CERVICAL LENGTH SCREENING AS A PREDICTOR OF SPONTANEOUS PRETERM BIRTH IN LOW RISK SINGLETON PREGNANCY

BY

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ABSTRACT

Preterm birth is the most common cause of perinatal mortality and morbidity. Although the survival rate has improved, the surviving neonate carries risk of long term neurological impairment, respiratory and gastrointestinal problems. Two third of preterm birth are spontaneous. Various prediction methods of preterm birth were found to have limited predictive ability. Transvaginal cervical length measurement is a safe and gold standard method. Cervical length screening in high risk patient was recommended, however limited scientific evidence in universal cervical length screening for a low risk women. This research is aim to predict spontaneous preterm birth in singleton pregnancies of low risk primigravida through their cervical length measurement. This is a prospective observational study in 380 primigravidae. Pregnant mothers between 18 to 24+6 weeks gestation were recruited and cervical length (CL) screening done by transvaginal ultrasound. They were followed up until delivery. 380 primigravida were screened and 4.8% were delivered preterm (<37 weeks) of which only 0.5 % had cervical length of < 2.5 cm. Further statistical analysis found that 2.6% of total recorded deliveries were preterm birth with cervical length < 3.5cm and the mode is 3.1cm. Cervical length < 3.5cm between 18 to 24 + 6 weeks gestation, gives a positive predictive value of 37% and negative predictive value of 98%. Based on ROC curve, cervical length is a good predictive tool to predict term delivery in a low risk population. From the study it shows that cervical length < 2.5cm carries risk of preterm birth. However the percentage of short cervical length is very small and it would not be a feasible screening method due to limited resources in our health care centre. Further study with larger sample size should be conducted to focus on cervical length < 3.5cm to predict preterm birth.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion; it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Master of Obstetrics and Gynaecology.

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This dissertation was submitted to the Department of Obstetrics and Gynaecology and is accepted as a partial fulfilment of the requirements for the degree of Master of Obstetrics and Gynaecology.

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DECLARATION

I hereby declare that this dissertation is the result of my own investigation, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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LIST OF ABBREVIATIONS

CL	Cervical Length
HSNZ	Hospital Sultanah Nur Zahirah
MFM	Maternal Fetal Medicine
PTB	Preterm Birth
ROC	Receiver Operating Characteristics
SD	Standard Deviation
TVS	Transvaginal Ultrasound

CHAPTER ONE

INTRODUCTION

Preterm birth defines as delivery before 37 completed weeks. The incidence of preterm birth in the develop country is 7-12% (Dewhurst & Edmonds, 2012) and the number increased in the developing and 3rd world country. Severe prematurity is the major cause of death and handicap in newborn babies worldwide. Morbidity and mortality are inversely related to gestational age at birth. Besides that preterm birth also contribute to the economic burden to the country starting from the intrapartum and neonatal period, early intervention programmed for disable child with developmental delay, and later on establishment of special education services.

Preterm birth is not a disease on its own, but is a symptom that may have one or more causes. There are multiple recognizable causes of preterm birth, however two third of preterm births are spontaneous (McIntosh, Feltovich, Berghella, & Manuck, 2016). Preterm birth has been associated with cervical incompetence, extensive cervical surgery or damage, abnormalities of haemostasis, infection within the uterus, placenta abruption or decidua haemorrhage, and multiple pregnancy. Other than that, teenagers and women over 30 have increased risk of preterm birth and it was higher in first pregnancy. Social disadvantages also contribute to the risk of preterm birth such as marital status, cigarette smoking, environmental stress, poor nutrition, use of alcohol and recreational drugs (Dewhurst & Edmonds, 2012).

Recently the concept of cervical competence in preterm birth is continuingly evolved. Several studies have shown a strong relationship between cervical length and the risk of preterm birth. A short and partially dilated cervix may allow ascending

infection and leads to cervical ripening, shortening and subsequently preterm birth. The short and weak cervix not only leading to second trimester miscarriage but also contributing to risk of ascending infection and leads to classical spontaneous preterm labour.

Prevention is better than cure. However for an obstetrician to prevent the disease, early prediction is a first step. Early identification of women at risk of preterm birth and prophylaxis intervention is good approaches to reduce perinatal morbidity and mortality due to preterm birth. Women with history of previous preterm birth have increased risk of preterm birth in subsequent pregnancy. However this cannot be applied to the primigravida. At present, there are no specific screening tests which are routinely applied to primigravida who are not at high risk for preterm birth. Different methods of predicting preterm birth has been proposed, however these were found to have limited predictive ability.

Cervical length measurement has been proposed as one of the methods of predicting spontaneous preterm birth and preventive measures could be given early before they become symptomatic.

There are various methods in measuring cervical length such as through a direct physical examination or by sonographic. Clinical digital examination is still usually used but the results is individual as it's varies among examiners.

Transvaginal sonographic measurement of cervical length is the best methods to predict the risk of preterm birth and is a gold standard compared to other sonographic methods. Transabdominal ultrasound was the preferred when the ultrasonographic measurement was first instigated. However it is unreliable since it has a poor image quality due to distance from probe to the cervix and difficult to visualize cervix adequately. Transabdominal ultrasound also need full bladder to produce a good image,

which can compress the cervix leading to an error in measurement. Translabial (transperineal) ultrasound is another sonographic method however it is more difficult to learn and the presence of gas in the rectum will obscured the view of the external os.

Cervical length screening can be done as a serial measurement of cervical length throughout 2nd and 3rd trimester or a single cervical length measurement at 18-22 weeks. Serial measurement is more superior compared to the single measurement, however it is more costly and time consuming.

Cervical length measurement at 20-24 weeks was found to be more predictive to predict preterm birth. Before 14 weeks, the small gestational sac has not sufficiently expends the lower part of the uterus, therefore it is difficult to distinguish between lower uterine segment from the endocervical canal. Cervical length should not be done before 14 weeks of gestation due to the above reason. Cervical length measurement at 10–14 weeks was not reliable for predicting preterm birth (Ozdemir, Demirci, Yucel, & Erkorkmaz, 2007).

Cervical length screening in high risk patient has been recommended and practices worldwide, however there are limited studies and evidence in cervical length screening of low risk women. Cochrane review did not find sufficient evidence to recommend routine cervical length screening for all pregnant women, they suggested more studies to allow better assessment and evaluation of the cervical length measurement in low risk women (Berghella & Saccone, 2019).

CHAPTER TWO

LITERATURE REVIEW

Transvaginal ultrasound is a gold standard examination to measure cervical length for predicting and preventing preterm birth. It is a safe and acceptable method of assessing the cervical length. Transvaginal ultrasound is accepted by >99% of the women and pain is reported in < 2% of the cases (Dutta & Economides, 2003). Transvaginal ultrasound will not increase the risk of ascending infection to the mother or fetus even in women with preterm pre labour rupture of membranes (Carlan, Richmond, & Obrien, 1997).

Universal cervical length screening has been implemented about 68% at MFM fellowship training centre In United states of America since 2015 by using transvaginal and transabdominal ultrasound (Khalifeh, Quist-Nelson, & Berghella, 2017).

Previous study on cervical length stated that cervical length measurement has a better diagnostic accuracy in comparison to digital examination of the cervix in predicting preterm birth in a low risk population (Matijevic, Grgic, & Vasilj, 2006). Measurement of cervical length at 20 weeks of gestation also provides sensitive prediction of severe preterm birth (Heath, Southall, Souka, Elisseou, & Nicolaides, 1998) .

Cervical length screening has been known to be effective in prediction of preterm birth in high risk population. A cervical length of <20 mm was significantly associated with preterm delivery with an odds ratio of 4.88 (95% confidence limit, 1.15 - 20.73) (Orzechowski, Boelig, Baxter, & Berghella, 2014) .

The cervical length at 20–24 weeks was significantly shorter in the preterm birth group (28.4 mm) compared to those who had term deliveries (37.8 mm) ($P < 0.001$). The cervical shortening was more observable in the group that delivered prematurely (from 38.6 to 28.4 mm) than in term deliveries (from 40.9 to 37.8 mm) (Ozdemir et al., 2007).

Another study at King's College Hospital London involved 2567 singleton pregnancies women at 23 weeks showed that 2% of the population whose has cervical length < 1.5cm were delivered prematurely. 90 were delivered at 28 weeks and 60% delivered at 32 weeks. This data showed that cervical length screening provides an accurate prediction of preterm birth (Heath et al., 1998). However another study was contradicted as it shown that cervical length screening in general population at 20 to 24+6 weeks of gestation show weak correlation between cervical length and gestational age at delivery and it is not a good predictor for preterm birth, ROC 0.693, (95% CI, 0.512 to 0.874) (Peixoto et al., 2017).

About 35% of women with history of preterm birth in singleton pregnancy has short cervix in subsequent pregnancy and 40% with no prior history of preterm birth. The positive predictive value is approximately 20-30% and majority of low risk singleton pregnancy with cervical length < 2.5cm will deliver after 35 weeks unless they had prior preterm birth (Bohîlțea et al., 2016).

Society for Maternal Fetal Medicine (SMFM) recommend routine transvaginal cervical length screening for women with singleton pregnancy and history of prior spontaneous preterm birth (Mcintosh, Feltovich, Berghella, & Manuck, 2016) . However the issue of universal transvaginal ultrasound cervical length screening for a low risk singleton pregnancy for prediction of preterm birth is still debatable. Current Society for Maternal Fetal Medicine guidelines state universal cervical length screening

in singleton pregnancy without prior preterm birth is not a necessity. Even so, implementation of such a screening method is reasonable, and can be considered by individual practitioners as it is safe and reproducible.

CHAPTER THREE

RESEARCH HYPOTHESIS AND OBJECTIVES

3.1 OBJECTIVE

General Objective

- To establish the relation between cervical length and risk of spontaneous preterm birth in primigravida with singleton low risk pregnancy.

Specific Objective

- To define the cervical length at risk to develop preterm birth
- To ascertain the cervical length in normal population deliver at term

3.2 RESEARCH HYPOTHESIS

Primigravida with low risk singleton pregnancy with a cervical length less than 2.5cm has increased risk of spontaneous preterm birth.

CHAPTER FOUR

METHODOLOGY

This prospective research and analysis were organized and carried out in the Obstetrics Clinic Hospital Sultanah Nur Zahirah Kuala Terengganu. This prospective study was approved by the Clinical Research Centre of the Hospital Sultanah Nur Zahirah as well as Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) NMRR-17-3122-38181.

About 380 primigravida between 18 to 24+6 weeks gestation that fulfilled the criteria were offered to participate in this study. They were explained on the study and its objectives and those who agreed to participate were given an information sheet about the study for their own reference.

4.1 INCLUSION AND EXCLUSION CRITERIA

Primigravidae with singleton pregnancy, age 18 and above and between 18 to 24 + 6 weeks gestation was included in this study.

The exclusion criteria for this study were women with serious medical problems, congenital uterine anomaly, fetal demise or anomaly, history of cervical surgery, IVF pregnancy and patient on vaginal progesterone or cervical cerclage.

4.2 TERMINOLOGY

4.2.1 Preterm Delivery

Delivery which occurs between 22 and 37 completed weeks of gestation.

4.2.2 Cervical Length

Length of the cervix measured along the endocervical canal between the internal and external os.

4.2.3 Short Cervix

Defined as length of the cervix measured by transvaginal ultrasound less or equal to 20mm in women with no prior preterm delivery and less or equal to 25mm in women with a prior preterm delivery.

4.3 SAMPLE SIZE

In 2016, HSNZ has recorded a total delivery of 15831 out of which 497 are preterm birth. Therefore for this study, a sample size is selected to be 317 with confidence level of 95% with 5% margin of error. Including 20% dropout rate, making the grand total of 380 patients in this study.

4.4 STUDY PROTOCOL

Every primigravida who was suitable and followed the above criteria was counselled about the study during clerking at obstetrics clinic. They were informed regarding the aims, methods, and benefits of the study. Once they agreed to participate in the study, consent was taken and the confidentiality will be kept in check at all times during the study.

General history taking, physical and obstetric examinations was carried out as per hospital protocol. Ultrasound was done using an ultrasound machines LOGIQ V5 from GE Healthcare and Samsung H60. Routine transabdominal ultrasound was done to look for liquor volume, fetal parameters and normality. Additional transvaginal

ultrasound was done to measure cervical length. TVS was done in total duration of 5 minutes. Step in doing TVS was summarized in table 4.1. All the ultrasound measurements were done by the same ultrasonographer (principal investigator).

Patient continued their antenatal follow up at respective health clinic. Delivery time and mode of delivery were updated from patient's respective health clinic and HSNZ delivery record. The entire document was kept in patient record in computer (hospital information system). Only authorised person (medical practitioner involve in patient's management) can enter the patient's medical record.

Table 4.1 Technique of TVS of Cervical Length Measurement

- Procedure was explained to the patient and examination was done with the present of chaperone.
- Bladder was emptied and patient placed in dorsal position
- Condom covered probe was used and probe was inserted at vagina and directed into anterior fornix
- Excessive pressure must be avoided during TVS to prevent shortening of the cervix from the ultrasound
- Sagittal sonographic view of the cervix was obtained and image was enlarged two third of the ultrasound screen
- Entire endocervical canal should be visualized (internal os at flat angle and symmetric view of external os)
- Measurement was taken from the internal os to external os along entire cervical canal
- 3 measurements were taken and the shortest measurement was used
- Total duration of TVS was about 5 minutes

4.5 DATA ANALYSIS

Cervical length measurement and gestational age of delivery were analysed using IBM SPSS version 20. Results were described as mean ± standard deviation (±SD), or frequencies (number of cases) and percentages accordingly. Independent t-test was used to compare the numerical variables between the study groups. For comparing categorical data Chi-square (X^2) test were used. P value of less than 0.05 (p value < 0.05) was considered as statistically significant. Linear regression is used to look for correlation between CL and PTB while receiver operating characteristics curve analyse the ability of CL to predict PTB.

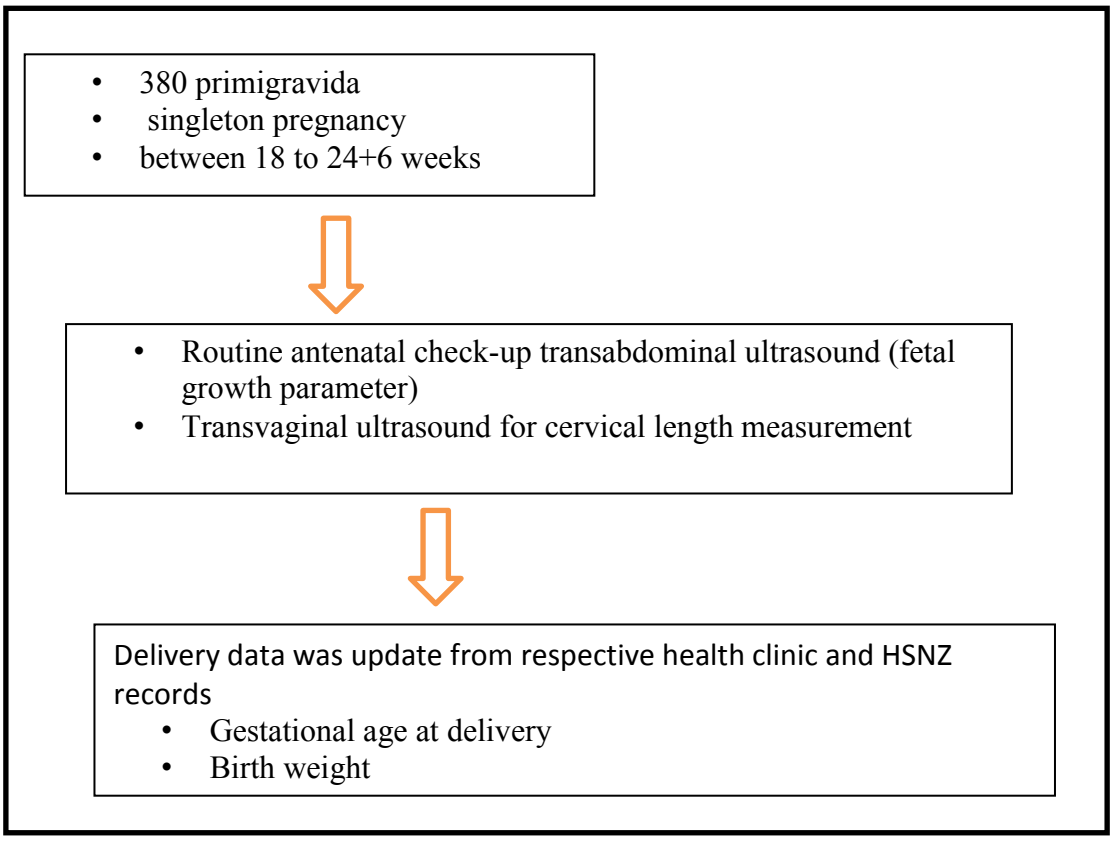

Figure 4.1 Flow chart of patient recruitment and test procedure

CHAPTER FIVE

RESULT

Figure 4.1, shows the flow chart of patient recruitment. 380 primigravidae recruited in this study from June 2018 until November 2018. 380 primigravidae was recruited and undergoing routine second trimester ultrasound. A total of five patients were excluded from this study due to the following causes: one fetal demise, two induced preterm for medical reason, and another two were induced for PPROM. For statistical analysis, 375 primigravidae fulfilled the inclusion criteria. The demographic characteristics of the patients are demonstrated in table 5.1.

Table 5.1 Patient's Clinical Characteristic Data

Characteristics	PTB (n=18)	Term birth (n=357)	P value
Maternal Age (years) (mean ±SD)	26.67 ± 3.4	27.46 ± 4.6	0.36
Gestational Age during scan (weeks), (mean ±SD)	21.06 ± 1.51	21.55 ±1.58	0.19
Gestational Age at delivery (weeks), (mean ±SD)	34.72 ± 3.23	38.56 ± 1.01	< 0.001
Cervical length (cm), (mean ± SD)	3.79 ± 0.93	4.36 ± 0.56	< 0.001
Birth weight (kg), Mean (SD)	2.22 ± 0.62	3.43 ± 0.72	< 0.001

There were no statistically significant differences in maternal age, gestational age during scan between the group that delivered at term and preterm group. The mean maternal age of the preterm and term groups were 26.67 ± 3.4 and 27.46 ± years respectively (P =0.36). Spontaneous delivery before 37 weeks occurred in 18 women (4.8%). The mean gestational age during scan was not statistically different between the group of women delivered at term (21.06 ± 1.51) and the preterm group (21.55 ±1.58).

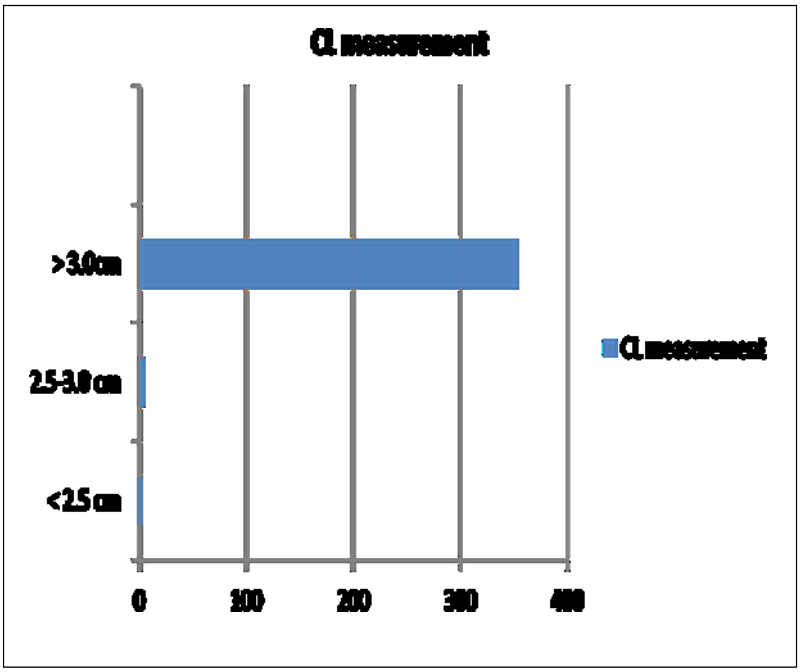

Figure 5.1 Cervical Length Measurement

Figure 5.1 shown the Cervical Length Measurement of 375 patients screened, 369 was found to have cervical length >3cm, four patients between 2.5-3cm and two patients with cervical length <2.5cm.

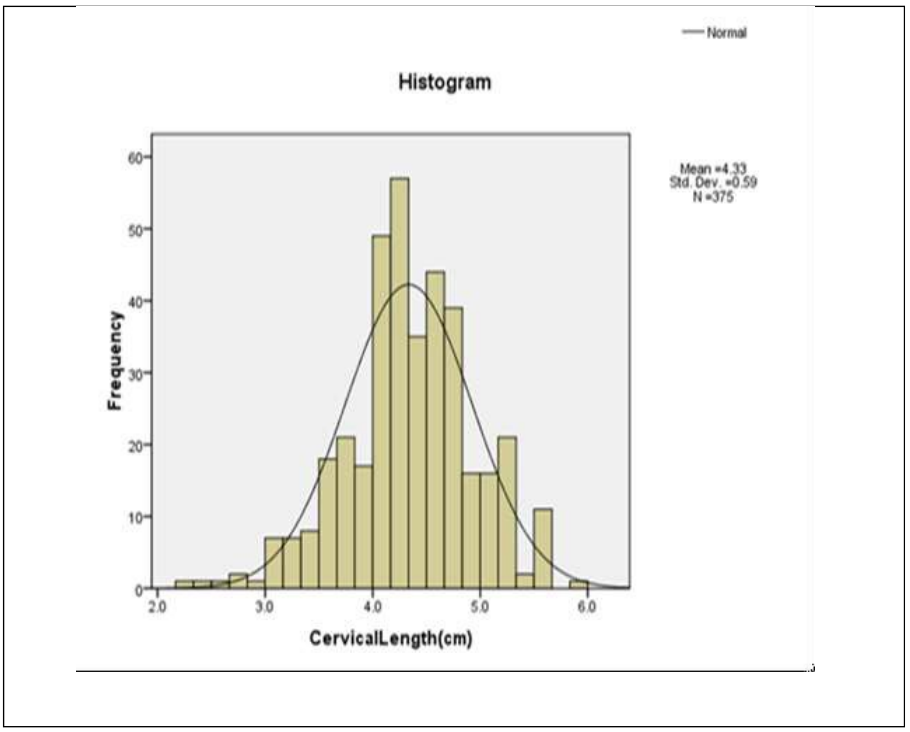

Figure 5.2 Histogram on Distribution of Cervical Length Measurement

The mean cervical length in 2nd trimester in primigravida was 4.3cm and this data was normally distributed.

Table 5.2 Cervical Length Measurement and Time of Delivery

Cervical length	< 34 weeks (n=1)	34-36 weeks (n=17)	37 and more (n=357)
>3cm		16	353
2.5 – 3 cm			4
<2.5cm	1	1	

The percentage of preterm birth < 37 weeks was 4.8%. Birth < 34 weeks occurred in 50% of <2.5cm cohort and it was statistically significant ($p < 0.001$).