**Deanship of Graduated Studies**
**Al-Quds University**

# Consanguinity and other Risk Factors in Relation to Congenital Malformations in Live Newborns at Al-Makassed Hospital

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# Consanguinity and other Risk Factors in Relation to Congenital Malformations in Live Newborns at Al-Makassed Hospital


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**A thesis submitted in Partial Fulfillment of Requirement for the degree of Master of Public Health/School of Public Health.**

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# Dedication

“I would like to dedicate this work to my father`s soul, and express a special thanks to my mother and brother, who exhibited patience and understanding during this project, and to all the staff at the health facility who made this project possible”.

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## Thesis Approval

# Consanguinity and other Risk Factors in Relation to Congenital Malformations in Live Newborns at Al-Makassed Hospital

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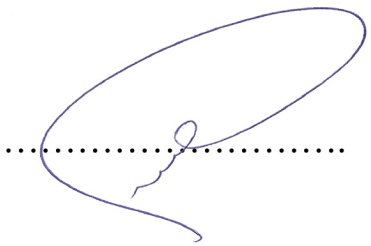
**Jerusalem - Palestine**

**1432 / 2011**

# 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 part of the same) has not been submitted for a higher degree to any other university or institution.



**Ahmad Masri**

Date: **17-02-2011**

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I sincerely hope that this study will be beneficial to the Palestinian community.

# Abstract

Congenital malformations occur all over the world and constitute an impenetrable core of perinatal mortality in developed countries. In developing countries like Palestine, with the decline of other causes of perinatal mortality, congenital malformations are acquiring importance. The significance of congenital malformations lies not only in their contribution to mortality but also in causing disability and handicaps. Our country, with its limited financial resources for health can hardly afford to rehabilitate these children and the meager amount available for the same can be better utilized for salvaging normal babies by preventing congenital malformations. The aim of this study was to investigate the association between consanguinity, other risk factors, and congenital malformations. This is to provide reliable information to be as a baseline data for further studies, which may help in improving the quality of health care for both mothers and the newborns.

A quantitative approach was adopted to investigate the prevalence and the most risk factors of congenital malformations in the maternity department of Al-Makassed Hospital, which is a private paying institution where about 60% of the deliveries were booked earlier and 40% came as emergency cases. A retrospective study done on 5729 live babies born consecutively over a period of 24 months from 1$^{st}$ June 2007 to May 2009. An instrument was developed specially for this study to collect the data. Descriptive statistic methods were used and the findings were statistically interpreted using the statistical package for Social Science (SPSS). Results showed the frequency of congenital malformations was 5%. The predominant system involved was cardiac system. Major malformations constituted 55.3% of the total. A statistically significant increase in the frequency of congenital malformations was observed with decreasing gestation and birth weight. There was a significant correlation between maternal factors, like previous abortions, drug intake during pregnancy period, diabetes mellitus, pre-eclampsia toxemia, and congenital malformations in the baby. The results also showed that 45.9% of the cases were the product of consanguineous mating, most of them were first cousins. The inability to discover the causes of congenital malformations is one of the most miserable failures of modern medicine. There is a clear need for genetic counseling services and ante-natal diagnostic tests to be offered specially for those mothers at risk. Current legal and religious attitudes towards the options available for people at genetic risk should be considered.

## ملخص الدراسة

من المسلم به، بأن التشوهات الخلقية تحدث في مختلف أنحاء العالم، حيث أنها تعتبر أهم العوامل الأساسية (التي لا يمكن تجاهلها) المسببة لحالات الوفاة أثناء فترة الحمل أو خلال فترة الولادة في البلدان المتقدمة. ففي البلدان النامية، كما هو الحال في فلسطين، ومع تراجع أسباب الوفاة الاخرى (غيرالتشوهات الخلقية) لدى المواليد اثناء الحمل وخلال الولادة، فان هذه الظاهرة (التشوهات الخلقية) تكتسب مكانه بالغة الأهمية. حيث تكمن هذه الاهمية ليس فقط في مساهمة هذه التشوهات في حدوث وفيات في المواليد، ولكن أيضا في إحداث العجز والإعاقة لدى أولئك المواليد بعد الولادة. ففي بلد محدود الموارد المالية المخصصة لقطاع الصحة، كفلسطين، فانه سيكون من الاجدر تأمين هذه الموارد المحدودة للتقليل من حدوث مثل هذه التشوهات، بدلا من تأمينها لاعادة تأهيل الاطفال ذوو الاعاقات والتشوهات الخلقية.

فكان الهدف من هذه الدراسة هو استقصاء العلاقة التي من الممكن ان تربط بين عامل القرابة، وعوامل أخرى قد تسبب مثل هذه التشوهات الخلقية. حيث ان مثل هذه الدراسات ستقوم بتوفير معلومات موثقة قد تكون بمثابة قاعدة بيانات أساسية لمزيد من الدراسات المستقبلية، التي قد تساعد في تحسين نوعية الرعاية الصحية للأمهات والأطفال حديثي الولادة على حد سواء.

واعتمد النهج الكمي الوصفي في هذه الدراسة للتحقق من هذه الظاهرة وعلاقتها بأهم العوامل المسببة لخطر التشوهات الخلقية وما مدى انتشارها. حيث تمت هذه الدراسة في قسم النسائية والتوليد لمستشفى جمعية المقاصد الخيرية الاسلامية بالقدس، الذي يعد من أهم مستشفيات فلسطين من حيث جودة الرعاية المقدمة، وقد بلغ معدل الامهات المسجلات للرعاية الصحية خلال فترة الحمل (ما قبل الولادة) ما نسبته 60% من مجمل العينة، وما نسبته 40% كحالات طارئة.

وهذه دراسة استعادية استرجاعية أجريت على 5729 طفلا أحياء، ولدوا على التوالي خلال فترة 24 شهرا من الاول من حزيران للعام 2007 الى 31 من أيار للعام 2009. حيث صممت استبانة خصيصا لهذه الدراسة لجمع البيانات. وعولجت النتائج إحصائيا باستخدام الحزمة الإحصائية للعلوم الاجتماعية (SPSS) بأساليب إحصائية وصفية. فكانت وتيرة التشوهات الخلقية التي أظهرتها النتائج 5%. وكانت التشوهات الخلقية سائدة في الجهاز القلبي، حيث شكلت ما نسبته 55.3% من أجمالي التشوهات الكلية.
لوحظ من النتائج وجود زيادة ذات دلالة إحصائية في وتيرة التشوهات الخلقية مرتبطة بفترة الحمل وانخفاض وزن الجنين. وقد كان هناك ارتباطا كبيرا بين العوامل المرافقة لفترة الحمل، مثل حالات الإجهاض السابقة، تناول الأدوية خلال فترة الحمل، وداء السكري، وتسمم الحمل، والتشوهات الخلقية في

الجنين. كما أظهرت النتائج أن 45.9% من مجمل الحالات، كانت نتاج زواج أقارب معظمها من الدرجة الاولى.

عدم القدرة على اكتشاف أسباب مثل هذه التشوهات الخلقية يعد واحدا من أسباب فشل الطب الحديث. وهناك حاجة ماسة للاختبارات التشخيصية والاستشارات الوراثية قبل الولادة وخلال فترة الحمل ، لعرضها خصيصا لأولئك الأمهات المعرضين للخطر. وينبغي الأخذ بعين الاعتبار المواقف القانونية والدينية نحو الخيارات المتاحة للناس المعرضين لخطر مثل هذه التشوهات.

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**List of Abbreviations**

| | |
|---|---|
| ACE inhibitors | Angiotensin-Converting Enzyme Inhibitors |
| ANL | Abnormal |
| CHD | Congenital Heart Deformities |
| CM | Congenital Malformations |
| DUSS | Detailed Ultra Sound Screening |
| FAS | Fetal Alcohol Syndrome |
| Ges. D/M | Gestational Diabetes Mellitus |
| H/O | History Of |
| ICD | International Statistical Classification of Diseases |
| IUGR | Intra Uterine Growth Retardation |
| MCH | Maternal and Child Health Care |
| NICU | Neonatal Intensive Care Unit |
| NL | Normal |
| NTD | Neural Tube Defect |
| PCBS | Palestinian Central Bureau of Statistics |
| PMOH | Palestinian Ministry of Health |
| S.V.D | Spontaneous Vaginal Delivery |
| TGA | Transposition of Great Arteries |
| U/S | Ultra Sound |
| UK | United Kingdom |
| USA | United States of America |
| VUR | Vesico-Ureteric Reflux |
| WHO | World Health Organization |

# Chapter I

## 1.1 Introduction

Congenital malformations account for a significant proportion of infant morbidity and mortality, as well as fetal mortality. Based on World Health Organization report (WHO 98,99) about 3 million fetuses and infants are born each year with major congenital malformations (Rosano A, 2000). Furthermore, congenital malformations account for nearly 500,000 deaths worldwide each year. Several large population-based studies showed that the incidence of major malformations ranges between 2–3% of all live births; this incidence is known to be much higher among still births (Rosano A, 2000).

The underlying causes for most of the known congenital anomalies remain obscure. It has been estimated that around 15%-25% of congenital malformations are due to recognized genetic conditions as in chromosomal abnormalities and single gene defects, 8%-12% are due to known environmental factors (maternal-related conditions, drugs or chemical exposures) and 20%-25% are thought to be of multifactorial causes. Still the majority of congenital anomalies, 40%-60%, have unexplained causes (Rosano A, 2000; Nelson K, 1984).

It is known that congenital malformations arise at the time of conception, or during intrauterine development, and thus all are present at birth, though some may not be apparent. The prevalence of genetically determined disorders increases in populations with known high consanguinity rates, as this will increase the risks of recessively inherited diseases and multifactorial disorders (Clayton et al, 1997).

The term ‘‘consanguinity’’ is used to describe unions between individuals who are known to share genes inherited from one or more common ancestors, i.e. refers to the relation in blood. Marriage between closely related individuals is known as consanguineous marriage (Al-Awadi et al., 1985). The possibility of parents being carriers of the same gene is increase if both are related, and hence consanguineous marriages are prone to produce offspring who inherit some congenital malformation in higher frequency than those of unrelated parents. Many harmful traits in humans are inherited in a recessive manner, so will be easily passed to the offspring. This confers an increased chance for expression of recessive genes that are hidden in

heterozygous carrier parents, resulting in children affected with the disease that is carried by both parents. The risk increases with the degree of consanguinity and may influence the rates of congenital malformations (Clayton et al, 1997; Al-Awadi et al., 1985).

Consanguineous marriages are of different patterns including: uncle-niece (marrying one's sister's daughter) or aunt-nephew (marrying his father's sister) both types are prohibited in Islam. First cousins which can be either cross (marriage between the children of a brother and sister), or parallel (marriage between the children of two brothers or two sisters), and second-cousins (marriage between the children of two first-cousin). For the purpose of this study consanguineous marriages were classified as: double first-cousin, first-cousin, first-cousin once removed, second-cousin, second-cousin once removed, and third cousin (Saedi-Wong S et al., 1989; Al-Gazali LI et al., 1997).

Arab populations and Middle Eastern societies in general, are characterized by close family relationships. The preference for marrying relatives is a deeply rooted cultural trait. Even though major religions discourage consanguineous mating, it is still very prevalent in Palestine. The frequency of consanguineous marriages varies greatly between populations depending on geographical, ethnic, and socioeconomic characteristics. The rate being very high in Kuwait (54.2%) (Al-Awadi et al., 1985), Saudi Arabia (54.3%) (Saedi-Wong S et al., 1989), Emirates, and other Gulf countries (50.5%) (Al-Gazali LI et al., 1997). This rate was also found to be high in Egypt (22%) (Hafez M et al., 1983), Lebanon (25%) (Khlat M et al., 1984), Syria (33%) (Prothro ET. et al., 1974), Jordan (41%) (Khlat M et al., 1984), Algeria (23%) (Benallegue A et al., 1984), and among Arab communities in Israel (44.3%) (Jaber L. et al., 1994).

The estimated prevalence of consanguineous marriages (first cousin) in the last Palestinian census in 2007 had shown a total rate of 27.4% that represents 24.6% in West Bank, and 32.2% in Gaza strip, 45% of total consanguineous marriages (PCBS. 2007). Congenital malformations are found in 2-6% of all newborns, including some which are not of serious impact; another 2-6% of infants discovered to have malformations during the first year of life. Approximately 0.5-1.3% of newborns have more than one malformations recognized at birth (PCBS 2007), (New York State Congenital Malformations Registry 2006).

This study was conducted at AL Makassed hospital in east Jerusalem, with the aim to have some basic epidemiological information and investigate the association between consanguinity, other risk factors and congenital malformations in Palestine.

### 1.2. Possible intervention

The genetic implications of consanguinity should be addressed by providing genetic counseling for individual families, as well as the identification of other possible risk factors that can lead to congenital disorders, mainly environmental factors.

Development of an appropriate genetic counseling services and prenatal health care and education is a high priority in this area to reduce the associated infant mortality and morbidity. The following may be possible interventional approaches:

1- Adoption of primary preventive approaches such as food fortification or avoid using medications and smoking depend highly on pre-conception information for families.

2- Integrate the subject “consanguineous marriages; scope and effects” through the student curriculum. This subject needs clear and deep scientific discussions with the students to dispel misconceptions and to clarify advantages and disadvantages.

3- Family planning program may provide a suitable focus for advice about future pregnancies.

4- Identification of other areas for research in public health services.

### 1.3. Research questions

- How common congenital malformations in Palestine are?
- What are the risk factors associated with congenital malformations among women and their newborns in Palestine?
- What are the implications of the results of this study in order to improve the preventive approach?

### 1.4. Aim of the Study

The aim of this study was to have basic epidemiological information, and investigate the association between consanguinity, other risk factors, and congenital malformations in Palestine.

### 1.5. General Objectives

1- To delineate the relationship between consanguinity and different kinds of congenital malformations.

2- To investigate other risk factors associated with congenital malformations in the study population.

3- To have some basic epidemiological information about congenital malformations.

### 1.6. Specific Objectives

1- To investigate the association between consanguineous marriages and congenital malformation among newborns of consanguineous parents.

2- To study the association between the socio-economic status, lifestyle, cultural factors and congenital malformations among the population under study.

3- To explore the relationship between maternal health status during pregnancy and congenital malformations among their newborns.

4- To explore the relationship between the mother's previous medical history and congenital malformations among their newborns.

5- To explore the relationship between medication use /radiation exposure among mothers and congenital malformations in their newborns.

### 1.7. Problem Statement

Congenital malformations have been reported to affect 2-6% of all live births (Clayton et al, 1997). Several factors can contribute to the etiology of congenital malformations. Consanguineous marriages have been described as one of the important factors known to increase the risk of congenital malformations (Teebi AS, 1994). Consanguinity has been a long-standing social practice among some communities, especially in Muslim populations. In different Middle Eastern countries the rate of consanguineous marriages varies from 23.3% to 57.9% (Teebi AS, 1994). This study intends to investigate the association between consanguinity, other risk factors and congenital malformations in live newborns at a tertiary hospital in East Jerusalem (AL-Makassed Hospital).

### 1.8. Importance of the study

The result of this study may help those in a position of planning, to set out suitable strategies, in term of developing the primary health care services in the area focusing on pre-conception information and counseling. This will facilitate better planning of health education programs regarding genetic counseling, pre-conception and during pregnancy information.

### 1.9. Significance of Study

While parental consanguinity is known to increase the risk of congenital malformations in the off-springs, it is hard to quantify this risk in populations where consanguinity is prevalent. The prevalence of consanguineous marriages in the Palestinian society may be as high as 48%, while in Europe it is less than 1% (Bittles AH, 1998). WHO periodically estimates that 34% of infant`s mortality rate is due to genetic factors (WHO 98, 99) (Rosano A, 2000). In Palestine, infant`s mortality has been shown to be caused by either prematurity or congenital abnormalities (PMOH 2005). Congenital malformations were categorized by ICD-10 as minor and major malformations, which can be familial and of prenatal origin. Remarkably few studies have been conducted in the Palestinian area in relation to the incidence of these birth defects and malformations and its association with parental consanguineous marriages, or other related risk factors.

# Chapter II

# Literature Review

## 2.1. Introduction

Congenital malformations or birth defects are common among all races, cultures, and socioeconomic classes. Birth defects can be isolated abnormalities or part of a syndrome and continue to be an important cause of neonatal and infant morbidity and mortality (Clayton et al, 1997).

Based on a World Health Organization (WHO) report, about 3 million fetuses and infants are born each year with major congenital malformations; and these accounted for an estimated 495,000 deaths worldwide in 1997 (Rosano A, 2000). The incidence of major malformations about 2–3% of all live births according to several large population-based studies (Leppig KA et al., 1987; Marden PM et al., 1964; Van Regemorter N et al., 1984).

An approximately equal number of additional major anomalies are diagnosed later in life. Of all congenital malformations diagnosed by the end of first year of life, nearly 60% are identified in the first month and about 80% by the end of 3 months (Czeizel AE, 1997). The prevalence of major congenital malformations is even higher among stillbirths with significant birth defects reported in Hungarian about 15–20% of all stillbirths (Czeizel AE, 1997).

With the introduction of prenatal ultrasound in obstetric care, many major congenital malformations are diagnosed prenatally, allowing parents to have the option of terminating the pregnancy. In UK, it was found that termination of pregnancy for fetal malformations increased from 23 to 47 per 10,000 births between the years 1985 and 2000. The same study also reported that the diagnostic accuracy of prenatal ultrasound in detecting congenital anomalies exceeds 90% for anencephaly and abdominal wall defects but is still less than 70% for diaphragmatic hernia, bladder outlet obstruction, and many major skeletal defects

(Richmond S et al., 2005). Similarly, many cardiac defects diagnosed in the first year of life were unsuspected before or at birth.

Several recent reports on secular trends in the prevalence of congenital malformations from Europe, Canada, and Asia have also shown that prenatal diagnosis rates and pregnancy terminations have gradually increased over the last two decades but the overall total prevalence of major malformations has been unchanged (Richmond S et al., 2005; Rankin J et al., 2005). Other studies have reported a gradual decline in the total prevalence of non-chromosomal anomalies and an increase in chromosomal anomalies (Rankin J et al., 2005). No consistent evidence of seasonality has been reported for common birth defect groups (Siffel C et al., 2005).

A higher overall rate of birth defects is reported in males and black infants (Petrini J et al., 2002). A study from the UK reported a higher risk of non-chromosomal congenital anomalies with increasing socioeconomic deprivation, and speculated that this increase in the risk was probably related to differences in nutritional factors, lifestyle, environment, occupational exposures, access to healthcare, maternal age, and ethnicity (Vrijheid M et al., 2000). However, more research is necessary to confirm these findings and to better understand the reasons for the increased risk of congenital malformations with increasing socioeconomic deprivation, if any.

Detailed information from population-based studies on the incidence and prevalence of minor malformations is limited, less reliable, and less accurate because of difficulties and inconsistencies in definitions, identification, documentation, and reporting of these non-life threatening birth defects (Marden PM et al., 1964; Richmond S et al., 2005).

## 2.2. **What is a Congenital Malformation?**

A congenital malformation is an abnormality of structure, or function that is present at birth (even if not diagnosed until later in life) and results in physical or mental disability (March of Dimes, 2006).

A birth defect is defined as a major deviation from normal morphology or function that is congenital in origin. Birth defects are common; with 2-6% of all newborns born globally have

a major structural malformation detectable at birth. By 1 year of age, malformations or developmental disorders have been identified in 7% of babies. This number increases to 12 to 14% by the time children enter school, and to 17% before they reach age 18 (Boyle CA et al., 1994). Most malformations are not inherited, and less than one third of patients seeking counseling for birth defects have a genetic condition. A smaller proportion-about 10% of congenital abnormalities is caused by teratogens. Only a small number of teratogens have been confirmed (Kimmel CA et al., 1993).

### 2.3. Classification of Congenital Malformations

Congenital malformations can be classified as being major or minor.

1. **Major malformations:** are anatomic abnormalities which are severe enough to reduce life expectancy or compromise normal function, such as neural tube defects, renal agenesis, etc. Major malformations can be further divided into lethal or severe malformations.

   A malformation is considered lethal if it causes stillbirth or infant death in more than 50 percent of cases. Major malformations are considered as severe life-threatening without medical intervention (Czeizel AE, 1997).
2. **Minor malformations:** structural alterations which either require no treatment or can be treated easily and have no permanent consequences for normal life expectancy.

   Minor malformations are most frequent in areas of complex and variable features such as the face and distal extremities.

   Minor malformations are relatively frequent and a higher incidence may be noted among premature infants and infants with intrauterine growth restriction (Czeizel AE, 1997).

The incidence of minor malformations has been reported to vary from about 7 percent to as much as 41 percent among newborn infants. In addition, the majority of birth defect registries collect data only on congenital anomalies diagnosed before, at, or soon after birth; few collect data on cases diagnosed from birth to the age of 1 year. However, many minor malformations of internal organs are diagnosed later in life, if at all (Marden PM et al., 1964; Richmond S et al., 2005).

In general, minor malformations are more subtle, (have low validity of diagnosis) and are not reported consistently. They are nevertheless significant as they may be an indication for the presence of a major malformation and may also provide critical clues to the diagnosis (Leppig KA et al., 1987).

The risk of having a major malformation increases with the number of associated minor malformations. It is estimated that infants with three or more minor defects have a 20–90% risk of a major malformation; those with two minor defects have 7–11% risk; and those with one minor defect have a 3–4% risk compared to infants with no minor malformations who have a 1–2% risk of a major malformation (Leppig KA et al., 1987; Marden PM et al., 1964). Some of this variability in risk is probably related to variability in definition, documentation, and validity of minor malformations diagnoses in different studies.

### 2.4. Causes of Congenital Malformations

The causes of congenital anomalies are divided into four broad categories; genetic, environmental, multifactorial, and unknown. Initially, as many as 50–60% of all congenital anomalies were considered to have an unknown etiology but with recent advances in genetics, the etiology of many syndromes is being identified. Based on earlier data, a genetic cause was considered to be responsible for as many as 10–30% of all birth defects, environmental factors for 5–10%, multifactorial causes for 20–35%, and unknown causes were found in 30–45% of the cases (Clayton et al, 1997; Hobbs CA et al., 2002; Brent RL, 2004). However, more recent data indicate that the etiology of congenital malformations is unknown in only17% of the cases (Czeizel AE, 1997).

Genetic factors are responsible for the vast majority of congenital malformations with known causes and play an important role in disorders of multifactorial inheritance. A chromosomal abnormality occurs in 1 of 170 live births. A chromosomal abnormality leading to a congenital malformation can be either numerical or structural. Among chromosomally abnormal neonates, one third have an extra sex chromosome, one-fourth have trisomy of an autosome, and the remaining have an aberration of chromosomal structure such as a deletion or translocation. Earlier studies reported that nearly 10% of infants with lethal multiple

congenital malformations have abnormal cytogenetic studies. However; this proportion is likely to be much higher today with advances in genetics (McLean S, 1999).

Examples of numeric chromosomal abnormalities include Down syndrome (trisomy 21) and Turner syndrome (45, XO monosomy). Structural chromosomal abnormalities may include translocations, deletions, micro deletions, duplications, or inversions. With better understanding of the human genome and improved techniques in molecular cytogenetics, more and more structural chromosomal abnormalities are being identified as a cause of congenital anomalies previously considered to be of unknown etiology. Furthermore, there are genetic abnormalities such as single gene disorders. Single gene disorders are genetic conditions caused by the alteration or mutation of a specific gene in the affected person's DNA. Single gene disorders are heritable and often run in families. Individuals with a family history of a single gene disorder may be at risk for passing the condition onto their children. Examples of single gene disorders include cystic fibrosis, sickle cell anemia, Tay-Sachs disease, myotonic dystrophy, Duchenne and Becker muscular dystrophies, Fragile X syndrome and spinal muscular atrophy (Clayton et al, 1997; McLean S, 1999).

Environmental factors also play an important role in the etiopathogenesis of many congenital malformations. Maternal exposure to certain environmental agents can lead to disruption of the normal developmental process and result in both minor and major congenital anomalies. These agents with the potential to induce a structural anatomic anomaly in the developing fetus are termed *teratogens* (Greek: teratos [monster] and gen [producing]) (Brent RL, 2004).

The following table summarizes some common examples of teratogens in different categories and the associated congenital malformations. The exact mechanisms by which each teratogen induces anomalies are not clearly known but include altered gene expression, histogenesis, cell migration and differentiation, protein or nucleic acid synthesis and function, or supply of energy. The risk of having a congenital anomaly after exposure to a teratogenic agent depends on the nature and the dose of the agent, timing and duration of exposure, presence of concurrent exposures, and the genetic susceptibility of the embryo. It is likely that the interactions between genes and environmental factors are responsible for most birth defects related to teratogenic exposures (McLean S, 1999).

The teratogenic risks associated with most maternal environmental exposures are not well established. Even less understood are the effects of paternal environmental exposures. For the most part, environmental exposures involve multiple agents and other confounding elements, creating difficulty in identifying the underlying cause(s).

Table 2.1 Some Common Teratogens and Associated Anomalies (adopted from McLean S, 1999)

| | **Vulnerable Period** | **Associated Congenital Anomalies** |
|---|---|---|
| **Teratogen Drugs** | | |
| ~ Antihypertensive | | |
| ACE inhibitors | 13th week-term | renal failure, pulmonary hypoplasia, death |
| ~ Anticonvulsants | | |
| Phenytoin | 18–60 days | Cleft lip/palate, congenital heart defect, hypoplasia of nails |
| Valporic acid | 18–60 days | nails dysplasia, cleft lip/palate, limb defects, microcephaly |
| ~ Retinoid | 18–60 days | CNS/ear defects, cleft lip/palate, heart defects, eye anomalies |
| ~ Anticoagulants | | |
| Warfarin | 6–9 weeks | Nasal hypoplasia, eye anomalies, Hypoplastic phalanges |
| ~ Androgens | 2–24 weeks | Genital tract abnormalities |
| **Infections** | | |
| ~ Rubella | First trimester | Cataract, microcephaly, microopthalmia, heart defects |
| ~ Varicella zoster | 8–20 weeks | Microcephaly, limb hypoplasia, cutaneous scars |
| ~ Toxoplasmosis | 7–22 weeks | Hydrocephaly, microopthalmia, mental retardation. |
| **Maternal Disorders** | | |
| ~ Diabetes | First trimester | Neural tube defects, cardiac defects, caudal regression syndrome |
| ~ Phenylketonuria | First trimester | IUGR, microcephaly, dysmorphic features, maxillary and mandibular hypoplasia, cardiac defects, cleft lip/palate |
| ~ Maternal Starvation | Pregnancy period | IUGR, abortion, NTDs. |
| ~ Tobacco Smoking | Pregnancy period | Abortion, IUGR, and stillbirth. |
| **Miscellaneous** | | |
| ~ Alcohol | First trimester | Microcephaly, maxillary hypoplasia, heart defects |
| ~ Ionizing Radiation | Pregnancy period | Increased the risk for some fetal effects such as microcephaly or growth retardation, but for mental retardation is higher. |
| ~ Thalidomide | First trimester | Deafness, atonia, preaxial limb reduction defects, ventricular septal defects and GI atresia. |

The essential principles for determining a cause and effect relationship between environmental exposures and congenital anomalies are: an assessment of the strength of the association; evidence for biologic credibility; consistency of the findings with other studies; specificity of the association; and evidence of both time-exposure and dose-response relationships (Trasler JM et al., 1999).

Proving an exposure to environmental agent is teratogenic requires a well-designed epidemiologic research using high quality, population-based surveillance data. Examples of infectious agents that can be transmitted to the fetus and have an adverse effect include rubella, cytomegalovirus, varicella toxoplasma, and others. A number of drugs have clearly been shown to be teratogenic (Vrijheid M et al, 2000). The global epidemic of thalidomide-induced limb defects seen in the 1960s resulted in today's practice of monitoring for congenital anomalies worldwide. Other examples of teratogenic agents include folic acid antagonists, anticonvulsants (Dilantin, Tegretol), Coumadin derivatives and retinoid (Accutane) (Trasler JM et al., 1999; Hennekens CH et al., 1987).

Currently, the most widely used teratogenic agent is alcohol. Fetal alcohol syndrome (FAS) has been recognized in Canada as one of the leading causes of preventable birth defects and developmental delay in children (Canadian Centre on Substance Abuse, 1996; Reprotox, 2001). A wide spectrum of effects of alcohol on the fetus has been demonstrated. Although these relationships are not fully understood, the magnitude of the risk and the nature of harm to the fetus are dependent on the amount of alcohol intake, the gestational age at exposure and the maternal/fetal genetic predisposition. An estimate of the incidence of fetal alcohol syndrome is 1:1,000 births (Canadian Centre on Substance Abuse, 1996).

Despite public concerns regarding exposures from the physical environment, actual evidence for the human teratogenic effects from these exposures is limited. Recent researches have reported increased risks of structural birth defects and chromosomal abnormalities with air pollution and proximity to hazardous waste sites (Ritz B et al., 2002); however, further studies are required to interpret and to prove these findings. Other physical environmental factors with inconclusive findings include maternal pesticide exposure (Shaw GM et al., 1999), tri-

halomethane by-products in public water supplies (Dodds L et al., 2001), and industrial areas heavily polluted with lead (Vinceti M et al., 2001).

Maternal age is a risk factor for congenital anomalies; specifically chromosomal problems (Yang Q et al., 2006). Maternal health conditions that contribute to increased risks for congenital anomalies include obesity, epilepsy controlled with anticonvulsant medications, and insulin-dependent diabetes. More recent but somewhat contradictory research has implicated maternal thyroid disease, even when treated, as increasing the risk for congenital anomalies (National Institute of Child Health and Human Development, 2002).

### 2.5. What is consanguinity?

Two individuals are considered consanguineous if they have at least one ancestor in common. The term usually refers to an individual mating with a third-degree relative such as a first cousin, second cousin, or a more distantly related individual. First-degree relatives share half, second-degree relatives share one fourth, and third-degree relatives (cousins) share one eighth of their genes. Because of the potential for sharing deleterious genes, consanguineous unions are at increased risk to produce children with autosomal recessive or multifactorial diseases (Bittles AH, 1998).

First-cousin marriages, the most frequent consanguineous mating, carry a twofold increased risk of abnormal offspring if there is no family history of genetic disease. If one of the partners has a sibling with an autosomal recessive disease, the risk of affected offspring is many times higher than if he or she had chosen an unrelated partner. Thus, in general terms, inbreeding is associated with loss of biological fitness. It is however appropriate to note that, even in the absence of preferential consanguinity, alleles which are rare in large populations can rapidly increase to high frequency in a breeding pool of restricted size, because of factors such as founder effect and random genetic drift. In the USA, first-cousin marriage is legal in 30 states and is actually preferred in some countries, for example, some parts of the Middle East (Bennett RL et al., 1999).

Incest is defined as a relationship between first and second degree relatives, such as parent and child or brother and sister and is universally illegal. Progeny of such unions carry the highest

risk of abnormal outcome, and up to 40 percent of offspring are abnormal as a result of recessive and multifactorial disorders (Bennett RL et al., 1999).

### 2.6. Global Distribution of consanguineous marriage

In clinical genetics a consanguineous marriage is most commonly defined as a union between couples related as second cousins or closer. That is, the parental couple share 1/8 of their genes inherited from common ancestors, and on average their children have identical gene copies at 1/16 of all genes.[40] Using this definition, human populations can be subdivided into several major groupings: Societies in which fewer than 1% of marriages are consanguineous, as in Western Europe, North America, Australasia, and Russia; or Societies in which 1 to 10% of all marriages are consanguineous, such as South America. In the majority of North and sub-Saharan Africa, West, Central and South Asia, about 20 to more than 50% of marriages are consanguineous (Bittles AH, 1998).

There is no reliable information on consanguineous marriages for over 20% of the world's population, including many of the highly populous countries in Asia and Africa. By using Indonesia as an example, a review of anthropological sources indicated that first- or second-cousin marriages were preferred or permissible in 12 of 17 different subpopulations studied (Murdock GP, 1981). Thus it seems likely that a sizeable but unknown proportion of current marriages in many Eastern populations have been contracted between spouses who are biological relatives, and a similar situation may exist in many other countries where data are so far unavailable.

In most countries the positive or negative attitudes towards consanguineous marriages reflect long-standing religious or cultural beliefs. First-cousin unions are the most prevalent form of consanguineous marriages, and they are generally preferred within Buddhism, Confucianism, Judaism, Islam, and the Zoroastrian/Parish religion (Bittles AH et al., 2001). Religion and traditional beliefs can also determine the specific types of consanguineous marriage that are permissible, and so in Arab Muslim communities' first-cousin unions between a man and his father's brother's daughter are preferred, as opposed to the mother's brother's daughter pattern of first-cousin marriage prescribed by the Muslim populations of South Asia (Bittles AH,

1994). In the countries of the eastern Mediterranean region the preference for consanguineous marriage is by no means restricted to Islamic communities; first cousin marriage is also common in some Christian and Jewish communities (Goldschmidt E et al., 1960).

Social and economic considerations are important in the preference for consanguineous marriage. In social terms, consanguineous marriage is believed to strengthen family ties and at the same time help to avoid health or financial uncertainties that may arise through marriage with a spouse from another family or community (Hussain R, 1999). Consanguineous unions also greatly simplify premarital arrangements and the relationship of the bride and her in-laws (and relatives by birth) is predictably closer and more risk to produce congenital anomalies (Khlat M, 1989). In countries where either dowry (payment from the bride's family to the groom) or bride-wealth (payment from the groom to the bride's family) is the norm, a marriage arranged within the family is an effective mean of minimizing the financial costs, which increases the consanguineous marriage prevalence to the highest rate among the poorer and less educated populations (Shami SA et al., 1991; Al-Thakeb FT, 1985).

The prevalence of consanguineous marriage was higher (52.9%) among Bedouin families who do not participate in Israeli MOH prenatal services than in those who participate (38%). The socioeconomic status shows, that 91% of the prenatal care non-users lived in shantytowns and encampments, with fewer economic resources (The Avicenne Initiative, 1998). This usually result in younger female and male age at marriage and at first birth, which is likely to increase family sizes and hence the likelihood that a recessive disorder will be expressed (Bittles AH et al., 1991).

In the early 20th century, consanguineous marriages in Western countries was generally rare and largely restricted to remote and under populated rural areas, and to religious isolates in the USA (Bittles AH, 2003). However, as a result of the large-scale migration from less developed countries to Western Europe, North America, and Australia during the last 50 years, many permanent migrant communities have been established in which consanguineous marriages is regarded as the norm. For example, in the UK Pakistani community of 0.5 to 0.6 million, an estimated 50 to more than 60% of marriages are consanguineous with evidence that their prevalence is increasing (Darr A et al., 1988), and a similar trend of increasing consanguinity has been reported among Moroccan and Turkish immigrants in Belgium (Reniers G, 1998).

Consanguinity is a predominant feature of Palestinian marriages, with 28% of ever-married women (aged 15–54 years) married to a first cousin and 17% married to other relatives within their Hamula (extended family) in 2006(PCBS 2007).

Among communities in the Eastern Mediterranean Region in which cousin marriages are preferred, the highest rates are consistently reported in the more traditional rural areas. Thus it is important for neonatologists and pediatricians to be aware of the possibility that their patients may be born to biologically related parents and to be conversant with the circumstances and outcomes of such unions (Al-Thakeb FT, 1985; Bittles AH et al., 1991).

## 2.7. Clinical Outcomes of Consanguineous Marriage

### 2.7.1. Consanguinity, Fertility, Prenatal Losses and Birth Measurements

Despite the widespread and erroneous belief that fertility is reduced in consanguineous unions, lower levels of pathological sterility have been reported in first-cousin progeny (Bittles AH et al., 2002). Data on fetal losses and stillbirths have been contradictory, with most studies indicating no consanguinity-associated effect (Shami SA et al., 1991; Tunçbilek E et al.,1994; Jaber L et al., 1997; Abdulrazzaq YM et al., 1997), but also some reports showed increased rate of losses (Bas¸aran N et al., 1989; Schull WJ et al., 1972; Hussain R et al., 1998).

Data on the relation between consanguinity and birth measurements (Birth weight, length, and head circumference) have also been mixed, with a number of surveys suggesting that babies born to consanguineous parents were smaller and lighter (Silbert JR et al., 1979; Magnus P et al., 1985; Kulkarni ML et al., 1990; Shami SA et al. 1991), whereas other studies failed to detect a significant difference in the East Mediterranean Region. Studies in Kuwait reported a decline in low birth weight in a small-scale with parental consanguinity (El-Alfi OS et al., 1969). Similar studies conducted in Iraq (Ramankutty P et al., 1983), Lebanon (Khlat M, 1989), and the Kingdom of Saudi Arabia (Saedi-Wong S et al., 1989) showed no association between consanguinity and low birth weight.

### 2.7.2. Consanguinity and Early Mortality

Although almost all studies based on adequate sample sizes have shown that early postnatal mortality is higher in the progeny of consanguineous unions, there has been a substantial

downward revision in the estimates of excess consanguinity-associated mortality throughout time (Bittles AH et al., 1988).

The most recent representative mortality estimate, based on a multi-national study of over 600000 pregnancies and live births, showed that deaths from approximately the sixth month of pregnancy to a median age of 10 years are 4.4% higher in first-cousin progeny than among the offspring of non-consanguineous unions, even after controlling for all potential confounding factors (Bittles AH et al., 1994).

Most studies of outcomes of consanguineous marriages have been conducted in developing countries, with consanguinity-associated deaths largely occurring during the first year of life (Jaber L et al., 1997; Hussain R et al., 2001). In the majority of cases no specific cause of death was identified because of poor diagnostic facilities and/or parental disagreement to do prenatal examinations. Multiple deaths also have been reported in specific consanguineous families from developing and developed countries, risk directly related to the degree of consanguinity (Stoltenberg C et al., 1999).

### 2.7.3. Consanguinity and Congenital Malformations

Studies about the prevalence of birth defects largely depend on the diagnostic criteria employed, and in less developed countries diagnoses may overlap with, and reflect late fetal and neonatal survival rates (Zlotogora J, 2002).

The incidence of birth defects reported in first cousin progeny, is 0.7 to 7.5% greater than in non-consanguineous couples, with the higher values reported in the more recent studies (Zlotogora J, 2002). Congenital defects with a complex etiology appear to be more common in consanguineous families (Jaber L et al., 1997), possibly reflecting rare or even unique recessive mutations, with a greater likelihood of recurrence (Stoltenberg C et al., 1999).

Many single gene disorders are present at increased prevalence in consanguineous progeny, including autosomal recessive non-syndromal hearing loss, blindness caused by early onset retinal dystrophies, childhood glaucoma, anophthalmos and microphthalmos (Rahi JS et al., 1995). In Saudi Arabia bilateral retinoblastoma has been reported to be more common in consanguineous couples (Al-Idrissi I et al, 1992). Both mild and severe mental retardation

tend to increase in consanguineous offspring (Al-Ansari A, 1993), and in the UK Pakistani population elevated rates of cerebral palsy have been reported (Sinha G, 1997).

Beside elevated levels of α- and β-thalassaemias (El-Hazmi MAF et al., 1997), rare complex haemoglobinopathies involving both α- and β-chain mutations, and other hematological disorders including coagulation deficiencies, have been reported at increased prevalence in consanguineous progeny (Giordano PC et al., 1999). There are also elevated levels of acute lymphocytic leukemia and childhood cancers in some communities (Bener A et al., 2001), This is also true for a wide range of inborn errors of metabolism that have been diagnosed in different indigenous and immigrant populations, including rare lysosomal storage disorders and cerebral lipidosis (Christopher R et al., 2002).

Global studies have shown a significantly higher incidence of major congenital malformations in the offspring of consanguineous parents. However, surveys in Saudi Arabia, Pakistan, and Jordan were unable to detect a significant increase in perinatal mortality or birth defects (Jaber L et al., 1992; Swailem AR et al., 1988; Yaqoob M et al., 1993; Aqrabawi HE, 2008).

### 2.8. Prevention of Congenital Anomalies

Reducing the prevalence and associated mortality and morbidity of congenital anomalies in Palestine is an attainable goal.

- Primary preventive efforts are clearly the optimal approach for ensuring the best possible pregnancy outcomes for Palestinian women. Food fortification with folic acid, promoting folic acid-containing multivitamin use in the periconceptional period, pre-pregnancy immunization against rubella, and interventions to reduce smoking and medications use in pregnancy are examples of important primary preventive measures.

- Prenatal diagnosis and subsequent termination of pregnancies with babies affected with lethal or hopeless congenital malformations, as well as in-utero treatment of some of the prenatally detected congenital anomalies (still experimental), are two secondary preventive strategies. As the scope of in-utero treatment remains limited, secondary prevention is mainly achieved through selective abortion.

- Prenatal diagnosis also contributes to tertiary prevention in cases where an early prenatal diagnosis improves postnatal management and reduces or avoids neonatal complications.

- Integrate the subject “consanguineous marriages; scope and effects” through the student curriculum. This subject needs clear and deep scientific discussions with the students to dispel misconceptions and to clarify advantages and disadvantages.

Successful implementation of these various initiatives will be dependent on community cooperation. They will not be aided by well-meaning but misconceived advice from external agencies that consanguineous, and even intercommunity marriage, simply should be avoided. Directive interventions of this nature run counter to a basic precept of genetic counseling. More importantly, they underestimate the central and valued role that consanguineous marriage has traditionally played in the lives of many different populations.

**2.9. Intervention approaches**

Prevention of congenital malformations is recognized as the ultimate goal, a goal that has not yet been reached despite much progress in the diagnosis, and treatment of birth defects. In addition to quests for the causes of congenital malformations and the removal of these causes, preventive methods must be sought that could aid in eliminating these malformations as sources of children's morbidity and mortality.

Morphology and embryology in abnormal human development were well established by the 19th century, and early in the 20th century many causative factors were discovered and preventive measures introduced. Identifying causative factors including genetics, disease entities, drugs, environment and nutrition, will always be required for the prevention of fatal abnormalities.

Primary prevention of genetic and congenital disorders depends largely on preconception information, screening, and counseling. Parents of affected children with genetic and congenital disorders should be informed of the fact that 50% of their brothers and sisters and

25% of their nephews and nieces may be carriers. Many carriers for an increasing number of inherited diseases can be detected through carrier testing (WHO 1997).

Researches demonstrate that folic acid intake by women before and during the first weeks of pregnancy can reduce the risk of some congenital malformations in offspring. Well documented is the impact of folic acid supplementation on decreasing the risk of neural tube defects (NTDs). Findings of many studies suggested, that maternal use of folic acid during periconceptional period can be effective for prevention of other congenital malformations, including defects of the heart, limb, urinary system and oro-facial clefts. The preventive programs of NTDs are conducted in many countries all over the world, which lead to popularization of everyday diet rich in folate and folic acid supplementation among women in childbearing age, and the food fortification with folic acid (Milunsky A et al., 1989).

As primary health providers, we should know the basic principles of the Epidemiology of congenital anomalies to provide adequate counseling to women in reproductive age, and to identify couples and pregnancies at risk, taking into consideration previous reproductive outcomes. A summary of common primary preventive measures is given in (table 2.2).

Table 2.2: Primary prevention of congenital malformations (Adopted from Rankin, Hobbs, Brent)

| Etiology of congenital malformations | Primary preventive recommendations |
|---|---|
| **Genetic** | |
| ~ Chromosomal disorders | Counsel on advanced maternal age risk |
| | Chromosomal rearrangement carrier detection in recurrent abortion |
| ~ Single-gene disorders | Counsel on advanced paternal age |
| | Offer genetic counseling to affected individuals |
| | Offer genetic counseling to consanguineous couples |
| | Offer screening for carrier detection |
| **Multi-factorial** | Offer genetic counseling to couples at risk |
| | Recommend consumption of periconceptional folic acid |
| | Counsel on and adapt treatment of maternal diseases |
| **Environmental agents** | |
| ~ Physical | Avoid radiation and treat hyperthermia |
| ~ Chemical | Avoid unnecessary drug exposure during pregnancy |
| | Avoid alcohol, tobacco, and other common substances abuse |
| | Counsel on occupational exposure |
| ~ Biological | Screening for potential teratogenic infection |
| | Indicate rubella vaccine when appropriate |

## 2.10. Conceptual Framework

Conceptual frameworks represent a less formal attempt to organizing phenomena than theories, which can serve to guide research and support theory development. Conceptual framework, like theories, can serve as springboard for the generation of research hypotheses. The following framework of congenital malformation has five main dimensions that show how congenital malformations can affect and been affected. These dimensions are socio-economic and behavioral characteristics, parent's age, environmental characteristics, maternal characteristics, and the obstetrical characteristics.

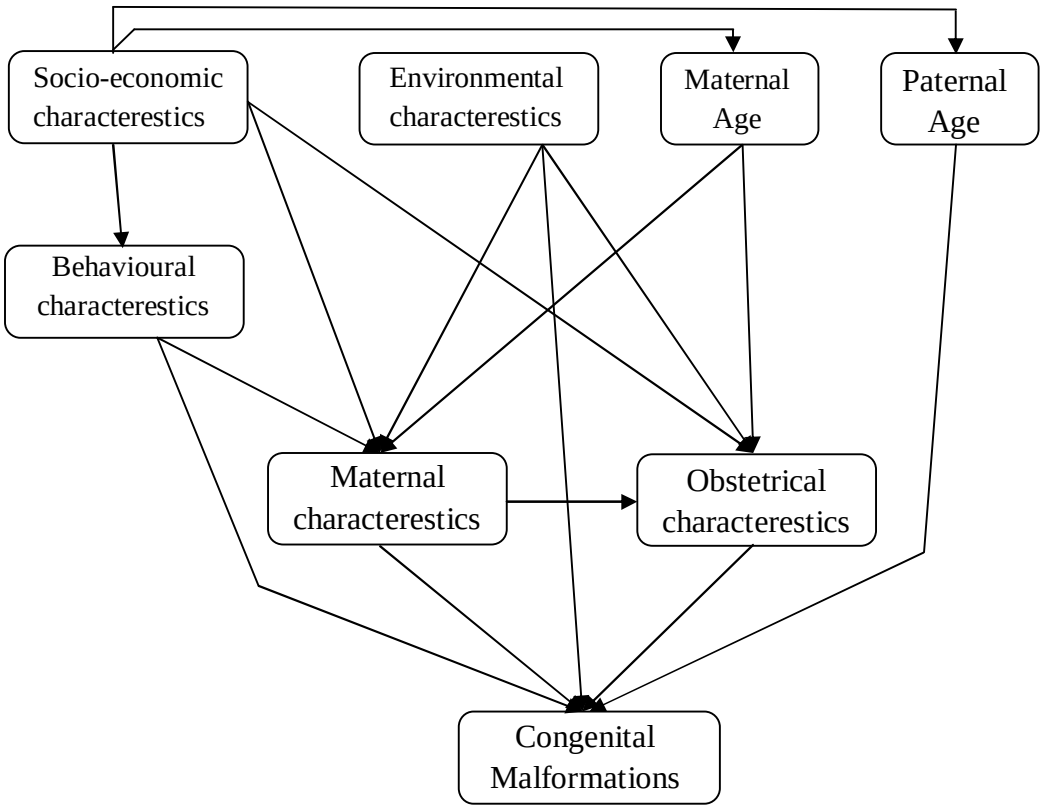


*Figure 2.1 Conceptual framework-factors that influence congenital malformations*

In order to decide what actions are needed to decrease the prevalence of the congenital malformations and hence promote the health of the infants, we need to be able to identify the reasons and the presumed influences of the congenital malformations. The model postulates that health-seeking behavior is influenced by a person's perception of a threat posed by a health problem and the value associated with actions aimed at reducing that threat.

## 2.11. Conclusion

Congenital malformations are one of the most miserable failures of modern medicine. The problem has been described as 'an epidemiologist's nightmare'. While much progress has been made in early detection of congenital malformations, the area of etiopathogenesis is still shrouded with darkness. Genetics, drugs, viruses and environment all have a role in causation but for vast majority of malformations the exact cause is not known. Thus, it may not always

be possible to prevent congenital malformations but mortality and morbidity secondary to these can be reduced by early detection and proper management. Awareness of local prevalence and pattern of malformations with associated factors in mother if any, can help the doctors rendering medical care to identify 'at risk' cases early, and plan appropriate and effective intervention.

# Chapter III
# Research Design: Methodology

## 3.1. Introduction

The main purpose of the study is to investigate the association between consanguinity, other risk factors, and congenital malformations in Palestine. This chapter describes the methodology, research design and sampling method that will be used in this study. Population and sample will be described; ethical consideration related to the study will be presented; and the instrument used in the study and methods of data analysis will be described.

### 3.2. Study design

A retrospective chart review study conducted at the maternity and neonatal departments of Al Makassed hospital in East Jerusalem, during the period June, 2007 till May, 2009.

### 3.3. The study population

The study population included all live born babies delivered at the maternity department of Al Makassed hospital between June 2007 and May 2009. The neonatal unit policy in the hospital implies that all newborns are examined twice by a senior pediatric resident within the first 24 hours of birth, after delivery and on discharge, any congenital malformation usually recorded in details.

During the study period, there were 5567 deliveries giving birth to 5729 live newborns, of these 291 babies were found to have congenital malformations.

### 3.4. Sampling method

The delivery and neonatal records of all newborns delivered at the maternity department of Al Makassed hospital during the study period were reviewed and relevant data were collected in a specific data collection form designed for the study. Relevant data were obtained in details including antenatally, prenatally and neonatally. Maternal data including parity, consanguinity, mother's age, father's age, age at first pregnancy, residency, educational level,

birth order, smoking, exposure to radiation, performing antenatal tests and examinations, family history for medical and genetic illnesses, significant maternal illnesses, ingestion of drugs, previous delivery of abnormal babies, mode of delivery, and other relevant information. Also all neonatal data were recorded in details including birth weight, gender, gestational age, and any abnormality found during clinical examination (appendix 1).

Anomalies were then divided into two major categories based on anatomic classification according to the International Classifications of Diseases (ICD-10).

1. **Major malformations:** anatomic abnormalities which are severe enough to reduce life expectancy or compromise normal function (Czeizel AE, 1997).

2. **Minor malformations:** structural alterations which either require no treatment or can be treated easily and have no permanent consequences for normal life expectancy (Czeizel AE, 1997).

### 3.5. Setting Background

This study was conducted at Al-Makassed hospital in East Jerusalem. The hospital is the main referral centre for people living in East Jerusalem, West Bank and Gaza strip where it provides tertiary and quaternary levels of care. The hospital has a busy obstetric department with around 3000 deliveries per year, supported by a well equipped and staffed NICU, which is considered the largest NICU in Palestine

All deliveries are registered in a special registry kept in the delivery department where all the maternal demographic data, the delivery details, and the newborn data are recorded. The newborns also have special registry where all the neonatal data are recorded. All newborns are examined twice by a senior pediatric resident, after delivery and on discharge, and all physical findings including congenital anomalies are recorded in details.

### 3.6. Sample size

Since the prevalence of congenital and genetic disorders among newborns is relatively low. The actual sample size was 5567 mothers, giving birth to 5729 live newborns, of these 291 babies were found to have congenital anomalies.

### 3.7. Data collection form

All the neonatal records were reviewed and the data were entered in a specific data collection form made specifically for this study (appendix 1).

1. Personal information: including file number of mother and infant, residency, age of both mother and father.
2. Socioeconomic factors including number of years of education for the mothers and fathers, age at marriage for mothers and fathers, religion, and consanguinity among the couples.
3. Obstetric history including age at first pregnancy, parity, gestational age, interval between marriage and first delivery, abortions, stillbirths, infants and children deaths, cesarean sections, pregnancy health-related problems, medication use, smoking alcohol consumption, radiation exposure, family history of genetic or congenital disorders.
4. Infant's data and the infant status such as birth weight, sex, and mode of delivery.

### 3.8. Ethical and confidentiality matters

An official letter of approval to conduct the research was obtained from the hospital administration "the only authorized official body to give permission for researches in the hospital" (appendix 2). For confidentiality purposes no names were used, and the patients were coded by the file number, also the data collection sheets were only accessible for the primary investigator and the supervisor. The data entry into the computer was also coded using file numbers and no names used.

### 3.9. Data collection

The neonatal records of all live newborns delivered during the study period were reviewed, and those with any congenital abnormality were included in the study. The maternal charts, the clinic visit charts, and the birth certificate office charts for these babies were also reviewed. Data entered into the designed data collection form, and after that into the computer.

### 3.10. Analysis of data

Data analyzed using computer based SPSS version 17 to reveal the relationship between independent variables, such as consanguinity, mother`s age, father`s age, age at first pregnancy, residency, maternal illnesses, educational level, birth order, use of medications, smoking, exposure to radiation, performing the antenatal tests and examinations, family history for medical and genetic illnesses, and newborn status such as birth weight, sex, gestational age, and the dependent variable, which is congenital malformations. Data was analyzed using the descriptive analysis, and Bivariate /Multivariate associations. Logistic regression utilized to investigate the association between the parental consanguinity and its effect on the congenital malformations with adjusting for all known confounders. The level of probability was set at $p \leq 0.05$.

### 3.11. Conclusion

Congenital malformations occur all over the world. The significance of congenital malformations lies not only in their contribution to mortality but also in causing disability and handicaps.

The main purpose of the study is to investigate the association between consanguinity, other risk factors, and congenital malformations in one of the Palestinian hospitals. A retrospective cohort descriptive method was used in this study; the sample size was 5567 mothers with 5729 newborns. Data collection form was designed especially for this study.

# Chapter IV

# Results

## 4.1. Introduction

This chapter presents the findings of the congenital malformations and the common risk factors.

### 4.2. Description of Sample

During the study period between June 2007 and May 2009, there were 5729 live births resulting from 5567 delivers, with 114 pairs of twins, 15 sets of triplets, and 6 sets of quadruplet. Of these 3014 were females and 2715 were males. Out of the 5729 live births, 292 babies were found to have congenital malformations, with an overall incidence of 5%. There were 130 (44.7%) minor malformations and 161 (55.3%) major malformations (Table 4.1). The incidence of malformations was significantly higher among male babies vs. females (56.7% vs. 42.6% respectively).

Table 4.1: Study Population Profile

| Details | Number | % |
|---|---|---|
| Total live Births | 5729 | |
| ~ Males | 2715 | |
| ~ Females | 3014 | |
| ~ Twins | 114 | pairs |
| ~ Triplets | 15 | sets |
| ~ Quadruplets | 6 | sets |
| Babies with malformation | 291 | (5) |
| ~ Major malformations | 161 | (55.3) |
| Minor malformations | 130 | (44.7) |

### 4.3. Socio-demographic Variables

The studied socio-demographic variables include: mother's age, father's age, place of residency, the mother's level of education, the father's level of education, age at marriage, age at first pregnancy, number of pregnancies, and number of living children.

#### 4.3.1. Age at Delivery

The mothers' age at delivery showed that 26 babies (8.9%) in our study population their mothers were between the ages (15-19), which gives a reflection of the rate of teenage pregnancy (less than 19 years old) at our country, and also the rate of early age at marriage. In our cohort we found that 149 mothers (51.2%) were married before age 19, while in fathers that was only 1.7%.

Results showed that 43 babies (14.7%) were born for women who 35 years and older at time of delivery, while in men 100 (34.6%) were above 35 years.

Most of the babies who born for mothers who were in the age group (20-34) years, 222 babies (76.2%) were born for mothers in this age group, of them 119 babies found to have major malformations, and the other 103 babies born with minor congenital malformations.

#### 4.3.2. Age at Marriage

It was observed that 149 babies with congenital malformations were born for women who were married before the age of 19 years (51.1%), 77 babies (51.7%) of them had major malformations, compared to 142 (48.8%) babies born to women married between age (20-34) years, where 84 of them (59.1%) found to have major malformations.

None of the mothers in our cohort were married $\geq$ 35 years. The difference between the three groups by congenital malformations was not statistically significant. The average age at marriage for mothers was 20.5 years.

#### 4.3.3. Education

The majority of the babies in our study, 185 (63.4%), their mothers had 12 or less years of education, and the same applied for fathers 182 (62.3%). On the other hand the high education group (BA degree & higher education groups) represent about one third of the fathers and even less in the mothers group: 78 (26.7%) in mothers and 88 (30.2%) in fathers.

In the study 185 babies with congenital malformations (63.3%) were born to mothers who were illiterate or having an educational level of 12 years or less, of them 101 babies (54.6%) had major malformations, and 84 (45.4%) had minor ones.

We found that 106 babies in our cohort were born to mothers with higher educational level, of them 62 (58.9%) had major congenital malformations, and 44 (41.1%) minor ones.

The mean number of years of education for women was 10.6 years. Level of education was not statistically significant.

The locality was divided into four groups; the highest number of delivers came from the middle region accounting for 163 babies (56%), because of the relative distance from the hospital, and the boundaries that put obstacles for easy access to the hospital. Mothers from the northern part of the country represent 68 (23.3%), and only 59 (20.2%) came from the southern part (Table 4.2).

Table 4.2: Distribution of malformations by some social variables, age at marriage, age at delivery, education, and locality

| Variables | Congenital malformations | | | | | | P value |
|---|---|---|---|---|---|---|---|
| | Total | | Major | | Minor | | |
| | No. | % | No. | % | No. | % | |
| **Mother's age at Marriage** | | | | | | | |
| 15-19 | 149 | 51.2 | 77 | 51.7 | 72 | 48.3 | 0.718 |
| 20-34 | 142 | 48.8 | 84 | 59.1 | 58 | 40.9 | |
| 35 and above | 0 | 0 | 0 | 0 | 0 | 0 | |
| **Age at delivery** | | | | | | | |
| • Mother 15-19 | 26 | 8.9 | 12 | 46.1 | 14 | 53.9 | 0.039 |
| 20-34 | 222 | 76.2 | 119 | 53.6 | 103 | 46.4 | |
| 35- and above | 43 | 14.7 | 30 | 69.7 | 13 | 30.3 | |
| • Father 15-19 | 5 | 1.7 | 3 | 60 | 2 | 40 | 0.017 |
| 20-34 | 186 | 63.9 | 96 | 51.6 | 90 | 48.4 | |
| 35- and above | 100 | 34.3 | 62 | 62 | 38 | 38 | |
| **Education** | | | | | | | |
| • Mother 12 years and less | 185 | 63.5 | 101 | 54.6 | 84 | 45.4 | 0.417 |
| 2 years collage | 29 | 9.9 | 14 | 48.2 | 15 | 51.8 | |
| BA University | 72 | 24.7 | 43 | 59.7 | 29 | 40.3 | |
| Post Graduate | 5 | 1.9 | 3 | 60 | 2 | 40 | |
| • Father 12 years and less | 182 | 62.5 | 102 | 56 | 80 | 44 | 0.573 |
| 2 years collage | 22 | 7.6 | 10 | 45.5 | 12 | 44.5 | |
| BA University | 74 | 25.4 | 39 | 52.7 | 35 | 47.3 | |
| Post Graduate | 13 | 4.5 | 10 | 76.9 | 3 | 23.1 | |
| **Locality** | | | | | | | |
| Middle | 163 | 56.0 | 85 | 52.1 | 78 | 47.9 | 0.756 |
| North | 68 | 23.3 | 46 | 67.6 | 22 | 32.4 | |
| South | 59 | 20.2 | 29 | 49.2 | 30 | 50.8 | |

## 4.4. Consanguineous Marriage

In our cohort, 134 of babies were born to consanguineous couples, which give a prevalence of consanguineous marriage in our study group of 45.9%

### 4.4.1. Degree of consanguinity

Among the consanguineous marriages, 101 (75.4%) were first-degree cousins, in 52 of them (51.5%) anomalies were major, and 49 (48.5%) had minor defects.

Marriages with less than first cousins were 33 (13.4%), of them 9 had major congenital malformations and the other 9 were born with minor anomalies.

Those in the not relatives group were the largest group comprising 157 (54%), 89 (56.7%) of them found to have major malformations, and 68 babies (43.3%) with minor one, P value showed no test significance. ($p > 0.05$)

Table 4.3: Distribution of the congenital malformations by the degree of consanguinity

| **Degree of Consanguinity** | **Congenital malformations** | | | | | | P Value |
|---|---|---|---|---|---|---|---|
| | **Total** | | **Major** | | **Minor** | | |
| | *No.* | *%* | *No.* | *%* | *No.* | *%* | |
| First degree cousin | 101 | 34.7 | 52 | 51.5 | 49 | 48.5 | 0.236 |
| Less than First cousin | 33 | 11.3 | 20 | 60.6 | 13 | 39.4 | |
| Not Relatives | 157 | 54.0 | 89 | 56.7 | 68 | 43.3 | |
| **Total** | **291** | **100** | | | | | |

## 4.5. Obstetric history of the women

### 4.5.1. Age at First Pregnancy:

It was observed that 80 babies (27.4%) of our study population were born for mothers who were 19 years or less at their first pregnancy, and (2.7%) of them were 16 years old or less. Of these 80 babies, 43 (53.8%) had major malformations, and 37 (46.2%) had minor congenital anomalies. 210 newborns were born to mothers who were between age (20-34) years at their

first pregnancy, representing (72.1%) of the total study population. Of these, 121 (57.6%) had major congenital malformations, and 89 babies (42.4%) born with minor anomalies.

The mean age at first pregnancy for the study population was 21.9 years. There was no statistical significance for age at first pregnancy and congenital malformations.

### 4.5.2. Number of living children

It was observed that most of the babies with congenital malformation were born to mothers who had three living children or less. One hundred eighty babies (61.8%) of the total study population were born for mothers who had three or less living babies, of them 98/180 babies (54.5%) had major congenital malformations, and 82/180 (45.5%) had minor ones.

While there were 84 babies (28.8%) of the total study population born for mothers who had between four to six living children, of them 48/84 babies (57.1%) born with major congenital malformations, and 36/84 babies (42.9%) were born with minor ones.

Only 27 babies (9.4%) were born for mothers who had seven living babies or more. 19/27 babies (70%) had major malformations, and 8/27 babies (30%) had minor congenital malformations.

The differences between the groups reach the level of statistical significance ($p < 0.05$).

### 4.5.3. Total pregnancies

It was observed that most of the babies with congenital malformations, in our cohort were born for mothers who had three or less pregnancies. The results showed that 151babies (51.9%) fall in this category, of them 79/151 babies (52.3%) had major congenital malformations, and 72/151 babies (47.7%) had minor malformations. Ninety seven babies (33.3%) were born for mothers who got pregnant more than four times, of them 53/97 babies (54.6%) born with major congenital malformations, and 44/97 babies (45.4%) with minor ones.

Babies with congenital malformations who were born to mothers who got pregnant seven times and more, were 43 babies (14.7% of the total study population), of them 29/43 babies (67.4%) were found to have major congenital malformations, and 14/43 babies (32.6%) minor ones. The differences between the groups were statistically significant at $p < 0.05$.

Table 4.4: Distribution of the CM by age at first pregnancy, # of pregnancies, and living children per woman

| Variables | Congenital malformations | | | | | | P value |
|---|---|---|---|---|---|---|---|
| | Total | | Major | | Minor | | |
| | No. | % | No. | % | No. | % | |
| **Age at first pregnancy** | | | | | | | |
| 15 - 19 | 80 | 27.5 | 43 | 53.8 | 37 | 46.2 | 0.439 |
| 20 - 34 | 210 | 72.1 | 121 | 57.6 | 89 | 42.4 | |
| 35 - and above | 1 | 0.4 | 1 | 100 | 0 | 0 | |
| **Total pregnancies** | | | | | | | |
| 3 or less | 151 | 51.9 | 79 | 52.3 | 72 | 47.7 | 0.021 |
| Between 4-6 | 97 | 33.3 | 53 | 54.6 | 44 | 45.4 | |
| 7 or more | 43 | 14.8 | 29 | 67.4 | 14 | 32.6 | |
| **Total of living children** | | | | | | | |
| 3 or less | 180 | 61.8 | 98 | 54.5 | 82 | 45.5 | 0.026 |
| Between 4-6 | 84 | 28.8 | 48 | 57.1 | 36 | 42.9 | |
| 7 or more | 27 | 9.4 | 19 | 70.3 | 8 | 29.7 | |

### 4.5.4. Birth Order

It was observed that most of the babies with congenital malformations were born for mothers who delivered for the first time. Results showed that 70 (24%) babies were born for mothers who delivered for the first time, (the first baby), of them 37/70 babies (52.9%) born with major congenital malformations, and 33/70 babies (47.1%) with minor congenital malformations.

The results also showed that the congenital malformations decreased by increasing the birth order. The second and the third birth order gives respectively 60 (20.5%), 50 (17.1%) malformed babies, of them 33/60 (55%), 28/50 (56%) with major congenital malformations, and 27/60 (45%), 22/50 (44%) with minor malformations. Babies with congenital malformations who were the eighth or ninth in birth order were 8 babies (2.7%) of them 6/8 babies (75%) with major congenital malformations and 2/8 babies (25%) with minor

congenital malformations. The difference between the birth order was statistically significant. ($P < 0.05$)

Table 4.5: Congenital malformations by birth order

| Birth Order | **Congenital malformations** | | | | | | P value |
|---|---|---|---|---|---|---|---|
| | Total | | **Major** | | **Minor** | | |
| | No. | % | No. | % | No. | % | |
| The First | 70 | 24.0 | 37 | 52.9 | 33 | 47.1 | 0.042 |
| The Second | 60 | 20.6 | 33 | 55 | 27 | 45 | |
| The Third | 50 | 17.2 | 28 | 56 | 22 | 44 | |
| The Fourth | 41 | 14.1 | 24 | 58.5 | 17 | 41.5 | |
| The Fifth | 30 | 10.3 | 15 | 50 | 15 | 50 | |
| The Sixth | 13 | 4.5 | 9 | 69.2 | 4 | 30.8 | |
| The Seventh | 13 | 4.5 | 7 | 53.8 | 6 | 46.2 | |
| The Eighth | 8 | 2.7 | 6 | 75 | 2 | 25 | |
| The Ninth | 6 | 2.1 | 6 | 100 | 0 | 0 | |
| **Total** | **291** | **100** | | | | | |

### 4.5.5. Health Problems during the last pregnancy

The total number of babies delivered for women who had health problems during their last pregnancy was 111 (38%) of the total study population. The majority of them 73/111 (65.8%) of babies were had major congenital malformations, compared to only 38/111 of babies (34.2%) with ones. The differences between the health problems and the congenital malformations were statistically significant. ($P < 0.05$)

The frequent health problems for the mothers who delivered the malformed babies who were involved in this study were gestational D/M, D/M, HTN, Infections, Heart diseases, and some other health problems which were the less frequent. Twenty one babies 21/111 (18.9%) were born for mothers who developed Gestational D/M during last pregnancy. Of them 13/21 babies (61.9%) were born with major congenital malformations, and 8/21 of them were born with minor congenital malformations. Nine babies 9/111 were (8.2%) born for mothers who had a history of either D/M or HTN. Seven of them were born with major congenital

malformations, while 2/9 babies were born with minor congenital malformations. Also 3/111 babies (2.7%) were born for mothers who were had heart diseases before and during her last pregnancy, all of them were born with major congenital malformations. Anemia, pre-eclampsia and hypo-hyperthyroidism were less frequent in those mothers who delivered the malformed babies. Sixty six babies out of one hundred eleven (59.4%) were born for mothers who were had the less frequent problems. Forty six of them 46/66 (69.7%) were born with major congenital malformations, and the rest of them 20/66 (30.3%) were born with minor congenital malformations.

It was observed that there was statistical significance between the outcome (congenital malformations) and the group of the health problems that were mentioned in the data collection tool, and it was seen in the percentage of these problems which were higher among the major congenital malformations than the minor ones.( $p < 0.01$)

Table 4.6: Congenital malformations by health problems & their kinds during last pregnancy.

| **Variables** | Congenital malformations | | | | | | P value |
|---|---|---|---|---|---|---|---|
| | Total | | Major | | Minor | | |
| | No. | % | No. | % | No. | % | |
| **Health Problems** | | | | | | | |
| Yes | 110 | 37.8 | 72 | 65.8 | 38 | 34.2 | 0.018 |
| No | 174 | 59.7 | 89 | 51.1 | 85 | 49.9 | |
| No Data | 7 | 2.5 | 4 | 57.1 | 3 | 42.9 | |
| **Kind of Health Problems** | | | | | | | |
| Ges. D/M | 21 | 18.9 | 13 | 61.9 | 8 | 38.1 | 0.009 |
| HTN & D/M | 9 | 8.2 | 7 | 77.8 | 2 | 22.2 | |
| Infectious | 12 | 10.8 | 4 | 33.3 | 8 | 66.7 | |
| Heart Disease | 3 | 2.7 | 3 | 100 | 0 | 0 | |
| Others | 66 | 59.4 | 46 | 69.7 | 20 | 30.3 | |

{Others: pre-eclampsia, Anemia, hypo-hyperthyroidism, Thrombophilia, Hydramnios, DVT, Gastritis, Hyperemesis, Falling Down, Head Trauma}

### 4.5.6. History of miscarriages, stillbirths, and congenitally malformed babies

The following table (4.7) shows that the number of the babies with congenital malformations who were born for mothers with no history of miscarriages was 175 babies (60.1%) of the total study population, 91/175 babies (52.0%) were born with major congenital malformations, compared to 84/176 babies (48%) with minor malformations. One hundred six babies (36.5%) of the total population were born for mothers who had a history of 1-2 miscarriages, 62/106 of them (58.5%) were found to have major congenital malformations, and 44/106 (41.5%) with minor ones. Only 10 babies (3.4%) were born for mothers who had history of three or more miscarriages, 9/10 babies (90%) of them were born with major congenital malformations, and only one baby with minor ones. The differences between the history of miscarriage and the congenital malformations were statistically significant. ($P < 0.05$)

The same table (4.7) shows that the total number of babies with congenital malformations born for mothers who had a history of one stillbirth were 17 (5.8%), of them 14/17 (82.3%) had major malformations, and 3/17 had minor ones. For those babies with congenital malformations who born to mothers had no history of stillbirths were 274 babies which equal (94.1%) of the total study population. One hundred forty eight of them (148/274) babies were found with major congenital malformations and 127/274 babies were with minor malformations. The differences between congenital malformations and stillbirth did not reach the level of statistical significance.

Furthermore, the table (4.7) shows babies with congenital malformations who born for mothers who had a history of previous babies in their families with congenital malformations. Two hundred twenty nine (78.4%) babies with congenital malformations born to mothers had no history of congenitally malformed babies. Out of them, 128/229 babies (55.9%) born with major congenital malformations, and 101/229 babies (44.1%) with minor congenital malformations. Only 62 babies (21.4%) of the total study population, were born for mothers who had a history of previous congenitally malformed babies in their families. 33/62 babies (53.2%) of them born with major malformations, and 29/62 babies (46%) with minor malformations. The test was not statistically significant.

Table 4.7: Congenital malformations by miscarriage, stillbirths, and H/O CM per woman

| Variables | Congenital malformations | | | | | | P value |
|---|---|---|---|---|---|---|---|
| | Total | | Major | | Minor | | |
| | No. | % | No. | % | No. | % | |
| **Miscarriages** | | | | | | | |
| No abortion | 175 | 60.1 | 91 | 52 | 84 | 48 | 0.014 |
| Between 1-2 | 106 | 36.5 | 62 | 58.5 | 44 | 41.5 | |
| More than two | 10 | 3.4 | 9 | 90 | 1 | 10 | |
| **Stillbirths** | | | | | | | |
| Yes (one or more) | 17 | 5.9 | 14 | 82.3 | 3 | 17.7 | 0.732 |
| No | 274 | 94.1 | 147 | 53.6 | 127 | 46.4 | |
| **H/O congenital malformations** | | | | | | | |
| Yes (one or more baby) | 62 | 21.4 | 33 | 53.2 | 29 | 46.8 | 0.383 |
| No (no H/O CM babies) | 229 | 78.6 | 128 | 55.9 | 101 | 44.1 | |

## 4.6. Ante-natal care

Prenatal consultations might also influence maternal health states. One of the objectives of prenatal care is to prevent and detect major congenital problems. Maternal health status might consequently be better when attending prenatal clinics. It can play an important role in assisting women to maintain healthy lifestyles.

Results showed that the percentage of babies in our study population whose mothers had their antenatal care at Al-Makassed hospital (booked at Al Makassed hospital clinics) was 150 (51.5%).Of these, 87 (58.0%) born with major congenital malformations, and 63 babies (41.7%) with minor ones.

The rest of the babies (141 babies), which represent (48.3%) of the total study population, their mothers were not booked at Al Makassed Hospital, 74 of them (52.5%) had major congenital malformations, and 67 (47.5%) had minor ones, with no test significance.

In General we found that 255 of our babies (87.6% of the total study population), their mothers attended antenatal care for two or more visits either at Al-Makassed hospital or elsewhere. In this group, 139 babies (54.5%) were born with major congenital malformations, and 116 babies (55.5%) with minor ones. Babies with congenital malformations who born for mothers who had no antenatal care, or Just one visit represent (12.4%) of the total study population, 22 (61.1%) of these babies had major congenital malformations, and 14 (38.9%) minor malformations, and no statistical test significance.

Ultrasound imaging and specifically detailed ultrasound scanning is currently an integral part in antenatal maternity care. Results showed that 162 babies (55.6%) in our study were born to mothers who had examined by ultrasound at least three times or more during their antenatal care visits. Of them, 92/162 babies (56.8%) were born with major congenital malformations. Of those babies who born for mothers who had examined by ultrasound, only 212 babies (72.6%) of the total study population their mothers had performed the detailed ultrasound exam. One hundred twelve babies (112/212) had born with major congenital malformations.

Other antenatal screening tests, the triple test, also called triple screen, which is an investigation performed during pregnancy in the second trimester to classify a patient as either high-risk or low-risk for chromosomal abnormalities (and neural tube defects). Only 55 babies (20.5%) with congenital malformations born to mothers who had performed the triple test. Of them, 39/55 babies (71%) were with major congenital malformations, and 16/55 babies (29%) with minor ones.

Amniocentesis test is a medical procedure used in prenatal diagnosis of chromosomal abnormalities and fetal infections. Only 14 babies (4.7%) were born to mothers who had performed the offered test. Ten babies out of 14 were with major congenital malformations.

Table 4.8: Distribution of congenital malformations by ante-natal care per woman

| Variables | Congenital malformations | | | | | | P value |
|---|---|---|---|---|---|---|---|
| | Total | | Major | | Minor | | |
| | No. | % | No. | % | No. | % | |
| **Booking at al-Makassed Hosp.** | | | | | | | |
| Booked | 150 | 51.5 | 87 | 58.0 | 63 | 42.0 | 0.299 |
| Unbooked | 141 | 48.5 | 74 | 52.5 | 67 | 47.5 | |
| **Number of the clinic visits** | | | | | | | |
| More than 2 visits | 255 | 87.6 | 139 | 54.5 | 116 | 55.5 | 0.115 |
| One visit or never | 36 | 12.4 | 22 | 61.1 | 14 | 38.9 | |
| **No. U/S examination** | | | | | | | |
| 1 – 2 times | 112 | 38.6 | 59 | 52.6 | 53 | 47.4 | 0.062 |
| 3 times and more | 162 | 55.6 | 92 | 56.8 | 70 | 43.2 | |
| No Data | 17 | 5.8 | 10 | 59.0 | 7 | 41.0 | |
| **Detailed U/S** | | | | | | | |
| Done | 212 | 72.8 | 122 | 57.4 | 90 | 42.6 | 0.357 |
| Not Done | 64 | 22.0 | 29 | 45.3 | 35 | 54.7 | |
| No Data | 15 | 5.2 | 10 | 66.7 | 5 | 33.3 | |
| **Triple test** | | | | | | | |
| Yes | 55 | 18.9 | 39 | 75 | 16 | 25 | 0.935 |
| No | 222 | 76.2 | 112 | 50.4 | 110 | 49.6 | |
| No Data | 14 | 4.9 | 10 | 83.3 | 2 | 16.7 | |
| **Amniocentesis Exam** | | | | | | | |
| Yes | 14 | 4.9 | 10 | 66.7 | 4 | 33.3 | 0.243 |
| No | 260 | 89.3 | 139 | 53.4 | 121 | 46.6 | |
| No Data | 17 | 5.8 | 12 | 78.6 | 5 | 21.4 | |

## 4.7. Congenital malformations and the sensitivity of some prenatal tests

### 4.7.1. Detailed Ultrasound

As mentioned previously, only 212 (72.6%) of our babies, their mothers had detailed ultrasound done. It was observed from the results of this study that, 113 babies (38.7%) had abnormal detailed U/S findings. Of them 106/113 babies born with major congenital malformations, and 7/113 babies had minor malformations. The remaining 99 babies, (33.9%) had normal detailed ultrasound test result, of them 16/99 babies born with major congenital malformations, and 83/99 babies were found to have minor ones.

Babies with congenital malformations born to mothers who did not perform detailed ultrasound were 62 babies, of them 27/62 babies born with major congenital malformations, and 35/62 had minor ones. The differences between the groups were highly reaching the level of statistical significance. ($p \leq 0.001$)

### 4.7.2. Amniocentesis test

As mentioned in the previous section, 14 babies (4.7%), in our cohort, their mothers had amniocentesis test done, despite the fact that 44 of our babies their mothers were older than 35 years old during the pregnancy, also 13 mothers had abnormal triple test result, and 113 babies their mothers had abnormal detailed ultrasound. Four out of the 14 babies their mothers had abnormal amniocentesis test result. All of these babies were born with major congenital malformations.

On the other hand, 10/14 babies (3.4%) with congenital malformations born to mothers who had normal amniocentesis test results, six of those babies born with major congenital malformations and 4/10 babies had minor ones.

Two hundred forty nine babies (85.6%) of the total study population born to mothers who did not perform this test. Of them 131/249 babies (52.6%) born with major congenital malformations, and 118 babies born with minor ones.

Eleven babies were born for mothers who refused to do the amniocentesis test, 8/11 of them were found to have major congenital malformations.

The differences between the groups did not reach the level of statistical significance.

### 4.7.1. Triple test

We were surprised to find that 210 (72.1%) of babies in our study their mothers did not have the triple test done, of these 103 babies (49.0%) were born with major congenital malformations, and 107/211 babies with minor anomalies.

Only in 55 babies (18.8%) in our study the mothers underwent triple test, 13 had abnormal test result and all of them were born with major congenital malformations.

In the 42 babies whose mothers had normal triple test results, 26/42 babies (61.9%) were born with major congenital malformations, and 16/42 babies (38.1%) had minor anomalies.

Table 4.9: Congenital malformations by the sensitivity of some prenatal tests

| **Variables** | **Congenital malformations** | | | | | | P value |
|---|---|---|---|---|---|---|---|
| | Total | | Major | | Minor | | |
| | No. | % | No. | % | No. | % | |
| **Detailed U/S Findings** | | | | | | | |
| Abnormal test | 113 | 38.7 | 106 | 93.8 | 7 | 6.2 | 0.001 |
| Normal test | 99 | 33.9 | 16 | 16.2 | 83 | 83.8 | |
| Refused | 2 | 0.7 | 2 | 100 | 0 | 0 | |
| No Data | 15 | 5.2 | 10 | 66.7 | 5 | 33.3 | |
| Not Done | 62 | 21.3 | 27 | 43.6 | 35 | 54.4 | |
| **Amniocentesis Findings** | | | | | | | |
| Abnormal test | 4 | 1.4 | 4 | 100 | 0 | 0 | 0.935 |
| Normal test | 10 | 3.4 | 6 | 3.7 | 4 | 3.1 | |
| Refused | 11 | 3.8 | 8 | 4.9 | 3 | 2.3 | |
| No Data | 17 | 5.8 | 12 | 7.4 | 5 | 3.8 | |
| Not Done | 249 | 85.6 | 131 | 52.6 | 118 | 47.4 | |
| **Triple test Findings** | | | | | | | |
| Abnormal test | 13 | 4.4 | 13 | 100 | 0 | 0 | 0.238 |
| Normal test | 42 | 14.4 | 26 | 61.9 | 16 | 38.1 | |
| Refused | 12 | 4.1 | 9 | 75 | 3 | 25 | |
| No Data | 14 | 4.8 | 10 | 71.4 | 4 | 28.6 | |
| Not Done | 210 | 72.1 | 103 | 49.0 | 107 | 51.0 | |

**When trying to put the three test results together we found**:

In our cohort only 4 babies were born for mothers who had normal test results for all of the previously mentioned antenatal diagnostic tests (DUSS, Amniocentesis, and triple test), 3/4 of them born with minor congenital malformations, and only one newborn found to have major anomalies.

Only one baby was born with major congenital malformations for a mother who had a normal detailed ultrasound and amniocentesis, with no triple test. Also one baby with major malformations was born for a mother who underwent a normal detailed ultrasound and triple test with no amniocentesis test.

Thirteen babies (4.5%) born for mothers who had normal detailed ultrasound and triple test results, with no amniocentesis test. Only 3/13 babies of them had major congenital malformations, and 10/13 babies were born with minor defects.

Seventy four babies were born for mothers who underwent a normal detailed ultrasound, with no amniocentesis or triple tests. Out of them 10/74 babies were born with major congenital malformations, and 64/74 babies with minor anomalies.

The 21 babies born to mothers who had abnormal detailed ultrasound, and normal or not done triple tests, and amniocentesis test results, all had major malformations.

Five babies born with major congenital malformations were for mothers who had an abnormal detailed ultrasound and triple test, and did not perform amniocentesis test.

Sixty nine babies delivered for mothers with an abnormal detailed ultrasound test result, and did not undergo either the triple test or amniocentesis test. Out of them 63 babies were with major congenital malformations, and only 6 babies with minor ones.

Two babies with major congenital malformations, born for mothers who underwent an abnormal detailed ultrasound with an abnormal triple test, and refused to perform the amniocentesis test. Another 2 babies were delivered for mothers who had an abnormal detailed ultrasound with a normal triple test, and refused to do an amniocentesis test. One of them was with major malformation, and the other with minor malformation.

Three babies were with major congenital malformations, born for mothers that underwent an abnormal detailed ultrasound, and refused to perform the other two tests (amniocentesis & triple tests).
One mother did not undergo a detailed ultrasound, and performed amniocentesis and triple tests, with an abnormal result, delivered a baby with major congenital malformations.

The total number of babies born for mothers who did not undergo any prenatal diagnostic tests was 53 (18.2%) of the total study population, 22 babies (41.5%) born with major congenital malformations, and 31 babies (48.5%) with minor anomalies

Table 4.10: Distribution of congenital malformations and the utilization of the prenatal tests

| **DUSS NL /ANL** | **AMNIO. NL / ANL** | **Triple Test NL / ANL** | **Congenital malformations** | | | | |
|---|---|---|---|---|---|---|---|
| | | | Total | Major | | Minor | |
| | | | No. | No. | % | No. | % |
| NL test | NL test | NL test | 4 | 1 | 25 | 3 | 75 |
| NL test | NL test | Not Done | 1 | 0 | 0 | 1 | 100 |
| NL test | Not Done | NL test | 13 | 3 | 23.1 | 10 | 76.9 |
| NL test | Not Done | ANL test | 1 | 1 | 100 | 0 | 0 |
| NL test | Not Done | Not Done | 74 | 10 | 13.5 | 64 | 86.5 |
| NL test | Not Done | Refused | 2 | 0 | 0 | 2 | 100 |
| NL test | No Data | Not Done | 2 | 1 | 50 | 1 | 50 |
| ANL test | NL test | NL test | 3 | 3 | 100 | 0 | 0 |
| ANL test | NL test | Not Done | 2 | 2 | 100 | 0 | 0 |
| ANL test | ANL test | ANL test | 3 | 3 | 100 | 0 | 0 |
| ANL test | Not Done | NL test | 16 | 16 | 100 | 0 | 0 |
| ANL test | Not Done | ANL test | 5 | 5 | 100 | 0 | 0 |
| ANL test | Not Done | Not Done | 69 | 63 | 91.3 | 6 | 8.7 |
| ANL test | Not Done | Refused | 4 | 4 | 100 | 0 | 0 |
| ANL test | No Data | No Data | 1 | 1 | 100 | 0 | 0 |
| ANL test | Refused | NL test | 2 | 1 | 50 | 1 | 50 |
| ANL test | Refused | ANL test | 2 | 2 | 100 | 0 | 0 |
| ANL test | Refused | Not Done | 2 | 2 | 100 | 0 | 0 |
| ANL test | Refused | Refused | 3 | 3 | 100 | 0 | 0 |
| Not Done | Not Done | NL test | 4 | 2 | 50 | 2 | 50 |
| Not Done | Not Done | Not Done | 52 | 21 | 40.3 | 31 | 59.7 |
| No Data | No Data | No Data | 10 | 8 | 80 | 2 | 20 |
| Refused | Not Done | Refused | 2 | 2 | 100 | 0 | 0 |

### 4.8. Environmental risk factors

Results showed that 171 babies (58.8%) were born for mothers who used to take periconceptional medications (Folic acid, Iron, and Vitamins) during their last pregnancy, of them 86/171 babies (50.3%) were born with major congenital malformations, and 85 babies (49.7%) with minor ones.

Twenty four babies in our cohort their mothers used to take different other kinds of medication during their last pregnancy; 21 of them were born with major congenital malformation, and only three with minor anomalies.

Eleven babies (3.8%) of the total study population were born for mothers who used to smoke during their last pregnancy, 4 Of them (36.3%) born with major congenital malformations.

Only one of the babies (0.3%) in our cohort, the mother was exposed to therapeutic radiation during pregnancy, and born with major congenital malformations.

The differences between these groups did not reach the level of the statistical significance.

Table 4.11: Congenital malformations by some environmental risk factors

| **Variables** | **Congenital malformations** | | | | | | P value |
|---|---|---|---|---|---|---|---|
| | Total | | Major | | Minor | | |
| | No. | % | No. | % | No. | % | |
| **Using of Medications during Preg.** | | | | | | | |
| ~ Iron, Folic acid, and Vitamins | 171 | 58.8 | 86 | 50.3 | 85 | 49.7 | 0.610 |
| ~ Other Medications | 24 | 8.3 | 21 | 87.5 | 3 | 22.5 | |
| ~ Nothing/No Data | 96 | 32.9 | 54 | 56.3 | 42 | 43.7 | |
| **Smoking** | | | | | | | |
| ~ Yes | 11 | 3.8 | 4 | 36.3 | 7 | 63.7 | 0.327 |
| ~ No | 277 | 95.1 | 156 | 56.3 | 121 | 43.7 | |
| ~ No Data | 3 | 1 | 1 | 33.3 | 2 | 66.7 | |
| **Exposure to X-Ray radiation** | | | | | | | |
| ~ Never | 290 | 99.7 | 160 | 55.2 | 130 | 44.8 | 0.155 |
| ~ Once or more | 1 | 0.3 | 1 | 100 | 0 | 0 | |

{Other medications: Eltroxin, Coumadin, B. Aspirin, Clexane, Anti-hypertensive, Paragesic, Anti-biotic, Anti-emetic, Calcium}

## 4.9. Baby Status

### 4.9.1. Birth weight

The results of our study showed that 9 babies were born with a birth weight of less than 1500 grams, which represent (3.1%) of the total study population, out of them 7/9 babies (77.8%) had major congenital malformations, and 2/9 babies (22.2%) had minor ones.

The majority of our babies 227/292 babies (77.7%) were born with a birth weight between (2501-4000) gram, of them 119/227 babies (52.5%) were born with major congenital malformations, and 108/227 babies (47.5%) with minor anomalies.

Sixteen babies (5.5%) had a birth weight more than 4 kilograms, 11/16 of them had major congenital malformations.

During the study period, the total number of live births born with a birth weight of < 2500 gm was 608 babies, with 49 babies having congenital malformations (8%). Those born with birth weight more than 4 kg were 265, of them 16 had congenital malformations (6%). The majority 4839 babies had birth weight between 2500-4000gm, of them 226 had congenital malformations (4.7%)

The incidence of congenital malformations decreased with increasing birth weight, till reaching the 4000 gm (Statistically significant)

### 4.9.2. Newborn gender

In our study, only 2 newborns (0.7%) were born had ambiguous genitalia, 165 males (56.7%) of the total study population, and 124 females (42.6%) with ratio of (M: F) 1:1.3

There was no significant difference in the distribution of congenital malformations between the two sexes.

### 4.9.3. Gestational age

The study showed that 4 babies (1.4%) in our cohort had a gestational age of 28 weeks and less, 3had major malformations. Thirty tow babies (11%) were born with gestational age between 29-34 weeks of them 21 babies (65.6%) born with major congenital malformations, and 10 babies (34.4%) with minor ones

Babies born between (35-36) weeks gestational age were 32 (10.9%) of the total study population, 20 babies (63.6%) of them were born with major congenital malformations.

Most of the babies in our study (223 babies, that equals 76.3%) had a gestational age of 37 weeks or more, f them 117 babies were born with major congenital malformations, and 106 with minor anomalies.

During the study period 19 babies were born with a gestational age of 28 weeks or less and 4 of them (21%) had congenital malformations. Those babies born between 29-34 weeks GA were 238, of them 32 (13.4%) had congenital malformations. The incidence of congenital malformations in babies born with a gestational age between 34-36 weeks was 9.3% (33/354). Babies born with a gestational age of 37 weeks or more, were 5110 with 223 babies having anomalies (4.4%)

Statistically there is a significant fall in the incidence of congenital malformations with increasing the gestational age. This was highly significant at the level 0.01.

### 4.9.4. Mode of delivery

It was observed that, the total number of the babies delivered vaginally was 194 (66.4%) of the total study population, of them 93 babies (47.9%) had major congenital malformations and 101 babies (52.1%) born with minor ones. Mode of delivery no statistical test significance. While 93 babies (32.2%) were born through caesarian section, of them 67 babies (72%) were born with major congenital malformations, and 26 babies (28%) were with minor anomalies. Only 4 babies (1.4%) of the total study population were born by vacuum mode, of them one baby was born with major congenital malformations, and the other 3 babies were with minor ones.

Table 4.12: Congenital malformations by newborn gender, gestational age, mode of delivery, and birth weight

| Variables | All Babies | | Congenital malformations | | | | | | P value |
|---|---|---|---|---|---|---|---|---|---|
| | Total | | Malformed | | Major | | Minor | | |
| | No. | % | No. | % | No. | % | No. | % | |
| **Newborn Gender** | | | | | | | | | |
| Male | 3156 | 55.1 | 165 | 56.7 | 90 | 54.5 | 75 | 45.5 | 0.623 |
| Female | 2571 | 44.9 | 124 | 42.6 | 69 | 55.6 | 55 | 44.4 | |
| Ambiguous | 2 | 0.03 | 2 | 0.7 | 2 | 100 | 0 | 0 | |
| **Gestational Age** | | | | | | | | | |
| 28 and less | 19 | 0.4 | 4 | 21 | 3 | 75 | 1 | 25 | 0.000 |
| 29 - 34 | 238 | 4.2 | 32 | 13.4 | 21 | 65.6 | 11 | 34.4 | |
| 35 - 36 | 354 | 6.2 | 32 | 9.0 | 20 | 63.6 | 12 | 36.4 | |
| 37 – and more | 5110 | 89.2 | 223 | 4.4 | 117 | 52.5 | 106 | 47.5 | |
| **Mode of Delivery** | | | | | | | | | |
| S.Vaginal Delivery | | | 194 | 66.4 | 93 | 47.9 | 101 | 52.1 | 0.900 |
| Caesarian Section | | | 93 | 32.2 | 67 | 72.0 | 26 | 28.0 | |
| Vacuums | | | 4 | 1.4 | 1 | 25 | 3 | 75 | |
| **Newborn Weight** | | | | | | | | | |
| 1500 and less | 117 | 2.1 | 9 | 7.7 | 7 | 77.8 | 2 | 22.2 | 0.339 |
| 1501 - 2500 | 491 | 8.6 | 40 | 8.2 | 25 | 62.5 | 15 | 37.5 | |
| 2501 - 4000 | 4839 | 84.6 | 226 | 4.7 | 118 | 52.2 | 108 | 47.8 | |
| More than 4000 | 265 | 4.7 | 16 | 6 | 11 | 68.8 | 5 | 31.2 | |

## 4.10. Infants Morbidity:

The following classification of the congenital malformations was adopted according to the international classification of diseases (ICD 10).

### 4.10.1. Distribution of Congenital Malformations

We found that the number who had congenital anomalies was 291, born to 287 women. The incidence rate was calculated to be 5% during the study period. There were 161 babies (55.3%) with major malformations, and 130 babies (44.7%) with minor ones. Cardiac malformations were the commonest, with 101 babies (18.3 per 1000 births) affected, and this accounted for almost one third of the defects recorded. Musculoskeletal malformations came second, with 72 babies (12.5 per 1000 births) affected, then genitourinary tract abnormalities with 69 babies affected (12 per 1000 births), gastrointestinal tract with 37 babies affected (6.5 per 1000 births), renal system with 31 babies affected (5.4 per 1000 births), chromosomal syndromes 22 (3.8 per 1000 births), pulmonary defects 8 (1.4 per 1000 births). The following table illustrates all the congenital malformations reported in our study.

Table 4.13: Systemic Distribution of Congenital Malformations

| System and type of defects | Num | Incide/1000 live births |
|---|---|---|
| **1. Cardiac anomalies** | **101** | 18.3 |
| **2. Musculoskeletal** | **72** | 12.5 |
| **3. Genitourinary** | **69** | 12 |
| **4. Gastrointestinal system** | **37** | 6.5 |
| **5. Renal system** | **26** | 4.5 |
| **6. Central nervous system** | **22** | 3.8 |
| **7. Respiratory defects** | **7** | 1.2 |
| **8. Syndromes** | **22** | 3.8 |
| **9. *Miscellaneous*** | **29** | 5 |

### 4.10.2. Congenital cardiac anomalies

It was observed that one third of the defects reported in our study involve the heart, with 101 babies involved (15/1000 live births). The commonest cardiac defect was atrial septal defect (ASD) which was present in 29 babies (28.7% of all cardiac defects). Ventricular septal defects (VSD) found with 24 babies (23.8% of all cardiac defects). Fifteen babies (14.8%) found to have Patent Ductus Arteriosus (PDA). Five babies (5.7%) born with Hypoplastic

heart. Three babies were born with Ebstein's anomaly (4.4%), and another one with tetralogy of fallout (TOF). While two babies were born with transposition great arteries (TGA).

Table 4.14 Frequency of cardiac anomalies

| Cardiac Anomalies | N | % |
|---|---|---|
| o Atrial septal defect | 29 | 28.7 |
| o Ventricular septal defect | 24 | 23.8 |
| o Patent ductus arteriosus | 15 | 14.8 |
| o Mitral valve regurgitation | 6 | 5.9 |
| o Hypoplastic heart | 5 | 4.9 |
| o *Ebstein's anomaly* | 3 | 2.9 |
| o *Pulmonary artery atresia* | 3 | 2.9 |
| o *Tetralogy of Fallout* | 1 | 0.9 |
| o Aortic stenosis/ring | 3 | 2.9 |
| o TGA | 2 | 1.9 |
| o Pulmonary valve stenosis/ thickness | 4 | 3.9 |
| o Pentalogy of fallout | 1 | 0.9 |
| o Subaortic membrane | 1 | 0.9 |
| o Absent pulmonary artery | 1 | 0.9 |
| o Complete heart block | 1 | 0.9 |
| o Complex CHD | 1 | 0.9 |

### 4.10.3. Musculoskeletal Anomalies

The study showed that 70 babies (12.2 per 1000 births) were found to have musculoskeletal anomalies. The commonest musculoskeletal anomalies were feet deformities with 18 babies affected, followed by congenital dislocation of the hip in 13 babies. Musculoskeletal anomalies also occurred as major malformations such as in Osteogenesis Imperfecta (1), and Arthrogryposis Multiplex (1). The following table illustrates all the musculoskeletal anomalies reported in our study.

Table 4.15: Frequency of Musculoskeletal anomalies

| Musculoskeletal anomalies | N | % |
|---|---|---|
| o Feet Deformities | 18 | 25.7 |
| ▪ Club Feet | 10 | |
| ▪ Calcaneovalgus | 7 | |
| ▪ Equinusvalgus | 1 | |
| o Congenital dislocation of hip | 13 | 18.5 |
| o Inguinal Hernia | 11 | 15.7 |
| o Umbilical hernia | 2 | 2.9 |
| o Polydactyly | 10 | 14.2 |
| o Syndactyly | 2 | 2.9 |
| o Achondroplesia | 3 | 4.2 |
| o Clinodactyly | 3 | 4.2 |
| o Amniotic band amputation | 3 | 4.2 |
| o Arthrogryposis Multiplex | 1 | 1.4 |
| o Osteogenesis Imperfecta | 1 | 1.4 |
| o Short limbs (Ventral Bowing) | 1 | 1.4 |
| o Compomelic Dysplesia | 1 | 1.4 |
| o Hyperextension of Knee | 1 | 1.4 |

### 4.10.4. Genitourinary anomalies

Hypospadias of its different grades or types (glandular or mid-shaft or other sites), was the commonest genitourinary tract anomalies with 36 babies affected. Followed by undescended testicles which were in 11 babies, chordae in 9 babies, imperforated hymen in 9 babies, and ambiguous genitalia in 2 babies. The following table shows all the genitourinary anomalies.

Table 4.16: Frequency of Genitourinary anomalies

| Genitourinary Anomalies | N | % |
|---|---|---|
| • Hypospadias | 36 | 52.1 |
| • Undescended testes | 11 | 15.9 |
| • Chordae- | 9 | 13 |
| • Imperforated Hymen | 9 | 13 |
| • Ambiguous genitalia (CAH) | 2 | 2.9 |
| • Micropenis | 1 | 1.4 |
| • Epispadias | 1 | 1.4 |

## 4.10.5. Gastrointestinal tract anomalies

Out of the total congenital malformations, 37 of them involved the gastrointestinal tract (6.4 per 1000 live births). The commonest anomaly of them was cleft lip with 9 babies affected, followed by tracheo-esophageal fistula / atresia which was described in 5 babies.

Table 4.17: Frequency of Gastro-intestinal anomalies

| Gastro-intestinal Anomalies | N | % |
|---|---|---|
| o Cleft lip | 9 | 24.3 |
| o Trachio-esophageal fistula/atresia | 5 | 13.5 |
| o Anteriorly displaced anus | 5 | 13.5 |
| o Cleft palate | 3 | 8.1 |
| o Duodenal atresia | 3 | 8.1 |
| o Imperforated anus | 3 | 8.1 |
| o Hirsch sprung disease | 3 | 8.1 |
| o Gastroschisis | 2 | 5.4 |
| o Jujenal atresia | 1 | 2.7 |
| o Omphalocele | 1 | 2.7 |
| o Natal teeth | 1 | 2.7 |
| o Tongue tie | 1 | 2.7 |

### 4.10.6. Respiratory anomalies

Anomalies involving the respiratory system were 7, with 5 babies born with diaphragmatic hernia out, and two babies with hydrothorax.

Table 4.18: Frequency of Respiratory anomalies

| Respiratory Anomalies | N | % |
|---|---|---|
| o Diaphragmatic hernia | 5 | 71.4 |
| o Hydrothorax | 2 | 29.6 |

### 4.10.7. Syndromes

In our study, syndromes had an incidence of 3.8 per 1000 live births, compared to the international incidence of 1.4 per 1000 live births. The most common category was Down syndrome, which was confirmed in 17 of our babies.

Table 4.19: Frequency of Syndromes

| Syndromes | N | % |
|---|---|---|
| o Down syndrome | 17 | 77.3 |
| o Klippel-fiel | 1 | 4.5 |
| o Robinow | 1 | 4.5 |
| o Trisomy 13 | 1 | 4.5 |
| o Trisomy 18 | 1 | 4.5 |
| o Turner`s | 1 | 4.5 |

### 4.10.8. Central nervous system

The incidence of neural tube defects (NTD), which include anencephaly, spina bifida and encephalocele, was found to be 3.5 per 1000, which is relatively the same as the global incidence. The incidence of NTD in the United Kingdom (in certain parts of Wales, Ireland

and Scotland) is as high as 4-8 per 1000 live births. In general, all NTD are of multifactorial inheritance.

Table 4.20: Frequency of Central nervous system anomalies

| **Central nervous system** | N | % |
|---|---|---|
| o Hydrocephalus | 7 | 35 |
| o Microcephaly | 3 | 15 |
| o Joubert syndrome | 2 | 10 |
| o Meningomyelocele | 2 | 10 |
| o Macrocephalus | 2 | 10 |
| o Pfeiffer syndrome | 1 | 5 |
| o Holoprosencephaly | 1 | 5 |
| o Dandy-walker syndrome | 1 | 5 |
| o Lissencephalus | 1 | 5 |

### 4.10.9. Renal system

The incidence of renal system anomalies was found to be 4.5 per 1000 live births. The most frequent was polycystic kidney disease (1.7 per 1000) and hydronephrosis (1.7 per 1000).

Table 4.21: Frequency of Renal system anomalies

| **Renal system** | N | % |
|---|---|---|
| o Polycystic kidney disease | 10 | 38.4 |
| o Hydronephrosis | 10 | 38.4 |
| o Absent kidney | 2 | 7.7 |
| o Ectopic kidney | 2 | 7.7 |
| o Nephrocalcinosis | 1 | 3.8 |
| o Kidney cystic lesion | 1 | 3.8 |

### 4.10.10. Miscellaneous defects

The following table illustrates the other miscellaneous congenital malformations, which count 24 of the total congenitally malformed babies. The most common anomaly was multiple dysmorphic features (short neck, protruded tongue), which found with six cases.

Table 4.22: Frequency of Miscellaneous anomalies

| Miscellaneous defects | N | % |
|---|---|---|
| o Multiple dysmorphic features (short neck, protruded tongue) | 7 | 28 |
| o Single umbilical artery | 3 | 12.5 |
| o Collodion baby | 2 | 8.4 |
| o Haemingioma | 2 | 8.4 |
| o Hydrops fetalis | 2 | 8.4 |
| o Congenital stridor | 2 | 8.4 |
| o Skin tags | 2 | 8.4 |
| o Alopecia totalis | 1 | 4.1 |
| o Ear thin helix deformity | 1 | 4.1 |
| o Low set ear | 1 | 4.1 |
| o Micro-otia | 1 | 4.1 |
| o Micro-ophthalmia | 1 | 4.1 |

# Chapter V

# Discussion

## 5.1. Introduction

The results of this study have identified some possible factors that may influence the congenital malformations in the newborns at Al-Makassed Hospital. This study had shown interconnection between congenital malformations and possible risk factors such as consanguinity, socio-economic factors, obstetric history and maternal morbidity, and other factors mentioned before. The results of this study matched those found in other similar studies in some findings and differed in others.

## 5.2. Congenital malformations incidence

We found that the incidence of congenital malformations at Al-Makassed Hospital falls within the world range of 2.5-6%. It is thought that the majority of such anomalies have a multifactorial origin, caused by the joint action of a genetic liability (polygenic inheritance) and environmental factors.

The frequency of congenital malformations in our study was found to be 5%. The reported incidence from other areas varies from 0.25% to 5.5%. A prospective study done in India on 2462 babies along one year (August 1978 to August 1979) showed the frequency of congenital malformations as 3.7% (Nair MKC, 1981). Another study also done in India showed the frequency as 3.6%.[87] The rate of congenital malformations in a multicentric study by WHO in 2006 was 3.1%, which was similar to those done in our region (Khlat M, 1989; Ramankutty P et al., 1983; Saedi-Wong S et al., 1989), and slightly less than what our present study showed. This may be to some extent explained by the fact that Al-Makassed hospital is a tertiary referral health center, and many of the delivered cases are of the high risk type.

### 5.3. Socio-economic factors

It was found that the prevalence of the customary consanguineous marriages among the parents of the babies involved in our study was (45.9%), which is a similar rate compared with other areas, in Kuwait, the rate being very high (54.2%) (Al-Awadi et al., 1985), and Saudi Arabia (54.3%) (Saedi-Wong S et al., 1989), and in Egypt (22%) (Hafez M et al., 1983), Lebanon (25%) (Khlat M et al., 1984), Syria (33%) (Prothro ET. et al., 1974), Algeria (23%) (Benallegue A et al., 1984), and Jordan (41%) (Khlat M et al., 1984), and Arab communities in Israel (44.3%) (Jaber L et al., 1994). In the Emirates, like the rest of the Gulf countries, the consanguineous marriage rate was found to be also high (50.5%) (Al-Gazali LI et al., 1997).

It is well known that consanguineous marriages are at increased risk for birth defects and genetic diseases, different studies report diverging estimates. The differences could be due to various factors, such as different definitions of birth defects, different methods of case detection, as well as differences inherent to the populations studied. In several distinct inbred communities, the risk for malformations and genetic diseases in the offspring of parents who are first cousins varies from 0.7% to 7.5% (Al-Idrissi I et al., 1992). Most of these differences may be overcome by looking at the ratio between the malformations in babies from the consanguineous parents and non-consanguineous parents within each study.

First-degree cousin marriage was found in 34.6% of the babies in our study population (101 out of 292). We may infer that the high prevalence of consanguineous marriage in the localities can be attributed to multiple factors that probably operate concurrently to produce the differences among the localities. These factors can be summarized as follows:-

- Promotion of family ties, security to the families and preservation of its properties.
- Easy way of marriage negotiation.
- Trends of family traditions.
- Women`s education: women are more educated among non-consanguineous group. *67/107 babies (62.7%) were born for mothers educated more than 12 years ($p<0.01$)*
- Women`s age at marriage: women in the age groups less than 19 years at the time of marriage were higher among the consanguineous marriage. *78/149 babies were born for mothers married at age 19 years or less with p value<0.05*

- Father`s age at marriage: fathers in consanguineous marriages tend to marry after the age of 19 years more than the first group. *Only 4 babies born for fathers married before age 19 years. (p> 0.05)*

It is difficult to explain correctly the main reasons supporting and encouraging the consanguineous marriage due to its social and cultural values.

These socio-cultural findings were similar to the findings of Haldan in 1963 when he reported a rapid reduction in the prevalence of consanguineous marriages among the higher literacy rate groups and low family size. Hafez in 1983 reported a high rate of consanguineous marriages within more traditional rural areas.

Results of the study were similar to the other results in other parts of the world. For example, in Beirut, Lebanon, Khlat M. in 1989 found that choosing to marry a cousin is associated with the strengthening of family ties and the maintenance of properties. Also in Kuwait, Al-Thakeb FT in 1985 found an association between cousin marriage and the poorer and less educated sections of the society. From my point of view the prosperity and social stability could reduce the need for such strong family ties, and offer increased possibilities for satisfaction through individual and professional self-development.

Moreover, marriage before the age of 19 years put the woman to a higher risk of poor pregnancy outcomes throughout her reproductive life and not merely during the first pregnancy only. In this study we found that (51.1%) of the babies who involved in the study were born for mothers who were married at age 19 years or less. Many studies around the world concluded that early age at marriage might be a confounding factor. It was observed through the results that there was no association between age at marriage and congenital malformation ($P > 0.05$).

It was observed that the higher the rate of mothers has no congenitally malformed babies, the higher is the rate of educated mothers. There was no association between the educational levels of the parents and the proportion of babies reported with birth defects. Maternal education is seen as an important determinant of maternal age at conception. Mothers with higher education levels delay their time to conceive for different reasons: difficulties of

combining family and education, longer absence of income (during education), desire to benefit from time spent to education through a remunerated work (desire of working is greater than the desire for children).

The more consanguineous marriages, the more crowding in the families are. The study results showed an impression that the consanguineous parents have total number of living children more than those are not consanguineous. Results of our study were similar to other results either locally or in the region. It must be taken into consideration that the prevalence rate in this study represents the population who delivered at Al-Makassed Hospital during the period between June 2007 and May 2009.

The socioeconomic variables, investigated in this study, were proxy indicators. Those variables included parents` education, locality, parents' age, and age at marriage.

Age of the mother and father has an impact on the risk of congenital anomalies. Indeed, the general health status of the mother is influenced by her age. Results gave a significant positive association between mothers` age and fathers` age in relation to congenital malformations. This increasing risk has been well documented For example; Q.Yang et al. (2006) show a higher frequency of sperm chromosome aberrations in older men. They mention that chromosomal abnormalities are partly due to paternal genetic factors; also they note that maternal age might also affect the risk of congenital heart defects.

### 5.4. Obstetric history and maternal morbidity.

In this study, it was observed that there were significant differences in many of the women's` obstetric history by the congenital malformations. Results showed that there was no significant difference of the age at marriage and malformations ($P>0.05$).

Our sample showed that there was an association between health problems related to pregnancy e.g. anemia, gestational diabetes, bleeding and toxemia of pregnancy and congenital malformation ($P<0.05$). It seems that mother's health state has an impact on the risk of congenital anomalies. Past studies in medicine showed that a deficiency in vitamin B-12, obesity or diabetes is risk factors for congenital anomalies. For example, Waller et al.

(1994) found that obesity might be a risk factor of congenital anomalies and more particularly of neural tube defects. Their study was based on women living in California and Illinois; 1370 women participated in the survey (836 mothers having an offspring with congenital anomalies and 534 without). The effect was still present after controlling for maternal age, race, education and family income. Moore et al. (2000) found a significant relation between major non chromosomal congenital defects and obesity or diabetes, 22951 pregnant women have been included in the sample. Garne (2004),in a short review of the literature on the link between maternal diabetes and congenital anomalies, mentioned that *the risk of congenital malformations for diabetic pregnancies even with optimal metabolic control is at least twice as high as for non-diabetic pregnancies*. The results of this study are comparable with studies from other areas, and confirmed similar results.

It was observed also that, there was an association between the birth order and congenital malformations ($P<0.05$). Selvin and Garfinkel (1972) showed that birth order has an impact on the risk of fetal loss. Their study was based on 1.5 million pregnancies occurring in the State of New York. Data were collected during 1959 and 1967. In order to avoid unexpressed causal relationship, the authors included maternal age as well as paternal age in their model. Many studies have also concluded that longer birth intervals decrease the risk of feto-infant mortality and morbidity. Our sample showed similar association.

It was observed also in this study that the number of pregnancies, and the total number of living children was relatively higher among women who had babies with major congenital malformations compared to mothers who had babies with minor anomalies. In terms of gross fertility, Bittles AH. 2002 in his study “the influence of congenital malformations on reproductive behavior in India and Pakistan” found a positive association between the total fertility and congenital malformations. Bittles has analyzed reported data on congenital malformations and fertility. A significant positive association between congenital anomalies and fertility was found at level ($P < 0.05$).

Any insult during the first trimester, the period of organogenesis, is likely to result in congenital abnormalities. It is said that no drug is safe during the first trimester including vitamins. In our study, 8.2% of the malformed babies were born for mothers who gave a

history of drug intake (other than folic acid and vitamins) during the whole period of pregnancy. In Nair`s study the incidence of drug intake during first trimester was 6.4%. Mishra and Baveja reported that 13.3% of mothers with malformed babies gave history of drug intake during the first trimester. Because of the fact that our study is a retrospective one, it was difficult to know in which trimester they insult they took these drugs. Further prospective cohort studies are needed in order to assess this variable, so there was no significant association between ingestion of drugs and congenital malformations.

### 5.5. Prenatal Care and Utilization of Diagnostic tests

As numerous works pointed out, while fees for prenatal services are often major barriers, there are other issues involved in the adequate utilization of these services. Upon registration with a MCH clinic, all pregnant women in Al-Makassed clinic are given a mother-held prenatal follow-up card which includes all prenatal care information filled out by all providers of pre-natal care (physicians and nurses). Women are asked to bring it to the hospital upon each visit and when coming to give birth. In our institution almost all women comply with this request. The card is filed along with the women's birth and hospitalization records. The hospitalization records as well as the prenatal follow-up records were the sources of the data used in this study.

The adequacy of initiation of prenatal care was determined according to the timing of prenatal diagnostic tests as follows: early initiation of care before 18 weeks of gestation (allowing for referral to all standard diagnostic tests to detect congenital anomalies); intermediate: between weeks 18 and 22 (allowing only for referral to second-trimester ultrasound); late: after 22 weeks of gestation (no referrals can be made as termination of pregnancy could not be considered if the fetus was affected).

Utilization of prenatal diagnostic procedures: (a) triple test and/or amniocentesis (these tests were grouped together as very few women underwent amniocentesis, and in some cases women planning to undergo amniocentesis chose not to take the triple test); (b) second-trimester fetal sonographic scan, and (c) at least one of these tests.

Results showed that, the use of some of the prenatal tests was not satisfactory. Many factors could be affecting the utilization of these prenatal tests to detect fetal anomalies. Such as:

failures of previous pregnancies, personal experience of coping with a child affected by a chronic condition, exposure to western culture in general, and low economic status.

Although (87.7%) of the babies were for mothers who attended antenatal clinics more than two times, the quality of care is still need to be emphasized. As only (18.8%) of the total study population were for mothers who had performed a triple test, and only (72.6%) of the total study population were for mothers underwent the detailed ultrasound test. While only 14 (4.7%) of the babies were for mothers who had performed the amniocentesis test. Despite the fact that 44 (15.1%) of the babies were for mothers who were 35 years or older at time of pregnancy. Of them 3 performed the triple test with an abnormal test and 113 babies (38.7%) were born for mothers who had an abnormal detailed ultrasound test result.

Our results emphasized the fact, that detailed ultrasound when performed by experienced radiologist had a good specificity. As 106/113 of women with abnormal detailed ultrasound had major congenital malformations, while those in which detailed ultrasound was normal were 99 babies of them only 16 babies only had major congenital anomalies.
Many studies have also shown a lower rate of utilization of prenatal services, and a few deal specifically with prenatal diagnostic tests. Halliday et al. (1995) reported that nonusers in Victoria, Australia, tended to be immigrants or born in foreign-language-speaking countries, as well as living in rural areas. Kupperman et al. (1996) showed that utilization of amniocentesis in San Francisco varied by racial ethnic groups. These consistent findings have been explained by financial constraints, low level of education, and by cultural, religious, and social characteristics forming attitudes towards prenatal testing and abortions, as well as towards raising an affected child.

All these barriers exist in our traditional and religious study population: most women of reproductive age are of a very low level of education (63.3%) which makes written communication about prenatal testing not effective. Moreover, educational differences between care-givers and women and their families further widen the communication gap and sometimes create distrust and suspicion.

Additional studies are needed in order to better understand the reasons for use and avoidance of prenatal testing as well as the mechanisms of trust-building towards health services in

traditional societies such as the population involved in this study. Meanwhile, several intervention programs aiming at reducing barriers towards the utilization of prenatal testing have been implemented in the past few years in our country. These interventions include introduction of a genetic counseling clinic, a special educational program for high-school students, education and instruction at MCH clinics with specific interventions to be targeted to those high-risk families. Educational material for each type of intervention was designed for a population with limited ability to understand written information with an emphasis on its cultural appropriateness.

### 5.6. Birth weight and Gestational age

A fetus needs 37 weeks of gestation to be considered as term or be fully developed. Consequently, the infant's mortality and morbidity decreases, with advancing gestational age. Similarly, infant's mortality decreases with increasing weight at birth. A birth weight of at least 500 gram or gestation age of at least 22 weeks is the minimal thresholds recommended for declaration by the World Health Organization (Gourbin and Masuy-Stroobat (1995).

Results showed that the prevalence of low birth weight infants in our study was {49/608 (8%)} (birth weight less than 2500g), while the premature babies with gestational age of 34 weeks or less were {36/257 (14%). The differences of congenital malformations by low birth weight were statistically significant ($P < 0.001$).

Ramankutty P, et al (1983) mentioned that low birth weight (LBW) *contributes to neonatal deaths*. Gestational age and birth weight are highly associated however. In this perspective, our study has shown that gestational age and relative weight at each gestational age are related to perinatal mortality and morbidity.

### 5.7. Congenital malformations

Majority of studies reported that anomalies involving the musculoskeletal system are commonest types of malformations. However, the frequency of congenital cardiovascular malformations (prevalence 18 per 1000) has certainly been under estimated in most studies, as diagnosis can be difficult and many cases present later in childhood. The commonest system involved in this study was the cardiovascular system, other studies the system most commonly

involved was CNS, Musculoskeletal system, or the gastrointestinal tract (respectively (Czeizel AE, 1997; Richmond S et al., 2005; Rankin J et al., 2005)).

Worldwide studies reported a higher incidence of major malformations among offspring of consanguineous parents. A preliminary survey conducted in Pakistan by Shami SA, Qaisare R, Bittles AH. In 1991 suggested that some major diseases of adult life, including some forms of cardiovascular disease and cancer, might be more prevalent in the offspring of consanguineous parents. This suggestion still needs further investigation, keeping in mind the strong influence of social factors on the epidemiology of these disorders.

### 5.8. Future Developments

The last few decades have not seen an increasing success in congenital anomaly prevention, as evidenced by the lack of decline in the prevalence. Implementations of current knowledge with effective policies, as well as research into causes of congenital anomalies, have the potential to change this situation with political well.

Prenatal screening and diagnosis have seen rapid development. The near future will bring less invasive technologies for the detection of chromosomal anomalies, and greater sensitivity and specificity of the diagnostic tests used. The challenge for these is also to reduce the number of women having to consider termination of pregnancy as an option by achieving effective primary prevention, and improving the outcome of affected children and their families in terms of health, quality of life and participation.

# Chapter VI
# Conclusion and Recommendations

## 6.1. Conclusion

Although the causes of most birth defects remain unknown, the potential impact of the pathophysiology and risk factors for congenital malformations is profound and far reaching. With the exponential increase in the knowledge of medicine and technology, primary care physicians may frequently be expected to explain reported findings to patients and parents. The pediatrician and other health care practitioners will need sufficient familiarity knowledge about the etiology of birth defects to recommend prevention strategies and to help families negotiate testing and treatment options.

The reasons of inconsistency between our results which represents the largest series of genetics and congenital abnormalities ever investigated in Palestine and other studies are probably as follow:

Some of the congenital anomalies are not diagnosed at birth and may be evident later in life, therapeutic advances, application of appropriate preconception care, adequate number of geneticists and prenatal diagnosis programs. Also this inconsistency might be explained by the diagnosis of both minor and major congenital malformations in all systems, the large number of cases and the different sex ratio between male and female newborns. Moreover the possible role of various factors such as different geographical distribution, and socioeconomic differences must not be disregarded.

Counseling, prenatal diagnosis and proper management of congenital malformations present a challenge to obstetricians. Periconceptional intake of folic acid has proved to be effective in preventing the recurrence of NTD, and probably the occurrence of this and other anomalies. Second-trimester screening by biochemical markers for NTD and Down's syndrome has proved to be effective. Ultrasound is a highly valuable diagnostic tool for prenatal diagnosis of congenital malformations, but is not yet widely accepted as a screening method in low-risk pregnancies. Ultrasound and Doppler techniques are useful for the detection of congenital cardiac defects.

We indicated in our study that, parental consanguinity plays an important role in the incidence of congenital malformations. In the present study, almost 45.9% of the couples studied were consanguineous, and nearly two third of them were first cousins. Clearly, any attempt to reduce the incidence of consanguineous marriages in this population must be approached with great care and handled with sensitivity, since such marriages have been practiced for hundreds of years and are deeply ingrained in Arab communities. Nonetheless, there are ways of tackling the issue, such as the various control programs already mentioned. The objectives of any such program must be:

- To inform the community about the risks of congenital malformations associated with consanguineous marriages.
- To identify the prevalent genetic disease in each community in order to be able to screen for carriers where possible.
- To advise couples about the importance of premarital testing, emphasizing its accuracy and significance in terms of making a contribution to their health.
- To inform them of the religious opinion regarding permission to terminate a pregnancy during the first 120 days in the event of a severely affected fetus.
- To provide prenatal and genetic counseling services, including prenatal diagnosis, and to educate as many people as possible to utilize these services.
- To provide folic acid supplements 2 months prior to a planned pregnancy until the end of the first trimester.

Once the women themselves accept the concept that termination of pregnancy is permissible in these circumstances, this should have a significant impact on the incidence of malformed live-born children.

There are no preventive programs in this area and genetic services are inadequate. The high incidence of abnormalities with a high recurrence risk in this study indicates that there is a need to develop a comprehensive preventive program for congenital abnormalities in this country. Apart from the routine maternal care in pregnancy, there should be a special and sensitive educational program about the genetic consequences of consanguineous marriage. Genetic counseling supported by the availability of antenatal screening and prenatal diagnostic technology when appropriate should be an essential component of such a program. This

should form the basis of a community based genetic service which is an integral part of preventive medical care.

In conclusion, this retrospective descriptive study has produced a detailed analysis of the pattern of congenital malformation in a Middle Eastern medical district.

## 6.2. Recommendations

It has been said that "Prevention is the best cure". Regarding the risk factors of congenital malformations, prevention is the best way to confine and humble the expected malformation or disorders that might occur as a result of the exposure of such risk factors.

We need to emphasize the importance of antenatal care, with the introduction of a designed program by the ministry of health, which should be followed by all obstetricians and primary care providers who provide antenatal care for women in their regions. This should include a National Antenatal care form, with all the antenatal tests that should be done, pregnancy information and test results should be recorded in this form (all tests should be offered, and made available to all women, and if refused should be indicated in the forms). In relation, the following interventions are recommended:

- To introduce peri-conception information (antenatal diagnostic tests and screening) and counseling services. That has to focus on primary prevention of genetic and congenital malformations, which depends largely on pre-conception information, screening and counseling. Worldwide, primary health care services need strengthening in this important subject. This calls for identification of an appropriate infrastructure, reinforcement of prenatal diagnostic services, and development of educational material for mothers and primary health care staff, and training in basic genetic counseling for primary health care personnel. Incorporation of these services into the maternal and child health program can, in some countries represents a great opportunity for the prevention of congenital genetic malformations.

- To incorporate genetic counseling services into maternal and child health program which may provide a suitable focus for advice about future pregnancies.

- To introduce the subject of consanguineous marriage in the school curriculum especially at preparatory and secondary level, and to adopt awareness campaign and educational activities as a part of reproductive health program in the school.
- To implement community based health education programs using mass media, and involving participation of community nurses, school health program to increases the awareness of women on the risk of consanguineous marriages.
- Standardized and comparable studies are needed to provide data that can be used in developing health policies, such as pilot studies of the feasibility of the prenatal diagnostic tests and genetic counseling for those families at risk of genetic and congenital malformations.

Other in relation interventions are recommended:

- Reducing the occurrence of congenital abnormalities such as neural tube defects, and avoiding the sequel of micronutrient deficiencies such as mental retardation due to iodine deficiency by promoting healthy nutrition for women.
- Preventing congenital rubella syndrome by immunizing against rubella infection.
- Reducing congenital abnormalities and stillbirths by better control of maternal diabetes prior to and during pregnancy.
- Reducing the risk of miscarriage, congenital abnormality and fetal growth retardation through avoidance of smoking during pregnancy.
- Avoiding congenital abnormalities caused by certain infections by prevention, early detection and prompt treatment.

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Appendix (1)

## Data Collection Form

Baby`s File #: _____ Mother's file #:_____

==========

Mother: □ Age:_____Yrs. □ Fathers Age: _____Yrs.

Relationship: Consanguineous □ Y, □ N

□ Mother to father: _____

□ Father to mother:_____

Religion: □ Muslim □ Christian □ Others _____

Occupation: □ Mother _____ □ Father _____

Address: _____ □ Region_____□ City □ Village / Town □ Camp

Age at marriage _____

Educational level:

Mother: □ ≤ 12 years □ 2 years college □ BA – University □ Post Graduate

Father: □ ≤ 12 years □ 2 years college □ BA – University □ Post Graduate

Obstetrics and Family Hx:

□ Age at 1st pregnancy: _____Yrs. □ Birth Order: _____

Gestational age: _____wks. □ G_____, □ P_____, □ Ab_____

Prenatal Care □ Yes □ No

Rubella: □ Immune, □ non immune / HBsAg: □ Neg, □ pos / Blood group_____

Detailed U/S □ N, □ Y _____

Triple test □ N □ Y_____

Amniocentesis: □ N, □ Y_____

Smoking: □ N, □ Y _____

Meds: Iron □Y, □ N / vit: □Y, □ N (folic acid)/ other drugs □ N, □ Y _____

X-ray during preg: □ N, □ Y _____

Infections during preg: □ N, □ Y_____

History of: □ Abortion_____ □ Still birth_____

□ Deaths:_____

□ Congenital anomalies:_____

□ Genetic diseases:_____

==========

**Newborn**

Date of birth_____, Sex □ M □ F, Delivered by: □ SVD □ C/S □ Other

□ B.Wt_____, □ HC_____, □ LT_____ (IUGR: □ Y, □ N)

Dysmorphic: □ N, □ Y _____

Congenital anomalies: □ N, □ Y_____

_____

Admitted to: □ NN, □ NICU, □ discharged home

PKU done: _____, □ Abn

Anomalies involve: □ CNS, □ Heart, □ Renal, □ Skeletal, □ GIT □ Urogenital

Was the anomaly diagnosed antenatally: □ Y, □ N

Heart murmur: □ Y, □ N

Hip click: □ Y, □ N

Club foot: □ Y, □ N

Undescended testicle □ Y, □ N

Hypospadias □ Y, □ N

(Take copy of the newborn exam sheet, or NICU discharge summary for those with anomalies)

**Appendix (2)**
**Approval letter**

MAKASSED ISLAMIC
CHARITABLE HOSPITAL
MOUNT OF OLIVES
Jerusalem
P.O.Box: 19482
Tel.: 02-6270222
Fax:02-6288392

مستشفى
جمعية المقاصد الخيرية الاسلامية
القـــــدس
ص.ب. ١٩٤٨٢
تلفون: ٠٢-٦٢٧٠٢٢٢
فاكس: ٠٢-٦٢٨٨٣٩٢

Ref.No. .....
Date: June 13th, 2009

رقم الشاره: .....
التاريخ: .....

**Dear Mr. Ahmad Masri**
**Neurosurgical Department**

I would like to give you the approval to collect data in connection to your thesis related to "Consanguinity, other risk factors in relation to Congenital Malformation in Newborns at Al-Makassed Hospital".

Hoping you success.

Sincerely,

T. Hasheesh

Taleb Hasheesh
Deputy Nursing Director

نموذج رقم ٧٢٠٢١٩٠