, with a TSB level measurement

combined with each zone (Queensland Maternity and Neonatal Clinical Guidelines Program, 2009).

2.2.9.2 Risk assessment

To identify newborns at risk for severe hyperbilirubinemia and to prevent bilirubin encephalopathy, guidelines have been developed on an evidence-based approach for the management of jaundiced neonates. An American Academy of Pediatrics' Subcommittee on Hyperbilirubinemia adapted a guideline for hyperbilirubinemic infants of 35 or more weeks of gestation. The focus of this guideline is to reduce the incidence of severe hyperbilirubinemia and bilirubin encephalopathy in addition to minimizing the risks of unintended harm such as maternal anxiety, decreased breastfeeding, and unnecessary costs or treatment (AAP, 2004a).

The best documented method for assessing the risk of hyperbilirubinemia on later is to measure the total serum bilirubin and or total transcutaneous bilirubin level; it is noninvasive, fast, and relatively inexpensive technique for measuring serum bilirubin and plots the results on a nomogram (Annex 2.2).Bilirubin nomogram is tool identifies risk zones based on the newborn's age in hours. An infant whose TSB is in the low-risk zone is at very low risk of developing severe hyperbilirubinemia (AAP, 2004a).

2.2.10. Treatment

The most common therapeutic modalities in the treatment of newborn with hyperbilirubinemia are phototherapy and exchange transfusion (Hansen, 2014)**.**

2.2.10.1 Phototherapy

Phototherapy is the most widespread treatment in neonates with unconjugated hyperbilirubinemia. This therapeutic technique was discovered unintentionally in England in the 1950s, now it is considered the traditional therapy used in newborns (Hansen, 2014). This treatment method using blue-green light that aids in destructing the serum bilirubin level (AAP, 2004a).The clinical response of exposed newborn to phototherapy depends on the efficacy of the phototherapy device, as well as the infant's rates of bilirubin production and elimination (Bhutani and the committee fetus and newborn, 2011).

In 2011, an AAP published a technical report, "Phototherapy to Prevent Severe Neonatal Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation." Their goal was to standardize the use of phototherapy in the management of hyperbilirubinemia that the most important intervention for infants with severe hyperbilirubinemia is to initiate phototherapy immediately (Bhutanim and Committee on Fetus and Newborn, 2011).The annex (2.3) illustrates the recommended levels for the phototherapytreatment according to gestational and postnatal ages (AAP, 2004a).

2.2.10.2 Exchange transfusion

Exchange transfusion is one of the most common strategies for the treatment of neonatal hyperbilirubinemia. It prevents kernicterus by removing bilirubin from the circulation also maternal antibodies in Rh-hemolysis disease (Smits-Wintjens et al., 2008). American Academy of Pediatrics (2004a) recommended guidelines for exchange transfusion according to gestational and postnatal ages, with thresholds given for phototherapy (Annex 2.4).

The complications of exchange transfusions have been reported in many studies. In a retrospective study lasted to 15 years comparing the incidence of severe complications between healthy and ill infants, (2%) of 106 infants with a variety of illnesses died after exchange transfusion, and (12%) had severe complications. None of the 81 healthy infants died, but 1 had severe necrotizing enterocolitis requiring surgery (Jackson, 1997).

2.2.10.3 Breast feeding

Increasing the frequency of feedings is recommended in jaundiced newborn. Optimal breastfeeding (eight to 12 times per day) enhances removal of bilirubin through the gastrointestinal tract. Infants with inadequate oral intake, excessive weight loss (more than 12 percent of birth weight), or dehydration should receive supplemental breast milk or formula. Intravenous fluids should be given if feeding is insufficient and the infant is dehydrated (AAP, 2004a).

2.2.10.4 Pharmacologic therapy

Medications are not usually administered in newborns with physiologic NNJ. However, in certain conditions, phenobarbital has been used to enhance bilirubin metabolism. Several

studies have shown that phenobarbital is effective in reducing TSB. Phenobarbital may be administered to the mother prenatally or the infantpostnatally (Hansen, 2014).The recommended dose for Intravenous immunoglobulin is 0.5–1.0 g/kg in case of Rhesus hemolytic disease (AAP, 2004a).

2.2.11 Summary

Table (2.2): Summary for the main literature review findings of neonatal hyperbilirubinemiarisk factors

Author(s)	Study type	Title of Paper	Study Population Description	Significant finding
Davies et al. Year:(1973) Country: England	Prospective study	Neonatal Jaundice and Maternal Oxytocin Infusion	• Blood bilirubin was obtained on the 2nd and 5th day. • Rhesus and ABO incompatibility were excluded. • Group A:Spontaneous labor, no oxytocin • Group B: Spontaneous labor, oxytocin given. • Group C: Labor artificially, oxytocin given.	* 2nd day: - Mean group A: 4.8 (2.8) - Mean group B: 5.4 (2.9); (P > 0.05) - Mean group C: 6.8 (2.3); (P < 0.05) * 5th day: - Mean group A: 4-3 (4 2) - Mean group B: 2-8 (3 2); (P > 0. 05) - Mean group C: 7-0 (4 2); (P < 0.05)
Chalmers et al. Year:(1975) Country: United Kingdom	Retrospective controlled study	Use of Oxytocin and Incidence of Neonatal Jaundice	• Group A:Oxytocin administration • Group B:Spontaneous Labor, no oxytocin	* Group A: Infants born after oxytocin administration became jaundiced: (12.4%); RR: 1.61 (P< 0.000001). * Group B: Infants born after spontaneous laborbecame jaundiced: (8.1 %)
Friedman et al. Year:(1978) Country: London	Retrospective study	Factors influencing the incidence of neonatal jaundice	• Infants without multiple birth, Rh or ABO incompatibility & G6PD deficiency were observed for 1st week of birth.	* BW:(P <0.001) * Ventouse extraction:(P <0.001) * Oxytocin: (P<0.001)
Wood et al. Year:(1979) Country: England	Retrospective cross sectional study	Factors affecting neonatal jaundice	• Plasma bilirubin was estimated on the 6th day of life. • Preterm, low birth weight, Coombs, positive and ventose delivered babies were excluded.	*Mother age:>25years (52.6%). * Feeding method Artificial: (12.3%); (P<0.001) Breast: (25.3%); (P < 0.05) Mixed: (23.6%) * Labor onset Spontaneous: (19.1%) Induced, prolonged Pregnancy: (14.6%) Induced, other: (24.6%) *No effect of maternal age, delivery type &ABO blood group on neonatal hyperbilirubinemia.
Buchan Year: (1979) Country: England	Retrospective cross sectional study	Pathogenesis of neonatal hyperbilirubinaemia after induction of labor with oxytocin	• 95 healthy newborn infants (44 boys, 51 girls) • Birth weights: 3005-4108 • Apgar scores exceeding 7 at one minute.	* Infants born after oxytocin-induced labor had an increased plasma bilirubin concentration (P< 0.001) than others.
Saigal et al. Year: (1982) Country: Canada	Prospective study	Serum bilirubin levels in breast- and formula-fed infants in the first 5 days of life	• 485 infants who delivered during March to July 1979 in maternity unit in Hamilton, Ont. were enrolled • Eligibility criteria: • Healthy, term, singleton , delivered SVD or CS, weight appropriate for gestational age and expected to stay in hospital for at least 4 days. • Exclusion criteria: • All infants with congenital	* Mean TSB (including the peak level) were significantly higher in the breast-fed group than formula-fed infants on each postnatal day (P < 0.001). * The proportion of babies with peak bilirubin levels at or above 12 mg/dl was higher in the breast-fed group (26% v. 7%, P < 0.001).

			malformations, diabetic mothers, had problems or separated from their mothers for medical reasons longer than 12 hours were excluded	
Khoury et al. Year: (1988) Country: United States	Retrospective cross sectional study	Recurrence Risk of Neonatal Hyperbilirubinemia in Siblings	• 3301 live infants born between1966 and 1986 to 1669 male US Army veterans. The study population included 580 sibships with one infant, 679 with two, and 410 with three or more.	* The risk of NHB in newborns who have one or more prior siblings with NHB was 3.1 times higher than that of newborns who have prior siblings without NHB (10.3% vs 3.6%).
Narang et al. Year: (1997) Country: India	Retrospective cross sectional study	Neonatal Jaundice: An Analysis of 551 Cases	• 551 live births at Nehru Hospital between April 1994 and June 1995 who admitted with diagnosis of NNJ irrespective of other illnesses were studied. • Group A: TSB ≤ 15 mg/dl • Group B: TSB >15 mg/dl	* Incidence of significant neonatal jaundice: (14.56%) *Birth weight: - < 1500gram: (65.6%) - < 2500gram :(34.5%) ***** incidence of NJ three times higher in LBW babies compared to babies above 2500 g**.**
Grupp-Phelan et al. Year: (1999) Country: United States.	Population-based case-control study	Early newborn hospital discharge and readmission for mild and severe jaundice	• Cases: 750 infants readmitted to the hospital for jaundice in the first 2 weeks of life. • Controls: 3192 infants not readmitted.	***** Healthy infants sent home at younger than 30 hours were between (10%) & (64%) more likely to be readmitted to the hospital for jaundice than similar infants with longer neonatal stay. ***** No difference in readmission for jaundice between infant discharged from the hospital early and those discharged late - Infants staying ≤2 days: (OR, 1.35 [95% CI, 1.12 1.63]. - Infants staying >2 days: (OR, 1.43 [95% CI, 1.01-2.04].
Srivastav et al. Year: (1999) Country: India	Comparative study	A study of serum bilirubin in neonates in relation to the maternal age	• 122 healthy newborns were selected that TSB was done. • Mothers were divided into two groups i.e. <30 years and >30 years of age.	* No significant difference between two groups on day of birth and day 5 but significant difference was observed on day 3 (P <0.05). * Statistically significant higher serum bilirubin levels in younger age group mother on day 3 (1.36±0.59 mg/dl) *In both the groups of mothers, serum bilirubin levels in their neonates raised to highly significant levels on day 3 (P value <0.001). *No significant difference observed on day 5(6.3±1.47 mg/dl.), however slightly higher in older age group mothers.
Bertini et al. Year: (2001) Country: Italy	Hospital-based prospective study	Is Breastfeeding Really Favoring Early Neonatal Jaundice?	• GA ≥ 37 weeks • Participants with asphyxia, infections, abnormal direct serum bilirubin values, malformations, or other pathologic conditions were excluded.	*Supplementary feeding: positive correlation (P=0.001). * Breastfeeding : negative correlation (P= 0.001) * Vacuum delivery: (P= 0.001)
Hung Year: (2004) Country: Taiwan	Case-control study	Risk Factors for Severe Hyperbilirubinemia in Neonates	• Cases with peak serum bilirubin levels ≥342 µmol/L • Control with peak serum bilirubin levels <256µmol/L	* Breast feeding: OR: 4.6 (P< 0.001).
Al-Hakeem Year: (2006) Country: Saudi Arabia	Hospital-based prospective study	Pregnancy outcome of gestational diabetic mothers: Experience in a tertiary center	• 685 pregnant women were diagnosed with gestational diabetes were studied.	*The commonest complication in babies of gestational diabetic mothers and leading cause for NICU admission was NNH(41.2%) compared to (6.4%) for neonates of non-diabetic mother.

Gupta et al. Year: (2006) Country: India	Hospital-based prospective study	Length of Postnatal Stay in Healthy Newborns andRe-hospitalization Following their Early Discharge	• 1134 healthy babies were enrolled over a period of 2 months in the postnatal ward of a tertiary care government hospital in Delhi. • Newborn weighing < 1800 g, < 34 wk gestation, or with asphyxia, major congenital anomalies, pathological hyperbilirubinemia and those requiring admission to NICU were excluded	* Neonatal jaundice was the most frequent problem seen in 105 (54.4%) children on follow-up. Only 16 (8.3%) newborns needed re-hospitalization; the most common indication being neonatal jaundice (n=9).
Kuzniewicz et al. Year: (2008) Country: USA	Nested Case-Control Study	Risk Factors for Severe Hyperbilirubinemia among Infants with Borderline Bilirubin Levels	• GA ≥ 34 weeks gestation • BW ≥ 2000 g • TSB of 17 to 22.9 mg/dL at age ≥ 48 hours.	* Family history of jaundice: OR = 3.8 (0.93 - 15.7). * Bruising: OR = 2.36 (1.17- 4.77). *Cephalohematoma :(p value = 0.5). * Exclusive breast feeding: OR 2.0 (1.03–4.0)
Kavehmanesh et al. Year: (2008) Country: Iran	Comparative study	Prevalence of Readmission for Hyperbilirubinemia in Healthy Newborns	• Women who gave birth to their children in Najmieh Hospital, Tehran, from 2004-2005 were conducted. • 340 infant rehospitalized for hyperbilirubinemia and 2362 infants were nonhospitalized were compared as icteric and non-icteric babies. • Weighing ≥2500 gm. • Singletons	* Prevalence of readmission for jaundice: (12.6%). *Maternal age, mean (SD): 27.71 (5.4) years; (P = 0.45) Jaundiced: 28.1 (5.6) hours Non- jaundiced : 27.6 (5.4) hours *Maternal blood groups:(P =0.3) B: OR= 1.06;(CI: 0.67 - 1.66) AB: OR= 1.17;(CI: 0.69 1.98) O: OR= 1.14;(CI: 0.53 -2.45) *Maternal Rh: OR= 1.30 ;(CI: 0.67 2.52) Rh-negative mothers: (P=0.01), *ROM: (11.4%); (P=0.7). *Oxytocin used: (34.5%); (P =0.4) * Birth weight, mean (SD): (P = 0.41) Icteric: 3284.6 (392.9) Non-icteric: 3303.5 (395.9) * Child order: (p = 0.55); OR= 0.74; (CI: 0.50-1.09) First: Icteric: (12.9%) Non-icteric: (87.1%) Subsequent: Icteric: (12.1%) Non-icteric: (87.9%) *length of stay, mean(SD)::0.2(23.9) hrs.; (P <0.001) Icteric: 27.7 (9.9%) Non-icteric: 30.6 (25.3%) *Maternal oxytocin consumption: OR=1.20;(0.54-2.64)
Olusanya et al. Year: (2009) Country: Nigeria	Cross sectional community-based study	Infants with severe neonatal jaundice in Lagos, Nigeria: incidence, correlates and hearing screening outcomes	• 5266 mothers attending four of the seven primary healthcare centers which administered BCG immunization from July 2005 to June 2007 were enrolled.	*Incidence of NNJ: - Need phototherapy: 5.5% (95% CI: 4.9–6.2) - Requiring blood exchange: 1.9% (95% CI: 1.5–2.3) * Mothers age (Years): Mean : 28.0 ± 5.18 years < 20: (3.3%) 20–35 (88%) >35: (8.7%) * Mothers employment: Infants of mothers without full-time employment were significantly less likely to have severe NNJ than those with fully employed mothers. *Parity Primiparous: (40.9%) Multiparous: (59.1%) *Education Tertiary: (16.1%)

				Secondary: (66.3%) Primary: (14.8%) None: (2.8%) *<u>Mode of delivery</u> NVD: (94.7%) C/S: (5.3%) *<u>Exclusive breast feeding</u> No: (0.7)% Yes: (99.3)%
Kalakheti et al. Year: (2009) Country:	Prospective cohort Study	Risk of neonatal hyperbilirubinemia in babies born to 'O' positive mothers: a prospective cohort study	• 199 women having 'O' positive blood group admitted to the Department of Gynae and Obstetric were included in the study from July 2002 to June 2003.	37 (18.5%) babies had developed hyperbilirubinemia and among them 14 (38%) were from group of babies having 'O' positive blood group and 23 (62%) were from group of babies having other than 'O' positive blood group. There was 2.6 times higher chance of having hyperbilirubinemia in the babies with ABO incompatibility than 'O' positive babies
Heydarian and Majdi Year: (2010) Country: Iran	Descriptive cross sectional study	Severe Neonatal Hyperbilirubinemia;Causes and Contributing Factors Leading to Exchange Transfusion at Ghaem Hospital in Mashha	• Weight: ≥2kg who had exchange transfusion in	*****<u>ABO incompatibility:</u> (38.1%) *<u>Rh incompatibility</u>: (16.1%) *****Mothers delivery: NVD: (63.6%) C/S: (36.4%) * <u>Feeding Method:</u> Exclusive breast milk: (57.6%) Breast milk and formula: (26.3%) Formula alone: (11%) No oral feeding: (5.1%)
Boo et al. Year: (2011) Country: Malaysia	Cross-sectional study	Malaysian Mothers' Knowledge & Practices on Care of Neonatal Jaundic.	• 400 women consisting of 200 Malays, 100 Chinese and 100 Indians who admitted to the obstetric wards in the hospital Tuanku Jaafar from 1 March 2008 to 31 July 2008 were recruited.	***** Mean duration of <u>education</u>: 11 (SD=2.7) years. *****<u>Mother occupation</u>: Housewives: (47.7%) Professionals: (5.8%) Skilled workers: (20.3%) Semi-skilled workers: (25.0%).
Dubal and Joshi Year: (2012) Country: India	Retrospective cross-sectional study	Maternal factors affecting Neonatal Jaundice in Saurashtra region of Gujarat	• 50 neonates with NNJ with TSB >5mg% were examined who admitted from May 2010 to May 2011. • Neonates TSB <5mg% and with severe congenital malformation like hydrocephalus were excluded.	*<u>Primi mothers:</u> (44%) with TSB (20.4 ± 5.6); (P =0.003) * <u>Birth order</u>: lower the birth order higher TSB level (P <0.005). *<u>Mode of delivery</u>: TSB in neonates born by C/S was higher (20.5 ± 5.6) as compared to those delivered by normal vaginal delivery (14.5 ± 4.0); (P =0.001)
Ogunlesi, T. and Ogunlesi, F Year: (2012) Country: Nigeria	Retrospective cross-sectional study	Family socio-demographic factors and maternal obstetric factors influencing appropriate healthcare seeking behaviors for newborn jaundice in Sagamu, Nigeria	• 182 mothers whose babies were referred to a Nigerian tertiary hospital with jaundice were studied**.**	***** Low maternal education had a significant relationship with delayed health care-seeking for newborn jaundice
Iskander et al. Year: (2012) Country: Egypt	Retrospective cross-sectional study	Root causes for late presentation of severe neonatal hyperbilirubinaemia in Egypt	• Age ≥ 6 days over an 18 month	* <u>Mather education:</u> Literate: (75.4%). Illiterate: (24.6%). * <u>Mather occupation:</u> Working: (42.3%) Non-working: (57.7%). *<u>ABO incompatibility</u>: (25.4%). * <u>Rh incompatibility</u>: (5.8%). *<u>Delivery method:</u> NVD: (72.3%) CS: (27.7%). *<u>Type of feeding:</u> Breast fed: (66.9%) Bottle fed: (8.5%) Both: (4.6%),

				Breast milk fed and others: (20%) *Parity: Primipara: (67.7%) Multipara: (32.3%) * Mothers discharge: In ≤ 24 hours: (79.2%) Within 25–48 hours: (14.4%) In > 48hours: (6.4%)
Henny-Harry and Trotman Year:(2012) Country: India	Retrospective descriptive study	Epidemiology of Neonatal Jaundice at the University Hospital of the West Indies	• 170 neonates at the University Hospital of the West Indies with clinically significant jaundice between January 1, 2006 and June 30, 2007 were studied. • Neonates who had a direct serum bilirubin level greater than 20% of the value of their TSB level were excluded.	* BW: > 2500 gram: (65.3%) 2000- 2500 gram: (34.7%) Range: 670 - 4830g Mean of 2696 ± 799 *Day of life jaundice first noted : Day 1: (27%) Day 2: (43%) Day 3–4: (26%) Day 5–6: (3%) * Admission age: Mean: 1.8 SD: 2.4 days *Parity Para 0: (54%) Para 1–2: (39%) Para 3–6: (7%) * Diabetic mother: (14%) * Mather age: Range: 16-46 years Mean: 29.4 ± 6.3. *Delivery type NVD :(66%) C/S: (34%) Vacuum delivery: (1%) *Oxytocin induction: (15%) * Feeding method Exclusive breastfeed: (52%) Supplemented/formula feed: (21%) * Blood group Mothers' blood group O: (66%) Rhesus negative mothers: (12%) Infants with blood group O: (38%) Infants with blood groups A or B: (59%) *Prolonged rupture of membranes: (9%) *Cephalohaematoma: (2%) *Excessive bruises: (6%) * Previous sibling treated for jaundice: (4%). Etiology * ABO incompatibility :(35%). *Rhesus incompatibility: (3.5%) *Infection: (18%) *Infant of a diabetic mother: (6%) *Dehydration: (5%) * Cephalohaematoma: (1%) * Excessive bruising: (4%) *Minor group incompatibility: (2%)
Al-Khalifah et al. Year: (2012) Country: Saudi Arabia	Retrospective case-control Study	Neonatal Short-Term Outcomes of Gestational Diabetes Mellitus in Saudi Mothers	• 419 pregnant women with gestational diabetes mellitusand 347 controls with their babies were included during Jan to Dec 2007.	*Jaundice requiring phototherapy were not significantly different between the infants born to gestational diabetes mellitus mothers compared to infants born to normal mothers
Israel-Aina and Omoigberale Year:(2012) Country: Nigeria	Retrospective study	Risk factors for neonatal jaundice in babies presenting at the University of Benin Teaching Hospital, Benin City	• 1784 babies who admitted from January 2006 to December 2008 at Special Care Baby Unit of the University of Benin Teaching Hospital, Benin City were recruited	* Mean GA: (37.36 ±2 .80) weeks. * Mean presentation age: (3.43 ± 3.76) days; (P =0.00) *Mean maternal age: (30.44 ± 5.63) years; (P = 0.62) * Mean birth weight:(2,990± 640) gm.; (P=0.86)

				* ABO incompatibility: (7.6%) *Sepsis: (45%)
Elhissi Year:(2012) Country: Palestine	Prospective cohort study	Mother Work and Pregnancy Outcome in the Gaza Strip	• 590 pregnant women were followed up during their 3rd trimester and their neonates were examined.	* Physiological jaundice appeared in 28.1% of newborns; (31%) of working pregnant women gave birth to jaundiced infants while (27.9%) housewives gave birth to jaundiced infants.
Bilgin et al. Year:(2013) Country: Turkey	Prospective study	Factors Affecting Bilirubin Levels during First 48 Hours of Life in Healthy Infants	• 388 study infants were recruited to measure cord 24 hours' and 48 hours'. • Infants with severe problems like congenital anomaly, asphyxia, traumatic birth caused by vacuum extraction, respiratory insufficiency, infection, metabolic diseases, and hemolytic diseases (i.e., Rh & ABO incompatibility) were excluded. • GA >34 weeks	*****Without hemolytic disease ABO incompatibility: (23.96%) Rh incompatibility: (6.44%) *Feeding method Breastfeeding alone: (58.5%) Mixed feeding: (41%) Formula feeding: (0.5%) ***** Mode of delivery and feeding route had no effect on bilirubin levels during first 48 hours in healthy neonates**.** ***** Vaginally delivered mothers initiated breastfeeding earlier and needed nutritional support for their babies less frequently than mothers delivered with c/s. *Delayed first feeding and high cord bilirubin levels were related to be in higher risk zone for later hyperbilirubinemia.
Najib et al. Year:(2013) Country: Iran	Prospective cross sectional study	Incidence, Risk Factors and Causes of Severe Neonatal Hyperbilirubinemia in the South of Iran (Fars Province)	• 170 infants referred to Namazi Hospital from February 2009 to February 2010 due to severe indirect hyperbilirubinemia were included. • Age less than 28 days	* Mean BW: 3068 (526) g,ram Range: 1550-4300g * Mean time of first feeding after birth: 3.99 (9.99) hrs, Range: 0.5-72 hrs. * Mean TSB on admission: 2.059(5.81) mg/dl, Range: 42- 9.5- 42. *****Jaundice in first 24 hours after birth: (11.4%) & (73.5%) developed jaundice after discharging from hospital. *Type of delivery: NVD: (73.5%) C/S: (26.5%) Oxytocin administration: (32.4%) * History of jaundice in siblings :(27.9%) [12.4% of need phototherapy and 5.3% of them need exchange phototherapy]. *Cephalhematoma :(4.7%) *Bruising: (7.7%) Causes: * ABO and Rh incompatibility: (5.9%) [Infants born to mothers with type O blood (66.7 %)]. * Sepsis: (12%) Risk factor *History of jaundice in siblings :(P = 0.006) *Early discharge:(P = 0.035) *NVD: (P = 0.027). *Brest feeding: (P =0.038)
Yahya and Alajeely Year: (2013) Country: Iraq	Descriptive study	Incidence and Risk Factors of Hyperbilirubinemia in Neonatal in Mosul City	• 440 neonates attending the Al-Khansaa Teaching Hospital and Ibin-Sena Teaching Hospital in neonatal intensive care units throughout 28th December 2009 to the end of 28th April 2010.	*****Birth weight: Mean BW: 2.674, SD = 570.35 Range 1.750 - 4.800 Normal weight: (63%) Low birth weight :(34%) Macrosomia: (3%) * Mean TSB level: 13.67, SD = 4.801, Range 5 - 25 * RHincompatibility: (5%) *ABO incompatibility: (28%) * Breast feeding**:** (88%),(P value= 0.00) Artificial feeding: (6%) Mixed feeding: (6%) * History of jaundice in sibling: Positive history: (68%).

				Negative history: (32%). * Stepwise regression used to find factors independently associated with hyperbilirubinaemia. -Positive family history:(P value= 0.00) -Breast feeding: (P value= 0.00) -Not read and write:(P value= 0.005) -Mother age (25-35 years): (P value= 0.008) -Poor feeding:(P value=0.02)
Akgül et al., Year: (2013) Country: Turkey	Retrospective descriptive	Neonatal hyperbilirubinemia due to ABO incompatibility: does blood group matter?	• 166 cases with ABO hemolytic disease who were born to blood group O mothers and had no other predisposition to indirect hyperbilirubinemia., • Risk factors for the severity of jaundice were compared in infants with blood group A or B. • Infants with congenital anomalies were excluded.	* No statistically significant differences in hematological parameters including initial and final indirect bilirubin levels and hemolytic findings between the both blood group A or B.
Titi and El Sharif Year: (2013) Country:Palestine	Follow-up comparative study	Prenatal and postnatal care of gestational diabetes and gestational hypertension in clinics for high-risk pregnancies in the West Bank, occupied Palestinian territory	• 60 women who had gestational diabetes or gestational hypertension from Oct 1, 2010, to Jan 31, 2011, we followed up all during their pregnancy and delivery of their baby in 2009.	* Infants born to mothers with gestational hypertension or gestational diabetes: (34%); (P =0.002)
Mesic al. Year: (2014) Country: Europe	Retrospective cross sectional study	Unconjugated Pathological Jaundice in Newborns	• 800 newborns were conducted in the department of Pediatrics of the University Hospital of Osijek at the beginning of August until the end ofDecember of the same year.	* Birth order: first -born infants. (P>0.05). *Maternal infection in pregnancy: (p< 0.05). * Preeclampsia: (P >0.05). *Gestational diabetes: (P >0.05). * Mode of delivery: spontaneous :(P<0.05). * Premature rupture of the membranes: (P <0.05)
Kulkarni et al. Year: (2014) Country: India	Retrospective cross sectional study	Risk factors of neonates with indirect hyperbilirubinemia in teriary care hospital.	• 120 hospitalized neonates at department of Pediatrics of Shree Vasantrao Naik Govt. Medical College and hospital, Yavatmal from, June 09 to May10. • TSB >10 mg\dl.	* Idiopathic: (35%) *Physiological: (30%) * ABO incompatibility: (15%) * Rh incompatibility: (6.67%) * Septicaemia: (n8.33%) * Rh incompatibility: (6.66%) * Cephalhematoma: (3.33%)
Olusanya et al. Year: (2015) Country: United States	Systematic Review and Meta-Analysis	Risk Factors for Severe Neonatal Hyperbilirubinemia in Low and Middle-Income Countries	• A total of 13 studies with 1,951 subjects and 32,208 controls from India, Nigeria, Pakistan, Nepal and Egypt were studied between January 1990 and June 2014.	* Primiparity: OR= 1.59; (CI: 1.26-2.00) * ABO incompatibility: OR=4.01; (2.44-6.61) * Rhesus incompatibility: OR =20.63;(CI: 3.95-107.65) * sepsis :OR=9.15;(2.78-30.10)

Chapter 3

Methodology

3.1 Introduction

This chapter presents all aspects of research methodology used to answer the research questions. It clarify the design, study population, the sample and setting, the period of study, the process of data collection and analysis, the strategies and plans to ensure of the validity ad and reliability of study tools and instruments that will be used for data collection. Finally, the restriction of the study and ethical issues are included.

3.2 Study design

This study was quantitative approach; the design was a hospital-based case-control study was used for the purpose of achieving the objectives of the study. Case-control study has specific advantages compared to other study designs. It is relatively quick, easy, inexpensive, and generally requires few study participants. Farther it is highly appropriate to study association of a disease with multiple exposures. Case-control study is particularly appropriate to study rare diseases or outcomes (Lewalle and Courtrigh, 1998).

3.3 Study setting

The study was conducted in MOH centers. Cases were carried out within two governmental hospitals in GS; Al- Nassir pediatric hospital and Naser Medical Complex especially at NICU. Controls were chosen from two primary health centres**;** Martyrs Khanyounis clinic and Martyrs Al-Remal clinic.

3.4 Study population

The study population consisted of two groups, the first group was cases (all hospitalized newborns aged 28 days or less who were staying in NICU in the previously mentioned hospitals during the study period and having NNHas confirmed by doctor, and the second group was controls (all newborns aged from 29 to 49 days and didn't have NNHor history

of other diseases as confirmed by specialized doctor who presenting in a regular check-up post natal careof the selected two primary health canters.

The participants weren’trandomized to the exposed or unexposed groups, rather they were observed in order to determine both their exposure and their outcome status and the exposure status was thus not determined by the researcher.

3.5 Sample size and sampling process

The sample of this study was convenience sample, GS was divided into two areas; south and north, Naser Medical Complex represented the south area of Gazaand Al-Nassir Pediatric Hospital represented the north area of Gaza. The participants were collected from NICU in previously mentioned hospitals and primary health centres. The size of the sample determined using the statistical calculator of the EPI-Info software V.20, based on literature review (Annex 3.1). The sample size was 158, 79cases and 79controls with a ratio of one case to one control at (α= 0.05, power= 0.8) matching was done by gestational age, gender and geographic area. To enhance the representation of our sample we increased the sample to 180, 90 cases and 90 controls.

3.6 Period of the study

The study consumed 9 months; it started in April 2015 after the acceptance of the proposal, then conducting the administrative procedures and gaining ethical approval. Pilot study conducted in June 2015. Data collection and data entry started in July 2015 and continued to September 2015. Data analysis continued in October 2015, and writing final report continued till the end of November 2015. Annex 3.2 describes the activities of the research and duration for each activity.

3.7 Eligibility criteria

3.7.1 Inclusion criteria for cases

A Case is a neonate diagnosed as NNH as confirmed by specialized doctor from birth until age of 28 days and no history of other diseases.

3.7.2 Exclusion criteria for cases

- Neonates with age more than 28 days.

- Neonates with a history of other diseases such as RDS and birth asphyxia.

- Neonates admitted to the intensive care unit for any reason.

- Those neonates whose guardians or parents declined to give consent.

3.7.3 Inclusion criteria for controls

A control is a healthy neonate who doesn't have currently nor had a history of NNHor other diseases as confirmed by specialized doctor from 29- 49 days.

Controls were chosen from the previously mentioned primary health centers who in visit for a regular check-up and to take the first dose of plio immunization (1month). After doctor assessment, we applied the criteria for controls selection and matching done by gender, gestational age, and geographical are. For example, a case male 37weeks newborn in Naser Medical Complex matched with a control male 37weeks newborn inMartyrs khanyounis clinic.

3.8 Instrument of the study

- After reviewing previous studies and literature, the questionnaire was arranged in a logical sequence to facilitate the interview and was written in English language (Annex 3.3 & Annex 3.4). The questions were closed- ended questions.

-The questionnaire is divided into three parts and covered the following areas:

- First part about socio-demographic factors: contains information about mother age, mother education, mother occupation and family income.
- Second part is maternal factors: contains mother blood group and Rh type, parity, pregnancy disorders, delivery type, premature rupture of membranes, oxytocin drug use, and length of stay in postnatal department by hours.
- Third part about neonatal factors: includes neonate order, birth weight, cephalhematoma and bruising, previous sibling with jaundice, and feeding practices.

3.9 Validity and reliability

3.9.1 Face and content validity

The researcher submitted the questionnaire to expert's panel (Annex 3.5) with scientific knowledge and personal experience in pediatrics and neonatology and in public health to revise and evaluate its quality and to make the needed suggestions.

3.9.2 Instrument standardization

The researcher used a calculator to exactly compute the gestational age. Estimated date of delivery for cases and controls calculated from Last Menstrual Period. Using the birth date and estimated date of delivery, the calculator yields the gestational age (Annex3.6) (Medscape, 2015).

3.10 Pilot study

Pilot study conducted before starting data collection. The piloting process aiming to help in identifying problems in the research design; test data collection tools for clarity, validity, reliability, and objectivity. Further, it allows the data collectors to gain an experience in dealing with data collection instruments and participant's characteristics who will be included in the study.

Piloting performed on 20 participants, 10 cases and 10 controls were included which obtained from the selected hospitals and primary health centres.

3.11 Data collection

Data was collected using structured interviews (face-to-face interviews questionnaire). All information gathered from babies' mothers and medical records. The researcher herself filled up the questionnaire. The time for every interview to fill questionnaire was 15-20 minutes.

3.12 Data management and statistical analysis

- The collected data introduced to the computer using SPSS (Statistical Package for Social Sciences version 20).

- Statistical methods carried out as follow:

- Reviewing the records and filling out the questionnaires.
- Developing an appropriate data- entry model.

- Coding the participant data.
- Defining and recording the variables.
- Cleaning the data.
- Descriptive statistics such as frequencies, percentages, means, and SDanalysis.
- Bivariate analysis was used via person's chi-square to show if there are statistical significant associations between factors and neonatal hyperbilirubinemia such as socio-demographic factors and other factors.
- Multivariate analysis was used by binary logistic regression to determine which pure independent variables affect the probability of an outcome of NNH and results were presented with beta coefficients, AOR with CI 95% and p- value.

3.13 Ethical and administrative considerations

The researcher committed to all ethical considerations required to conduct a research which include:

- An official letter of approval to conduct the study obtained from the Helisinki Committee (Annex 3.7) and School of Public Health at Al-Quds University (Annex 3.8).
- An official letter of request obtained from the general director of MOH (Annex 3.9) and the director of Primary health centersAdministration(Annex 3.10) to conduct the study in the governmental hospitals.
- To guarantee participants rights, a covering letter indicating that the participation is voluntary and the right to refuse was preserved.
- Confidentiality was given and maintained during and after finish the study.
- Every participant in the study was provided by complete explanation about the research, purpose and benefits of the results on community health.

3.14 Limitations of the study

The obstacles of this study were as the following:

- Absence of computerized information system in MOH hospitals.
- Limited time available to conduct the study.
- Lack of local researches about the study topic.
- Limited scientific resources like books and journals.

- Few numbers of cases and difficulties of accessing matched participants in the control group.
- Frequent electricity cuts affected the ability to accomplish the work in a timely manner.
- Financial costs, self-funded study (Annex 3.10).
- Transportation.

Chapter Four

Results and Discussion

4.1 Introduction

This chapter illustrates the results of statistical analysis of the data, firstly includes descriptive analysis that presents the participants characteristics and demonstrates the variations between cases and controls thatthe researcher used descriptive statistics including frequencies and percentages. Secondary, the different risk factors socio-demographic, maternal or neonatal that contributed to the development of NNH was illustrated using advanced statistical procedures such aschi-square test. After that, multiple logistic regression model was presented to show the most important and independent risk factors.Finally, these results were discussed in comparison with literature review and related previous studies.

4.2 Descriptive analysis

4.2.1 Selected socio-demographic characteristic of the study population

The study sample consisted of 180 newborn, divided into two groups; case group consisted of 90 (50%) neonates who have NNHand control group consisted of 90 (50%)who haven't NNH.

Table (4.1): Frequencies of study population according to governorate, residence, and citizenship

Variable		Case		Control	
		N	%	N	%
Governorate	Gaza	47	52.2	47	52.2
	Khanyounis	43	47.8	43	47.8
	Total	**90**	**100**	**90**	**100**
Residence	City	31	34.4	55	61.1

	Camp	37	41.2	3	3.3
	Village	22	24.4	32	35.6
	Total	**90**	**100**	**90**	**100**
Citizenship	Non-refugee	50	55.6	86	95.6
	Refugee	40	44.4	4	4.4
	Total	**90**	**100**	**90**	**100**

Table (4.1) showed that approximately fifty two percentage (47 cases and 47 controls) were from Gaza and 86 (47.8%) (43 cases and 43 controls) were from Khanyounis. The observed equality between both cases and controls was because of matching. Concerning the living area, the researcher found that 31 (34.4%) of cases are living in cities, 37 (41.1%) are living in camps and 22 (24.4%) are living in villages compared to 55 (61.1%), 3 (3.3%), and 32 (35.6%) of controls respectively. About fifty (55.6%) from cases were non-refugee and 40 (44.4%) were refugee compared to 86 (95.6%) and 4 (4.4%) of controls respectively.

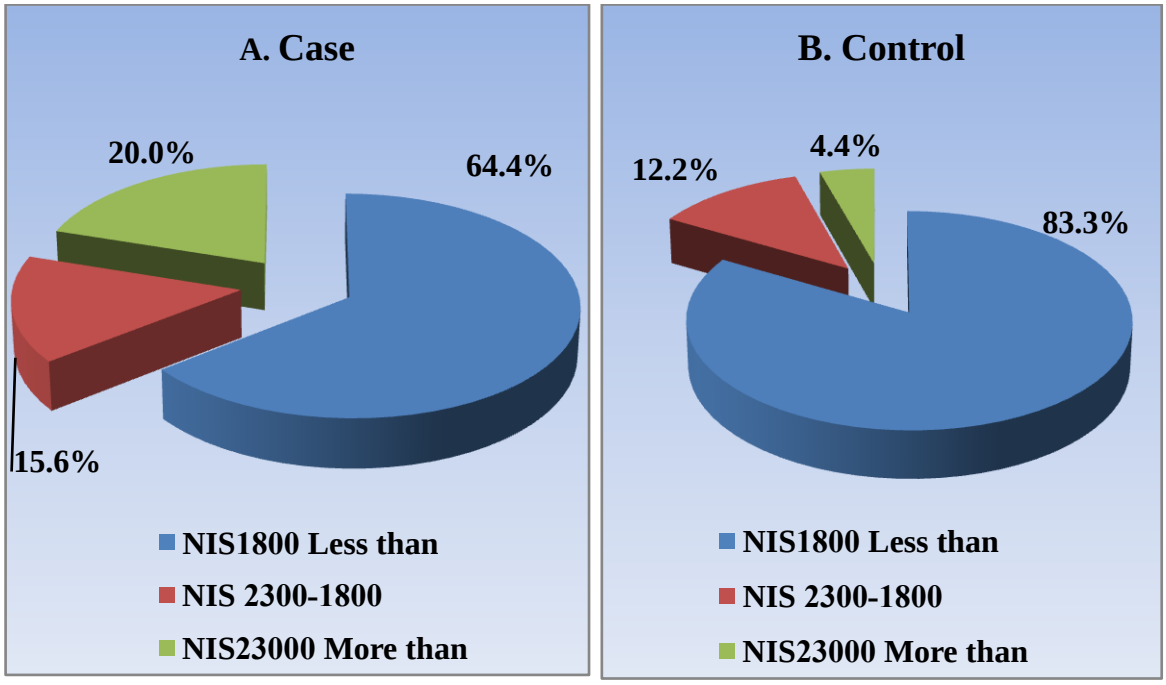

Figure (4.1): Percentage distribution of study population according tofamily income

Figure (4.1) showed that the largest percentage of the study sample their income was less than 1800 NIS; 75 (83.3%) of controls and 58 (64.4%) of cases. Fourteen (15.6%) of cases and 11 (12.2%) of controls had income from 1800 to 2300 NIS. The smallest group which

represented eighteen (20.0%) of cases and 4 (4.4%) of controls had income more than 2300 NIS.

4.2.2 Selected parents characteristic of the study population

Table (4.2): Frequencies distribution of study population according to mother age, father age, mother education, father education, and mother occupation

Variable		Cases		Control	
		N	%	N	%
Mother age	16-25 years	45	50	47	52.3
	26-35 years	35	38.9	31	34.4
	36-47 years	10	11.1	12	13.3
	Total	**90**	**100**	**90**	**100**
Father age	19-29 years	43	47.7	39	43.3
	30-39 years	32	35.6	35	38.9
	40-61 years	15	16.7	16	17.8
	Total	**90**	**100**	**90**	**100**
Mother education	Below secondary	10	11.1	8	8.9
	Secondary	38	42.2	45	50
	University	42	46.7	37	41.1
	Total	**90**	**100**	**90**	**100**
Father education	Below secondary	13	14.4	16	17.8
	Secondary	34	37.8	38	42.2
	University and higher	43	47.8	36	40.0
	Total	**90**	**100**	**90**	**100**
Mother occupation	Employed	8	8.9	3	3.3
	Unemployed	82	91.1	87	96.7
	Total	**90**	**100**	**90**	**100**

According to the table (4.2), half of cases 45 (50%) and 47 (52.2%) controls, their mother's age ranged between 16-25 years. Also, 35 (38.9%) of mother's cases and 31 (34.4%) of mother's controls were with age 26-35 years. Only10 (11.1%) of mother's cases and 12

(13.3%) of mother's controls were from 36-47 years old. Regarding father age, 43 (47.7%) who their age 19- 29 years were cases and 39 (43.3%) were controls.Also, 35 (38.9%) of fathers who their age between 30 and 39 years were controls and 32 (35.6 %) were cases. About fifteen (16.7%) of the fatherswho their age 40 -61 years were cases and 16 (17.8 %) were controls. The mean age of mothers was 26.74 ± 6.188 years while the mean age of fathers was 31.58 ± 5.18 years.

Moreover, the study results indicated that 10 (11.1%) of mothers cases and 8 (8.9%) of mothers controls were below secondary education. There were 38 (42.2%) of mothers cases and 45 (50%) of mothers controls were secondary education. University education accounted for 42 (46.7%) of mothers cases and 37 (41.1%) of mothers controls. At the same time, the results show that 13 (4.4%) of fathers cases and 16 (17.8%) of fathers controls were below secondary education. Thirty four (37.8%) of fathers cases and 38 (42.2%) of fathers controls were secondary education. Forty three (47.8%) of fathers cases and 36 (40.0%) of fathers controls were university education or higher. Regarding employment, the results shows that the majority of controls and cases were to unemployed mothers as 87 (96.7%) and 82 (91.1%) respectively. As well as, about 8 (8.9%) of cases mothers and 3 (3.3%) of control mothers were employed.

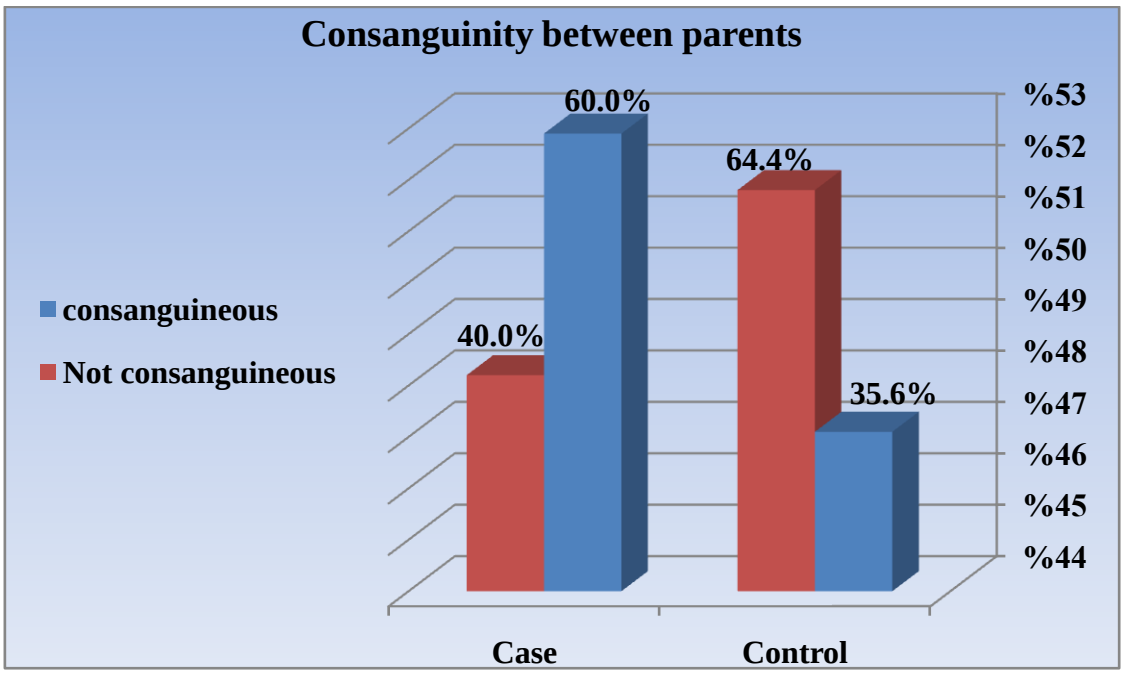

Figure (4.2): Percentage distribution of study population according to consanguinity between parents

According to the figure (4.2), the fifty four (60.0%) of cases were consanguine parents and 36 (40.0%) were not consanguine parents. On the other hand, 58 (64.4%) of controls were not consanguine parents and 32 (35.6%) of them were consanguine parents.

4.2.3 Selected neonatal characteristic of the study population

Table (4.3): Frequencies of study population according to gender, gestational age, and neonate order

Variable		Cases		Control	
		N	%	N	%
Gender	Male	51	56.7	51	56.7
	Female	39	43.3	39	43.3
	Total	**90**	**100**	**90**	**100**
Gestational age	35-36 wks.	6	6.7	6	6.7
	37-39 wks.	54	60.0	54	60.0
	40-41 wks.	30	33.3	30	33.3
	Total	**90**	**100**	**90**	**100**
Neonate order	First	25	27.8	17	18.9
	Subsequent	65	72.2	73	81.1
	Total	**90**	**100**	**90**	**100**

The table (4.3)showed that gender and gestational age were equal because of matching, there was no difference between both cases and controls. Fifty one (56.7%)of our sample was males and 39 (43.3%) were females. Alsothe table demonstrated that the highest percentage of study population 54 (60.0%) among cases and controls were 37-39 weeks, followed by gestational group 40-41 weeks which represented 30 (33.3%),and the gestational age 35-36 weeks was the smallest group which represented 6 (6.7%). The mean gestational age for the entire sample was 38.74 with SD ±1.333.

Concerning neonate order, the table (4.3) showed that the prominent group was subsequent born neonates (72.2% of cases and 81.1% of controls). The reminding group; first-born neonates were (27.8% of cases and 18.9% of controls).

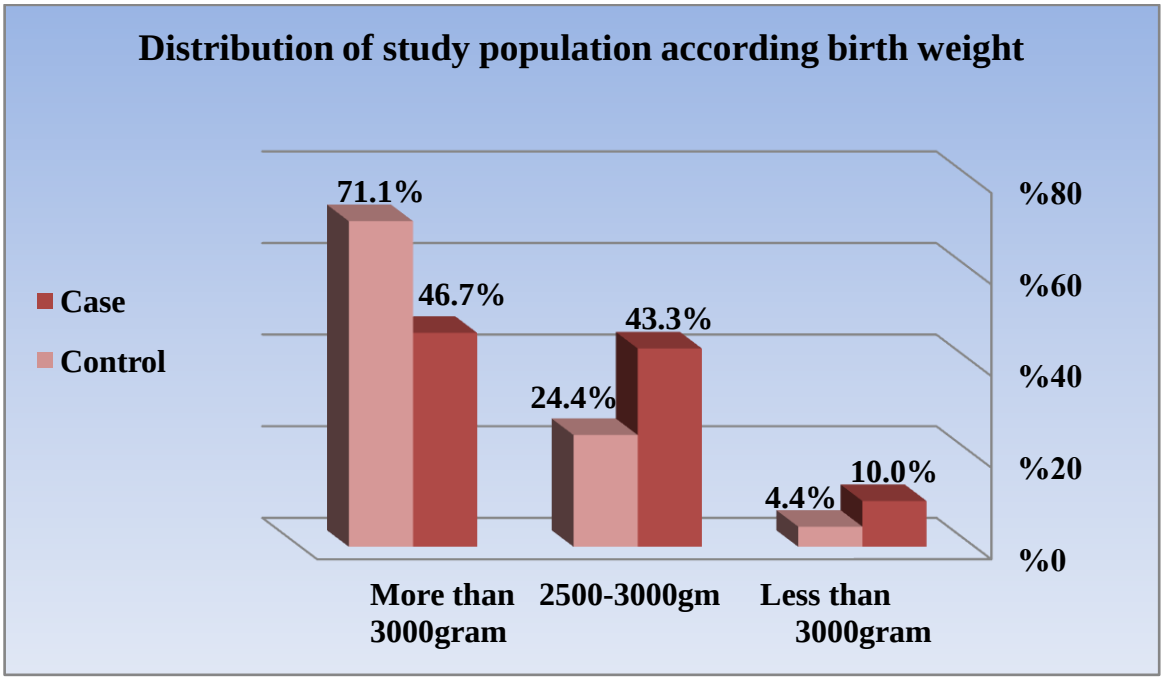

Figure (4.3): Percentage distribution of study population according to birth weight

Regarding birth weight of newborn, the figure (4.3) showedthat the highest percentage of cases (46.7%) and (43.3%), their weight were more than 3000gram and 2500-3000gram respectively. Seventy one percentage and (24.4%) of controls, their weight were more than 3000gram and 2500-3000gram respectively.Generally birth weight ranged from 1800 - 4600gram. The mean was 3214.44 with SD ±503.271.

In Najib et al. (2013) study, birth weight ranged from 1550 - 4300gram and the mean was 3068 with SD (526) gram. Furthermore, Yahya and Alajeely (2013) study revealed that birth weight ranged from1750 - 4.800gramand the mean was 2.674, SD = 570.35.

4.2.4 Distribution the characteristic of study cases

Table (4.4): Distribution of admission characteristics for the study cases

Characteristics	Range	Mean	SD
Infant age at jaundice	1 – 14 day	2.89 day	1.974 day

apparent			
Hemoglobin level	7.7 - 20.9 g/dL	14.440 g/dL	2.5887 g/Dl
RBCS	2.7 – 6.1 million/microliter	5.245 million/microliter	10.0224 million/microliter
TSB	7.5- 34.7 mg/dL	17.133 mg/dL	5.6127 mg/dL
Direct bilirubin level	0.3 – 8.6 mg/dL	1.086 mg/dL	1.0707 mg/dL

The case sample as shown in table (4.4), hemoglobin level ranged from 7.7 - 20.9 g/dL with a mean ± SD 14.440 ± 2.5887. RBCs count ranged from 2.7- 6.1 million /microliter with a mean ± SD 5.245 ± 10.0224.TSB ranged from 7.5 - 34.7 mg/dL with mean ± SD17.133 ±5.6127. Direct bilirubin level ranged from 0.3- 8.6 mg/dL with mean ± SD 1.086 ± 1.0707. First day jaundice was observed in 16 (8.9%) case. Thirty two (17.8%) of cases started jaundice in the second day and 35(19.4%) from the 3-5 day of life (table 4.4). Iskander et al. (2012) study showed that onset of the mean age of jaundiced neonates was observed at 4.1 days of life, the mean age of presentation at the hospital was 9.4 days. In Olusanya et al. (2009) study, the median age of the jaundiced infants at thetime of visiting the hospitals was 11 days.

All cases in our study received phototherapy. Exchange transfusion was used in 9 (5%) of the cases; 2 cases in Naser Medical Complex and 7 cases in Al-Nassir Pediatric Hospital. Two cases had signs of kernicterus and 2 cases had dysmorphic features (Down syndrome).

Henny-Harry and Trotman (2012) study showed that the mean ± SD age of admission was 1.8 ± 2.4 days.Neonatal jaundice was noted on day 1 to 2 in most cases (119; 70%).Concerning total serum bilirubin, Yahya and Alajeely (2013) study showed that it rangedfrom 5 – 25 md/ dL with mean 13.67 and SD = 4.801.

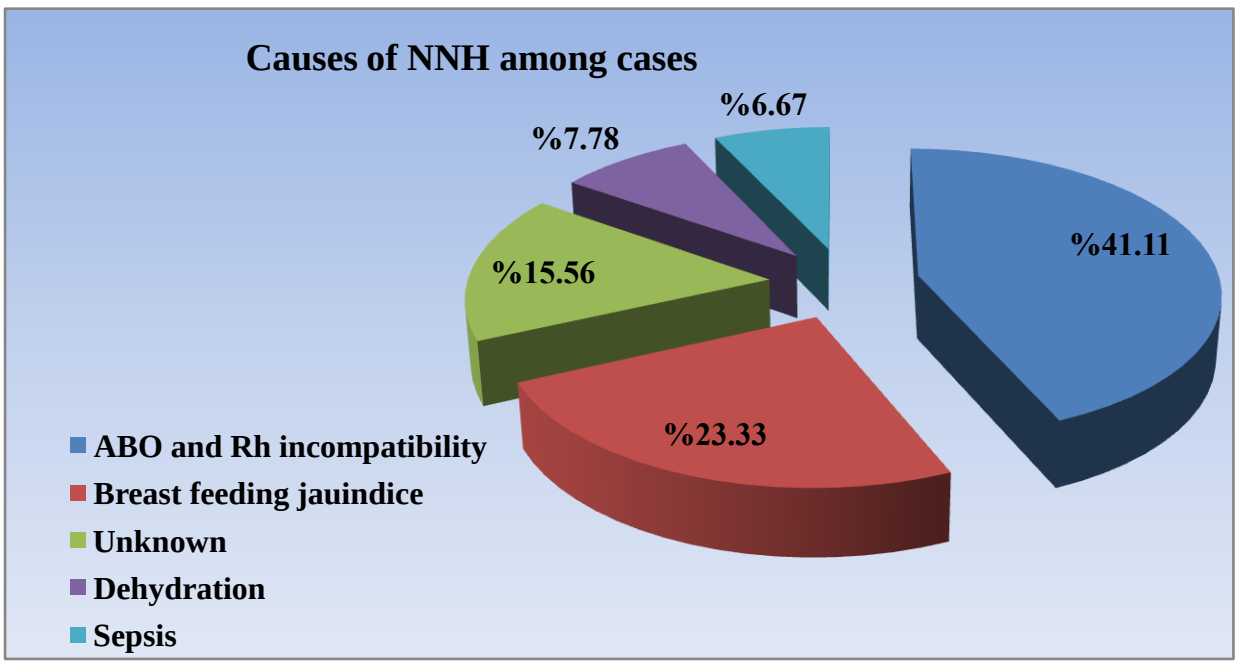

Figure (4.4): Percentage distribution of study cases according to causes of NNH

As shown in figure (4.4), the prominent cause for the development of NNHwas ABO and Rh incompatibility (41.11%), followed by breastfeeding jaundice (23.33%) and in (15.56%), the cause was unknown. Dehydration represented (7.78%), while sepsis reached (6.67%).

There wasa consensus between our results and international studies that the risk of developing NNHis higher in infants with ABO and Rh incompatibility. Henny-Harry and Trotman (2012) study founded that ABO incompatibility percentage was (35%) similarly to Bhat and Kumar (2012) study which showed that ABO incompatibility was observed in (17.3%). Furthermore, Heydarian and Majdi (2010) study explained that the most common cause of exchange transfusion was ABO incompatibility (38.1%) and Rh incompatibility (16.1%). Moreover, Elhissi (2012) stated that physiological jaundice appeared in (28.1%) of newborns. In addition, Yahya and Alajeely (2013) study showed that ABO incompatibility was (28%), RH incompatibility: (5%) and breast feeding percentage reached (88%), (P value = 0.00). Finally, Kulkarni et al.(2014)study showed that idiopathic cause for jaundicerepresented (35%), Physiological was (30%), while ABO incompatibility reached (15%) and Rh incompatibility was (6.67%), and (8.33%)was septicemia.

4.3 Inferential statistics

4.3.1 Bivariate analysis

4.3.1.1 Risk factors of Neonatal Hyperbilirubinemia

4.3.1.1.1 Socio-demographic variables

The researcher supposed that the socio-demographic variables of the participants may play a role as predisposing risk factors of hyperbilirubinemia among neonates. These variables include mother age, mother education, mother occupation and family income.

Table (4.5): Association between socio-demographic factors and neonatal hyperbilirubinemia among case and control group

Variable		Cases		Control		$\chi 2$	*p* value
		N	%	N	%		
	16-25 years	45	50	47	52.3		0.791

Mother age	26-35 years	35	38.9	31	34.4	0.468	
	36-47 years	10	11.1	12	13.3		
	Total	**90**	**100**	**90**	**100**		
Mother education	Below secondary	10	11.1	8	8.9	1.129	0.569
	Secondary	38	42.2	45	50		
	University	42	46.7	37	41.1		
	Total	**90**	**100**	**90**	**100**		
Mother occupation	Employed	8	8.9	3	3.3	2.421	0.120
	Unemployed	82	91.1	87	96.7		
	Total	**90**	**100**	**90**	**100**		
Family income	<1800NIS	58	64.4	75	83.3	11.442	**0.003***
	1800-2300 NIS	14	15.6	11	12.2		
	>2300NIS	18	20.0	4	4.4		
	Total	**90**	**100**	**90**	**100**		

*P value ≤0.05

Table (4.5) showed that there was no statistically significant effect of mother age on the risk for NNH($\chi 2$ = 0.468, P value = 0.791). These findings were supported by the results of both Israel-Aina and Omoigberale (2012) and Kavehmanesh et al. (2008) studies which explained that mother age didn't differ between the jaundiced and non- jaundiced babies as (P value = 0.45) and (P value = 0.62) respectively. On the other hand, Henny-Harry and Trotman (2012) study founded that mother age ranged from 16 to 46 years with a mean of 29.4 ± 6.3. The mean age of mothers was 28.0 ± 5.18 years that (88%) of mothers age were between 20 – 35 years old in Olusanya et al. (2009) study. The researcher observed that absence of significant association could be attributed high rate of early marriage in our society or type of the study.

The same table showed that there was no significant association between NNHand mother education($\chi 2$ = 1.129, P value = 0.569).Iskander et al. (2012) study agreed with our findings which explained that (75.4%) of the mothers' cases were literate and (24.6%) were illiterate. These results inconsistent with Yahya and Alajeely (2013) study which showed a significant relationship between mother educational level and hyperbilirubinemia with high proportion not read and write. Absence of significant association could be attributed to that the Palestinian population highly educated.

Also the results showed that there was no significant association between mother occupation and NNH($\chi 2$ = 2.421, P value = 0.120). Ng and Chong (2014) study revealed that approximately half of the mothers were housewives (53.0%) while (40.4%) were working and Iskander et al. (2012) study explained that (42.3%) of cases mothers were

working and (57.7%) of them non-working. On the other side, Olusanya et al. (2009) study showed incongruent results that infants of mothers without full-time employment were significantly less likely to have severe NNHthan those with fully employed mothers. These incongruences may be due to high rates of unemployment in the Palestinian society which reached (23%) for those 15 years of age or older in 2012 (MOH, 2014).

With regard to family income, there was a statistically significant association between family income and NNH ($\chi 2 = 11.442$, P value = 0.003).These results are incongruent with Olusanya et al. (2015) meta-analysis study which examined the role of social class on severe hyperbilirubinemia that the results did not show any significant association (Pvalue = 0.090). Also, Ng and Chong (2014) study verified that the mean family income was not associated with an increased risk of severe hyperbilirubinemia (Pvalue = 0.682).

4.3.1.1.2 Maternal variables

The researcher supposed that the maternal variables may play a role as predisposing risk factors for NNHamong newborns. These variables include parity, mother's blood group and Rh type, pregnancy disorders, PROM, oxytocin use, delivery type and discharged from postnatal department.

Table (4.6): Association between maternal factors among case and control group

Variable		Cases		Control		$\chi 2$	*p* value
		N	(%)	N	(%)		
Para	1-2	46	51.1	38	42.2	1.825	0.402
	3 –4	24	26.7	25	27.8		
	More than 4	20	22.2	27	30.0		
	Total	**90**	**100**	**90**	**100**		
Mother's blood group type	O	52	57.8	25	27.8	17.248	**0.001***
	A	21	23.3	33	36.7		
	B	11	12.2	24	26.7		
	AB	6	6.7	8	8.9		
	Total	**90**	**100**	**90**	**100**		
Mother's Rh type	Positive	75	83.3	82	91.1	2.443	0.118
	Negative	15	16.7	8	8.9		
	Total	**90**	**100**	**90**	**100**		
PROM	< 24hrs	86	95.6	83	92.2	0.871	0.351
	>24hrs	4	4.4	7	7.8		

	Total	**90**	**100**	**90**	**100**		
Oxytocin use	Yes	24	26.7	27	30.0	0.246	0.620
	No	66	73.3	63	70.0		
	Total	**90**	**100**	**90**	**100**		
Delivery type	Vaginal	67	74.5	74	82.3	1.832	0.400
	Caesarean	20	22.2	13	14.4		
	Vacuum	3	3.3	3	3.3		
	Total	**90**	**100**	**90**	**100**		
Discharge from maternity department	< 6hrs.	56	62.2	63	70.0	1.523	0.467
	6 – 24hrs.	19	21.1	17	18.9		
	>24 hrs.	15	16.7	10	11.1		
	Total	**90**	**100**	**90**	**100**		

*P value ≤0.05

Table (4.6) showed that half of mothers cases 46 (51.1%) were para 1-2, twenty four (26.7%) of them were para 3-4, and 20 (22.2%) had more than 4children. Our results even though showed that parity had no statistical significant association withNNH($\chi 2$ = 1.825, P value = 0.402). These results were congruent with Henny-Harry and Trotman (2012) study which revealed that (54%) of mothers was primiparous, (39%) were para 1–2, and (7%) were para 3–6. Similarly, Iskander et al. (2012) study showed that (67.7%) of patients mother were primipara and (32.3%) were multipara. Also, Olusanya et al. (2015) study, which cleared that primiparity with (OR, 1.59, 95% CI: 1.26 - 2.00).

On the other hand, Ng and Chong (2014) study revealed a large proportion of the mothers were multiparous with (61.6%) having 2 to 5 children and (8.1%) having more than 5 children. This inconsistency may be referred to the study type or the sample size.

According to the results in table (4.6), P value reached the high statistical significant difference between mother's blood groupsamong the study groups of cases and controls and NNH ($\chi 2$ = 17.248, P value =0.001).But, there was no statistical significant association between mother's Rh type and NNH ($\chi 2$ = 2.443, P value = 0.118).These results show that the prominent mother's blood group among cases was O (57.8%). The percentages of mothers with blood group A were (36.7%, 23.3%) and B were (26.7%, 12.2%) for both controls and cases.

These results agreed with Henny-Harry and Trotman (2012) study which founded that the highest percentageof mothers had blood group O (66%) and 20 (12%) had Rh negative mothers. Furthermore, Najib et al. study (2013) showed that the percentage of infants born to mothers with type O blood was (66.7 %).

On the other hand, in Kavehmanesh et al. (2008) study, the results showed that there were no significant effect of maternal blood groups ; O (reference group), A, B, and AB on jaundice as [(OR: 1.14, 95% CI: 0.53 -2.45), (OR: 1.06, 95% CI: 0.67-1.66), and (OR: 1.17, 95% CI:0.69 - 1.98)] respectively, but Rh-negative mothers had more jaundiced infants (17.9%) compared with Rh-positive mothers (12%) (P value = 0.01).This inconsistency may be referred to the study type and the sample size or that our study is case control that compared commonly with cross sectional studies.

Table (4.6) also indicated that the duration of membranes rupture had no statistical significant association with NNHamong the both groups of cases and controls ($\chi 2 = 0.871$, P value = 0.351).Like our findings, Kavehmanesh et al. (2008) study revealed that premature rupture of membrane was in (11.4%)of the cases which not reached to the statistically significant level; (P value = 0.7), but Mesic et al. (2014) study confirmed an association between the onset of jaundice in newborns and their mothers with premature rupture of membrane; (P value < 0.05).

In additionally, table (4.6) showed no statistical significant association between oxytocin use and NNH ($\chi 2 = 0.246$, P value = 0.620). Our study finding in relation to oxytocin use was congruent to Kavehmanesh et al. (2008) study which revealed that oxytocin used in (34.5%) of the cases which not reached to the statistically significant level; (P value =0.4). On the other hand, Buchan (1979) illustrated that infant born after oxytocin-induced labor had an increased plasma bilirubin concentration (P value < 0.001) than others. Also, Chalmers et al. (1975) study revealed that infants born after oxytocin administration became jaundiced with significant higher risk (P value < 0.000001) than others.

Moreover, table (4.6) showed that association between neonatal hyperbilirubinemia and delivery type ($\chi 2 = 1.832$, P value = 0.400), so we accepted the null hypothesis and rejected an alternative hypothesis (There was no difference between the delivery vaginally or by c/s and the risk to deliver baby had risk to NNH).

This result agreed with Wood et al. (1979) study which mentioned that no effect of type of delivery on NNH. Moreover, Bertini et al. (2001) study showed no statistically significant correlation between jaundice and delivery by neither vaginal delivery (P value= 0 .67) nor cesarean section (P value= 0 .79).

On the other hand, our result disagreed with Dubal and a Joshi (2012) study which showed that a positive, statistically significant correlation between high TSB and delivery by vacuum extractor (Pvalue = 0.001). Additionally, Mesic et al. (2014) study revealed that jaundice is more common in newborns that were born by stimulating or inducing labor than in those born spontaneously (Pvalue< 0.05). Moreover, Friedman et al. (1978) study showed that neonates with jaundice delivered by ventouse extraction reached to statistically significant level (P value< 0.001). This inconsistency in these results may be due to small sample size and/or the type of this study as most of previous studies were cross-sectional ones in comparison to this case-control study.

The above table (4.6) additionally showed that the time of discharge from postnatal department had no effect on the occurrence risk of NNH ($\chi 2 = 1.523$, P value = 0.467). The findings related to length of stay in postnatal department congruent to Maisels and Kring (1998)study which showed that infants whose length of stay was < 48 hours were at no greater risk for readmission for jaundice or other causes than those whose length of stay was ≥ 48 hours to < 72 hours; [length of stay < 48 hours (OR, 2.40; CI: 1.09 - 5.30) and 48 to < 72 hours (OR: 3.15, CL: 1.40 - 7.09) versus ≥ 72 hours], but discharge at any time < 72 hours significantly increases the risk for readmission to hospital and the risk for readmission with hyperbilirubinemia when compared with discharge after 72 hours.

On the other hand, Escobar et al. (2005)studyshowed that newborns, whose stay was less than 72 hours, were at a significantly greater risk for readmission than those who had longer stays. Furthermore, Kavehmanesh et al. (2008) study mentioned that mean (SD) length of primary nursery stay was 30.2 (23.9) hours. Mean neonatal stay in jaundiced babies was 30.6 (2.5) hours, but in non-jaundiced babies was 27.7 (9.8) hours, that is significantly longer in non-jaundiced infants (P value < 0.001). This inconsistency may be because of exaggerated rates of delivers in our society in relation to the shortage in bed numbers so, almost all infants delivered by vaginal method leave the hospital before6 hours of birth.

Table (4.7): Association between pregnancy disorders as maternal factors among case and control group

Variable		Cases		Control		$\chi 2$	*p* value
		N (%)		N (%)			
Pregnancy disorders	Yes	66	73.3	79	78.8	5.994	**0.014***
	No	24	26.7	11	12.2		
	Total	**90**	**100**	**90**	**100**		
Gestational diabetes	Yes	2	2.2	5	5.6	1.338	0.247
	No	88	97.8	85	94.4		
	Total	**90**	**100**	**90**	**100**		
Pregnancy induced hypertension	Yes	8	8.9	13	14.4	1.348	0.246
	No	82	91.1	77	85.6		
	Total	**90**	**100**	**90**	**100**		
Urinary tract infection	Yes	41	45.6	50	55.6	1.800	0.180
	No	49	54.4	40	44.4		
	Total	**90**	**100**	**90**	**100**		
Vaginal infection	Yes	35	38.9	35	38.9	0.000	1.000
	No	55	61.1	55	61.1		
	Total	**90**	**100**	**90**	**100**		
Anemia	Yes	36	40	57	63.3	9.811	**0.002***
	No	54	60.0	33	36.7		
	Total	**90**	**100**	**90**	**100**		
Perinatal hemorrhage	Yes	10	11.1	7	7.8	0.585	0.445
	No	80	88.9	83	92.2		
	Total	**90**	**100**	**90**	**100**		

*P value ≤0.05

Table (4.7) cleared that pregnancy disorders showed statistically significant association with NNH ($\chi 2$ = 5.994, P value = 0.014). Most study population their mothers had pregnancy disorders, which represent (73.3%) of cases and (78.8%) of controls.Of these disorders; gestational diabetes, pregnancy induced hypertension, urinary tract infection, vaginal infection, and perinatal hemorrhage indicated no statistical significant association

with NNH among both cases and controls group as [(χ2 = 1.338, P value = 0.247)], [(χ2 = 1.348, P value =0.246)], [(χ2 = 1.800, P value =0.180)], [(χ2 = 0.000, P value =1.000)], [(χ2 = 0.585, P value =0.445)] respectively. Only anemia as pregnancy disorder showed statistical significant association with NNH (χ2 = 9.811, P value = 0.002).

These results were consistent with Al-Khalifah et al. (2012) study which showed that newborns of gestational diabetic mothers wasn't significantly different in comparison with normal mothers [(OR= 1.02, 95% CI: 0.95-1.10); p value = 0, 55]. Also Bertini et al. (2001) study showed that there is no statistically significant except correlation between jaundice onset and maternal diabetes (6.6%); (P value= 0 .59). In addition, Mesic et al. (2014) study showed that (8 out of 34) jaundiced newborn, their mothers reported no statistically significant association between diabetes mellitus or gestational diabetes and NNH(P value>0.05), additionally, there was no statistically association between jaundice and preeclampsia, (P value >0.05). Moreover, Bertini et al. (2001) study explained that there was no statistically significant correlation between jaundice onset and maternal hypertension (5.4%), (P value = 0.75).

Some studies wereinconsistent with our findings as in Al-Hakeem study (2006)which revealed that the gestational diabetic mothers of neonates with hyperbilirubinemiawere (41.2%) compared to (6.4%) for neonates of non-diabetic mother. Moreover, Mesic et al. (2014) study explained a statistically significantdifference between jaundice onset and maternal infection during pregnancy (P value < 0.05). Also, Titi and El Sharif(2013) study mentioned that infants born to mothers with gestational hypertension or gestational diabetes: (34%); (Pvalue = 0.002).This inconsistency in these results may be due to small sample size and/or the type of previous studies was cross-sectional ones in comparison to this case-control study.

4.3.1.1.3 Neonatal variables

The researcher supposed that the neonatal variable of the participants may play a role as predisposing risk factors of hyperbilirubinemia in neonates. These variables include; neonate order, birth weight, cephalhematoma and bruising, history of previous sibling with jaundice, and feeding practices**.**

Table (4.8): Association between neonatal factors and hyperbilirubinemia among study population

Variable		Cases		Control		$\chi 2$	P Value
		N	%	N	%		
Neonate order	First	25	27.8	17	18.9	1.988	0.159
	Subsequent	65	72.2	73	81.1		
	Total	**90**	**100**	**90**	**100**		
Birth weight	<2500g	9	10.0	4	4.4	11.227	**0.004***
	2500-3000	39	43.3	22	24.4		
	>3000g	42	46.7	64	71.1		
	Total	**90**	**100**	**90**	**100**		
Cephalhematoma	Yes	1	1.1	1	1.1	0.000	1.000
	No	89	98.9	89	98.9		
	Total	**90**	**100**	**90**	**100**		
Bruising	Yes	0	0.0	2	2.2	2.022	0.155
	No	90	100	88	97.8		
	Total	**90**	**100**	**90**	**100**		
Previous sibling with jaundice	Yes	30	33.3	26	28.9	0.415	0.520
	No	60	66.7	64	71.1		
	Total	**90**	**100**	**90**	**100**		

*P value ≤0.05

The above table showed that there was a statistically significant association between birth weight and NNH ($\chi 2$ = 11.227, P value = 0.004). The highest percentage of babies with birth weight more than 3000gm were (71.1%) for control in comparison with (46.7%) for cases.Our results consistent with Olusanya et al. (2015) study, in which underweight/weight loss was statistically associated with NNH(OR, 6.26; 95% CI: 1.23-31.86). Moreover, Friedman et al., (1978) study reported that there was significantly association between neonatal jaundice and birth weight (P <0.001).On the other hand, Kavehmanesh et al.(2008) study revealed that mean (SD) neonatal birth weight was 3301.1 (395) grams in jaundiced babies and 3303.5 (385.9) in non- jaundiced babies] that there was no statistically significant association between groups (P value = 0.41).

Add to that, table (4.8) showed that there was no significant association between neonate order and NNHamong the both groups of cases and controls ($\chi 2 = 1.988$, P value = 0.159). These finding were congruent with Mesic et al. (2014) study which showed that jaundice was most common in first-born infants; (98 out of 341) jaundiced neonate were first-born infants, but the association not reached to statistically significant level (P value > 0.05). On the other side, Dubal and Joshi (2012) study revealed that birth order was found to be associated (P value < 0.05) with level of TSB in neonatal jaundice. This inconsistency may be referred that most of previous studies were cross-sectional ones in comparison to this case-control study.

In addition, table (4.8) showed that there was no significant association between cephalhematoma or bruising and NNH as [($\chi 2 = 0.000$, P value = 1.000)] and[($\chi 2 = 2.022$, P value = 0.155)] respectively. These results agreed with Hung (2004) who showed that cephalhematoma and bruising weren't statistically significant risk factor identified with the univariate logistic regression models [(AOR: 7.39, 95% CI: 0.84–64.66; P value = 0.071)]. On the other hand, Bertini et al. (2001) study demonstrated statistically significant positive correlation was found between hyperbilirubinemia and cephalohematoma; (P value <0.001). Add to that, Kuzniewicz et al. (2008) study explained that bruising doubled the risk of severe hyperbilirubinemia (AOR = 2.36; 95%CI = 1.17 - 4.77). This inconsistency in these results may be due to small sample size and/or the type of this study and the compared studies. Also may be this due to rare occurrence of cephalohematoma or bruising in neonates.

The above table also indicated that newborn who had a history of previous sibling with jaundiceshowed no statistically significant association with NNH ($\chi 2 = 0.415$, P value = 0.520). Our results were inconsistent with the literature review as in Kuzniewicz et al. (2008) study which revealed that a family history of jaundice appeared to increase the risk of severe hyperbilirubinemia by almost 4 fold (AOR = 3.83; 95% CI = 0.93 - 15.7). This inconsistency in these results may be due to characteristic of our sample and its identity that other factors may be theprominent risk for NNH.

Table (4.9): Association between neonate feeding practices and neonatal hyperbilirubinemia among study population

Variable		Cases		Control		$\chi 2$	P value
		N	%	N	%		
Feeding method	Exclusive	67	74.4	30	33.3	40.895	**0.000***
	Bottle	6	6.7	1	1.1		
	Mixed	17	18.9	59	65.6		
	Total	**90**	**100**	**90**	**100**		
Feeding initiation time	First hour	29	32.2	62	68.9	24.973	**0.000***
	2-4 hours	47	52.2	24	26.7		
	More than 4hours	14	15.6	4	4.4		
	Total	**90**	**100**	**90**	**100**		
Feeding difficulty	Yes	49	54.4	16	17.8	26.223	**0.000***
	No	41	45.6	74	82.2		
	Total	**90**	**100**	**90**	**100**		
Feeding frequency	On demand	26	28.9	66	73.4	43.304	**0.000***
	Every 2-3hrs.	36	40.0	22	24.4		
	More than3hrs.	28	31.1	2	2.2		
	Total	**90**	**100**	**90**	**100**		
Number of wet diapers / 24 hours	0-1	12	13.3	3	3.3	8.006	**0.018***
	2-4	72	80.0	74	82.3		
	5-7	6	6.7	13	14.4		
	Total	**90**	**100**	**90**	**100**		

*P value ≤ 0.05

Table (4.9) showed an association between feeding practices in neonates and NNH. According to the results, there was highly statistically significant association between feeding method had statistically significant association with NNH as ($\chi2$ = 40.895, P value = 0.000). Approximately seventy five of cases and (33.3%) of controls had exclusive feeding compared with (65.6%) of controls and (18.9%) of cases had mixed feeding. Feeding initiation timealso in table (4.9) showed that feeding initiation time had statistically significant association with NNH($\chi2$ = 24.973, P value = 0.000).The highest percentage (68.9%) of controls initiated their feeding immediately after delivery within the firsthour compared with (32.2%) of controls.

According table (4.9), the percentage of cases and controls who had feeding difficulty were (54.4%) and (17.8%) respectively that this reached tostatistically significant association with NNH occurrence as ($\chi2$ = 26.223, P value = 0.000).Regarding feeding frequency, the same table explained that (73.4%) of controls and (28.9%) of cases had feeding on demand which reached a statistically significant level($\chi2$ = 43.304, P value = 0.000). Finally, the results of (4.9) table showed statistically significant association between jaundice and number of wet diapers/ 24 hours ($\chi2$ = 8.006, P value = 0.018).

The previous study findings mostly agreed with our findings. Heydarian and Majdi (2010) study explained that the majority of jaundiced neonates fed breast milk exclusively (57.6%), (26.3%) fed breast milk and formula,(11%) took formula alone, (P value = 0.000). Moreover, Saigal et al. (1982) study showed that mean TSB were significantly higher in the breast-fed infants than formula-fed infants on each postnatal day (P value < 0.001). Also, Najib et al. (2013) study revealed that the time of first feeding of jaundiced cases was 3.99 (9.99) hours after birth (Min: 0.5 hour, Max: 72 hours). Thirty three neonates (18.8%) had poor feeding irritability and letharginess on admission when started 4.65(6.58) hours after birth (Min: 1hr, Max: 24 hours).

On the other side, Bertini et al. (2001) study demonstrated a statistically significant positive correlation between patients with a TSB>12.9mg/dL and supplementary feeding [refers to infants who were breastfed and received additional formula supplements.] (13.1%), (P value <0.001) with mean 478 (22%); oppositely, breastfeeding showed negative correlation between patients with a total serum bilirubin concentration >12.9 mg/dL (221 mmol/L) (2.7%), (P value <0.001) with mean 1595 (73.4%).

4.3.2 Multivariate analysis

Multiple logistic regression analysis was employed to predict the probability that a neonate less than 28 days would suffer from hyperbilirubinemia. Bivariate analysis applied to all participants and which have statistical significance association with hyperbilirubinemia were selected as predictors. They were: family income, mother's blood group type, pregnancy disorders, maternal anemia, birth weight, feeding method, feeding initiation time, feeding difficulty, feeding frequency, and number of wet diapers / 24 hours.

Table (4.10): Final model of risk factors for neonatal hyperbilirubinemia in Gaza Strip

Variables		B Coefficient	Adjusted OR (95% CI)	P value
Family income	less than 1800 NIS	**3.150**	**23.345 (2.083-261.688)**	**0.011***
	1800 – 2300 NIS	2.580	13.192 (0.881-197.565)	0.062
	More than 2300 NIS®			
Mother's blood group type	O	- 0.118	0.889 (0.061-12.966)	0.931
	A	0.775	2.170 (0 .122-38.634)	0.598
	B	- 0.813	0.443 (0.029-6.681)	0.557
	AB®			
Pregnancy disorders	Yes	0.647	1.909 (0.317-11.506)	0.480
	No®			
Maternal anemia	Yes	**1.683**	**5.383 (1.035-27.998)**	**0.045***
	No®			
Birth weight	<2500g	-2.254-	0.105 (0.009-1.266)	0.076
	2500-3000g	**-2.144-**	**0.117 (0.028-0.498**	**0.004***
	>3000g®			
Feeding method	Exclusive	**-4.089-**	**0.017 (0.003-0.093)**	**0.000***
	Bottle	**-5.182-**	**0.006 (0.000-0.141)**	**0.002***

	Mixed®			
Feeding initiation time	First hour®			
	2-4 hrs	-1.216-	0.296 (0.081-1.085)	0 .066
	More than 4hrs	**-3.088-**	**0.046 (0.004-0.586)**	**0.018***
Feeding difficulty	Yes	**-2.543-**	**0.079 (0.019-0.328)**	**0.000***
	No®			
Feeding frequency	On demand®			
	Every 2-3hrs.	**-2.223-**	**0.108 (0.026-0.448)**	**0.002***
	More than 3 hours	**-5.842-**	**0.003 (0.000-0.045)**	**0.000***
Number of wet diapers / 24 hrs.	0-1	-2.383-	0.092 (0.002-3.646)	0.204
	2-4	-1.838-	0.159 (0.015-1.667)	0.125
	5-7®			

The dependent variable is neonatal hyperbilirubinemia N= 180. This model is correctly specified and didn't have omitted relevant variables. Multiple Logistic Regression, ®Reference group, *P value ≤0.05

Table (4.10) showed the final model of risk factors for NNHafter adjusting the odd ratio. The results showed that the newborns who had families with more than 2300 NIS have increased odds of having NNH 13.192 times than families who had 1800 – 2300 NIS which was marginal significant and the newborns who had families with more than 2300 NIS have increased odds of having NNH 23.345 times than families who had less than 1800 NIS which was statistically significant.

The probability of NNH occurrence among neonates their mothers hadn't anemia was 5.383times than neonates their mothers had anemia which reached the statistically significant level. This mean that infants who their mothers hadn't pregnancy disorders had higher risk for NNH development.

The newborns with birth weight less than 25000gram have decreased the odds (0.105) of having NNH than newborns with birth weight more than 3000gram that was marginal significant and newborns with birth weight 2500-3000gram have decreased the odds (0.117) of having NNH than newborns with birth weight more than 3000gram that reached the statistically significant level.This means that the probability of NNH development was higher in neonates less than 3000gram.

Neonates who had exclusive and bottle feeding methods have decreased odds of having NNH by 0.017and 0.006 times respectively than neonates who had mixed feeding. Also, newborns who had feeding difficulty have decreased odds of having NNH by 0.079 times than newborns who didn't. This mean positive association between feeding difficulty and increase risk for NNH.

The probability of NNHdevelopment was significantly lower among neonates who had their feeding on demand. The odds of NNH occurrence was lower among neonates who had their feeding on demand compared to neonates who fed every 2-3 hours (OR0.108).This means that infants who fed on demand had lower risk (negative association) for development NNH.

The probability of NNHdevelopment was significantly lower among neonates who initiated their feeding immediately within 1 hour of delivery. The odds of NNH occurrence was 0.046.In other meaning, there was negative (protective) association between early feeding initiation and the risk of NNH occurrence.

On the other hand, mother's blood group type, pregnancy disorders and number of wet diapers/24 hours weren't significant predictors of development NNH development as shown in table (4.10).

Our results were consistent with others international literature. In Scrafford et al. (2013) study showed that the exclusive breastfeeding and difficulty feeding significantly associated with jaundice. A significant interaction between exclusive breastfeeding and difficulty feeding was observed (P value for interaction= 0.006) among infants with difficulty feeding, exclusive breastfeeding showed an increased risk of jaundice [RR = 1.28 (95% CI: 0.89–1.84)]. However, among infants with no report of difficulty feeding, exclusive breastfeeding was protective [RR = 0.72 (95% CI: 0.58– 0.88)].

Also, Hung (2004) study showed that breast feeding was statistically significant risk factor related to NNH identified with the univariate logistic regression models [AOR:4.60. 95% CI:2.40 - 8.81; ($P < 0.001$)] and similarly, multivariate logistic regression models adjusted for the breast feeding confirmed the statistical significance of these factors [AOR:4.64. 95% CI: 2.25–9.57; ($P < 0.001$)]. Additionally, Kuzniewicz et al. (2008) study

demonstrated in their multivariate model that infants who exclusively breast-fed after their qualifying TSB had an AOR of 2.03 (95% CI = 1.03 to 3.99),

Chapter Five

Conclusion and Recommendations

5.1 Conclusion

This study aimed to identify the main risk factors which are associated to hyperbilirubinemia among hospitalized neonates in Gaza governorates. A case-control study was undertaken to hospitalized newborns in Naser Medical Complex and Al- Nassir pediatric hospital and neonates attending Martyrs Khanyounis clinic and Martyrs Al-Remal clinic. The target population consisted of two groups, the first group were cases (all hospitalized newborns aged 28 days or less who were staying in NICU in the previously mentioned hospitals during the study period and having NNH as confirmed by doctor), the second group were controls whoall newborns aged from 29 to 49 days and don't have NNH or history of other diseases as confirmed by specialized doctor that presenting in a regular check-up post natal care of the selected two primary health canters. A convenience sample was consisted of 180 newborn (90 cases and 90 controls) matched with gender, gestational age, and geographical area. A validated questionnaire was distributed to all 180 neonates during July and September 2015.

The study population consisted of 180 newborn, 90 (50%) were cases and 90 (50%) were controls. Ninety four (52.5%) (47 cases and 47 controls) were from Gaza and 86 (47.8%) (43 cases and 43 controls) were from Khanyounis. Fifty one (56.7%) from males were cases and the same were controls, thirty nine (43.3%) from females were cases and the same were controls.

Among socio-demographic factors; bivariate test was used by person's chi-square, the results showed that there was a significant association between hyperbilirubinemia and family income ($\chi2 = 11.442$, P value = 0.003).Other factors were statistically insignificant risk factors for developing hyperbilirubinemia including mother age, mother education and mother occupation as ($\chi2 = 0.468$, P value = 0.791), ($\chi2 = 1.129$, P value = 0.569), and ($\chi2 = 2.421$, P value = 0.120) respectively.

The results of bivariate test using person's chi-squarerevealed that there was a significant association between maternal factors and NNH such as mother's blood group type as ($\chi2 = 17.248$, P value = 0.001).Among overall pregnancy disorders; the results showed that it had a statistically significant association with hyperbilirubinemia ($\chi2 = 5.994$, P value =

0.014). Of these disorders, anemia revealed statistically significant association ($\chi2 = 9.811$, P value = 0.002). Other factors were statistically insignificant risk factors for developing hyperbilirubinemia including: gestational diabetes, pregnancy induced hypertension, urinary tract infection, vaginal infection, and perinatal hemorrhage as [($\chi2 = 1.338$, P value = 0.247)], [($\chi2 = 1.348$, P value =0.246)], [($\chi2 = 1.800$, P value =0.180)], [($\chi2 = 0.000$, P value =1.000)], [($\chi2 = 0.585$, P value =0.445)] respectively. The remindingmaternal factors were statistically insignificant risk factors for developing hyperbilirubinemia which include parity, Rh type,PROM, oxytocin use, delivery type, and discharge from postnatal department as ($\chi2 = 1.825$, P value = 0.402), ($\chi2 = 2.443$, P value = 0.118), ($\chi2 = 0.871$, P value = 0.351), ($\chi2 = 0.246$, P value = 0.620), ($\chi2 = 1.832$, P value = 0.400), and ($\chi2 = 1.523$, P value = 0.467)respectively.

Among neonatal factors; the results of bivariate test by person's chi-squarerevealed that there was statistically significant association between birth weight and ($\chi2 = 11.227$, P value = 0.004). Other factors were statistically insignificant risk factors for developing hyperbilirubinemia including neonate order ($\chi2 = 1.988$, P value = 0.159), cephalhematoma and bruising [($\chi2 = 0.000$, P value = 1.000)] and [($\chi2 = 2.022$, P value = 0.155)] respectively, and previous sibling with jaundice ($\chi2 = 0.415$, P value = 0.520).

Also, feeding practices as neonatal factors were explained by bivariate test, a significant association with NNHand as: feeding method ($\chi2 = 40.895$, P value = 0.000), feeding initiation time ($\chi2 = 24.973$, P value = 0.000), feeding difficulty ($\chi2 = 26.223$, P value = 0.000), feeding frequency ($\chi2 = 43.304$, P value = 0.000), and number of wet diapers/ 24 hours ($\chi2 = 8.006$, P value = 0.018).

Multivariate analysis of risk factors for hyperbilirubinemia among neonates aged less than 28 years was done using multiple regression to show the important and independent factors. Results showed that there was a significant association between development of NNH and family incomegroups; > 2300 NIS (reference group) and < 1800NIS [(AOR: 23.345, 95% CI: 2.083-261.688); P value = 0.011], maternal anemia [(AOR: 5.383, 95% CI: 1.035-27.998); P value = 0.045], birth weight groups; > 3000gram (reference group) and 2500 - 3000gram [(AOR:0.117, 95% CI:0.028-0.498); P value =0.004]. All feeding practices showed statistically significant association with NNH occurrence except number of wet diapers / 24 hours as following: feeding method groups; exclusive [(AOR: 0.017, 95% CI: 0.003-0.093); P value = 0.000], bottle [(AOR: 0.006, 95% CI: 0.000-0.141); P

value = 0.002], and mixed (reference group), feeding initiation timegroups 1st hour (reference group)and more than 4 hours [(AOR: 0.046, 95% CI:0.004-0.586); P value = 0.018], feeding difficultygrouped as yes [(AOR: 0.079, 95% CI:0.019-0.328); P value = 0.000], and no(reference group) , lastly feeding frequencywhich grouped to: on demand (reference group), every 2-3 hours[(AOR: 0.108, 95% CI:0.026-0.448); P value = 0.002], and more than 3 hours [(AOR: 0.003, 95% CI:0.000-0.045); P value = 0.000].

5.2 Recommendations

In the light of the study results, the researcher suggests the following recommendations:

1. Enforce using evidence base risk assessment chart (Nomogram) for all delivered neonates before discharge which is effective method in stratification babies and predicting highly risk newborns thereforeapplying effective and appropriate prevention measures and follow up.
2. Routinely monitoring TcB for all delivered neonates before discharge to identify infants at risk for NNH.
3. A automatically cord blood drown for all newborns born to mothers with the blood type O or Rh negative to measure blood group, Rh type, Coombs test, and cord bilirubin level.
4. Evaluate all breastfeeding mothers by a lactation consultant during their delivery hospitalization and give needed health education.
5. Conduct a special continuous health education programs and give information for mothers and/or care takers upon discharge to increase their awareness about the risks of hyperbilirubinemia.
6. Encourage effective feeding practices and adopting programs to enhance babies feeding practices among mothers.
7. Paying special attention to pregnant women about the importance of nutritional diet, closing monitoring to alleviates risk delivery of low birth weight baby.

5.3 Suggestions for further studies

- To conduct cost effectiveness studies on ongoing screening for all delivered neonates in relation to decrease the readmission and morbidity rates.

- To carry out a study regarding adherence to effective feeding practices and their impact on NNH development.

- To study in depth the relationship between mother blood group and Rh type and risk for NNH.

- Further studies emphasize on additional risk factors and causes not explored yet such as G6PD, congenital hypothyroidism, and Infant Error Of Metabolism.

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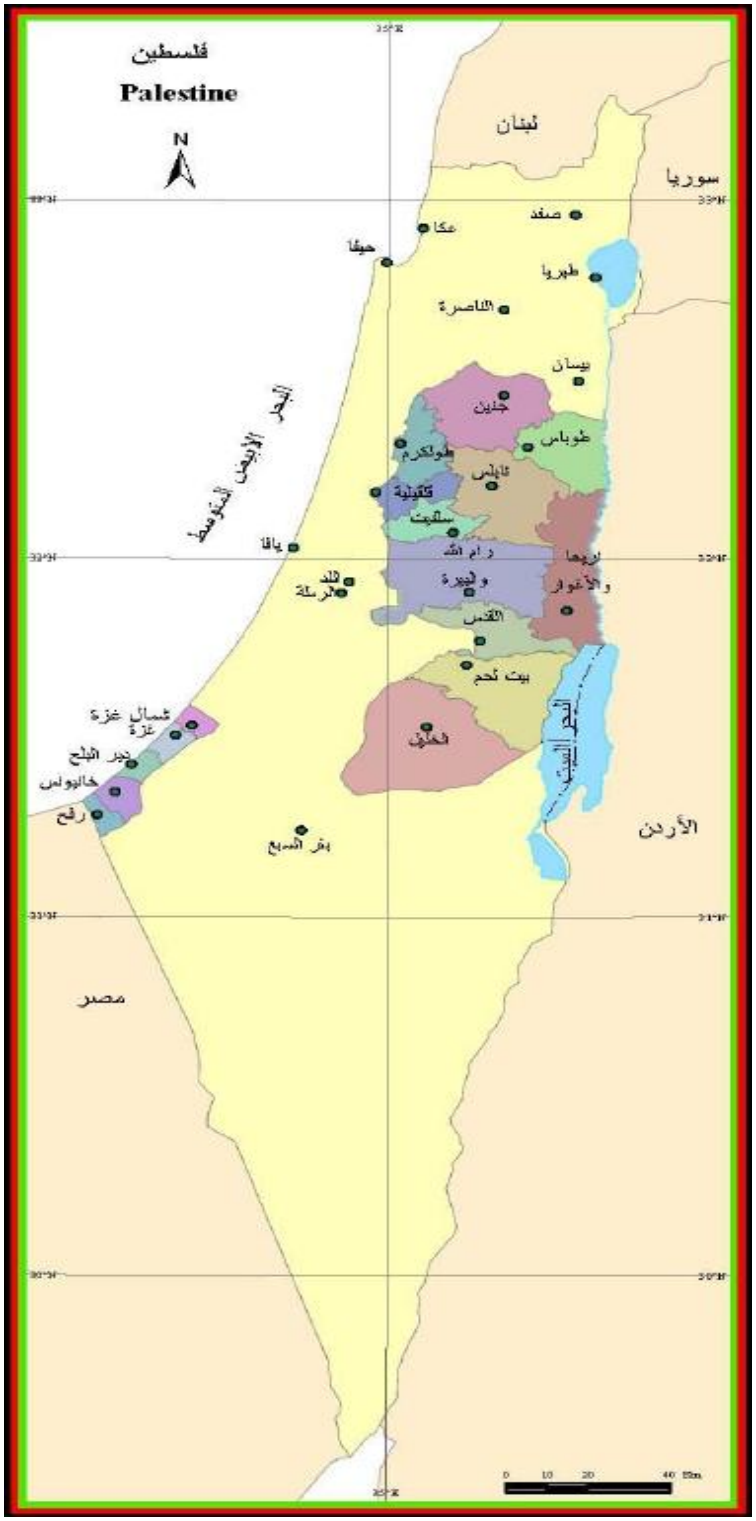
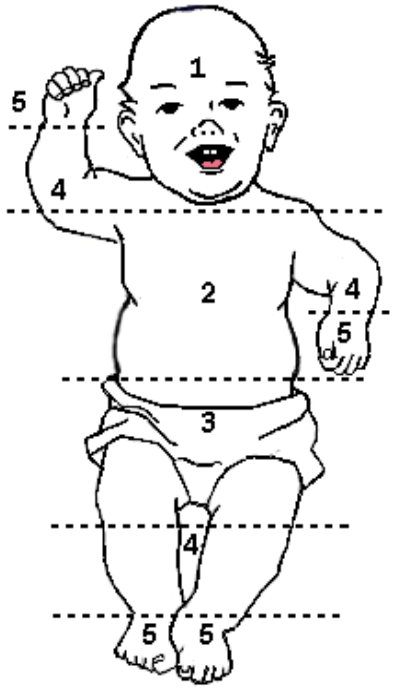
Annexes

Annex (1.1): Map of Palestine



PCBS, 2014

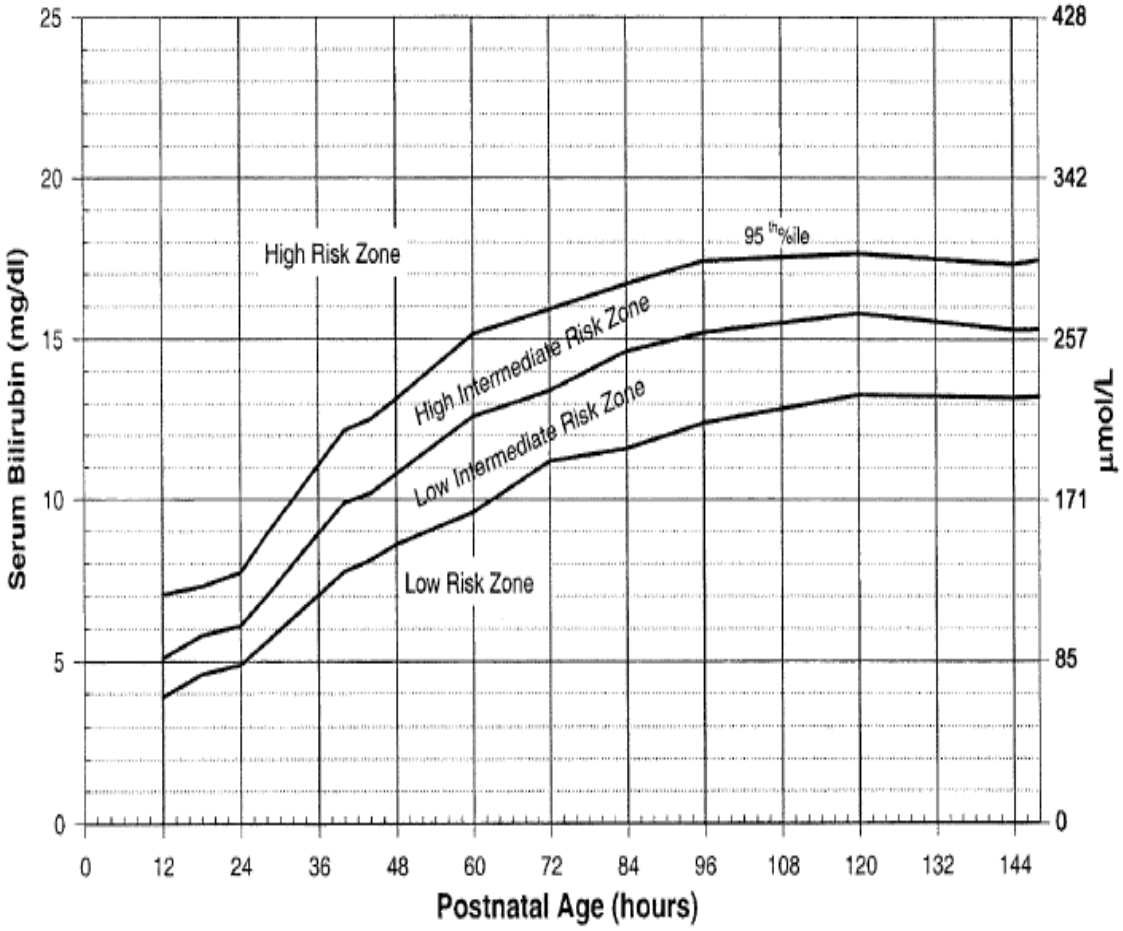
Annex (2.1): Kramer's Rule



Zone	1	2	3	4	5
Definition	Head and neck	Upper trunk	Lower trunk and thighs	Arms and lower legs	Palms and soles
TSB (micromol/L)	100	150	200	250	>250

(Queensland Maternity and Neonatal Clinical Guidelines Program, 2009**)**

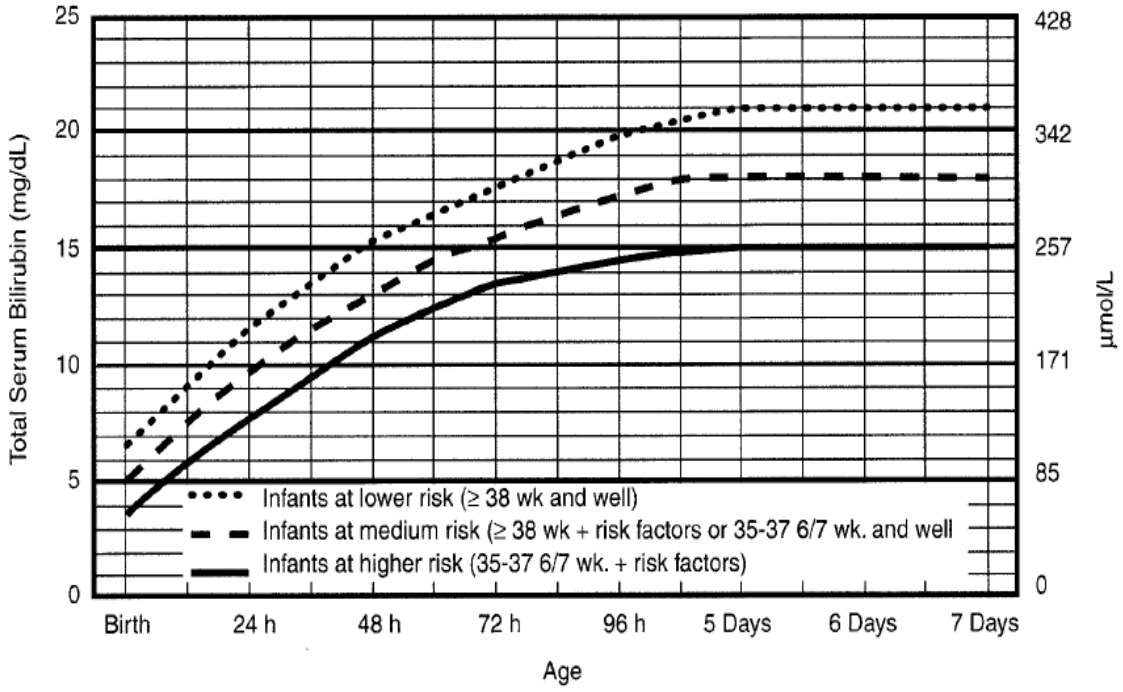
Annex (2.2): Nomogram for designation of risk in newborns



Nomogram for designation of risk in well newborns at 36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values. The serum bilirubin level was obtained before discharge, and the zone in which the value fell predicted the likelihood of a subsequent bilirubin level exceeding the 95th percentile (high-risk zone).

(AAP, 2004a)

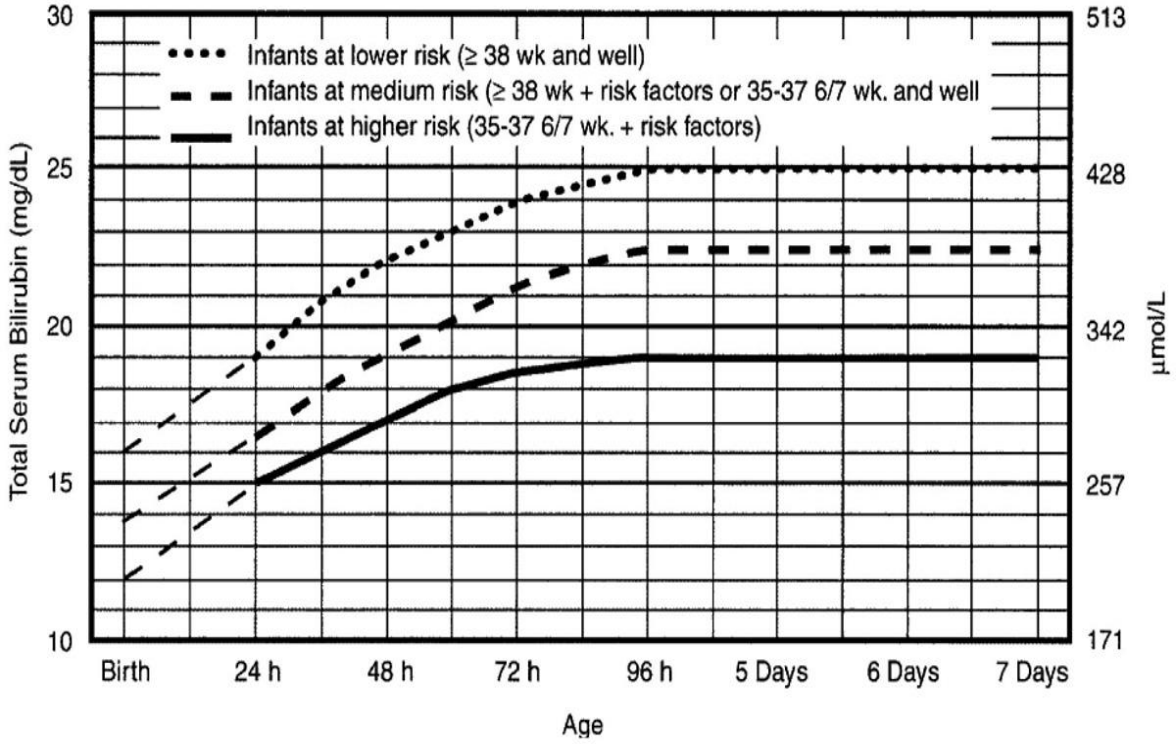
Annex (2.3): **Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation**



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

(AAP, 2004a)

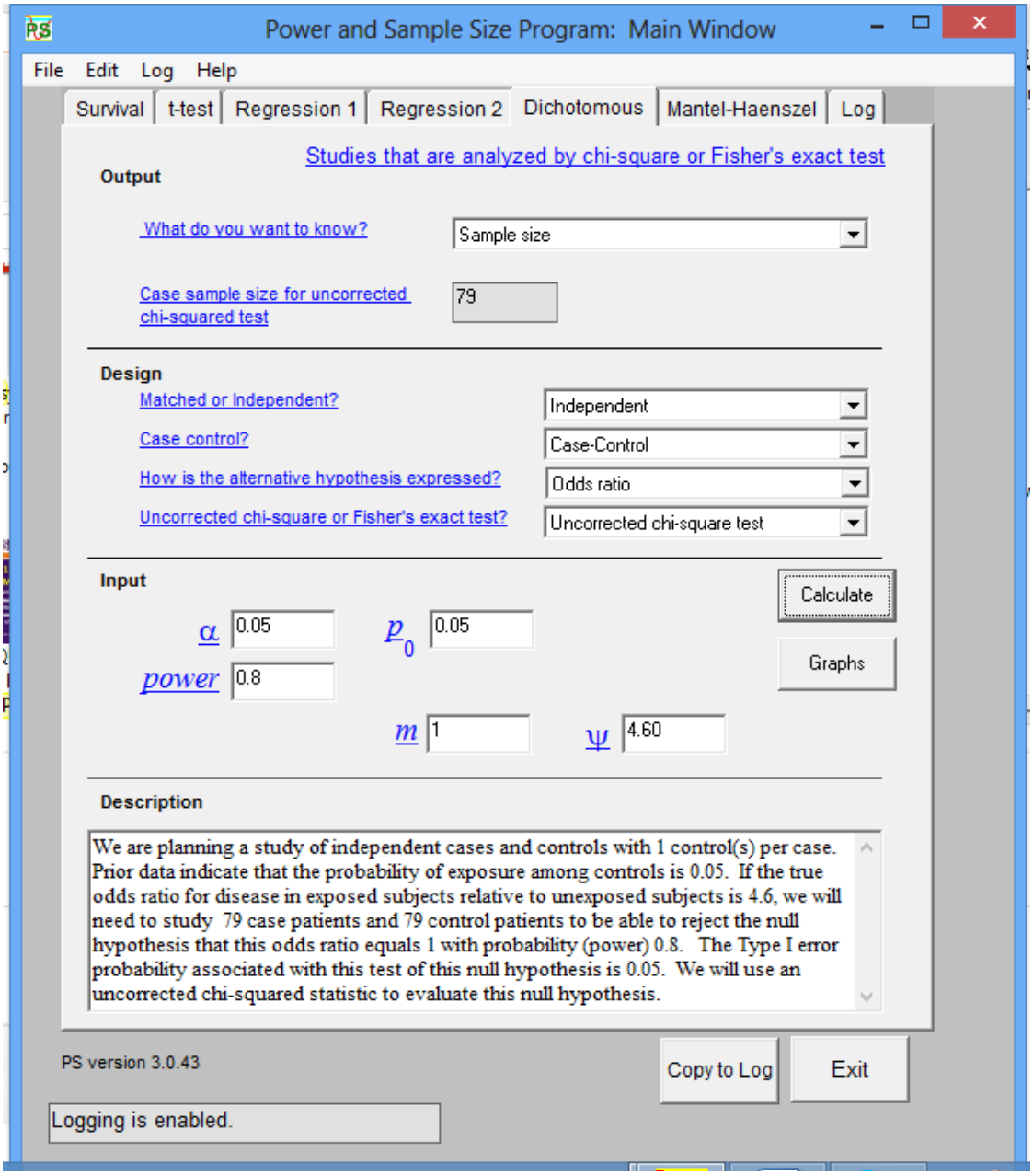
Annex (2.4): Guidelines for exchange transfusion in infants 35 or more weeks' gestation



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 µmol/L) above these lines.
- Risk factors - isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (See legend)
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

(AAP, 2004a**)**

Annex (3.1): Sample size calculation



Annex (3.2): Study activities time table

Activity	Duration	3	4	5	6	7	8	9	10	11
Proposal writing	1 month									
Proposal defense and approval	1 month									
Expert committee check for validity of instruments	1 month									
Pilot Study	2 weeks									
Modifications	2 weeks									
Data Collection	3 months									
Data Entry	3 months									
Data Analysis	2 months									
Research writing	2 months									

Annex (3.3): Interviews questionnaire(English copy)

Cover Letter

Risk Factors of Hyperbilirubinemia among Admitted Neonates in Gaza Governorates: Case Control Study

Our participant:

This study is carried out by the researcher as a part of the requirements for master degree of public health at Al-Quds University, School of Public Health-Palestine. The study is self-funded.

Kindly, I would like to inform you that your child has been selected to be part of my study research **" Risk Factors of Hyperbilirubinemia among Admitted Neonates in Gaza Governorates: Case Control Study"**. You are selected because you have met the selection criteria for participation and your facility has been thoroughly selected as a source of data by filling a well and comprehensive questionnaire.

The purpose of this study is to investigate the main risk factors that contribute to neonatal hyperbilirubinemia among admitted neonates in Gaza Governorates.

The researcher thankfully appreciates your effective participation in this study through answering the interviewer's questions that don't take more than 15 minutes. The researcher would like to emphasize that all the data given from your side is top confidential and only for the purpose of scientific research. Accordingly, we will not need to mention names. Although I welcome your participation, participation is optional and no information given would be used against you whatsoever.

Thanking you in advance for your cooperation

Researcher

Safaa Abu Mostafa

Mobile: 0592430253

Interviews Questionnaire

Serial Number:	**File Number:**
Date of interview: ……/…../2015	**Date of admission:** ……/…../2015
Place of admission:□ Nasser medical complex □ Al- Nasser pediatric hospital	
Participant:□ Case □ Control	
1. Socio-demographic Information	
1.1 Address:……	**1.2 Telephone/mobile:**……..…
1.3 Date of birth: …./……/2015	**1.4 Father's status:**□ Alive □ Ill □ Dead
1.5 Mother age:□□years	**1.6 Father age:**□□years
1.7 Mother's educational level: □ Illiterate □ Primary □ Preparatory □ Secondary □ University □ Higher than University	
1.8 Father's educational level:□ Illiterate □ Primary □ Secondary □ University □ Higher than University	
1.9 Mother's work: □ Employed □ Unemployed **1.10 If employed, what is the type of work?** …….	
1.11 Is there relation between parents?□ Yes □ No	
1.12 If (Yes), what the degree of relation?□ First degree □ Second degree	
1.13 Governorate:□Gaza □ Khanyounis	**1.14 Citizenship:**□Refugee□Non-refugee
1.15 Residence:□City □ Camp □Village	**1.16 Monthly income:**□□□□□ NIS
2. Maternal Factors	
2.1 Medical history:	
2.1.1 What is mother's blood group? □ A □ B □ O □ AB	
2.1.2 What is mother's Rh type?□ Positive □ Negative	
2.1.3 Did you have history of any type of hepatitis?□ Yes □ No **2.1.4** If (Yes), which the type? ……..	
2.2 Past obstetric history	
2.2.1 Is this your first pregnancy?□ Yes □ No	
2.2.2 If (No), answer the following: …… Gravidity …… Para	
2.3 Present obstetric history	

2.3.1 Did you have any disorder associated with the last pregnancy? Yes No

2.3.2 If (Yes), circle the appropriate:

Gestational diabetes Pregnancy Induced Hypertension

Urinary tract infection Vaginal infection

Perinatal hemorrhage Anemia

Others, specify…….

2.3.3 For how long did your membranes ruptured before delivery?

< 18hrs 18hrs - 24hrs >24hrs

2.3.4 Was oxytocin used during labor? Yes No

2.3.5 Which type of delivery did you have?

Vaginal delivery Caesarean Section Instrumental delivery: Vacuum

2.3.5 The outcome of this pregnancy: Single Twins Triplet Quadruplet

2.4 Feeding practices

2.4.1What is the feeding method?

Exclusive breast feeding Bottle feeding Mixed Others, specify……

2.4.2 When did you initiate feeding? Hr.

2.4.3 How many times has the baby been usually fed?

On demand Every 2-3 hours More than3 hours

2.4.4 Did your baby have feeding difficulty before admission? Yes No

2.4.5 How many wet diapers usually have been changed within 24 hours? Diapers.

2.4.6 When did you discharged from maternity department?

< 6h 6 - 24hr 25-48hr 49-72hr >72hr

2.4.7 Had any history of newborn's previous sibling with jaundice? Yes No

3. Neonatal Factors

3.1 General information

3.1.1 Gender: Male Female	**3.1.2 Neonate age on admission:** Days
3.1.3 Gestational age: wks.	**3.1.4 Birth weight:** gm.

3.1.5 Neonate order:

3.1.6 How old was the baby when you first noticed jaundice? Day

3.1.7 Cause of jaundice:

□ ABO incompatibility □ Rh incompatibility □ Breast-feeding jaundice □ Breast-milk jaundice □ Dehydration □ Prematurity □ UTI □ Sepsis □ Birth asphyxia □ G6PD deficiency □ Liver disease □ Hypothyroidism □ Idiopathic (Unknown) □ Others, specify…...…….
3.1.8 Neonate treatment:□ Increase feeding □ Stop breast feeding □ Phototherapy □ Exchange blood transfusion □ Others, specify ……[Antibiotics, IV fluid, blood transfusion, Intravenous Immunoglobulin (IVIG) or phenobarbital].
3.2 Laboratory findings:
3.2.1 Neonate's blood group:□ A □ B □ O □ AB □ Unavailable
3.2.2 Neonate 's Rh type:□ Positive □ Negative □ Unavailable
3.2.3 Bilirubin level on admission: a. Total**: ……..** mg/dl □ Serum □ Transcutaneous b. Direct**: …..……..** mg/dl□ Not measured c. Indirect**: …..……..** mg/dl□ Not measured
3.2.4 Complete blood count on admission: a. Hemoglobin level ……..…. g/dl □ Not measured b. Total WBC count …… c. Total RBC count…….. d. Total platelet count …….
3.2.5 Direct coombs test : □ Positive □ Negative □ Unavailable
3.2.6 Peripheral blood film:□ Normal □ Abnormal □ Unavailable
3.2.7 Urine analysis:□ Positive □ Negative □ Unavailable
3.2.8 Urine culture:□ Positive □ Negative □ Unavailable
3.2.9 Blood culture:□ Positive □ Negative □ Unavailable
3.3 physical examination:

3.3.1 Temperature on admission:□°C	**3.3.2 Dysmorphic features?** □ Yes □ No
3.3.3 Umbilical infection?:□ Yes □ No	**3.3.4 Bruising after birth?**□ Yes □ No
3.3.5 Cephalhematoma after birth?□ Yes□No	**3.3.6 Kernicterus signs?** □Yes □ No

Annex (3.4): Suggested interviews questionnaire(Arabic copy)

إستبيان المقابلة

عزيزتى الام, مرحبا

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

عوامل الخطر التى تؤدى إلى اليرقان لدى الاطفال حديثي الولادة في محافظات غزة

يسعدني موافقتك على المشاركة بالاستبيان, وأرجو التكرم بالإجابة على جميع اسئلة الاستبانة, مع العلم أن مشاركتك هذه الدراسة طوعية, كما أن البيانات التي سيتم جمعها سيتم استخدامها لغرض البحث العلمي فقط, يرجى الإجابة على الأسئلة بكل امانة وصدق و لا داعى لكتابة الاسم

هذه الاستبانة سوف تستغرق حوالى 15 دقيقة لاستكماله، مهما كانت المعلومات التي تعطيها سوف تبقى سرية وطي الكتمان ولن يطلع عليها أحد باستثناء الباحث.

اشكرك حسن تعاونك

الباحثة: صفاء أبو مصطفي

رقم المحمول:0592430253

الإسبيانة

رقم الملف:	**الرقم التسلسلى:**
تاريخ الدخول: ...\...\ **2015**	**تاريخ المقابلة:** ...\...\ **2015**
مكان الدخول: مجمع ناصر الطبي مستشفى النصر للأطفال	
المشارك : مريض سليم	
1. المعلومات الاجتماعية و الديموغرافية	
1.1العنوان:.....	2.1 **رقم الجوال:**.....
3.1 تاريخ الولاده: : ...\...\ **2015**	**4.1حالة الأب:** سليم مريض متوفي
5.1 عمر الأب: سنه	**6.1 عمر الأم:** سنه
7.1 مستوب تعليم الأم: أمي ابتدائي إعدادي ثانوي جامعة أعلي من الجامعة	
8.1 مستوي تعليم الأب: أمي ابتدائي إعدادي ثانوي جامعة أعلي من الجامعة	
9.1 عمل الأم: تعمل لا تعمل **10.1إذا كانت الأم تعمل، ماهو نوع العمل؟**.....	
11.1هل يوجد صلة قرابة بين الأب والأم: نعم لا **12.1إذا كانت الإجابة نعم, ماهي درجه صلة القرابة؟** درجة أولي درجة ثانية	
13.1 **المحافظة:** غزة خانيونس	**14.1المواطنة:** مواطن لآجئ
15.1الإقامة: مدينة مخيم قرية	**1.16 الدخل الشهرى بالشيكل:** شيكل
2. العوامل المتعلقة بالأم	
1.2التاريخ الطبي:	
1.1.2 ماهي فصيلة دم الأم؟ A B O AB	
2.1.2 ما هو العامل الريزيسي للأم؟ إيجابي سلبي	
3.1.2هل لديك تاريخ من أي نوع من أنواع التهاب الكبد؟ نعم لا **4.1.2إذا كانت الإجابة نعم, ماهو النوع؟**.....	
2.2 تاريخ الولادة الماضي	
1.2.2هل هذا حملك الأول؟ نعم لا **2.2.2 ذا كانت الإجابة لا، حددي عدد ما يلي:** حمولات ولادات	
2.2 تاريخ الولادة الحالي	
1.2.2 هل لديك أي اضطراب المرتبطة بالحمل الماضي؟ نعم لا 2.2.2 **إذا كانت الإجابة نعم, ضع دائرة حول الإجابة الصحيحة:** سكري الحمل ضغط الحمل التهابات المسالك البولية الالتهابات المهبلية نزيف ما قبل الولادة نزيف ما بعد الولادة فقر الدم أخرى، حددي	
3.2.2 ما المدة التي استمر فيها تمزق الغشاء المحيط بالجنين قبل الولادة ؟	

□<18 ساعة □ 18-24 ساعة □> 24 ساعة

4.2.2 هل تم استخدام الطلق الصناعي خلال الولادة؟

□نعم □ لا

5.2.2 ما هو نوع الولادة؟

□ ولادة مهبلية طبيعية □ عملية قيصرية □ولادة بالأدوات: الشفط.

6.2.2 ماهي نتيجة الحمل الأخير؟

□طفل واحد□ توأم □ ثلاثة توائم □ أربعة توائم

3.2 ممارسات التغذية

1.3.2 ماهي طريقه تغذيتك لطفلك ؟

□رضاعة طبيعية حصرية □رضاعة بالزجاجة □ مختلطة □ أخرى، حددي.....

2.3.2 متي كانت أول محاوله لتغذيه طفلك؟□ساعة

2 .3.3 كم عدد المرات التي يتم فيها تغذية طفلك عادة؟

□ على الطلب □كل 2-3 ساعات □ أكثر من 3 ساعات

2 **.4.3 هل عاني طفلك من صعوبة بالتغذية؟**□ نعم □ لا

2 .5.3 كم عدد الحفاظات الرطبة التي يتم تغييرها خلال 24 ساعة عادة؟ □ حفاظة

2 .6.3 ماهي المدة الزمنية التي مكثت بها في قسم الولادة قبل الخروج؟

□< 6 ساعات □6- 24 ساعة □25- 48 ساعة □ 49 - 72 ساعة □> 72 ساعة

2 .7.3 هل كان هناك تاريخ مرضي لإخوة سابقين مع اليرقان؟ □نعم □ لا

3. عوامل متعلقة بالطفل

1.3 معلومات عامة:

1.1.3 الجنس:□ ذكر □ أنثي	**2.1.3 عمر الطفل عند الدخول:**□ يوم.
3.1.3الوزن عند الولادة:□□□□ جم.	**4.1.3 العمر الرحمي(سن الحمل)عند الولادة:** □□أسبوع

4.1.3 ترتيب الطفل : □

5.1.3 كم كان عمر الطفل عند أول ملاحظه لليرقان؟ □ يوم.

6.1.3سبب اليرقان:

□ عدم توافق فصيلة الدم □عدم توافق العامل الرايزيسي□ يرقان الرضاعة الطبيعية
□ يرقان لبن الأم □الجفاف □ الخداج
□إلتهاب المسالك البولية □الإنتان (إلتهابات الدم) □اختناق الميلاد
□ نقص انزيمG6PD□ أمراض الكبد □نقص إفراز الغدة الدرقية
□ مجهول السبب □ أخرى، حدد .....

7.1.3العلاج:

□ زيادة تغذية □ وقف الرضاعة الطبيعية
□ العلاج بالضوء □ تبادل نقل الدم
□ أخرى، حدد ..... [المضادات الحيوية، السائل الوريدي، ونقل الدم، الغلوبولين المناعي الوريدي (IVIG) أو الفينوباربيتال].

2.3 النتائج المخبرية:

1.2.3 **فصيلة دم الطفل:** □ A □ B □ O □ AB □ غير متوفر

2.2.3**العامل الريزيسي للطفل:** □إيجابي □ سلبي □غير متوفر

3.2.3 مستوى البيليروبين عند الدخول: أ. المجموع : .... ملغ / دل □ المصل □ عبر الجلد□ غير مقاس ب. مباشر: .... ملغ / دل ج. غير المباشر: ... . ملغ / دل	
4.2.3 تعداد الدم الكامل على الدخول: أ. مستوى الهيموجلوبين ..... غ / دل□ غير مقاس ب. مجموع عدد كرات الدم البيضاء ..... ج. مجموع عدد كرات الدم الحمراء ..... د. مجموع عدد الصفائح الدموية	
5.2.3 اختبار كومبس المباشر: □ إيجابي □ سلبي □ غير متوفر	
6.2.3 فيلم الدم: □ طبيعيي□ غير طبيعي□ غير متوفر	
7.2.3تحليل بول:□ إيجابي □ سلبي □ غير متوفر	
8.2.3 مزرعة بول:□ إيجابي □ سلبي □ غير متوفر	
9.2.3 مزرعة دم:□ إيجابي □ سلبي □ غير متوفر	
3.3 الفحص البدني:	
1.3.3 درجة الحرارة عند الدخول:□س°	**2.3.3 علامات تشوه خلقي؟:**□ نعم□ لا
3.3.3 عدوي التهاب الحبل السري ؟: نعم □لا	**4.3.3كدمات بعد الولادة؟:**□نعم □لا
5.3.3ورم دموي رأسي بعد الولادة؟: □ نعم □ لا	**6.3.3علاماتمضاعفاتعلي الدماغ؟:** □نعم □ لا

شكرا جزيلا لتعاونك

الباحثة: صفاء أبو مصطفى

Annex (3.5): Expert's Panel

1. Dr. Yehia Abed	Al-Quds University
2. Dr. Bassam Abu Hamad	Al-Quds University
3. Dr.Khitam Abu Hamad	Al-Quds University
4. Dr. Ashraf El-Jedi	Islamic University
5. Dr. Ahmad Al-shir	Islamic University
6. Dr.Abed-Alkareem Radawan	Islamic University
7. Dr.Areefa AL-Beheery	Islamic University
8. Dr. Nabeel Al-Baraquony	Al-Naser Pediatric Hospital
9. Dr. Shireen Aabed	Al-Naser Pediatric Hospital
10. Dr. Mohammad Zakoot	Naseer Medical Complex
11. Dr. Tareq Al-Daghma	Naseer Medical Complex
12. Dr. Yousef Abu Rreesh	MOH

Annex (3.6): Gestational age calculation

Gestational Age from Estimated Date of Delivery (EDD)

Share

Input:

Current Date: Nov 17 2015

Estimated Date of Delivery: MM DD YYYY

Results:

Current Gestational Age by EDD

References

1. Mul T, Mongelli M, Gardosi J. A comparative analysis of second-trimester ultrasound dating formulae in pregnancies conceived with artificial reproductive techniques. *Ultrasound Obstet Gynecol*. 1996 Dec;8(6):397-402.
2. Westerway SC, Davison A, Cowell S. Ultrasonic fetal measurements: new Australian standards for the new millennium. *Aust N Z J Obstet Gynaecol*. 2000 Aug;40(3):297-302.
3. Altman DG, Chitty LS. New charts for ultrasound dating of pregnancy. *Ultrasound Obstet Gynecol*. 1997 Sep;10(3):174-91.

Adress: http://reference.medscape.com/calculator/gestational-age-est-delivery-date

Annex (3.7): Approval from Helsinki committee –Gaza governorate

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: 03\08\2015 Number: PHRC/HC/44/15

Name: الاسم: صفاء عواد أبومصطفي

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 Hyperbilirubinemia among Admitted Neonates in Gaza Governorates: Case Control Study

The committee has decided to approve the above mentioned research. Approval number PHRC/HC/44 /15 in its meeting on 03/08/2015 و قد قررت الموافقة على البحث المذكور عاليه بالرقم والتاريخ المذكوران عاليه

Signature

Member Member

Chairman

Genral Conditions:-

١٦. Valid for 2 years from the date of approval.
١٧. It is necessary to notify the committee of any change in the approved study protocol.
١٨. 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 (3.8): An official letter of request

Al-Quds University
Jerusalem
School of Public Health

جامعة القدس
القدس
كلية الصحة العامة

التاريخ: 2015/7/5
الرقم/: ك ص ع –غ/ 2015/55

حضرة الدكتور ناصر أبو شعبان المحترم
مدير عام تنمية القوى البشرية–وزارة الصحة

تحية طيبة وبعد،،،

الموضوع: تسهيل مهمة للطالبة صفاء أبو مصطفى

تقوم الطالبة المذكورة أعلاه بإجراء بحث بعنوان:

Risk Factors of Hyperbilirubinemia among Admitted Neonates in Gaza Governorates: Case Control Study

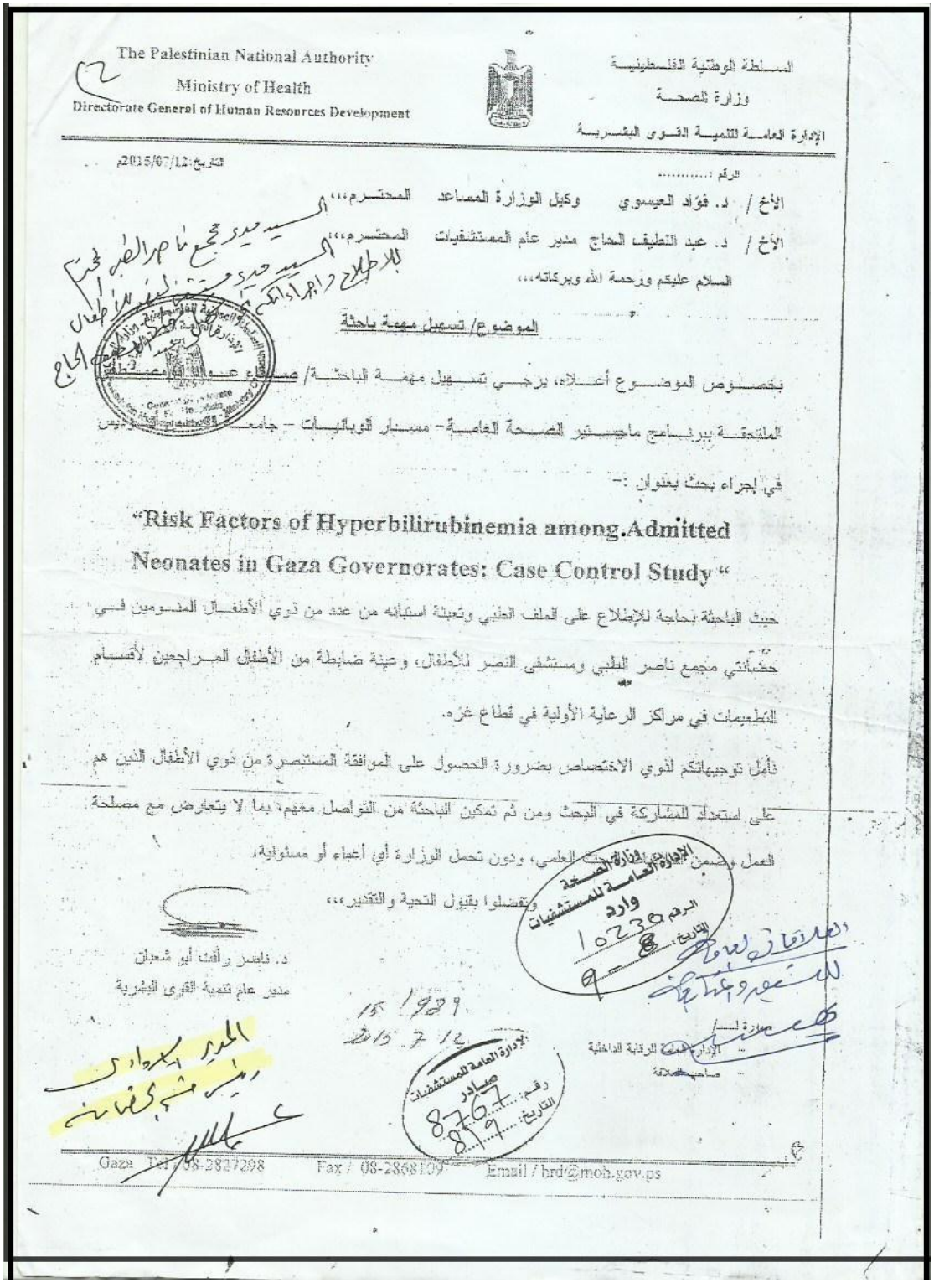
كمتطلب للحصول على درجة الماجستير في الصحة العامة–مسار علم الأوبئة وعليه نرجو التكرم بالموافقة والايعاز لمن يلزم بتسهيل مهمة الطالبة بجمع البيانات الخاصة ببحثها من ملفات الأطفال حديثي الولادة المدخلين لمستشفى النصر للأطفال ومجمع ناصر الطبي ومركزي شهداء الرمال وشهداء خانيونس التابعة لادارتكم الموقرة ، كم سيتم إجراء مقابلة مع الأمهات لاستكمال البيانات . علماً بأن المعلومات ستكون متوفرة لدى الباحث والجامعة فقط وسنطلعكم على النتائج في حينها .

و اقبلوا فائق التحية و الاحترام،،،

د. بسام أبو حمد
منسق عام برامج الصحة العامة
فرع غزة

نسخة
- الملف

Annex (3.9): An agreement letter from MOH Hospitals General Administration



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

السلطة الوطنية الفلسطينية
وزارة الصحة
الإدارة العامة لتنمية القوى البشرية

التاريخ: 2015/07/12م
الرقم: .....

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 باحثة

بخصوص الموضوع أعلاه، يرجى تسهيل مهمة الباحثة/ صفاء عبد الله محمد ناشي الملتحقة ببرنامج ماجستير الصحة العامة- مسار الوبائيات - جامعة القدس في إجراء بحث بعنوان :-

"Risk Factors of Hyperbilirubinemia among Admitted Neonates in Gaza Governorates: Case Control Study "

حيث الباحثة بحاجة للإطلاع على الملف الطبي وتعبئة استبانه من عدد من ذوي الأطفال المنومين في حضانتي مجمع ناصر الطبي ومستشفى النصر للأطفال، وعينة ضابطة من الأطفال المراجعين لأقسام التطعيمات في مراكز الرعاية الأولية في قطاع غزه.

نأمل توجيهاتكم لذوي الاختصاص بضرورة الحصول على الموافقة المستبصرة من ذوي الأطفال الذين هم على استعداد للمشاركة في البحث ومن ثم تمكين الباحثة من التواصل معهم، بما لا يتعارض مع مصلحة العمل وضمن الإطار العلمي، ودون تحمل الوزارة أي أعباء أو مسئولية.

وتفضلوا بقبول التحية والتقدير،،،

د. ناصر رأفت أبو شعبان
مدير عام تنمية القوى البشرية

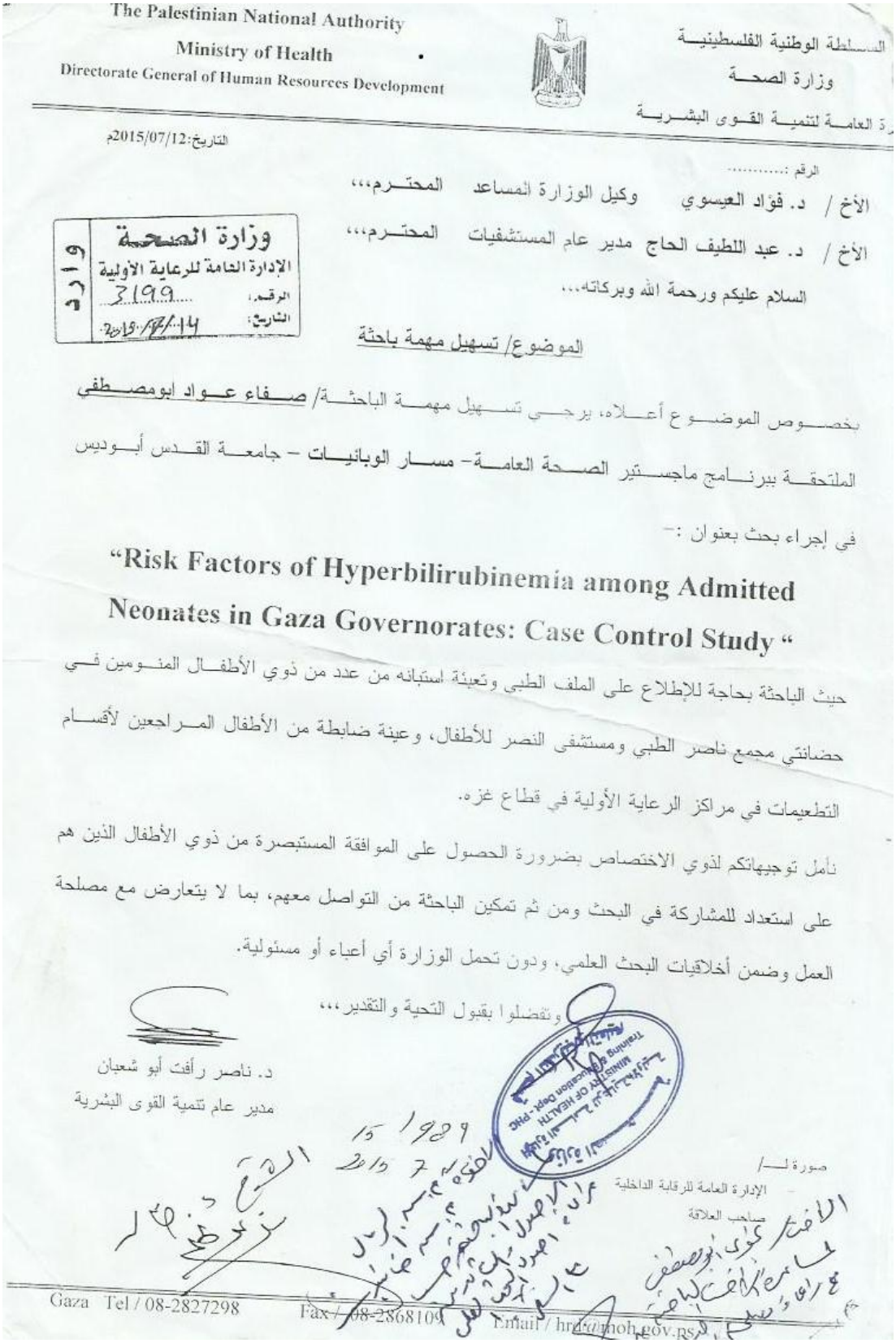
الإدارة العامة للمستشفيات
وارد
الرقم 10230
التاريخ 8/7/2015

الإدارة العامة للرقابة الداخلية

الإدارة العامة للمستشفيات
صادر
رقم 8767
التاريخ 8/7/2015

Gaza Tel / 08-2827298 Fax / 08-2868109 Email / hrd@moh.gov.ps

Annex (3.10): Approval from Primary Health CentersAdministration



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

السلطة الوطنية الفلسطينية
وزارة الصحة
المديرية العامة لتنمية القوى البشرية

التاريخ:2015/07/12م

الرقم :.....

الأخ / د. فؤاد العيسوي وكيل الوزارة المساعد المحترم،،،

الأخ / د. عبد اللطيف الحاج مدير عام المستشفيات المحترم،،،

السلام عليكم ورحمة الله وبركاته،،،

وزارة الصحة
الإدارة العامة للرعاية الأولية
الرقم: 3199
التاريخ: 2015/7/14

الموضوع/ تسهيل مهمة باحثة

بخصوص الموضوع أعلاه، يرجى تسهيل مهمة الباحثة/ صفاء عواد ابومصطفى الملتحقة ببرنامج ماجستير الصحة العامة- مسار الوبائيات – جامعة القدس أبوديس في إجراء بحث بعنوان :-

"Risk Factors of Hyperbilirubinemia among Admitted Neonates in Gaza Governorates: Case Control Study "

حيث الباحثة بحاجة للإطلاع على الملف الطبي وتعبئة استبانه من عدد من ذوي الأطفال المنومين في حضانتي مجمع ناصر الطبي ومستشفى النصر للأطفال، وعينة ضابطة من الأطفال المراجعين لأقسام التطعيمات في مراكز الرعاية الأولية في قطاع غزه.

نأمل توجيهاتكم لذوي الاختصاص بضرورة الحصول على الموافقة المستبصرة من ذوي الأطفال الذين هم على استعداد للمشاركة في البحث ومن ثم تمكين الباحثة من التواصل معهم، بما لا يتعارض مع مصلحة العمل وضمن أخلاقيات البحث العلمي، ودون تحمل الوزارة أي أعباء أو مسئولية.

وتفضلوا بقبول التحية والتقدير،،،

د. ناصر رأفت أبو شعبان
مدير عام تنمية القوى البشرية

صورة لـــ/
الإدارة العامة للرقابة الداخلية
صاحب العلاقة

Gaza Tel / 08-2827298 Fax / 08-2868109 Email / hrd@moh.gov.ps

Annex (3.11): Estimated budget

No	Item	Unit	Expected USD
1	Study tools	Questionnaire	$200
2	Transportation	Three months- all Gaza Governorates	$1,000
3	Data collectors	300* $5 per questionnaire	$1,500
4	Training workshop	For data collectors	$200
5	Data entry and analysis		$1000
6	Photocopying for research papers		$500
Total US $			**$ 4,500**

ملخص الدراسة

عنوان الدراسة: عوامل الخطر التي تؤدي إلي اليرقان لدي الأطفال حديثي الولادة في قطاع غزة: دراسة مقارنة

إعدادالباحث: صفاء عواد أبومصطفي
إشراف :د/ يوسف الجيش

مقدمة:

يعتبر اليرقان عند الأطفال حديثي الولادة من أكثر المشاكل الصحية شيوعا في جميع أنحاء العالم حيث أن حوالي 60٪ من الأطفال مكتملي النمو و80٪ من الخدج يصاب باليرقان في الأسبوع الأول من الحياة.

أهداف الدراسة:

لقد هدفت هذه الدراسة إلى التعرف على عوامل الخطر التي تؤدي إلي حدوث اليرقان بين المواليد في محافظات قطاع غزة.

منهجيةالدراسة

كانت منهجية الدراسة عبارة عن دراسة مقارنة (الحالات والشواهد) بين حالات مرضية وحالات سليمة، وتكونت عينة الدراسة من 180 مولود (90 مريض باليرقان و 90 سليم)، وقد تم اختيار الحالات المرضية من مستشفى النصر للأطفال ومجمع ناصر الطبي في حين تم اختيار الحالات السليمة من مراكز الرعاية الصحية الأولية (عيادة شهداء خان يونس وشهداء الرمال). لقد تم استخدام استبيان محكم أعد لقياس متغيرات الدراسة وقام الباحث بإجراء اختباراتالص دق له، وقد تم استخدام برنامج الحزمة الإحصائية للعلوم الإنسانية في تحليل البيانات التي تم جمعها حيث تم إجراء العديد من الاختبارات الإحصائية بما في ذلك إحصاءات وصفية، التحليل الثنائي باستخدام اختبار الكاي ومعامل الانحدار المتعدد.

أهم النتائج

- كشفت نتائج التحليل ثنائ المتغير أن هناك علاقة ذات دلالة إحصائية بين بين اليرقان والعوامل الاجتماعية والديموغرافية مثل دخل الأسرة الشهري (P value < 0.05) ، بينما العوامل

الأخرى مثل (عمر الأم، عمل الأم، والمستوي التعليمي للأم) فلم تظهر علاقة ذات دلالة إحصائية (P value > 0.05).

- من بين العوامل المتعلقة بالأم؛ فقد بين التحليل ثنائي المتغير وجود علاقة ذات دلالة إحصائية بين اليرقان و(نوع فصيلة الدم للأم، وفقر الدم ، واضطرابات الحمل(P value < 0.05)
- من ناحية أخرى؛ أظهرت النتائج أنه لا توجد علاقة ذات دلالة احصائية بين اليرقانو(عدد الولادات، نوع العامل الرايسيسي للأم، التمزق المبكر للأغشية المحيطة بالجنين، استخدام الأكسيتوسين، نوع الولادة، سكري الحمل، ضغط الحمل، التهاب المسالك البولية، التهاب المهبل، نزيف ما حول الولادة، الخروج المبكر بعد الولادة من المستشفى(P value > 0.05).
- أما العوامل المتعلقة بالمولود، أظهر التحليل ثنائي المتغير أن وزن الطفل عند الولادة، وممارسات الرضاعة (طريقة الرضاعة، صعوبة التغذية ،وقت أول محاولة للرضاعة، المسافة الزمنية بين وجبات الرضاعة، وعدد الحفاضات الرطبة خلال 24 ساعة) أنها عوامل ذات دلالة إحصائية للإصابة باليرقان (p value < 0.05)، كما أظهرت عوامل أخرى تعلقت بترتيب الطفل في الإنجاب وحدوث ورم دموي رأسي أو وكدمات، وتاريخ أخ سابق مصاب باليرقان عن عدم وجود علاقة ذات دلالة احصائية (p value > 0.05).
- وقد تم استخدام الانحدار المتعدد للكشف عن العوامل المستقلة الهامة المرتبطة بالإصابة باليرقان عند المواليد، وأظهرت النتائج أن دخل الأسرة،وفقر الدم عند الام، ووزن الطفل عند الولادة، وغالب ممارسات الرضاعة (طريقة الرضاعة، ووقت أول محاولة للرضاعة، وصعوبة الرضاعة، والمسافة الزمنية بين وجبات الرضاعة) عوامل خطر ذات دلالة إحصائية لحدوث اليرقان عند حديثي الولادة في قطاع غزة.

<u>أهم التوصيات</u>

في الختام، حيث أن نتائج الدراسة أظهرت أن العديد من عوامل الخطر التي تؤدي إلي اليرقان يمكن التحكم بها وتفاديها، فإننا نوصي بضرورة الاهتمام بالفحص الشامل والمراقبة الدقيقة لحديثي الولادة خاصة الأكثر عرضة منهم لعوامل الخطر. وأخيرا تعزيز التثقيف الصحي بشأن ممارسات التغذية الفعالة أملا في الوقاية والكشف المبكر وللحد من حالات الدخول المتزايدة من مرضي اليرقان.