PREVALENCE AND ASSOCIATED FACTORS OF NEONATAL MICROCEPHALY IN THAILAND 2014-2018

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ความชุกและปัจจัยที่เกี่ยวข้องกับภาวะทารกแรกเกิดศีรษะเล็กในประเทศไทย ปี พ.ศ. 2557 - 2561

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วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาสาธารณสุขศาสตรมหาบัณฑิต
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หลังจากที่มีการระบาดของการติดเชื้อไวรัสซิกาไปทั่วโลก ความกังวลเกี่ยวกับภาวะทารกแรกเกิดศีรษะเล็กได้เพิ่มขึ้นเป็นอย่างมาก ประเทศไทยเป็นประเทศหนึ่งที่ได้รับผลกระทบจากการระบาดของไวรัสซิกา ดังนั้นการประเมินความชุกของภาวะทารกแรกเกิดศีรษะเล็กจึงจำเป็นในการเตรียมพร้อมและการรับมือ นอกจากนี้ลักษณะทางระบาดวิทยาของทารกแรกเกิดศีรษะเล็กที่จำเพาะต่อประชากรไทยยังสำคัญต่อการพัฒนาแนวทางการจัดการทางคลินิกของภาวะทารกแรกเกิดศีรษะเล็กอีกด้วย การศึกษานี้มีวัตถุประสงค์เพื่อประเมินความชุก อธิบายลักษณะทางระบาดวิทยา และหาปัจจัยที่เกี่ยวข้องกับภาวะทารกแรกเกิดศีรษะเล็กในประเทศไทยระหว่างปี พ.ศ. 2557-2561 โดยทำการศึกษาแบบภาคตัดขวางและใช้ข้อมูลจากระบบคลังข้อมูลด้านการแพทย์และสุขภาพของกระทรวงสาธารณสุข ประเทศไทย ซึ่งครอบคลุมทารกแรกเกิดมีชีพเฉลี่ยร้อยละ 69 จากทารกแรกเกิดมีชีพทั้งหมดในประเทศไทย ทารกแรกเกิดศีรษะเล็กคือ ทารกแรกเกิดที่มีเส้นรอบศีรษะน้อยกว่าเปอร์เซ็นไทล์ที่ 3 ของเส้นรอบศีรษะมาตรฐาน การวิเคราะห์หาความสัมพันธ์ต่อภาวะทารกแรกเกิดศีรษะเล็กจะใช้สถิติ chi-square และ multiple logistic regression ตามลำดับ ผลพบว่า ระหว่างปี พ.ศ. 2557-2561 มีข้อมูลของทารกจำนวน 121,448 คน ที่สามารถประเมินขนาดของศีรษะได้ ความชุกของภาวะทารกแรกเกิดศีรษะเล็กคือ ร้อยละ 14.5 จากการวิเคราะห์พหุตัวแปรพบว่า ภาวะทารกตัวเล็ก (Adjusted OR 5.34, 95% CI 3.24, 8.81, P-value <0.001), ทารกตัวสั้น (Adjusted OR 2.92, 95% CI 1.36, 6.29, P-value 0.01), การตั้งครรภ์ในสตรีอายุมาก(Adjusted OR 1.84, 95% CI 1.07, 3.18, P-value 0.03), และทารกครรภ์แรก(Adjusted OR 2.01, 95% CI 1.37, 2.95, P-value <0.001) มีความสัมพันธ์กับภาวะทารกแรกเกิดศีรษะเล็กอย่างมีนัยสำคัญทางสถิติ โดยสรุปความชุกของภาวะทารกแรกเกิดศีรษะเล็กในประเทศไทยสูงกว่าที่คาดการไว้ การใช้มาตรฐานของนานาชาติอาจไม่เหมาะสมกับบริบทของทารกในประเทศไทย ปัจจัยที่มีผลต่อภาวะทารกแรกเกิดศีรษะเล็กคือ ภาวะทารกตัวเล็ก, ทารกตัวสั้น, การตั้งครรภ์ในสตรีอายุมาก และทารกครรภ์แรก ส่วนปัจจัยที่เกี่ยวข้องอื่นอาจมีการศึกษาต่อไปในอนาคต

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The concern of neonatal microcephaly became high after Zika outbreaks occurred worldwide. Thailand was one of the affected countries. The estimation of neonatal microcephaly prevalence was crucial for public health preparedness and response. The epidemiological characteristics of microcephaly specifically to Thailand were vital to developing clinical management and guideline. The objectives of this study were to estimate the prevalence, describe the epidemiological characteristic and identify associated factors of neonatal microcephaly in Thailand during 2014-2018. This study was a cross-sectional study using data from the health data center, ministry of public health Thailand, 69% of live birth in Thailand was included in this database. Neonatal microcephaly is a newborn who has head circumference (HC) less than the 3rd percentile of standard HC by gestational age (GA) and sex. Univariate and multivariate analyses were performed to identify associated factors by using chi-square and multiple logistic regression, respectively. During 2014-2018, we obtained 121,448 records of a newborn who can evaluate the head size. The prevalence of neonatal microcephaly was 14.5%. Multivariate analysis showed that small for gestational age (SGA) (Adjusted OR 5.34, 95% CI 3.24, 8.81, P-value <0.001), birth length less than the 10th percentile of standard (Adjusted OR 2.92, 95% CI 1.36, 6.29, P-value 0.01), elderly pregnancy (Adjusted OR 1.84, 95% CI 1.07, 3.18, P-value 0.03), and 1st gravida (Adjusted OR 2.01, 95% CI 1.37, 2.95, P-value <0.001) were significantly associated factors of neonatal microcephaly. The prevalence of neonatal microcephaly in Thailand was higher than expected. The international head circumference chart may not suitable for the Thai newborn. The associated factors were birth weight, length, maternal age, and gravida. The standard head circumference for the Thai newborn is needed. The other associated factors may study in the future.

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CHAPTER I

INTRODUCTION

1.1 Background and Rational

Neonatal microcephaly is a condition of head that presented by a newborn born with a smaller head size (head circumference), less than 2 standard deviation (SD) or less than the 3rd percentile, when compared with other newborn in the same gestational age and sex by using a standard reference[1-3] such as the World Health Organization (WHO) standard growth charts[3], INTERGROWTH 21st standard head circumference charts[4], and Fenton growth chart for preterm infants[5].

The complication or consequence of neonatal microcephaly varies from mild to severe symptoms due to the severity of microcephaly. Some microcephaly case shows significantly smaller head size but they can grow with normal intelligence and normal in other development. Some microcephaly case may develop other abnormalities such as seizures, delay speech development, learning disabilities, hearing loss or vision problem in the future when they grow older. In severe case, the newborn with microcephaly may die at birth.[1-3, 6] Seventy-nine point seven percent of microcephaly cases can survive more than or equal to 1 year (95% confident interval = 7.36 – 84.6 %).[7] Life expectancy of microcephaly is around 35 years. The impact of microcephaly was calculated to disability-adjusted life year (DALY) and direct medical cost. The data from Latin America and the Caribbean showed that microcephaly can cause patient loss of 29.95 DALY per case and has an expenditure for this condition about $91,102 per year.[8]

Normally, microcephaly may be a result of abnormal brain development. Recently, the cause of microcephaly remains unclear. However, the most common causes are abnormal genetic (Down syndrome, Edward syndrome, and Cri-du-chat syndrome), infections (Toxoplasmosis, Syphilis, Rubella, Campylobacter pylori, herpes, cytomegalovirus, HIV and Zika virus), or exposure to toxic chemicals (arsenic, mercury, alcohol, radiation, and smoking) during pregnancy.[1-3, 6]

Prevalence of microcephaly is various in different places. According to the World Health Organization (WHO) report, microcephaly is a rare condition. The prevalence of microcephaly is 1 case per several thousand live-births.[3] In the United State of America, Centers for Disease Control and Prevention (US-CDC) reported that microcephaly is not a common disease, there were microcephaly cases around 2 to 120 microcephaly cases per one hundred thousand live-births.[1] Data from the Western Australian Register of Developmental Anomalies, they found that there were 55 microcephaly cases per one hundred thousand live-births in Australia during 1980-2009.[9] In Europe, data from the European surveillance of congenital anomalies, covering 570,000 births annually in 15 countries, reported that there were 15.3 microcephaly cases per one hundred thousand live-births in Europe between 1 Jan 2003-31 Dec 2012.[10] For Thailand, the data from national disease surveillance system of Bureau of Epidemiology, Department of Disease Control reported that there were 4.36 microcephaly cases per one hundred thousand live-births in 2014.[11]

The global concern of microcephaly was rising in 2016 after Zika virus infection epidemic in the world (evidence of Zika infection was reported from 86 countries and territories). Zika virus is a flavivirus. It is transmitted primarily by mosquitoes (*Aedes aegypti*). Moreover, it can be vertical transmission (from mother to fetus during pregnancy), sexually transmitted disease, blood transfusion disease, or organ transplantation. Most people who were infected with Zika virus was no symptom. In a patient who had symptoms, the symptoms of Zika virus infection is mild such as fever, rash, conjunctivitis, muscle and joint pain, malaise, and headache. The major complications of Zika virus infection were microcephaly, other congenital abnormalities in the developing fetus and newborn, Guillain-Barré syndrome, neuropathy and myelitis.[12] In 2015, the northeast of Brazil faced with Zika virus infection outbreaks. After that, they found an increase of congenital microcephaly cases. The prevalence of microcephaly between 1 and 31 December 2015 was 4.2 to 8.2% or 4200 to 8200 per one hundred thousand live-births. Different from the Brazilian live-births information system which reported that between 2012 and 2015, the prevalence of microcephaly in Brazil was 64 per one hundred thousand live-births.[13] The increasing rate of congenital microcephaly in Brazil and other relationship between microcephaly and other central nervous systems (CNS) and Zika virus infection from 17 countries were reported to WHO. Consequently, WHO declared that the cluster of microcephaly cases and other neurological disorders was a Public Health Emergency of International Concern (PHEIC).[14] Furthermore, the case-control study for finding an association between microcephaly and Zika virus infection was established in Brazil between January 15 and November 30, 2016. They found that the adjusted odds ratio was 73.1 (95% CI 13·0–∞) for microcephaly and Zika virus infection. This result can confirm the association between microcephaly and Zika virus infection.[15] In 2016, Thailand was one of the Zika affected countries. Bureau of Epidemiology (BoE), Department of Disease Control, Ministry of Public Health, Thailand reported more than 1000 cases of Zika virus infection from many parts of Thailand in 2016. Among these, two confirmed Zika-related microcephaly was reported. Consequently, BoE established the surveillance system to follow up any abnormality of pregnant women and their newborn.[16] However, this system was not included in an area where asymptomatic Zika virus-infected patient lives. The estimation of magnitude (prevalence) of microcephaly after endemic of Zika virus infection is crucial. We need this data for the improvement of public health preparedness and response. Moreover, the epidemiological characteristics of microcephaly specifically to Thailand are vital for a clinical management and develop a clinical practice guideline. However, there was no evidence about prevalence of microcephaly in Thailand after epidemic of Zika virus infection.

Head circumference plays an important role for screening genetic disorders, brain or neurological development, other development, and microcephaly diagnosis. The measurement of head circumference does not invade to newborn, easy and inexpensive.[17] In Thailand, head circumference measurement is the one routine neonatal care in every labor room. This variable was computed into the hospital information system (HIS) after measurement. Head circumference of a newborn may affect many factors such as low birth weight, length, maternal race, maternal age, maternal weight, maternal height, and parity.[18-25] However, there were controversial or cut-point in some factor such as maternal age. Kirchengast S (2013)[20] the results of this study show that the newborn who born with a young mother (12-16 years) had a smaller head circumference than the other groups. H. Shajari (2006)[19], this study showed newborn who had mother ages less than 20 years old had a head circumference smaller than a newborn who had mother ages equal and more than 20 years old. Sutan R (2018)[23], they found that the mother who had ages equal or less than 35 years old is the associated factor with microcephaly. Furthermore, the parity is one of an associated factor with microcephaly which has a controversy. Sutan R (2018)[23], the result of this study showed that the women who had parity equal or more than 5 had higher risk of gave a newborn with microcephaly more than the women who had parity less than 5. Nevertheless, there was another study showed the different result, Shajari (2006)[19], they found that the newborn who born with first parity had head circumference smaller than the newborn who born with multi-parity. However, there was no evidence showed a relationship between associating factor and microcephaly in Thailand.

1.2 Research Questions

1. What is the prevalence of neonatal microcephaly in Thailand after the epidemic of Zika virus infection?
2. What are the epidemiological characteristics of neonatal microcephaly specifically to Thailand?
3. What are the factors associated with neonatal microcephaly in Thailand?

1.3 Objectives of the study

1. To estimate the prevalence of neonatal microcephaly in Thailand.
2. To describe the epidemiological characteristic of neonatal microcephaly in Thailand.
3. To identified associated factor of neonatal microcephaly in Thailand.

1.4 Hypothesis

1. Null Hypothesis

   There is no association between the factors being studied and neonatal microcephaly in Thailand.
2. Alternate Hypothesis

   There is an association between the factors being studied and neonatal microcephaly in Thailand.

1.5 Conceptual Framework

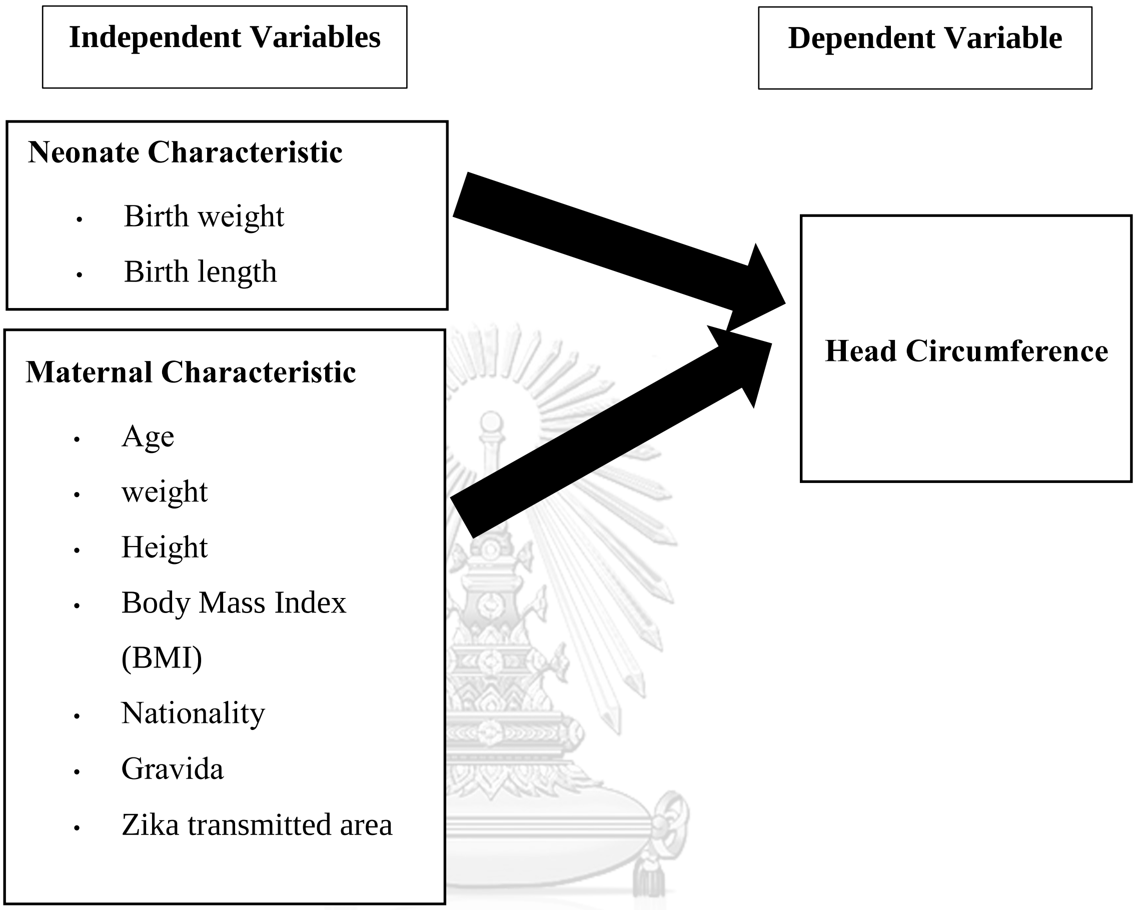

Figure 1 Conceptual Framework

1.6 Operation Definitions

- **Birth weight** is the weight that measured at the first time of life after delivery or after complete expulsion or extraction from their mother. This weight should be measured within 24 hours after birth (preferably within the first hour of life).[26]
- **Birth length** is the distance from crown to heel of a newborn.[26]
- **Gravida** is the number of pregnancies, current and past, regardless of the pregnancy outcome.[27]
- **Head circumference** is the size of a newborn head. It can measure by using the measuring tape placed on the newborn head. Practically, the measuring tape was placed on the possible widest head circumference or place on the prominent part of the newborn head (frontal part and occipital part).[28]
- **Head circumference measuring period:** According to the royal college of pediatricians of Thailand, a newborn should be measured their head circumference within 72 hours after birth.[29]
- **Maternal age** is the age of the mother at the time of delivery.[23]
- **Maternal body mass index** (BMI) is is a maternal weight in kilograms (kg) divided by her height in meters squared.[30]
- **Maternal height** is the height of mother at the first antenatal care visit.[23]
- **Maternal weight** is the weight of the mother at the first antenatal care visit.[23]
- **Microcephaly** is a newborn who had head circumference less than the 3rd percentile of the standard head circumference by age and sex[29]

- **Standard head circumference** for diagnosis microcephaly has criteria following[29]
    - Term or Mature newborn (gestational age $\geq$ 37 weeks)
        - Certain gestational age: Microcephaly is the newborn that have head circumference less than 3rd percentile or less than – 2 SD of the standard head circumference of WHO INTERGROWTH-21.[31]
        - Uncertain gestational age: Microcephaly is the newborn that have head circumference less than 3rd percentile or less than – 2 SD of standard head circumference of WHO child growth standards.[32]
    - Preterm newborn (gestational age < 37 weeks)
        - Microcephaly is the newborn that have head circumference less than 3rd percentile or less than – 2 SD of the standard head circumference of Fenton preterm growth.[5]
- **Zika transition area** is a province that reported Zika virus infection cases to Zika situation awareness team.[16]

1.7 Abbreviation

AGA	=	Appropriate for Gestational Age
BMI	=	Body Mass Index
BoE	=	Bureau of Epidemiology
CDC	=	Centers for Disease Control and Prevention
DALY	=	Disability-Adjusted Life Year
GA	=	Gestational Age
HC	=	Head Circumference
HDC	=	Health Data Center
HIS	=	Hospital Information System
LGA	=	Large for Gestational Age
MoPH	=	Ministry of Public Health
SD	=	Standard Deviation
SGA	=	Small for Gestational Age
WHO	=	World Health Organization

CHAPTER II

LITERATURE REVIEW

The aims of this study were estimating the magnitude or prevalence, describe the characteristics and identify associated factor of neonatal microcephaly in Thailand. Therefore, this literature review will be provided the information related to neonatal, head circumference, and microcephaly as below.

1. Neonatal
2. Microcephaly
3. Head circumference

2.1 Neonatal

2.1.1 Definition

The neonatal period is the first 28 days after birth. It can be divided into 2 periods. There are early neonatal period and late neonatal period.[33]

- Early neonatal period is the first 7 days after birth.
- Late neonatal period is the period after first 7 days of life up to 28 days of life.

2.2 Microcephaly

2.2.1 Definition[1-3]

Microcephaly is a condition of head that presented by smaller head size (head circumference) when compared with others in the same age and sex by using a standard reference. Figure 2 show, the comparison between typical head size, microcephaly, and severe microcephaly[1]

Figure 2 Typical Head Size, Microcephaly and Severe Microcephaly Comparison

2.2.2 Etiology[1-3]

The cause of microcephaly remains unclear. However, the cause of microcephaly can be classified into 2 groups. There are primary or genetic microcephaly and secondary or non-genetic microcephaly.

- Primary or genetic microcephaly: The most common causes include
    - Familial (autosomal recessive)
    - Autosomal dominant
    - Chromosomal syndromes such as Down syndrome (trisomy 21), Edward syndrome (trisomy 18), and Cri-du-chat syndrome (5 p-), etc.

- Secondary or non-genetic microcephaly: the most common causes may be
    - Infections in pregnancy period such as Toxoplasmosis, Syphilis, Rubella, Campylobacter pylori, herpes, cytomegalovirus, HIV and Zika virus.
    - Exposed to toxic chemicals such as arsenic, mercury, alcohol, radiation, and smoking during pregnancy period.
    - The injuries during brain developing period such as the problem of blood supply to the fetal brain during brain development.
    - Nutrition problems during pregnancy period such as severe malnutrition, not getting enough food.

2.2.3 Clinical manifestation[1-3]

Microcephaly may relate with brain development during pregnancy period or stop developing after birth. As a result, head size is small. Wide ranges of clinical manifestation among microcephaly cases were shown. It depends on the severity of microcephaly. Microcephaly cases may die at birth or develop other abnormalities in the future when they grow older as following

- Seizures, epilepsy or cerebral palsy
- Delay development such as speech, sitting, standing, or walking
- Intellectual disability or learning disabilities
- Decreased ability function in daily life
- Hearing loss and/or vision problem

2.2.4 Diagnosis

Microcephaly can diagnose by measuring newborn head circumference in the first 24 hours after birth then compare with WHO standards reference by age and sex.[3] According to the guidance for the evaluation and management of infants with possible congenital Zika virus Infection, promoted by the royal college of pediatricians of Thailand, newborn should be measured their head circumference within 72 hours after birth. The microcephaly can be divided into 2 types by severity. There are microcephaly and severe microcephaly.[29]

- Microcephaly is the newborn that have head circumference less than 3rd percentile or less than – 2 SD of standard head circumference in the same sex and gestational age.
- Severe microcephaly is the newborn that have head circumference less than – 3 SD of standard head circumference in the same sex and gestational age.

The standard head circumference reference for diagnosis microcephaly has criteria following;

a. Term or Mature newborn (gestational age ≥ 37 weeks)
    - Certain gestational age: Microcephaly is the newborn that have head circumference less than 3rd percentile or less than – 2 SD of the standard head circumference of WHO INTERGROWTH-21.[31]
    - Uncertain gestational age: Microcephaly is the newborn that have head circumference less than 3rd percentile or less than – 2 SD of standard head circumference of WHO child growth standards.[32]

b. Preterm newborn (gestational age < 37 weeks)

- Microcephaly is the newborn that have head circumference less than 3rd percentile or less than – 2 SD of the standard head circumference of Fenton preterm growth.[5]

2.2.5 Treatment and care

There is no specific treatment for this condition. Supportive treatment is a good thing. Due to the wide range of clinical manifestation (mild to severe), different treatment for each microcephaly cases may be seen. Some mild cases may not need intensive care. They may need an only routine check-up and monitor growth development. For a severe case, they will need care and treatment regarding their health problems. However, every microcephaly cases need early developmental services for assessing, improving and maximizing their physical and intellectual abilities.1-3

2.3 Head Circumference

2.3.1 Head circumference measurement

Head circumference refers to the size of the head. It can measure by using the measuring tape placed on the newborn head. Practically, the measuring tape was placed on the possible widest head circumference or place on a prominent part of the newborn head (frontal part and occipital part). Centers for Disease Control and Prevention (US-CDC) recommend the measuring technique. There is placing the tape around the head above the eyebrow, above the ears, and on the most prominent part on the occiput. The measuring tape should not be stretched. The newborn should be measured their head size three times the largest were selected. Head circumference should be recorded nearest 0.1 cm.[28] INTERGROWTH 21st recommend head circumference measurement technique as following[34]

- Use metal measuring tape for measurement. The tape must show the tape marked in centimeters and millimeters.
- Removing all interfere subjects such as hairpins or headbands from the newborn head before measurement.
- Holding the newborn on the assistant measurer lap.
- The measurer should sit by the side of the assistant.
- Take the centimeters side of measuring tape on the outside.
- Place the measuring tape around the head.
- Place the measuring tape above the eyebrows, with the zero points and wrap the tape around the fullest head circumference (the forehead anchor point is important for standardized measurement within and across sites).
- The marking point of the back is the fullest protuberance of the skull.
- Checking the position of measuring tape and marking point
- Pulling the measuring tape tight to compress the hair and skin. Be careful not to pull the tape too tight and cause injury to newborns.
- Reading the head circumference to the last completed 1mm.

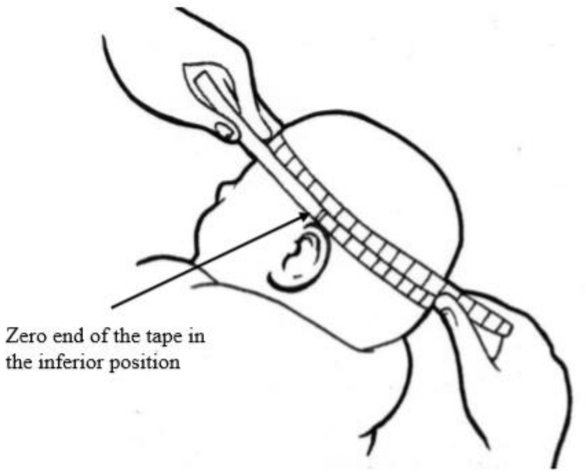

Figure 3 The position for head circumference measurement

In Thailand, head circumference measurement is the one of routine assessment in the labor room. Labor room nurses play an important role in this assessment. After delivery, newborn were measured their head by labor room nurses by using measuring tape. The recommended technic is occipitofrontal (OF), the measurement tape was placed on newborn head pass occipital protuberance and forehead.[35] The reliability of measurement among labor room nurses was assessed. The result shows that the circumference which measured by labor room nurse was good and useable.[36]

2.3.2 Associating factors with a head circumference

The factors that may be affected to newborn head circumference have many factors such as low birth weight, maternal race, maternal age, maternal weight, maternal height, and gravida.[18-23]

2.3.2.1 Low birth weight

Many studies concluded that head circumference associated with low birth weight. For example, the study of predicting factor of microcephaly among Malaysian child showed that the low weight at birth of children was associated with the small head circumference.[23] As same as the study in Nigeria, they found that the head circumference have a positive relationship with birth weight, the child who had low birth weight showed small head size more than the child who had normal birth weight.[18]

2.3.2.2 Length

Length is the one of neonatal assessment.[35] It refers to the distance between the crown and heel of the newborn or height of the baby.[26] The number of the clinical studies suggests that there was an association between height and head circumference. Saunders CL 2006[25], they assessed the relationship between head circumference and height in a normal healthy child by using the national cooperative survey in Argentina. From this study, they found that there was a relationship between height and head circumference. The study suggests that the assessment of head circumference should be interpreted with height. Moreover, Geraedts EJ 2011[24], they study the relationship between height and head circumference by using data from the Dutch nationwide survey. They found that head circumference had a strong correlation with height.

2.3.2.3 Maternal age

Not only characteristic of newborn which related with head circumference but the characteristic of the mother may affect with a head circumference of the newborn also. There are many research that studies about the characteristic of mother and head circumference such as Kirchengast S(2013)[20] the results of this study show that maternal age had an associated with neonatal head circumference, they found that the newborn who had a young mother (12-16 years) were significantly different of head circumference when compared with older mother (17-29 years). This newborn had a smaller head circumference than the other groups. H. Shajari (2006)[19], studied mother who had ages less than 20 years old compared with mother who had ages equal and more than 20 years old, they found that newborn who had mother ages less than 20 years old had a head circumference smaller than newborn who had mother ages equal and more than 20 years old. Sutan R (2018)[23], compared the neonatal head circumference between 2 groups of mother age (equal or less than 35 years old and more than 35 years old), they found that the mother who had ages equal or less than 35 years old is the associated factor with microcephaly.

2.3.3.4 Maternal height, pre-pregnancy weight, and pre-pregnancy body mass index

Height, pre-pregnancy weight, and pre-pregnancy body mass index (BMI) are one of factors that affect to head circumference of the newborn. Polzlberger E (2017)[22], study the relationship between maternal weight, height, BMI and newborn size, they found that all three variables were a positive relationship with the neonatal head circumference. The study in Malaysian mothers and newborn compared between mother who had height ≤ 145 cm and >145, they found that the mother who had height ≤ 145 cm is the risk factor of microcephaly.[23] The results of multiple regression analysis between pre-pregnancy weight and head circumference showed the positive moderate relationship between pre-pregnancy weight and head circumference.[18] Neggers Y. (1995)[21], they study the relationship between the pre-pregnancy weight of mother and head circumference of the newborn they found that the pre-pregnancy weight of mother can predict the head circumference of the newborn.

2.3.3.5 Parity

Parity is one of an associated factor with microcephaly and head circumference. Sutan R (2018)[23] showed the association between parity and microcephaly, they found that the women who had parity equal or more than 5 had higher risk of gave a newborn with microcephaly more than the women who had parity less than 5. H. Shajari (2006)[19], compared head circumference of the newborn who born with first parity and multipara, they found that there was a significantly different of head circumference between 2 groups in univariate analysis. However, it was not significantly different in multivariate analysis. According to the data source of this study, the parity is not included in this data base. So that, we use the gravidity replace the parity.

2.3.3.6 Zika virus infection

In recent year, Zika virus infection was pandemic worldwide. Many countries were affected. The most one of concern about the consequence of Zika virus infection was microcephaly. Microcephaly was declared that it is PHEIC in 2016 because they got many reports from many countries about the possible relationship between microcephaly and Zika virus infection.[14] The most affected country is Brazil. In 2015, there was an increasing rate of microcephaly among their newborn.[13] de Araújo TVB (2018)[15] conducted the case-control study compared between microcephaly cases and non-microcephaly cases (matching birth date and area of resident). The high odds ratio was shown in this study (odds ratio = 73.1). It means that the one who got Zika virus infection have odds of microcephaly more than the one did not who got Zika virus infection. The mechanism which may explain Zika virus infection and microcephaly was published. Zika virus can transition from pregnant women to their fetus (vertical transition) then Zika virus attack the brain of fetus and make abnormality development of fetus brain, finally, microcephaly can be seen.[37]

CHAPTER III

RESEARCH METHODOLOGY

3.1 Study Design

A cross-sectional study was used as a study design in this study for assessing the prevalence, epidemiological characteristic and associated factors of neonatal microcephaly among newborn who received a medical service in a public hospital under ministry of public health (MoPH), Thailand and other hospitals who interest to send the data to MoPH during 1 January 2014 to 31 December 2018.

3.2 Study Period

The period of this study was 1 January 2014 to 31 December 2018.

3.3 Study Population

All newborn, received a medical service in public hospital under the ministry of public health (MoPH), Thailand and other hospitals who interest to send the data to MoPH during 1 January 2014 to 31 December 2018.

Inclusion Criteria

- All newborn who birth during 1 January 2014 to 31 December 2018.
- Received a medical service in public hospital under the ministry of public health (MoPH), Thailand or other hospitals who interest to send the data to MoPH.

Exclusion Criteria

- Children who have no head circumference data in national health database or cannot evaluate gestational age were excluded from this study.

3.4 Study Area

The area of this study was all public hospital under the ministry of public health (MoPH), Thailand and other hospitals who interest to send the data to MoPH which established cover all parts of Thailand.

3.5 Data source

Passive national health database (43 files report) from the health data center (HDC), Thai MoPH was used as a data source in this study. This database was established by Thai MoPH in 2012 (fiscal year) and data was completed since 2014. The aim of this database was collecting health information among client who received a medical service in a public hospital under Thai MoPH for health strategic management and health policy planning. The information in this database (Table 1) include general information (such as sex, birthdate, address, and marital status), medical service information (such as physical examination, diagnosis, and treatment), and survey information (such as non-communicable disease (NCD) screening).[38] Figure 4 showed the data transferring process of this database. The data starts from each service provider such as health-promoting hospital, community hospital, and provincial hospital. In this step, data of client who received medical service was computed in the hospital information system (HIS). Next step, the data in HIS were prepared to 43 files format for transferring to the provincial health office. After the provincial health office receives the data from each provider, the data was stored in provincial HDC for backup and transferred to central HDC (MoPH)[39]. Nowadays, 1454 hospitals were involved by HDC (Table 2).[38] Since 2014, this database cover live birth around 47.1-85.4 % of total live birth in Thailand (Table 3).[40]

Table 1 Structure of national health database (43 files report), Thai MoPH

Collector files	Service files	Service and Semi-survey files
1. PERSON	1. FUNCTIONAL	1. REHABILITATION
2. ADDRESS	2. ICF	2. NCDSCREEN
3. DEATH	3. SERVICE	3. ANC
4. CHRONIC	4. DIAGNOSIS_OPD	4. POSTNATAL
5. CARD	5. DRUG_OPD	5. NEWBORN_CARE
6. HOME	6. PROCEDURE_OPD	6. EPI
7. VILLAGE	7. CHARGE_OPD	7. NUTRITION
8. DISABILITY	8. SURVEILLANCE	8. SPECIALPP
9. PROVIDER	9. ACCIDENT	
10. WOMEN	10. LABFU	
11. DRUGALLERGY	11. CHRONICFU	
12. PRENATAL	12. ADMISSION	
13. LABOR	13. DIAGNOSIS_IPD	
14. NEWBORN	14. DRUG_IPD	
	15. PROCEDURE_IPD	
	16. CHARGE_IPD	
	17. APPOINTMENT	
	18. DENTAL	
	19. FP	
	20. COMMUNITY_ACTIVITY	

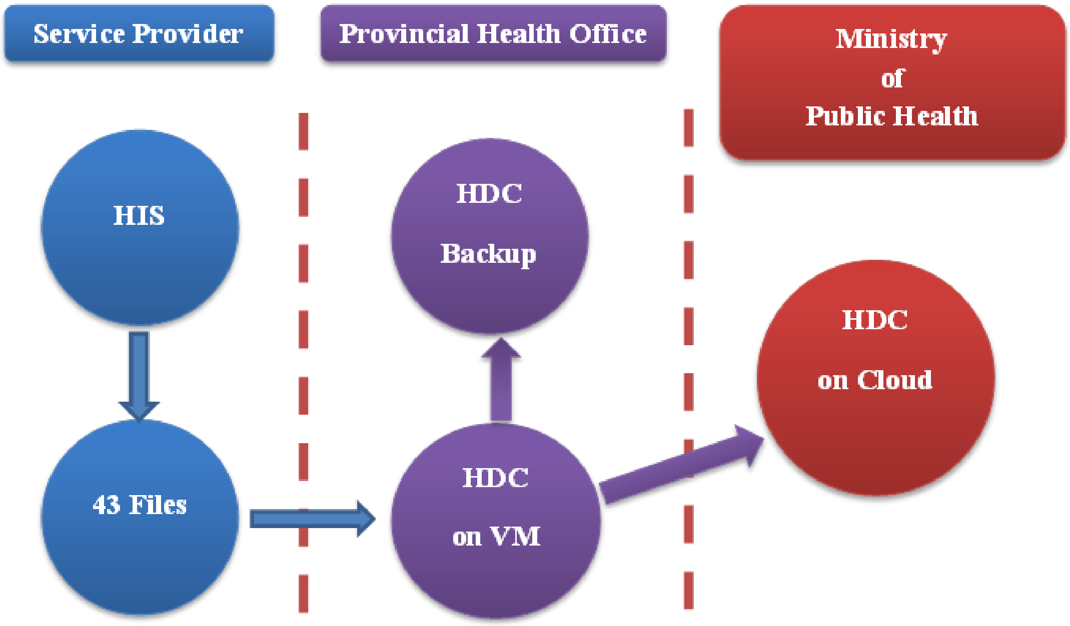

Figure 4 Data transferring process of the health data center, Thailand

Table 2 Hospital which enrolled in the national health database (43 files report), Thai MoPH

Hospital	No.
MoPH	
• Office of the Permanent Secretary	
○ Tertiary care hospital	34
○ Provincial hospital	82
○ Community hospital	781
• Non-Office of the Permanent Secretary	62
Non-MoPH	124
Private hospital	371

Table 3 The number of live birth in Thailand and the national health database (43 files report), Thai MoPH, 2014-2018

Year	**2014**	**2015**	**2016**	**2017**	**2018**
Live birth in Thailand (person)	711,805	679,502	666,207	656,571	NA
Live birth in HDC (person)	335,052	427,597	549,157	560,903	462,611
Percent (%)	47.1	62.9	82.4	85.4	-

3.6 Interested variables

Neonatal Variable

- Head Circumference *(centimeters)*
- Sex *(male, female)*
- Birth weight *(grams)*
- Gestational age *(weeks)*
- Length *(centimeters)*

Maternal Variable

- Age *(years)*
- Weight *(kilograms)*
- Height *(centimeters)*
- Gravida *(no.)*
- Zika transmitted area *(province)*

3.7 Data collection

The interesting variables were obtained from national health database by extracting data in varied files as table 2. Each variable was conjoined by using hospital code (Hospcode), personal ID (PID) and citizen ID (CID). We used NavicatTM version 11.1.3 as a data retrieve program. Age of mother was calculated by using birthdate of neonate in labor file – birthdate of mother in person file. The data about Zika transmitted area was obtained from the situation awareness team of Zika virus infection, Bureau of Epidemiology, Department of diseased control, Thailand.

Table 4 Variable, file, and code for extracting data from the national health database, Thailand

	Variable	File	Code
Neonatal	Head Circumference	NUTRITION	HEADCIRCUM
	Sex	PERSON	SEX
	Birth weight	NEWBORN	BWEIGHT
	Gestational age	NEWBORN	GA
	Parity	NEWBORN	GRAVIDA
	Length	NUTRITION	HEIGHT
Maternal	Age	LABOR	BDATE
		PERSON	BIRTH
	Weight	ADMISSION	ADMITWEIGHT
	Height	ADMISSION	ADMITHEIGHT

3.8 Data management

3.8.1 Neonatal data

After we obtained all interested data of all neonate who received a medical service in a public hospital under Thai MoPH. Then, we selected only the neonate who had head circumference (HC) and gestational age (GA). We managed duplication by grouping Hospcode, PID and CID, respectively (figure 5).

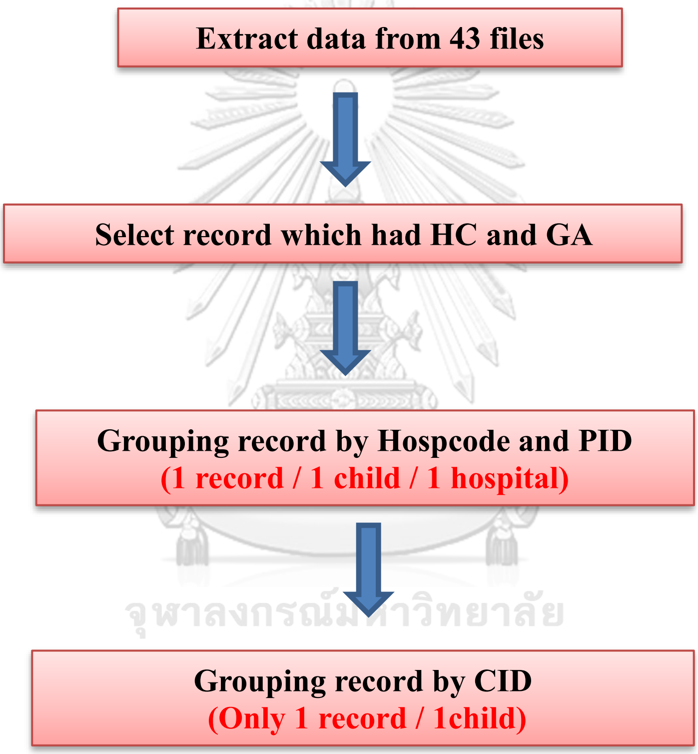

Figure 5 Neonatal data management

3.8.1 Maternal data

We managed duplication by grouping Hospcode, PID and CID, respectively (figure 6).

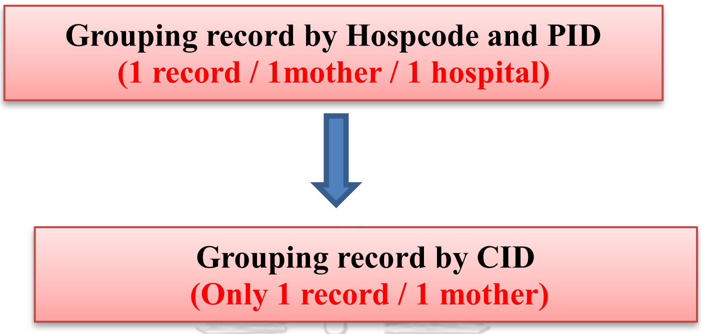

Figure 6 Maternal data management

Finally, we will join neonatal data and maternal data by using maternal CID.

3.9 Data analysis

The definition of microcephaly case was a newborn who had HC less than the 3rd percentile of standard HC by age and sex and Non-cases was a newborn who had head circumference more than or equal to 3rd percentile of standard HC by age and sex. We calculated microcephaly prevalence by Ms. Excel 2010 and Epi-info 7.0 programs and shown in proportion with 95% confidence limits, ratio, and percentage.

To analyze the factors associated with microcephaly, the dependent variable is microcephaly case or non-microcephaly case. The independent variables are birth weight (small for gestational age (SGA) is a newborn who has birth weight that below the 10th percentile of expected weight for their age and gender, appropriate for gestational age (AGA) is a newborn who has birth weight between the 10th – 90th percentile of expected weight for their age and gender, and large for gestational age (LGA) refers to a newborn who is larger than 90th percentile of expected weight for their age and sex), length (< 10th percentile or ≥10th percentile), maternal age (< 35 years or ≥35 years), maternal weight and height will be calculated to body mass index (BMI, <18.5 kg/m^2 = underweight; 18.5–23 kg/m^2 = normal range; 23–24.9 kg/m^2 = overweight; ≥ 25-29.9 kg/m^2 = obesity), gravida (1 or >1), and Zika transmitted area (Zika transmitted area or non- Zika transmitted area). Univariate analysis of each independent variables will use the Chi-square test or simple logistic regression. P value < 0.05 will be considered as a statistical significance. The variable which has P-value < 0.2 will be analyzed in the multivariate analysis by using multiple logistic regression.

3.10 Time schedule

Activities	2018				2019					
	September	October	November	December	January	February	March	April	May	June
Preparation and Literature review										
Proposal development										
Develop tool										
Proposal examination										
Editing proposal										
Apply for ethic approval										
Data collection										
Data analysis										
Conclusion and Writing report										
Presentation										
Editing report and Manuscript writing										
Publication										

Figure 7 Activities and time planning of the study

3.11 Budget and source of funding

Table 5 The budget estimation of the study

List	Total (Thai-Baht)
1. Transportation for data collection (10 times)	
1.1 Round trip (50 Baht per time) x 10 times	500
2. Copy fee	1,000
3. Printing fee	1,000
4. Final report preparation fee	2,000
5. Other	500
Total	**5,000**

The source of funding comes from the pocket of the researcher.

3.12 Limitation of the study

1. This study is a secondary data analysis using the national health database. It may not include all of the associated factors.
2. The national health database may not represent all newborn in Thailand because data were collected from a public hospital under the ministry of public health (MoPH), Thailand only, not include some public hospital outside MoPH or private hospital.

3.13 Expected outcome

1. The improvement of public health preparedness and response for microcephaly in Thailand.
2. The improvement of a clinical practice guideline for diagnosis and management microcephaly in Thailand.

3.14 Ethical consideration

This study was approved by the research ethics review committee for research involving human research participants, health science group, Chulalongkorn University, Thailand. COA no. 149/2019. The information does not include the name of patients (keep anonymous). All will be keep confidentially and use for study purpose only. After the end of the study, the data will be destroyed suddenly.

CHAPTER IV

RESULTS

This chapter presents the finding of this study which includes descriptive analysis and analytical analysis.

4.1 Descriptive analysis

During January 2014 – December 2018, a total of 2,335,320 newborns in Thailand were recorded in a database of the health data center, ministry of public health, Thailand. And in this number, only 134,004 persons (5.7%) had head circumference variable in their record. Among them, 121,448 persons (90.6%) can evaluate gestational age (Figure 8).

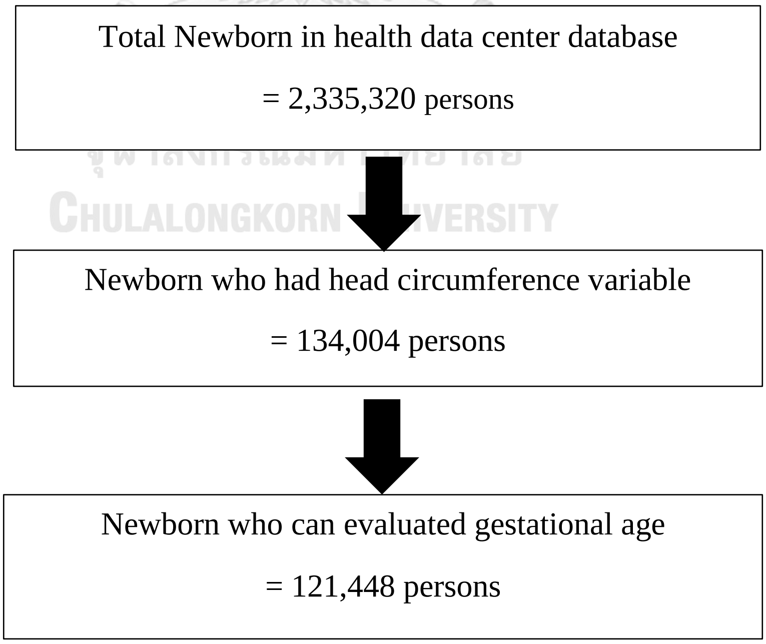

Figure 8 Data managing flow of newborns who were recorded in health data center database, 2014-2016

4.1.1 The characteristic of the study population

The characteristic of newborns in this study was illustrated in table 6. the total number of each variable were not equal due to the completeness of the data. Fifty-five point five percent was male. Male per female ratio was 1.06:1. The mean ± SD of birth weight was 3057.57 ± 421.74 grams. Around 80% of the newborn had birth weight in AGA group. The mean ± SD of birth length was 50.84 ± 2.67 centimeters. Most of the newborn (95.9%) had a birth length equal to or more than 10^{th} percentile of standard birth length by age and sex.

Table 6 The characteristic of newborns in this study

Variables	n	%	Total
Sex			121,448
Male	62,490	51.5	
Female	58,958	48.5	
Weight			121,390
SGA	12,671	10.4	
AGA	97,953	80.7	
LGA	10,766	8.9	
Mean ± SD: 3057.57 ± 421.74 grams			
Length (by Age and Sex)			121,301
< 10th percentile	5,008	4.1	
≥ 10th percentile	116,293	95.9	
Mean ± SD: 50.84 ± 2.67 centimeters.			

Table 7 presented the characteristic of a mother in this study. Most of the mother in this study (97.7%) had age less than 35 years old. The mean ± SD of maternal age was 28.9 ± 4.1 years old. The minimum and maximum age of the mother were 14 and 47 years old, respectively. The major groups of maternal body mass index (BMI) were a normal range (36.7%) and obesity (34.3%). The mean ± SD of maternal BMI was 23.5 ± 4.9 Kg/m^2. Most of the mother had a height equal to or more than 145 centimeters. The mean ± SD of maternal height was 156.7 ± 5.7 centimeters. The majority of maternal nationality was Thai (39.8%). The median of gravida was 2. Minimum and maximum gravida were 1 and 9, respectively. Fifty-seven point nine percent of mother live in Zika transmission areas and 42.1% live in non-transmission areas.

Table 7 The characteristic of mother in this study

Variables	n	%	Total
Age (year)			16,088
< 35	15,723	97.7	
≥ 35	365	2.3	
Mean ± SD: 28.9 ± 4.1 years old			
BMI (Kg/m^2)			86,942
<18.5	15,029	17.3	
18.5-22.9	31,917	36.7	
23-24.9	10,137	11.7	
≥25	29,859	34.3	
Mean ± SD: 23.5 ± 4.9 Kg/m^2			
Height (centimeter)			87,731
<145	449	0.5	
≥145	87,282	99.5	
Mean ± SD: 156.7 ± 5.7 centimeters			
Nationality			14,607
Thai	5,819	39.8	
Myanmar	2,155	14.8	
Laos	805	5.5	
Cambodia	447	3.1	
Other	5,381	36.8	
Gravida			88,439
1	37,991	43.0	
>1	50,448	57.0	
Median: 2, Min-Max: 1-9			
Zika transmission area			78,205
Yes	45,278	57.9	
No	32,927	42.1	

4.1.2 Prevalence of microcephaly, normal head size, and macrocephaly

Table 8 showed a prevalence of microcephaly, normal head size, and macrocephaly**.** During January 2014 – December 2018, head circumference of 121,448 newborns were evaluated. There were 17,558 newborns (14.5%) had head circumference less than 3rd percentile of standard reference (microcephaly). In addition, 8,370 newborns (6.9%) were macrocephaly. The trend of microcephaly was increasing since 2014 and hit to the peak (16.0%) in 2016 then the trend decreased. In another trend, the trend of macrocephaly is decreasing year by year from 10.1% in 2014 to 4.8% in 2018.

Table 8 Prevalence of neonatal microcephaly, normal head size, and macrocephaly, Thailand, 2014-2016

Year	2014		2015		2016		2017		2018		Total	
Microcephaly	2,700		3,565		5,717		2,415		3,161		17,558	
Normal head size	14,679		18,416		27,678		12,042		22,705		95,520	
Macrocephaly	1,958		1,925		2,324		865		1,298		8,370	
Total	19,337		23,906		35,719		15,322		27,164		121,448	
Prevalence of microcephaly (%)	14.0		14.9		16.0		15.8		11.6		14.5	
95%	**Upper**	**Lower**	**Upper**	**Lower**	**Upper**	**Lower**	**Upper**	**Lower**	**Upper**	**Lower**	**Upper**	**Lower**
Confidence limits	13.5	14.5	14.5	15.7	15.6	16.6	15.2	16.3	11.3	12.0	14.3	14.7
Prevalence of macrocephaly (%)	10.1		8.1		6.5		5.6		4.8		6.9	
95%	**Upper**	**Lower**	**Upper**	**Lower**	**Upper**	**Lower**	**Upper**	**Lower**	**Upper**	**Lower**	**Upper**	**Lower**
Confidence limits	9.7	10.6	7.7	8.4	6.3	6.8	5.3	6.0	4.5	5.0	6.8	7.0

4.1.3 The epidemiological characteristic of neonatal microcephaly and newborn with normal head size

The characteristics of a newborn who was microcephaly case and a newborn who had normal head size were shown in table 9. In the table, variables were divided into 2 groups, there were a neonatal factor and maternal factor. The major sex of newborn was male in both groups (56.2% in microcephaly and 51.2% in normal head size). The birth weight was compared with gestational age then divided into 3 groups. There were small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA). The main groups of microcephaly case were AGA and SGA, 63.4% and 36.1%, respectively. In a normal head size group, the most of newborn (85.8%) was AGA. The main birth length of both groups was the same. There were newborn who had length ≥ 10th percentile 86.3% and 97.6% in microcephaly and normal head size groups.

The maternal factors were maternal age, body mass index (BMI), height, nationality, gravida, and Zika transmission area. Most of the mother had age less than 35 years old, accounting for 98.2% and 97.6% in microcephaly and normal head size, respectively. BMI was divided into 4 groups according to BMI for *Asian* populations. The main groups of BMI were normal BMI range and obesity. We found that mother with underweight in microcephaly group (19.1%) was more than a normal head size group (16.7%). The maternal hight in both groups were higher than 145 centimeters. The major nationalities were Thai and Myanmar in both groups. Around half of the mother in both groups were first gravida. More than fifty percent of mother in both groups live in Zika transmission areas.

Table 9 The epidemiological characteristic of neonatal microcephaly and newborn with normal head size, Thailand 2014-2016

Variables	Microcephaly		Normal Head size	
	n	**%**	**n**	**%**
Neonatal factors				
Sex				
Male	9,871	56.2	48,908	51.2
Female	7,687	43.8	46,612	48.8
Weight				
SGA	6,341	36.1	5,974	6.3
AGA	11,128	63.4	81,942	85.8
LGA	81	0.5	7,576	7.9
Length (by Age and Sex)				
< 10th percentile	2,401	13.7	2,319	2.4
≥ 10th percentile	15,110	86.3	93,108	97.6
Maternal factors				
Age (year)				
< 35	2,355	98.2	12,095	97.6
≥ 35	43	1.8	295	2.4
BMI (Kg/m^2)				
<18.5	2,543	19.1	11,207	16.7
18.5-22.9	4,679	35.1	25,280	37.6
23-24.9	1,521	11.4	7,890	11.8
≥25	4,596	34.4	22,790	33.9
Height (centimeters)				
<145	60	0.4	353	0.5
≥145	13,407	99.6	67,445	99.5
Nationality				
Thai	1,124	51.4	4,420	38.1
Myanmar	310	14.2	1,752	15.1
Laos	131	6.0	624	5.4
Cambodia	84	3.8	341	2.9
Other	536	24.5	4,476	38.5
Gravida				
1	6,192	47.9	29,402	42.2
>1	6,723	52.1	40,242	57.8
Zika transmission area				
Yes	6,527	57.8	35,834	57.4
No	4,766	42.2	26,591	42.6

4.2 Analytical analysis

4.2.1 Univariate analysis

Univariate analysis of neonatal factors and microcephaly was performed to find an association between neonatal factors and microcephaly. The results were shown in table 10. From the analysis, we found that there was a statistically significant association between sex, birth weight, and birth length with microcephaly. The odds of male was 1.22 times (95% CI 1.18-1.26, P value <0.001) greater in microcephaly than female. The chance of microcephaly in SGA newborn was 7.82 times (95% CI 7.51-8.14, P value <0.001) more than AGA newborn. In contrast, the chance of microcephaly in LGA newborn is lower than AGA newborn (Odds ratio 0.08, 95% CI 0.06- 0.10, P value <0.001). A newborn who birth length less than 10^{th} percentile, compared with the same sex and age, had the chance of microcephaly than a newborn who birth length equal or more than 10^{th} percentile 6.38 times (95% CI 6.01-6.77, P value <0.001).

The association between maternal factors and microcephaly was presented in table 11. we found that the maternal age, mother with underweight (BMI <18.5 Kg/m^2) and obesity (BMI ≥25Kg/m^2), Myanmar, Laos and other nationality, and gravida had a statistically significant association (P-value 0.08, <0.001, <0.001, <0.001, 0.06, <0.001, and <0.001, respectively). The chance of microcephaly in advance maternal age (≥ 35 years old) was less than the mother who had age less than 35 years old (Odds ratio 0.75, 95% CI 0.54-1.03). The odds of a mother with underweight and obesity were 1.23 and 1.09 times greater in microcephaly than mother with normal BMI range (95% CI 1.16-1.29 and 1.04-1.14, respectively). The Myanmar, Laos, and other nationality of a mother had the chance of microcephaly less than Thai mother ((Odds ratio 0.70, 0.83, and 0.47), (95% CI 0.61-0.80, 0.68-1.01, and 0.42-0.53), respectively). The mother with the first gravida had the chance of microcephaly more than the mother who had gravida more than 1 (Odds ratio 1.26, 95% CI 1.21-1.31). In addition, some variable showed association with microcephaly but was not statistically significant such as mother with overweight had the chance of microcephaly more than mother with normal BMI range 1.04 times (95% CI 0.98-1.11, P value 0.21), the chance of microcephaly in mother with short stature (height < 145 centimeters) was less than mother who had height ≥ 145 centimeters (Odds ratio 0.86, 95% CI 0.65-1.12, P value 0.26), the Odds of Cambodian mother was 0.97 times (95% CI 0.76-1.24, P value 0.80) in microcephaly lesser than Thai mother, the mother who lives in Zika transmission area had a higher chance of microcephaly than mother who live in non Zika transmission area (Odds ratio 1.02, 95% CI 0.98-1.06, P value 0.44).

Table 10 Univariate analysis of neonatal factors and microcephaly among Thai newborn, 2014-2018

Variables	Microcephaly		Normal Head size		Odds Ratio	95% CI		P value*
	n	%	n	%		Lower	Upper	
Sex								
Male	9,871	16.8	48,908	83.2	1.22	1.18	1.26	<0.001
Female	7,687	14.2	46,612	85.8	ref.			
Weight								
SGA	6,341	51.5	5,974	48.5	7.82	7.51	8.14	<0.001
LGA	81	1.1	7,576	98.9	0.08	0.06	0.10	<0.001
AGA	11,128	12.0	81,942	88.0	ref.			
Length (by Age and Sex)								
< 10^{th} percentile	2,401	50.9	2,319	49.1	6.38	6.01	6.77	<0.001
≥ 10^{th} percentile	15,110	14.0	93,108	86.0	ref.			

* P value from Chi-square test

Table 11 Univariate analysis of maternal factors and microcephaly among Thai newborn, 2014-2018

Variables	Microcephaly		Normal Head size		Odds Ratio	95% CI		P value
	n	%	n	%		Lower	Upper	
Age (year)								
≥ 35	43	12.7	295	87.3	0.75	0.54	1.03	0.08
< 35	2,355	16.3	12,095	83.7	ref.			
BMI (Kg/m2)								
<18.5	2,543	18.5	11,207	81.5	1.23	1.16	1.29	<0.001
23-24.9	1,521	16.2	7,890	83.8	1.04	0.98	1.11	0.21
≥25	4,596	16.8	22,790	83.2	1.09	1.04	1.14	<0.001
18.5-22.9	4,679	15.6	25,280	84.4	ref.			
Height (centimeters)								
<145	60	14.5	353	85.5	0.86	0.65	1.12	0.26
≥145	13,407	16.6	67,445	83.4	ref.			
Nationality								
Myanmar	310	15.0	1,752	85.0	0.70	0.61	0.80	<0.001
Laos	131	17.4	624	82.6	0.83	0.68	1.01	0.06
Cambodia	84	19.8	341	80.2	0.97	0.76	1.24	0.80
Other	536	10.7	4,476	89.3	0.47	0.42	0.53	<0.001
Thai	1,124	20.3	4,420	79.7	ref.			
Gravida								
1	6,192	17.4	29,402	82.6	1.26	1.21	1.31	<0.001
>1	6,723	14.3	40,242	85.7	ref.			
Zika transmission area								
Yes	6,527	15.4	35,834	84.6	1.02	0.98	1.06	0.44
No	4,766	15.2	26,591	84.8	ref.			

* P value from Chi-square test

4.2.2 Multivariate analysis

We performed multivariate analysis by using multiple logistic regression for finding an association between possible variable and microcephaly. The variable which had p-value < 0.2 from the univariate analysis was selected into multivariate analysis i.e. sex of newborn, birth weight, birth length, maternal age, BMI of the mother, maternal nationality, and gravida. From the analysis, we found that the variable that had a statistically significant association with microcephaly was birth weight, birth length, maternal age, and gravida. As shown in table 12, a newborn with SGA had a chance of microcephaly more than AGA newborn 5.34 times (95% CI 3.24-8.81, P value <0.001), the odds newborn who had length < 10^{th} percentile was 2.92 times (95% CI 1.36-6.29, P value 0.01), The chance of microcephaly in advance maternal age was 1.84 times (95% CI 1.07-3.18, P value 0.03) more than the mother who had age less than 35 years old, and the chance of microcephaly in mother with the first gravida was higher than the mother who had gravida more than 1 (Adjusted Odds ratio 2.01, 95% CI 1.37-2.95, P value <0.001).

Table 12 Multivariate analysis of epidemiological characteristic and microcephaly among Thai newborn, 2014-2018

Variables	Adjusted Odds Ratio	95% CI		P value
		Lower	Upper	
<u>Neonatal factors</u>				
Sex				
Boy	1.03	0.72	1.49	0.87
Girl	ref.			
Weight				
SGA	5.34	3.24	8.81	<0.001
LGA	0.41	0.13	1.36	0.15
AGA	ref.			
Length (by Age and Sex)				
< 10th percentile	2.92	1.36	6.29	0.01
≥ 10th percentile	ref.			
<u>Maternal factors</u>				
Age (year)				
≥ 35	1.84	1.07	3.18	0.03
< 35	ref.			
BMI (Kg/m^2)				
<18.5	0.63	0.12	3.22	0.58
23-24.9	1.22	0.74	2.03	0.44
≥25	0.67	0.42	1.08	0.10
18.5-22.9	ref.			
Nationality				
Myanmar	1.38	0.13	14.07	0.79
Laos	1.77	0.17	18.71	0.63
Cambodia	2.22	0.21	23.00	0.50
Other	0.40	0.03	5.11	0.48
Thai	ref.			
Gravida				
1	2.01	1.37	2.95	<0.001
>1	ref.			

*analyzed by using multiple logistic regression

CHAPTER V

DISCUSSION, CONCLUSION, AND RECOMMENDATIONS

After the world epidemic of Zika virus infection, microcephaly is one condition which became highly concern. Thailand is one of many countries that was affected by Zika virus infection[14]. The objectives of this study estimated the prevalence, describe the epidemiological characteristic and identified associated factor of neonatal microcephaly in Thailand by using the database (43 files report) of the health data center (HDC), ministry of public health, Thailand.

This chapter was divided into 6 parts

1. Discussion about the database (43 files report)
2. Discussion on the prevalence of neonatal microcephaly in Thailand
3. Discussion on the associated factor of neonatal microcephaly in Thailand
4. Strengths and limitations of the study
5. Conclusion
6. Recommendations

5.1 Discussion about the database (43 files report)

Although 43 files report cover around 70% of the total of live-births in Thailand, only 6.5% of the newborn in 43 files report can evaluate the head size. The low completeness of head circumference data may come from noncompulsory data. The head circumference in this database is a noncompulsory variable, the service provider may send or not send up to the willingness. This reason can explain why more than 90% of the newborn has no head circumference data. As same as the head circumference, some interesting variable is noncompulsory variable. Therefore, this is the explanation of low compltness data in each variable.

5.2 Discussion on the prevalence of neonatal microcephaly in Thailand

The prevalence of neonatal microcephaly in this study is 14.5% or 14,500 persons per one hundred thousand live-births which higher than expectation and previous study. In this study, the definition of neonatal microcephaly is a newborn who had head circumference less than the 3rd percentile of the standard head circumference by age and sex[29]. It means that the expected prevalence of neonatal microcephaly is around 3%. The data from the previous study show that the prevalence of neonatal microcephaly was 4.36 cases per one hundred thousand live-births or 0.0000436%[11]. The higher prevalence may come from different methodology. Although the case definition of neonatal microcephaly in the previous study was the same with this study, the way to get microcephaly case is different. In this study, we used head circumference of each newborn compared with standard reference to identify microcephaly case directly but in the previous study, they did not compare by themselves. They use diagnosis code (ICD-10-CM = Q02, a congenital or acquired developmental disorder in which the circumference of the head is smaller than normal for the person's age and sex[41]) to identify microcephaly case. In 2017, Bureau of Epidemiology, Department of Disease Control, Ministry of public health, Thailand conducted the microcephaly reporting system evaluation, using 43 files database as a reporting system they found that sensitivity of this reporting system was 0.14%. it means that if microcephaly occurs 100,000 cases, only 140 cases will be reported Q02 in the system[42]. This is a reason why the prevalence of neonatal microcephaly in this study is higher than the previous study.

Another reason for high prevalence may come from using international standard reference which did not include Thailand. The number of studies in Asia countries[23, 43-45] mentions about international standard growth curve may not proper with their newborn such as They made the standard of head circumference from their newborn data and compared with the international standard reference, they found that local standard head circumference in each country are smaller than international standard head circumference. Therefore, using the international standard head circumference may induce a high prevalence of microcephaly. According to the national guideline,[29] the newborn with microcephaly is one of the criteria for congenital Zika syndrome investigation which have expensive cost. If using international standard head circumference, the newborn may receive unnecessary investigation and loss of expenditure wastefully. Therefore, the local standard head circumference specifically to Thai newborn is needed.

The highest prevalence of microcephaly in 2016 (16.0%) may come from a high concern about Zika related microcephaly case. At the beginning of 2016, 2 cases of Zika related microcephaly were reported in Thailand and many parts of Thailand face of the Zika virus outbreak. Consequently, the head circumference variable was entered into the database higher than last year. A lot of head circumference data may induce a high prevalence. Another reason may be the high intention when measuring the head circumference. If measurer pulls the measuring tape tightly, the head circumference may smaller than the real. This is the reasons why the prevalence increase. After 2016, the prevalence of microcephaly was decreasing. It may come from decreasing of head circumference value. In 2017, only 15323 of 560903 newborns (2.7%) have head circumference value. In 2018, the prevalence of microcephaly was significantly decreasing but the number of newborns who has head circumference value increase. The low prevalence may come from the increasing of the denominator. Another reason may be the increase intention of the measurer, do not pull the measuring tape tightly. This may be the reason why the prevalence decrease.

5.3 Discussion on the associated factor of neonatal microcephaly in Thailand

5.3.1 Neonatal factors

5.3.1.1 Birth weight

Birth weight in this study was divided into 3 groups. There were small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA). The univariates analysis of this study show that a newborn with SGA had a chance of microcephaly higher than a newborn with AGA, and a newborn with LGA had a chance of microcephaly less than a newborn with AGA. This result is the same with many studies such as (Mili F, et al)[46], they study the prevalence of birth defects, including microcephaly, among low birth weight infants. They divided infants into 5 groups. There were < 1,500 grams, 1,500 – 1,999 grams, 2,000 – 2,499 grams, 2,500 - 3999 grams, and ≥ 4000 grams. The results showed that the rate of microcephaly is highest in a newborn who had weight < 1,500 grams, and the trend of microcephaly decreased to lowest in the newborn who had more weight respectively. The study from Malaysia is the one study that reported low birth weight is associated with microcephaly. They found that a newborn who has birth weight < 2,500 grams have a chance of microcephaly higher than a newborn who has birth weight ≥ 2,500 grams 1.6 times. Moreover, the biostatistics study from Nigeria showed the linear relationship between birth weight and head circumference[18]. LGA in this study is a protective factor of microcephaly same the study from the USA[46]. From all study above, we can conclude that birth weight is associated factors of neonatal microcephaly.

5.3.1.2 Birth length

The birth length in this study showed an association with microcephaly. A newborn who has birth length < 10th percentile of standard reference by gestational age and sex, we can call short newborn, have a chance of microcephaly higher than a newborn who has birth length ≥ 10th percentile 2.92 times. The result is similar to previous studies. In Malaysia, a short newborn has a chance of microcephaly higher than a normal length newborn 1.82 times[23]. In Argentina, the assessment of the relationship between head circumference and height was studied. the results show that there was a relationship between height and head circumference[25]. Furthermore, the study of Dutch children showed a positive correlation between head circumference and length[24]. This finding may be explained by the concept of proportionality of head size[47]. This concept says that there is a relationship between head size and body size so a newborn who was short most likely to have a small head size. For assessment head circumference some study suggests that the assessment of head circumference should be interpreted with height[25].

5.3.2 Maternal factors

5.3.2.1 Maternal age

In this study, we divided the maternal age group into 2 groups. There was a mother who had age <35 years and ≥ 35 years. The result report that a mother who had age ≥ 35 years have a chance of microcephaly higher than mother who had age < 35 years 1.84 times. The result may be explained by a mother who had age ≥ 35 years or advanced maternal age is a risk group. There is a lot of report about complication during pregnancy in this group. The complications in advanced maternal age are gestational diabetes mellitus (GDM), gestational hypertension, preeclampsia, small for gestational age newborn (SGA), and preterm delivery[48]. Moreover, there is some study reported that advanced maternal age is a risk factor of intrauterine growth restriction (IUGR)[49]. IUGR is a condition of the fetus which unable to achieve a normal size. As a result, a fetus with IUGR may birth with lower birth weight or SGA[50]. In contrast, there is some studies report about younger mother associated with microcephaly such as Kirchengast S(2013)[20] the results of this study show that the head circumference of a newborn who had a young mother (12-16 years) was significantly different when compared with older mother (17-29 years). This newborn had a smaller head circumference than the other groups, H. Shajari (2006)[19], studied mother who had ages less than 20 years old compared with mother who had ages equal and more than 20 years old, they found that newborn who had mother ages less than 20 years old had a head circumference smaller than newborn who had mother ages equal and more than 20 years old. Both of the study mention that teenage pregnancy may cause of microcephaly. in this study Mean ± SD of maternal age among population is28.9 ± 4.1 years old. The maternal age of population quite far from teenage. This may be the reason why the result of maternal age showed like this. In a further study, the comparison between 3 maternal age groups (<20, ≥20 and <35, and ≥ 35 year old) will be considered to study.

5.3.2.2 Maternal height, pre-pregnancy weight, and pre-pregnancy body mass index

In this study maternal weight and height were calculated to body mass index (BMI) then divided into 4 groups. There were underweight (<18.5 kg/m^2), normal range (18.5–23 kg/m^2), overweight (23–24.9 kg/m^2), and obesity (≥ 25-29.9 kg/m^2). The result showed that there is no association between maternal BMI and microcephaly. This result is similar to previous studies such as Bonakdar SA and et al[51], they examined the relationship between pre-pregnancy BMI and birth size in the north-east part of Iran. The results showed that there was no relationship between head circumference and maternal BMI (normal range of BMI and overweight). Zoya T and et al[52], the study on pre-pregnancy BMI with newborn anthropometric characteristics. The results showed that there was no significant difference in the mean of head circumference when compared between maternal BMI groups. Gondwe A and et al[53] studied the associations between pre-pregnancy BMI and birth outcomes. They found that there was no significant difference in the mean of head circumference and prevalence of small head size between groups of maternal BMI. As the results of this study and previous studies, maternal BMI (pre-pregnancy period) may be not associated with microcephaly. The weight-related with head circumference factor is maternal gestational weight gain.[53, 54] A women with low weekly gestational weight gain was a greater risk of small head circumference when compared with women with normal weekly gestational weight gain.[53] In addition, a result of a study in China showed that a newborn who has a mother with excessive gestational weight gain have head circumference larger than the newborn who has a mother with adequate gestational weight gain.[54]

There is the number of studies show an association between maternal height and head circumference of the newborn. Hassan NE and et al[55] studied the relationship between characteristics of the mother and birth size. They found that maternal height had a significant positive correlation with a head circumference of the newborn. Similar to the study of Polzlberger E and et al[22], the result showed that maternal height had a highly significant correlation with a head circumference of the newborn. In contrast, there is no association between the height of the mother and a head circumference of the newborn in this study. We tried to compare the mean of maternal height between microcephaly and normal head size groups. The result showed a significant difference between both groups, the mean of maternal in normal head size groups was higher than microcephaly group. However, the maternal height may not be the best predictor. The best predictor may be gestational weight gain because it is the best to predict birth weight[56].

5.3.2.3 Gravida

Because parity was not included in 43 files database so we replace parity with gravida. In this study, a woman who was the first gravida had a chance of microcephaly higher than women with multigravida. The results of this study similar to the result of parity in the previous study. H. Shajari (2006)[19], compared head circumference of the newborn who born with first parity and multipara, they found that there was a significantly different of head circumference between 2 groups, the mean of neonatal head circumference in first parity group smaller than multiparity group. This result is similar to our study. In our study, a newborn with the first gravida had a chance of microcephaly higher than a newborn with multigravida 2.01 times. The result may be explained by the concept of low birth weight. Terán JM and et al[57] found that a newborn with the first parity has a chance of low birth weight higher than that a newborn with multiparity. The explanation of low birth weight may come from poor uterine blood perfusion in primiparous mothers, reduces the supply of oxygen and nutrients to the fetus. [58]

5.3.2.4 Zika transmission area

Although the association between Zika virus infection and microcephaly was confirmed, there is no association between a newborn who has mother live in Zika transmission area and microcephaly in this study. In the previous study, they performed a case-control study to find an association between Zika virus infection and microcephaly. For confirmation, they tested the serum of cases and controls for detection of Zika virus and IgM antibodies[15]. In this study, we cannot confirm the infection status of microcephaly case and normal head size case. This may the reason why there is no association between Zika transmission area and microcephaly in this study.

5.4 Strengths and limitations of the study

5.4.1 Strengths

- This study is the first study that provides information about the prevalence and associated factors of neonatal microcephaly in Thailand.

- This study used the data from the health data center (HDC) of the Ministry of Public Health, Thailand which 1,454 hospitals were involved by HDC. This database covers a public hospital under Thai MoPH and other hospitals (Outside MoPH and Private hospital). Regarding the population of this study, a newborn who received a medical service in a public hospital under Thai MoPH and other hospitals who interest to send the data to MoPH, 69% of live birth in Thailand were included in this database.

5.4.2 Limitations

- This study is secondary data analysis. Some variable may incomplete or absent such as the head circumference of the newborn. The head circumference in this database is a noncompulsory variable, the service provider may send or not send up to the willingness. In this study, only 6% of total live birth in HDC have head circumference value

- Some interesting factor such as gestational weight gain, nutrition during pregnancy, socioeconomic status, environmental, and lifestyle (stress, smoking and alcohol use) cannot be evaluated.

5.5 Conclusions

A total of 121,448 newborns who born at a public hospital under Thai MoPH and other hospitals who interest to send the data to MoPH in 2014-1018 were included in this study. There were 17,558 newborns (14.5%) had head circumference less than 3rd percentile of standard reference (microcephaly). The high prevalence of neonatal microcephaly in this study may come from the standard reference. Using international standard reference may induce misdiagnosis. The study to establish a local standard reference is needed.

From statistical analysis, the associated factors of neonatal microcephaly are a newborn who has birth weight in small for gestational age group, a newborn who has birth length < 10th percentile when compared with another newborn in the same sex and age, a newborn who born with advanced maternal age, and first gravida newborn. Another interesting variable such as gestational weight gain, nutrition during pregnancy, socioeconomic status, environmental, and lifestyle (stress, smoking and alcohol use) may study in the future.

5.6 Recommendations

5.6.1 Recommendation for policy maker

- A standard reference anthropometric chart for Thai newborn should be developed for preventing misdiagnosis and lose of expenditure for investigation.

- The guideline for diagnosis, investigation, and treatment neonatal microcephaly may be modified.

- Encourage health care provider to send the complete and correct data to the central level.

5.6.2 Recommendation for health care workers

- Health care workers should emphasize data entry because complete and correct data is valuable data.

5.6.3 Recommendation for further study

- The study to construct a standard reference anthropometric chart for Thai newborn should be considered.

- The study about possible associated factors such as gestational weight gain, nutrition during pregnancy, socioeconomic status, environmental, and lifestyle (stress, smoking and alcohol use) should be considered.

APPENDIX

APPENDIX A: STANDARD HEAD CIRCUMFERRENE CHARTS

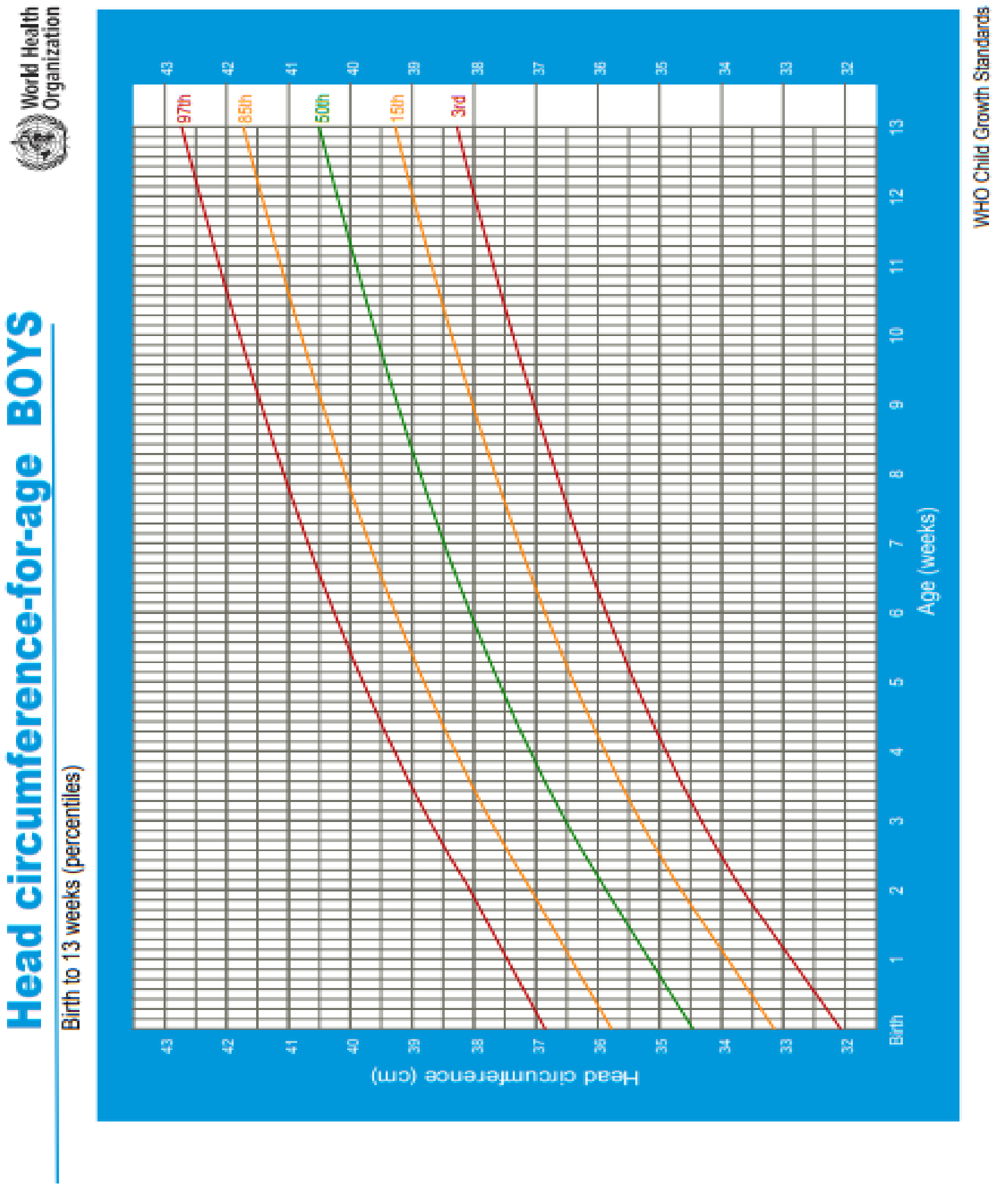

Figure 9 World Health Organization (WHO) standard growth charts for boys

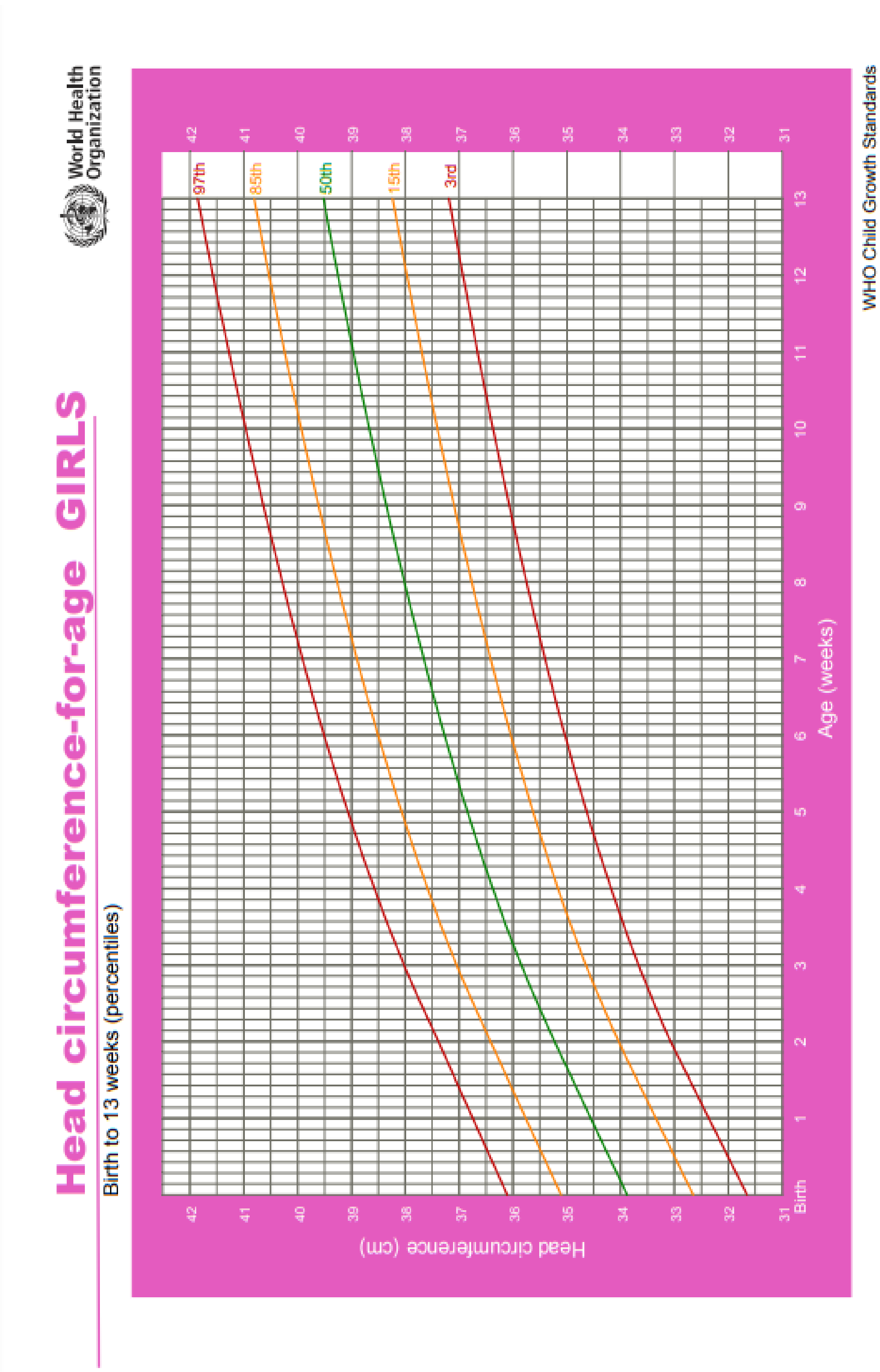

Figure 10 World Health Organization (WHO) standard growth charts for girls

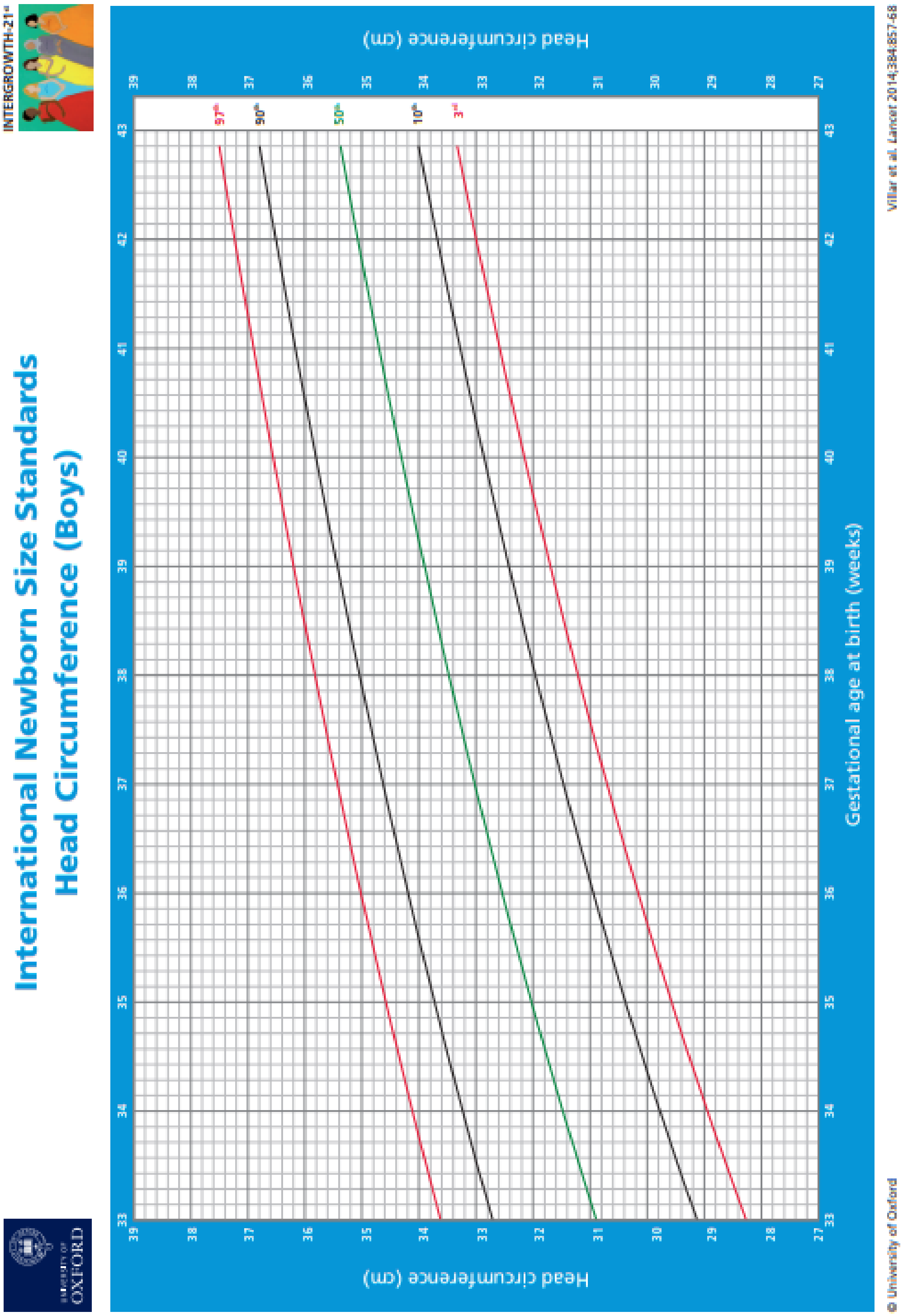

Figure 11 INTERGROWTH 21st standard head circumference charts for boys

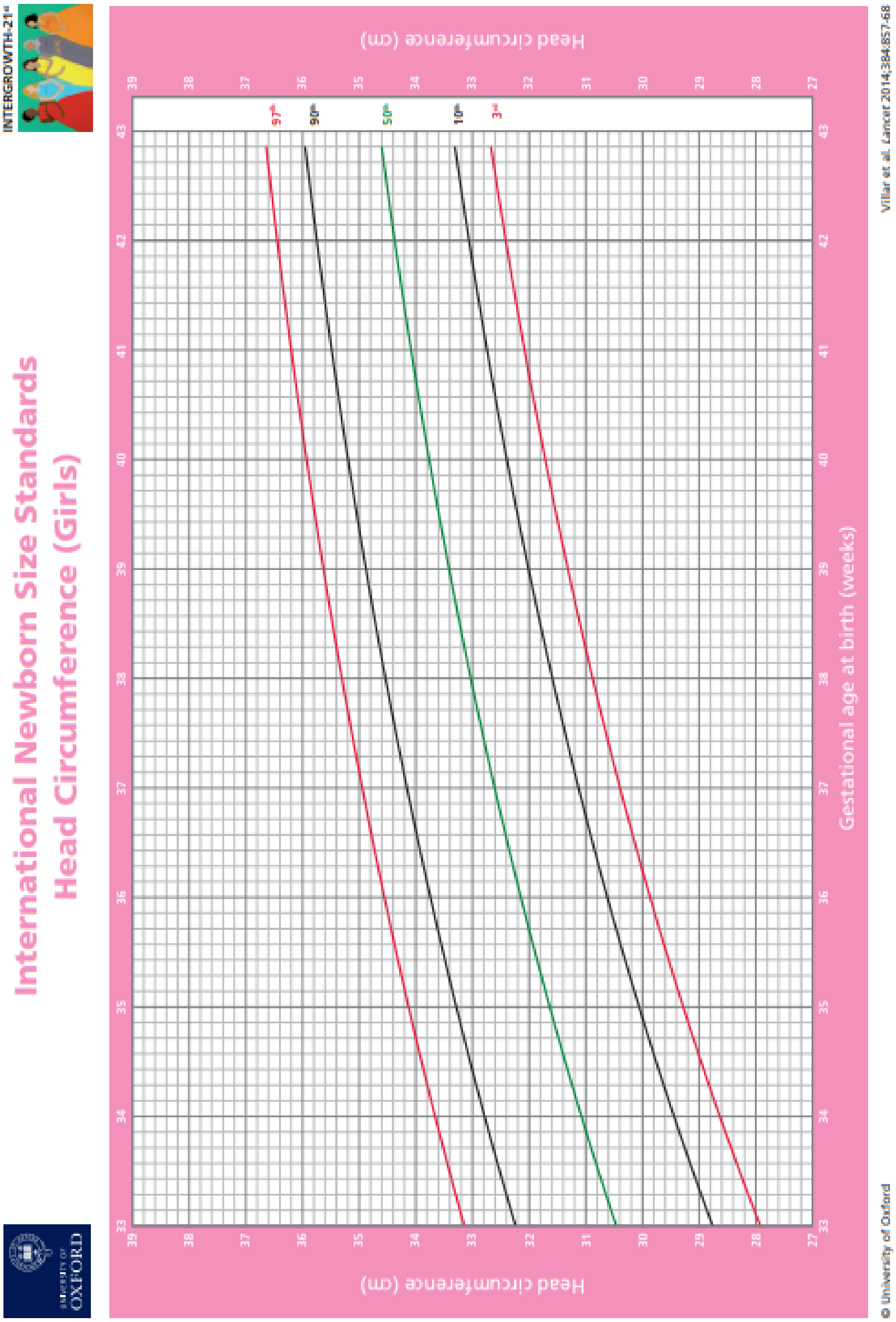

Figure 12 INTERGROWTH 21st standard head circumference charts for girls

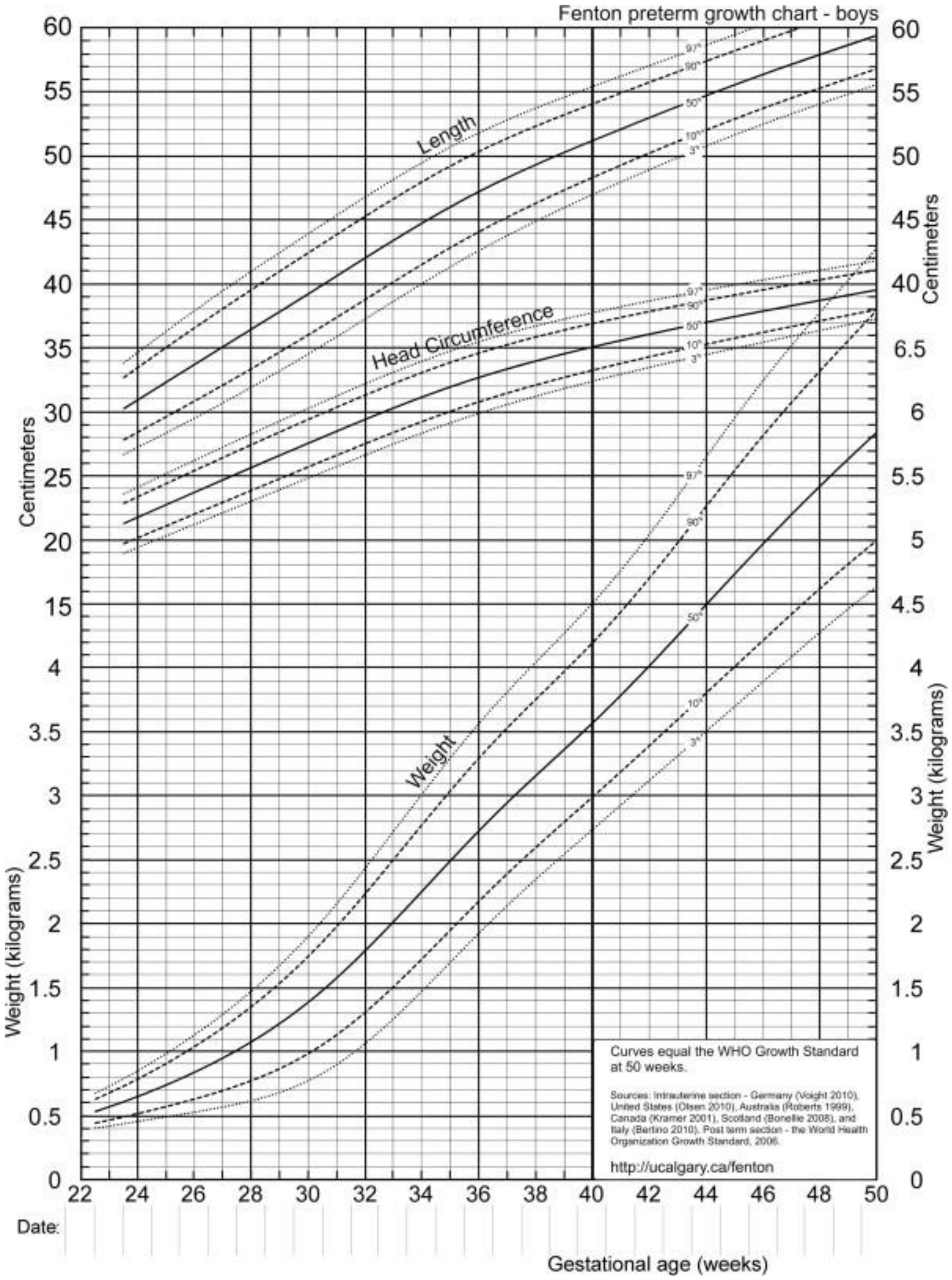

Figure 13 Fenton growth chart for preterm infants for boys

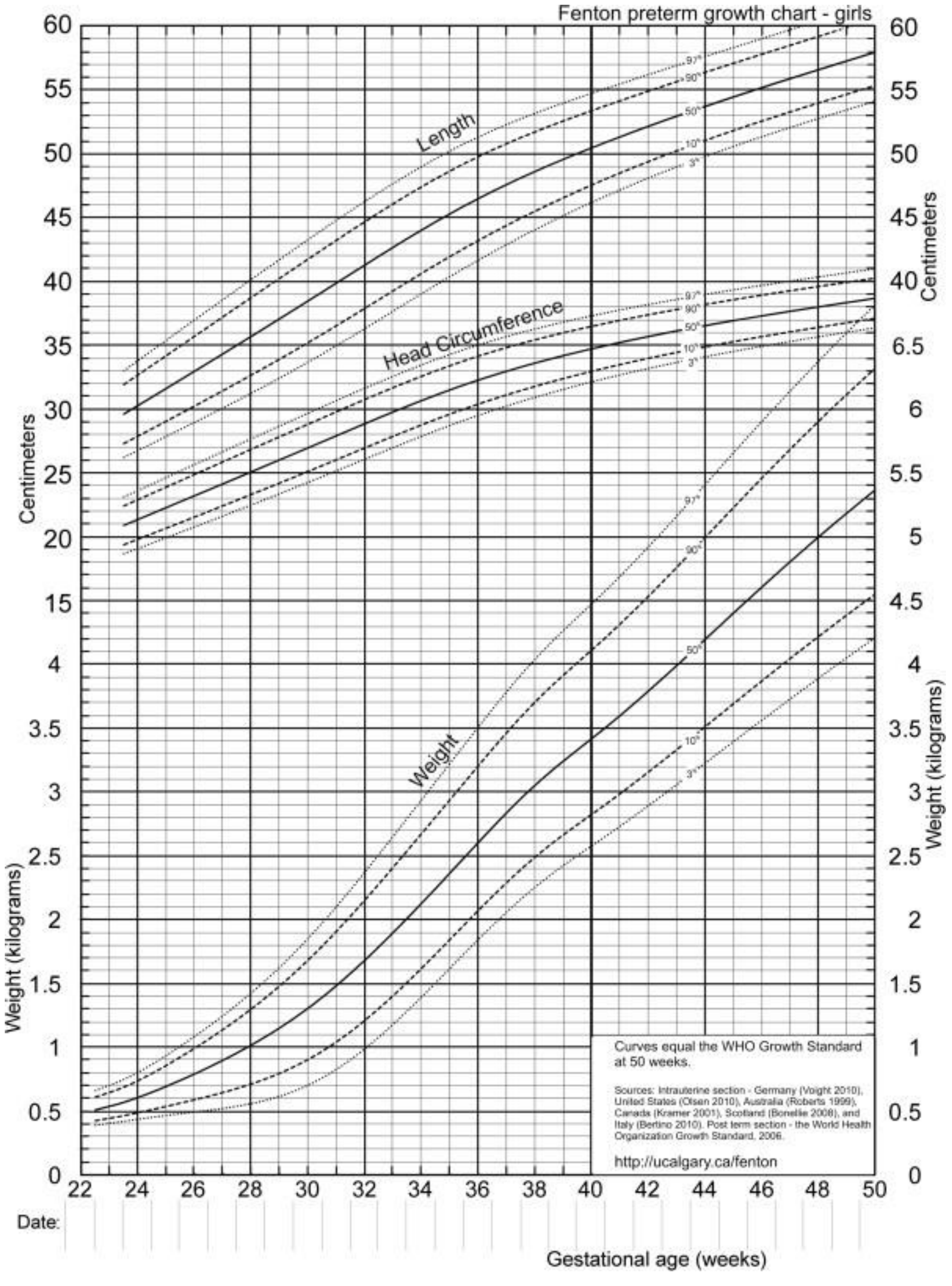

Figure 14 Fenton growth chart for preterm infants for girls

APPENDIX B: DATA COLLECTING FORM

Table 13 Data collecting form for newborn

ID	HOSPCODE	PID	CID	BIRTHDATE	GA	GRAVIDA	BWEIGHT	HEIGHT	DATE_SERVE	HEADCIRCUM	MATRNAL_CID
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
15											
16											
17											
18											
19											
20											

Table 14 Data collecting form for mother

ID	HOSPCODE	PID	CID	BIRTHDATE	DATE_SERVE	WEIGHT	HEIGHT	PARITY	PROVINCE
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
19									
20									

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