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Risk Factors Associated With Cerebral Palsy amongst Palestinian Children

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DEDICATION

FOR MY MOTHER.

Declaration

I certify that this thesis submitted for the degree of master in public health is the result of my own research, except where otherwise acknowledged, and this (or any part of the same) has not been submitted for a higher degree to any other university or institution.

Signed:……..

Suzanne Lewis Daher

Date:……

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Special thanks to my husband and children.

Abstract

Despite the large number of studies into cerebral palsy little is known concerning the risk factors operating before or during pregnancy that influence vulnerability in cerebral palsy. Indeed such studies that do exist focus on developed countries.

The purpose of this case control study is to investigate risk factors for cerebral palsy amongst Palestinian children. Risk factor examined in this study were known prenatal and perinatal, in addition three factors specific to Palestinian society, consanguineous marriage, delivery at private maternity homes lacking facilities, and lack of pre-natal doctor visits on the part of the mother were investigated.

A case-control study was conducted; the cases came from The Princess Basma Centre for Disabled Children which is the national centre for Palestinians. Medical records were combined into a questionnaire to gather information into risk factors for the period January-August 2011.In total one hundred and seven cases were examined, controls came from West Bank pediatric clinics. As the condition under study is considered rare 223 controls were enrolled.

The crude results were a high frequency of cerebral palsy from cesarean delivery [45.3%] OR= 2.65 95% C.I. [1.6-4.34] and a high frequency cases due to hypoxia [45.8%], OR= 65.76 95% C.I. [22.41-192.96]. Also of significance; low birth weight OR= 4.60 95% C.I. [2.60-8.14], gestational age OR=2.90 95% C.I. [1.67-5.03], jaundice OR=2.70 95% C.I. [1.39-5.55], multiple births OR=11.40 95% C.I. [2.45-52.97], infection during pregnancy, OR=4.8 95% C.I. [2.20-10.89], and delivery, OR= 5.00 95% C.I. [1.51-16.72], congenital abnormalities OR= 2.41 95% C.I. [1.31-4.44], and other children with disability in the family OR= 8.90 95% C.I. [2.89-27.62]. New, previously un-assessed population specific factors of significance were; consanguineous marriage, OR =2.85 95% C.I. [1.75-4.64], no medical care during pregnancy, OR=5.50 95% C.I. [1.89-16.07], and place of delivery, OR for Ministry of Health Hospitals=2.70 95% C.I. [1.69-4.38]. Associations were seen which remained significant after adjustment for gender, gestation and multivariable adjustment. The first model of risk factors for Palestinian children was produced.

Known risk factors proved significant as did population specific variables assessed for the first time in this study. Modifiable risk factors identified means the possibility of prevention is a reality through behavioral change.

عوامل المخاطرة المرتبطة بالشلل الدماغي لدى الاطفال الفلسطينيين

اسم الطالبه: سوزان فاين ظاهر

اسم المشرفه: الدكتوره لينا الخيري

الملخص

بالرغم من وجود عدد كبير من الدراسات حول الشلل الدماغي إلا ان هنالك قلة في المعرفة عن تأثير عوامل مخاطرة خلال فترة الحمل أو اثناء الولادة على حدوث الشلل الدماغي و معظم هذه الدراسات تركز على البلدان المتقدمه.

الهدف من هذه الدراسة هو تحري عوامل المخاطرة لحدوث الشلل الدماغي لدى الاطفال الفلسطينيين.

عوامل الخطر التي تم دراستها في هذه الدراسة هي عوامل المخاطرة في مرحلة ما قبل الولادة و ما حولها كنقص الاكسجين و الولادة المبكرة و تعدد الحمل و نقص الوزن عند االولاده و أعمار الوالدين و حدوث الاصفرار و حدوث التهابات أثناء فترة الحمل و وجود تشوهات خلقية أخرى و وجود مرض خثار الدم و عوامل اجتماعية اقتصاديه و عوامل عائليه. بالاضافة الى ذلك فقد تم دراسة بعض العوامل الخاصة بالمجتمع الفلسطيني مثل زواج الاقارب و الولادة بمستشفيات خاصة غير مجهزة بشكل جيد و عدم الحصول على الرعاية الصحية اثناء فترة الحمل.

لقد قورنت حالات الشلل الدماغي المدروسة بعينة ضابطه حيث أخذت الحالات من مبرة الاميره بسمه و التي تعتبر المركز الوطني للتعامل مع المصابين بالشلل الدماغي حيث يتم تحويل المصابين من كافة ارجاء الوطن من قبل وزارة الصحة الفلسطينية. لقد تم استخدام الملفات الطبية مع استبيان للامهات لجمع المعلومات خلال الفترة ما بين شهر كانون الثاني و شهر حزيران من عام 2011. لقد كان مجموع الحالات التي درست 107 حالات و قد أخذت العينة الضابطة من عيادات أطفال مختلفه من مختلف ارجاء الضفة الغربيه و كان حجمها 223 عينه.

دلت النتائج على وجود نسبه كبيره من الحالات من ولادات قيصريه (45.3%)
[1.6-4.34] C.I. 95% OR= 2.65 و عدد كبير ممن عانوا من نقص الاكسجين (45.8%)
[22.41-192.96] C.I. 95% OR= 65.76 أما العوامل الاخرى التي اظهرت فروقات احصائية فكانت:
الوزن القليل عند الولاده [2.60-8.14] C.I. 95% OR= 4.60 والولادة المبكره
[1.67-5.03], C.I. 95% OR=2.90 والاصفرار [1.39-5.55] C.I. 95% OR=2.70 و الحمل المتعدد
[2.45-52.97] C.I. 95% OR=11.40 و الالتهاب اثناء الحمل [2.20-10.89] C.I. 95% OR=4.8 و
الالتهاب اثناء الولاده [1.51-16.72] C.I. 95% OR= 5.00 و وجود تشوهات خلقيه
[1.31-4.44] C.I. 95% OR= 2.41 و وجود اطفال آخرين في العائلة مع إعاقات
[2.89-27.62] C.I. 95% OR= 8.90.

أما عوامل المخاطرة التي لم تتم دراستها مسبقاً و كانت لها تأثيرات احصائيه فكانت: زواج الاقارب [1.75-4.64] C.I. 95% OR =2.85 و عدم الحصول على رعايه طبية أثناء الحمل OR=5.50 [1.89-16.07] C.I. 95% و مكان الولاده حيث كانت نسبة المخاطرة للمستشفيات الحكومية 95% 2.70 C.I. [1.69-4.38]

لقد تمت ملاحظة علاقات احصائية للعوامل منفصله كما تم التعديل حسب الجنس, فترة الحمل و باقي العوامل مجتمعه.

لقد بينت هذه الدراسه انه يوجد علاقات ذات دلاله احصائيه بين عوامل الخطر المعروفه و أيضاً عوامل الخطر الخاصه بالمجتمع الفلسطيني و التي تمت دراستها لاول مره.

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1) Chapter One.-Background.

1.1 Introduction.

Cerebral palsy is the most common and visible motor disability, it can be defined as brain damage that results in neurological and motor deficits (Case-Smith *et al*, 1989). There are no known prevalence studies for Palestine or indeed developing countries (Stanley. *et al,* 2000). Prevalence in a Turkish county has been estimated using house to house survey data as 5.6 per 1000 children below six years of age- 95% confidence interval 3.5-7.7, (Okan *et al* 1995). Data available comes from the U.S.A. where it is estimated there are 764,000 children and adults with cerebral palsy (Nelson 2008). Since 1950 worldwide rates for overall cerebral palsy have remained around 2-2.5 per 1000 live births (Robertson *et al* 1998).

The causes remain under debate and vary from medical mismanagement to multifactorial steps which are part of a causal pathway (Keogh and Badin 2006). The risk factors identified from the literature review are hypoxia, pre-term, low birth weight, maternal and paternal age, jaundice, inflammation and infection during pregnancy and delivery, congenital abnormalities, thrombophilia, trauma, socio-economic status and familial risk (Adding *et al,* 2006, Cohen *et al* 1982, Eastman 1955, Krigger , 2006, Laisram 1992) .Two other risk factors were identified from the literature review but will not be included in this study. The first, cerebrovascular event [stroke], diagnosis cannot be confirmed without neuro-imaging procedures, such as magnetic resonance (Kraus 1999). There has been no test of consensus in reading films for validity purposes when reviewing research (Kraus 1999). Also many of those children participating in this project will not have had access to such tests due to financial and limited availability of the equipment needed. This would make the investigation of this risk factor subjective. The second variable to be excluded is apgar score; studies have revealed an association between cerebral palsy and apgar (Nelson and Grether 1998) score however this can be seen as a sign of potential problems but not seen as a risk factor.

The Princess Basma Centre for Disabled Children was founded in 1965 as a home for physically disabled children, primarily suffering with paralytic polio. Today the focus is on children with cerebral palsy although other types of disability are also treated. The centre's services are comprised of occupational therapy, physiotherapy, nursing, play therapy,

hydrotherapy and special education. In addition the centre focuses on community based rehabilitation to integrate their clients into the community. Children attend the centre to be assessed and during their stay receive a planned program of rehabilitation, the majority of which is carried out at home. Staff therefore work with both the child and the mother or primary care-giver to teach them how to manage and aid their child‘s development.

The context of this research is that although there are no statistics available nationally and unlike other countries there is no cerebral palsy register, from the numbers of children who attend it is evident cerebral palsy is a major disability amongst Palestinian children. There is a wealth of data in the form of hand written admission reports, medical summaries, which is as yet un-interpreted or analyzed and the opportunity to gather data from mothers/caregivers attending the centre.

Upon admission full medical history and medical reports are documented by nursing staff. The quality of the information can be seen by the centre’s achievement and maintenance of ISO-9004, giving the researcher the benefit of accurate and complete data. The centre receives children from three months until fifteen years of age. Treatment is residential for a period of three weeks; the child is accompanied by the mother or primary care giver. Entrance to the centre is free for the parents with the full cost being borne by the Ministry of Health, and open to Jerusalem I.D. and West Bank I.D. Palestinians. The centre is able to provide the child and caregiver with permits allowing access to the centre.

1.3 Problem Statement.

If we can better identify the risk factors that place a particular baby at high risk for cerebral palsy we may be able to devise new preventative and treatment strategies. So this research identifies that there is a gap in academic research into risk factors globally and locally and seeks to investigate suspected risk factors with additional factors specific to the Palestinian population. The identification of risk factors significant to Palestine is the first step towards prevention.

1.4 Principle objective.

To identify the risk factors for cerebral palsy among Palestinian children.

1.5 Specific objectives.

1. To examine the association between cerebral palsy and the known risk factors, pre-natal and peri-natal for Palestinian children
2. To establish whether there is an association between consanguineous marriage and cerebral palsy for Palestinian children.
3. To establish whether there is an association between location of delivery and cerebral palsy for Palestinian children.
4. To establish whether there is an association between lack of medical care when pregnant and cerebral palsy for Palestinian children.

1.6 Significance.

Firstly of significance this study will add to the body of knowledge in cerebral palsy research. It is a subject of public health importance, children with this condition and their families require significant additional support from medical, educational and social services. An additional cultural belief is that a child with a disability is due to some fault on the part of the mother. There is also some overlap with the studies justification which is the significance of investigating new and established risk factors as they relate to a specific population- the Palestinians.

1.7 Expected outcomes

To identifying new factors and assessing the known risk factors can provide information which may be utilized for prevention. A disabled child changes the whole dynamics of the family, and signals the start of a cycle of doctor visits, hospital appointments and rehabilitation. The burden of care is with the mother and eventually other siblings. In addition to the extra financial burden there is the burden of social stigma [Harper 2010]. This study will assist in establishing cause on a host of risk factors which may be the basis of other studies which would ultimately see a reduction in the numbers of children with cerebral palsy. Should a greater number of cases of cerebral palsy result depending on where the delivery takes place, perhaps policy changes could be instigated to regulate or improve regulation of these establishments. Through this study the case for a national cerebral palsy register can be highlighted. This is standard in most developed countries in

order to ascertain the impact of future public health and other preventative measures aimed at reducing the frequency of brain injury. Also such a register could be used for monitoring frequency and characteristic of children with cerebral palsy amongst the Arab population. Whilst the scope and scale of this study is limited it may provide information for future research. There is no known study to date that has addressed cerebral palsy including new, population specific risk factors in Palestine.

Despite the existence of data including admission reports and medical documentation there has yet to be any interpretation or analysis into the risk factors leading to cerebral palsy in Palestine. From the numbers of children who attend The Princess Basma Centre for the Disabled it is apparent this is a condition of public health concern.

1.8 Explanation of structure.

The first chapter presents the background for the study. This chapter includes the justification for the research, the problem statement together with the principal objective and study questions to be answered. The significance of the study and the expected outcomes will be given.

The second chapter is the literature review; this will include the history of cerebral palsy, definitions of the condition, epidemiology, diagnosis and clinical features. The main body of this chapter will present the risk factors for cerebral palsy.

The third chapter will detail the conceptual framework in diagrammatic form with a discussion.

The fourth chapter will present the methods used, the study design, sampling, research tools and ethical considerations.

The remaining chapters will present research findings, analysis and discussion of the results, concluding with recommendations.

2) Chapter Two- Literature Review.

This literature review will first examine the history of the identification of cerebral palsy. Leading on from this modern definitions of the condition will be presented. The epidemiology and risk factors found in the literature and their inclusion in this study will be discussed.

2.1 History.

Cerebral Palsy was first reported in 1862 and known as Little's disease, after the doctor who first described and documented cases (Nelson 2008). The cause of Little's disease was thought connected solely with birth. Freud's view was that intrauterine development abnormalities were responsible; it was decades before his views were given credence (Reddihough and Collins 2003). For the next hundred years the idea related to Little's beliefs were held, that most cases of cerebral palsy were due to asphyxia in labor or in the perinatal period. The rates of cerebral palsy were seen as outcome measures of obstetrics practice and neo-natal care. It was therefore thought that improved medical management would prevent cerebral palsy. However despite improvement in care and new equipment such as, fetal monitoring and caesarian sections the cerebral palsy rate remained constant. Only the number of still births and the neo-natal death rate declined. It was a ground breaking study in 1955 by obstetricians (Eastman and Delon 2008) who presented one of the first controlled studies of factors involved in cerebral palsy. They found that the majority of cerebral palsy arose in infants born at term. That hypoxia due to placental abruption, a birth trauma was indeed more common in children with cerebral palsy but did not contribute a major proportion of cerebral palsy cases. They noted that half of the term infants who went on to develop cerebral palsy were in good condition in the delivery room, with none of the findings usually taken to indicate asphyxia. They identified factors which led them to believe other causes were in existence, for example babies born to women who were febrile in labor had a seven times greater chance of cerebral palsy than women who were not febrile. The results of their observations stimulated research which had been lacking and made it apparent that birth injury or birth asphyxia accounted for only a small minority of cerebral palsy cases.

The past twenty years has seen a change from a wait and see attitude, deferring a definitive diagnosis and therefore the start of treatment until the child had reached three or four years.

Now the opposite is believed and accepted, that early therapeutic intervention takes advantage of the plasticity of the developing nervous system. Accurate prediction of outcome can not only aid prevention but the timely provision of appropriate services and stop the loss of time in the early months/ years when therapy can be most effective. At present the decision to treat or not depends on case history and early neo-natal findings. Risk factors play an important part in that history (Keogh and Badawi 2006).

Coming up to date the goal of management of cerebral palsy is not to cure or to achieve normalcy but to increase functionality, improve capabilities and sustain health in areas of; locomotion, cognitive development, social interaction and independence.

2.2 Definition

Cerebral palsy is one of the major causes of chronic disability of the central nervous system. The National Institute of health defines cerebral palsy as a non-progressive motor disorder of early infant onset, involving one or more limb with resulting muscular spasticity or paralysis (Krigger 2006).

An additional definition describes cerebral palsy as non-progressive motor disorders of movement and posture due to deficit or lesions of the developing brain (Sundrum.S. *et al* 2005). The disorder can manifest as global mental and/or physical dysfunction or isolated disturbances in gait, cognition, growth or sensation. Complications of cerebral palsy include spasticity, contractures, feeding difficulties [choking, long feeding time, non-oral feeding], weight [under nourished, overweight, obese], drooling, communication problems, visual and hearing problems, osteopenia, osteoporosis, chronic pain, epilepsy, vomiting, incontinence and constipation. Further mortality and morbidity from ischemic heart disease, cerebrovascular disease, cancer and trauma are higher in people with cerebral palsy than in the general population (Shankaran 2008).

2.3 Diagnosis.

In clinical practice cerebral palsy is diagnosed based on observations or parental reports that the child has failed to reach major motor milestones- sitting, pulling to stand, or walking for examples. Posture is evaluated along with deep tendon reflexes and muscle tone. Infants with perceived neurological abnormalities are observed in the early months of life and motor impairments may or may not be resolved during the first or second year. As

neurological abnormalities maybe transient definitive diagnosis is based on repeated examination (Reddihough and Collins 2003).

2.4 Clinical features and distribution.

2.4.1 Types of motor dysfunction- Tone.

Cerebral palsy manifests in a number of physical pattern, the first is spasticity. Affected limbs show increased deep tendon reflexes, tremors, muscular hyper tonicity, weakness and scissor gait with toe walking. The athetoid or dyskinetic type of cerebral palsy is characterized by slow, writhing movements of the hands, feet, arms or legs exacerbated if the person is under stress and absent during sleep. It usually manifests as bizarre patters of muscular activities. The rarest form, ataxic cerebral palsy is characterized by balance and co-ordination impairment. The person walks with a wide based gait and has tremors which complicate normal daily function. Usually ataxia is generalized but may be confined to one side of the body or one extremity. Tone in individuals with cerebral palsy can be further characterized by chorea which is faster than athetosis and is typically seen in the trunk and large muscles of the extremities. The motion is jerky, random and complex. The involuntary movement is often incorporated into voluntary motion. Ballismus is also characterized by fast and forceful movements, typically the shoulder but may also include the hips. Ballismus may occur with athetoid and choreiform movements. Finally tone maybe characterized by hypotonic movements. This type of motor dysfunction is characterized by lack of normal muscle tone or tension with muscle flaccidity or weakness (Case-Smith. *et al* 1996).

2.4.2 Distribution/location of motor dysfunction.

The distribution of limb involvement can be classified in traditional terms and includes monoplegia, which involves weakness or paralysis of a single extremity. The location can be hemiplegic, involving both upper and lower extremities on one side. Diplegia is defined as one area more involved than the other, for examples both upper extremities, and/or both lower extremities. Triplegia is where three extremities are involved, and quadriplegia involves all four extremities (Nelson 2008).

2.4.3 Condition impact.

This can be defined as mild, moderate, severe, and profound. Mild means that due to the condition the individual will require some intervention but activities are not limited. Moderate means that the condition does have an impact on activities and the individual is limited by this. Severe means the condition has a major impact on activities in terms of limitation and precluding. For profound the individual is dependent in all areas and activities (Case-Smith. *et al* 1996).

In diagnosis the tone, location and condition are used in combination, for examples moderate spastic diaplegia which is bilateral spasticity with leg involvement greater than arm. Another example could be mild spastic hemiplegia which is unilateral spasticity not limiting the individual's activities. Research has begun to connect risk factors with resulting pattern and distribution; results have been inconclusive for most but the strongest known risk factors (Nelson 2008).

2.5 Epidemiology.

In developed countries the rate is stable; however there is an increase in the survival of pre-term infants. This coupled with the increase in longevity of those with cerebral palsy has resulted in an increase in the overall prevalence. Cerebral palsy is considered the most common infant disability, but despite this it is also rare with the incident put at 2/1000 live births (Noetzelm 2006). Statistics from the U.S.A. reveal 8, 000 infants diagnosed annually with an additional 1200-1500 pre-schoolers. At present it is calculated there are 764,000 children and adults with cerebral palsy (Nelson. 2008). There are no extensive population based birth prevalence studies of cerebral palsy in developing countries. Prevalence in a Turkish study has been estimated using a house to house survey at 5.6 per 1000 in children below the age of six (Okranetal 1995), and for rural Kashmir as 1.46 per1000 children below 14 years old, (Razdan et al 1994). One small scale prevalence study conducted in Turkey found a 1.1 cases of cerebral palsy per 1000. This low figure was found due to insufficient neonatal care resulting in low survival in preterm and low birth weight children and poor postnatal care of children with cerebral palsy (Ozturk et al 2007). Another Egyptian study based on a small door to door survey in El-Kharga found a prevalence rate of 2.04/1000 with the main cause being hypoxia (El-Tallaway et al 2011). According to Duggan and Ogala, most of the population estimates for developing countries are well

above developed. Further cases are more severe with more cases due to lack of oxygen and kenicterus (Duggan and Ogala, 1982). Finally a small community based study in Saudi Arabia found 6.85 per 1000 for neurological disorders of which cerebral palsy was included (Al-Salloun et al 2011).

2.6 Risk Factors.

Risk factors identified from the literature will now be discussed – hypoxia, premature birth, inflammation and infection, stroke, multiple gestation, low birth weight, medical mismanagement, family member disabled, socio-economic status, trauma, jaundice, congenital anomalies and thrombophilia (Adding *et al* 2006, Cohen *et al* 1982, Eastman 1955, Krigger 2006, Laisram 1992) Of importance to this research and fitting in with the culture of Palestine consanguineous marriage, whether the mother went for pre-natal check-ups and the type of delivery facility will be discussed. The timing of cerebral palsy can be categorized into pre-natal, perinatal or post natal (Reddihough and Collins2006) some of the factors can also overlap and be involved in more than one category (Reddihough and Collins 2006). It is believed that the above mentioned risk factors alone or in combination may result in cerebral palsy. One theory is that cerebral palsy may be the result of a sequence of events, a causal pathway which culminates in disease (Blair1996). Some of these factors can be further separated into infants of all gestations, whilst others are only associated with either full term or premature infants (Nelson 1999). The nature of the condition under research as a new area means many concepts are included in the literature review.

2.6.1 Hypoxia

This risk factor is perhaps the only one that can be considered causal. It has been demonstrated repeatedly in controlled population based studies that birth hypoxia equals cerebral palsy (Odding *et al*, 2006). However it has also been recognized that interruption of the oxygen supply to the fetus does not account for most cerebral palsy. In one population study for example only six percent of children with cerebral palsy had had a recognized complication capable of interrupting oxygen supply to the fetus (O'Shea 2008]. Here hypoxia in this study can also be perinatal/postnatal where insufficient oxygen to the brain due to breathing problems or poor blood flow in the brain. The lack of oxygen acts as

a trigger for the uncontrolled release of excitatory neurotransmitters. Cell damage is enhanced by the production of free radicals and nitric oxide that attack the structural components of the neurons which results in periventricular encephalomalacia [PVL], damage to the brain tissue located around the ventricles. The resulting encephalopathy can be mild, moderate or severe, statistics show that 16-20% of children with cerebral palsy have hypoxic-ischemic brain injury, from these 15-20% will die (O'Shea 2008). Neonates with mild encephopathy do not have an increased risk of motor or cognitive deficits. Neonates with severe encephalopathy have an increased risk of death and an increased risk of cerebral palsy and mental retardation amongst survivors. Neonates with moderate encephalopathy have significant deficits, memory impairment, visual motor or visual perceptive dysfunction, increasing hyperactivity and delayed school readiness. There is no clear diagnostic test for hypoxia, other etiologies are excluded and a delayed cry or a baby born blue and flaccid. (Page 1986). Not all hypoxia cases are of acute origin, so optimal obstetrical care may not prevent all of the hypoxia causing cerebral palsy, but optimal care in performing the necessary interventions at the appropriate time can indeed reduce the incidence of cerebral palsy (Page 1986) Permanent motor deficits can be caused by hypoxia if the hypoxia is severe and prolonged, it can also occur at different times during gestation (Blair 1996).

2.6.2 Pre-term newborns/ low gestational age <37 weeks.

Much of the literature on cerebral palsy examines pre-term newborns, which account for an estimated ten to twelve percent of all live newborns in developed countries, and represent a high risk population for brain damage (Nelson and Grether 1999). Co-morbidity for mental retardation is present in eighty-two percent of pre-term children with quadriplegia, forty-four percent with diaplagia. Also pre-terms without cerebral palsy and/or mental retardation show a lower I.Q. score at school age compared to their full term peers. Learning disabilities are considered common in the pre-term population who are three to five times more likely to be affected by reading, spelling, and math and writing disorders. Pre-term children are more likely to be hyperactive and inattentive than their term school peers (Suvanand *et al* 1997). The most common type of pre-term damage is periventricular leukomalacia and intraventricular hemorrhage [IVH] (Curatolo *et al* 1999).Whether brain damage in pre-term newborns is part of a series of developmentally adverse events leading to pre-term labor, or as a result of organ immaturity is unclear

(Odding *et al* 2006). The cerebral palsy that arises in pre-term infants is commonly spastic diaplegia. Birth too early in gestation is evidently a very important risk factor and highlights the need for interventions which either prolong gestation or decrease the risk of pre-term delivery thus decreasing the risk of cerebral palsy. In addition there is the question of whether post 40 weeks gestation time before delivery is a factor so this will also be incorporated in operationalzing this particular variable even though it is a factor that has not received much attention in the literature published to date (Moster *et al* 2010). Relevant to this study one Turkish study found low birth weight to be a top risk factor along with pre-term birth and hypoxia (Erkin et al 2011). Also from research in Turkey, a retrospective case-control study of 101 cerebral palsy children low birth weight was the only significant factor (Matin 2006).

2.6.3 Infection and inflammation.

Other brain damage routes are what the literature refers to as the inflammation pathway (Noetzel 2006). There is a large body of experimental evidence which indicates that pre-term labor in the setting of intrauterine infection is triggered by an uncontrolled maternal-fetal inflammatory reaction to the presence of invading micro-organisms. Research has demonstrated an increased rate of pre-term birth after chorioamnionitus, also in full term infants where the relative risk has also been proven. For pre-term this infection is considered the most important factor (Blair 1996) it is believed that an infection results in the release of large amounts of cytokines which lead to early labor, they act as inflammatory mediators and take part in the brain damage of pre-term newborns. High levels of pro-inflammatory cytokines in umbilical blood have been associated with an increased risk of developing cerebral palsy; this has also been confirmed in term infants. Cytokines are essential in all stages of nervous system development. (Kraus.1999). Nelson *et al* reported a relative risk ranging from 6.6 -30.5 for different types of newborn infections (Nelson and Grether.1999). Also one study from India reported encephalitis and tubercular meningitis as possible etiological factors (Odding *et al* 2006). A final study for use as an example examined the role of neonatal infection in 6903 children between 1993-2001. Nearly 2/3 had acquired infections in the newborn period, and of these over forty percent developed a brain injury resulting in cerebral palsy, or cognitive impairment or both. Cerebral palsy was found in sixteen percent of children, who had neonatal infection compared with eight percent in the absence of infection (Nelson 2008).

Other studies in the literature reveal a link between cerebral palsy and maternal infection and inflammation during labor. One study (Nelson and Grether 1998) reported that women who were febrile in labor had babies with seven times the rate of cerebral palsy as women who were not febrile during labor; further women who were febrile with urinary tract infections had infants whose intelligence was lower, even after adjustment for socio-economic factors. In addition examinations of the placenta found that moderate or severe inflammatory infiltrates in the umbilical cord were associated with heightened risk of cerebral palsy in both term and pre-term infants (Baptiste-Roberts *et al* 2008). This same study found the administration of antibiotics prior to delivery was not associated with the risk of cerebral palsy. In a population study in northern California evidence of maternal infection or fever during admission for delivery was associated with risk of cerebral palsy in infants of normal birth weight and associated with admission to neonatal intensive care unit for seizures, and meconium aspiration (Eastman 1955). Other studies concur regarding term and near term infants in finding an association of maternal infection or fever with low Apgar score, neonatal encephalopathy, seizures and cerebral palsy risk. (Nelson and Grether 1998). To date there has been little systematic study of infections or inflammatory maternal conditions that occur in pregnancy before admission for delivery as risk factors for cerebral palsy. Inflammation can to some extent co-exist with the next risk factor to be discussed, stroke. It is believed that cytokines could cause a blood flow restriction in cerebral areas with an immuno-induced mechanism. This reduction in blood flow may eventually cause ischemia (Nelson and Ellenberg 1981).

2.6.4 Ischemia.

Prenatal stroke, defined as a cerebovascular event occurring during fetal or neonatal life during the twenty eight days after birth (Nelson and Grether 1999). Arterial ischemic stroke in the perinatal period has been recognized as a major cause of cerebral palsy only in recent years. Advances in technology with the advent of computer tomography and magnetic resonance imaging have been applied with increasing frequency to infants and children. A stroke diagnosis cannot be confirmed without such imaging procedures as the clinical signs are variable and often non-specific. In a study in which magnetic resonance was employed unilateral strokes were identified in 1:2300 term infants in the nursery period (Keogh and Badawi 2006). Newborn infants with stroke seldom display asymmetrical movement or strength as would be expected. The most common reason

leading to a stroke diagnoses are seizures. Some infants who appear without disability at birth maybe diagnosed in later months or years when the child fails to meet developmental milestones, or is able to reach with one hand but not the other-indicating hemiparisis. Retrospective diagnosis depends on neuro-imaging, there has been no test of consensus in reading films, this needs to be borne in mind for validity purposes when reviewing research. (Bax 2006)

Stroke is more common in the perinatal period than during any other time of childhood or until later life. Thromboses at other sites are also relatively common in the period surrounding birth. It is believed unlikely that maternal pregnancy related stroke is most common in the few days immediately before or after birth, a period when coagulation status is altered in both mother and baby. Prime parity, pre-eclampsia and a history of fertility treatment have been presented as associations for stroke (Suvannand *et al* 1997). Retrospective observational study on maternal or family history of thrombophilic disease, advancing maternal age, obesity, surgery, dehydration or shock and prolonged bed rest are risk factors for thrombosis (Nelson *et al*. 2002). Infection and inflammation are important triggers of thrombosis, pre-eclampsia and are maternal risk factors for stroke in the infant (Bax 2006).

2.6.5 Multiple gestations.

Multiple gestations are increasing because of personal and medical decisions. Therefore the increased risk of cerebral palsy in multiple births is of concern with increased fertility interventions. For twins the risk of developing cerebral palsy is given as 4.8 times more likely than singletons. Death of a co-twin increased the risk by a factor of six compared with when both twins were live born. Twins were more likely to develop spastic quadriplegia while singletons were more likely to develop dyskinetic or ataxic cerebral palsy (Petterson *et al* 1993). Another study re-in forces the increased risk, with 8% incidence of cerebral palsy in singletons, and 9% in twins born at thirty-two weeks or less. Many variables were considered in the analysis in the study, birth sequence, and mode of delivery, presentation, size, and size discrepancy. The evidence suggests that two factors are predominant in contributing to cerebral palsy risk in multiple gestation; the tendency of twins and higher order multiple births to be born premature and the death of one infant. In one study which included a million births the highest rates of cerebral palsy were in surviving twins whose co-twin was still born, 4.5% died soon after birth, 11.8% had

cerebral palsy. Cerebral palsy risk after the death of a co-twin was similar for same sex, and for different sex pairs. The reason for the high risk is due to conjoined circulations in the placenta. The death of one twin is followed by vascular collapse in the survivor. If this happens early in gestation, congenital abnormalities can be the result in the survivor. There may be other mechanisms of brain injury in the survivor of a co-twin death, in addition anything that harms one infant lethally might harm the other sub lethally (Nelson and Grether 1999). The 'vanishing' twin is fairly common in early pregnancy, some children who were twins early in gestation maybe born as singletons and bear the consequence of co-twin loss. In one study triplet pregnancies produced a child with cerebral palsy forty-seven times more often than singleton (Nelson *et al* 2002). Another study notes the considerable increase in multiple gestations. The average five yearly increase was 3.9% in twins and 67% for triplets (Nelson and Grether 1998). This has contributed to a significant annual increase in the proportion of multiple births associated with cerebral palsy cases. Rates of multiple births are rising not only because of the increased use of treatments for infertility but also due to the rise in births to older women. This study calls for the limiting of number of embryos transferred in vitro fertilization (Nelson and Grether 1998).

2.6.6 Birth weight

Babies who are small for their dates at birth have been found to be at risk for cerebral palsy (Bax *et al* 2006). In this particular study low birth weight is stated as the second highest risk factor. Also babies who are large for their dates are at increased risk. It is apparent that heightened risk is associated with growth abnormalities at both ends of the scale. Many factors can influence birth size- chromosomal abnormalities, infections [toxoplasmosis, rubella, cytomegalovirus, herpes virus, malaria and H.I.V.], pre-eclampsia, systematic maternal vascular disease or thrombophilia. For larger than normal size the excess risk maybe due to the problems associated with delivering large babies. Additionally a classic risk factor for large babies is maternal diabetes (Bax *et al* 2006). Another example of how many of these risk factors are interwoven is that excessively small/large babies are at higher risk for perinatal stroke than infants near the mean weight for dates (Kraus 1999) Low birth weight can bring with it many problems; cardio-vascular, respiratory complications mean prolonged ventilation, sepsis, and seizures for examples (Nelson and Grether 1997).

2.6.7 Low Apgar score

Many of the studies revealed an association between low Apgar scores and cerebral palsy. An Apgar score of 0-3 at five minutes gave an 81 fold increased risk of cerebral palsy (Cohen *et al* 1982). However whilst this is noteworthy such studies highlight signs not risk factors.

2.6.8 Medical management.

Whilst it is now recognized that quality of care during pregnancy is not solely the causative factor of cerebral palsy research can be found that that still sees this as a valid risk factor. One study (Sundrum *et al* 2005) investigated the relationship between quality of obstetrical care in the management of fetal distress and cerebral palsy. The conclusion was that if intrapartum fetal distress could be completely eliminated the incidence of cerebral palsy might be lowered by sixteen percent. Yehezkely-Schildkraut *et al* reported an incidence of seven percent of cerebral palsy in fetuses with signs of fetal distress who received sub-optimal care (Yehezkely-Schildkraut 2005). Clinical management and medical facilities are critical in dealing with and preventing complications (Giles 1996). Another study investigating obstetric mishaps maintains only a small number of mishaps may occur leading to cerebral palsy. In their work 26% of mothers with cerebral palsy children had caesarean deliveries, indicating the obstetrician was well aware that the infant was in difficulties. Although a proportion of these may have had difficulties due to inattention, many would not. They therefore deduce obstetrician malpractice is low. (Suvanand *et al* 1997)

2.6.9 Location of delivery.

In the West Bank the existence of small private maternity homes is a recent and growing phenomenon. There are thirty-seven such homes and many have grown as a response to difficulties in gaining access to hospitals due to occupation. Ministry of Health hospitals were seen as dirty, overcrowded and under-resourced (Wick 2006). There is no known regulatory body to oversee standards; quality and dictate what provisions should be available. There are no known facts or figures relating to Palestine; however reports by rehabilitation professional at Princess Basma state there is a disproportionate amount of cerebral palsy from private nursing homes. This research sought to calculate the number of

cases of cerebral palsy to see if this is in fact the case and further research warranted: is lack of medical care at these private facilities leading to higher rates of cerebral palsy?

2.6.10 Inter-marriage.

Concerning consanguineous marriage which is common in Palestine no local and few international studies were found. One study based on Turkish children with cerebral palsy found consanguineous marriage to be a top risk factor (Delialioglu *et al* 2008). This research will be the first to investigate this in Palestine. Another Swedish study based on a cerebral palsy data base also reported inter-marriage as a factor. This same study (Thorngen-Jerneck 2008) also examined a number of maternal and pregnancy related conditions that are risk factors for cerebral palsy and concluded that a strong contribution of multiplicity of risk factors to cerebral palsy etiology means that a linear casual chain is often not evident. A more recent study from Jordan examined global developmental delay and included cerebral palsy under this definition, consanguinity was found to be a major factor (Masri et al 2011).

2.6.11 Socio-economic Status.

Three studies were reviewed which found a relationship between cerebral palsy and socio-economic status. This was only partially accounted for by known social gradients in birth weight and gestational age. Increased odds ratio's were observed not only for the most deprived groups but in all groups when compared with the least deprived group, 31-51% of cases of cerebral palsy can be attributed to socio-economic inequality (Odding 2006). In another study social factors were found to be of importance in developmental outcome. General cognitive ability, verbal, and language skills in particular tend to correlate more closely with the responsiveness of the caretaker, whereas gross motor and perceptual motor performances are correlated more closely with adverse perinatal history (Sundrum *et al* 2005). A statistically significant linear association was observed between the risk of cerebral palsy and social economic status, in relatively affluent areas of the U.K. The percentage of cerebral palsy attributed to social inequality was estimated by comparing the overall population risk of cerebral palsy with the risk that would have been found if the risk in the least disadvantaged groups applied to the whole population. The increased odds ratio was observed not only in the most deprived groups but in all groups compared to the

least deprived group. Father's occupation was used to define social economic status (Odding 2006).

2.6.12 Congenital anomalies.

It has been consistently observed that children with cerebral palsy have more congenital abnormalities than children without cerebral palsy (Reddihough and Collins 2003). As such it is a risk factor contributing to cerebral palsy. Recent studies linking population based registries for cerebral palsy and for congenital malformations re-enforce previous observations noting congenital malformations of head, clefts of lips and palate. This is because children with anomalies outside the central nervous system also have congenital brain malformations. Modern imaging techniques enable more children with this condition to be identified and therefore knowledge about the cortical dysplasias of which some have a genetic base is increasing rapidly (Pharoah 2007).

2.6.13 Thrombophilia.

A clotting disorder, thrombophilia can be inherited or acquired, the impact on the fetus is via placenta vascular injury and clotting in the fetal vessels (Hemminiki *et al* 2007). This can be compared to a stroke and perinatally acquired can occur in 1: 4000 pregnancies and underlies a significant proportion of hemiplegic cerebral palsy, some spastic quadriplegia and neo-natal seizures. It is believed that thrombophilia has an accumulative effect and is part of a causal sequence, leading as an example to perinatal stroke. One study on an Arab population in Israel found a significant level of factor V Leiden mutation, a common cause of hereditary thrombophilia and cerebral palsy (Yehezkely-Schildkraut 2005).

2.6.14 Trauma.

One result of trauma found in the literature is neonatal encephalopathy which is a syndrome of disturbed neurological functions referred to earlier characterized by difficulty in initiating and maintain respiration, depressed tone, reflexes, subnormal levels of consciousness and seizures. The trauma that is responsible for this syndrome are uterine rupture, cord prolapse or major placenta abruptions, placenta embolism, and reduced placenta blood flow This is however a highly under researched area but a risk factor with cerebral palsy is suggested (Giles *et al* 1996). Another area where trauma can be sustained

is in instrument assisted delivery. The incident of cerebral palsy increases sharply in cases of instrument assisted delivery or in abnormal presentation. Over the last twenty years this has reduced along with the reduction in the use of forceps and vacuum delivery which are thought to result in subdural hemorrhage (Cohen *et al* 1982).

2.6.15 Jaundice, kernicterus.

Neonatal jaundice is another suggested risk factor. If jaundice is not treated early the newborn will suffer brain damage due to high levels of billarubin in the blood. Billarubin easily passes through the blood brain barrier and causes neurotoxicity. Treatment is by way of phototherapy or exchange transfusion, when levels are detected via blood tests that the levels in the blood could cause damage. Results from one study place neonatal jaundice fourth in their analysis of significant factors (Reid *et al* 2006). The need for early intervention is well known in the neo-natal period so that the exposure time of the developing brain to this adverse factor can be reduced. Many studies were found concerning jaundice, one Dutch study found striking results (Van de Bor 1989). From their study it was found that the risk of disability increased 30% for each 50 mmol/l [209mg/dl] increase of maximal serum total of billirubin concentration, this suggests a casual neuro-developmental outcome. Another study sees jaundice as a re-emerging threat in the U.S.A., early hospital discharge before the extent of jaundice is known and signs of brain damage have appeared are believed responsible. Other reasons proffered are, a lack of adequate concern for the risks of severe jaundice in healthy or term infants, medical cost constraints and limitations within health care systems to monitor outpatient jaundice (Bhutani and Johnson 2003).

2.6.16 Parental Age

Parent's age has also been found to be of significance, rates of cerebral palsy are higher for mothers over forty years of age, likewise under twenty one years. Parental age is also significant for post natal cerebral palsy with mothers aged less than twenty one at delivery, mainly for non-accidental head injuries. For fathers a parental age of below twenty one is significant (Fletcher and Foley 1993).

2.6.17 Familial Risk

A final suggested variable is familial risk, which whilst un-common has been found to be significant. One study puts the figures at 1.6% of all cerebral palsy cases, however for parents who had one affected child the risk of recurrence in another child was considerably increased. Parents of one affected child had a 4.8 fold risk of having a second affected child. Where the siblings were twins, the risk was 29-fold. Familial risk was found to be high within certain groups for examples; 17-25 in singletons and 37-155 in twins, including hemiplegia, diaplegia and quadriplegia. The researchers argue that this high familiar risk is hard to explain without the contribution of heritable factors. (Hemminiki *et al* 2007)

2.6.18 Lack of medical Care in Pregnancy.

A new risk factor introduced in this study and proffered by Princess Basma's rehabilitation doctor (personal communication 2010). Is lack of medical care during pregnancy resulting in higher cerebral palsy cases? It is related to Palestine which does not have a national health system so attendance for pre-natal checks depends on the individual. Therefore there is no literature available.

2.6.19 Post- natal acquired cerebral palsy.

Postnatal acquired cerebral palsy is believed to be of particular importance to developed countries (Groholt 1995). The main causes of which being meningitis, motor vehicle accidents, and septicemia. It should be noted that this acquired cerebral palsy later in childhood is unconnected to events before the child was born or during the birth process. It is the easiest to isolate causes, as opposed to risk factors and is therefore outside the scope of this research.

2.7 Developed and developing countries.

Social and medical practices may affect rates and profiles of etiologies in developing countries when compared with developed countries. As most of the existing research was conducted in developed countries this remains very much a concept since there are no population based birth prevalence data from developing countries. Most developing

countries such as Palestine do not have cerebral palsy registers. It can be hypothesized that many more cases die, or are more moderate to severe. Even international comparisons between developed countries are problematic due to differences in criteria. For developing countries which may have unique factors it is important that suspected causes are recorded in detail even if numbers are small and therefore of parochial interest.

The limited data that does exist suggests differences, for example research in Africa (Duggan and Ogala 1982) place febrile convulsions due to malaria as an important risk factor. Research in India (Laisram et al 1992) report cerebral infections [cause not specified] as a primary risk factor. In developed countries there are also differences, for example Sweden has the lowest number of post-natally acquired cerebral palsy, [Hagberg et al 1996]. In other countries such as Saudi Arabia [Taha and Mahadi 1984] post-natally acquired cerebral palsy is stressed due to high numbers of home accidents, measles and respiratory tract infections. Although post natal cerebral palsy is not included in this research such studies collaborate the concept that there may be difference between countries and populations within countries.

2.8 Conclusion.

From the literature review potential variables to be included in this study have been identified. It is also important to note that even if a child does have a risk factor it does not mean that the child will definitely have cerebral palsy. It means that the chance of a child getting cerebral palsy is increased. Factors identified can be pre-natal, perinatal and post-natal. Pre-natal can include stroke, death of a twin, maternal infection and inflammation, trauma and congenital anomalies. Perinatal can include jaundice, problems associated with size and/or delivery. Finally post natal, acquired infections, and accidents form the main factors for cerebral palsy. From the review it is evident that there has been a change in thinking from simplistic theories about one single cause per child to the realization that it may be a ‘cascade of contributing events’ (Groholt 1995). It has also shown that there is a need for more studies which explore observable differences between the maternal, birth, prenatal and perinatal histories of babies. It is only through such research that preventative strategies maybe feasible.

3. Chapter Three – Conceptual Framework.

3.1 Definitions utilized.

Cerebral Palsy; Motor impairment due to brain injury (Tapers 1971).

Hypoxia; Deficiency in the amount of oxygen reaching body tissue (Tapers 1971).

Preterm birth; A baby of less than 37 weeks of gestational age (Nelson 2011).

Gestational age; The age of a newborn, expressed in weeks dating from the first day of the mother's menstrual period (Nelson 2011).

Multiple births; Where one or more fetus is carried to term in a single pregnancy (Nelson 2011).

Low birth weight; A baby less than 2500g in weight (Nelson 2011).

Paternal age; On the birth of the child more than forty years or less than twenty one years (authors own).

Maternal age; On the birth of the child more than forty years or less than twenty one years (authors own).

Jaundice; Hyperbilrubinemia in the blood (Tapers 1971).

Infection; Invasion and multiplication of pathogenic micro-organisms in a bodily part or tissue which may produce/ progress to disease (Tapers 1971).

Congenital abnormalities; A condition which is present at the time of birth and varies from the standard presentation (Tapers 1971).

Thrombophilia; The propensity to develop thrombosis due to an abnormality in the system of coagulation (Tapers 1971).

Trauma; Serious/ critical bodily injury or shock (Tapers 1971).

Ischemia; A restriction in blood supply with resultant damage or tissue dysfunction (Tapers 1971).

Apgar score; Heart rate, breathing, muscle tone, reflexes and skin tone measured periodically after birth (Tapers 1971).

Social economic status; An individuals or groups position within a hierarchical social structure (Authors own).

Consanguineous marriage; A union between two people genetically related (Tapers 1971).

Ministry of Health hospital; Health services operated under the Palestinian national Authority (authors own).

Private maternity home; An institution/ hospital operated outside the confines of the state/ government system (authors own)

3.2 Introduction.

The conceptual framework is interwoven in the study objectives, hypothesis and expected results. There are differences in etiology between developed and developing countries, that there are population specific factors which produce unique risk. This study introduces three new un-assessed risk factors under this conceptual framework; consanguineous marriage, lack of medical care in pregnancy and location of delivery. Therefore an adapted model based on existing concept headings was devised (Al-Sharif 2010).

3.3 Difference in risk factors due to specific population differences.

Research is also limited concerning population differences but enough to offer this idea as a concept. In studies of mixed racial groups it has been found that the rate of cerebral palsy in the black population is 1.6 times that of whites (Murphy et al 1993). Further in Australia aboriginal rates are six times those of caucasians (Blair and Stanley 1982).

Differences between developed and developing countries and population specific factors form part of the conceptual framework. Additionally from the literature review research has sought to identify causes from single factors, strong, un-confounded associations. The example of this type of direct cause has been given-hypoxia. The concept in this study is to identify the significance of less dramatic factors. The importance of this can be given in the possibility of prevention. Earlier factors may increase the chances of later factors, for example if pre-term birth pre-disposes babies to cerebral palsy additional exposure to the environment when they are not ready could lead to cerebral palsy. Pre-term is not enough, as many pre-term babies do not have cerebral palsy. Therefore in the analysis all variables will be regressed simultaneously, also a stepwise model will present etiology for Palestine.

3.4 Development of The conceptual framework diagram.

There are no known conceptual framework models for cerebral palsy which include wider societal issues. From the literature review studies measure single quantifiable risk factors. This study seeks to do this as well but in recognizing that population specific factors may be of importance the unique background to these factors also requires recognition. With no existing models in order to present the study in diagrammatic form an adapted model was used. Two headings were used – service factors and socio-culture-economic from a lecture on research methodology (Al-Sharif 2010). Other headings and design were added by the researcher- political and medical treatment. Study factors were then organized into categories and a conceptual framework for cerebral palsy suggested. The concept that there is a difference between developed and developing countries and that there are population specific factors necessitated the development of a model.

3.5 Explanation of the conceptual framework diagram.

The risk factors may be put under four headings; service factors, medical/ treatment factors, political and socio-cultural economic factors which all are relevant in terms of background. Many of the issues forming the bigger picture are outside the scope of this study. They do however need to be borne in mind and influence the risk factors under study. In this sense the conceptual framework can be said to be ecological, this is illustrated below in fig 3-1, showing the conceptual framework for cerebral palsy. Factors of concern to the study are depicted in figure 3-2.

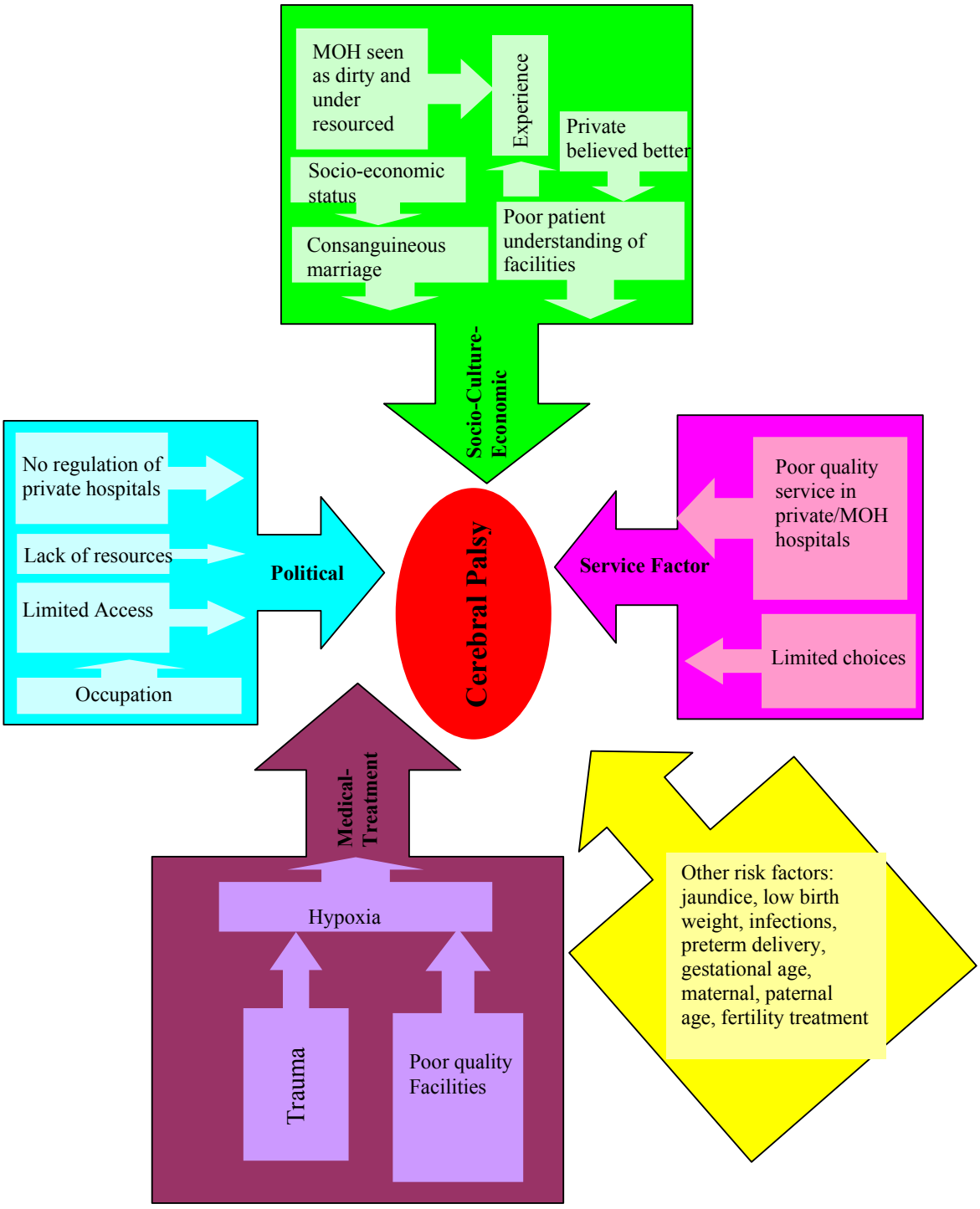

Figure 3-1: Theoretical model for cerebral palsy.

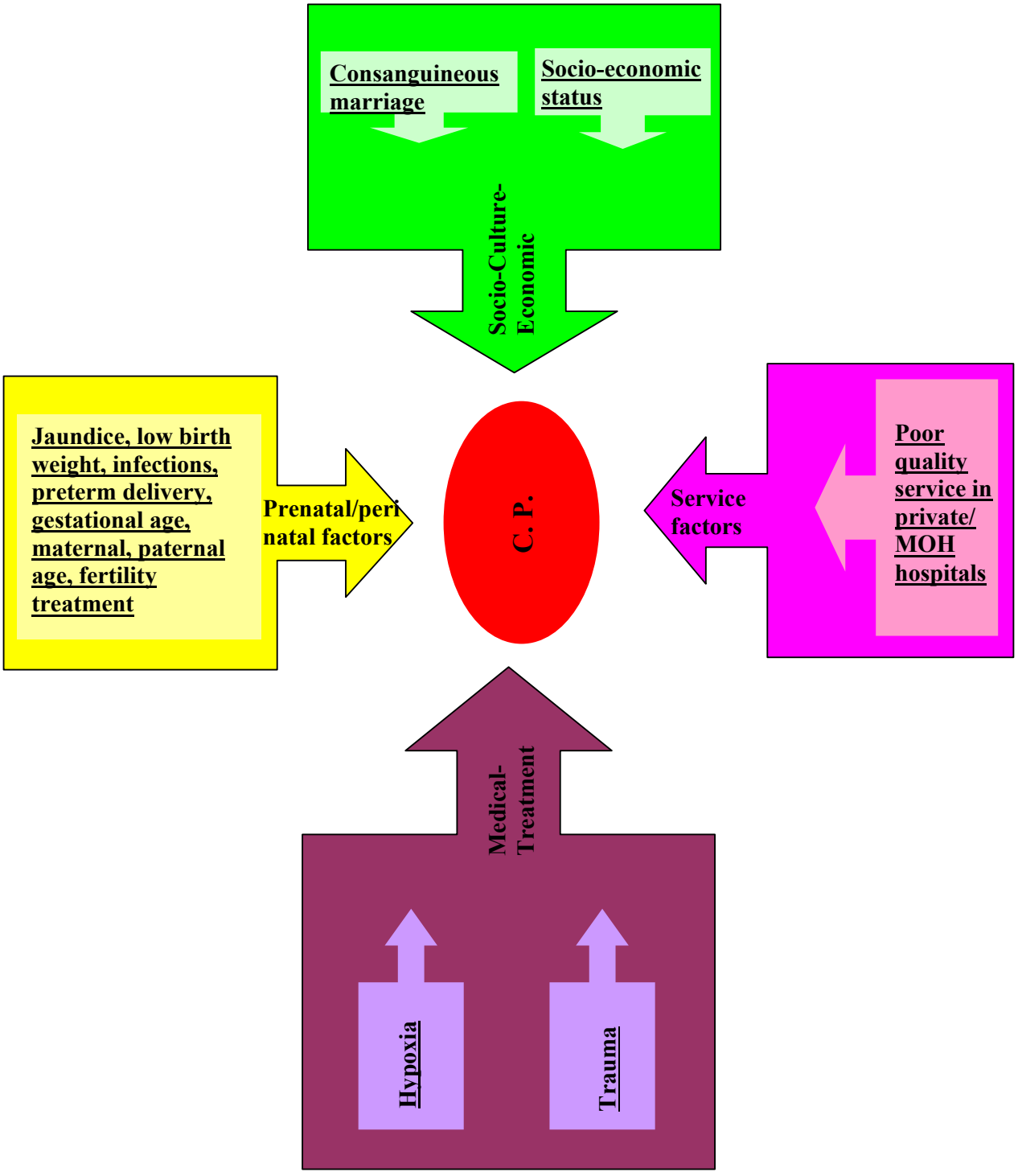

Figure 3-2: Study conceptual framework for cerebral palsy.

3.6 Conclusion.

As societies change and develop causes may change and diversify rather than disappear entirely. Perhaps infection as a risk will reduce as medical services improve; this may also apply to hypoxia. Population factors may grow in importance, for Palestine may be consanguinity will increase. The unique situation of the Palestinians may lead to unique risk factors. This framework will be used to assess the risk factors for cerebral palsy.

4) Chapter Four - Methodology.

4.1 Study design.

The study design is a case control study which is conducive to the study's aims. The aim is to study more than one possible etiologic factor; in addition the condition is rare which also lends itself to case control. This methodology was utilized because case control studies can be of a short duration, relatively inexpensive, of benefit when exposure is apparently frequent and a small sample can be sufficient to gather data.

4.2 Sample Population.

For the cases the sample population is Palestinian children who have been diagnosed with cerebral palsy and are attending The Princess Basma Centre for the Disabled from January 19th- June 19th 2011. For the controls; Palestinian children who were attending outpatient clinics with a variety of diagnosis except for cerebral palsy from July 19th- August 29th 2010.

4.3 Sample.

A unique method with similarities to random probability sampling was used to select cases from the mothers and children who were present at the centre, a total of 107 cases were obtained. Numbers were assigned to the mothers on a weekly basis who were then randomly selected to participate [Numbers were put into a bag]. There were 223 controls, as cerebral palsy is a rare condition a ratio of 1:2 cases and controls was used. The controls were selected from outpatient clinics from M.O.H., Azariah, Jerusalem district, U.N.W.R.A. and Arab Health Care. Ramallah,-UNWRA, M.O.H., Arab Health Care. Nablus, - UNWRA, private pediatric clinic, and M.O.H. Tulkarim. Hebron, - M.O.H. UNWRA Bethlehem, private pediatric clinic- Bethlehem. Every other child attending the clinic and fitting the inclusion criteria was selected.

The controls were from the different health care providers in Palestine, Ministry of Health, UNWRA, and private. Controls were representative of the population in terms of geographical area. The country was divided into central, south and northern areas.

4.3.1 Exclusion and inclusion criteria for cases and controls.

a. Any medical documentation which was absent for particular cases/controls resulted in exclusion.
b. Before one year it is unlikely that a diagnosis of cerebral palsy can be definitive, so cases and controls under one year of age were excluded. The age range was therefore from one year to fifteen years old; this is the age range of children treated at The Princess Basma Centre.
c. Cases attending The Princess Basma Centre for treatment other than cerebral palsy were excluded.
d. For cases a doctor diagnosis of cerebral palsy, for controls, any diagnosis except cerebral palsy.
e. For cases, every child attending the Princess Basma Centre with the primary caregiver, for controls every child attending an outpatient clinic with their primary caregiver.
f. Boths males and females were included in the study.

4.4 Sample size

The importance of sample size lies in the ability to make statistical inferences and produce accurate data. Unlike other study designs sample size calculation does not depend on incidence in case control studies. It is based on the relative risk of the exposure and size of sample from existing published studies. This is combined with the desired power of the statistical test.
Whilst not all risk factors were calculated examples are given below. The first being low birth weight, as relative risk is an important component this variable was chosen as the relative risk was lower than for other risk factors in the study. This was evident when further sample sizes were calculated, hypoxia and infection.

$$| N = \left(p_0 q_0 + p_1 q_1\right)(Z_{1-\alpha/2} + Z_{1-\beta})^2 \Big/ (p_1 - p_0)^2$$

Where:

p_1 = Proportion of exposure among cases

p_0 = Proportion of exposure among controls

$q_1 = 1 - p_1$

$q_0 = 1 - p_0$

$\alpha = 0.05$

$\beta = 0.2$ – power of 80%

Low birth weight

$p_0 = 0.049$, $p_1 = 0.049$ X 3.4 (RR) = 0.1666

$$N = [(0.049 \times (1 - 0.049)) + (0.1666 \times (1 - 0.1666))] \times [(1.96 + 0.84)^2] \Big/ (0.1666 - 0.049)^2$$

N = 105 for both cases and controls.

The numbers substituted are from Murphy 1993, for hypoxia O'Brien et al 1966 and for infection Nelson and Grether 1998.

The sample size required for hypoxia was 25 and for infection 30.4 for both cases and controls.

4.5 Study limitations, validity and reliability.

There is a need to be mindful of confounding difficulties as outcome is already known which leads to questions about reliability and validity. Provision to avoid confounding has been made in the planning stage of this research. The population is a homogenous group; controls represented the population in terms of geographical area. However there maybe differences between Palestinians who hold Jerusalem identification and Palestinians who hold West bank identification. Despite representative numbers there may be a possible bias; those with Jerusalem identification have additional access to different medical facilities in Israel. If this is a factor in the etiology of cerebral palsy is not known. It will also be kept in mind that education and father's occupation which will be used as a determinant of socio economic status are possible confounders. In depth reading in order to identify possible confounders has also been

completed, however the nature of observational studies makes this area problematic. Confounding will also be addressed in the analysis with checks for co-efficient uniformity in the regressions; where there is no evidence of confounding data will be analyzed in its crude form leading to more precision. Risk factors will also be adjusted for gender and gestation. In addition to confounding many issues such as exposure specificity and recall bias become relevant. For some of the risk factors interviews with mothers are the means of data collection, they may not have known about some exposures. In addition misclassification bias may occur; mild cases may not be detected and referred and so cases may have therefore been amongst the controls having gone undetected. There is also the possibility of selection bias where again mild cases were not referred and detected. In defense of this last point there is nothing in the literature that says mild cases have a different set of risk factors. Mothers themselves maybe reluctant to give away facts about the prenatal period for fear of being blamed for the child's condition. However many of the variables are document medical facts, examples being birth weight, gestational age, type of delivery, diagnosis, jaundice, multiple birth, where the child was delivered, whether incubated and for how long. Others do not lend themselves to recall bias, for examples whether they are related to their spouse and how close this relationship is, age etc. Care was needed in variables where the mother was asked whether their child was one of a twin who did not survive infection at time of delivery or during pregnancy as access to medical records for this is not always available. In defense of this last point it should be noted that internationally the practice of predicting long term outcomes for infants is still more an art that a science (Groholt 1995). Another source of bias maybe in terms of incident/prevalence bias, incident studies are deemed better on the basis that before they become prevalent cases some additional change occurs. Perhaps this is not applicable to cerebral palsy which is by definition a non progressive condition. Whilst the medical records contain much information they cannot verify or rule out stroke. The existence or not of stroke is not usually investigated in children with cerebral palsy in Palestine unlike many other countries. Limited medical facilities may play a part in this which means this is a limitation of this study.

Finally this research incorporates a non-standardized questionnaire as a means of data collection and this is a weakness in terms of reliability and validity. However there is no standardized questionnaire in existence to address the areas of study.

4.6 Data collection methods and procedures.

Data was gathered from the centre's admission form/medical records and combined into a questionnaire to gather data regarding additional risk factors. Medical files served to cross check the information obtained from the caregiver. The only medical variables that could not be cross checked were infection during pregnancy/ delivery, and fertility treatment; this fact will be clearly stated and taken into account when drawing conclusions from the results.

The same questionnaire was used to gather data from the controls whose medical file were also used to cross check the information obtained. The questionnaires were completed by the investigator in all but twenty-four of the cases. Also present during the interview was either an occupational therapist from Princess Basma, or nurses from the different clinics to make sure there were no inaccuracies due to language difficulties.

4.7 Medical Records available and content.

- A case summary written by the referring physician.
- A medical report containing many variables of importance to this study. Contains; diagnosis, age, address, delivery details [when, where, type of delivery, if and what trauma took place, whether incubated, for how long, whether child was jaundiced], gestational age, birth weight, disappearing twin. Any salient complications.

4.8 The Questionnaire.

The format of the questionnaire arose from a combination of risk factors contained on the Princess Basma admission form/medical records and questions which arose from the literature review. The questions directly ask about the relevant risk factor and its applicability.

The first section is comprised of mainly demographic data, profession and education of parents. This first section also includes the child's diagnosis, the distribution, tone and severity. This leads onto questions about the pregnancy and delivery before

questions about the child. Early medical history concludes with place of delivery and the age of the parents when the child was born [see appendix A].

The format is mixed in terms of mainly dictatonamous and option questions; the pilot study was used to verify that the questions are clear, the duration is reasonable, and that the questions although of a personal nature are not embarrassing. The questions seemed to have face validity; this was judged to be the case after the pilot study. The same judgment was made for content validity, for criterion validity, the use of medical records has importance.

In the formulation of the questionnaire experts in the field of cerebral palsy were consulted and asked to review the questionnaire, two specialist pediatricians. Further the questionnaire was reviewed by two general practitioners. Discussions as to the content and format took place prior to consultations with multi-disciplinary professionals who work at Princess Basma.

4.9 Pilot study.

Five questionnaires were tested to check the feasibility and improve the design. As a result the question regarding the families income was removed, there was no objective way of verifying this. Social economic status was therefore evaluated based on education and father's profession. Minor modification was made to the order of questions improving the flow of the questionnaire. The pilot also highlighted one practical logistical difficulty namely that more time than had originally been anticipated would be needed for the completion of the questionnaire.

4.10 Implementation and operational variables.

<u>Risk factor variables confirmed from the centers admission form/ medical records.</u>

1. Lack of oxygen. Yes/no
2. Low birth weight. <1500g, < 2500 exact weight.
3. Premature Yes/no, Exact gestational age.
4. Type of delivery, trauma. NVSD, instrument assisted [forceps, vacuum], Caesarian, breech birth. Reason for caesarian.
5. Jaundice. Yes/ no. Bilarubin levels if documented, length of time with jaundice.

6. Other family members disabled. [any physical/cognitive disability] Yes/ No. disability to be specified.
7. Inter- marriage. Yes/no. 1st cousin, 2nd cousin, from the family.
8. Child incubated. Yes/no. length of time.
9. Did the Baby suffer; hemorrhage/bleeding difficulty breathing, lack of oxygen, bilirubinemia, others to be specified.
10. Socio-economic status. Occupation of father and mother. Classified using ISCO. [International Labor Organization, 2008]
11. Education – Classified into; Below Tawghi, Tawghi, College Diploma, and University.
12. Disappearing twin, Yes/no
13. Multiple pregnancies, Yes/no
14. Congenital abnormalities, Yes/no
15. Place of delivery

Risk factor variables to be obtained from questionnaire- operational in the questionnaire and not available from medical records.

1. Fertility treatment? Specify what kind.
2. Infection and inflammation, Yes/no, during pregnancy, during delivery.
3. Thrombophilia. - Clotting disorder, Yes/no.
4. Parent's age. Specified for mother and father.

4.11 Statistical analysis.

Analysis was by SPSS19, 2010 beginning with descriptive statistics including mean, standard deviation and t-test, univariate analysis, Chi squared test for cross tabulation, and t-test for difference in means. Fischers exact was used for variables with small numbers. Data was stratified and adjusted for gestational age and gender and use made of multivariate regression models. Binary logistical regression, the main analysis method for unmatched case control studies was central. Forced entry all variable regression and stepwise entry was used in model building. All analysis was conducted, two tailed with p=0.05 considered significant. [IBM SPSS version 19]

Logistic regression analysis was used to adjust for potential confounders and to identify independent risk factors. The risk factors included were; low birth weight,

mode of delivery, hypoxia, gestational age, jaundice, multiple birth, other disabilities in the family, infection during pregnancy and delivery, congenital abnormality, disappearing twin, ages of parents and socio-economic status were analyzed. Population specific factors assessed were consanguineous marriage, whether medical care was received during pregnancy, and location of delivery, [Ministry of Health Hospital, private maternity home, Makassad Hospital and Hilal Hospitals.]. Each risk factor was adjusted firstly for gestational age of less than 37 weeks and gender and secondly for all other risk factors. Crude odds ratio's showed significance, also with adjustment for gestational age, and gender. With adjustment for all other variables many of the known variables lost their significance. Specifically; caesarean, gestation, jaundice, infection during pregnancy, infection during delivery, and place of delivery. This was not the case with most of the population specific variables. This result is summarized in tables 5.9 and 5.1

4.12 Ethical considerations.

As part of the research is concerned with examining numbers as they relate to the risk factors no names or personal information is of relevance. Permission to use the centre's data was granted likewise permission from M.O.H., U.N.W.R.A., and private clinics were obtained. For the questionnaire a consent form was offered and mothers/ caregivers of both cases and controls were free to participate or not. Ethical considerations were minimal.

4.13 Issues arising in the research process.

After the first ten cases it was necessary to add an additional question, the reason for cesarean, if known. As the mothers were residential all cases were asked this question. The qualitative variables pertaining to the mothers evaluation of hospital services was omitted. This was because it was clear that mothers of cases blamed the medical services for their child's condition. Whilst in some cases this may have been valid the fact that it could not be objectively confirmed was the reason for omission. Regarding the question of jaundice, only where this was significant enough to be noted in the medical records was it recorded which may mean there is the possibility of missing data. During the research period, from January 19th-July 19th there were a total of

thirteen case exclusions, six of the cases at Princess Basma were residential for the treatment of autism, five were post-natally acquired cerebral palsy, and two were diagnosed with Down's syndrome. In addition two of the mothers left the centre early and due to the nature of probability of the sample missed inclusion. None of the cases refused to participate and only three controls declined.

The medical records from the M.O.H. and the UNWRA were the same forms and contained similar information to that recorded at Princess Basma. However the private clinics do not have such a detailed and extensive medical history. The questionnaire was administered without cross-checking medical records. However only a small proportion of the sample came from private clinics.

It was initially proposed that the questionnaire would be administered by the researcher and the occupational therapists at the centre. However due to staff shortages this soon became impracticable, all 330 interviews except for 24 were conducted by the researcher

4.14 Conclusion.

Work completed in preparation for this research highlighted the need for more studies on the risk factors for cerebral palsy, especially in developing countries. The need to incorporate specific population factors as important risk factors was also evident. It is thought a case control methodology was fitting for the research question. The extensive planning meant that the research progressed smoothly and on schedule.

5) Chapter Five: Results.

5.1 Introduction.

In this chapter the socio-demographic characteristics of the study population will be presented. Birth characteristic of the sample are given before bi-variate analysis for each risk factor. This will be followed by single crude or univariate associations. To identify possible confounders adjustment will be made for gestational age and gender. Forced entry binary logistic regression will be shown for all variables. A stepwise model giving the risk factors for cerebral palsy amongst Palestinian children will then be presented. This model will show the importance of population specific risk factors.

5.2 Socio-demographic characteristic of the study.

The socio-demographic characteristics of the study population are shown in table 5-1.There were 107 cases and 223 controls in the study population. More males than females were found in group totals, however the increase was marginal and the ratio varied from 1.12 – 1.18. The slightly higher number of males cases indicates the representativeness of the sample, as cerebral palsy is slightly more prevalent in males at a ratio of 1:1.3 for females and males. Father's profession for cases and controls were classified by International Classification of Occupation 2008, International Union of Labor. Variations of father's professions of both groups follow similar patterns. Mother's profession by cases and controls were also classified using the same system. The vast majority of mothers of both groups are housewives, where mothers do work a higher proportion are in professional employment. Due to small numbers occupation was further classified using categories decided by the researcher. There was no statistically significant difference between the age of mothers of the case group and the control group, nor was there a difference between the father's ages. The analysis showed that 68.2% of the total sample were not related, leaving 31.8% with an inter- family relationship. Table 5-3 show the birth characteristics of the sample which were; gestational age, birth weight, duration of jaundice, incubator stay, low birth weight (<2500 gm) and premature delivery (<37 weeks). There was no statistically significant difference between the mean age of the cases and the mean age of the control group. The standard deviation is indicative of the wide age range

included in the sample. There was a statistically significant difference between the mean weight of cases and controls on delivery, the cases were of lower birth weight. Again the standard deviation is indicative of the wide range of birth weights. Incubator time and CP are also shown in this table, in this study, sixty –three cases as opposed to fourteen controls were incubated after delivery. Independent t-test sample means for time of jaundice for cases and controls are shown with cases of a longer duration.

Table 5-1: Social-demographic characteristics of the study population.

	CP Cases (n=107) (%)	Control (n=223) (%)	P value
Age of children.(Y)Mean ±SD	3.87±2.71	4.17±3.94	0.47**
Gender			0.83*
Male	58 (54%)	118 (53%)	
Female	49 (46%)	105 (47%)	
Sample location			
Princess Basma	107 (100%)	0 (0%)	
UNRWA	0(0%)	109 (49%)	
Private	0(0%)	22 (10%)	
MOH	0(0%)	92 (41%)	
Region			0.45*
North	43 (40%)	88 (39%)	
Middle	53 (50%)	101 (45%)	
South	11 (10%)	34 (15%)	
Mother's education			0.17*
Below Tawjihi	68 (64%)	123 (55%)	
Tawijhi	14 (13%)	40 (18%)	
Collage	8 (7%)	9 (4%)	
University	17 (16%)	51 (23%)	
Father's education			0.73*
Below Tawjihi	65 (61%)	121 (54%)	
Tawijhi	22 (21%)	53 (24%)	
Collage	9 (8%)	19 (9%)	
University	11 (10%)	30 (13%)	
Other children with disability	15 (14%)	4 (2%)	

*: Chi-square test.

**: t-test

Table 5-2: Continued Socio-demographic characteristics of the study population

	CP Cases (n=107)	Control (n=223)	P value
Mother's profession			0.47*
Professionals	5 (4.7%)	15 (6.7%)	
Tech/associate/prof	0 (0%)	1 (0.4%)	
Clerical	3 (2.8%)	3 (1.3%)	
Service/sales	0 (0%)	4 (1.8%)	
Elementary	0 (0%)	2 (0.9%)	
Housewife	96 (89.7%)	195 (87.4%)	
Student	3 (2.8%)	3 (1.3%)	
Mother's profession			0.57
Professional	5 (4.7%)	15 (6.7%)	
Skilled/semiskilled	3 (2.8%)	10 (4.5%)	
Unemployed	99 (92.5%)	198 (88.8%)	
Father's profession			< 0.05*
Armed forces	3 (2.8%)	2 (0.9%)	
Mangers	0 (0%)	1 (0.4%)	
Professional	15 (14%)	25 (11.2%)	
Tech/associate/prof	2 (1.9%)	6 (2.7%)	
Clerical	1 (0.9%)	16 (7.2%)	
Service/sales	6 (5.6%)	16 (7.2%)	
Skilled/agricultural	2 (1.9%)	0 (0%)	
Craft/trade	10 (9.3%)	19 (8.5%)	
Plant/machine/operators	13 (12.1%)	8 (3.6%)	
Elementary	43 (40.2%)	86 (38.6%)	
Unemployed	11 (10.3%)	41 (18.4%)	
Deceased	1(0.9%)	2 (0.9%)	
Father's profession			0.30
Professional	17 (16%)	32 (14.5%)	
Skilled/semiskilled	32 (30.2%)	59 (26.8%)	
Manual	46 (43.4%)	88 (40.0%)	
Unemployed	11 (10.4%)	41 (18.6%)	
Consanguinity			< 0.001*
Not related	56 (52.3%)	169 (75.8%)	
1st cousin	37 (34.6%)	40 (17.9%)	
Second cousin	9 (8.4%)	3 (1.3%)	
Further relation	5 (4.7%)	11 (4.9%)	

*: Chi-square test.

Table 5-3: Birth characteristics of the study population.

	CP Cases (n=107)	Control (n=223)	P value
Gestational age (W)Men ± SD	36.41± 5.19	38.48± 2.19	< 0.001*
Birth weight (g)Mean ±SD	2686±901.7	3183±600.3	< 0.001*
Time jaundice lasted (day)Mean±SD	2.29±6.85	0.65±3.90	< 0.05*
Time spent in incubator (day)Mean±SD	15.4±23.21	0.82±5.14	< 0.001*
Low birth weight <2500 gm n%	41 (38.3%)	17 (7.7%)	< 0.001**
Gestational age < 37 weeks n%	35 (32.7%)	32 (14.3%)	< 0.001**

*: t-test.

**: Chi-square

5.3 Patterns of cerebral palsy amongst cases.

Current research has attempted to link risk factors and resulting patterns of cerebral palsy. As presented in the literature review there has been some evidence to link hypoxia with spastic quadriplegic cerebral palsy. The most common pattern of cerebral palsy amongst the cases was moderate spastic quadriplegic cerebral palsy which gives credence to the finding that 45.8% of cases suffered hypoxia as shown in table 5-4.

Table 5-4: Pattern of cerebral palsy amongst cases

		Tone					
		Spastic	Athetoid	Attaxic	Chorea	Hypotone	Total
Severity	Mild	10 (9.3%)	1 (0.9%)	0 (0%)	0 (0%)	9 (8.4%)	20 (18.7%)
	Moderate	41 (38.3%)	8 (7.5%)	1 (0.9%)	0 (0%)	7 (6.5%)	57 53.3%)
	Severe	22 (20.6%)	3 (2.8%)	0 (0%)	0 (0%)	2 (1.9%)	27 (25.2%)
	Profound	2 (1.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.9%)

5.4 Risk Factors for Cerebral Palsy.

5.4.1 Bivariate association between risk factors and CP

Both known risk factors and new population specific risk factors were investigated and assessed with chi squared to test for association, p values are reported (table 5.5). Fischer's exact was used with small numbers and showed that significance in the chi was not necessarily true. The results indicated significant associations between cerebral palsy and hypoxia, consanguinity, lack of pre-natal checkups, low birth weight, gestational age, incubation, jaundice, disappearing twin, delivery at Ministry of Health hospital, or Makassad/Hilal Hospital, cesarean delivery, multiple pregnancy, infection during delivery, infection during pregnancy and other disabilities in the family. There was no significant association for cerebral palsy and delivery at private maternity homes, breech delivery, profession of mother and father, education of mother and father, congenital abnormality, thrombophilia and age of mother and father. The Tables 5-5, 5-6, 5-7 and 5-8 summarize this association.

Table 5-5: A) The relationship between known factors and cerebral palsy

Factor	Groups		Observed outcomes		Total	P value
			Yes	No		
Hypoxia	status	cp	49 (45.8%)	58 (54.2%)	107	0.000*
		control	4 (1.8%)	204 (98.4%)	208	
	Total		53	242	295	
			<2500	2500-4000		
Low birth weight.	status	cp	41 (38.3%)	66 (61.7%)	107	0.000
		control	25 (11.2%)	185 (83.0%)	210	
	Total		66	251	317	
			<37 weeks	>37 weeks		
Gestation	status	cp	35 (32.7%)	70 (65.4%)	105	0.000
		control	32 (14.3%)	191 (85.7%)	223	
	Total		67	261	328	
			Yes	No		
Jaundice	status	cp	20 (18.7%)	87 (81.3%)	107	0.003
		control	17 (7.6%)	205(91.9%)	222	
	Total		37	292	329	
			Yes	No		
Disappearing twin	status	cp	6 (5.6%)	101 (94.4%)	107	0.001*
		control	0 (0%)	223 (100%)	223	
	Total		6	324	330	
			Yes	No		
Cesarean delivery	status	cp	48 (44.9%)	51 (47.7%)	99	0.000
		control	58 (26%)	163 (73.1%)	221	
	Total		106	214	320	

Table 5-6: B) The relationship between known factors and cerebral palsy

Factor	Groups		Observed outcomes		Total	P value
			Yes	No		
Breech delivery	status	cp	5 (4.7%)	102 (95.3%)	107	0.535*
		control	7 (3.1%)	216 (96.9%)	223	
	Total		12	318	330	
			Yes	No		
Multiple birth	status	cp	10 (9.3%)	97 (90.7%)	107	0.000*
		control	2 (0.9%)	221 (99.1%)	223	
	Total		12	318	330	
			Yes	No		
Infection during Pregnancy	status	cp	20 (18.7%)	87 (81.3%)	107	0.000
		control	10 (4.5%)	213 (95.5%)	223	
	Total		30	300	330	
			Yes	No		
Infection during delivery	status	cp	9 (8.4%)	98 (91.6%)	107	0.006*
		control	4 (1.8%)	219 (98.2%)	223	
	Total		13	317	330	
			Yes	No		
Congenital Abnormality	status	cp	10 (9.3%)	97 (90.7%)	107	0.306*
		control	0 (0%)	223 (100%)	223	
	Total		1	319	330	
			Yes	No		
Other children with disabilities in the family	status	cp	15 (14%)	92 (86.0%)	107	0.000*
		control	4 (1.8%)	219 (98.2%)	223	
	Total		19	311	330	
			Yes	No		
Fertility Treatment	status	cp	2 (1.9%)	105 (98.1%)	107	0.104*
		control	0 (0%)	223 (100%)	223	
	Total		2	328	330	
			Yes	No		
Thrombophilia	status	cp	5 (4.7%)	102 (95.3%)	107	0.635*
		control	8 (3.6%)	215 (96.4%)	223	
	Total		13	317	330	

*: Fisher's exact test

Table 5-7: The relationship between population specific factors and cerebral palsy

Factor	Groups		Observed outcomes		Total	P value
			Yes	No		
Consanguinity	status	cp	51 (47.7%)	56 (52.3%)	107	0.000
		control	54 (24.2%)	169 (75.8%)	223	
	Total		105	225	330	
			Yes	No		
Medical Care In Pregnancy	status	cp	95 (88.8%)	12 (11.2%)	107	0.001*
		control	218 (97.8%)	5 (2.2%)	223	
	Total		313	17	330	
			Yes	No		
Ministry of Health Hospital	status	cp	67 (62.6%)	40 (37.4%)	107	0.000
		control	85 (38.1%)	138 (61.9%)	223	
	Total		152	178	330	
			Yes	No		
N.G.O. Makassad/Hilal Hospitals	status	cp	26 (24.3%)	81 (75.7%)	107	0.003
		control	91 (40.8%)	132 (59.2%)	223	
	Total		117	213	330	
			Yes	No		
Private maternity home	status	cp	13 (12.1%)	94 (87.9%)	107	0.106
		control	43 (19.3%	180 (80.7%)	223	
	Total		56	274	330	

*: Fisher's exact test

Table 5-8: The relationship between descriptive/socioeconomic factors and cerebral palsy

Factor	Groups		Observed outcomes		Total	P value
			Yes	No		
Incubated	status	cp	63 (58.9%)	44 (41.1%)	107	0.000
		control	14 (6.3%)	209 (93.7%)	223	
	Total		77	253	330	
			Unemployed	Employed		
Fathers employment	status	cp	11 (10.3%)	96 (89.7%)	107	0.059
		control	41 (18.4%)	182 (81.6%)	223	
	Total		52	278	330	
			un-educated	Educated.		
Fathers education	status	cp	65 (60.7%)	42 (39.3%)	107	0.235
		control	120 (53.8%)	103 (46.2%)	223	
	Total		185	145	330	
			Unemployed	Employed		
Mothers employment	status	cp	96 (89.7%)	11 (10.3%)	107	0.549
		control	195 (87.4%)	28 (12.6%)	223	
	Total		291	39	330	
			Uneducated	Educated		
Mothers education	status	cp	68 (63.6%)	39 (36.4%)	107	0.148
		control	123 (55.2%)	100 (44.8%)	223	
	Total		191	139	330	
			<=21	22-39		
Mothers age	status	cp	20 (18.7%)	85 (79.4%)	105	0.584
		control	46 (20.6$)	166 (74.4%)	212	
	Total		66	251	317	
			>39	22-39		
Mothers age	status	cp	2 (1.9%)	85 (79.4%)	87	0.099*
		control	14 (6.3%)	163 (73.1%)	177	
	Total		16	248	264	
			<=21	22-39		
Fathers age	status	cp	1 (0.9%)	90 (84.1%)	91	0.430*
		control	6 (2.7%)	176 (78.9%)	182	
	Total		7	266	273	
			>39	22-39		
Fathers age	status	cp	20 (18.7%)	86 (80.4%)	106	0.302
		control	52 (23.3%)	165 (74.0%)	217	
	Total		72	251	323	

*: Fisher's exact test, un-educated=below Tawjghi examination.

5.4.2 Multivariate association between risk factors and CP.

Table 5-9: Crude and adjusted odds ratio for neo-natal risk factors and cerebral palsy.

	Number (%)		OR. [95%CI]£	OR. [95%CI]†	O.R. [95%C.I.]#
	Control (223)	CP (107)			
[1]: Normal weight >2500 Low birth Weight ≤2500	25 (38.3)	25 (11.9)	4.60[1] [2.60-8.14] **	3.74 [1.97-7.08]**	2.91 [1.08-7.83]*
[1]: N.V.S.D. Caesarean Delivery	58 (26.0)	48 (44.9)	2.65[1] [1.61-4.34]**	2.40 [1.43-3.98]**	1.25 [0.60-2.58]
[1]: No hypoxia Hypoxia	4 (1.8)	49 (45.8)	65.76[1] [22.41-192.96] **	61.19 [20.02-187.07]**	38.57 [11.42-130.27]**
[1]: Normal gestation 38-42 weeks Gestational age <37 weeks	32(14.3)	35(32.7)	2.90[1] [1.67-5.03]**	2.98 [1.71 – 5.17]* ††	1.08 [0.426-2.74]
[1]: No jaundice Jaundice	17 (7.7)	20 (18.7)	2.70[1] [1.39-5.55]*	2.22 [1.07-4.59]*	0.89 [0.30-2.67]
[1]: Singleton birth Multiple births	2 (0.9)	10 (9.3)	11.40[1] [2.45-52.97]**	8.76[1.83-41.97]**	8.31 [1.270-54.40]**
[1]: No congenital abnormalities. Congenital Abnormalities Cleft Palate Head malformation Other.	 0 (0) 0 (0) 1 (0.4)	 1 (9) 6 (5.6) 3 (2.8)	2.41[1] [1.31-4.44]**	000	000

* : <0.05, ** :< 0.01, £: Crude OR, †: Adjusted for gestational age <37 week/ gender, ††: Adjusted for gender #: Adjusted for all variables in table, [1]: Reference category.

Table 5-10: crude and adjusted odds Ratio for extra neonatal risk factors and cerebral palsy

	Number (%)		OR. [95%CI]£	OR. [95%CI]†	O.R. [95%C.I.]#
	Control (223)	CP (107)			
[1]: No infection during pregnancy Infection during Pregnancy	10 (4.5)	20 (18.7)	4.80[1] [2.20-10.89]**	4.23[1.85-9.64]**	1.86 [0.46-7.50]
[1:] No infection during delivery Infection during delivery	10 (4.5)	14 (13.1)	5.00[1] [1.51-16.72]*	3.32 [0.948-11.63]*	3.04 [0.39-24.03]
[1:] No other children with disabilities. Other Children with disabilities in family	4 (1.8)	15 (14)	8.90[1] [2.89-27.62]**	8.05 [2.52-25.65]**	8.85 [2.28-34.38]**
[1]: Not related. Consanguineous marriage	54 (24.2)	51 (47.7)	2.85[1] [1.75-4.64]**	3.25 [1.94-5.42]**	4.37 [2.20-8.64]**
[1:] Medical care in pregnancy No medical care in pregnancy	5 (2.2)	12 (11.2)	5.50[1] [1.89-16.07]**	6.33 [2.18-18.33]**	6.65 [1.77-24.97]**
[1]: Makassad and Hilal Hospitals, Private Maternity Homes Place of Delivery MOH	85 (38.1)	67 (62.6)	2.70[1] [1.69-4.38]**	2.70 [1.65-4.41]**	0.65 [0.06-7.43]
Mother's age ([1:] Ages 22-38) younger (<21) older (>39)	 46 (21.7) 14(7.9)	 20 (19.0) 2 (2.3)	 0.84[1] [0.47-1.53] 0.27[1] [0.06-1.23]	 0.86 [0.46-1.56] 0.28 [0.62-1.34]	1.17 [0.984-1.16][2]
Father's age ([1:] Ages 22-38) younger (<21) older (>39)	 6 (3.3) 52 (24.0)	 1 (1.1) 20 (18.9)	 0.33[1] [0.39-2.74] 0.74[1] [0.41-1.32]	 0.34 [0.004-2.95] 0.69 [0.38-1.26]	0.99 [0.92-1.05][2]
Place of delivery [1:] M.O.H/Makassad Private maternity home [1:] M.O.H./Private. Other-Makassad, Hilal hospital.	 85(38.1) 91(40.8)	 67(62.6) 26(24.3)	 0.58[1] [0.30-1.13] 0.46[1] [0.27-0.78] **	 0.65 [0.33-1.28] 0.44 [0.26-0.75]	 0.43 [0.03-5.20] 0.21 [0.02-2.56]

* : <0.05, ** :< 0.01, £: Crude OR, †: Adjusted for Gestational age <37 weeks/gender, #: Adjusted for all variables, [1]: Reference category, [2]: Adjusted for non-categorized age.

Tables 5-9 and 5-10 show that low birth weight retained significance after adjustment for gestational age, gender and multi-variable regression. The significance and odds ratio was reduced in regression but still present. The connection between low birth weight and gestational age is well established. Less than thirty-seven weeks was significant and un-confounded until adjustment for all variables. This indicates that birth weight is the most important factor but may form a causal pathway together with a pre-term delivery.

Cesarean section also maintained significance until regressed where it was superseded by other factors. Jaundice loses significance after adjustment for other factors in regression unlike multiple births which retains a strong odds ratio if a reduced significance.

Infection during pregnancy retains significance as crude and after adjustment for gestation and gender. Infection during delivery is confounded by gestational age and in the multi-variable regression. Crude and gender odds ratio show significance only. Infection for the infants produced too few numbers to allow analysis.

Congenital abnormality when adjusted as one variable with the different abnormalities in one group showed significance. However the presence of a 0 in the control group meant this could not be regressed by SPSS. Other children with disability in the family retained significance throughout the analysis. This was also the case with one of the original variables in this study consanguineous marriage. Another original variable, lack of medical attention during pregnancy again retained significance throughout the analysis, despite a reduction in significance by gestational age. For this variable it should be noted however that numbers in the study are small.

Continuing with the original population specific factors, place of delivery, the Ministry of Health remained significant until the all variable analysis here marginally significance was lost. Private maternity homes were not significant throughout which was against the study hypothesis. Makassad and Hilal hospitals {N.G.O.'s} were found to be of less risk in the early analysis until the all variable regression. Regarding cesarean and cerebral palsy the results present a significant association. Forty-five point three of the cases were delivered by cesarean. The reasons given for the cesarean differ between cases and controls are depicted below in fig 5-1. For cases more cesareans were due to long labor, premature rupture of membranes, multiple births and fetal distress. For the controls, reasons included all previous deliveries were

by cesarean, loss of amniotic fluid, no contractions and their health. Of note is that more controls [10%] were aware of the reason for their cesarean than cases [Fig 5-2].

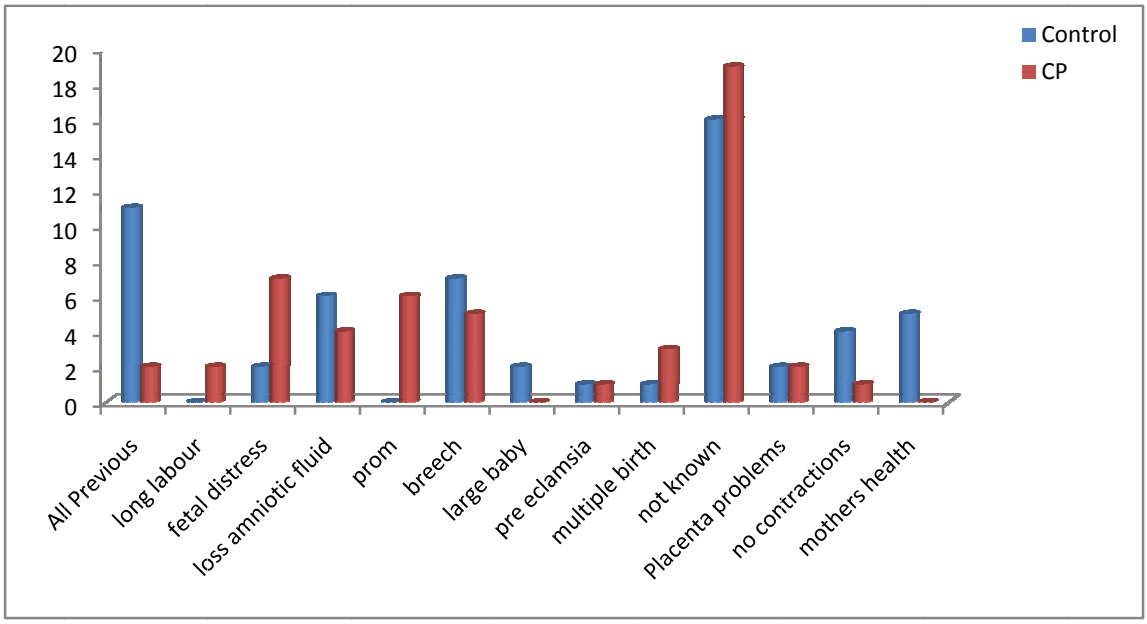

Figure 5-1: Reasons given for cesarean by respondents

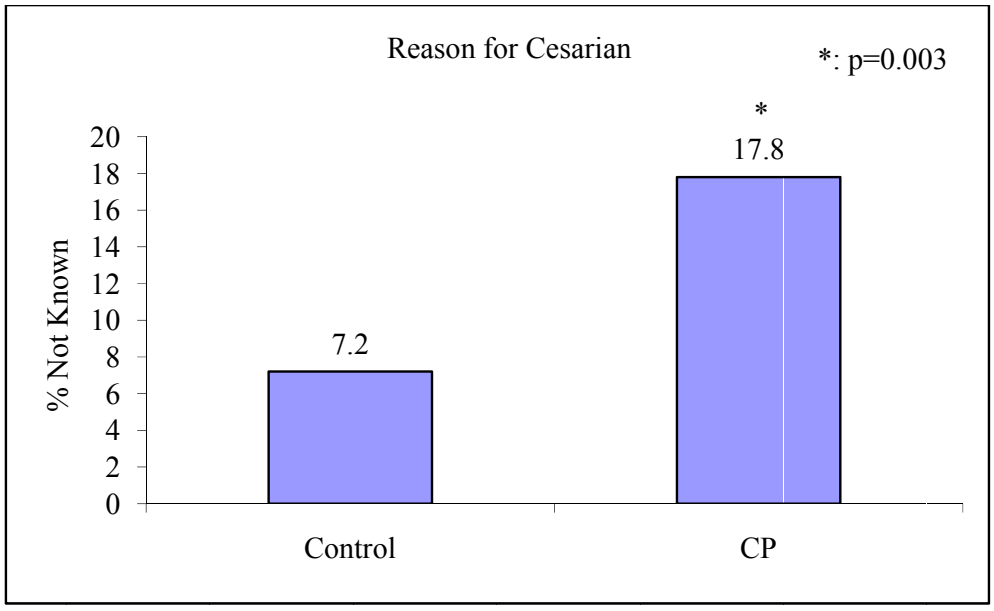

Figure 5-2: More controls were aware of the reason for their cesarean than cases

For hypoxia and cerebral palsy, the results show 45.8% of the cases compared with 1.8% of the controls suffered lack of oxygen. This association proved to be a major result in this study. Cesarean becomes insignificant when combined with hypoxia.

Table 5-11: The association between hypoxia and cesarean with cerebral palsy.

	O.R. C.I. 95%	P value
Hypoxia	58.26 [19.66-172.67]	.000
Cesarean	1.99 [.99-3.98]	0.51

Consanguineous Marriage and Cerebral Palsy, first and second cousins proved significant but no wider family relations showed significance. Table 5-12 below presents this result, of further note is the stronger relationship for cerebral palsy and second cousins.

Table 5-12: The association between consanguineous marriage and cerebral palsy.

	O.R. C.I. 95%	P value
First cousins	2.8[1.62-4.79]	0.000
Second cousins	9.1[2.37-34.61]	0.001
Wider	1.4[0.46-4.11]	0.573

The variables which proved insignificant at all levels of analysis were socio-economic status as defined by father's profession and low educational attainment. With reference to father's profession when split into fewer categories an initial slight significance was lost. This was also the case for mother's employment and education. Age of parents, below twenty one and above thirty nine proved insignificant as did breech birth, assisted, instrument delivery and thrombophilia.

5.5 The main risk factors for cerebral palsy amongst Palestinian children.

Using stepwise binary regression risk factors were individually introduced. Risk factors were removed if they showed no significance. The continuity of the co-efficient indicated no confounding. Variables were entered hierarchically based on significance. The results are displayed below in table 5-13.

Table 5-13: Step wise model of risk factors for cerebral palsy in Palestine.

Risk factor	O.R. C.I. 95%	P value
Low Birth Weight	4.98[2.01-12.32]#	0.001
Hypoxia	92.45 [24.45-349.62]#	0.000
Multiple birth[twins]	9.25 [1.29-66.75]#	0.027
Other disabled children.	12.73 [3.13-51.70]#	0.000
Consanguineous Marriage	4.62 [2.07-10.31]#	0.000
No medical care In Pregnancy	5.22 [1.18-23.14]#	0.029
Delivery at Makassad/Hilal Hospital [N.G.O.'s]	0.38 [0.16-0.91]#	0.030

Adjusted for all variables in the study.

From the known risk factors low birth weight, hypoxia, multiple pregnancies, other children in the family with disability, stayed in the model. Cesarean went out with the addition of hypoxia, gestational age immediately showed no significance as expected. Jaundice, infection during pregnancy, and infection during delivery also showed no significance. Large confidence intervals can be explained by small sample size.

From the original population specific risk factors consanguineous marriage remained, as did no medical care during pregnancy. Ministry of Health went out but N.G.O.'s [Makassad Hospital and Hilal hospitals] remained, giving a lower risk for cerebral palsy than Ministry of Health Hospitals.

6) Chapter six- Discussion.

6.1 Introduction

Ill health is due to behavior, environment, genetic constitution and all that may have gone on before in previous generations. Cerebral palsy has been researched as one condition arising from a variety of risk factors. This chapter will discuss what the results tell us about cerebral palsy in Palestine. For reliability purposes it should be noted that there are no major difference in the mean ages of cases and controls which lends itself to the sample being representative. The international prevalence of cerebral palsy occurs in a ratio of 1:1.3 for females to males in this study the ratio for the sample equates to a ratio of 1:1.2 Also of note the unemployment rate for Palestinian men is 16.7% (P.C.B.S, 2008), for this study the rate was calculated at 16%. Again this can be said to provide evidence for the representativeness of the sample.

6.2 Summary

The main study findings are high numbers of cases with documented hypoxia and high number of cases delivered by cesarean section. The study found strong correlation with many known risk factors and introduces new, previously un-assessed population specific risk factors. There were risk factors for which complete analysis was not possible. The reasons for this were presence of zero amongst the controls and small numbers. Post term gestation and cerebral palsy, baby's weight more than four kg and cerebral palsy could not be analyzed for the latter reason. There were also risk factors found to be of no significance.

6.3 Population specific risk factors and cerebral palsy

Of the new variables this study presents consanguineous marriage and cerebral palsy which produced consistent, strong results. Inter-marriage is common in Palestine, and is an accepted part of the culture. Cerebral palsy and marriage between first cousins was found to be significant at P = 0.0001. For marriage between second cousins the significance was found at P=0.0003, Fischer's exact due to small numbers. For the main analysis the categories were left in one group, the higher odds ratio for second cousins and cerebral palsy may not be overly significant, inter-marriage may have continued throughout many previous generations. For inter-marriage from the wider

family there was no significance. This factor was also important in the multi variable regression and the stepwise binary logistical model. This factor has received little attention in research in the past but maybe of importance in the etiology of cerebral palsy in Palestine. In this research this factor ranked the fifth highest in the ranking of odds ratios. In the existing research it was also found to be amongst the top risk factors (Delialioglu et al 2008).

Another population specific variable unique to this research is place of delivery and cerebral palsy. It was hypothesized that small private maternity homes in the West Bank had a higher correlation with cerebral palsy cases. However this was found to have no significance in this study. Of significance was M.O.H. hospitals. N.G.O.'s, being Makassad Hospital, East Jerusalem and Hilal, Red Crescent Hospitals in Jerusalem and the West Bank were found have less risk.

No medical care in pregnancy is another unique study risk factor. With no national health system in Palestine whether, when and how an individual seeks any medical care is solely in the control of the individual. Cerebral palsy and lack of regular pre-natal checkups and was found to be significant at P=0.001. It should be noted that numbers within the sample population were small, so a study with a larger sample is needed. Primary health care in Palestine is available and not expensive; the reasons for not having regular check-ups are not known and require further investigation. From this association we can assume that the benefits of routine ultra-sound in early pregnancy and other checks are important for prevention.

Blood clotting and cerebral palsy can be considered both a population specific factor and a known factor with thrombophilia high within Arab populations (Yehezkely-Schildkrant 2005).This study found no significance between thrombophilia and cerebral palsy.

6.4 The association between cerebral palsy and known risk factors.

For the known risk factors the first to be discussed is caesarian section and cerebral palsy. In the literature review caesarian was considered protective, or associated with a slight rise in risk in very few studies (Giles 1996). However dramatically in this study 45.3% of the cases were caesarian delivery, compared with 26.3% of controls. All participants were asked the reason for their caesarian, of particular interest is the high number, particularly amongst cases where the mother was unaware of the reason.

Indeed 10% more of the cases did not know why their child had been delivered by caesarian. In Palestine this is a decision taken by the doctor, there are no elective caesarian at 39 weeks of gestation as is common in other countries (O'Brien et al, 1966). This would require a shift from a dominant medical model to a partnership approach which does not exist at present. It should be remembered that with any observational study the data is collected post hoc and therefore we cannot be sure that the association is due to poor medical management and not a common confounding factor. How many cases are due to sub-optimal obstetric response [not expediting delivery] is not known. Clinical signs sufficient to warrant a caesarian may only be recognizable after the damage has occurred. Maybe an optimal response is for the mother to be given options to include a caesarian at 39 weeks pre-labor. The most common association was caesarian and hypoxia. Lack of oxygen is believed to be an important and preventable cause of cerebral palsy. Indeed this belief underpinned much of the justification for fetal monitoring in labor and the increase in caesarian rates. For many years no research was done into cerebral palsy to look at other factors as it was thought to be lack of oxygen. Research began with the knowledge that lack of oxygen only accounts for 10% of cerebral palsy cases in developed countries (Adding et al 2006).The picture is very different in Palestine with 45.8% of cases as opposed to 1.8% of controls; this figure is close to the figure for caesarian sections above. It is known that the potential for hypoxia is highest during caesarian section. There appears to be several options; With reference to congenital abnormalities and cerebral palsy, this was found to be significant at P=0.000. Visible manifestations included cleft palate, head malformations and additional digits. Many non-visible malformations of the brain or other organs are known to be due to teratogens causing structural malformations in early pregnancy. Visible defects in children with cerebral palsy suggest an exposure occurring early in pregnancy maybe responsible for both the malformation and the cerebral palsy (Pharoah 2007). Small numbers in this study mean inferences are difficult.

For disappearing twin and cerebral Palsy SPSS could not analyze this factor due to lack of controls Many twin pregnancies with early co-fetal losses are not recognized and may not even be recognized as twin conceptions which makes it difficult to estimate the true number of cases of cerebral palsy due to disappearing twin.

Findings for low birth weight and cerebral palsy in this study are the mean weight of 3183.24 kg for controls and 2685.66kg for cases. The correlation was significant,

different explanations can be suggested for this association firstly that low birth weight and cerebral palsy is epiphenomena in itself. Secondly that intrauterine growth restriction causes the conditions responsible for brain damage. Thirdly growth restriction or low birth weight makes the child more vulnerable to hypoxia. Finally that the damage has already occurred, maybe low birth weight is related to earlier pregnancy factors such as malformations or viral infections. The underlying mechanisms are unclear (Stanley et al 2000).

For gestational age and cerebral palsy both crude and adjusted significance was found at the P=0.000 level. Whilst the results show the lower the gestational age the higher the association with cerebral palsy it should be remembered that most children with cerebral palsy are born at term. It can be suggested that the changing gestational age profile of cerebral palsy that very pre-term cerebral palsy rates may depend on neo-natal care (Pharoah et al 1997). Such variables such as gestational age are less dramatic than lack of oxygen and were therefore included as having importance in a causal pathway addressed in a later section of the discussion. Interventions aimed at reducing the occurrence of very pre-term birth can only influence cerebral palsy rates if less than 32 weeks is on a causal pathway. The existence of unexplained early labor shows the limited understanding of pathways. Perhaps pre-term birth makes the child more vulnerable to hypoxia or damage to the motor cortex triggers early delivery itself (Stanley and Blair 1994).

For multiple pregnancy and cerebral palsy; in this study there were only cases/controls with twins, no higher order births. Twins and cerebral palsy proved significant at all levels of analysis. The small numbers are limiting in terms of the weight of the study. Multiple births have greater risks of complications particularly for the second child. Further they are associated with low birth weight, pre-term delivery and death of a co-fetus (Petteson et al 1993). To date there has been no studies of higher order multiple births with sufficient numbers to allow estimates of the rates of cerebral palsy compared to twins. It seems reasonable that with multiple births there is the greater potential for congenital defects than singleton pregnancies. Multiple births may lead to growth restriction, especially in the third trimester. A singleton pregnancy is more likely to produce an appropriately grown fetus at term, for which the like hood of cerebral palsy is lower.

For the association between jaundice and cerebral palsy with a variety of effective treatments this is one of the risk factors where the possibility of prevention is perhaps

one of the strongest. We can only hypothesis that a lack of available equipment may be the reason for its continued importance.

Other family members with disability was specified to include any close and extended family members with physical or cognitive deficits from birth. Due to this wide definition the possibility of confounding cannot be overlooked. This association was found to be significant at the P=0.000 level. As part of family history it may encompass a range of influences, direct and less direct, genetic factors or maybe intergenerational environmental effects. Further research is needed with perhaps a more specific definition. Other studies which focused on the risk of a second child having cerebral palsy where one child had already been diagnosed produced an O.R. of 1.6 of recurrence (Hemminiki et al 2007).

With reference to stroke, one of the frustrations of case-control research is events of interest are not always recorded or detected. Stroke is one such event, diagnosis by ultra sound or MRI. Presentation of stroke in newborns is non-specific so diagnosis is reliant on the above equipment. For the majority of Palestinian children they will be born in medical facilities without imaging capabilities. Where present the lack of such tests or diagnosis in the medical files may mean it is seldom used. One of the clinical signs maybe an apparent hypoxia so we can hypothesize that some of the cases did suffer a stroke but this cannot be quantified. Whether strokes are more or less likely in the presence of surgical delivery has not been investigated, but it is known surgery is a risk factor for coagulation disorders such as stroke (Suvannand et al 1997). This could be a factor especially given the high numbers of cesareans and cerebral palsy in this study.

6.5 Risk factors for cerebral palsy found to be of no significance.

The known risk factors incorporated into this study and found to be of no significance were; social economic variables [parent's occupation, education]. This parallels some studies but there are also studies which found associations for example (Odding 2006). Age of parents was also found to have no significance, for early and late birth, unlike existing research where young mothers were found to have increased risk,(Fletcher and Foley 1993).The average age was 27 and 32 for mothers and fathers respectively. There was no difference in the mean ages of parents between cases and controls. Fertility treatment and cerebral palsy was not significant, only two cases and

no controls were contained in the sample. Another study with bigger numbers is perhaps needed to investigate further. Instrument delivery, breech birth and cerebral palsy also proved insignificant, the same reason may apply- that of small sample numbers. This cannot be ruled out as a possible factor as research has linked type of delivery and cerebral palsy, (Cohen et al 1982).

6.6 Risk factors for cerebral palsy in Palestine –The first model.

The method used to build the model came from D. Bowers, 2009. All risk factors which revealed insignificant P values were excluded, [socio-economic variables, demographic, fertility treatment, breech birth and instrument assisted delivery]. All factors of significance were ordered lowest p values first after chi square tests. Where risk factors shared the same value their introduction into the model was arbitrary. Factors were entered into a binary logistical model and remained if significant and removed if not. The final model contained both known risk factors and population specific risk factors.

This model shows the most significant risk factors for cerebral palsy in Palestine to be hypoxia, low birth weight, multiple births and a family history of disability. This last variable gives credence to a possible genetic link reinforced by the presence of consanguinity in the model. Lack of medical care in pregnancy and location of delivery was also significant. If Palestinians deliver at either Hilal hospitals or Makassad hospital the chance of cerebral palsy is less compared to other possible delivery locations – Ministry of health Hospitals.

6.7 Parallels and differences with existing research.

The results in this study have parallels and differences with existing research. Of the known factors the ones that showed significance mirror many previous studies. Hypoxia as in other studies produces the most dramatic results, low birth weight, multiple births, infection during pregnancy and delivery, congenital abnormality, other disability in the family, jaundice all agree with current body of knowledge. Also as in other studies when adjusted by all variables most appear confounded. In some studies all risk factors are confounded indicating the possibility of multiplicity of risk

factors in cerebral palsy. In this research some remained significant after adjustment and in regression. For some factors as already discussed small numbers meant analysis was not complete so no comparison can be made. The difference between this research and other studies is in the new variables introduced as having importance amongst Palestinians, consanguineous marriage, lack of medical care when pregnant, and location of delivery. The only other difference is the risk of caesarean and cerebral palsy which others studies show as protective, this can be explained by the lack of elective caesarean sections performed in Palestine. This study is unique in that it is the first to present a model of risk factors for cerebral palsy for Palestinians.

The significant results for the new risk factors can be explained by the belief that in addition to renowned factors which were discovered through research in developed countries that there are specific population factors that also increase the risk of cerebral palsy. Location of delivery is an issue due to occupation, access to hospitals outside the confines of the West bank is denied to many resulting in private maternity homes. Primary health care in Palestine is comparable with many developed countries however there is a widely held belief amongst professionals and the Palestinians themselves that at the tertiary level Ministry of Health Hospitals are lacking in terms of service and standards. This was evident when conducting the research, many mothers would have preferred to deliver at Makassad but access was not possible. The protective nature of N.G.O.'s confirmed by this study is merely reinforcing what is commonly known by the population. The results for the known risk factors can be explained by the fact that population specific risk factors are only part of the etiology and people from different societies share commonalities as they are all human beings

6.8 Strengths and weaknesses of the study.

The strengths of this study are firstly it is presenting unique risk factors and adding to the body of knowledge regarding risk factors for cerebral palsy. This has been possible due to the unique characteristics of Palestinian society and the way the people are forced to live. The methodology was implemented rigorously and accurately. However the study is a small scale observational study, many small numbers meant some factors could not be analyzed completely. Some of the questions in the interview could have been open to bias, for example perhaps a mother with a

child having a congenital defect would not have wished to say. There is also the possible bias between the different types of identification, a unique attribute of Palestinian society under occupation. When the answers were checked against the medical records all information was confirmed. The mother's did of course provide more detail than was contained in the files, their openness and honesty was humbling.

6.9 Study conclusions.

The major findings of this study are the importance of population specific factors, high numbers of cerebral palsy and cesarean delivery and the large proportion of cases due to hypoxia. Suggested explanations have been presented in the discussion. With respect to cesarean delivery, this is a doctor decision so maybe it is time to respect women's autonomy. Women should play a major role in what is essentially a risk assessment. Our inability to identify and prevent risk factors for events such as cerebral palsy could be of minimal importance if there was a switch to early cesarean as risk avoidance. This intervention could be seen as a social or public health policy replacing currently late intervention, medical care applied to an already compromised mother or neonate. Whilst caesarian at 39 weeks pre-labor is common in developed countries few studies have examined the effects of elective cesarean on outcome. Also for this study it needs to be recognized that as an observational study strong associations do not necessarily signify causation, confounders or epiphenomena can be alternative explanations.

For consanguineous marriage, this is a social issue which needs to be addressed by government and non-government agencies. For many inter-marriage has many perceived benefits, keeping the money in the family, the families are known to each other and to be of good character to name but two examples (Barbour and Salameh 2009) However the down side needs to be known, there is an increased risk of disability because of inter-marriage and not due to something the mother did wrong.

For cerebral palsy there are many emerging factors yet to be researched not just population specific factors incorporated into this study for examples the effects of nutritional supplements, or maternal dehydration during delivery (Stanley 2000). In addition we still fail to understand the complex pathways[s] which include social, cultural and behavioral factors that cause cerebral palsy. Many significant brain damaging events go un-noticed because of this.

In summary, with the exception of private maternity homes increasing the risk of cerebral palsy the study objectives achieved. Evidence has been presented that whilst important there are more than just simple associations between single risk factors and cerebral palsy. Developed and non developed countries differ in terms of population specific risk factors - consanguineous marriage, whether medical care in pregnancy was given. Also factors differ in their importance, the high number of cesarean sections and cerebral palsy, the high number of hypoxia and cerebral palsy in Palestine compared to developed countries. Other factors apply equally between countries, some such as hypoxia, disappearing twin are so dramatic the result is cerebral palsy. Others are less dramatic and occur in combination. It is perhaps this latter point that will be the focus of cerebral palsy research because here is the possibility of prevention. There is also the possibility of prevention in offering elective cesarean.

6.10. Current Recommendations

In conclusion there are five current recommendations, and four for future consideration; this study has found that modifiable risk factors are resulting in cerebral palsy in Palestine. Strategies for prevention could include the following.

1. The need for heightened awareness about the link between consanguinity and cerebral palsy. This requires a cultural change perhaps realized through health promotion incorporating advice from health providers and social marketing campaigns. Deep seated cultural practices are obviously hard to change and require time.
2. There is the need for heightened awareness of the importance of regular pre-natal check-ups. This requires an educational change so mothers are made aware of the importance of visits for their health and their baby's health.
3. Mothers need to be involved in decisions about the birth of their children, which requires a behavioral change. A change from the dominant medical model to a partnership approach with the start of birthing plans
4. Where a case of cerebral palsy is identified at birth there is the need for an in hospital committee aimed at possible improvement and future avoidance, an organizational change. This can be constructive not geared to apportion blame.

5. Finally for a National Palestinian Cerebral Palsy Register vital for monitoring, dissemination of knowledge and further research. This is a bureaucratic surveillance change, surveillance is carried out in Palestine, and the number of cases of cerebral palsy in Palestine is justification for the addition.

All recommendations require a shift in attitudes and behavior which may reduce the occurrence of cerebral palsy. The future recommendations are more broad in focus concerning but not exclusive to Palestine.

6.11. Future Recommendation

1. For research to include new risk factors not previously studied, for example diabetes. Not just whether the mother has diabetes but perhaps also its existence in the wider family. It was noticed by the researcher that this factor was documented in the medical records of the cases during data collection. No known research into diabetes and cerebral palsy exists.
2. For research into medical technology to identify the exact location and extent of the injury in the brain. The condition of cerebral palsy is an umbrella word for all injuries, may be through research links can be made between the site of the injury and the risk factors. Therefore a convergence of academic disciplines could be beneficial.
3. To consider that each risk factor itself may have its own causal pathway. Perhaps if research were to step back to try to untangle what factors are behind individual variables. This requires a change in perspective; this may lead to explanations relating to the confounding of variables when regressed as in this study.
4. Finally for more research into cerebral palsy in Palestine, this study was the first so more is needed to confirm the results. Data is readily available and the sample size was easily reached in a short period- five months. This means that logistically further studies could include many more cases. Etiology and the hypothesis could be further strengthened.

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Appendix A.

Questionnaire.

File number:_____

Distribution:_____

Diagnosis;_____ Description of tone:_____

Mild / Moderate / Severe.

1.

Name of child::	D.O.B
Address:	

2. Information about parents

Father	
Profession	DOB
Education	
Mother	
Profession	DOB
Education	
Relation to spouse:	Number of children:

3. Are there any other children with disability in the family

□ Yes □ No

If yes, what:

4. Did the mother receive any medical care during pregnancy

□ Yes □ No

If yes, what:

5. Type of delivery
   a. Trauma Specify_____
   b. NVSD
   c. Instrument assisted
   d. Caesarian: if caesarian, why?
   e. Breech birth
6. Weight of child on delivery:……..

7. The gestational age of the baby:……..

8. Was the baby put in the incubator

□ Yes □ No

If yes, for how long:

9. Did the baby Suffer from
    a. Hemorrhage or bleeding
    b. Difficulty breathing
    c. Lack of oxygen
    d. Bilirubinemia
    e. Others:

    ……

    ……

    ……

10. If the baby suffered from bilirubinemia
    a. What was the level
    b. For how long

11. Did you receive any fertility treatment prior to your pregnancy with this child?

□ Yes □ No

If yes,

i. What type of treatment:…….

ii. Was it multiple pregnancy, How many

12. Was this child one of a twin who died before birth?

□ Yes □ No

13. Where did you deliver?

M.O.H._____,Private maternity home_____, Other, specify

Name of medical facility_____.

14. Did you have any infections/ illness during pregnancy?

□ Yes □ No

If yes

what:_____

- Did you have any treatment

□ Yes □ No

If Yes: what?_____

_____

- Do you have any concerns about the treatment you and your child received?

Please specify_____

___.

_____

_____

- Would you classify the treatment received as

Excellent Acceptable Bad

15. Did you have any infections/ illness during delivery?

□ Yes □ No

If yes

what:_____

- Did you have any treatment

□ Yes □ No

If Yes: what?_____

_____

- Do you have any concerns about the treatment you and your child received?

Please specify_____

___.

_____

_____

- Would you classify the treatment received as

Excellent Acceptable Bad

16. Do you know if you suffer from any blood clotting disorder?

□ Yes □ No

If Yes, What disorder_____

17. Does the child have any congenital abnormalities?
    a. Cleft palate
    b. Cleft lip
    c. Head malformation
    d. Other _____.

18. Mother's age when child born
19. Father's age when child born

إستبيان

رقم الملف_____

التوزيع_____

التشخيص_____ وصف

التون_____

قليل / متوسط / بالغ

تاريخ الميلاد:	إسم الطفل:
العنوان:	

1)

2) معلومات عن الوالدين

	الأب
تاريخ الميلاد:	المهنه:
	التحصيل العلمي
	الام
تاريخ الميلاد:	المهنه:
التحصيل العلمي	
عدد الاطفال	صلة القرابه بين الوالدين

3) هل يوجد أطفال اخرين في العائله لديهم إعاقات

□ نعم □ لا

إذا كان الجواب نعم, ما هو نوع الإعاقه:_____

4) هل تلقت الام أي عنايه طبيه خلال فترة الحمل

□ نعم □ لا

إذا كان الجواب نعم, ما هي

5) ما نوع الولاد

a. قصريه مع إصابه

b. طبيعيه

c. بمساعدة أدوات مثل ملقط أو شفاطه

d. بعمليه قيصريه: إذا كانت قيصريه, لماذا:_____

e. ولدة بريتش (الارجل أولاً)

6) وزن الطفل عند الولاده:_____

7) عمر الحمل للطفل:_____

8) هل وضع الطفل في الحاضنه

□ نعم □ لا

إذا كان الجواب نعم, ما هي المده الزمنيه

9) هل عانى الطفل من

a. نزيف

b. صعوبة تنفس

c. نقص أكسجين

d. صفار

e. غير

ذلك:_____

10) إذا عانى الطفل من الصفار

a. كم كانت نسبة الصفار في الدم

b. كم المده الزمنيه التي عانى فيها من الصفار

11) هل تلقيت أي علاج للإخصاب قبل الحمل بهذا الطفل

□ نعم □ لا

إذا كان الجواب نعم,

- ما هو نوع العلاج_____

- هل كان هنالك أثر من جنين واحد كم عددهم:

12) هل كان لهذا الطفل أخ/أخت توأم توفي قبل الولاده؟

☐ نعم ☐ لا

13) أين وضعت طفلك

مستشفى حكومي_____مستشفى خاص_____

غير ذلك(الرجاء التحديد)_____

14) هل عانيت من أي أمراض أو إلتهابات أثناء الحمل؟

☐ نعم ☐ لا

إذا كان الجواب نعم, الرجاء التحديد_____

_____

__

- هل تلقيت أي علاج؟

☐ نعم ☐ لا

  - إذا كان الجواب نعم, الرجاء التحديد_____

_____

هل لديك أي تحفظات أو ملاحظات على العلاج الذي تلقيته انت أو طفلك , الرجاء التوضيح_____

_____

_____

_____

- هل تصنفين العلاج الذي تلقيته على أنه

ممتاز مقبول سيء

15) هل عانيت من أي أمراض أو إلتهابات أثناء الولاده؟

□ نعم □ لا

إذا كان الجواب نعم, الرجاء التحديد_____

_____

__

- هل تلقيت أي علاج؟

□ نعم □ لا

o إذا كان الجواب نعم, الرجاء التحديد_____

_____

__

هل لديك أي تحفظات أو ملاحظات على العلاج الذي تلقيته أو تلقاه طفلك , الرجاء التوضيح_____

_____

_____

- هل تصنفين العلاج الذي تلقيته أو تلقاه طفلك على أنه

ممتاز مقبول سيء

16) هل تعرفين إذا كنت تعانين من أي من أمراض تخثر أو تجلط الدم

□ نعم □ لا

إذا كان الجواب نعم, الرجاء التحديد_____

17) هل يعاني طفلك من أي تشوهات خلقيه:

a. انشقاق سقف الحلق
b. انشقاق الشفاه
c. تشوهات في الرأس
d. غير ذلك _____

18) كم كان عمرك وقت ولادة الطفل؟_____

19) كم كان عمر الاب وقت ولادة الطفل؟_____

Appendix B

نموذج موافقه

عنوان الدراسه:
عوامل المخاطره التي قد تسبب الاصابه بالشلل الدماغي لدى الاطفال في فلسطين

أنت مدعوة للمشاركة في هذه الدراسه من خلال الإجابة على إستبيان و الذي لا يستغرق أكثر من عشر دقائق.

لا يترتب عليك أي مجازفة أو مخاطره , لأن الهدف من الدراسه معرفة الأسباب التي تؤدي إلى الإصابة بالشلل الدماغي.

لأسباب تتعلق بطريقة البحث العلمي سيتم جمع معلومات عن أطفال غير مصابين بالشلل الدماغي بالإضافة الى الأطفال المصابين بالشلل الدماغي.

كل المعلومات الوارده في هذه الدراسه ستكون معلومات سريه و لن يكون هنالك أي ذكر لشخص المشاركين في أي تقارير سواء كانت شفوية أو كتابيه.

المشاركه في الدراسة هي مشاركة طوعية و لا يترتب عليها أي تبعات ماليه.

لقد قرأت المعلومات الواردة أعلاه و تلقيت نسخة من هذا النموذج و لا مانع لدي من المشاركة في هذه الدراسه.

توقيع المشارك

التاريخ:

معلومات عن منفذ الدراسة