"ROLE OF CERVICAL LENGTH EVALUATION WITH TRANSVAGINAL ULTRASOUND FOR PREDICTION OF PRETERM DELIVERY IN LOW RISK PREGNANCY- A PROSPECTIVE STUDY"

By

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IN

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Under the guidance of

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ABSTRACT

BACKGROUND: Preterm birth (PTB) is estimated to affect approximately 13 million births worldwide as per the censes of year-2005 which accounts to 9.6% of all births. India is one among the top 10 countries with the greatest number of preterm births - 35,19,100 preterm births every year[4]. Transvaginal ultrasound (TVU) measures various cervical parameters in the prediction of preterm birth. Cervical length < 25 mm is considered as the best cervical parameter with a good predictive accuracy for preterm birth in most populations.

OBJECTIVES:

PRIMARY OBJECTIVES:

1. To study the role of cervical length measurement in predicting preterm labour by Trans vaginal sonography (TVS).
2. To measure cervical length and follow up cases to study the fetal outcome.

SECONDARY OBJECTIVE :

1. To study the efficacy of TVS in evaluation of cervical length.

MATERIALS AND METHODS :

Single Centre prospective study was conducted on one hundred and thirty four low risk single ton pregnant women between 16 - 24 weeks of gestational age after fulfilling the selection criteria and recruiting for the study. The exclusion criterias were severe anemia, heart diseases, previous history of surgery on cervix (cervical dilatation, conisation), multiple pregnancy, prior preterm birth and polyhydramnios. After emptying the bladder transvaginal ultrasound scanning was done with high

frequency endovaginal probe (5-7Mhz) covered with a condom and it is guided into the anterior fornix of vagina. Sagittal long-axis view of endocervical canal along the entire length is obtained and the length of cervix from external to the internal os is measured. Atleast three measurements should be obtained and the best shortest measurement in millimeters is recorded. Transfundal pressure should be applied for 15 seconds and cervical length is obtained again and other cervical changes are also noted. The cases are followed till delivery and outcome is noted.

CONCLUSION :

Transvaginal sonography when performed between 16 - 24 weeks of gestational age could identify all the women having short cervical length and also with other changes of cervix. Out of 134 study group of low risk women, 8 women had preterm birth which accounts to the overall incidence of 5.9%.

6 women out of the 12 women with short cervical length (<25mm) had preterm birth which accounts to the incidence of 50% and sensitivity of 75%. Using a cervical length threshold of 25 mm and spontaneous preterm birth before 37 weeks' of gestation as the reference standard, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of our study are 75%, 95.2%, 50%, 98.4%, 94% respectively. Among the 134 newborns, majority of the admissions (14) were due to birth asphyxia followed by meconium aspiration syndrome (11). Others admissions were due to IUGR, hyperbilirubinia and low birth weight. No perinatal mortality was noted in the immediate first week of birth.

Keywords: Preterm Birth, Cervical length, Transviginal, Ultrasound.

LIST OF ABBREVATIONS:

TVU	- Transvagial Ultrasound
CL	- Cervical length
PTB	- Preterm birth
BW	- Birth weight
TVS	- Transvaginal Sonography
TAS	- Trans abdominal Sonography
MAS	- Meconium Aspiration Syndrome
LBW	- Low Birth Weight
IUGR	- Intra Uterine Growth Restriction

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INTRODUCTION

The average duration of normal human pregnancy is 267 days after conception or 280 days or 40weeks calculated from the first day of last normal menstrual period.Preterm birth is defined by WHO as the one that occurs after 20 weeks of gestation and before completion of 37 menstrual weeks of gestation regardless of birth weight[1](BW).

65Preterm birth (PTB) is estimated to affect approximately 13 million births worldwide as per the censes of year-2005 which accounts to 9.6% of all births.Africa and Asia accounted for almost 11 million preterm births[2].Higher preterm birth rates are recorded in Africa (11.9%) and North America (10.6%) and lower rates in Europe(6.2%)[1].According to thereviewed version of WHO - november 2016, each year, 15 million babies are born preterm.This accounts to more than 1 in 10 babies. Among children of age less than 5 years, prematurity is considered as the prime cause of death.[3] Whencompared with other causes, preterm birth accounts for large number ofcomplications related to newborn and infant death.India isone among the top 10 countries with the greatest number of preterm births - 35,19,100 preterm births every year[4].

Preterm labour is defined by WHO as the onset of labour before 37 completed weeks of gestation (or) 259 days of pregnancy. The lower limit of the gestational age varies from 20 -28 weeks[5]. Every year, nearly 1 million children die with the complications of preterm birth (2013). Across184 countries, preterm birth rate is in between 5% to 18% of new born babies. In India, every year 27 million babies are born (2010 data),among them 3.5 million babies are born premature.[6]

The onset of labour can be determined by documented uterine contractions (atleast one every 10 min) and ruptured fetal membranes or documented cervical changes with an estimated cervical length of less than 1cm (or) cervical dilation of more than 2 cm. Threatened preterm labour is diagnosed when there are documented uterine contractions but no evidence of cervical changes. Despite of these apparently clear definitionsand because the suspected preterm labour needs early intervention clinicians usually make the diagnosis before just discussed criteria are met. Hence reported incidence of threatened preterm labour is greater than the actual preterm labour (at least double).

When the preterm labour is being discussed, a glance should be given on certain terminology and definitions, as they are interlinked. Based on the gestational age preterm birth is inturn divided as

- Early preterm - Those who deliver before 33 weeks 6 days.
- Late preterm - Those who deliver between 34 and 36 completed gestational weeks.

Gestational age & birth weightare related by these terms

- Small for gestation– Birth weight below 10^{th} percentile for gestational age.
- Appropriate for the gestational age – Birth weight between 10^{th} and 90^{th} percentile.
- Large for gestational age – Birth weight above 90^{th} percentile.

Thus infants born before term can be small/large for GA but still fit into the definition of preterm.

- Low birth weight (LBW) refers to neonates weighing between 1500 to 2500 grams
- Very low birth weight (VLBW)refers to those between 500 to 1500 grams
- Extremely low birth weight (ELBW)refers to those between 500 to 1000grams.

The gestational boundaries of 20 and 37 weeks are historical and not scientific.[7].

Risk Factors for preterm labour are prior preterm birth, priorconization, polyhydramnios, short cervix, placental abruption, placenta previa and uterine malformations. Apart from the clinical manifestations of preterm labour like persistent contractions, intermittent abdominal crampings,pelvic pressure, vaginal bleed,various tests can be performed for diagnosing preterm labour. They include sterile speculum examination to assess the pH of the cervical secretions, fern pattern and to obtainfibronectin swabs and cervical and vaginal cultures, digital examination of cervix to assess the effacement and dilatation of cervix, transabdominal ultrasound and transvaginalultrasound examination of cervix.Cervical ripening and decidual activation are the other features of parturition which can be tested to improve the diagnostic accuracy of preterm birth.[8,9]Both thesetests helpthe diagnosis primarily by reducing the false positive results. A negative fibronectin test in women with symptoms before 34 weeks of gestation with cervical dilatation less than 3 cms rules out the possibility of preterm labour.

NEED FOR THE STUDY

Preterm birthpossess a major health burden to the society due to its long - term morbidity, perinatal mortality and high financial expenditures associated with it. It is responsible for more than half of all neonatal deaths.[10] Various factors account for the rise in the rate of preterm birth like socioeconomic conditions, cervical incompetence, previous preterm birth, smoking. Factors related to pregnancy that increase preterm birth rate include polyhydramnios, multiple gestation, uterine anomalies, vaginal bleeding and excessive uterine contraction.

The gestational age at birth is inversely related to the morbidities associated with preterm birth and perinatal mortality. Respiratory distress syndrome, intraventricular hemorrhage, bronchopulmonary dysplasia, retinopathy, sepsis, necrotizing enterocolitis are the various morbidities associated with preterm birth. Not only the baby which is born preterm, but the entire family bears the burden of its preterm birth in various ways like psychologically, medically, financially, socially. If an infant is born preterm the risk of death in the first year of life is 40 times greater compared with an infant born at term.[12] Infants born preterm represent half of the children with cerebral palsy, one third of those with abnormal vision, one quarter of those with chronic lung disease, and one fifth of children with mental retardation. Even in their adulthood the ones with preterm birth pose various struggles in their day to day life like lower IQ status and thus low education levels, behavioral problems, reproductive problems and higher incidence of preterm birth in their offspring. Thus keeping in view of all these hazards it is essential to recognize women at increased risk of preterm birth.[12]

The various pathological changes which lead to preterm birth can be determined at their initial stages by evaluation of the cervix. The most important factor of preterm birth that can be quantitatively assessed is cervical length. Previously, cervical length (CL) was assessed by digital examination of cervix. It being subjective, varies between examiners and cannot assess the true anatomic length. Transvaginal ultrasonographic measurement is an effective and objective way of measuring the cervical length. When compared with transvaginal ultrasound measurement of cervix, digital examination is considered inferior because it cannot measure[13,14] the cervical length beyond the vaginal fornices unless there is two cm or more of dilation

Since 1980s several studies were done on transvaginal ultrasound (TVU) to measure various cervical parameters in the prediction of PTB. Cervical length < 25 mm is considered as the best cervical parameter with a good predictive accuracy for preterm birth in most populations.Betweeen 14 to 34 weeks of gestational age transvaginal ultrasound (TVU) measurement of cervical length (CL) is considered to predict preterm birth (PTB) more accurately. But cervical length shortening during other gestational ages also leads to PTB.[15] Transvaginal sonagraphic measurement of CL, predicts preterm birth not only in asymptomatic low-risk women but also among those presenting with threatened preterm labor. Even though TVU carries the advantage of identifying short CL and predicting preterm birth earlier, it also has high false-positives.

OBJECTIVES OF THE STUDY

PRIMARY OBJECTIVES:

3. To study the role of cervical length measurement in predicting preterm labour by Trans vaginal sonography (TVS).
4. To measure cervical length and follow up cases to study the fetal outcome.

SECONDARY OBJECTIVE :

2. To study the efficacy of TVS in evaluation of cervical length.

REVIEW OF LITERATURE

Dennis JG et.al studied various literature and recent advances regarding the use of cervical length in the prediction of preterm birth and came to a final conclusion that cervical length measurement by transvaginal ultrasound as the best, reliable, safe, valid and well accepted procedure. At 16 to 24 weeks of gestation, cervical length less than 25 mm is identified as a reliable marker in identifying those at increased risk of preterm birth. Cervical length is inversely related to the risk of preterm birth. The risk rate goes even higher if shortening starts at earlier periods of gestation. Pregnant women with a prior history of preterm birth or a early trimester loss can be benefited by ultrasound - indicated cerclage if they develop cervical length < 25mm when measured by transvaginal ultrasound at 16 – 23 weeks of gestation. Thus, in addition to the prediction of preterm birth at an earlier stage cervical length assessment by trans vaginal ultrasound also helps in preventing further complications of preterm birth [16].

Moroz LA et al. studied 2,695 pregnant women between 20-33 weeks of gestation and followed them till delivery by conducting serial transvaginal ultrasound - cervical length measurements to study predictors of preterm birth. They observed that in pregnant women with shorter cervixes, a 3% rise in the odds of spontaneous preterm birth was seen with every 1mm shortening of cervical length between the ultrasounds done at various gestational ages. Change in cervical length was associated with spontaneous preterm birth for women with cervical length less than 25 mm. After controlling age, race, BMI, use of tobacco, and fetal fibronectin test status association between spontaneous preterm birthand change in cervical length remained significant. Thus, in those women diagnosed to have a short cervix sono- graphically,

spontaneous preterm birthis associated with the rate of change in cervical length, which is independent of fetal fibronectin test and other important risk factors for spontaneous preterm birth [17].

Barber MA et al. have measured cervical length in 2351 women between 18 - 22 weeks of gestation. Preterm birth was categorized as before 37 weeks, before 34 weeks, and before 30 weeks. In assessing preterm birth, the specificity, sensitivity, positive and negative predictive values of cervical length were 98%, 26%, , 63.6%, 93.57% for the 3rd percentile; 97%, 34%, 51%, 94% for the 5th percentile; and 92%, 39%, 31% and 94% for the 10th percentile. But cervical length measurement at early period of gestation is recommended in all asymptomatic pregnancies. Till 18 weeks of gestation, cervical length is not considered as a reliable predictor of PTB. Hence cervical length measurement by transvaginal ultrasound when done during 18 - 22 weeks of pregnany helps in identifying asymptomatic women at risk for preterm delivery[18].

Vaisbuch E et al. had conducted a study with 109 asymptomatic pregnant women who had a cervical length ≤ 15 mm at 14 – 24 weeks of gestational age. They have excluded women with cervical dilatation of > 2 cm , multifetal gestation, cervical cerclage. They divided the study population based on the gestational age at diagnosis (<20 weeks POG vs. 20–24 weeks POG) and also based on cervical length (≤10 mm vs 11–15 mm). They have studied diagnosis to delivery interval and preterm birth at < 28 and < 32 weeks of gestation as the main outcome variables. At the time of diagnosis of a short cervix, before 20 weeks and between 20 –24 weeks, the median gestational age was 18.9 and 22.7 weeks. Higher preterm birth rate was seen in women diagnosed before 20 weeks i.e, <28 weeks (76.9% vs. 30.9%; P < 0.001) and at < 32 weeks (80.8% vs. 48.1%; P=0.004) and a shorter diagnosis to delivery

median interval (21 vs. 61.5 days, P=0.003) than those diagnosed at 20–24 weeks of gestation. Patients who had a short cervical length at < 20 weeks of gestation had higher rate of amniotic fluid sludge when compared to those pregnant women between 20 and 24 weeks (92.3% vs. 48.2%; P < 0.001). Thus, they concluded that those women who remained asymptomatic and who had a short cervical length (≤15 mm) detected prior to 20 weeks of gestation were reported to have a higher rate of preterm birth those women detected at 20 - 24 weeks of gestation[19].

Honest H et al. studied 9 different databases which included 31,577 pregnant women. They divided the study population into two subgroups - symptomatic and asymptomatic. 13 studies in symptomatic and 33 studies in asymptomatic women were done. They observed that transvaginal ultrasound can identify women at higher risk of spontaneous preterm birth. Wide variations were reported in these studies like gestational age at testing, threshold of abnormality definition and reference standard definition as these can affect the accuracy of transvaginal ultrasound in predicting spontaneous preterm birth. The most commonly reported sub-group was testing of asymptomatic women at < 20 weeks of gestation using a threshold cervical length of 25 mm with spontaneous preterm birth before 34 weeks gestation as the reference standard. Among asymptomatic women, cervical length assessment and funneling, whether used in combination or alone, help in predicting spontaneous preterm birth. But among symptomatic women, transvaginal ultrasound measurement of cervical length was not accurate in predicting spontaneous preterm birth. Thus, among symptomatic women with this limitation the degree of funneling was observed to be predictive of spontaneous preterm birth [20].

Crane J .M. J et al. studied 2,258 women by using a common cervical length of 25mm or less. Six studies had 663 women with a prior history of spontaneous

preterm birth. Cervical length at <20 weeks had LR+ = 11.30 and at 20–24 weeks had LR+ = 2.86 which was considered to be at a higher level in comparison with the LR of the standered levels which correspond to < 25mm. Only limited data was available regarding the use of cervical length at > 24 weeks in this group with 42 pregnant women. In those who had undergone excisional cervical procedures, cervical length at < 24 weeks was predictive of spontaneous preterm birth at < 35 weeks (LR+=2.91) when compared to cervical length > 24 weeks. In the study of 64 women with uterine anomalies, cervical length was predictive of spontaneous preterm birth at < 35 weeks (LR+=8.14). Thus in asymptomatic high-risk women transvaginal ultrasound measurement of cervical length is predictive of spontaneous preterm birth at < 35 weeks. But this is not applying for prediction in women after 24 weeks of gestation, with prior history of spontaneous preterm birth and in those with uterine anomalies[21].

Ozdemir I et al. studied 152 asymptomatic singleton pregnancies at 10 - 14 and 20 – 24 weeks of gestation and assessed their cervical length by transvaginal ultrasound. Their spontaneous preterm delivery rate was 10.5%. They recorded a mean cervical length of 40.5 and 37.1 mm at 10 – 14 and 20 – 24 weeks of gestation. No significant difference in the cervical length was observed at 10 - 14 weeks of gestation between term deliveries (40.9 mm) and preterm deliveries (38.6 mm). But the cervical length of pregnant women at 20–24 weeks who had preterm deliveries (28.4 mm) was significantly shorter than those of term deliveries (37.8 mm) (P < 0.001). Cervical length shortening was prominent in those who had premature delivery (38.6 mm to 28.4 mm) than those who had term deliveries (40.9 to 37.8 mm). Thus, cervical length measurement at 20 – 24 weeks of gestation in asymptomatic singleton pregnancies was helpful in identifying women who are at high risk of preterm delivery. But in contrast, cervical length assessment at 10 –14 weeks of

gestation was identified as not a very good and sensitive predictor of preterm birth. They observed that the mean cervical length gradually tapered from initial to the next scan and there is a high risk of preterm delivery in those who had a more faster cervical shortening[22].

Berghella V et al. have conducted study to identify the role of transvaginal ultrasound in screening pregnant women for preterm birth based on cervical length measurement. They have included all pregnant women between 14 to 32 weeks period of gestation taken from various randomized controlled trials. Among all those trials, 12 were identified and out of them 5 were found to be eligible according to their criteria. Three trials had singleton pregnancies with preterm labour; one had singleton pregnancy with preterm premature rupture of membranes; one had twin pregnancies without or with preterm labour. Based on the results of these studies they came to the conclusion that further research is required to be done focusing on specific populations separately (twins vs single ton pregnancies); symptoms (preterm labour symptoms present or not present), outcomes of pregnancy including perinatal and maternal and cost-effectiveness analyses. This is because no predominant association was found among the symptomatic women between the results of TVU cervical length and incidence of preterm labour at less than 37 weeks of gestation. Thus for easy evaluation, they advised the future studies to have a clear cut protocol to manage pregnant women depending on the results of transvaginal measurement of cervical length[23].

Jasmina Begum, Ashok Kumar Behera conducted a study in fifty one women to evaluate cervical length by transabdominal and transvaginal ultrasonography at 14-24 weeks of gestation in asymptomatic women for predicting women at risk of

preterm delivery and to find out the one method which is more accurate of the two. Women with cervical incompetence, multiple gestation, maternal medical diseases, previous cervical surgery were excluded. Each woman underwent a transabdominal and transvaginal ultrasonographic cervical length measurement and the period of gestation at delivery in these women was then correlated with sonographic findings. On analysis, prediction of risk of preterm delivery by cervical length cut off value on the basis of the median at earlier weeks, 35 mm for transabdominal and 30 mm for transvaginal sonography, it was observed that transabdominal sonography with a sensitivity of 63.15% and specificity of 71.8%, predicted relative risk of 2.47 which was not significant (P <0.1) but transvaginal sonography with sensitivity of 78.9% and specificity of 81.2 predicted relative risk of 5.35 which was significant (P <0.001). They concluded that transvaginal ultrasonography seems to be the optimal method for assessment of cervical length in the second trimester and for screening for spontaneous preterm delivery[24].

Hernandez-Andrade et al. Used transabdominal and transvaginal ultrasound (US) and conducted a study on 220 pregnant women. They studied the accuracy of transabdominal ultrasound in diagnosing women with cervical length < 25mm. Transabdominal ultrasound could identify only 43% (n =9) of women who had a short cervical length. They found that transabdominal ultrasound overestimated cervical length by 8 mm among pregnant women who had short cervix and under diagnosed 57% of cases. Hence concluded that cervical length cannot be measured accurately by transabdominal ultasound among those who have a short cervical length as it overestimates cervical length among them and further transvaginal ultrasound is needed. Transvaginal ultrasound has to be utilized to diagnose women with short cervical length as a primary modality. It prevents the under diagnosing of shorter

cervical length and identifies various other cervical changes like sludge which cannot be diagnosed by transabdominal ultrasound accurately and relied upon. 13 women with funneling and 6 women with sludge were identified with transvaginal ultrasound whereas only 3 women with funneling and one women with sludge were detected by transabdominal ultrasound. Primary prevention and effective treatment of preterm birth cannot be provided to women with short cervical length due to the under diagnosis of cervical length by transabdominal ultrasound [25] .

Antsaklis P et al. Conducted a meta-analysis of current available literature to know the relationship between risk of preterm birth and cervical length. After assessing various cervicometry findings in the first and second trimesters, they came to the conclusion that for the prediction of preterm birth, the cervical length measurement at 11 - 14 weeks of gestation is not well defined yet. But this is concluded from limited studies. Newer studies proposed that promising results for prediction of the preterm birth can be obtained by measuring the endocervical length and by avoiding the length of the isthmic part. Further more research is required to assess if transvaginal ultrasound before 14 weeks can give any information regarding the individual risk of preterm birth and if at that particular gestational age, cervical length of women having preterm birth will have any differences with those delivering at term[26].

Celik E et al. have conducted a prospective observational study in 58,807 singleton pregnant women during the period between January 1998 and May 2006. They measured the cervical length of these women using transvaginal ultrasound between 20 to 24 weeks of gestation during the routine antenatal checkups. Results of extreme, early, moderate and mild spontaneous preterm birth rates were obtained as 0.23%, 0.24%, 0.57%, 2.93%. Spontaneous preterm birth was best predicted by

cervical length. Obstetric history aids further in its prediction. Considering the screen-positive rate to be 10%, sensitivity of 80.6%, 58.5%, 53.0% and 28.6% was obtained for combined model of cervical length and obstetric history for extreme, early, moderate and mild spontaneous preterm birth. Thus their study concluded that in the routine antenatal checkups, antenatal history taking should be combined with cervical length screening by transvaginal ultrasound. Preterm birth rate also its associated mortality and morbiditycan be significantly reduced by this combined approach[27].

Friedman MA et al. studied cervical length of 1,217 women by transvaginal ultrasound during regular antenatal checkups. Before performing transvaginal cervical length measurement, cervix was measured transabdominally before and after voiding in each patient. Based upon the sensitivity and specificity obtained from their studies they concluded that transabdominal measurement of - cervical length screening, will successfully identify very low risk women for short transvaginal cervical length. Thus, transabdominal ultrasound screening may decrease the burden of universal cervical length screening significantly by allowing 40% of women approximately to avoid transvaginal ultrasound. But in order to prove the high sensitivity of transabdominal ultrasound screening, 60% of patients approximately will need transvaginal ultrasound measurement of cervical length [28].

According to O'Hara S et al. The best method for accurate measurement of maternal cervix is transvaginal ultrasound and the shortened cervical length is a strong predictor for preterm birth. There are not many studies till date to compare the transabdominal ultrasound and transperineal ultrasound approaches for cervical length measurement to the transvaginal ultrasound measurement of cervical length approach in the mid-trimester. There is conflicting data to include transvaginal approach in

common practice for measuring the maternal cervix using in women who are considered to be at a historically 'low risk' for PTB in their pregnancy and hence further research is needed. The accurate measurement of cervical length in mid trimester of pregnancy helps in prolonging the pregnancy to more than 34 weeks. There have been conflicting studies in preferring transvaginal over transperineal for imaging cervix in pregnancy which were based on feedback from patients. Thus, feedback from patients plays major role in confirming these early reports in different studies comparing different measurement approaches[29].

Lim K et al. Studied various literature in the PubMed searches and the Cochrane Library up till 2009 December and came to a conclusion that cervical length measurement by transvaginal ultrasound as a effective, safe and acceptable technique in predicting the high risk of preterm birth. Transperineal route is used in cases who do not prefer transvaginal examination. Unnecessary interventions can be prevented among those at high risk of preterm birth if their results are reassuring. But, the available present evidence does not support regular use of transvaginal ultrasound for measurement of cervical length in low-risk pregnancies[30].

Hof M V et al. Studied various reviews of bibliographies in identified articles and several medline searches. In their study they analyzed that cervical length measurement by transvaginal ultrasound as effective and safe procedure among selected pregnant women for assessing cases at high risk for preterm delivery. Transvaginal ultrasound measurement of cervical length is found to have good (class B) evidence in identifying pregnant women at high risk of preterm birth. Its high negative predictive value provides a good advantage in proper assessment cervical length among the pregnant women at low risk and further aids in avoiding unnecessary interventions for women found to be low risk. However, the present

available evidence is not sufficient to advice for routine prenatal transvaginal ultrasound screening of cervical length. Randomized trials are required further to identify if routine interventions will have any effect on maternal and perinatal outcomes, even though the normal results aids in avoiding unnecessary interventions, given cervical shortening[31].

Preterm labour is defined by WHO as the onset of labour after the viability of gestation period (20 - 28 week, depending on definition) and before 37 completed weeks or 259 days of pregnancy[32-34].

Threatened pretem labour is diagnosed when there are documented uterine contractions but with no evidence of cervical changes.

Preterm birth - Epidemiological Factors :

There are various maternal and fetal risk factors which account for the preterm birth.Preterm birth is not always spontaneous and not all spontaneous onsets of preterm parturition will result in preterm birth.Manifestations of spontaneous preterm parturition are cervical ripening and softening, decidual activation / uterine contraction.Among these changes, the initial evidence which suggests the start of parturition is cervical softening[35].

The risk factors which play role in the spontaneous onset of preterm labour are explained below

Genital tract infections

Cervical and vaginal infections have a major role in the onset of preterm labour.

Lactobacilli is predominant organism present in the lower genital tract.

When these predominant lactobacilli are replaced by anaerobic gram negative bacteria like Pronotelle, Bacteroids, Mycoplasma and Mobilunuous species largely, the ecosystem of vagina is altered and results in bacterial vaginosis (BV).

BV has a two fold increased risk of spontaneous preterm birth and the risk rate further increases if the BV is detected early in pregnancy.

Use of antibiotic for eradication of BV does not reduce the risk of preterm birth consistently.

Lower genital tract flora are commonly found in the placenta and membranes, amniotic fluid which includes Mycoplasma hominis, Ureaplasma urealyticus, Fusobacterium species, Peptostreptococcus, Bacteroids, Gardenella vaginalis species in women with intact membranes and spontaneous preterm labour.

The frequency of positive culture increases along with gestation from 60% at 23-24 weeks to 20 - 30% after 30 weeks.

Apart from the genital tract infections, UTI and intra-abdominal infections like appendicitis and pyelonephritis also lead to preterm birth. It occurs due to the release of tumor necrosis factors and interleukins by maternal macrophages which in turn trigger production of prostaglandins.[1]

Other infections

Alimentary tract and genitourinary tract are major areas of microbial colonization where host immunity acts locally to protect the body. Hence periodontal disease has high risk for preterm birth.

But periodontal care / Rx has no effect on reducing the risk of PTB.[1]

Congenital abnormalities of uterus:

Depending on the type of malformation, the risk of preterm birth range between 25 to 50%.

These are the mullerian fusion defects like uterine septum and others that result in preterm birth.

Classical examples of anatomic abnormalities of cervix causing preterm birth are seen in women exposed to diethylstilbesterol during intrauterine life and women who had / LEEP/ extensive conization.

Among them, most clinically significant abnormalities are septate and bicornuate uterus.

They have high incidence of spontaneous abortion (~27%) and the incidence of preterm birth varies between 16 to 20 % after 20 weeks of gestation.

Women who present with recurrent PTB's / abortion / malpresentation should be suspected to have congenital malformation of uterus.[1]

Abnormal Placentation:

One of the etiologic agents causing preterm birth is abnormal placentation. It is proved by histological examination of placenta which shows the underdevelopment of spiral arteries.

It is seen in 40% of women who had preterm birth in whom the spiral arteries have not acquired completely the necessary physiological changes of a normal gestation.

Other feature like placental infarcts, fibrosis, calcification, spiral artery thrombosis are also seen.

Doppler studies have proven that the incidence of preterm birth is grossly higher in women with abnormal Doppler in early weeks of gestation.

The most accepted hypothesis is utero-placental blood flow restriction which causes fetal stress, which in turn increases corticotrophin releasing hormone production and activation of renal pathways.

Cervical length (CL):

Cervical lengthmeasured by transvaginal ultrasound is related inversely to preterm birth. Cervical length< 25 mm at 22 to 24 weeks of gestational age has 6.5 times high risk of preterm birth before 35 weeks of gestational age and 7.7 times high risk of preterm birth before 32 weeks of gestational age when compared with those whose cervical length was more than 75th percentile.[36]

Progesterone supplementation can slow down the progression of cervical shortening and when started before 24 weeks of gestational age in women with / without a previous preterm birth, the risk can be reduced.[37]

Endovaginal ultrasound can identify changes in anatomy of cervix but is not helpful in identifying the pathological process causing the abnormality.

Thus the findings of endovaginal ultrasound are only suggestive of a short cervix but not diagnostic of incompetent of cervix.

Till date various studies have proved preterm cervical shortening as an active process.[35]

Nutritional factors:

Women with pre pregnancy BMI< 19.8 kg/m^{22} have reported to have an high risk of preterm birth.[38]

Smoking has a high risk of preterm birth.

Studies identified that consumption of 1 / > servings of fish per month would help women to have decreased rates of preterm birth when compared with women who never / rarely eat fish.[39]

Present pregnancy risk

Assisted reproductive techniques are associated with increased rate of preterm birth due to increased occurrence of multiple gestations but assisted reproductive techniques' are also associated with increased rates of preterm birth's in single ton pregnancy as well. Almost two fold high risk of preterm birth is seen in single tons conceived by various assisted reproductive techniques.[40] When women of multiple gestations conceived with assisted reproductive techniques were compared with women with multiple gestation conceived spontaneously , there was no difference in the risk rates of preterm birth, hence the reason for increased rates in single ton pregnancies is not clear. Super ovulation side effects, upper genital tract colonization of micro organisms, high stress levels in infertile couples and high birth defect rates have been proposed.

Ante partum hemorrhage and vanishing twins

The risk of preterm birth was observed to be more among women who had un explained per vaginal bleed after the first trimester and risk rate is proportional to the number of episodes

Pregnant women with high levels of unexplained maternal serum alpha fetoprotein with a vanishing twin were also identified to have increased rates of preterm birth.[1]

MULTIPLE GESTATIONS :

It is prime risk factor for preterm birth. The number of preterm birth's increase proportionally with increase in the number of fetus indicating that uterine over distention and fetal signaling are important base to initiation of early labour.

Delivery usually occurs before 37 weeks in > 50 % of twins. Among the twin gestations, chorionicity is a prime factor predicting any adverse outcome of pregnancy. Monochorionicity carries increased risk for neuromorbidity and necrotizing enterocolitis than di-chorionicity among the newborns. But among the monochorionic twins, what is the exact rate of excess preterm birth due to spontaneous versus induced is still not known.[1]

SPONTANEOUS PRETERM BIRTH -RISKFACTORS :[1]

- African Americans
- Unknown cause of bleeding during any trimester
- History of prior preterm birth
- Uterine anomalies
- Multi fetal gestation
- Assisted reproductive techniques
- Lower genital tract infection/ instrumentation
- UTI and bacteriuria
- Bacterial vaginosis

- STI – HPV, Trichomonalis, Gonorrhea, Chlamydia
- Periodontal disease
- Poor nutrition and low pre pregnancy BMI (<19.6)
- Low socioeconomic status/ income/ education
- High levels of stress
- Poor prenatal care

Placental Disorders

Placenta previa

Placental premature separation

Chronic/acute (preeclampsia) hypertension

Medical Disorders

Maternal HIV/ HSV

Obesity

Connective tissue disorders

Smoking

Asthma and chronic bronchitis

Seizures

Advanced maternal age

Thromboembolism

Fetal Disorders

Fetal Compromise

Chronic - Causes poor fetal growth

Acute - Causes fetal distress

Blood group alloimmunization

Birth defects

Polyhydramnios / Oligohydramnios

Hydrops fetalis

Fetal complications of multi fetal gestation

Ex: Growth deficiency, twin to twin transfusion syndrome

Sometimes preterm birth is indicated for several reasons of maternal and fetal origin as follows

Obstetrical risks in the present pregnancy

Preeclampsia

Prior uterine surgeries (ex: previous cesarean birth via classical / T shape uterine incision)

Diabetes, diagnosed before / during pregnancy

Cholestasis

Pathophysiology :

Preterm and term labour have common pathways which include increased cervical ripening, membrane rupture, uterine contractility leading to fetal prematurity and damage patho physiology of preterm labour[41]. Spontaneous labour at term is the result of physiologic activation the common pathway of parturition, but preterm labour is the result of the pathologic activation which in turn activates other components of the common pathway via similar or alternative mechanisms[42]. The common pathway of parturition includes anatomic, biochemical, immunologic, endocrine and clinical changes[43]. Studies regarding the anatomic and clinical events have been evaluated in detail, but immunologic, biochemical, endocrine events are not well understood.[43] There are several factors released in to the peripheral circulation and also within the uterine environment along with the changes of parturition. But till today, no single factor has been identified as the prime regulator which controls the parturition, and the debate still continues upon it.

The physiologic activation of the common pathway of parturition leads to spontaneous onset of preterm labour. This includes increased uterine contractility, cervical ripening and decidual / membrane activation. This is not the same with preterm labour as it is the result of pathologic activation of this pathway. The stimulus which initiates the process causes recruitment of each pathway asynchronously.

Asynchrony is identified clinically as

- Cervical insufficiency when the cervix is involved predominantly.
- Preterm uterine contractions when the myometrium is involved predominantly.

- Preterm premature rupture of membranes when the chorioamniotic membranes are involved predominantly. Preterm labour with intact membranes results from synchronous activation in the preterm gestation.

Even if the labour is described as a process of smaller duration, parturition is actually a lengthier process which has a preparatory phase for the key organs involved in the common pathway. This preparatory phase includes cervical changes for few weeks, increased myometrial contractility prior the start of labour, and presence of fetal fibronectin in the cervicovaginal mucous. This indicates degradation of extracellular matrix, indicating activation of the decidua and membranes.

In spontaneous preterm birth, preterm rupture of membranes and preterm cervical effacement and dilation in absence can be seen. It results from multiple etiologies presenting alone or in a combination.

Increased Uterine Contractions and Uterine Pressure :

There occurs a characteristic change in the intrauterine pressure pattern during the labour. Uterine contractures start initially as uncoordinated episodic form lasting few minutes but gradually acquire a coordinated pattern lasting for minimal duration and result in marked rise of intra- uterine pressure that finally effect delivery. It usually start at night, which suggests neural control. Inflammation also result in increased uterine contractions like maternal infection or any abdominal surgery. Decidua and the periventricular nuclei of the hypothalamus produce oxytocin, which indicates the endocrine and paracrine control over it. The magnitude of uterine contractions depends on the plasma concentration of oxytocin, which indicates that oxytocin plays a role in the circadian rhythm of uterine contractility.

Myometrial contractions are a hallmark of parturition, both at term and before term. During labour, the individual myocytes contract together as a functional syncytium. This increased coordination is induced by gap junction formation, which increases cell to cell communication. Gap junctions develop in myometrium before labour and disappear after delivery.[44] Connexin-43 is a gap junction protein produced in myometrium during term and preterm labour.[45] Before the onset of parturition, there occurs the transformation of contractures to contractions which is aided by increased expression of connexin-43 and gap junctions.[46] The main hormones of pregnancy like progesterone, estrogen and prostaglandins help in the formation of gap junction and connexin-43 expression.[47,48]

CERVICAL CHANGES DURING PRETERM BIRTH :

Cervix plays a prime role during parturition. Apart from it, even during the pregnancy it undergoes various structural changes to facilitate the passage of fetus during delivery. Cervix attains most of its tensile strength through the collagen, and viscoelasticity through the glycosaminoglycan's (GAGs). Extracellular matrix is composed of GAGs, the long unbranched polysaccharides. They maintain tissue hydration, viscosity and also the architecture of the extracellular matrix.

Cervical adaptation and remodeling is a complex process. Because the processes of term and preterm cervical ripening and dilation have been associated with various inflammatory events, inflammation is considered as the final common pathway of parturition.[49] This hypothesis was supported by data that demonstrated that in the absence of infection interleukin-6, interleukin-8 and monocyte chemotactic protein-1 were significantly elevated both in term and preterm cervical tissues.[50] As shown, asymptomatic women with intra-amniotic infection or inflammation had

higher degrees of cervical shortening and dilation. Thus, it is reasonable to assume that in some clinical circumstances, a short or a dilated cervix favors microbial invasion of the gestational sac via an ascending mechanism.[51] Structural support is provided by the tight junctions present in between the cervical epithelial cells which play role in regulating the fluid fluxes. Cervical epithelial functions include proliferation, maintenance of fluid balance, differentiation, protection from environmental hazards, and transport of solutes via paracellular tight junctions. The turnover of extracellular matrix is high in the cervix. The clinical implication is that presence in the cervicovaginal fluid of specific biomarkers may reflect activation of signaling pathways involved in premature ripening, cervical dilation, and premature birth.

Most of these biomarkers are part of the innate immunity defense mechanism of the cervix and are constitutively expressed in the cervical mucus.[52] Comprehensive survey of the cervicovaginal fluid proteome showed that calgranulin-A, calgranulin-B, azurocidin, insulin-like growth factor–binding protein-1 and defensins were found up regulated in the cervicovaginal fluids of women at risk for preterm birth. Their differential expression may mediate the process of leukocyte infiltration, which are involved in cervical remodeling. With respect to the profile of cervical inflammatory infiltrate, Holt and coworkers suggested that there might be differences between various mechanisms involved in triggering preterm birth.[53] The monocyte population dominated the progesterone withdrawal mechanism, whereas neutrophils governed the process of endotoxin - induced preterm birth.

But this differential expression of immune pathways is not seen in term labour. Genes responsible for the expression of various cytokines (Interleukin-6, Tumor necrosis factor -α, Interleukin-1β) were up regulated in the cervix of animals

with intra- uterine infection.[54] Increased expression of cytokines was not seen in term cervices but was present during postpartum period. These findings argue that, in the postpartum period, cytokines may play an important cervical reparative role or may confer immune protection. Premature cervical ripening occurs in multiple gestations and also is rarely seen in diethylstilbestrol-exposed women. Interleukin-8, prostaglandins and nitric oxideare released during amniochorion stretch have role in the control of cervical ripening. These mediators cause degradation of extracellular matrix of the cervix.

Estrogen causes collagen degradation and helps in the ripening of cervix. Progesterone has antiestrogenic effects and thus by administration of progesteron can delay or even reverse ripening. Further, cervical ripening can be induced by progesterone receptor antagonist. Nitric oxide (NO), acts as an inflammatory mediator and can cause cervical ripening .

Cervical ripening on clinical examination is assessed from softening and thinning of the cervix and on ultrasound cervical "funneling" and endocervical canal length shortening indicates cervical ripening. These changes of cervix proceed to preterm birth within a few weeks.

Decidual Membrane Activation :

Decidual activation infers to a complex set of pathophysiologic changes that cause separation of amniochorionic membranes of fetus from the decidua, bleeding, spontaneous rupture of membranes, activation of myometrial contractility, and expulsion of the placenta.

During gestation, chorioamniotic membranes gradually fuse with the decidua. Before delivery, biochemical and molecular changes occur that allow separation and expulsion of the fetal membranes. Fibronectins have multiple binding sites to permit cell binding and interaction with cytoskeletal organization to effect cell migration, adhesion, and decidual cell differentiation.[55,56] Detection of fetal fibronectin into cervical and vaginal secretions before preterm parturitions one of the most clinically useful biomarkers of preterm birth.[57] Elastase-induced release and degradation of the glycosylated cellular fibronectin (fetal fibronectin) diminishes the binding ability of this glycoprotein for components of the extracellular matrix, thereby facilitating separation of the fetal membranes from the decidua. Many of the molecular events responsible for decidual activation and abruption are inflammatory. The acute lesions of chorioamnionitis and funisitis (e.g. fibrin deposition, hematoma, hemosiderin-laden histiocytes compressed villi,) are frequently associated with histologic abruption.[58]

The most frequent histopathologic lesions suggestive of chronic decidual bleeding are infarction and necrosis, chronic deciduitis and villitis, spiral vessels with absence of physiologic transformation and large number of circulating nucleated erythrocytes, vascular thrombosis, and villous fibrosis and hypovascularity. The extra villous trophoblasts by penetrating the spiral arteries of uterus (without causing hemorrhage) enter into the maternal circulation, which is essential for the development of embryo into fetus. Any minor error in this highly controlled and synchronized mechanism at a molecular level near the maternal-fetal interface can increase the risk for hemorrhage leading to abortion, abruption, and stillbirth. The main histological feature of placental abruption is hemorrhage in the decidua basalis.[59]This hemorrhage is due to disarray in the pathologic processes damaging the vascular endothelium.

As per the analysis of the expressed decidual transcripts and proteins, there are different transcriptional profiles for each spontaneous, abruption-associated, infection-induced preterm delivery. Studies demonstrating that inflammatory reactions (dependent or independent of infection) can activate the coagulation pathways emphasize the important role of inflammation in decidual bleeding.[60] Cytokines (e.g- Inierleukin-1β,6) by acting on decidual vascular surfaces increase the expression of leukocyte interactive proteins such as E-selectin, P-selectin, intercellular adhesion molecule-1,vascular cell adhesion molecule-1. This phenomenon may lead to decidual neutrophil infiltration, vascular damage, access of coagulation factors (factor VII) to the perivascular adventitial tissue factor and generation of thrombin. Tissue factor ,the prime initiator of coagulation is present abundantly in the decidua.

Thrombin is released by various processes that lead to vascular disruption and the interaction of circulating factor VIIa with decidual cell membrane –bound tissue factor. This explaines that abruption and disseminated intravascular coagulation are strongly interlinked. The mechanisms responsible for the onset of myometrial contractions due to intrauterine hemorrhage and the specific role played by the thrombin have been defined.[61] Myometrial contractions can also be induced by in vitro by fresh whole blood transfusion and it can be partially blunted by hirudin, a thrombin inhibitor.

Among the genes responsible for the normal phenotypic and morphologic remodeling processes of the human decidua, the homeobox (HOX) gene family appears to be critical. In vitro, thrombin decreased gene expression of HOX A9, HOX A10, and HOX A11. Furthermore, thrombin decreases HOX A10 mRNA and protein levels. Interleukin-1β, a cytokine with important regulatory roles in prostaglandin

production,[62] mimicked the effect of thrombin on HOXA10 gene expression. These observations provide proof of the concept that two recognized mediators of decidual inflammation and preterm birth, thrombin and IL-1β may operate by reducing the expression of HOXA10 gene.

The inflammatory events that follow abruption can occur dependent on or independent of progesterone. Progesterone appears to create both a haemostatic and an anti- proteolytic milieu in the decidua. Using a primary cell culture experimental setup, Schatz and colleagues demonstrated that first-trimester decidua expresses tissue factor and plasminogen activator inhibitor-1 (PAI-1), which is considered a fast inhibitor of the primary fibrinolytic agent - tissue plasminogen activator (tPA). With injury to decidua, cytokines get released whichfurther increase the synthesis of Matrix metallo proteinases (MMPs) and vascular endothelial growth factor (VEGF).Additionally, tumor necrosis factor-α, Interleukins-1β,6,8,11 are also involved. Other cytokines such as granulocyte-macrophage colony–stimulating factor (GM-CSF), monocyte chemoattractant protein-1 and colony-stimulating factor-1 (CSF1), may be implicated in the regulatory process of decidual activation and bleeding.[62]

In addition to controlling the decidual homeostasis, progestins also inhibit the proteolytic activity of collagenases - matrix metallo proteinases 1 and 3.Because antiprogestins (e.g:RU486) reverse the progestin - inhibited expression of matrix metallo proteinases, an attractive hypothesis is that progesterone withdrawal may induce an increase in the decidual expression of MMP-1 and MMP-3, which would promote extracellular matrix and fibrillar collagen degradation, preceding bleeding, premature separation of the placenta, and preterm premature rupture if membranes.

The mechanism by which progesterone function is balanced in the setting of high maternal circulatory levels is unknown. Abruption-associated preterm birth is accompanied by reduced immunostaining for progesterone and thrombin inhibits progesterone protein and mRNA expression in cultured term decidual cells.Epidemiologic studies suggest that for some women, the recurrence risk for placental abruption is higher than the general background risk and that thromboembolic events occur more commonly among female relatives of women with placental abruption.[63]

Intrauterine infection, abnormal allograft reaction, allergy - induced causes, uterine ischemia, uterine over distention, cervical insuffienency and endocrine disorders are various processes implicated in the preterm parturition syndrome.

Intrauterine infection :

Preterm labour can also be induced by maternal systemic infections like pyelonephritis and pneumonia frequently

Intrauterine infection may induce PTB suggested by atleast three lines of evidence. First - Spontaneous preterm labour can be induced by systemic administration microbial products (bacterial endotoxin) or by intrauterine infection.

Second - Subclinical intrauterine infections are always result preterm labour and preterm birth in humans.

Third - Pregnant women with intra-amniotic infection or inflammation have an increased risk of spontaneous preterm birth later in that pregnancy.[64]

Microorganisms commonly seen in the fetal membranes and amniotic fluid infection are Ureaplasma urealyticum, Mycoplasma hominis, Gardnerella vaginalis, Streptococcus group (GBS), Bacteroides species, and Escherichia coli. Listeria monocytogenes is a much rarer participant. Infection accounts to 25% to 40% of cases of preterm delivery as per the histopathologic and microbiologic studies.[65]

Cultures cannot measure accurately the extent to which microbial pathogens are involved in the process. Approximately 13% prevalence of positive amniotic fluid cultures is identified in women with preterm labour, with additional instances infection that are identifiable using PCR techniques rather than culture. Reasons for this include prevalence of these organisms, their slow growth or prevalence to being cultured in conventional media, and their growth requirements.

The cornerstone of genomics-based detection methods are sequencing of full or variable regions of the bacterial 16S ribosomal RNA (rRNA) gene.[66] This gene is characterized by a high degree conservation and a clustering of the variable regions of the gene into discrete taxonomic units; the latter allows in depth characterization of species richness and the diversion of complex microbial communities.

Various cytokines and inflammatory factors that take part in host immunity are similar to those that play role in parturition. Thus, preterm labour is considered as a host defense mechanism to intrauterine infection where mother's survival is given prime importance and later to fetus survival. The most advanced stage of intrauterine infection is fetal infection. In 33 % of fetuses with positive culture and in 4% of those with negative cultures, fetal bacterimia was found in blood obtained by cordocentesis.

Role of Inflammation , stress in parturition - TERM AND PRETERM :

Increasing evidence suggests that parturition at term is a type of inflammatory process. It was first proposed by Liggins that cervical ripening as a inflammatory event, and this hypothesis is supported by data showing a profound leukocytic (macrophage and neutrophilic) invasion into the cervix during normal parturition.[67] Meanwhile, increased expression of cell adhesion molecules occurs in the myometrium, along with it chemotactic agents like pro inflammatory cytokines, Interleukin - 8 and leukocyte activation occurs in the peripheral blood.But still its has not been concluded whether these factors are just a epiphenomenon or the crucial events in the initiation of labour.

For normal term parturition in humans, complex biochemical and neurohormonal interactions among fetal, placental and maternal compartments has to occur which are reflected by the normal maturation of maternal fetal - hypothalamic - pituitary adrenal - placental axis. Stimulating factors for these events can be stress subsequent to malnutrition, vascular damage, infection , psychosocial factors[68].

In patients with spontaneous preterm delivery, placental histological changes associated with infection and ischemia induced fetal stress are more common than in controls with idiopathic preterm and term births. But hyperactivity of hypothalamo pituitary axis is related with maternal mood depression. Carriers of a polymorphism in the gene encoding for 11beta HSD - type -1 have a higher level of hypothalamo-pituitary axis activity and are more susceptibility to depression[69.]

Uterine Over Distension :

Uterine over distension as seen in cases of polyhydramnios and multiple gestation is reported to trigger preterm labour. Multiple gestation accounts for 12 to 25% of preterm deliveries.

Mechanical force activates protein kinase C and mitogen-activated protein kinases which further increase the expression of G protein and other substances that induce myometrial contraction. Progesterone blocks the stretch - induced gene in the myometrium. Mitogen - activated protein kinases mediate the expression of stretch-induced c-fos mRNA in cells of myometrium.

Stretch also has its effects on membranes. In vitro studies have demonstrated an increased expression of prostaglandin E2 (PGE2), collagenase, Interleukin - 8 and cytokine pre–B-cell colony-enhancing factor in response to the mechanical forces acting in distended uterus and also in cases of ruptured membranes[1].

Fetal Membrane Stretch and Term and Preterm Birth :

The human fetal membranes are complex tissues composed of specialized epithelial and mesenchymal cells present in an extracellular matrix which is composed primarily of collagen and proteoglycans. The prime structural components maintaing the mechanical integrity of the membranes are the predominating type I and III interstitial collagens.[70]A significant decrease is noted in the elasticity of membranes that ruptured before labour independent of gestational age. Several alterations in the membranes like altered structure of collagen, decreased collagen content and increased pro-inflammatory and collagenolytic activity are related to preterm premature rupture of membranes and preterm birth. In vitro, stretching of the fetal membranes induces collagenase activitywhich increases uterine contractions to the point of rupture and preterm birth. After exposure of the whole membranes and amnion cells to mechanical stretch, synthesis of pro-inflammatory cytokines like Interleukins-1β,8 are increased. Notably, expression of Interleukin-8 was upregulated in both amnion and chorion, but not in decidua.[71]

Altered Allograft Reaction :

Fetoplacental unit is one of the most successful semi-allograft in the nature. Few women who had spontaneous preterm labour had shown the features of chronic villitis in their histopathological examination of placenta which indicates placental rejection. In cases of preeclampsia, recurrent pregnancy loss and intrauterine growth restriction abnormal recognition and adaptation to fetal antigens is identified as one of the mechanisms.

Allergy-Induced Preterm Labour :

Preterm labour can be induced by allergy mechanisms (type I hypersensitivity reaction). Myometrial contractility can be induced by histamine and prostaglandins produced by mast cells present in the uterus. Uterine allergy is represented by high levels of eosinophils in the amniotic fluid of those with preterm labour .

Cervical insufficiency :

It is responsible for a wide spectrum of diseases like recurrent pregnancy loss and spontaneous preterm birth. The latter often presents with bulging of membranes even in the absence of significant uterine contractility or rupture of the membrane, as well as with precipitous labour at term. In most cases, cervical insufficiency represent pathologic entities apart from the primary cervical disease which lead to premature remodeling. Infection accounts for 50 % of cases who present with acute cervical insufficiency.[72]Rising evidence implicates that treatment for pre-invasive cervical carcinoma can be a risk factor for preterm birth. Treatments like cold knife conization and large loop excision are associated with an increased risk of preterm birth .Cold

knife conization has a greater effect on delivery before 30 weeks of gestation. The risk for prematurity is related to the depth of the excision, with an estimated 6% increase in risk for each additional 1 mm of tissue excised. Recent survey suggests that cervical pre-invasive disease and spontaneous preterm labour may share common risk factors but are not directly linked. Human papilloma viruses and other microbial infections in the cervix or defects in the immune response are the other common risk factors.[73]

Endocrine Dysfunctions

Estrogen induces cervical ripening before labour by increasing the uterine contractions. Progesterone is essential for myometrial quiescence and for inhibition of cervical ripening. Though there occurs no fall in levels of serum progesterone levels before parturition, inhibition of progesterone action can result in parturition. Increased expression of progesterone receptors PR-A relative to PR-B in uterine myometrium decreases the responsiveness of progesterone. This functional progesterone withdrawal can also be explained by activation of nuclear factor-kB in amnion which suppresses the progesterone function.

Gene-Environment Interactions

The extent to which the host immune system defends its own body when exposed to infectious environment is dependent on host's genetic makeup.[74] This is explained based on the association of bacterial vaginosis and preterm birth.[75] It is known that bacterial vaginosis is the predominant risk factor for spontaneous preterm birth. But treatment of bacterial vaginosis cannot prevent it. One explanation to it goes back to the genetic makeup of the women who has bacterial vaginosis. Those women with allele 2 of tumor necrosis factor (TNF) are at increased risk of

spontaneous preterm birth. Though both bacterial vaginosis and TNF-a allele 2 are known risk factors for spontaneous preterm birth, simultaneous presence of both is known to have increased risk of spontaneous preterm birth, than when they are present alone.

DIAGNOSIS OF PRETERM LABOUR

Recurrent pelvic symptoms like uterine contractions occurring at a frequency of six > / per hour, cervical effacement of 80 %, cervical dilation of 3 cm, bleeding and ruptured membranes are suggestive of preterm labour. When these symptoms last longer than an hour during the second half of pregnancy, preterm labour should be suspected. Other symptoms like increased vaginal discharge, pelvic pressure, preterm labour, backache also suggest preterm labour when they occur at a higher severity. Pathologic uterine contractility never occurs alone, it usually starts in combination with decidual membrane activation and cervical ripening. Usually, these two pathological changes tend to start before uterine contractions become evident clinically. Cervical resistance offered characterizes the uterine contractions as painless or painful.

Diagnostic Tests for Preterm Labour

Though there are various tests for prediction of preterm labour, cervical dilatation and effacement are more important. But they present a diagnostic challenge when cervical dilation < 2 cm and effacement < 80%. In such cases other features of parturition like decidual activation and cervical ripening are to be considered. Cervical ripening can be assessed by measuring of cervical length by transvaginal

ultrasound. Cervicovaginal fluid levels of fetal fibronectin are used to assess the decidual activation.[76,77]

ROLE OF ULTRASOUND IN PREDICTION OF PRETERM LABOUR:

Before proceeding to know the ultrasound image of cervix at different trimesters, it is essential to have a glance over the normal anatomical structure of the cervix. The cervix occupies the lower part of uterus, and is surrounded above by the uterine isthmus. The histological and anatomical junction of the fibrous cervical stroma and muscular uterus is the internal os. The small distance between the external and internal osis identified as the endocervical canal. As pregnancy advances, cervical canal undergoes physiological shortening, cervical length measurement by ultrasound was found to be a reliable marker for assessing the preterm birth. It is unlikely to have a preterm labour in symptomatic women when cervical length measured by endovaginal ultrasound is > / 30 mm .

Extensive and major research was made in the last decade with the ultrasound of cervix during pregnancy. Since then major advances took place to signify the role of ultrasound of cervix as screening test in the prediction of preterm labour.

Ultrasound measurement of uterine cervical length can be useful in evaluating the likely hood of early labour in those known to be at risk for prematurity.

The specificity and sensitivity of this measurement was not high enough in most studies to record its use in low risk gravida.

However radiologists from American college recommends that the lower uterine segment and cervix can be seen in the second trimester as part of the obstetric ultrasound inspite of its low specificity and sensitivity.

But ACOG does not endour the routine ultrasound measurement of cervical length in low risk patient.

With this broader introduction about the need of ultrasound for cervical length measurement we will know have a short overview on various methods / techniques of ultrasound that can be used for the assessment of cervical length and to conclude the best technique among all other.

TECHNIQUES – ULTRASOUND OF CERVIX

Transabdominal Ultrasound (TAU)

Transabdominal Ultrasound goes way back to 1970's when the initial attempts were made in examining the cervix. But this technique carries various pros and cons which affects its reliability / validity like

- Fetal parts (after 20 weeks) can obscure the cervical visualization.
- Increased distance between the probe and cervix results in decreased quality of image.
- Adequate bladder fullness is often required for good visual image but full bladder causes elongation of cervix which obscures funneling of the internal os when present[78].

All these loop holes make Transabdominal Ultrasoundnot to be recommended for cervical assessment, not even as a screening test because of its very low sensitivity (8%). It is much lower the other techniques described later, in the prediction of disease.

TRANSLABIAL ULTRASOUND

Also known as transperineal ultrasound.

It was initially described in early 1980's in France.

During this procedure the women has to lie on table with flexion maintained at her hips and knee. A gloved transducer is then introduced between labia majora in sagittal position.

Women's hips should be elevated with a certain fox to improve visualization.

- This technique carries following advantages over the transabdominal ultrasound :
  - No obstruction by the fetal parts.
  - Technique is well accepted by most women.
  - Bladder need not be full.
  - Transducer does not enter vagina.
  - Additional transducer is not required.
- Disadvantages over transabdominal ultrasound :
  - Expertise over the technique is needed, as this technique is more difficult to master than transvaginal ultrasound.
  - Visualization of cervix can be affected by the presence of gas in the rectum.
  - This technique can be considered as a method of choice in patients objecting transvaginal ultrasound or in women with premature rupture of membranes, as a precautionary method to avoid infection which occurs with use of transvaginal ultrasound [79].

TRANSVAGINAL ULTRASOUND

Recently, transvaginal ultrasound is being used as a reliable method in the examination and assessment of the cervix and its changes during pregnancy. The initial use of transvaginal ultrasound goes back to the late 1980's where studies of human cervix were started. Andersen et al had initially published regarding the prediction of preterm birth by measuring cervical length by transvaginal ultrasound. They discovered that before 30 weeks of gestation, a cervix with cervical length less than 39 mm has a significant risk of early delivery. Till date, several studies are being conducted by using various risk scoring systems based upon the digital examination of cervix or epidemiological data to assess the onset of preterm labour. But as digital examination of cervix has its own limitations and being non objective, transvaginal ultrasound is now being widely used in the obstetric and gynecological practice. When compared to the above mentioned techniques, transvaginal ultrasound has the advantage to provide accurate, repeatable and objective measurements of cervical length. Approximately, it takes about 5 minutes to perform transvaginal ultrasound of a cervix. It is used often as a screening test for the prediction of preterm birth.

Currently, following recommendations are used while performing the transvaginal ultrasound:[80]

- Women should empty her bladder.
- Clean vaginal probe covered by a condom should be prepared.
- Insert the probe (women can insert the probe for more comfort).
- Probe should be guided towards the anterior fornix of the vagina.
- A sagittal view along the entire length of endo-cervical canal should be obtained.

- Probe should be withdrawed till the image is blurred and adequate pressure should be reapplied again till image restores.
- Image should be enlarged until cervix occupies two-thirds of the screen and both internal and external os are well visualized.
- Cervical length from internal to external os should be measured.
- Atleast 3 measurements should be obtained and the shortest measurement in millimeters should be recorded.
- Transfundal pressure should be applied for 15 seconds and cervical length should be recorded once again.

Transvaginal ultrasound requires expertise and skill to obtain accurate measurements. Keeping in view of the above mentioned criteria, one can perform transvaginal ultrasound of cervix . But initial 50 transvaginal ultrasound examinations of the cervix by a sonographer should be supervised to gain adequate expertise and accuracy.

FIGURE 1 : PORTABLE ULTRASOUND MACHINE AND TRANSVAGINAL ULTASOUND PROBE

To obtain the best results, one should keep the following points in mind while performing transvaginal ultrasound.

- Distance from posterior lip to the cervical canal should be equal to the distance from the anterior lip to the cervical canal.
- Internal os when compared with respect to the uterus should be flat or form an isosceles angle.
- The entire length of cervix should be seen.
- Echogenicity in the cervix should be avoided (sign of excessive pressure) .

FIGURE 2 : TRANSVAGINAL FETAL ULTRASOUND

ADVANTAGES OF TRANS VAGINAL ULTRASOUND:

- The intraobserver and interobserver variability of transvaginal ultrasound are both less than 10%. Such less variability is obtained by following proper technique and with adequate training under supervision [79,80].
- Transvaginal ultrasound of cervix is more acceptable and safer procedure. There occurs no inoculation of bacteria with the probe and can be used even in women with preterm premature rupture of membranes.
- The initial changes at internal os like opening of internal os, cervical shortening, cervical widening along the endocervical canal are always asymptomatic and can be detected by transvaginal ultrasound only.
- Cervical length measurement by transvaginal ultrasound has a stronger prediction of preterm birth than that by digital assessment of cervix. This is because digital examination is subjective (interobserver variability of 52%) [81], non specific (16% of primiparous women and 17% - 35% of multiparous women who had term deliveries have cervical dilatation of 1 - 2 cms by digital examination in the late second trimester) [82] and not accurate for evaluating the internal os (as the entire length of cervix is not measured by this method). Hence transvaginal ultrasound is superior to manual examination for prediction of preterm labour and for evaluation of cervix.

Excessive pressure should not be applied on the cervix as it causes elongation of cervix. When the image is magnified up to 70% to 75% of the screen, cervix can be visualized clearly and even the endocervical mucosa is seen along the endocervical canal. The calipers should be located at internal and external os and shape of cervix along with any funneling if present should be recorded.

This funneling or opening of cervical os could be obscured by the pressure exerted by full bladder. Hence prior emptying of the bladder is most important prerequisite. Apart from this, uterine segment contractions also appear to be as funneling of internal os. At such times we can observe a rounded myometrium around the cervix and a normal cervix distal to the contraction. A curved cervix is measured either as a curvature or as a straight line between internal and external cervical os.

The use of three dimensional multi planner volume increases the positive predictive value of cervical ultrasonography in predicting preterm delivery. High risk women can be screened by the two dimensional ultrasonography and their diagnosis of preterm labour can be improved by the 3D multi planner ultrasound assessment of cervix. Whereas in women with low risk cervical length was identified to be superior to cervical volume assessment by the 3D ultrasound in identifying women at increased risk of spontaneous preterm labour.

Various cervical parameters can be evaluated by transvaginal ultrasound as predictors of preterm birth. Cervical length, funneling, funnel length, endocervical canal dilatation, cervical index (funnel length+1/funnel length), cervical angle, anterior and posterior cervical length, cervical width, lower uterine segment thickness, contour of cervical canal (striaght/curved), visibility of chorioamnion membranes at the internal os, vascularity, cervical position (horizontal/vertical), sludge, cervical gland area and othersare the various cervical parameters.[83]

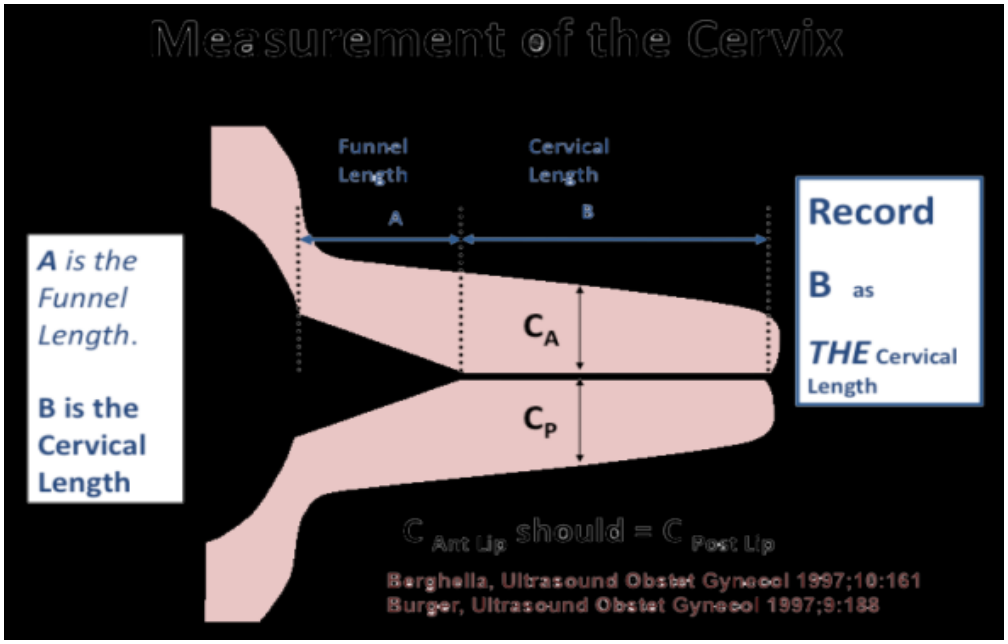


FIGURE 3 :MEASUREMENT OF THE CERVIX

Among all the parameters, cervical length is considered to be the most reliable and predictive factor. There is no sufficient evidence to prove that addition of any of these parameters to the cervical length would enhance its predictive accuracy

The distance between the internal os and external os is usually measured as the cervical length. Curved cervical canal indicates that cervical length is > 25 mm. Cervical length remains as the only parameter that can be assessed when cervical canal is closed.

FIGURE 4: CERVICAL LENGTH MEASUREMENT

Funneling also is reported to have similar predictive accuracy for preterm birth. Among 25 % to 33% of high risk women and 10 % [84] of low risk women, the internal os will be open. The length of open portion of cervix is measured as the funnel length and the funnel width is obtained from diameter of internal os. For the regular use and for prediction of preterm birth by sonography, term cervical length usually refers to functional cervical length . The closed portion of endocervical canal is measured as functional cervical length. Total cervical length is the sum of functional length and funnel length. During funneling, the cervical canal usually follows the order from the normal T shape, to Y shape, then V shape and finally U shape[85].

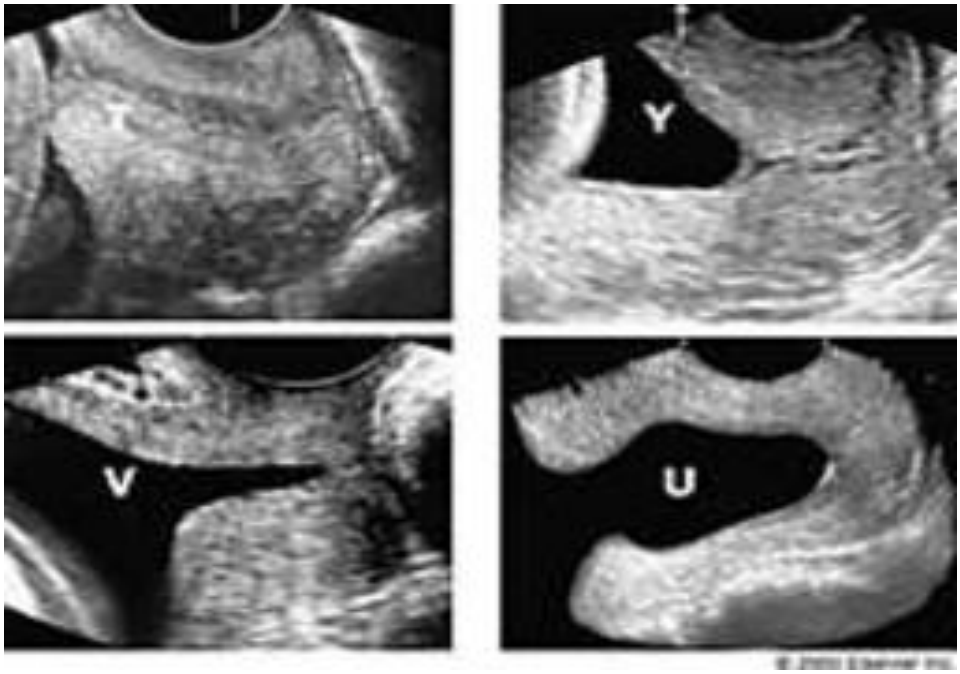


FIGURE 5: DIFFERENT SHAPES OF FUNNELING - T, Y, V, U SHAPES

But the disadvantage is the higher variability between observers among researchers and different centers. If the funneling is < 25% there is no increased risk of preterm birth. Mostly, in the presence of funneling, the cervical length is less (25 mm). In those women with a normal length cervix , risk of preterm birth will not be increased even with the presence of funneling. But the presence of both short cervix and funneling will increase the risk of preterm birth[86]

Application of transfundal pressure while performing transvaginal ultrasound, shortens cervical length in approximately 5% of women. Conflicting evidence persists whether transfundal pressure increases the screening potential of cervical length. However, larger studies on this factor have proved that dynamic changes improve the predictive accuracy, hence its best to consider the shortest cervical length.

All the above discussion confines to the skill of performing the transvaginal ultrasound. To obtain the accurate results, importance should also be given to the

weeks of gestation at which the transvaginal ultrasound is being performed. Prior knowing its significance, the normal cervical length at varies gestational ages should be noted.

From 14 to approximately 30 weeks of gestational age, a cervical length of 25 to 50 mm is considered as normal. For low risk single ton gestations, 25 mm is the 10% percentile and 25% percentile for high risk singleton gestations.[79,87.]

A short cervical length is the one less than 25 mm at these gestational ages, with best prediction for preterm birth obtained at 16 - 24 weeks of gestational age[84]. A short cervical length predicts a early preterm birth than later preterm birth. However, cervical length > 50mm is also considered normal because it reflects a measurement that includes lower uterine segment, as often happens before 16 weeks of gestation usually.

In the first trimester or before 14 weeks of gestationalage, preterm birth cannot be predicted by the measurement of cervical length. Before 14 weeks of gestational age, most of the women including those who eventually will have an early preterm birth and women with high risk for prerterm birth generally have a CL > 25 mm. Only a very minimal percentage (5%) of women mostly those who had a previous history of second trimester loss, those who had a large cervical cone biopsy in the past will have cervical length < 25 mm before 15 weeks of gestational age. During this time period the prediction of preterm birth has a very low sensitivity, because most women destinated to have a preterm delivery will have shortening of cervix usually detected > / 16 weeks of gestational age.

It is due to the poorly lower uterine segment. For expansion of lower uterine segment, the gestational sac should be developed to an adequate size required to separate lower uterine segment from the endocervical canal, which usually cannot occur by 14 weeks of gestational age.

Also between 14 - 18 weeks of gestational age, due to the presence of

Braxton - hick's contractions, the lower uterine segment gets closed, which makes it difficult to obtain cervical length as there will be no distinction between these structures.

Recently, Greco et al. came up with an new idea of measuring cervical length during the first trimester of pregnancy, to make a seperation between the isthmus and the endocervix , which looks like a myometrial thickening between the endocervix and the gestational sac. According to them, the vertical distance between the two ends of the endocervical canal (endocervical length) and the shortest distance between the gestational sac (isthmic length) and the glandular area of endocervix, seperating the endocervix and the isthmus has to be measured. Though their study of measuring of length of endocervical canal in the first trimester of pregnancy have shown some predictive value for preterm birth, still the results from bigger size studies are needed.

Usually, cervical length gradually decreases beyond 30 weeks of gestational age. Hence cervical length of 25 mm especially between 15 to 24 mm, beyond 30 weeks of gestation can be a part of normal process and has no increased risk of preterm birth in case of asymptomatic women.

Usually funneling or short cervix develops between 18 to 22 weeks of gestational age [79,80]. Hence for any screening program of preterm birth in asymptomatic women with the criteria of a single cervical length measurement, the

most effective timing would be between 18 - 22 weeks of gestational age. But according to the various studies done for evaluating the predictive accuracy of cervical length measurement by transvaginal ultrasound for preterm birth revealed that the screening interval is usually between 16 and 24 weeks of gestational age[84,87]. Most common primary outcome is spontaneous preterm birth at less than 34 weeks of gestation [88,89,90.].

However, high risk women for preterm birth will have cervical changes at an earlier gestational ages. These women will be benefited with early transvaginal ultrasound (14 - 18 weeks), as it may determine the necessity of early interventions. This is because the risk of preterm birth is higher when the short cervical length is identified at an earlier gestational age. In most of these high risk women, one cervical length measurement by transvaginal ultrasound at 14 - 18 weeks of gestation and one more between 18 - 22 weeks of gestation is reassuring[86]. But this does not apply in cases of all high risk women. Women with additional high risk factors like those with very early spontaneous preterm birth or previous second trimester loss, cervical length measurement by transvaginal ultrasound should be done every two weeks, at least between 14 - 24 weeks of gestational age.

MATERIALS AND METHODS

MATERIALS:

134 pregnant women with singleton pregnancy who attended outpatient department or admitted for antenatal care in BLDE University's Shri B. M. Patil Medical College, Hospital & Research Centre, Vijayapura were included in the study.

Duration of study: December 2015 to June 2017 (18 months).

DETAILS OF THE STUDY

INCLUSION CRITERIA:

- Singleton pregnancy.
- Gestational age between 16 and 24 weeks.
- Informed consent to participate in the study and to undergo transvaginal ultrasonography.

EXCLUSION CRITERIA:

- Severe anaemia
- Multiple pregnancy
- Heart diseases
- Previous history of surgery on cervix (cervical dilatation, conisation)
- Prior preterm birth
- Polyhydramnios.

METHOD OF COLLECTION OF DATA:

- Pregnant women with inclusion criteria are selected.
- Appropriate care and counselling regarding the procedure is given to selected pregnant women.
- Informed written Consent for the Procedure will be obtained.
- Detailed history of the patient is obtained
- Bladder should be emptied.
- Transvaginal ultrasound scanning will be done with high frequency endovaginal probe (5-7Mhz).
- A clean probe covered with a condom is prepared.
- Probe is inserted and guided into the anterior fornix of vagina.
- Sagittal long-axis view of endocervical canal along the entire length is obtained.
- The probe is withdrawn until the image is blurred and just enough pressure should be reapplied to restore the image (to avoid excessive pressure on the cervix, which can elongate it).
- Image should be enlarged so that cervix occupies at least two-thirds of the image and both the external and internal os are seen.
- The length of cervix from external to the internal os is measured along the endocervical canal.
- At least three measurements should be obtained and the best shortest measurement in millimetres recorded.
- Transfundal pressure should be applied for 15 seconds and cervical length is obtained again.

- Cervical changes like funnelling, funnel length, funnel width, cervical index, anterior cervical width, posterior cervical width are noted.

SAMPLING:

With 95% confidence level, anticipated incidence of preterm deliveries as 9.6% and desire precision as ± 5%.

The minimum sample size is 134.

$$n = \frac{Z^2 P(1-P)}{d^2}$$

n = sample size

d= precision.

z = z statisticfor a level of confidence.

P = expected incidence.

Design of study : Single centre prospective study.

Statiatical analysis : Data will be presented as

- Mean ± SD
- t-test for comparision of mean.
- Chi-square test for significance of association.

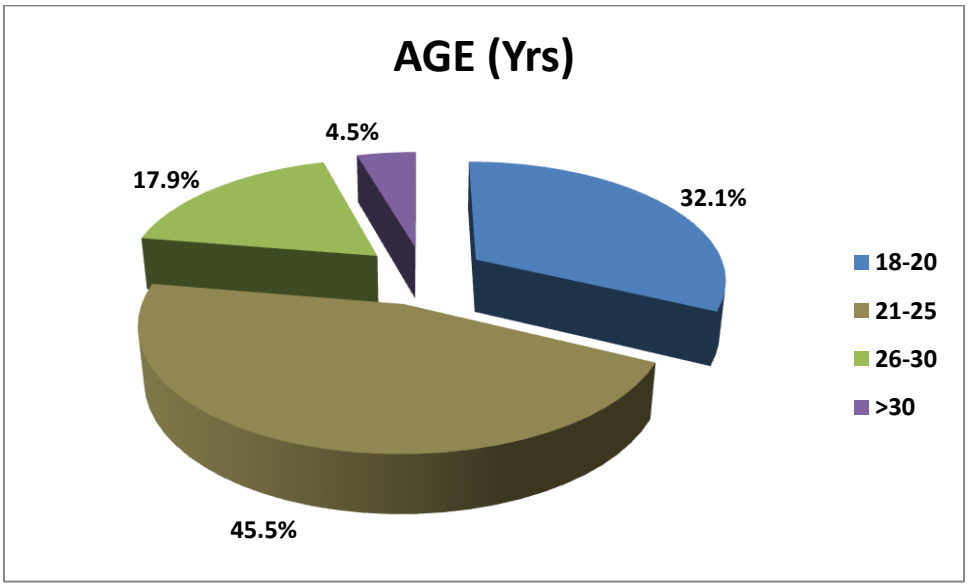
RESULTS

The study group of 134 women include women between 18 years to 30 years of age and above. The table and graph shows the distribution of age in the study group.

TABLE: 1.DISTRIBUTION OF CASES ACCORDING TO AGE

AGE (Yrs)	N	%
18-20	43	32.1
21-25	61	45.5
26-30	24	17.9
>30	6	4.5
Total	134	100

FIGURE: 1.DISTRIBUTION OF CASES ACCORDING TO AGE



Maximum number of women (61) are in the age group between 21-25 years.

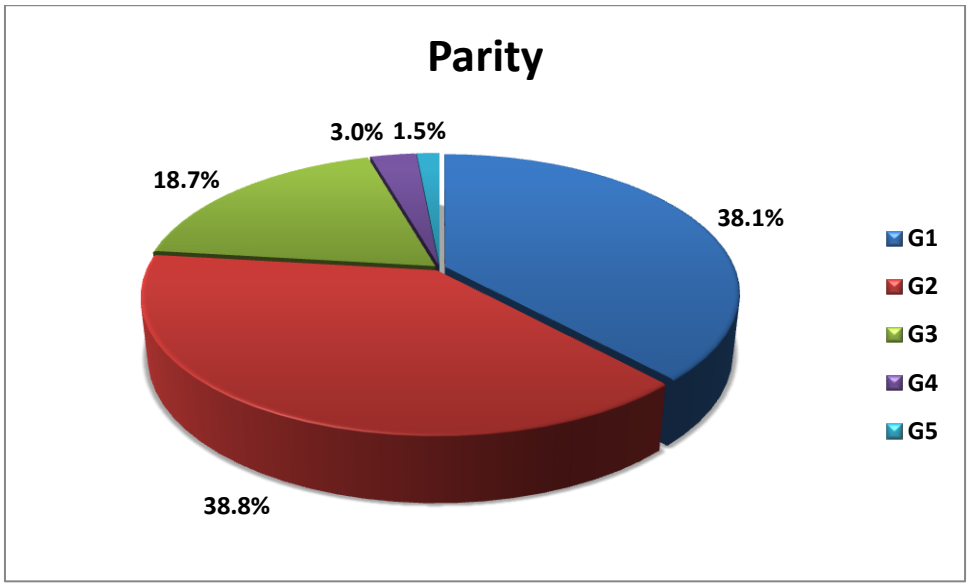
The study group of 134 women had Primpara's and Multipara's.

The table and graph shows the distribution of parity in the study group.

TABLE: 2. DISTRIBUTION OF CASES ACCORDING TO PARITY

Parity	N	%
P1	51	38.1
P2	52	38.8
P3	25	18.7
P4	4	3
P5	2	1.5
Total	134	100

FIGURE: 2.DISTRIBUTION OF CASES ACCORDING TO PARITY



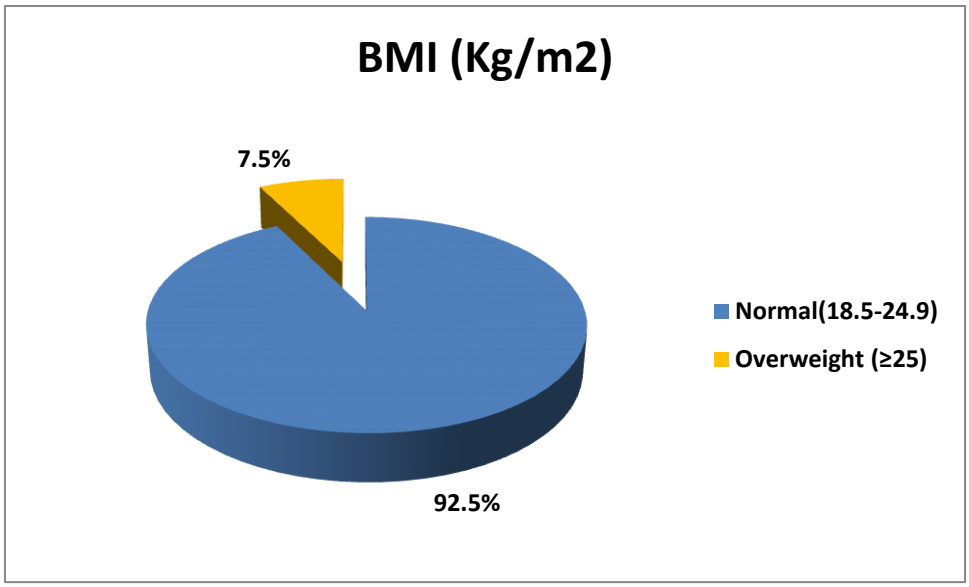
Maximum number of study (52) women are second para 2. Minimum number (2) are para five.

The table and graph shows the distribution of BMI in the study group.

TABLE: 3. DISTRIBUTION OF CASES ACCORDING TO BMI

BMI (kg/m2)	**N**	**%**
Normal(18.5-24.9)	124	92.5
Overweight (≥25)	10	7.5
Total	134	100

FIGURE: 3. DISTRIBUTION OF CASES ACCORDING TO BMI



Among 134 women, maximum number (124) of women are having the BMI in the normal range.

10 women were overweight.

The table shows the distribution of cervical length in the study group.

TABLE: 4. DISTRIBUTION OF CASES ACCORDING TO THE CERVICAL LENGTH

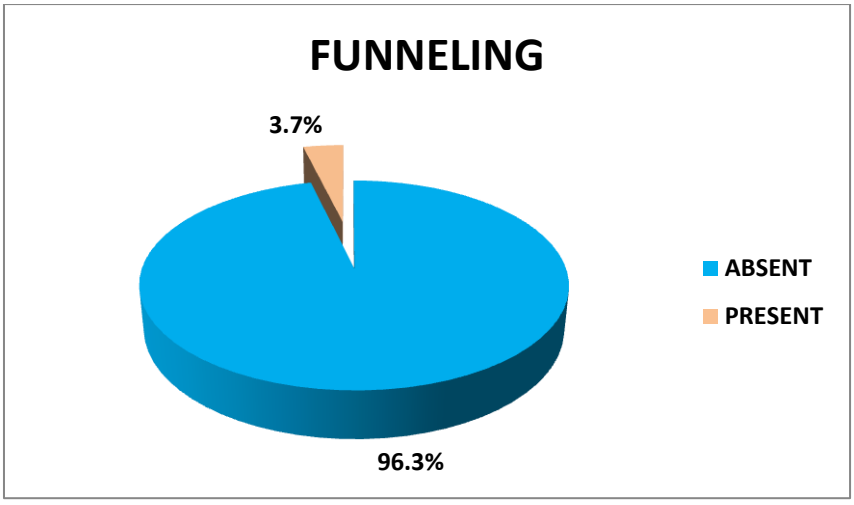
Length	CERVICAL LENGTH (mm)
Shortest	22.5
Longest	58.8
Mean	39.09
SD	6.7

The table and graph shows the distribution of funneling in the study group.

TABLE: 5. DISTRIBUTION OF CASES ACCORDING TO FUNNELING

FUNNELING	N	%
ABSENT	129	96.3
PRESENT	5	3.7
Total	134	100

FIGURE: 4. DISTRIBUTION OF CASES ACCORDING TO FUNNELING



Among the study group of 134 women, 5 women had funneling.

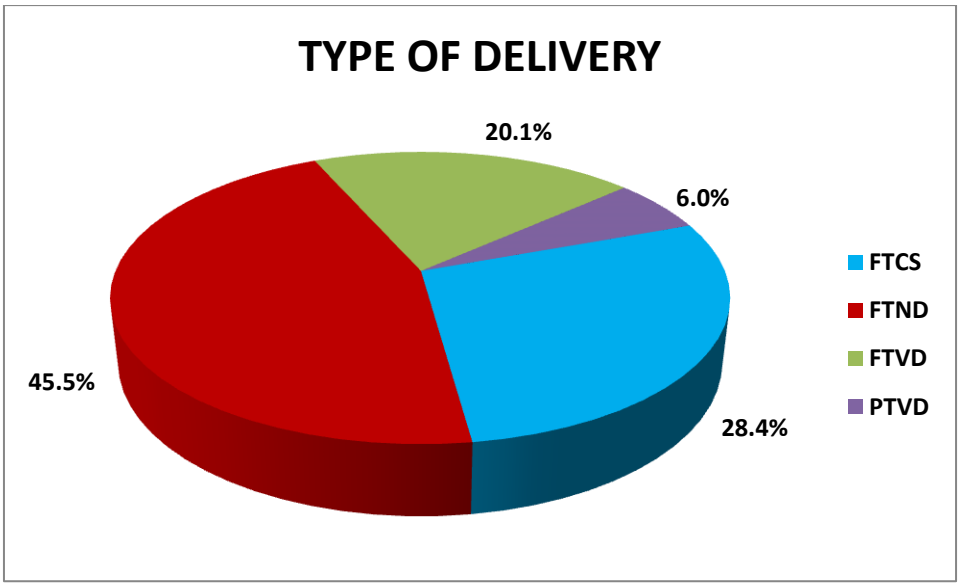
Among the study group of 134 women, follow up was done regarding their mode of delivery.

The table and graph shows the distribution of mode of delivery in the study group.

TABLE: 6. DISTRIBUTION OF CASES ACCORDING TO THE MODE OF DELIVERY

TYPE OF DELIVERY	N	%
FTCS	38	28.4
FTND	61	45.5
FTVD	27	20.1
PTVD	8	6.0
Total	134	100.0

FIGURE: 5. DISTRIBUTION OF CASES ACCORDING TO THE MODE OF DELIVERY



In the total of 134 deliveries, maximum were FTND - 61 and minimum were PTVD- 8.

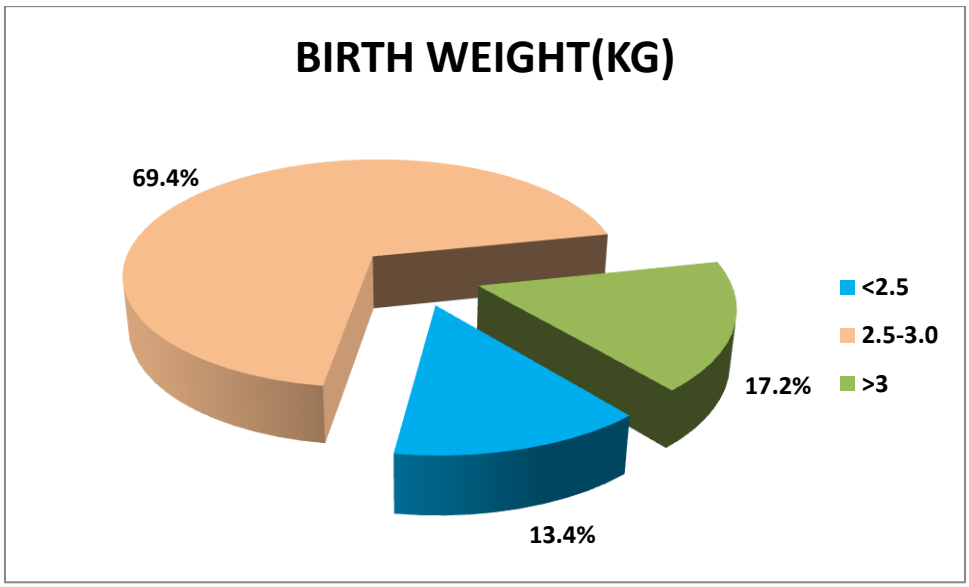
Among the study group of 134 women, follow up was done till delivery and the birth weight of their newborns was noted.

The table and graph shows the distribution of birth weight of newborns.

TABLE: 7. DISTRIBUTION OF CASES ACCORDING TO BIRTH WEIGHT

BIRTH WEIGHT(KG)	N	%
<2.5	18	13.4
2.5-3.0	93	69.4
>3	23	17.2
Total	134	100

FIGURE: 6. DISTRIBUTION OF CASES ACCORDING TO BIRTH WEIGHT



Maximum number (93) of newborn had birth weight in the range 2.5 - 3 kg. 18 newborn babies had birth weight < 2.5 kg.

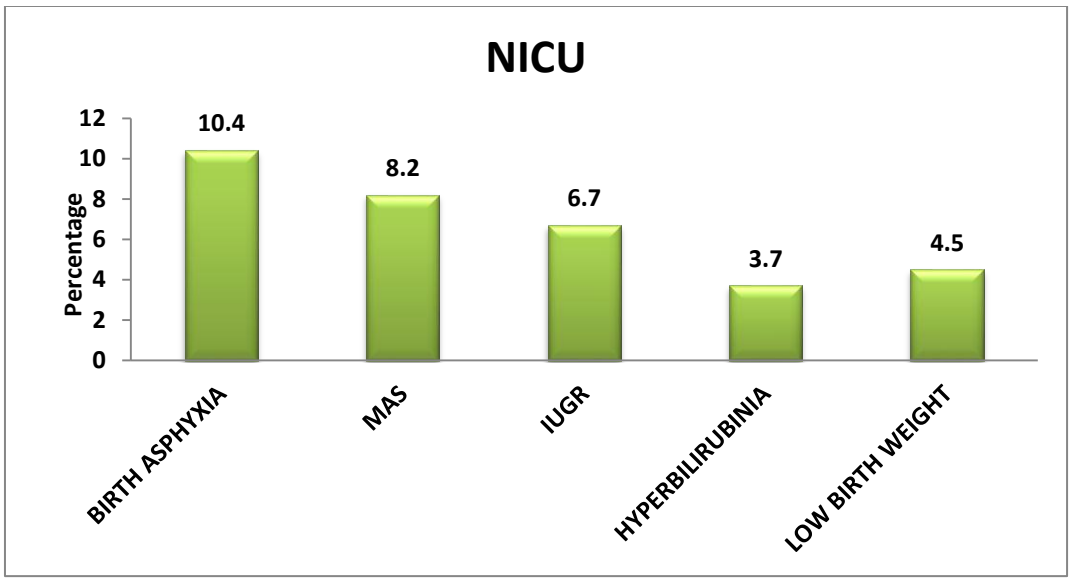
Among the 134 study group, 45 newborn babies had NICU admissions for various indications.

The table and graph shows the distribution of newborns according to their indications for NICU admissions.

TABLE: 8. DISTRIBUTION OF CASES ACCORDING TO THE INDICATIONS FOR NICU ADMISSIONS

NICU	N	%
BIRTH ASPHYXIA	14	10.4
MAS	11	8.2
IUGR	9	6.7
HYPERBILIRUBINIA	5	3.7
LOW BIRTH WEIGHT	6	4.5

FIGURE: 7. DISTRIBUTION OF CASES ACCORDING TO THE INDICATIONS FOR NICU ADMISSIONS.



Among the 134 newborns,majority of the admissions (14) were due to birth asphyxia followed by meconium aspiration syndrome (11). Others admissions were due to IUGR, hyperbilirubinia and low birth weight. No perinatal mortality was noted in the immediate first week of birth.

Various parameters of the study have been correlated in the following way.

The table and graph shows the correlation between various parameters and CL

TABLE: 9. PEARSON CORRELATION COEFFICIENT BETWEEN CL AND OTHER PARAMETERS

	r value	p value
AGE (Kg)	-0.244	0.004*
BMI (Kg/m2)	0.029	0.741
GA (Wks)	-0.349	<0.001*
BIRTH WEIGHT(KG)	0.296	0.001*

Note: * significant at 5% level of significance ($p<0.05$)

The above table shows the statistical correlation between various parameters and CL.

Age and Gestational age have negative correlation with the CL and are statistically significant.

Birth weight has a positive and statistically significant correlation with CL.

CL is in a positive correlation between birth weight of the newborn, BMI of the women.

FIGURE: 8. CORRELATION BETWEEN CL AND BIRTH WEIGHT

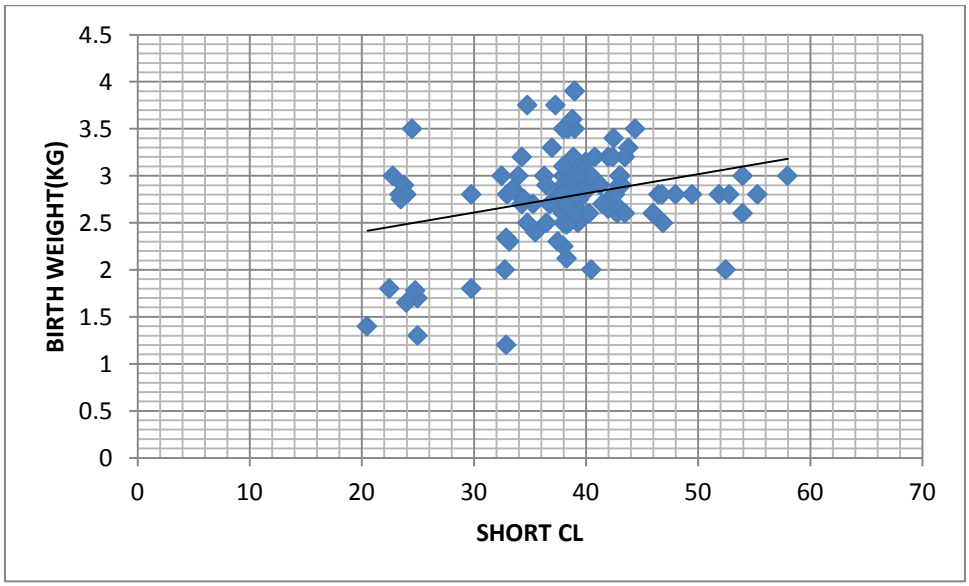
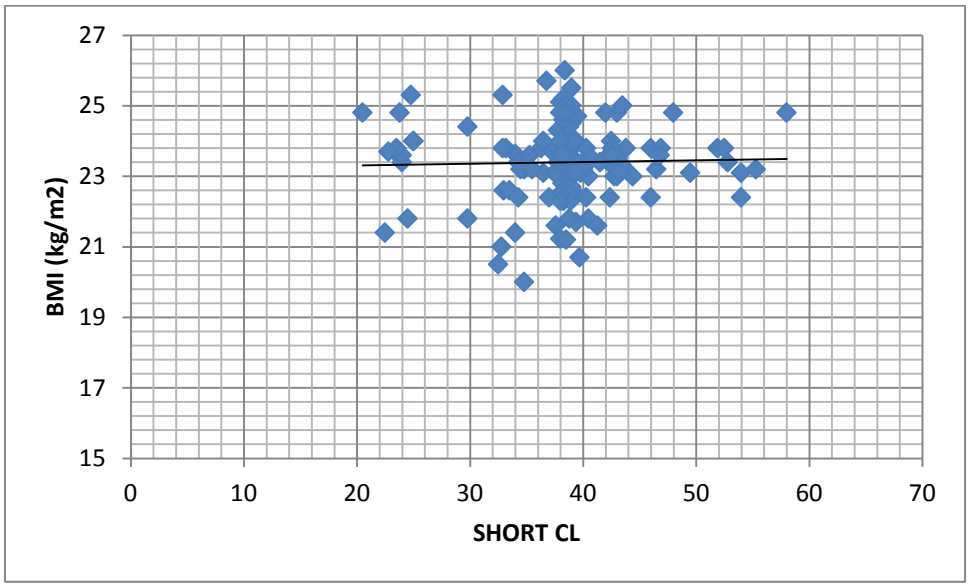


FIGURE: 9. CORRELATION BETWEEN CL AND BMI



CL is in negative correlation with GA and age of pregnant women.

FIGURE: 10. CORRELATION BETWEEN CL AND GA

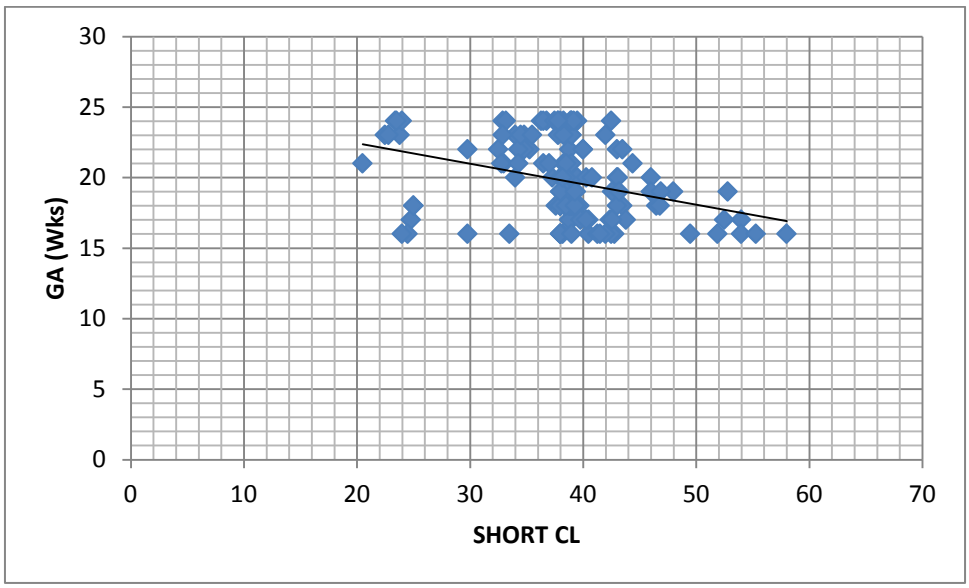
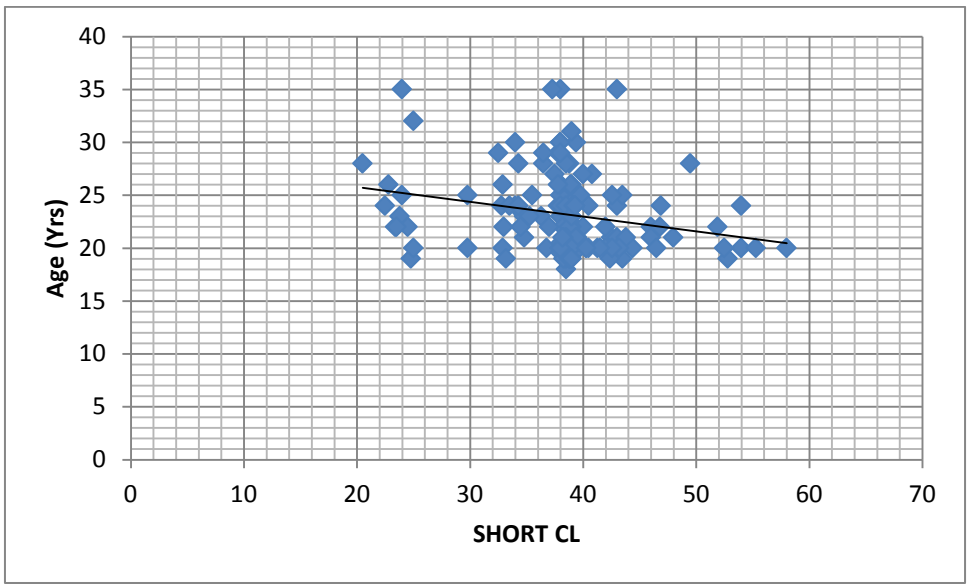


FIGURE: 11. CORRELATION BETWEEN CL AND AGE



These findings are in the favor of our present study and aid in predicting PTB by assessing the cervical length by transvaginal ultrasound among the low risk women.

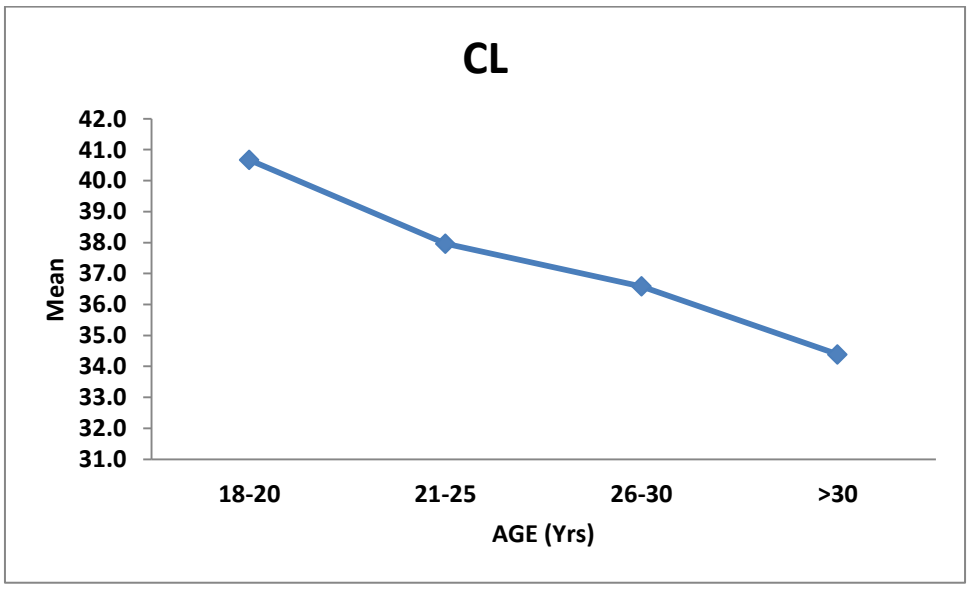
The table and graph shows the relation between mean of the shortest cervical length among the different age groups of study population.

TABLE: 10. STATISTICAL CORRELATION BETWEEN MEAN CL ACCORDING TO AGE

AGE (Yrs)	SHORTEST CL		p value
	Mean	SD	
18-20	40.7	6.7	0.024*
21-25	38.0	6.5	
26-30	36.6	5.6	
>30	34.4	7.9	
Total	38.4	6.6	

Note: * significant at 5% level of significance (p<0.05)

FIGURE: 12. STATISTICAL CORRELATION BETWEEN MEAN CL ACCORDING TO AGE



The correlation between age and mean of shortest cervical length was found to be negative and statistically significant (p value 0.024), which interpret that with lower cervical length was found with higher age.

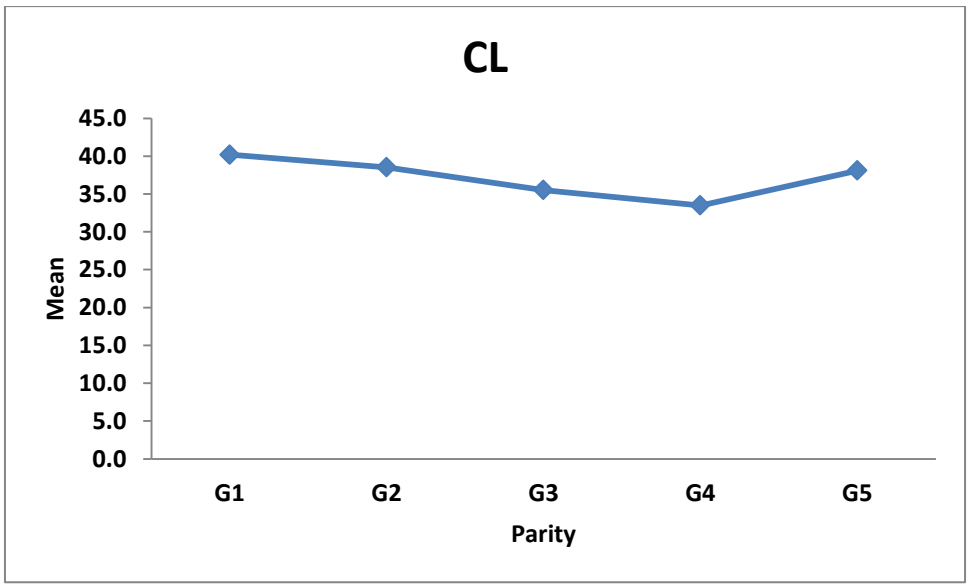
Table and Graph shows mean of shortest CL and its statistical correlation with parity of study group women.

TABLE: 11. STATISTICAL CORRELATION BETWEEN MEAN CL ACCORDING TO PARITY

PARITY	SHORTEST CL		p value
	Mean	SD	
G1	40.2	5.1	0.026*
G2	38.5	6.9	
G3	35.5	7.7	
G4	33.5	6.6	
G5	38.1	0.4	
Total	38.4	6.6	

Note: * significant at 5% level of significance ($p<0.05$)

FIGURE: 13. STATISTICAL CORRELATION BETWEEN MEAN CL ACCORDING TO PARITY



These findings suggest that the correlation between the mean of shortest CL and parity is negative and statistically significant (p value =0.015). It interprets that as the parity increases the CL decreases, except for a slight increase at highest parity.

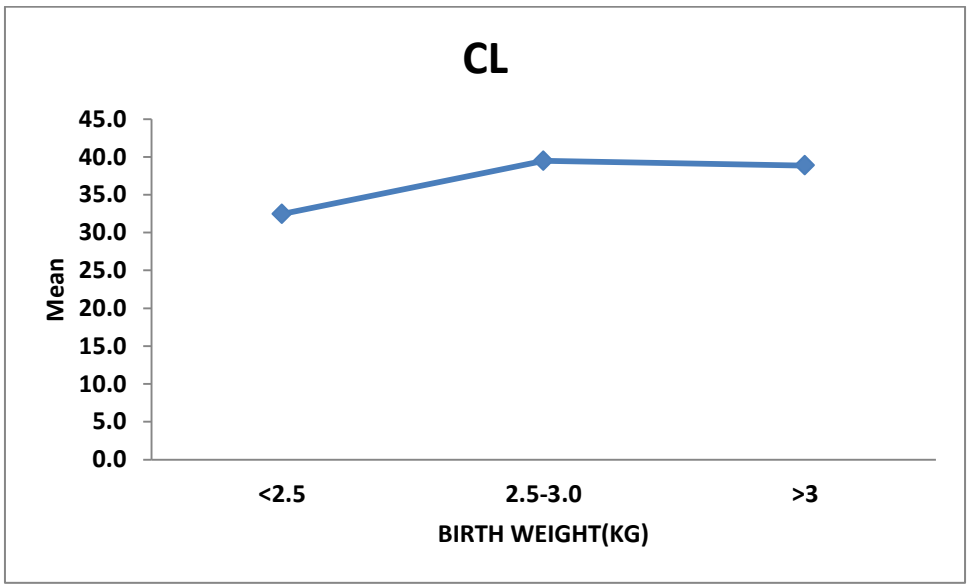
Table and Graph shows mean of shortest CL and its statistical correlation with birth weight of newborn of study group women.

TABLE: 12. . STATISTICAL CORRELATION BETWEEN MEAN CL ACCORDING TO BIRTH WEIGHT

BIRTH WEIGHT(KG)	SHORTEST CL		p value
	Mean	SD	
<2.5	32.4	8.0	<0.001*
2.5-3.0	39.5	6.3	
>3	38.9	4.1	
Total	38.4	6.6	

Note: * significant at 5% level of significance (p<0.05)

FIGURE: 14. . STATISTICAL CORRELATION BETWEEN MEAN CL ACCORDING TO BIRTH WEIGHT



These findings suggest that the correlation between the mean of shortest CL and birth weight are positive and statistically significant (p value < 0.001). It interprets that as the cervical length increases the birth weight also increases.

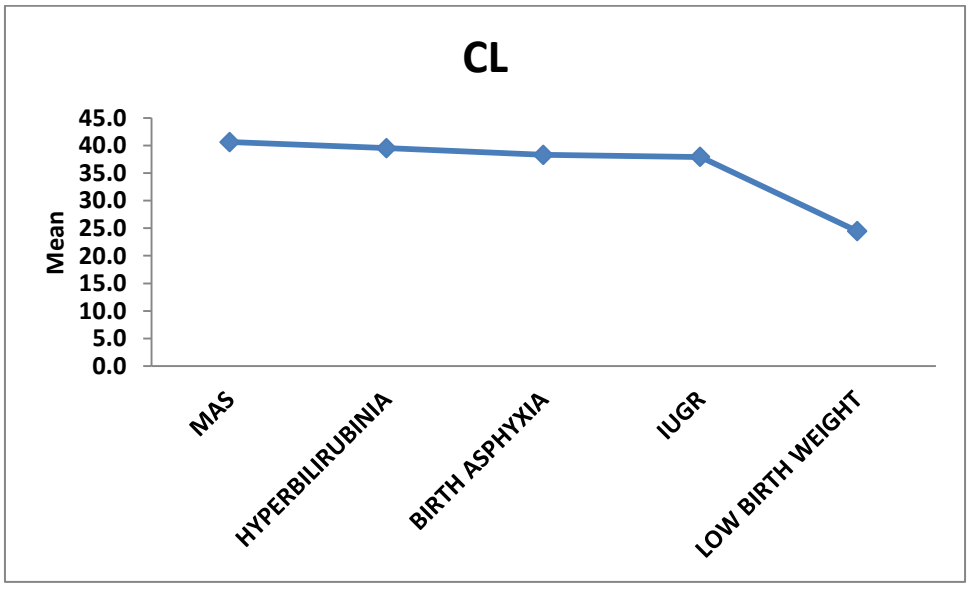
Table and Graph shows mean of shortest CL and its statistical correlation with indications for NICU admissions of study group women.

TABLE: 13. STATISTICAL CORRELATION BETWEEN MEAN AND INDICATIONS FOR NICU ADMISSIONS.

NICU	SHORTEST CL		p value
	Mean	SD	
MAS	40.6	3.7	<0.001*
HYPERBILIRUBINIA	39.5	9.3	
BIRTH ASPHYXIA	38.3	3.7	
IUGR	37.9	6.1	
LOW BIRTH WEIGHT	24.5	4.0	
Total	38.4	6.6	

Note: * significant at 5% level of significance (p<0.05

FIGURE: 15. STATISTICAL CORRELATION BETWEEN MEAN CL ACCORDING TO NICU



The correlation between indications for NICU admissions among the newborn of 134 women and shortest cervical length is statistically significant (p value < 0.001). Meconium aspiration syndrome is associated with longest mean CL of 40.6 mm. Low birth weight is associated with shortest mean CL.

Table and Graph shows mean of shortest CL and its statistical correlation with the mode of delivery among the study group women.

TABLE: 14. STATISTICAL CORRELATION BETWEEN MEAN CL AND MODE OF DELIVERY

CERVICAL LENGTH (mm)	Mean	FTCS		FTND		FTVD		PTVD		Total	p value
		N	%	N	%	N	%	N	%		
20-29	24.53	0	0.0	6	42.9	1	7.1	7	50.0	14	<0.001*
30-39	37.52	25	31.3	33	41.3	21	26.3	1	1.3	80	
40-49	43.18	11	33.3	18	54.5	4	12.1	0	0.0	33	
50-59	54.07	2	28.6	4	57.1	1	14.3	0	0.0	7	
Total	39.09	38	28.4	61	45.5	27	20.1	8	6.0	134	

FIGURE: 16. STATISTICAL CORRELATION BETWEEN CERVICAL LENGTH AND MODE OF DELIVERY

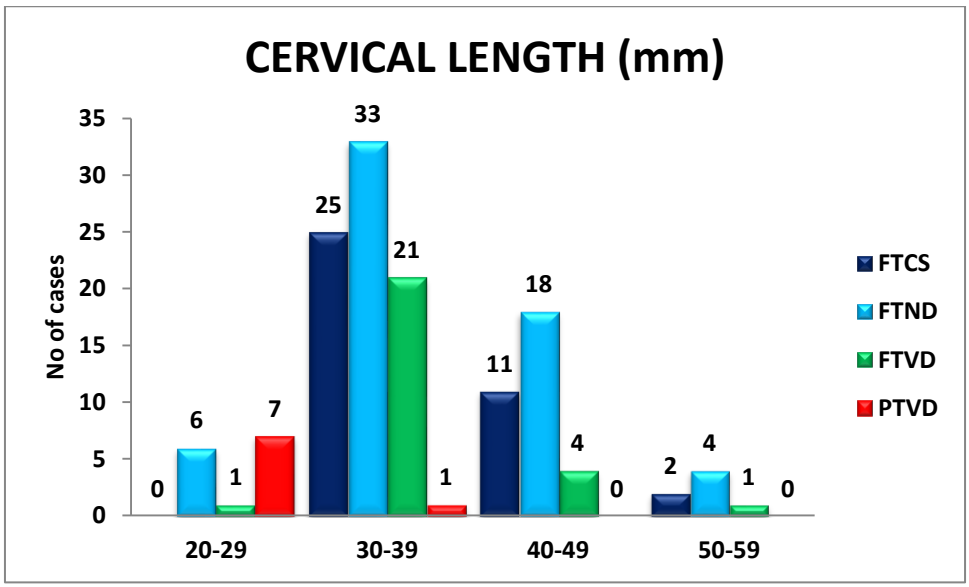


Table: 15. Shows the Sensitivity, Specificity, Positive Predictive value (PPV), Negative Predictive Value (NPV) among the study group women.

	CERVICAL LENGTH (mm)
	≤25
Sensitivity	75.0%
Specificity	95.2%
PPV	50.0%
NPV	98.4%
Accuracy	94.0%

DISCUSSION

Preterm birth possess a major health burden to the society due to its long - term morbidity, perinatal mortality and high financial expenditures associated with it. It is responsible for more than half of all neonatal deaths.[10] At present times, incidence of preterm birth is increasing inspite of the good perinatal care. With the recent advancements made in assisted reproductive techniques ,it is being used frequently with associated higher incidence of multiple pregnancy. This indirectly is leading to high incidence of preterm birth.

PREDICTION OF PRETERM LABOUR

Transvaginal ultrasound (TVU) is useful in diagnosing short cervix during pregnancy. Transvaginal sonagraphic measurement of cervical length predicts preterm birth not only in high risk group but also in asymptomatic low-risk women.

The present study was carried out in the Department of Obstetrics' and Gynecology of BLDE Universities' Shri BM Patil Medical College and Research Center, Vijayapura during 2015 - 2017. One hundred and thirty four low risk women between 16 - 24 weeks of gestation who fulfilled the selection criteria were recruited for the study. Maximum number of cases were found in the age group of 20 - 25 years (45.5%) and majority women of the study group were multipara (61.9%).

In our study group of 134 low risk women, 8 had preterm birth with a overall incidence of 5.9%.

In our study group of 134 low risk pregnant women, 12 had cervical length less than 25 mm on transvaginal ultrasonography when measured between 16 - 24

weeks of gestation. Out of 12 women with short cervical length, 6 women had preterm birth before 34 weeks of gestation (50%) with a sensitivity of 75%.

The sensitivity, specificity, PPV, NPV, recorded in our study are 75%, 95.2%, 50%, 98.4% respectively.

In our study group of 134 low risk women, cervical length was assessed between 16 - 24 weeks of gestation. At this period of gestation, cervical length assessment by transvaginal ultrasound could predict cervical changes and preterm birth.

In our study, eight preterm births were recorded. Among them 5 women had funneling of cervix and short cervical length of less than 25 mm. All these 5 women had preterm birth. This shows that the combined presence of shorter cervical length and funneling is better predictor of preterm birth than short cervix alone.

Among the 134 newborns ,majority of the admissions (14) were due to birth asphyxia followed by meconium aspiration syndrome (11). Others admissions were due to IUGR, hyperbilirubinia and low birth weight. No perinatal mortality was noted in the immediate first week of birth.

Studies conducted by **Hernandez-Andrade et al**[25] and **Friedman M A et.al**[28]concluded that cervical length cannot be measured accurately by transabdominal ultrasound and transvaginal ultrasound measurement of cervical length is a superior method.

Using a similar reference standered **Dennis JG et.al** reviewed studies on different population subgroups like low risk women,prior preterm birth, prior LEEP, prior cold knife cone, prior multiple D&Es, uterine anomalies, twins, triplets to assess the predictive accuracy of cervical length measured by transvaginal ultrasound in predicting preterm labour. In the study they included 2915 low risk pregnant women

and assessed the cervical length between 22- 25 weeks of gestation. The preterm birth rate was 4.3%.Their sensitivity, specificity, PPV, NPV was 47%, 84%, 35, 90 and the sensitivity, specificity, PPV, NPV, recorded in our study are 75%, 95.2%, 50%, 98.4% respectively. Perhaps because they assessed the cervical length starting from 22 weeks period of gestation, and may have missed some shorter cervical lengths and hence our values are comparatively a little higher than their study. Thus our study proves that transvaginal ultasound aids in predicting PTB in low risk population[16].

Barber MAet. al have measured cervical length in 2351 women between 18 - 22 weeks of gestation with the reference standered cervical length as 25 mm. In assessing preterm birth the specificity, sensitivity, positive and negative predictive values of cervical length were 98%, 26%, , 63.6%, 93.57% respectively.

Compared to their study , our study has recorded better specificity and higher sensitivity in predicting the preterm birth[18].

Lim K et al studied various literature in the PubMed searches and the Cochrane Library up till 2009 December and came to a conclusion that cervical length measurement by transvaginal ultrasound as a effective, safe and acceptable technique in predicting the preterm birth. Cervical length is inversely related to the risk of preterm birth in asymptomatic women. The largest study of this relationship noted that when compared with women who had values above the 75th percentile of cervical length, those with a shorter cervix at 24 weeks had the following relative risks: approximately 4 if length was < 30 mm (25th percentile), 6 if < 26 mm (10th percentile), 9 if < 22 mm (5th percentile), and 14 if < 13 mm (1st percentile). However, the positive predictive values (6 to 44%) and sensitivities (47%) were poor in this low-risk population. In our study, the positive predictive value and sensitivity obtained are 50% and 75% respectively. Compared to their study , our study has

recorded higher positive predictive value and sensitivity in predicting the preterm birth.[30]

Dalali M et.al conducted a observational cohort study in a total of 450 women from 508 eligible participants between 21-24 weeks of gestation. 47 cases had preterm labour out of 450 cases and 6 cases had positive funneling. Duration of pregnancy and cervical length significantly differed between women with and without funneling (p=0.001). The sensitivity and specificity of screening based on cervical length of 25mm were 55.5% (50.9-60.1%) and 93.6% (91.2-96%) respectively. They concluded that transvaginal ultrasound assessment of cervical length in low risk women has an acceptable reliability for screening of preterm labor and early diagnosis of spontaneous preterm deliveries in low risk women. The sensitivity, specificity recorded in our study are 75%, 95.2%, respectively. Compared to their study, our study has a higher sensitivity and specificity[89].

CONCLUSION

It is concluded from our study that transvaginal sonography (TVS) is a useful technique in assessing the cervical changes during pregnancy and predicting the preterm birth. Transvaginal sonography when performed between 16 - 24 weeks of gestational age could identify all the women having short cervical length and also with other changes of cervix. Out of 134 study group of low risk women, 8 women had preterm birth which accounts to the overall incidence of 5.9%.

6 women out of the 12 women with short cervical length (<25mm) had preterm birth which accounts to the incidence of 50% and sensitivity of 75%. Using a cervical length threshold of 25 mm with spontaneous preterm birth before 37 weeks'of gestation as the reference standard, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of our study are 75%, 95.2%, 50%, 98.4%, 94% respectively. These results prove that transvaginal ultrasonography between 16 - 24 weeks of gestation aids in accurately assessing cervical length and predicting the preterm birth before 37 weeks of gestation among low risk women. Thus, transvaginal ultrasonography can be used to caution the women at risk of preterm delivery and can be considered for necessary precautionary measures and interventions to prevent preterm birth.

Among the 134 newborns ,majority of the admissions (14) were due to birth asphyxia followed by meconium aspiration syndrome (11). Others admissions were due to IUGR, hyperbilirubinia and low birth weight. No perinatal mortality was noted in the immediate first week of birth.

SUMMARY

The present study entitled "Role of cervical length evaluation with transvaginal ultrasound for prediction of preterm birth in low risk pregnancy" was carried out in the Department of Obstetrics and Gynecology done of BLDE Universities' Shri BM Patil Medical College and Research Center, Vijayapura during 2015 - 2017.

One hundred and thirty four low risk women between 16 - 24 weeks of gestational age fulfilling the selection criteria were recruited for the study. The exclusion criterias were severe anemia, heart diseases, previous history of surgery on cervix (cervical dilatation, conisation), multiple pregnancy, prior preterm birth and polyhydramnios .

Ultrasound is being used as a reliable method in the examination and assessment of the cervix and its changes during pregnancy. Among the different techniques of ultrasound, transvaginal ultrasound is considered to be the best method in assessing the cervix and its changes during pregnancy.

When compared to different techniques, transvaginal ultrasound has the advantage to provide accurate, reproducibility and objective measurements of cervical length and it takes about 5 minutes to perform transvaginal ultrasound of a cervix. It is used often as a screening test for the prediction of preterm birth.

There are various tests for the prediction of preterm labour. Clinically assessing, cervical dilatation and effacement are more important. But they present a diagnostic challenge when cervical dilation < 2 cm and effacement < 80%. In such cases other features of parturition like decidual activation and cervical ripening are to

be considered. Cervical ripening can be assessed by measuring of cervical length by transvaginal ultrasound. Cervicovaginal fluid levels of fetal fibronectin are used to assess the decidual activation.

Various cervical parameters can be evaluated by transvaginal ultrasound as predictors of preterm birth. Cervical length, funneling, funnel length, endocervical canal dilatation, cervical index (funnel length+1/funnel length), cervical angle, anterior and posterior cervical length, cervical width, lower uterine segment thickness, contour of cervical canal (striaght/curved), visibility of chorioamnion membranes at the internal os, vascularity, cervical position (horizontal/vertical), sludge, cervical gland area and othersare the various cervical parameters.

Among all the above mentioned parameters, cervical length is considered to be most accurate and reliable parameter in predicting the preterm birth. In our study group of 134 low risk women, the shortest, longest and mean cervical length recorded was 22.5 mm, 58.8 mm, 39.09 mm respectively.

Out of 134 cases, maximum number of women belong to 21-25 years of age (61) ; normal range BMI (124); Para two (52).

All 134 low risk women underwent transvaginal assessment of cervical length between 16 - 24 weeks of gestational age and all these women were followed up till delivery.

Out of 134 deliveries, 126 women had full term deliveries and 8 women had preterm vaginal deliveries . 38 women had caesarean section among the 126 women with full term deliveries.

In the study group of 134 low risk women, 12 women had cervical length less than 25mm. Out of these 12, 6 women had preterm birth and the other 6 women had fulterm birth. Using a cervical length threshold of 25 mm with spontaneous preterm birth before 37 weeks' gestation as the reference standard, the incidence of preterm birth was 50% and the sensitivity of our study is 75% .

Among these 12 women with cervical length less than 25mm, 5 women had additional funneling changes of cervix and all the 5 women had preterm birth.

Among 134 women 2 women had cervical length more than 25 mm, but resulted in preterm.

The overall incidence of preterm birth in our study was 5.9% (n=8). 50% of low risk women with cervical length less than 25 mm had preterm birth before 37 weeks of gestation.

Maximum number (93) of newborns had birth weight in the range 2.5 - 3 kg and 18 newborns had birth weight < 2.5 kg.

In our study, cervical length of the women is statistically significant and has a negative correlation with the age of women (r value = -0.244 ; p value = 0.004) and her gestational age (r value = -0.349 ; p value = <0.001). Birth weight has a positive and statistically significant correlation (r value = 0.296 ; p value = 0.001) with cervical length.

Using a cervical length threshold of 25 mm and spontaneous preterm birth before 37 weeks' of gestation as the reference standard the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of our study are 75% ,95.2%, 50%, 98.4%, 94% respectively.

Among the 134 newborns,majority of the admissions(14) are due to birth asphyxia followed by meconium aspiration syndrome (11). Others admitions are due to IUGR, hyperbilirubinia and low birth weight. No perinatal mortality was noted in the immediate first week of birth.

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ANNEXURES

ETHICAL CLEARANCE CERTIFICATE

B.L.D.E.UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR – 586103
INSTITUTIONAL ETHICAL COMMITTEE

No/58/2015
20/11/15

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 17-11-2015 *at* 03 pm *scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.*

Title "Role of cervical length evaluation with transvaginal ultrasound for prediction of preterm delivery in low risk pregnancy"

Name of P.G. Student : Dr Sirupa venkata Geetika Reddy
Dept of Obstetrics & Gynaecology

Name of Guide/Co-investigator : Dr. S.R. Mudanur
Professor

DR.TEJASWINI VALLABHA
CHAIRMAN
CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College,BIJAPUR-586103.

Following documents were placed before E.C. for Scrutinization

1)Copy of Synopsis/Research Project
2)Copy of informed consent form.
3)Any other relevant documents.

INFORMED CONSENT FORM:

TITLE OF THE PROJECT **:** ROLE OF CERVICAL LENGTH EVALUATION WITH TRANSVAGINAL ULTRASOUND FOR PREDICTION OF PRETERM DELIVERY IN LOW RISK PREGNANCY- A PROSPECTIVE STUDY

PRINCIPAL INVESTIGATOR **:** DR.SIRUPA VENKATA GEETIKA REDDY
POST GRADUATE,
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CENTER, VIJAYPUR– 586103,
KARNATAKA.

CO-GUIDE : DR. BHUSHAN N. LAKHKAR
PROFESSOR AND HOD OF
DEPARTMENTOF RADIO-
DIAGNOSIS AND IMAGING.
B.L.D.E.UNIVERSITY'SHRI B.M.
PATIL MEDICAL COLLEGE
HOSPITAL AND RESEARCH
CENTRE, VIJAYAPUR-586103,
KARNATAKA.

PURPOSE OF RESEARCH:

I have been informed that this will be a prospective study to know the efficacy of transvaginal measurement of cervical length in the prediction of preterm labour in women visiting to BLDE University's Shri B.M. Patil Medical College Hospital & Research Centre, Vijayapur, Karnataka.

I have been explained about the reason for doing this study and selecting me /my ward as a subject for this study. I have also been given free choice for either being included or not in the study.

PROCEDURE:

I/my ward have been explained that, I/my ward will be subjected to general physical examination and investigations in pregnant women with preterm delivery risk factors visiting our hospital.

I/my ward will be followed up with certain routine blood and urine investigations, USG until I/my ward will be discharged.

RISKS AND DISCOMFORTS:

I/my ward understand that I/my ward would not have any discomfort with my study. I/my ward understand that necessary measures will be taken to reduce any kind of complications as and when they arise.

BENEFITS:

I/my ward understand that my participation in this study will help to analyse the role of transvaginal measurement of cervical length in predicting preterm labour in pregnant women.The rationale behind the use of transvaginal measurement of cervical

length is to prevent preterm delivery and its potential for disastrous complications and relatively high morbidity rates.

CONFIDENTIALITY:

I/my ward understand that medical information produced by this study will become a part of this Hospital records and will be subjected to the confidentiality and privacy regulation of BLDE University's Shri B.M. Patil Medical College Hospital and Research Centre, Vijayapur, Karnataka. Information of a sensitive, personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code key connecting name to numbers will be kept in a separate secure location.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers such as photographs and audio or video tapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. Dr. Sirupa Venkata Geetika Reddy is available to answer my questions or concerns. I/my ward understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me and that a copy of this consent form will be given to me for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I/my ward understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I/my ward also understand that Dr. Sirupa Venkata Geetika Reddy will terminate my participation in this study at any time after he has explained the reasons for doing so and has helped arrange for my continued care by my own physician or therapist, if this is appropriate.

STUDY SUBJECT CONSENT STATEMENT:

I/my ward confirm that Dr. Sirupa Venkata Geetika Reddy has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I/my ward have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(Witness to above signature) Date

CASE SHEET PROFORMA

Name : DATE :

Age/Sex :

I.P.NO : Ph No. :

Occupation : Case no :

DOA : DOD :

Address :

Chief complaints :

History of presenting complaints:

ANTENATAL HISTORY

I. Trimester :

II. Trimester :

III. Trimester :

Obstetric history

- Married life :
- Obstetric score :

Menstrual history

- Past menstrual cycle :
- LMP :
- EDD : POG:

Any Preterm births, cervical incompetence surgeries on cervix

Past history :

Family history :

Personal history :

GENERAL PHYSICAL EXAMNIATION:

Build and nourishment:

P.R :

Height : B.P :

Weight : BMI :

R.R :

Temp :

Breast :

Thyroid :

Spine :

Pallor/ icterus/ cyanosis/clubbing/odema /lymphadenopathy.

SYSTEMIC EXAMINATION:

CVS :

RS :

PER ABDOMEN:

Uterine height : Presentation :

FHS : Uterine contraction :

PER SPECULUM EXAMINATION:

(IF REQUIRED)

PER VAGINAL EXAMINATION:

(IF REQUIRED)

Effacement :

Os Dilatation :

INVESTIGATIONS / INTERVENTIONS:

1. BLOOD INVETIGATIONS
   - CBC :
   - Blood grouping and Rh typing :
   - BT :
   - CT :
   - RBS :
2. Urine Examination
   - Urine Routine :
   - Urine microscopy :
3. HIV & Hbs Ag :

4. First trimester ultrasound examination :

- Date :
- Crown rump length :
- Gestational age :

  EDD (with CRL) :

<u>Transvaginal Ultrasound examination for cervical length</u>

Date:

Gestational age (by Reliable LMP/1st Trimester USG) :

Cervical length (CL) :

1.

2.

3.

Shortest CL :

Other features-

Cervical funnelling :

Funnel length :

Funnel width :

Cervical index :

Anterior cervical length :

Posterior cervical length :

Others :

EDD (with reliable LMP) :

EDD by 1st trimester USG :

FOLLOW UP

Antenatal events :

Delivery date :

Gestational Age :

Type of delivery : FTVD/ Preterm delivery /LSCS

Fetal outcome :

Birth Weight :

Live and healthy/ Stillborn /AGA/IUGR/Asphyxia

NICU Admission :

Others :

REMARKS

KEY TO MASTER CHART

SLNO - Serial number

Pt NO - Patient Number

GA -Gestational age

BMI - Body mass index

CL - Cervical length

BW - Birth weight

EDD - Expected Date of Delivery

WK - Week

FTND - Full Term Normal Delivery

FTVD - Full term Vaginal Delivery

FTCS - Full Term Cesarean Section

PTVD - Preterm Vaginal Delivery

LBW - Low Birth Weight

MAS - Meconium Aspiration Syndrome