

**CHARACTERISTICS AND ASSOCIATED
FACTORS OF PRETERM BIRTH AT HOSPITAL
UNIVERSITI SAINS MALAYSIA (HUSM) IN 2016**

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LIST OF ABBREVIATIONS

ABO	ABO blood group system
ART	Assisted Reproductive Technology
BMI	Body Mass Index
HUSM	Hospital Universiti Sains Malaysia
HRPZ	Hospital Raja Perempuan Zainab II
iMOMz	Database system used at the Obstetrics & Gynaecology Department, HUSM
IUGR	Intrauterine Growth Retardation
LBW	Low Birth Weight
LMP	Last Menstrual Period
MCH	Maternal Child and Health
NOR	National Obstetric Registry
NCD	Non-Communicable Disease
pPROM	Preterm Premature Rupture of Membranes
SGA	Small for Gestational Age
USM	Universiti Sains Malaysia
WHO	World Health Organization

LIST OF SYMBOLS

Symbol	Description
$>$	More than
$<$	Less than
$=$	Equal to
\geq	More than and equal to
\leq	Less than and equal to
α	Alpha
β	Beta
$\%$	Percentage
p	p-value

**CIRI-CIRI DAN FAKTOR BERKAITAN KELAHIRAN BAYI PRAMATANG
DI HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM) PADA TAHUN
2016**

ABSTRAK

Latar Belakang: Di seluruh dunia, kelahiran pramatang tetap menjadi ancaman kesihatan awam yang signifikan memandangkan trendnya yang semakin meningkat dan impaknya yang serius pada kesihatan. Begitu juga di Malaysia di mana perkadaran kelahiran pramatang dan kematian neonatal yang berkaitan diperhatikan meningkat sejak tahun 2011. Akan tetapi, setakat ini penerbitan kajian mengenai kelahiran pramatang tempatan adalah terhad khususnya kajian mengenai ciri-ciri dan faktor risiko kelahiran pramatang.

Objektif: Kajian ini adalah bertujuan untuk mengkaji ciri-ciri dan faktor kelahiran pramatang di HUSM pada tahun 2016.

Kaedah: Pemerhatian rekod secara retrospektif pada data sekunder dijalankan dengan menggunakan bentuk kajian keratan-rentas dalam Bahagian I (n=4,246) dan bentuk kajian kes-kawalan dalam Bahagian II (n=472). Data mengenai ibu-ibu yang bersalin di HUSM pada tahun 2016 telah diekstrak daripada pangkalan data iMOMz. Analisis deskriptif digunakan dalam Bahagian I untuk menentukan perkadaran kelahiran pramatang dan perkadaran kelahiran pramatang berdasarkan ciri-cirinya (sub-kategori, jenis dan status hidup neonatal). Analisis univariat dan multivariat digunakan dalam Bahagian II untuk mengenalpasti faktor kelahiran pramatang.

Keputusan: Perkadaran kelahiran pramatang dalam kalangan kelahiran hidup di HUSM pada 2016 adalah 6.5%. Kesemua 278 kelahiran pramatang jatuh dalam sub-

kategori sederhana hingga lewat pramatang dan kebanyakannya adalah jenis spontan (74.5%). Hanya 1.8% daripada bayi-bayi yang dilahirkan pramatang ini meninggal dalam tempoh masa 28 hari yang pertama. Masalah hipertensi telah dikaitkan secara signifikannya dengan kelahiran pramatang. Ibu dengan masalah hipertensi mempunyai 2.46 kemungkinan yang lebih tinggi untuk mengalami kelahiran pramatang berbanding dengan ibu yang tidak mempunyai masalah hipertensi apabila disesuaikan dengan ibu dengan status kod merah (OR=2.46, 95% CI: (1.06, 5.72), p=0.037). Di samping itu, ibu dengan status kod merah juga dikaitkan secara signifikannya dengan kelahiran pramatang. Ibu dengan status kod merah mempunyai 2.06 kemungkinan lebih tinggi untuk mengalami kelahiran pramatang berbanding dengan ibu tanpa status kod merah apabila disesuaikan dengan ibu dengan masalah hipertensi (OR=2.06, 95% CI: (1.37, 3.10), p=0.001).

Kesimpulan:

Terdapat perkaitan yang signifikan di antara masalah hipertensi dan status kod merah dengan kelahiran pramatang. Oleh itu, mengoptimalkan kawalan tekanan darah sebelum dan semasa mengandung bagi mencegah terjadinya pra-eklampsia dan perkembangannya ke eklampsia merupakan salah satu strategi yang disyorkan, untuk menambahbaikkan status hasil kelahiran dan mengurangkan kadar kelahiran pramatang. Walaubagaimanapun ‘model of fitness’ dalam kajian ini menunjukkan bahawa ia mempunyai penggunaan terhad untuk meramal kelahiran pramatang. Kajian pada masa depan perlu menyertakan semua faktor risiko lain yang tidak dikaji kerana pembolehubah ini dapat meningkatkan kesahihan dalaman dan kesahihan hasil kajian dalam meramal kelahiran pramatang berdasarkan faktor risikonya.

KATA KUNCI: Kelahiran pramatang, ciri-ciri kelahiran pramatang, kematian neonatal, faktor kelahiran pramatang

**CHARACTERISTICS AND ASSOCIATED FACTORS OF PRETERM
BIRTH AT HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM) IN 2016**

ABSTRACT

Background: Worldwide, preterm birth remains a significant public health threat in view of its increasing trend and devastating health effects. Similarly, in Malaysia the proportions of preterm birth and related neonatal death were observed to be rising since 2011. However to date, there are limited publications on local preterm birth specifically on its characteristics and associated factors.

Objectives: The study aimed to investigate on preterm birth in terms of its characteristics and associated factors at HUSM in 2016.

Methodology: Retrospective record review on secondary data was conducted by means of a cross-sectional study design in Part I (n=4,246) and a case-control study design in Part II (n=472). Data on mothers attending HUSM for deliveries in 2016 were extracted from the iMOMz database. Descriptive analysis was used in Part I to determine the proportions of preterm births and the proportions of preterm births based on its characteristics (sub-categories, types and neonatal outcomes). Univariate and multivariate analyses were used in Part II to identify the associated factors of preterm birth.

Results: The proportion of preterm birth among live births at HUSM in 2016 was 6.5%. All of the preterm births (n=278) fell under the sub-category of moderate to late preterm and predominantly were spontaneous type (74.5%). Only 1.8% of the neonates of these preterm births died within the first 28 days of their lives. The presence of hypertension was significantly associated with preterm birth. Mothers

with hypertension had 2.46 higher odds to experience preterm birth compared to mothers with no hypertension when adjusted for mothers with red-tagging (OR=2.46, 95% CI: (1.06, 5.72), p=0.037). Additionally, the presence of red-tagging was also significantly associated with preterm birth. Mothers with red-tagging had 2.06 higher odds to experience preterm birth compared to mothers with no red-tagging when adjusted for mother with hypertension (OR=2.06, 95% CI: (1.37, 3.10), p=0.001).

Conclusion:

There were significant associations between hypertension and red-tagging with preterm birth. Thus, optimising blood pressure control prior to and during pregnancy as well as preventing the occurrence of pre-eclampsia and its progression to eclampsia are essentially some of the recommended measures, which may improve pregnancy outcomes and reduce the preterm birth rate. In this study however, the model of fitness suggests that it has limited use for prediction. Therefore, future studies need to include all other risk factor variables which were not studied as these variables may improve the internal validity and outcome of studies on predictive risk factors of preterm birth.

KEYWORDS: Preterm birth, characteristics of preterm birth, neonatal death, associated factors of preterm birth

CHAPTER 1

INTRODUCTION

1.1 Background

Preterm birth is a significant global public health threat as it is increasing in countries with reliable data and has tremendous health effects both immediate and long term. Paradoxically, unlike the other maternal and child health indicators, the incidence of preterm birth is no different among rich and poor countries. India, Nigeria, Brazil and the United States are among the countries with the highest numbers of preterm birth suggesting that preterm birth is truly a global problem (Blencowe *et al.*, 2012).

Worldwide, preterm birth is estimated to occur in 11.1% of all live births in 2010 (Tielsch, 2015). In the United States, nearly 12 out of every 100 babies born alive in 2010 were preterm, and this rate has increased by 30.0% since 1981 (Institute of Medicine, 2007). Whereas in a developing country such as Malaysia, its rate fell in the below 10.0% category based on the global preterm birth ranking statistics by the WHO in 2010. However, this rate began to rise markedly by 39.5% between the years 2010 to 2012 (National Obstetric Registry, 2015).

Preterm birth outcomes including related mortality and morbidity rates are important indicators of the general health of a population as the problem affects individuals and families throughout their life cycle. Additionally, preterm birth outcomes measure the quality of health care services provided for mothers and their babies, which is vital in monitoring and evaluating the impact of the evolving health care practices. As compared to their counterparts (full term infants), preterm infants have an

increased risk of death during the neonatal period (Smith *et al.*, 2003). Furthermore, Slattery and Morrison (2002), found that survivors of preterm birth often face lasting adverse health in three major domains which are mental (neuro-developmental impairment), physical (neuro-motor development) and sensory (vision, hearing).

1.2 Definition, sub-categories and types of preterm birth

According to the WHO (2017), preterm birth is defined as babies born alive before 37 weeks of gestational age. In Malaysia, the Perinatal Care Manual (2013) defines a preterm baby as any baby of less than 37 weeks gestation. Conventionally, gestational age refers to the time interval between a woman's first day of her last menstrual period (LMP) right up to delivery. Although insemination usually happens after two weeks of the LMP, gestational age takes into account this two-week time gap.

There are various means in the determination of gestational age in a pregnant woman. Firstly, it is based on a woman's recall or record of her LMP. Secondly, it is based on the gestational age estimation by ultrasound, which is importantly done within the first trimester. Thirdly, is the determination of gestational age assisted by a physical assessment of the gravid uterus. Most accurate means to gauge gestational age is by ultrasound i.e. either trans-vaginal or trans-abdominal, done within the first trimester supported by comparison of the estimated due date with the pregnant woman's LMP (if known) and substantiated by an obstetric abdominal examination. These methods of gestational age estimation used in combination would lead to lowered frequencies of post-term inductions due to wrong dates.

According to Hack and Fanaroff (2000), preterm birth can be classified into the following categories, which are moderate to late preterm, very preterm and extremely preterm. The corresponding gestational age for these sub-categories are as illustrated in Table 1.1 below.

Table 1.1: Sub-categories of preterm birth based on gestational age

Sub-categories	Gestational age (weeks)
Moderate to late preterm	32 to <37
Very preterm	28 to <32
Extremely preterm	<28

Majority of preterm birth fall in the moderate to late preterm sub-category and survival rates typically improve with gestational age (Blencowe *et al.*, 2012). Across sub-categories, disparities in the survival rate are apparent among the low and high-income countries.

There are two main types of preterm birth, which are spontaneous and provider-initiated (Goldenberg *et al.*, 2008). According to Savitz *et al.* (1991), spontaneous preterm birth refers to live births before 37 completed weeks of pregnancy preceded by either spontaneous preterm labour or; following preterm premature rupture of membranes (pPROM). Whereas, provider-initiated preterm birth are live births before 37 completed weeks of pregnancy via induction of labour or; elective/emergency caesarean-section for maternal or foetal indications (Tucker *et*

al., 1991). Most of the preterm births are occurring as a result of spontaneous causes; about 45.0% with intact membrane and approximately 30.0% following pPROM (Goldenberg *et al.*, 2008).

1.3 Causes and risk factors

The proposed pathways leading to preterm birth include intrauterine infection/inflammation i.e. single gene polymorphism link; precocious foetal endocrine activation; decidual bleeding and uterine over-distension (Frey and Klebanoff, 2016). Efforts have been focused on understanding the exact causality of spontaneous preterm birth associated with the change from uterine quiescence to active contractions and to birth before 37 completed weeks of gestation. However, no clear conclusions have been drawn; the cause of almost half of all cases remains unknown (Menon, 2008). What is known is that spontaneous preterm birth is of multi-factorial origin resulting from the multiple interactions of various maternal, foetal, environmental as well as social factors. Additionally, Steer (2005) has reported that the precursors to spontaneous preterm birth actually vary by gestational age.

Nonetheless, across gestational age sub-categories, several common evidence-based factors in the preconception and pregnancy stage have been identified and found to increase the risk of preterm birth (Institute of Medicine, 2007). Although these risk factors seem of practical use providing extensive knowledge on preterm birth however, an association does not necessarily establish causality. These factors can be broadly categorised into six divisions including: (i) Socio-demographic & community factors; (ii) Medical & pregnancy conditions; (iii) Genetic &

constitutional factors; (iv) Psychosocial & behavioural factors; (v) Nutritional factors; and (vi) Environmental toxicants (Institute of Medicine, 2007).

1.4 Economic and societal costs of preterm birth

As a result of extended hospital stay and extensive medical care requirement, financial spending related to preterm birth are often costly. The average length of stay is nine times longer in a preterm as compared to term babies (Institute of Medicine, 2007; Kaewluang, 2015). In 2005, the socio-economic cost combining medical, educational and loss of productivity associated with preterm birth in the United States was estimated to amount to \$26.2 billion annually (Hodek *et al.*, 2011). During that same year, the average first-year medical costs, including both inpatient and outpatient care, were about 10 times greater for preterm (\$32,325) than for term infants (\$3,325). While most of the medical cost incurred as a result of prematurity is covered by the health insurance plan, however out-of-pocket expenses remains substantial and significantly higher among preterm infants as compared to term, uncomplicated infants (Blencowe *et al.*, 2013).

The Global Burden of Disease study reported that for all ages and causes, complications from preterm birth make up the seventh greatest cause of disability-adjusted life years in developing countries (Misganaw *et al.*, 2017). The high financial burden and far-fetched socio-economic implications of prematurity have drawn the attention of policy-makers particularly in both developed and developing countries including Malaysia to re-evaluate their existing strategies in facing this unresolved global issue.

1.5 Statement of the problem

Preterm birth contributes largely to the perinatal, neonatal, infant and under five mortality rates. Up to three-quarters of perinatal deaths occurred with preterm infants and these infants make up the second highest proportion of deaths among infants (Mattison *et al.*, 2001). Out of the four million neonatal deaths around the world, approximately one-third were caused by preterm birth (Blencowe *et al.*, 2012). Every year, 7.6 million children die before their fifth birthday with preterm birth being an important cause of death after pneumonia (E Lawn *et al.*, 2005).

Additionally, the long-term morbidities related to preterm birth are very extensive. It is associated with complications involving the majority of the body system including the central nervous system, cardiovascular system, respiratory system, gastrointestinal system, hematologic system and the immune system (Laas *et al.*, 2012). Furthermore, it is responsible for almost 50.0% of all congenital neurological disability (Moore *et al.*, 2012). Preterm infants are also at increased risk of other various permanent lifelong devastating problems such as metabolic syndromes, cerebral palsy, blindness, deafness, developmental & behavioural abnormalities that collectively lead to significant economic and social burden (Saigal and Doyle, 2008). Moreover, developmental and behavioural disorders such as attention deficit hyperactivity disorder (ADHD), autistic spectrum disorder and other learning & social-communication difficulties are found to be increased among those who were born preterm (Harris *et al.*, 2013).

In Malaysia, preterm birth remains a major public health problem in view of its significant increasing trend in its frequency and related mortality and morbidity rates.

The steady nationwide escalation in the proportion of preterm births was observed over the years; with 8.1% reported in 2010, to 10.4% in 2011 followed by a highest record of 11.3% in 2012 (J Tan *et al.*, 2017). Separately by state, for example in Kelantan, the proportion of preterm births was 11.8% in 2012, which is an increase as compared to 10.7% in 2011 (National Obstetrics Registry, 2015).

Mortality and morbidity rates related to preterm birth in Malaysia reflect the distressing magnitude of the problem. Twelve percent of perinatal deaths are as a result of preterm birth complications including perinatal asphyxia, infections and congenital malformations (Ishak *et al.*, 2008). Approximately three-quarters of neonatal deaths are due to preterm birth, which are not associated with congenital malformations (Ministry of Health, 2015). The most common cause of deaths under the age of five in Malaysia are congenital malformations, deformations and chromosomal abnormalities accounting for 25.0% of their overall deaths which may be linked to preterm birth (Ministry of Health, 2015). The related morbidities in surviving preterm infants are high, increasing the overall long-term burden of the problem. This is evident from a study by Hovi (2007), reporting that 96.0% of 329 preterm babies had low birth weight (LBW), which is also a known risk factor for perinatal mortality and associated long-term morbidities.

The focus of preterm birth management has been on improving survival rates of preterm infants and catering to their long-term consequences of prematurity (Costeloe *et al.*, 2012). The advancement in health and technology particularly within the neonatal intensive care realm as well as the enhanced management of morbidities and disabilities associated with prematurity remain the core agenda in

most countries including Malaysia. In order to significantly reduce the burden of preterm birth holistically, the approach should follow a dual track: prevention and care. This means that the emphasis of preterm birth management should not only be on the care of those afflicted by prematurity but also should encompass radical prevention strategies.

Investigating the causes and risk factors of preterm birth is the first step to its prevention. The causes of preterm birth have been found to be multifactorial in nature; therefore, preventive solutions will not be in a form of a single discovery but rather a myriad of discoveries addressing multiple biological, clinical and social-behavioural risk factors. Comparatively, the aetiology of preterm birth is complex with much of its causality pathways not fully understood whereas its risk factors have been somewhat established internationally. This allows identification of at risk women or pregnant women and initiation of risk specific intervention or management.

The challenge in designing effective preventive strategies arises from insufficient evidence-based research on predictive risk factors of preterm birth in the local context. Therefore, although risk factors of preterm birth are heavily researched internationally, the findings may not be inferable to the Malaysian population specifically pregnant woman in Kelantan due to the marked multifactorial differences across populations worldwide. As risk factors of preterm birth may differ from country to country across time, identifying, quantifying and stratifying them in our settings remain a challenging task due to inadequate regional and national baseline data specifically on the subject under study.

1.6 Rationale of the study

This study is particularly relevant to a state like Kelantan, which is experiencing a marked rise in the proportion of preterm births with a latest finding of 11.8% in 2012 (National Obstetric Registry, 2015). The report stated that numbers of preterm birth was increasing in Kelantan and is topping the nationwide proportion of 11.3% in the same year. Therefore, understanding the characteristics and associated factors of preterm birth in Kelantan is crucial as part of the preliminary efforts in establishing an effective preventive strategy framework to minimise its rate of occurrence. It is vital to do so in view of the devastating impacts of preterm birth in relation to the overall burden of the problem and the associated mortality and morbidity rates.

Preterm birth deliveries are usually only conducted at tertiary (government) hospitals with neonatal intensive care support. In Kelantan, the four referral centres for such cases are Hospital Kuala Krai (HKK), Hospital Tanah Merah (HTM), Hospital Raja Perempuan Zainab II (HRPZ) and Hospital Universiti Sains Malaysia (HUSM). HUSM is chosen as the study site in view of the readily available obstetric secondary data through the iMOMz database. This database is unique to HUSM, which contains antenatal and delivery records of women representing the Kelantan population. Conducting this study would not only yield newer data on preterm birth in Kelantan i.e. providing data on preterm birth in 2016, but also provide an opportunity to explore preterm birth at a different tertiary centre i.e. HUSM. This exploration would complement findings from the National Obstetric Registry (NOR) which collated obstetric data back in 2010 to 2012 from HRPZ to represent the Kelantan population. The NOR report only focussed on distribution of preterm birth rather than its associated risk factors. The distribution categories that were reported include socio-

demographics, medical problems, parity, mode of delivery, birth weight and preterm outcome. Additionally, seeking knowledge in this area is critically required in view of the scarce published research on the risk factors of preterm birth in Malaysia. Up until now, most local studies on antenatal risk factors look at mainly the pregnancy outcome of LBW rather than preterm birth as the independent factor (Ho *et al.*, 1999).

This study will be investigating preterm birth in terms of its characteristics i.e. its proportions based on sub-categories, types and neonatal outcomes; as well as its associated factors, which would shed light on the frequency and trend patterns of the problem in a local context. The findings can be utilised to generate strategies to predict preterm birth, thus defining a population that is useful for studying specific interventions. The findings can also be used to determine at-risk women allowing initiation of risk-specific treatment. Moreover, the findings can aid stratification of preterm birth risk factors for prevention prioritisation or target areas; provide important insights into mechanisms leading to preterm birth; and facilitate establishment of effective strategies to improve pregnancy outcomes and reduce preterm birth rate.

Factors of preterm birth investigated across its sub-categories, types and neonatal outcomes could be studied to reap benefits of a more focussed knowledge of the problem. However, in view of the limited local data on factors of preterm birth in general regardless of its characteristics justifies the researcher's objectives aiming to investigate preterm birth and its factors in a more holistic approach. The results from

this broad investigation could serve as a reference point for local baseline data aiding further focussed exploration on the subject.

In studying risk factors for preterm birth, differentiating its types is particularly important in countries where caesarean birth is common (Joseph *et al.*, 2002). This applies to a country like Malaysia whereby caesarean section deliveries account for about a quarter of all deliveries in 2012 (National Obstetric Registry, 2015). However, in this study, factors of preterm birth will be explored without discrimination of its type; spontaneous or provider-initiated. This is because examination of provider-initiated preterm birth requires investigations beyond its causes and factors. In order to fully encompass investigations on provider-initiated preterm birth, data on indications and decisions for initiating induction or caesarean section, which inevitably results in preterm birth, need to be taken into consideration. Consistency of such practices with the existing evidence-based obstetric policies particularly on thresholds for caesarean section procedures require systemic evaluation. Since, data on indications and decisions for initiating induction or caesarean section is beyond the scope of this study, therefore the researcher has committed to studying factors of both spontaneous and provider-initiated preterm birth at HUSM.

Although there are several preterm birth outcomes used to measure the overall health status of a population, however for the purposes of this study the researcher has chosen to explore specifically on the neonatal outcomes. In view of preterm birth being a leading cause of neonatal mortality globally, the researcher is keen to look at the proportion of neonatal deaths among preterm births at HUSM. Critically

analysing data on such proportions in combination with available data from the national registry would help relevant authorities monitor the impact of policy initiatives on maternal and child health over time.

Most importantly, descriptive epidemiological research on preterm birth in our local setting is in line with the United Nation Development Programme goals to build a better life for the people of the world as outlined in The Global Strategy for Women's, Children's and Adolescent's Health 2016 - 2030 (Kuruvilla *et al.*, 2016). This study is also in harmony with and complements the WHO recommendations based on the 'Born Too Soon report' which emphasises on descriptive studies i.e. characterising the problem, as part of the initial or preliminary research pipeline strategies in advancing knowledge to address preterm birth (March of Dimes, 2012). To sum up, the far-fetched consequences and significant concomitant issues concerning preterm birth in Malaysia has given rise to the above justifications and rationales leading to the research questions, hypothesis and objectives of this study.

1.7 Research questions

1. What is the proportion of preterm births among all live births at HUSM in 2016?
2. What are the proportions of preterm births at HUSM in 2016 based on its sub-categories, types and neonatal outcomes?
3. What are the factors associated with preterm birth at HUSM in 2016?

1.8 Objectives

1.8.1 General objective

To study preterm birth in terms of its characteristics and associated factors at HUSM in 2016.

1.8.2 Specific objectives

1. To determine the proportion of preterm births among all live births at HUSM in 2016
2. To determine the proportions of preterm births at HUSM in 2016 based on its sub-categories, types and neonatal outcomes
3. To identify the factors associated with preterm birth at HUSM in 2016

1.9 Research hypothesis

There are associations between factors (socio-demographic & community factors, medical & pregnancy conditions and genetics & constitutional factors) and preterm birth among all live births of mothers residing in the North East region of Kelantan.

CHAPTER 2

LITERATURE REVIEW

2.1 Preterm birth: The life-course cycle

Physical and cognitive in utero development sets the stage for later-life progress making preterm birth a good predictor of various negative outcomes across the life course (Case *et al.*, 2005). Prematurity is associated with being small for gestational age (SGA), often grouped as LBW infants which also have been found to be associated with negative life outcomes (Hovi *et al.*, 2007).

A study in Sweden based on a national cohort study of infants born from the year 1973 to 1979 found that preterm birth is strongly associated with hypertension in young adulthood (Crump *et al.*, 2011). Babies who are born too soon face various life challenges and often need special care. A cohort study that followed preterm children (gestational age <32 weeks) at two, five and nine to fourteen years of age, found that in 40.0% of these children were not able to function as independent adults (Walther *et al.*, 2000). This not only takes a toll on the individual born preterm but the related lifelong disability adds a heavy burden on their families and the communities in which they live in (Institute of Medicine, 2007).

The relationship between the foundation of healthy early development and adult life outcome in terms of health, learning and behaviour has been described by Shonkoff (2010), illustrated in Figure 2.1 below. Positive early influences particularly during in utero development leads to typically more favourable long-term outcomes whereas

adverse early exposures tend to result in impaired learning process, maladaptive behaviour and poor health.

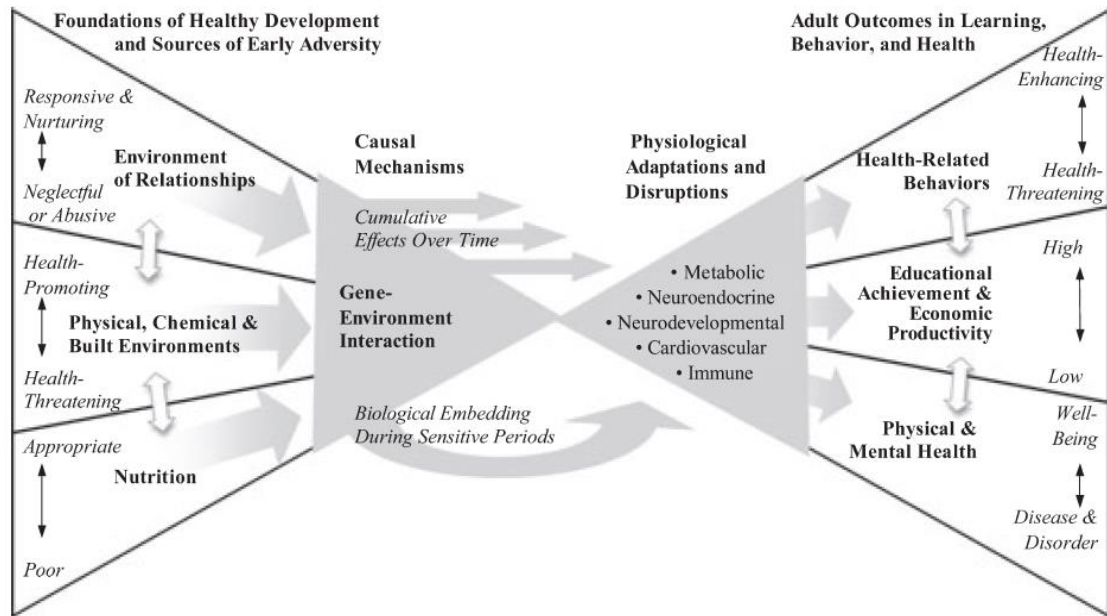


Figure 2.1: The bio-development framework of preterm birth (Shonkoff, 2010)

Furthermore, an intergenerational cycle of risks in relation to preterm birth and non-communicable diseases (NCD) have been observed (Hovi *et al.*, 2007). The epidemiological shift demonstrating an increase in NCD worldwide and its association with an elevated risk of preterm birth has warranted greater attention to maternal health, particularly in the antenatal management of NCDs and other conditions known to increase the risk of preterm birth. Reason being, pregnant women who go into pregnancy with uncontrolled co-morbidities are highly likely to deliver prematurely to an infant who would be at a greater risk of developing NCDs and other significant health conditions later in life.

These series of health events negatively feed the vicious intergenerational cycle even further as life outcomes continue to be influenced by the dynamic interplay of risk factors. These factors are not only the cumulative burden of risks of preterm birth; but are also influenced by the equally important buffering effects of protective factors (Shonkoff, 2010). Protective factors act by reducing the unfavourable effects of risk factors for example, presence of antenatal care. This refers to the provision of affordable, acceptable, high quality and accessible antenatal care and health facilities at rural or isolated areas, for example.

2.2 Frequencies of preterm birth

Based on the 'Born too soon report' by March of Dimes (2012), the rate of preterm birth is defined as all live births before 37 completed weeks (whether singleton or multiple) among every 100 live births.

Worldwide, an estimated 15 million infants are born prior to term in 2010 (Bick, 2012). The rate of preterm birth across 184 countries ranges from 5.0% to 18.0% of babies born (Goldenberg *et al.*, 2008). Across continents, around 85.0% of all preterm birth occur disproportionately in Africa and Asia i.e. 31.0% and 54.0%, respectively. In contrast, about 7.4% of such births occur in Europe and North America collectively (Blencowe *et al.*, 2013).

Disparities in the rates of preterm birth are apparent among the low and high-income countries. These inequalities could be explained due to the poor accessibility to antenatal care and facilities therefore depriving mothers in poorer countries of essential pregnancy monitoring (Blencowe *et al.*, 2013). Conversely, preterm birth

rates in certain high-income countries are also occurring but to a lesser extent. Reasons for this include the increased numbers of preterm birth reports secondary to enhanced gestational age measurement techniques; a rise among mothers of advanced age with underlying medical illness & associated pregnancy problems; the greater use of assisted conception and changes in obstetric practices resulting in preterm caesarean deliveries (Blondel *et al.*, 2006). Advanced maternal age, underlying maternal & pregnancy illness and infertility treatments leading to the occurrence of multiple pregnancies; are among the significant risk factors of preterm birth in the developing and developed countries (Felberbaum, 2007).

2.2.1 Proportion of preterm births among live births in Malaysia

The National Obstetric Registry (2015) reported on data on all live births from year 2010 to 2012 collated from 14 tertiary hospitals in Malaysia with one selected tertiary hospital representing each state. The national average proportion of preterm births in 2011 was 10.4% (135,932 live births) which increased to 11.3% in 2012. Likas Hospital, Sabah reported the lowest proportion of preterm births in 2011 at 3.5% (14,911 live births) followed by Hospital Sultanah Bahiyah, Kedah at 7.5% (10,428 live births). In 2012 Hospital Tengku Ampuan Afzan, Pahang reported the lowest proportion of preterm births at 4.9% (8,794 live births) followed by Likas Hospital, Sabah at 7.2% (13,798 live births).

Highest proportion of preterm births in 2011 occurred at Hospital Kuala Lumpur at 14.4% (11,745 live births) followed by Hospital Sultanah Aminah, Johor with 13.4% (12,532 live births). In 2012, Hospital Raja Permaisuri Bainun, Perak reported the highest proportion of preterm births at 15.2% (4,583 live births) followed by two

hospitals reporting proportions of 13.5% i.e. Hospital Tengku Ampuan Rahimah, Selangor (12,112 births) and Hospital Tuanku Ja'afar, Negeri Sembilan (6,241 live births). Data on proportion of preterm births for 2010 were not reported. Specifically to Kelantan, the proportion of preterm births at HRPZ was at 10.7% (13,116 live births) in 2011, which increased to 11.8% (11,034 live births) in 2012.

2.3 Characteristics of preterm birth

2.3.1 Sub-categories of preterm birth

The various sub-categories of preterm birth arise from the different gestational age range with sub-categories becoming less common as gestational age decreases. These sub-categories as outlined by Hack and Fanaroff (2000) include moderate to late preterm (32 to <37 weeks), very preterm (28 to <32 weeks) and extremely preterm (< 28 weeks). The ranges of gestational age are not always mutually exclusive, for instance very preterm may refer to babies born below 32 weeks without the further subdivision of extremely preterm.

More than 80.0% of preterm birth worldwide fall in the moderate to late preterm sub-category and most of these babies can survive with essential newborn care (Blencowe *et al.*, 2012). Approximately 10.0% fall in the very preterm sub-category followed by 5.0% in the extremely preterm sub-category (Goldenberg *et al.*, 2008). The Malaysian National Neonatal Registry (2012) reported that in 2008, majority of the preterm neonates were born in the moderate to late preterm sub-category (51.6%), followed by 35.1% in the very preterm sub-category and the remaining 13.3% in the extremely preterm sub-category. Similarly, a study on preterm birth in Malaysia reported that 55.0% of the preterm babies are born at 35 to 36 weeks & six

days; 30.0% are born at 32 to 34 weeks, and 15.0% are born at 22 to 31 weeks (Sunhare *et al.*, 2015).

As for preterm birth survival rate, it is typically observed to improve with increasing gestational age. In a study by Costeloe *et al.* (2012), the survival of live births at 22 weeks gestation was found to be 2.0%; at 23 weeks was 19.0%; at 24 weeks was 40.0%; at 25 weeks was 66.0% and; at 26 weeks was 77.0%.

2.3.2 Types of preterm birth

The types of preterm birth may arise from the following three clinical scenarios including:

- (a) Commencement of labour (with intact membranes)
- (b) Preterm commencement of labour with premature rupture of membranes (pPROM)
- (c) Medical interventions (induction or caesarean section) in the interest of either the pregnant woman herself or of her unborn child.

The former two clinical scenarios are collective known as spontaneous preterm birth whereas the latter is termed as provider-initiated preterm birth. Generally, about 40.0% to 45.0% of preterm births are spontaneous with intact membrane, 25.0% to 30.0% are spontaneous following pPROM and 30.0% to 35.0% are provider-initiated (Goldenberg *et al.*, 2008). Provider-initiated preterm birth represents a relatively smaller proportion of all births in developing countries as these pregnancies, if not delivered electively, will follow their natural history, and may frequently end in spontaneous preterm birth or stillbirth (Klebanoff and Shiono, 1995). In contrast, the

proportions of provider-initiated preterm birth are increasing in certain developed countries partly due to the more aggressive policies for caesarean section secondary to poor foetal growth (Joseph *et al.*, 2002).

In Malaysia, in terms of mode of delivery, 40.0% of preterm babies are born via caesarean section whereas 60.0% are born vaginally (National Obstetric Registry, 2015). However, to date there has not been any published data on the national breakdown of vaginal delivery i.e. whether deliveries occurred spontaneously or preceded with induction. Additionally most local studies on risk factors of preterm birth focus on one type of preterm birth commonly spontaneous preterm birth (J Tan *et al.*, 2017).

Distinguishing between spontaneous and provider-initiated preterm birth is of importance to programs aiming to reduce preterm birth rates (March of Dimes, 2012). However, provider-initiated preterm birth may unintentionally occur, thus complicating studies on its risk factors. Problems arise due to the absence of evidence-based medical indication among provider-initiated deliveries as reported by Gyamfi-Bannerman *et al.* (2011) and also as a result of discrepancies in gestational age assessment (Mukhopadhaya and Arulkumaran, 2007).

2.3.3 Neonatal outcomes of preterm birth

Neonatal outcome specifically neonatal mortality is one of the important preterm birth outcome indicators. Several other preterm birth outcome indicators including those measuring mortality and morbidity rates across different sub-categories and types of preterm birth assist the establishment of a high quality, internationally

recognised and sustainable mother and child health information system (Zeitlin *et al.*, 2013).

Worldwide, approximately 27.0% of neonatal deaths are a direct cause of prematurity (March of Dimes, 2012). However, in low-income countries with markedly high neonatal mortality more deaths occur secondary to infections and birth asphyxia (E Lawn *et al.*, 2005). Although the proportion of preterm birth related to neonatal deaths is lower in poor countries, the cause-specific rates are comparatively higher in low and middle-income countries than in rich countries. For example, in Japan the estimated cause-specific rate for neonatal deaths directly due to preterm birth is under 0.5 in every 1,000 live births whereas in Somalia it is 16 per 1,000 live births (Blencowe *et al.*, 2013). This could be due to the deprivation of simple and basic neonatal care for preterm babies leading to stark disparities in the survival rates of preterm birth between low and high-income countries (March of Dimes, 2012).

The relationship between neonatal mortality and prematurity is exponential (Alexander *et al.*, 2003). The more premature the baby is born, the higher the risk of life-threatening conditions or morbidity and neonatal death. Although only a minority of preterm birth occur in the very preterm sub-category, i.e. only about 3.0 to 4.0% but these cases contribute the most to the proportion of neonatal deaths (Mathews and MacDorman, 2011).

In Malaysia, 621 neonatal deaths out of 14,060 preterm births were reported in 2008, i.e. recording a proportion of 4.4% (Malaysian National Neonatal Registry, 2012). In

contrast to 938 neonatal deaths among 124, 096 term deliveries in 2008 i.e. reporting a proportion of 0.8%. Therefore, in 2008, neonatal deaths are occurring about five times more frequent among preterm deliveries as compared to term deliveries.

The high proportion of neonatal deaths resulting from decreasing gestational age of prematurity is mainly due to the poorly developed or underdeveloped organ system of preterm babies that put them at risk of various life-threatening conditions. High risk conditions faced by these preterm babies include infection & retinopathy of prematurity, hypothermia; bronchopulmonary dysplasia; hypotension; cardiovascular abnormalities including patent ductus arteriosus; intraventricular haemorrhage; necrotising entero-colitis; ineffective glucose regulation; and respiratory distress syndrome (Alleman BW, 2014).

2.4 Risk factors of preterm birth

The exact cause of preterm birth is still unknown however, several evidence-based risk factors have been identified (Institute of Medicine, 2007). These factors can be broadly classified into the following six categories:

- (a) Socio-demographic & community factors
- (b) Medical & pregnancy conditions
- (c) Genetics & constitutional factors
- (d) Psychosocial & behavioural factors
- (e) Nutritional factors
- (f) Environmental toxicants

2.4.1 Socio-demographic & community factors

Socio-demographic factors that increase the risk of preterm birth include maternal age at pregnancy, marital status, level of education, occupation or employment status, residential area, socioeconomic status, health insurance coverage and antenatal care.

(a) Maternal age at pregnancy

Maternal age as an obstetric risk factor has been widely reported to influence pregnancy outcome and therefore may affect pregnancy duration (Carolan and Frankowska, 2011). Many women tend to become pregnant at a later age. This could be due to the trend of delaying childbearing age among women in high-income countries (Martin *et al.*, 2011). Among women aged 35 to 39 years, the mean age of conceiving the first child had escalated significantly (Jacobsson *et al.*, 2004).

Increasing maternal age has been found to be related to preterm birth. As compared to mothers between 20 and 35 years of age, mothers older than 35 years of age had a higher risk for preterm birth. Majority of preterm birth were confined to mothers over 35 years of age (Rouget *et al.*, 2013). Many studies reported that poor foetal outcomes were related to increasing maternal age including preterm birth, LBW and stillbirth (El-Sayed *et al.*, 2012). Furthermore, women 35 to 48 years of age were linked to an increased risk of preterm birth, caesarean delivery, foetal distress, LBW and infant admission to the neonatal intensive care unit compared to younger women (Yüksel *et al.*, 1996). In the case of women over 35 years of age, the increased risk of preterm birth was related to the aging vascular system leading to higher likelihood of placental insufficiency (Muula *et al.*, 2011).

On the other extreme, young maternal age had been found to be related to poor foetal outcomes such as preterm birth, LBW, stillbirth and foetal death (Keeton and Hayward, 2007). This could be due to the lack of experience and knowledge on presentations of antenatal complications leading to delayed medical seeking behaviour. Smith and Pell (2001) found that the increased risk of preterm birth pertaining to very young women was related to their underdeveloped reproductive organs.

Some studies also found that both extreme spectrums of maternal age, i.e. women <20 years and ≥ 30 years of age had a higher preterm birth rate than women between the age 20 to 29 (Ziadeh, 2002; Morken *et al.*, 2005). However, a few research studies found that maternal age was not related to preterm birth (Reu *et al.*, 2011).

(b) Marital status

Beeckman *et al.* (2009) showed that single mothers give preterm birth more often. Several studies showed that being unmarried increases the risk of having a preterm birth (Candelaria *et al.*, 2011). The lack of social and emotional support among unmarried mothers had been linked with the risk of preterm birth and LBW (Rolett and Kiely, 2000) Moreover, unmarried mothers were likely to be less accessible to antenatal care putting them at risk of complications during pregnancy as well as poor nutrition that could lead to preterm birth (Zeitlin *et al.*, 2002b).

In contrast, Shah *et al.* (2011) reported that there was no association between marital status and preterm birth. This could be due to the homogenous distribution of married women in the population and the low divorce rate of 2.6%.