A STUDY ON B-HCG IN CERVICOVAGINAL SECRETIONS AS PREDICTOR OF PRETERM DELIVERY

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CERTIFICATE

This is to certify that the dissertation entitled **"A STUDY ON B-HCG IN CERVICOVAGINAL SECRETIONS AS PREDICTOR OF PRETERM DELIVERY** submitted by **Dr.RAGHAVI N** in the Institute of Social Obstetrics, Govt Kasturba Gandhi hospital (Madras Medical College) Triplicane , Chennai, in partial fulfillment of the university rules and regulations for award of MS degree in Obstetrics and Gynaecology under my guidance and supervision during the academic year 2014-2017.

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I solemnly declare that this dissertation entitled **"A STUDY ON B-HCG IN CERVICOVAGINAL SECRETIONS AS PREDICTOR OF PRETERM DELIVERY** was done by me at The Institute Of Social Obstetrics, Govt Kasturba Gandhi Hospital & Institute of Obstetrics and gynecology, Madras Medical College during 2014-2017 under the guidance and supervision of, **Prof. Dr. S. VIJAYA MD. DGO.** This dissertation is submitted to the TamilNadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.S. Degree in Obstetrics and Gynaecology.

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ABBREVIATIONS

B-HCG	-	Beta human chorionic gonadotropin.
FHR	-	Fetal Heart Rate
FLM	-	Fetal Lung Maturity
GA	-	Gestational Age
GBS	-	Group B Streptococcus
HMD	-	Hyaline Membrane Disease
IVH	-	Intra Ventricular haemorrhage
LN	-	Labour Natural
LMP	-	Last Menstrual Period
LSCS	-	Lower Segment Caesarean Section
NICU	-	Neonatal Intensive Care Unit
PROM	-	Premature Rupture Of Membranes
PPROM	-	Preterm Premature Rupture Of Membranes
RDS	-	Respiratory Distress Syndrome
ROM	-	Rupture of Membranes.
ROS	-	Reactive Oxygen Species.
USG	-	Ultrasono Gram

CONTENTS

Introduction

INTRODUCTION

Pregnancy is considered a unique, physiologically normal episode in a women's life. While most pregnancies and births are uneventful, all pregnancies are at risk. Around 15% of all pregnant women develop a potentially life-threatening complication which in turn require a major obstetrical intervention to survive.[1]

Labour is a naturally occurring phenomenon which usually starts on its own. Labour is defined as the spontaneous onset of regular painful uterine contractions associated with the progressive effacement and dilatation of the cervix and descent of the presenting part, with or without a 'show' or ruptured membrane.[2]

Preterm Labour (PTL) is defined by World Health Organization (WHO) as the onset of labour after the period of viability that is after 28 weeks of gestation and before 37 completed weeks or 259 days of pregnancy .It is estimated 15 million preterm births occur worldwide. Pre-term birth is associated with significant perinatal morbidity and mortality rates. About 35% of preterm birth follows preterm pre-labour rupture of membrane. The early detection of preterm labour or preterm rupture of membranes in traditional antenatal care is problematic because symptoms or signs may vary only a little from the normal physiological symptoms and signs of pregnancy.[3] Hence detailed guidelines required to screen or manage pre-term labour.

More than 1 in 10 of the world's babies born in 2010 were born prematurely making an estimated 15 million preterm births (defined as before 37 weeks of gestation), of which more than 1 million died as a result of their prematurity. Preterm birth is divided into several categories, based on weeks of gestational age:

1) Extremely preterm (<28 weeks)
2) Very preterm (28 to <32 weeks)
3) Moderate to late preterm (32 to <37 weeks).
4) Moderate preterm birth may be further split to focus on late preterm birth (34 - <37 completed weeks).

Preterm birth is a syndrome with a variety of causes which can be classified into two broad subtypes:

1) Spontaneous preterm birth (spontaneous onset of labour or following pre-labour premature rupture of membranes (PPROM)) and
2) Provider-initiated preterm birth (defined as induction of labour or elective caesarean birth before 37 completed weeks of gestation for maternal or fetal indications (both "urgent" and "discretionary"), or other non-medical reasons. Around 60% of preterm births in the world occur in Africa and South Asia, and it is truly a global problem. India had 3 519 100 preterm birth in 2010.[4]

Review of Literature

REVIEW OF LITERATURE

WHO defines Preterm labour as "*the commencement of regular uterine contractions, between viability and 37 weeks of gestation, along with cervical effacement and dilatation.*

Preterm delivery before 26 weeks or babies weighing less than 750 gm are at the current threshold of viability according to ACOG 2002, 2008 and suffer from many problems like medical, social. According to American Academy of Paediatrics current guidelines it is not necessary to resuscitate infants born prior to 23 weeks or those weighing less than 400 gm. Infants born at 22, 23, 24, or 25 weeks are considered to be under threshold due to immature organ systems. These infants are at higher risk for ischemic brain injuries as active brain development occurs during second and third trimester.

According to Tyson and associates (2008) factors improving the prognosis of preterm infants at the threshold of viability were singleton pregnancy, female gender, steroids given for foetal lung maturation, and higher gestational age.

In 2008 Mc Intire and Leveno reported that idiopathic natural preterm labour or premature tear of membranes constituted 80% of late preterm births and the rest of 20% was constituted by complications like hypertension, placental abnormalities.

REASONS FOR PRETERM DELIVERY

About 40-45% of preterm labour occurs spontaneously and 30% because of rupture of membranes (preterm) , and the rest 30-35% are induced preterm labours. One of the major reasons for preterm include multiple pregnancies. Etiology of preterm labour is multifactorial.

Some of the factors attributing to preterm are:-

- **Delivery for maternal or fetal indications**
- **Idiopathic preterm premature rupture of membranes**
- **High order births**
- **Uterine anomalies**
- **Foetal anomalies**
- **Genital tract infections**
- **Placental causes**
- **Foetal causes**
- **Unexplained reasons**

Delivery for maternal or foetal indications:

Indicated preterm delivery is done for various reasons. One third of preterm delivery is iatrogenic indicated for maternal or foetal reasons. These include:

Maternal causes

- Preeclampsia
- Placenta previa

- Abruption
- Chronic hypertension
- Diabetes
- Renal disease
- Cardiac disease

Foetal causes

- Foetal distress
- Severe foetal growth restriction due to utero placental insufficiency
- Rh iso immunisation
- Severe oligohydramnios
- Congenital malformation.

Idiopathic preterm premature rupture of membranes

Preterm rupture of membranes may occur due to reduction of membrane strength or due to increased intrauterine pressure theoretically. The amniotic membranes is a connective tissue and any defect in synthesis, degradation or collagen quality can result in preterm rupture of membranes.

High order births

Multiple gestation constitutes about 12-15% of all preterm births. Multiple gestations cause over distention of uterus resulting in initiation of preterm labour, infection, preterm rupture of membranes..Early activation of CRH and the physiological pathway for parturition,and over distention mechanical force

leading to activation of protein kinase. Mitogen –activated protein kinases and increased expression of G proteins that induce myometrium contractility are the proposed mechanisms of preterm labour.

Uterine Anomalies

Congenital anatomical abnormalities of uterus and cervix are seen in 1-3% of preterm births. They occur due to mullerian ducts defect and septate and bicornuate uterus are clinically significant. The rate of preterm delivery in these patients range about 16-20%. Overdistention of uterus caused by multiple gestation, polyhydramnios also contribute to preterm labour.

Cervical Abnormalities

About 5 % of preterm births are due to anatomical or physiological abnormalities of cervix. These include women exposed to diethylstilboestrol during intrauterine period, who had conisations or cervical surgeries.

Genital tract infections

Infection is one of the most common cause of preterm labour and responsible for 20-40% of all preterm cases. The most accepted mechanism is ascending infection. This theory suggests an occurrence of break in the normal physiological barrier present between the vaginal flora and the products of conception. The vaginal bacteria ascend through the breech and colonise the decidua and chorion and then enters the amniotic fluid and the foetus. This is supported by the fact that organisms secluded from the amniotic fluid and the vagina are similar. The vaginal flora is separated by the cervix and the cervical

mucus plug. Cervical changes and changes in mucus plug contribute to ascending infection. Common organisms include Chlamydia, group B streptococcus, trichomonas, Gonococcus. Repeated pelvic examination during pregnancy and sexual intercourse are also implicated.

According to Goldenberg and colleagues (2008b) these intrauterine infections trigger the innate immune system and activate preterm labour. These organisms initiate the release of inflammatory cytokines like tumour necrosis factor and interleukins which stimulates prostaglandins production which leads to uterine contractions there by leading to preterm labour.

Intra uterine infections – Chorioamnionitis

Acute chorioamnionitis diagnosis is clinical and is diagnosed by the presence of fever and 2 of the following features maternal or foetal tachycardia, bad smell of amniotic fluid, maternal leucocytosis, uterine tenderness. Labour in these patients occur as a protective mechanism.

Subclinical chorioamnionitis is an infection of the conceptus without clinical signs or symptoms of the disease. This condition occurs in preterm labour with ruptured membranes or incompetent cervix. Patients with subclinical chorioamnionitis present with uterine contractions. The diagnosis is by amniotic fluid analysis for Gram stain, white cell count, concentrations of interleukin 6, glucose, lactate dehydrogenase and cultures. The most common organisms isolated are Urea plasma urealyticum, Mycoplasma hominis,Fusobacterium species and Gardenella vaginalis.

The leukocyte count in amniotic fluid analysis WBC >12,000/mm3 or or left shift or bandemia (>9%) suggests chorioamnionitis. Concentration of glucose in amniotic fluid is also used as a method to diagnose chorioamnionitis. The best marker for chorioamnionitis is IL-6 concentration of greater than 7.9ng/ml in patients with ruptured membranes and more than 11.39 ng/ml in patients with intact membranes.

Extra uterine infections

Bacteria may acquire contact to the lower pole of the uterus though a normally functioning cervix, because of an increased number of virulent pathogens in the vagina, where they activate inflammatory mediators that leads to cervical ripening and shortening. **Placental causes**

- Abnormal placentation
- Anatomical abnormalities
- Placenta praevia
- Abruption placenta

Abnormal placentation

Abnormal placentation has been implicated as one of the causes of preterm labour. Histological studies of placenta (Arias et al.,1993) in preterm labour shows some defect in spiral arteries development, spiral artery thrombosis, and the placenta are small and have calcifications, infarctions and fibrosis . Decrease in uteroplacental flow causes foetal growth retardation and hence account for low birth infants in preterm labour(Lackman et al., 2001). Studies have shown that

patients with Doppler abnormalities in early gestation have higher incidence of preterm labour. Abnormal morphology, implantation, and functions of placenta also result in preterm labour.

Anatomical abnormalities

Marginal insertion of cord, battledore placenta, circumvallate placenta are also associated with preterm labour.

Abruption placenta

Placental Abruption is an abnormal premature separation of a normally implanted placenta. There are different kinds of abruption, based on the extent and region of separation.

Abruption of the placenta may lead to preterm labour, through the thrombin release, which encourages myometrial contractions by protease-activated receptors. With placental abruption, there is no time for pre-ripening of the uterine cervix to occur, hence the preterm labour with chorioamnionitis is mostly quick, whereas those with placental abruption, is less. (Phillip R.Bennet, 2011).

Placenta Previa

Placenta Previa can be defined as placenta inserted in wholly or partially in the lower uterine segment. This also causes preterm labour.

Foetal causes

Birth defects were associated in preterm deliveries according to Dolan and colleagues (2007).

EPIDEMIOLOGY

RACE

Preterm birth rates vary with different ethnicities and races. According to Goldenberg and colleagues in 2008 Black, African-American and Afro-Caribbean have a higher risk of preterm birth. Recurrent preterm birth is seen in black women according to Kistka and Colleagues, 2007.

Gene in 1996 reported that the rate of pre-term birth in African American women (2000) was not influenced by social and demographic factors.

AGE:

Preterm birth is associated with parity and maternal age. Young multiparae and older primiparae have higher risks of preterm delivery. According to Lumley Jm et al 1993 the incidence of preterm delivery is high in mothers less than 17 and more than 35 yrs. Very young maternal age can contribute to preterm labour (Amini et al, 1996). According to Hediger et al, (1997) adolescent girls less than 16 years, have twice the risk of preterm labour considering with older women. At the other end, women aging 35 and over too higher preterm delivery risks (Astolfi and Zonna 2002)

WEIGHT

Poor nutrition, pre pregnancy weight and weight gain during pregnancy play an important role in causing preterm labour. Hicklyand colleagues in 2005 have reported that low maternal weight gain is often associated with preterm birth.

STATURE

Short statured women have tendencies to deliver small babies. According to Lao and Ho, 1997 indicated that preterm delivery and labour risks was more in teenage pregnancies, and the occurrence was conversely related with maternal height. This proposed that the characteristic risk of preterm delivery in teenagers was short stature, which in turn could have been a reflection of young physical development during pregnancy.

SOCIOECONOMIC STATUS

The reasons for socioeconomic differences in preterm births are not clear, and have not been much explored. A number of reasons like maternal nutrition, smoking, abuse, activities, work and prenatal care have been implicated with preterm births. Women from lower socio economic status tends to be less educated and would not have satisfactory general, prenatal and antenatal care (Goffinet F 2005)

Low socioeconomic status on health appears to directly affect the incidence of preterm labour (Moutquin, 2003). Many studies show an correlation between preterm birth and numerous socioeconomic issues like societal class, education, marital status, earnings. Maternal nutrition before and during pregnancy have

contributed to the risk of preterm births, and this can be analysed by body mass index (WHO, 1995).

ADDICTIONS

Women who smoke and cocaine users are at increased risk of preterm labour (Bens 2004). The correlation between smoking and preterm birth was only existing among women with an increased intake of caffeine. Smoking more than 20 cigarettes per day has resulted in the increased incidence of pre-term birth under 34 week's gestation. Smoking initially associated with placental abruption, placenta praevia and pre mature rupture of membranes has now been linked with pre term delivery (Cnattingius 1998). Boer et al 1993, Volpe studied the increased incidence of pre-term birth in women addicted to opiods. Though, whether smoking alone effects the risk of preterm birth among heavy users of caffeine requires further investigation.

Studies show women who abuse cocaine have high incidence of preterm labour, and it was partly attributed to the abruption caused by cocaine addiction. (Boer et al)

Studies relating consumption of alcohol with the risk of pre-term labour are very few.

Occupational hazards

Those involved in manual work are more prone for preterm labour

PREDISPOSING FACTORS

Stress:

Preterm birth is associated with psychological factors such as depression, anxiety and chronic stress (Copper: 1996, Li 2008, Littleton 2007).Occupation which involve heavy physical work and psychological strain are associated with increased preterm births (Papiernik and Kaninski 1994).The utero placental flow decreases in prolonged standing and increases the frequency of placental infarcts causing intrauterine growth retardation. Preterm birth is increased in women who are subjected to physical abuse. Henribon et al 1995 reported that heavy vigorous exercise in the third trimester increased the risk of pre-term delivery while regular and moderate exercise were actually showing a reduced risk.

Coitus

Various theoretical mechanisms have been proposed for initiation of labour by sexual activity. These are nipple and genital stimulus may induce oxytocin release from the posterior pituitary, initiating uterine contractions.Prostaglandins that is released from mechanical stimulation of the cervix may be the reason of cervical ripening and prostaglandins in semen may also cause cervical ripening. Mills and co-workers found in singleton low-risk pregnancies sexual activity did not increase the frequency of preterm labour.

The influence of sexual interaction on recurring preterm delivery in women with history of prior spontaneous preterm birth was studied by Yost and colleagues at less than 32 weeks' gestation and concluded that sexual intercourse

had no effect on the occurrence of recurring preterm delivery. But the risk of recurrent preterm delivery increased with multiple sexual partners.

Reproductive History

a)Previous preterm birth

The risk of preterm delivery increases with a history of previous preterm delivery. Spong, 2007 concluded that previous preterm delivery was a major risk factor for preterm labour.

History of one previous preterm birth is associated with a recurrence risk of 16-41 % (Williams 22”’ edition).Preterm delivery risks increases with the number of preterm birth and decreases with term deliveries. This risk is on an increasing trend whenever the number of prior preterm births increases (Hoffinan 1981). Women having a prior preterm delivery have threetimes the risk of recurrence compared to a woman who has got a previous term delivery. This risk increases to eight fold whenever there is a history of two preterm deliveries. Though preterm delivery is an important risk factor to recurrent preterm delivery, previous preterm birth contributes to only 10% of total preterm births(Bloom and associates 2001). Factors such as cervical length and inherent biological property of the cervix may contribute to the recurrence of preterm births.

b) Previous abortion

Preterm deliveries increase in women who experienced one or more second trimester abortions. Earlier encouraged abortions were mainly linked with preterm delivery and the risk of preterm birth increased with the number of abortions. The

extent of association with previous induced abortion varied according to the cause of preterm delivery. Prior encouraged abortions mainly increased preterm delivery risks after idiopathic preterm labour, preterm premature rupture of membranes and ante-partum haemorrhage, but not preterm delivery after maternal hypertension. The strength of the correlation increased with decreasing gestational age at birth.

c) Cervical incompetence

Cervical Incompetence is diagnosed clinically by recurrent painless cervical dilation and spontaneous mid trimester abortions in the absence of membrane rupture, bleeding or infection. . This can lead to protrusion of the membranes into the vagina followed by expulsion of the immature foetus. This may repeat in future pregnancies if not treated.

Some of the causes are previous traumatization of the cervix caused by

- Dilatation and curettage
- Conisation
- Cauterisation
- Amputation of cervix

According to Albrechten and colleagues (2008) there is a fourfold risk of pregnancy loss before 24weeks in patients who had undergone cervical conisation.

d) Uterine anomalies:

e) Pregnancy complications

- Multiple pregnancies ,Hydramnios
- Preeclampsia
- Antepartum hemorrhage
- Second trimester bleeding not due to placental causes

Interval between pregnancies

Interval between pregnancies play a major role in preterm labour. Intervals shorter than 18 months and longer than 59 months has been considered as increased risk for preterm & small for gestational age infants (Conde - Agudelo 2006)

Preterm births was increased if the interval between childbirth and LMP of next pregnancy was less than 3 months. Bloom et al in 2001 found a threefold increase in risk if previous birth was preterm compared to a previous term pregnancy. A previous occurrence of preterm birth before 34 weeks may increase the risk of recurrence. (Krymko et al 2004)

Foetal Gender

Male babies have an increased chance of preterm delivery compared to female babies.

PATHOGENESIS OF PRETERM LABOUR

The normal labour involves three components namely cervical ripening, myometial and foetal membrane activation. Preterm labour can be physiological or pathological if it occurs prematurely or due to an abnormal stimulus respectively. Though etiology of preterm labour is multifactorial infection is implicated in initiation of preterm labour.

Withdrawal of progesterone theory established in parturition in sheep is not clear in humans. Increased synthesis of prostaglandins initiate parturition.

The intrauterine tissues synthesise prostanoids which play an important role in the commencement or maintenance of labour in a number of species. The amnion during labour produces more amount of PGE2 (Mitchell, 1986; Casey and MacDonald, 1986), which stimulates the physiological process leading to birth. Though the stimulus for preterm labour varies the final pathway involves the inflammatory mediators cytokines.

Cervical Ripening

This involves transformation of firm long cervix to soft distendable cervix. Cervix is predominantly made up of connective tissue namely fibroblasts and extracellular matrix. At end of pregnancy, there is increase in collagenase activity and hyaluronic acid production which decrease the collagen content and increase the water content of cervix.Sex steroids and prostaglandins are involved in initiation of parturition.

Activation of foetal membranes

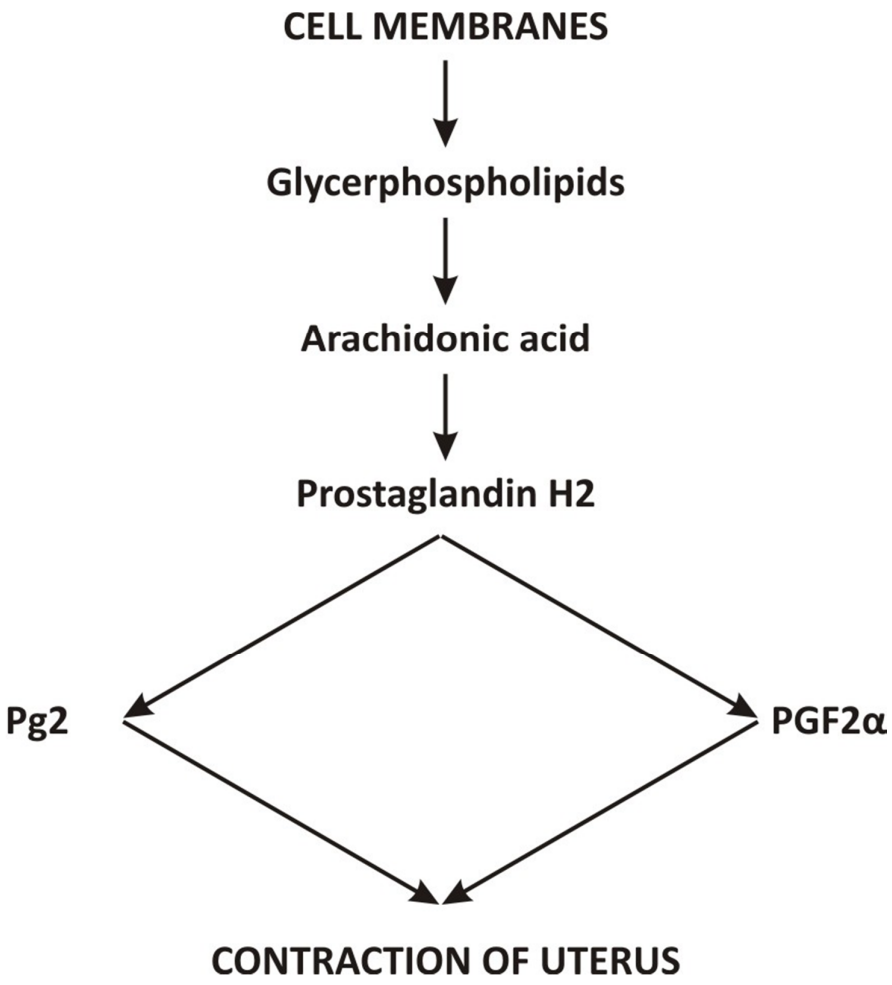
During pregnancy, the chorioamnionic membranes fuse with the decidua. Many biochemical reactions occur in term and preterm labour which cause the separation of the foetal membranes from the decidua which results in rupture of membranes. Fibronectins are present at the chorionic-decidual interface which are degraded and released into cervical and vaginal secretions immediately before term and preterm parturition. Beyond proteolytic degradation of the decidual and amniochorionic extracellular matrix by matrix-degrading enzymes, PROM is also associated with amnion epithelial apoptosis and localized inflammation. Enzymatic activity of matrix proteases are involved in the processof rupture of membranes and parturition with intact membranes.

Contraction of myometrium

In pregnancy uterine contractions are inhibited by progesterone, relaxin, and nitricoxide. At the end of pregnancy these substances reduce making the uterus respond to uterotonic agents. Increase in intracellular concentration of calcium is implicated in uterine contractions. Though uterine contractions play a vital role in preterm labour compared to cervical ripening or foetal membrane activation studies involving myometrial activity are limited.

Prostaglandins play an important role in preterm labour. Csapo (1961) proposed that labour commenced when the balance between myometrial stimulants and relaxants is lost. Prostaglandin endoperoxide H synthase increases the rate first, committed step of prostaglandin synthesis from arachidonic acid

(Smith et al, 1991). Prostaglandin endoperoxide H synthase activity increases in the amnion at parturition. According to DeWitt (1991) and Smith et al (1991), the prostaglandin endoperoxide H synthase expression is affected by various substances like growth factors, vascular cells, cytokines, steroids and tumour promoters in fibroblasts, and monocyte- and macrophage-like cells



Role of Cytokines in Preterm labour

Cytokines such as interleukin 1,2, 6 and 8 and tumour necrosis factor are implicated in preterm labour. Infection is associated with by a host-inflammatory response, which causes accumulation of inflammatory cells in the chorioamnionic membranes and thereby increasing the expression of cytokines .This inflammatory process can trigger the onset of preterm labour by myometrial contractions, PPROM and cervical ripening. This is supported by the fact that there is an increased cytokine levels (e.g. interleukin-6 [IL-6] and IL-8) in the amniotic fluid of patients with preterm labour. .Interleukin 1 and tumour necrosis factor cause rupture of foetal membranes.

In Sweden a study conducted about the association between the intra-amniotic microbial colonisation and the levels of IL-6 and IL-8, and their association with preterm birth revealed that microorganisms in the amniotic fluid were detected in 16% of women in preterm birth and 25% of women with PPROM. It was also found that a high ratio of cases with preterm labour (43%) and PPROM (57%) had raised IL-6 and or IL-8 levels in the amniotic fluid, indicating an inflammatory response.

Hence a solid relation between inflammation, microbialisation and preterm birth was established. Level of cytokines in amniotic fluid predicted preterm birth.

Interleukin-18 has also been found to play a major role in preterm labour. It is produced as a proform and is stimulated by the enzymecaspase-1. This in turn

activates intracellular signalling pathway through interface with the IL-18 receptor causing pro-inflammatory molecules, like interferon-g, tumour necrosis factor-a (TNF-a) and IL-1.Hence IL-18 can be considered to play a vital role in infection leading to preterm birth. Levels of IL-18 seem to be raised in the cervical and amniotic fluid of women in preterm labour compared with those not in labour at term.

DIAGNOSIS OF PRETERM LABOUR

Cunningham Gil and co-workers (2001) found that preterm labour is established when regular uterine contractions occur at least 4 in 20 minutes or 8 in 60 minutes with progressive change in cervical score with effacement 80% or more and dilatation more than 1 cm occurs.Preterm labour can be diagnosed by various factors .Preterm labour can be diagnosed by clinical methods and by investigations.

Threatened preterm labour is a condition in which uterine contractions occur in the absence of cervical changes.

PAPIERNIK SCORING SYSTEM

Points	Socioeconomic factors	Previous Obstetric /Medical History	Social	Aspects of current Pregnancy
1	Two living children low socioeconomic status	H/o 1 abortion / less than 1 year of last child birth	Employed	Unusual fatigue
2	Maternal age <20 or >40 years/single parent	H/o 2 abortions	Smoker 10 Cigarettes/ day/ moderate work	Gain <5g by 32 weeks
3	Very low socioeconomic status Ht< 150cm wt<45 kg	H/o 3 abortion	Heavy work / long distance traveling	Breech 32 weeks/ weight loss /head engaged at 32 weeks / febrile illness
4	Maternal age <18 year	Pyelonephritis		Bleeding after 12 weeks / short cervix open internal OS uterine irritability
5		Uterine anomaly second trimester abortion /DES exposure/cone biopsy		Placenta Praevia Hydramnios
6		Preterm delivery ,repeated second trimester abortion		Twins/ abdominal surgical procedure

SYMPTOMS

- Menstrual like cramps
- Low dull back ache
- Increase or change in vaginal discharge
- Uterine contractions 10 minutes apart or closer

CLINICAL ASSESSMENT

Uterine contractions

Uterine contractions is the main symptom of preterm labour. There should be regular uterine contractions of at least 4 in 20 minutes or 8 in 60 minute each lasting not less than 40 seconds.

Uterine Activity Monitoring

Although teaching a woman to self-monitor her uterine contractions is a simple inexpensive method, there are lot of subjective variations in it which makes it less reliable .The perception of the contractions in terms of frequency ,intensity, duration may vary between the health care providers hence a tocodynamometer can be used to assess the contractions. One of an earlier case control study reported a decrease in the preterm delivery rates on using the ambulatory monitoring system.(Katz et al 1986).

Current opinion is that for most patients home uterine monitoring is no better than frequent nursing care and support. Only patients, who cannot recognize the presence of uterine contractions adequately like multi foetal gestation and over distended uterus may benefit from home monitoring.

These contractions are accompanied by progressive cervicalchanges.

CERVICAL ASSESSMENT

The clinical diagnosis of labour is dependent on the presence of uterine activity with cervical effacement and dilation. One of the main sign of term or preterm labour is cervical change. When patients come with the complaint of pain after confirming uterine contractions pelvic examination is done. The following features are assessed namely position, consistency, dilatation, effacement of the cervix. This digital examination is not precise as there are inter- and intra-operator errors.

CERVICAL LENGTH

Cervical length measurement by digital examination formed the gold standard for diagnosis of preterm labour. Women with shorter cervices experienced increased rates of preterm birth.

The manual assessment of cervical length is subjective and has poor inter and intra observer variability. The cervix shortens and dilates at the level of internal cervical os. This process cannot be appreciated on a digital examination. Transvaginal ultrasound examination of cervical length is better than digital

examination in predicting preterm delivery. Hence cervical length measurement by ultrasound is used for prediction of labour.

The normal way of evaluating cervical length is by endo-vaginal ultrasound. Different measurements have been used to define short cervix. In patients with short cervical length, the “T” that is seen in ultrasound of cervix becomes “Y” and later on “U” as the amniotic sac descends. Though the conclusion of a short cervix does not mean incompetence and it is only a proposal, and neither can it identify, the pathological reasons for it. Before 1994, the studies done were surveyed by cerclage, making it harder to confirm. Later Jams et al; 1994, reported a means cervical length at 24 weeks around 35mm with progressively shorter cervix had more changes of preterm delivery.

Owen and co-workers concluded in 2003 that the value of cervical length to predict birth before 35 weeks is apparent only in high risk patients for preterm delivery .Studies by De Caralto et al 2005correlated the cervical length to preterm delivery. Hassan et al 2000 & 2001, found that when the cervical length was less than 25 mm, there was a high chance of preterm delivery with the normal mean length of cervix at 23 weeks of gestation being 35mm to 38 mm with the 10^{th} and 90^{th} percentile being 25mm and 45mm respectively.

A cervical length of 21mm at less than 20 weeks of gestation was shown by Cook et al (2000) to be associated with high risk preterm delivery. Owen et al (2001) showed at 3.3 time’s higher risk for preterm delivery if the cervical length

of 25 mm or less is seen at 16-19 weeks of pregnancy. An ultrasound screening every two weeks was also found to be significantly helpful (Andoers et al 2000).

FUNNELING

In women who are prone to deliver prematurely herniation of the foetal membranes occurs into the upper part of the endocervical canal.

Although the length, width and relationship of funnel to cervical length have been studied, there are no uniform criteria to describe funnelling. The reporting of funnelling as present or absent on ultrasound is a significant conclusion to be cited as its found equivalent to dynamic cervical changes. Rust et al (2005) showed the risk of preterm labour, higher incidence of complication and cerclage placement in women with both cervical shortening and funnelling.

Dynamic cervical changes

The opening of the internal os and descent of the foetal membranes on fundal pressure during ultrasound was found to be significant risk factor for preterm labour (Gwzman et al, 1994). Passive or dynamic ultrasound finding of shortening of the cervix between 15 and 22 weeks is a significant predictor of additional cervical shortening (Gwzman et al, 1997). The myometrial activity in painless uterine contractions leads to dynamic changes and is an indication that that the cervix is opening during these contractions.

Cervical dilatation

A study by Papiemik and his colleagues (1987) on cervical status before 37 weeks, concluded that risk of preterm labour is increased by precocious cervical dilatation. According to Levino and associates, one in four women who had dilated cervices (2-3cm) between 26 and 30 weeks, had their delivery before 34 weeks. Copper and associates (1995) have found that asymptomatic cervical dilation that occurs after mid pregnancy is significant preterm labour risk reason. Pereira and co-workers, (2007) identified cervical dilation as a predictor of a higher preterm delivery risk.

CERVICAL INCOMPETENCE

Premature cervical dilatation is associated with increased risk of preterm labour (Papiemik and colleagues 1987).In a study by Levino and associates one fourth of the women who cervices were dilated 2 to 3 cm between 26 and 30 weeks delivered before 34 weeks .Asymptomatic dilatation of cervix after mid trimester is considered as a risk factor for preterm labour. In a study by Cook and Ellwood. Cervical status of nulliparous and parous women between 18 and 30 weeks was followed up and both the groups gave birth to term. Copper and associates in 1995, Pereira and colleagues in 2007 have suggested cervical dilatation as an increased risk for preterm labour.

INVESTIGATIONS

Foetal fibronectin

Foetal fibronectin is produced in 20 different types of molecular forms by different kinds of cells. These includes hepatocycles, fibroblasts, endothelial cells and foetal amnion.Foetal fibronectin is found in high concentration in both maternal blood and amniotic fluid. They are thought to play an initial role in intercellular adhesion during implantation and in maintaining placental attachment to the exterior decidue according to Lesson and colleagues (1996).

Foetal fibronectin is found in cervical secretions in term patients and normal patients with intact membranes. This denotes stromal remodelling of the cervix before labour. It is normally found in cervico vaginal secretions before 16-18 weeks gestation before the fusion of the foetal membrane to thedecidual and then towards term prior to the onset of labour. It is usually not found between 22 and 37 weeks of gestation.

Lockwood and co-workers in 1991 reported that fibronectin in cervicovaginal secretions can be considered as a marker for impending preterm labour. Swabs taken from posterior fornix or cervix is used for the detection of foetal fibronectin by ELISA method with FDG 6 monoclonal antibody. Value exceeding 50 mg/ml is considered as positive. Quantitative tests takes a longer time to develop, hence bedside tests have been developed. High false positive rates are there if sample is contaminated with amniotic fluid, semen, maternal blood, patients with encirclage. Goldberg and co- workers in 2000 reported

detection of fibronectin in the vaginal or cervical secretions as an important predictor of preterm labour.

Leitich and co-workers performed a comprehensive meta-analysis on the efficacy of foetal fibronectin in identifying women at risk for preterm delivery. They noted that the test's usefulness was a result of its high specificity and was limited by the low sensitivity in identifying women who would go on to deliver prior to 34 weeks gestation. The sensitivity of the test decreased further in identifying women who would deliver prior to 37 weeks but increased when it was used serially.

In order to maximize foetal fibronectin, its use should be restricted to women with intact membranes, cervical dilation less than 3 cm, and gestational age between 24 and 34 completed week's gestation, and results should be available within 24 hours. False-positive foetal fibronectins may be obtained in women with recent intercourse or vaginal examinations or in the presence of bacterial vaginosis and vaginal bleeding.

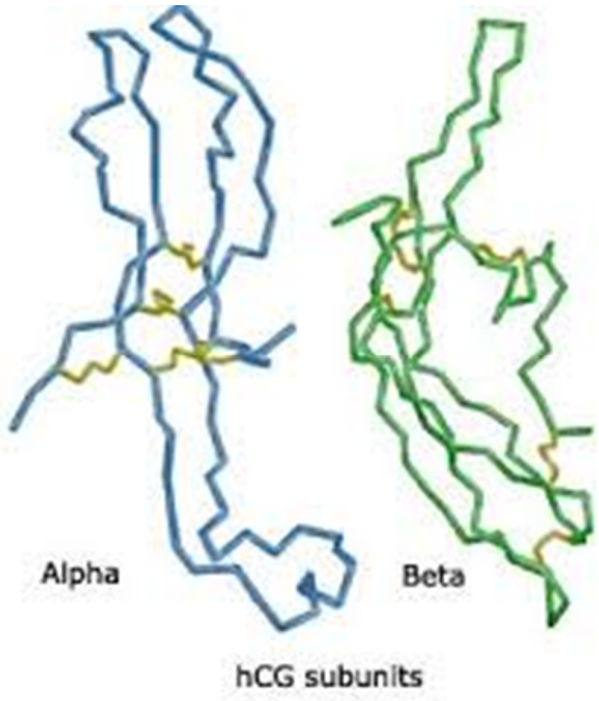
In general, the sensitivity of foetal fibronectin increases in symptomatic women, women with a cervical length of less than 2.5 mm, women with a history of prior preterm delivery, and women with bacterial vaginosis. The negative predictive value in women with preterm contractions ranges from 69% to 92% before 37 weeks gestation. Importantly, a negative foetal fibronectin has a 95% likelihood that delivery will not occur within 14 days of sampling..

The Preterm Prediction Study of the National Institute of Child Health and Human Development analysed the sensitivity, specificity and predictive values of Bishop Score, fibronectin test and cervical length in predicting preterm labour in asymptomatic women (Iams et al, 2001)

B-HUMAN CHORIONIC GONADOTROPHIN.

STRUCTURE:

HCG is a glycoprotein composed of 237 amino acids.Its molecular weight is of 25.7 kDa.[7]



hCG subunits

It is a heterodimer, with an α (alpha) subunit which shares structural similiarity luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH)

β (beta) subunit is unique to hCG.

The α (alpha) subunit is composed of 92 amino acids.while the β-subunit of hCG gonadotropin (beta-hCG) contains 145 amino acids.It is encoded by six highly homologous genes that are arranged in tandem and inverted pairs on chromosome 19q13.3

SYNTHESIS:

It is synthesized by syncytiotrophoblasts of human placenta.

Its levels mirror the growth rate of the developing embryo. beta-hcg is present in high concentrations in the amniotic fluid and maternal serum during pregnancy, with a close correlation between their concentrations. The concentrations of beta-hcg in the maternal serum and amniotic fluid rises gradually and peaks between the eighth and 12th weeks of gestation and then declines and remains plateau from the 18th week of pregnancy onwards (Bernstein,etal,1998). During the process of labour, the choriodecidual interface is disrupted releasing B HCG into the cervical secretions

Diagnosis of preterm labour poses a major problem. Any test that can precisely diagnose preterm labour will be of much help. One of the latest modality in predicting preterm labour is B-HCG in cervical secretions..There is contradictory literature on the role of beta-hcg as a marker of preterm delivery. Some investigators believe that there is an association between the presence of beta-hcg in maternal serum and preterm delivery (Lieppman et al, 1993; Oneroglu

et al, 1997; Van et al, 1999; Goffinet et al, 2001; Benn et al, 1996; Liu et al, 1999). However, there is also evidence suggesting that there is no relationship between them (Morssink et al, 1995, 1998). Alternatively the presence of beta-hcg in cervicovaginal fluid may be considered as a marker of preterm delivery, although the sensitivity, specificity, positive and negative predictive values vary between studies (Guvenal et al, 2001; Bernstein et al, 1998; Anai et al, 1997).

BHCG levels can be qualitatively estimated by ELISA using sandwich technique with Monoclonal antibodies specific to the Beta subunit .Quantitative estimation is accomplished with the aid of immune chromatographic techniques.

The purpose of this study was to determine the correlation between concentration of beta-hcg in cervicovaginal secretions and preterm delivery.

AMNIOCENTESIS TO DETECT INFECTION:

There are several tests to analyse intra-amniotic infections. Tests done by Romero and his colleagues in 1993 in 120 women with intact membranes and preterm labour, were used to assess the value of amniotic fluid that had increased leukocyte counts, elevated interleukin -6 concentration or a positive Gram stain, and reduced glucose level.

Those results with positive amniotic fluid culture were counted as infected. The experiments concluded that a negative Gram stain result was 99% to dismiss amniotic fluid bacteria. An increased value of interleukin-6 level, was 82% sensitive for finding out amniotic fluids that has bacteria.

There are other studies by Andrews and co-workers (1995) and Yoon and colleagues (1996) which have also proven that there exists a relation between the amniotic fluid inter leukin-6 levels (or leukocyte levels) and chorioamnio infections. Although these studies prove the relationship between the two, it is not confirmed that amniocentesis to identify infection is related with improved pregnancy results with or without rupture of membranes in women (Einstein and co-workers, 1986).It is determined that there is no indication to support routine amniocentesis to detect infection.

OTHER BIOCHEMICAL MARKERS

1. Salivary oestriol> 1.8/mi before 34 weeks has sensitivity of 68% and specificity of 76% for preterm labour before 35 weeks of gestation(Darne et al)
2. Serum collagenase
3. Tissue inhibitor of metalloproteinase (TIMP)/Matrix metalloproteinases
4. Relaxin
5. Corticotrophin Releasing Hormone

These are of less practical value in prediction of preterm labour

Mediators of Inflammation and Infection

a) C — Reactive protein

b) Granulocyte elastase

c) Cytokines (IL-6, TNF)

d) Amniotic Fluid Glucose Concentration

e) Zinc

f) Lipocortin -l (Romeo R et al)

g) Positive cultures

h) Granulocyte colony stimulating factor

These are not practically helpful in prediction of pre-term labour.

MANAGEMENT OF PRETERM LABOUR

The management of preterm labour includes

- To prevent preterm onset of labour if possible
- To arrest labour if not contraindicated
- Appropriate management of labour
- Neonatal care

PREVENTION OF PRE TERM LABOUR

Prevention is an important strategy in the management of a patient at high risk of preterm labour. The following guidelines are adopted:

i) Primary care

Aimed to reduce incidence by reducing the high risk factors.

ii) Secondary care

Screening for early detection and prophylactic treatment.

iii) Tertiary care

Aimed to reduce the perinatal morbidity and mortality after the diagnosis.

Basic care

Development of family support, education, supportive services from health care providers

- ❖ Behavioural and life style modifications
- ❖ Adequate nutrition.
- ❖ Cessation of smoking (Burguet et al)
- ❖ Avoidance of illicit drugs

Bed rest, hydration and sedation

Although bed rest and hydration are widely used as the first step of prevention, its practical benefit is questionable(Goldenberg et al).

Kovacevich et al in his studies showed that bed rest of more than three days was associated with an increased occurrence of thrombocmbolic events in women with threatened pre-term labour.

Some studies have reported the increased risk of development of pulmonary edema, when intravenous fluids are administered during tocolytic therapy. There is no substantial evidence of hydration therapy in causing pregnancy prolongation. Hydration therapy however has been rarely studied as a single therapy in prevention or treatment of pre-term labour.

Cochrane systematic review showed no significant difference in the risk of pre-term labour in women who received hydration therapy. Comparative trials have been conducted between combination of sedation with hydration vs

intramuscular opiods in reducing the occurrence of preterm delivery and the results were found to be similar in both groups.

Treatment of infections

About 25 — 40 percent of preterm births are estimated to result from intrauterine infections (Cunningham et al 2010) Morency and Buyold (2007) seemed to indicate that antibiotics given in the second trimester to females with a past of preterm labour would be effective in preventing reappearance of preterm labour.

Most Randomized control trials show that intra vaginal clindamycin cream used to treat bacterial vaginosis did not reduce the rate of preterm birth. Carey et al (2000) used oral metronidazole to treat bacterial vaginosis but did not find a reduction in preterm birth. Methodical evaluation determined that screening and treatment of asymptomatic bacteruria and bacterial vaginosis may lessen the occurrence of preterm in low risk population

Cervical encerclage

Primary cerclages are placed prophylactically in women considered at high risk of preterm birth based on obstetric history. Secondary cerclages are placed when ultrasound findings are indicative of cervical insufficiency in high risk women.

Tertiary cerclages are done as an emergency process in the presence of positive clinical examination findings.The 1993 MRC/RCOG Multicenter Randomized experiment determined that clear benefit was seen only in patients with a history of three or more spontaneous births or preterm deliveries (Mac Naughton et al 1993)

In 2001, CIPRACT Trial, Cervical Incompetence Prevention Randomised Cerclage Trial showed that patients with cervical insufficiency and cerclage placement had a lower incidence of preterm delivery prior to 34 weeks (ALTHUISIUS ET AL 2001)

Rest Ct al 2000 concluded that cerclage failed to alter any perinatal outcome Daskalakis et al (2006) reported the benefits of emergency cerclage. In preterm labour Dor et al 1982 and Roman et al 2005 reported that elective cerclage had no benefit in twin gestation. Two randomized trials by Lazr et al and Rush et al showed no benefit of routine cerclage in women at moderate risk for preterm labour.

EMERGENCY OR RESCUE CERCLAGE

There are certain studies that show that cervical incompetence and preterm labour together may lead to preterm delivery.Studies have analysed the importance of cerclage that is done after preterm labour initiates. If cervical incompetence is found with risk of preterm labour, emergency cerclage can be tried, although there is risks of pregnancy loss and infection (Harger, 1983). In an

experiment conducted by Althuisius and his co-workers, among 23 women with cervical incompetence before 27 weeks patients were subjected to bed rest with or without McDonald cerclage. The result was, that delivery delay was more in the group with cerclage than that of bed rest alone by 54 and 24 days respectively.

Another study was done by Terkildsen and his colleagues in 2003 that included 116 women for whom second trimester emergency cerclage was attempted. Membranes that extended outside the external cervical os and cerclage before 22 weeks, were linked with substantial decreased occurrence of pregnancy continuance to 28 weeks or more.

Progesterone

Progesterone given as weekly intramuscular injections of 17 hydroxyl progesterone caproate from 16-20 weeks to 37 weeks showed significant decrease in preterm labour (Meis et al 2003) .It is not beneficial in twin pregnancies (Rouse et al 2007) (.Fonseca et al 2007) Micronized progesterone for asymptomatic women with very short cervix (Less than 15mm) appear to be effective for prevention of preterm delivery.

As per AGOG (2008) progesterone is not recommended as a supplementary treatment to cervical cerclage for suspected cervical insufficiency or .as a preventive agent for asymptomatic women with a positive foetal fibronectin screen result or as a tocolytic agent. The role of progesterone in threatened preterm labour is uncertain (Cochrane Systematic Review 2006).

Cortico steroids

The potential for antenatal administered corticosteroids to accelerate lung maturity was discovered by Liggens. In 1995 National Institute of Health consensus Development Panel recommended corticosteroids for foetal lung maturation in preterm infants, antenatal corticosteroids are recommended for all pregnant women between 25 and 34 weeks who are at risk of preterm delivery within 7 days.

The initial reason for the usage of steroids in women with preterm delivery risk, was to avoid neonatal respiratory distress syndrome. After analysing a number of steroids administered pregnant women, it was revealed that there was another important benefit, which was the prevention of neonatal IVH. As there are such significant benefits of steroids administration, that overcome most of the theories that object such an approach about steroid usage, strong reasons must be justified for not using this treatment, especially in cases when preterm labour is going to occur before 30 weeks.

Cochrane systematic analysis reported that antenatal corticosteroids reduce neonatal death respiratory distress syndrome, intra ventricular haemorrhage, necrotizing enter colitis in first 48 hours of life as well as reduction in the need for intensive care monitoring & respiratory support later

For women with established preterm labour, a mix of betamethasone acetate (6mg) and betamethasone phosphate (6mg) must be administered intramuscularly, in consecutive two doses, with 24 hours interval, with no

contraindications for steroids. Some even prefer to use dexamethasone 4mg IM, for four doses every six hours.

Roberts and Daiziel (2006) reviewed antenatal corticosteroids for accelerating foetal lung maturity Bruschettini and colleagues (2006) studied equivalent of 12 mg versus 6 mg beta methadone and reported that the lower dose had less severe effects on somatic growth without affecting cell proliferation Eli main and co-workers (2007) reported that betamethasone and dexamethasone were comparable in reducing the rates of major neonatal mortalities in preterm infants.

According to Crowley, 1995, proposes that the effect of glucocorticoids, on foetal lung lasts not more than one week, through meta-analysis of random clinical trials. After this finding, the practice of administration of booster dose of betamethasone for every week for those who remained undelivered seven or more days after the early treatment, was adopted by many obstetricians.

Nevertheless, there are evidences that such a practice is linked with major fetal and neonatal side-effects, and it should be abandoned (Debbs et al, 1997; Banks et al, 1999; Vermillion et al 1999, Jobe et al, 1998; French et al, 1999)

Though the maximum benefit of corticosteroid administration is between 24 hours and 7 days after initiation of therapy they provide surgical advantage even when baby is delivered within 24 hours.

RESCUE CORTICOSTEROIDS

Rescue means giving a repetitive dose of corticosteroid when delivery is about to happen and more than 7 days have passed from the time of the first dose. It is said that rescue therapy should not be repetitively used and must be used mostly for clinical trials according to 2000 Consensus Development Conference.

In the trials conducted by Peltoniemi and his co-workers in 2007, that allotted 326 women to placebo or 12 mg betamethasone single dose rescue treatment. It concluded that the rescue dose increased the risk of respiratory distress syndrome. Later the American College of Obstetrics and Gynaecologists (2008) too recommends such method for trials.

Recently in a study of 437 women, less than 33 weeks who were administered rescue therapy or placebo, found that it reduced the rates of respiratory complications, and neonatal composite morbidity, with rescue corticosteroids according to Kurtzman and co-workers, 2009. However there were nil differences in perinatal mortalities and other morbidities. There are also evidences that treated infants had better respiratory compliance (Mc Evoy and associates, 2009).

PRINCIPLES OF MANAGEMENT IN WOMEN WITH PRETERM LABOUR

1. Steroids to the mother to enhance lung maturity.
2. Antenatal transfer of the mother to a centre equipped with NICU
3. Tocolytic drugs

4. Antibiotics
5. Careful intrapartum monitoring
6. Vaginal delivery preferred unless cesarean birth is indicated.

RECOMMENDED MANAGEMENT OF PRETERM LABOUR

AGE : 34 weeks or more

MANAGEMENT:

- Proceed to delivery, usually be initiation of labour
- Group B streptococcal prophylaxis is suggested

AGE: 32 weeks to 33 completed weeks

MANAGEMENT:

- Expectant management unless fetal pulmonary maturity is documented
- Group B streptococcal prophylaxis is recommended
- Corticosteroids-no consensus, but some experts recommend.
- Antimicrobials to prolong latency if no contracindications.

AGE: 24 weeks to 31 completed weeks

MANAGEMENT

- Expectant management
- Group B streptococcal prophylaxis is recommended
- Single course corticosteroids use is recommended.
- Tocolytics – no census
- Antimicrobials to prolong latency if no contraindications.

AGE: Before 24 weeks

MANAGEMENT:

- Patient counselling
- Expectant management or induction of labour
- Group B streptococcal prophylaxis is not recommended
- Corticosteroids use is not recommended.
- Antimicrobials-There are incomplete data on use in prolonging labour.

TOCOLYTIC AGENTS

Tocolysis is pharmacological suppression of uterine activity.

Tocolytic drugs have been used in an attempt to inhibit preterm labour. They are effective in reducing the likelihood of delivery within 48 hours but do not reduce the overall risk of preterm labour. (ACOG 2007)

Tocolytics may be required

1. To gain 48 hours to administer antenatal steroids for increasing pulmonary maturity
2. To permit in utero transfer of the patient to a tertiary care centre for Multi disciplinary management
3. Prepare for neonatal care
4. Preparing the patient for an operative delivery

Variety of drugs which act on uterine smooth muscle to interrupt contractions are available these include magnesium sulphate, calcium channel

blockers, oxytocin antagonists, Non-steroidal anti-inflammatory drugs (NSAIDS) and beta mimetic agonists.

As per ACOG 2003, choice of tocolytic agent is individualized and is usually based on the maternal condition.

Absolute Contraindications to tocolytic therapy

- Severe preeclampsia
- Severe abruption
- Severe bleeding, any cause
- Frank chorioamnionitis
- Foetal death
- Foetal anomaly incompatible with life
- Severe foetal growth restriction
- Mature lung studies
- Maternal cardiac arrhythmias

Relative Contraindications to Tocolytic Therapy

- Mild chronic hypertension
- Mild abruption
- Stable previa
- Maternal cardiac disease
- Hyperthyroidism
- Uncontrolled diabetes mellitus
- Foetal distress

- Foetal anomaly
- Mild intrauterine growth restriction
- Cervix greater than 4 cm dilated

β SYMPATHOMIMETICS

Cartis et al noted that small dose of epinephrine inhibited uterine hyperactivity .Efforts to produce an epinephrine like compound which lacked the cardiovascular stimulant effect culminated in the synthesis of beta agonists.

They react with β adrenergic receptors to reduce intracellular ionized calcium levels and prevent activation of myometrial contractile proteins Beta mimetics can cause mild fall in diastolic blood pressure and isused cautiously in patients of ante partum hemorrhage. They also cause a slight increase of blood sugar in non-diabetic patient and hence can cause gestational diabetes when used for a longer duration alter thyroid function, elevated transaminases hypo calcemia, anti-diuresis and hypokalemia are the other metabolic effects of beta mimetics..

Some of the neonatal side effects of beta mimetics include increased risk of hypo calcemia, hypo glycemia and intraventricular haemorrhage.In recent time better drugs have replaced beta mimetics in regard to tocolytic function due to better profile of safety and less of adverse effects.

CLASSIFICATION

1st Generation: Isoxsuprine, Orciprenaline, Isoprenaline

2nd Generation: Ritodrine, Terbutaline, Fenoterol

The most common used beta 2 agonist for tocolysis is ritodrine; then is terbutaline and salbutamol.

RITODRINE

Merkatz and colleages 1980 achieved a gestational age of 36 weeks in patients treated with ritodrine for threatened preterm labour.It is given as infusion at a dose of 50 ig/min and increased every 20 minutes until uterus is quiescent or side effects limit escalation of dose.

- However the drugs have been implicated as a cause of increased capillary permeability, disturbance of cardiac rhythm and myocardial ischemia.
- Side effects are palpitations, tremor, nausea, headache, chest pain dyspnea, pulmonary edema, hypokatemia, myocardial ischemia and arrhythmias.
- Ritodrine was withdrawn voluntarily in 2003, according to Federal Register, United States owing to its adverse effects.

TERBUTALINE

Not used as much as ritodrine, but is effective in temporary suppression of uterine contractions when given parenterally.

- intravenous dose 5-10 1g/min ,increased every 10-15 mm to a maximum of 80 g. 2.5 — 5 mg is the oral dose given every 4-6 hours and 250pg subcutaneously every 20-30 minutes given as 4-6 doses.
- Terbutaline causes more hyperglycemia than ritodrine

Like ritodrine it can cause pulmonary edema (Angel and associates 1988)

Gunin and associates (1998) reported no significant prolongation or improved neonatal outcome with terbutaline is not approved by the FDA and therefore it's not mentioned in any protocol for pre-term labour. Beta 2 agonists are no longer the first choice of drugs because of their side effects (RCOG 2002, Anotayanoth et al 2004)

Contraindications of beta 2 agonist :symptomatic cardiac disease, conduction disturbance, hyperthyroidism, sickle cell disease, uncontrolled diabetes mellitus, chorioamionitis, severe preeclarnpsia, multifetal gestation and severe obstetrical bleeding.

Prostaglandin Inhibitors

Acetylsalicylate (Aspirin), Indomethacin naproxen fenamate, sulindac inhibit prostaglandin syntheses enzyme responsible for the transformation of free arachidonic acid to prostaglandins thereby decrease the myometrial gap junctions and influx of calcium.

Indomethacin was first used as a tocolytic by Zuckerman and colleagues (1974) various trials compared indomethacin with other drugs like ritodrine;

Magnesium sulfate and found no difference in efficacy (Morales and coworkers (1989, 1193a).

Indomethacin is administered orally or rectally. A dose of 50 to 100 mg at 5 hours intervals, not to exceed 200 mg in 24 hours period.

Adverse effects reported are oligohydramnios, pulmonary hypertension due to constriction of ductus arteriosus. Intra cellular hemorrhage, necrotizing enterocolitis have also been reported.

Two randomized trials which compared the effect of indomethacin and placebo in delaying delivery showed no significant delay at 48 hours and 7 - 10 days.

MAGNESIUM SULPHATE

Ionic magnesium in a sufficiently high concentration can alter myometrial contractility. Its role is presumably that of a calcium antagonist causing less intracellular calcium (Ca2+) to participate in actins myosin interaction during smooth muscle contraction.Elliott in his study found that Magnesium sulphate was effective tocolytic in 87% cases.

Cox and associates in their study did not report any differences in the pregnancy outcome using magnesium sulphate.It affects neural transmission by modifying acetyl chloline release and sensitivity of motor end plate.

Drug concentration and effect

- Contractility is inhibited at serum level of 5 - 8 mEq/L.
- Deep tension reflexes are lost at 9 - 13 mEq/L.
- Respiratory depression occurs at> 14 Meq/ dl

Loading dose of 4g IV given over 20 minutes followed by maintenance dose of 1-2 g / hour.

Side effect is nausea, giddiness, flushing, hypocalonemia, respiratory depression, pulmonary edema and depressed motor respiratory activity in fetus. Contraindications of magnesium sulfate are myasthenia gravis, heart block, renal disease and recent myocardial infarction.

Neuro protective effect of magnesium sulfate was evaluated in (BEAM study-Beneficial Effects of Antenatal Magnesium Sulfate)According to Gowther et al 2002, Cochrane systematic review, magnesium sulfate is an ineffective tocolytic..Wilkens et al 1989 reported the occurrence of significant side effect of magnesium sulphate while being used concurrently with beta mimetics for tocolysis.

CALCIUM CHANNEL BLOCKERS

These agents act by reducing the influx of calcium ions into the cell membrane during the inward calcium current of action potential. They block the voltage sensitive L type of calcium channels. They also decrease the tone of

smooth muscles by inhibition of intracellular calciwn from sarcoplasmic reticulum .Nifedipine is the most commonly used calcium channel blocker.

King and colleagues 2003, Papatson's 1997 concluded that calcium channel blockers especially Nifedipine are safer and more effective tocolytic agents than are beta agonists and have lower neonatal morbidity No significant change in utero placental flow has been reported .Mari et al (1989)

TREATMENT REGIMEN

Optimal dose regimen of Nifedipine has not yet been defined. George et al 1991, Read and WeIlby (1986), showed that initial dose of 30 mg followed by 20 mg 8th hourly for 3 days had a success rate of 75% Andrenne et al gave a dosing regimen of 30 mg oral followed by a maintenance dose of 10 - 20mg orally every 4 - 6 hours.

Most trials advocated an initial loading dose of 30 mg of oral Nifedipine followed by 10 to 20 mg every 6 hours. Sublingual Nifedipine is no longer advocated due to risk of sudden hypotension. Onset of action is less than 20 minutes with peak plasma concentration within 15 - 90 minutes.

Having a half-life of 1.5 to 3 days. Elimination is mainly through kidneys (70%) and bowel 30%. Though the duration of action of a single dose can be as long as 6 hours, there is no apparent cumulative effect when administered every 6 hours.

Side effects include facial flushing, nausea vomiting, headache, hypotension and tachycardia. No significant alteration in blood glucose and serum electrolytes was reported.

OXYTOCIN ANTAGONIST (ATOSIBAN)

Nona peptide oxytocin analog is a competitive antagonist of oxytocin induced contractions.

Dosage

Recommended dose and administration schedule is a three step procedure. The initial bolus dose is 6.75 mg given over one minute, followed by an infusion of 18 mg/hour for three hours and 6 mg/hour for up to 45 hours. Treatment should not last longer than 48 hours and total dose given should not exceed 330 mg (RCOG, clinical Guidelines 2002)

Side effects include nausea, vomiting, chest pain, and dyspnoea.

In randomized clinical trials, artesian failed to improve relevant neonatal outcome and was linked with significant neonatal morbidity (Moutquin and coworkers, 2000 Romero and associates 2000)

However, RCOG clinical guidelines 2002 suggested the first choice on administration of tocolytics to be oxytocin antagonist or Nifedipine.

NITRIC OXIDE DONORS (GLYCERYL TRINTRATE)

It is a potent endogenous hormone having smooth muscle relaxant property. Main action affects vasculature, gut and uterus..Nitric oxide donors act by inhibiting CRH (Corticotrophin releasing hormone), a promoter of parturition.

Dosage 10 mg Glycerol Tri nitrate patch placed over fundal region of maternal abdomen. Dose can be repeated with another 10 mg after one hour, if tocolysis is not achieved, to a maximum dose of 20 mg in 24 hours. Maternal hypotension is a common side effect.

In randomized clinical trials, Nitroglycerine administered orally, trans dermal or intravenously was not effective and was no superior to other tocolytics (Bistis 2004, Clavin 1996, Rees 1999, Buhimschi 2002. DuckittK et al (2002) reported that nitroglycerine did not improve neonatal outcome or delay delivery on comparison with placebo, no treatment or alternative tocolytics.

POTASSIUM CHANNEL OPENERS

Diazoxide is related to thiazide diuretics and its main use is in the treatment of malignant hypertension. Its mechanism of action is inhibition of smooth muscle contractility, thereby causing uterine quiescence.

It is given in a dose of 5mg / kg, slow intravenous over 20-30 minutes. The drug is given after diluting with saline. Bolus dosage includes 50 -100 mg given every 5 minutes.

Side effects are tachycardia, hyperglycaemia, decreased blood pressure, and decreased utero placental flow secondary to hypotension in the mother. Hypoglycaemia and foetal distress are the side effects which occur secondary to maternal hypotension.

FETAL AND NEONATAL RISKS

Compromised foetal health is often the precipitating factor in threatened or actual preterm labour. Hence, intrauterine foetal death, intrauterine growth restriction, major congenital anomalies, unrecognized intrauterine infection, and complicated multiple pregnancy will all contribute tot he perinatal mortality and morbidity rates associated with preterm labour.

RISKS OF PREMATURITY

The gestational age at which threatened or actual preterm labour presents, together with the birth weight, influences both the management and the outcome. In women presenting between 20 and 24 weeks' gestation, the management decision after discussion with the parents may be to allow delivery to occur because of the maternal risks from treatment and the likely poor prognosis for the baby if, delivery can be postponed only for a few hours or days.

Foetal intrapartum hypoxia and birth trauma associated with preterm labour involving the very low birth weightinfant, whether birth is by the vaginal or abdominal route, will contribute to the perinatal risk. The risks in the neonatal period are those of congenital malformation, intrauterine growth restriction, respiratory distress syndrome, necrotizing enterocolitis, intracranial haemorrhage,

convulsions, and septicemia. The foetal and neonatal risks associated with the medical management of preterm labour have not been accurately quantified, but they require consideration in the overall management.

FETAL RISKS OF TOCOLYTIC AGENTS

Beta-sympathomimetic tocolytic agents cross the placenta and may cause foetal tachycardia and occasionally other adverse foetal cardiac effects, which may be significant in an already compromised foetus. The maternal hyperglycaemia commonly associated with the use of these agents may result in neonatal hypoglycaemia. There is a suggestion that neonatal interventricular haemorrhage may be associated with the use of oral beta-sympathomimetic drugs, although the data are preliminary. There have been only a few small studies of possible long-term ill effects for the neonate, and currently it appears there is no difference in developmental outcome.

Prostaglandin synthetase inhibitors (NSAIDs) cross from the mother to the foetus, potentially resulting in prolonged bleeding time, cardiopulmonary effects like premature closure or constriction of the ductus arteriosus and persistent foetal circulation, renal dysfunction, and reduced urinary output. Necrotizing enterocolitis and neonatal intra-ventricular haemorrhage have also been recorded in association with the use of these agents. Most studies have limited the use of prostaglandin synthetase inhibitors to short-term therapy (48–72 hours) before 32 to 34 weeks gestation. Newer and possibly more specific prostaglandin synthetase

inhibitors such as sulindac, ketorolac, and the COX-2selective agents (e.g., nimesulide) are considered to have fewer foetal side effects.

Magnesium sulfate also readily crosses the placenta and may compromise foetal cardiac activity, with reduced baseline variability of the foetal heart rate demonstrated by cardiotocography being a common association, which in turn may lead to unnecessary intervention. The neonate may exhibit hypotonia and hypocalcaemia as a consequence of the hypomagnesaemia. The more controversial aspects of magnesium sulfate are related to its possible foetal neuroprotective role, as several observational studies indicated a reduction in cerebral palsy rate in very low birth weight infants in association with its use.

Mitterdorf and associates,, have found in the ir small randomized controlled trial(MagNET trial) that there is a highly significant association between tocolytic magnesiumsulfate exposure and total neonatal mortality rates and worse out comes in relation to interventricular haemorrhage, periventricular leukomalacia, and cerebral palsy.

Crowther and associates (2003) presented the much larger ACTO MgSO4 trial and did not observe an increase in perinatal or neonatal mortality rate. A no significant reduction of adverse neurologic sequelae was reported.

Calcium-channel blockers have not been adequately evaluated with regard to foetal or neonatal effects, and the Cochrane reviewers recommended the assessment of different dose and formulations on maternal and neonatal outcomes.

Some animal studies have demonstrated profound metabolic alterations in the foetus, but these changes have not been confirmed in the foetuses of pregnant women.

Newer tocolytic agents such as nitric oxide donors and oxytocin receptor antagonists have not been sufficiently assessed. The maternal administration of thyrotropin-releasing hormone in association with corticosteroids was thought, from preliminary studies, to enhance the development of foetal lung maturity. The ACTOBAT Study demonstrated results to the contrary and hence, its use is discouraged.

Maternal corticosteroid administration to enhance foetal lung maturity is beneficial for the preterm neonate but may carry a number of risks, including infection, although the latest available data do not confirm this potential complication. These potential risks must be balanced against the proven beneficial effect on neonatal pulmonary function and the possible reduction in interventricularhaemorrhage and necrotizing enterocolitis.

The Dutch trial which studied the effects of maternal prenatal corticosteroid administration, suggesteda long-term increase in the incidence of pharyngeal and ear infections in infants of treated mothers but reported no clear evidence of significant foetal or neonatal infection in preterm labour associated with intact membranes. The former practice of repeated maternal corticosteroid administration encouraged by the NIH Consensus Statement (1994) for pregnancies at risk for preterm delivery between 24 and34 weeks' gestation is

questionable. Crowley and associates, in their studies, suggested that there was little evidence of adverse long-term outcomes with repeated maternal corticosteroid administration.

Walfisch and colleagues reviewed 280 articles on this topic and concluded that there are no well-designed randomized controlled trials (RCTs) in humans that support the advantages of multiple courses over a single course of antenatal corticosteroids.

They also commented that an increasing body of evidence raises the concern of adverse consequences from the use of repeated courses. This conclusion is consistent with the current Cochrane systematic review of three trials. However, fewer infants required surfactant and there were fewer cases of severe respiratory distress syndrome (RDS)

Aims & Objectives

AIM OF THE STUDY

- TO MEASURE BETA HUMAN CHORIONICGONADOTROPHIN LEVELS IN CERVICOVAGINAL SECRETIONS IN WOMEN PRESENTING WITH SYMPTOMS OF PRETERM LABOUR AND EVALUATE IT AS A PREDICTOR OF PRETERM DELIVERY.

PRIMARY OBJECTIVE

- TO DETERMINE THE RELATIONSHIP BETWEEN PRETERM DELIVERY AND CERVICOVAGINAL BETA HCG LEVELS.

SECONDARY OBJECTIVE

- TO EXPLORE THE ROLE OF NEW BIOCHEMICAL MARKERS IN PREDICTING SPONTANEOUS PRETERM BIRTH IN WOMEN WITH THREATENED PRETERM LABOUR.

Materials & Methods

MATERIALS AND METHODS

This study was conducted in Institute of Social Obstetrics, Govt. Kasturba Gandhi Hospital for Women and Children and Institute of obstetrics,Government hospital for women and children Egmore under Madras Medical College, Chennai for the period of 10 months from December 2015 to August 2016. Institutional Ethics Committee approval was obtained from Madras Medical College for this study.

Study Method

This was a prospective study which was carried out among pregnant women came with preterm pains from 28 weeks to 35 weeks 6 days(36 weeks) of gestational age. Sample size was calculated to 108 by using 7.72%[72] prevalence of Preterm delivery with 5% precision.

Only those patients who could be followed up till term were included under the study after explaining in detail about the procedure and getting informed written consent.

The study design was prospective cohort.

Out of the 108 mothers chosen for the study based on inclusion and exclusion criteria 8 were excluded from study as 3 developed Gestational diabetes mellitus,1 developed pregnancy induced hypertension and 4 were lost for followup.

INCLUSION CRITERIA:

Singleton gestation (confirmed by early second trimester ultrasound) gestational age between 28-36 weeks(by LMP and confirmed by ultrasound) without any co morbid complications with c/o preterm pains in this pregnancy.

EXCLUSION CRITERIA:

- Multiple gestation
- Gestational diabetes mellitus
- Pregnancy induced hypertension
- Hydramnios
- Cervical incompetence
- Cardiovascular disease
- Congenital fetal anamoly/malformation
- Abruption placentae
- Placenta previa

METHODS

All chosen mothers will be subjected to detailed history followed by general and obstetric examination following which cervico vaginal secretions are collected for Beta HCG measurement.

Sample collection:

For beta-hcg assay, cervicovaginal secretion samples will be obtained as follows .A cotton-tipped swab is placed first into the endocervical canal and

subsequently into the posterior fornix of vagina. The swab is placed in a sterile tube containing 1ml of saline solution and shaken for one minute. The swab is disposed and samples were refrigerated and assayed within 72 hours.

Laboratory Test

The beta-hcg levels of the samples were measured by an ELISA-based method using rapid EIA test kit Results will be reported in mIU/ml.

A cut off value of 25mIU/ml was considered to discriminate positive (>25mIU/ml) & negative(<25mIU/ml).

The patients were followed up till delivery and based on the gestational age at delivery were classified into preterm group and term group and the relationship of B HCG with gestational age at delivery was studied.

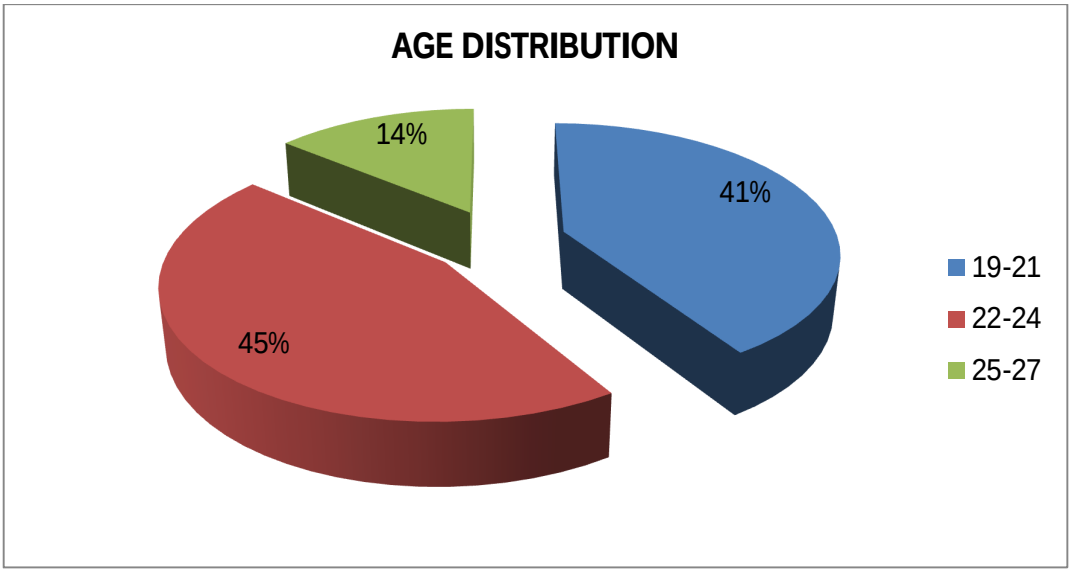
Observation & Analysis

OBSERVATION AND ANALYSIS

A.PROFILE OF CASES:

1.AGE DISTRIBUTION.

AGE GROUP	Frequency	Percent
19-21	41	41.0
22-24	45	45.0
25-27	14	14.0
Total	100	100.0



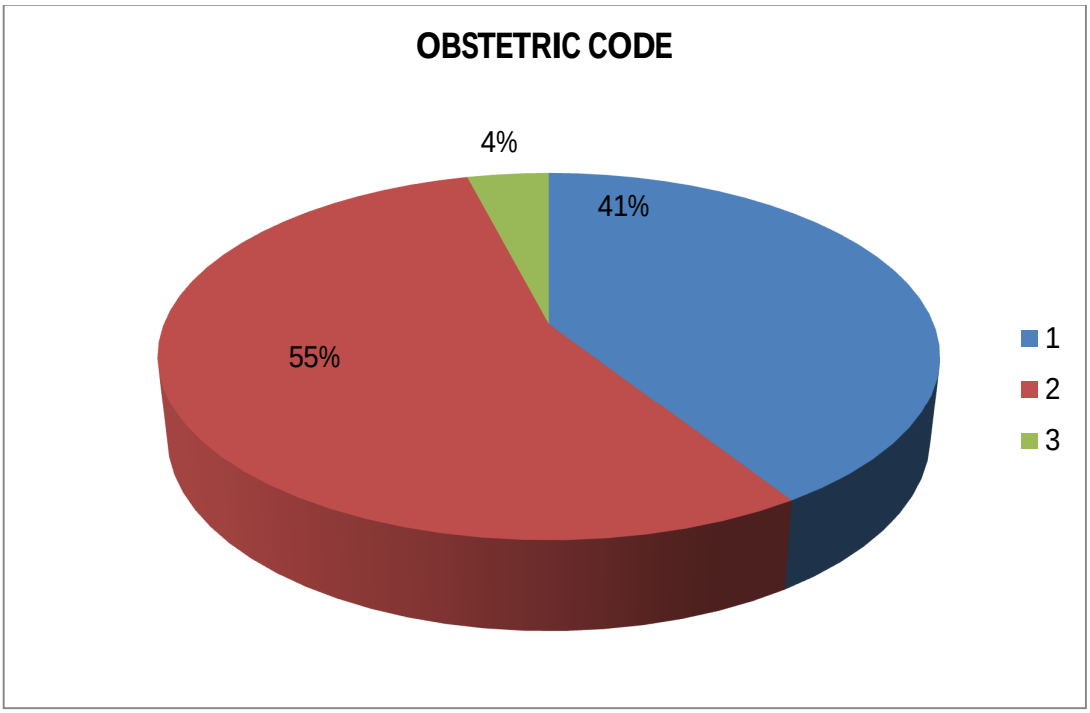
Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
VAR00005	100	19.00	27.00	22.2300	1.98405
Valid N (listwise)	100				

Among the mothers included in the study 41% were less than 20 years of age.

2. OBSTETRIC CODE.

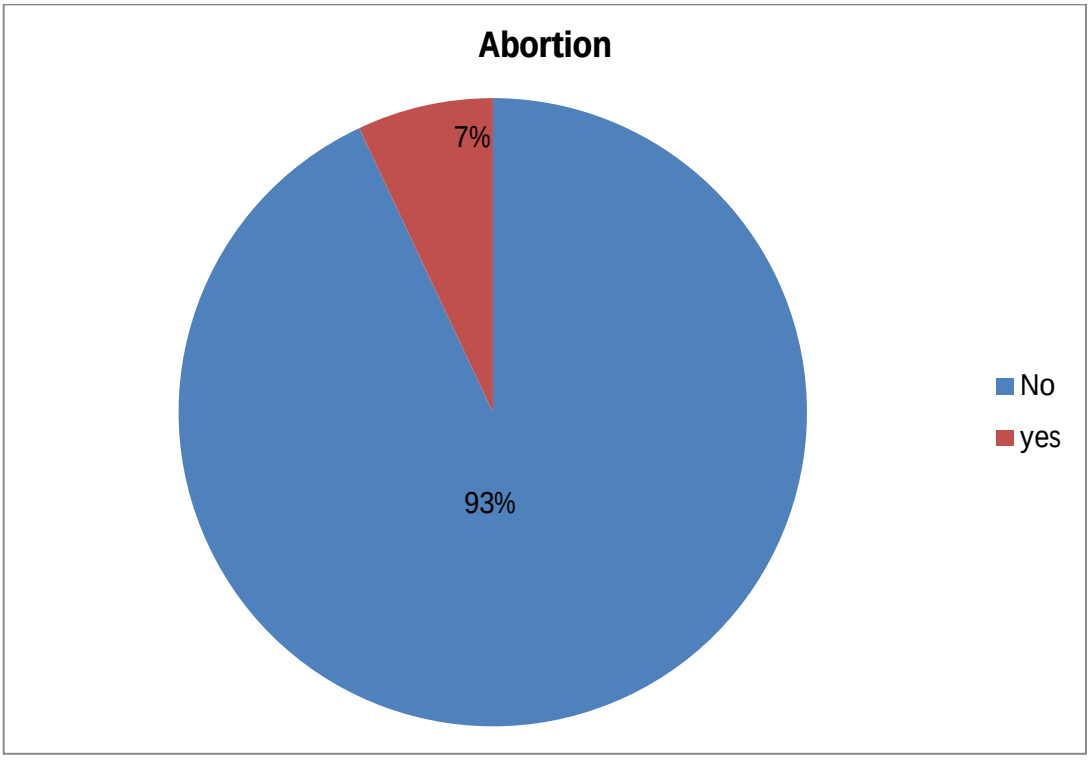
OBSTETRIC CODE	NO OF CASES	Percent
G1	41	41.0
G2	55	55.0
G3	4	4.0
Total	100	100.0

41% of the mothers included in the study were primis,rest were multigravida with 4% were third gravid and 55% were second gravidas.



ABORTIONS

PREVIOUS ABORTION	NO OF CASES	Percent
No	93	93%
yes	7	7%
Total	10	100.0

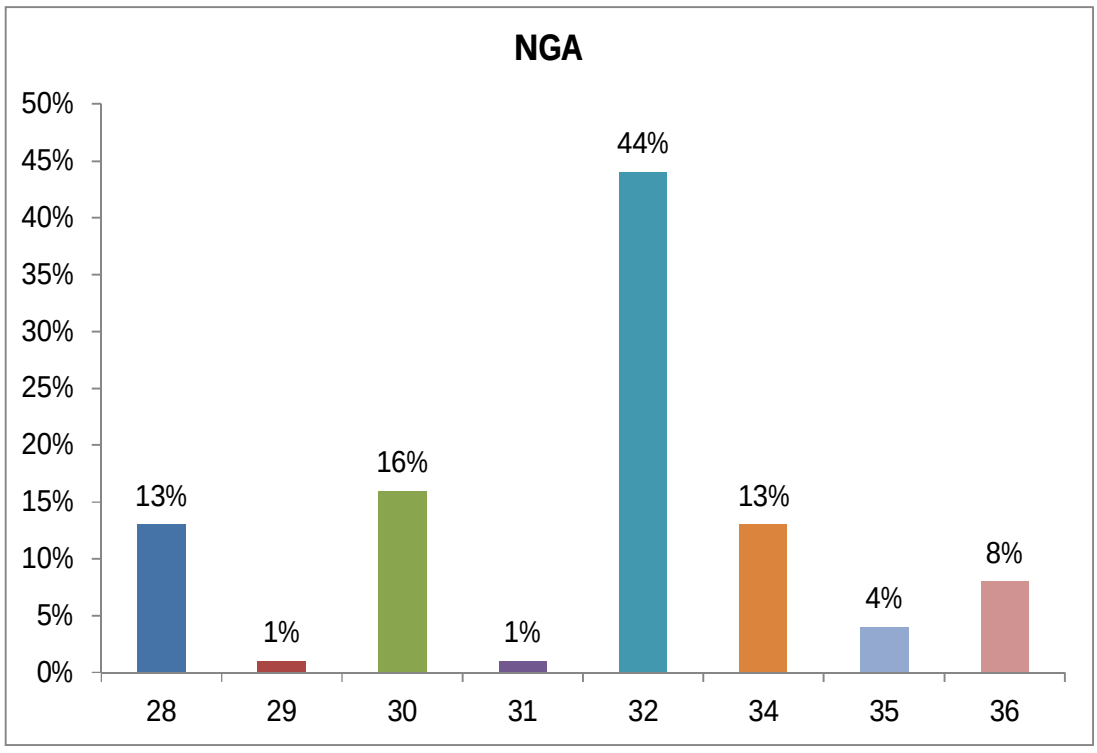


Only 7% of mothers had previous history of abortions.

3.GESTATIONAL AGE AT SAMPLE COLLECTION

Gestational age in weeks	No of cases	Percent
28	13	13.0
29	1	1.0
30	16	16.0
31	1	1.0
32	44	44.0
34	13	13.0
35	4	4.0
36	8	8.0
Total	100	100.0

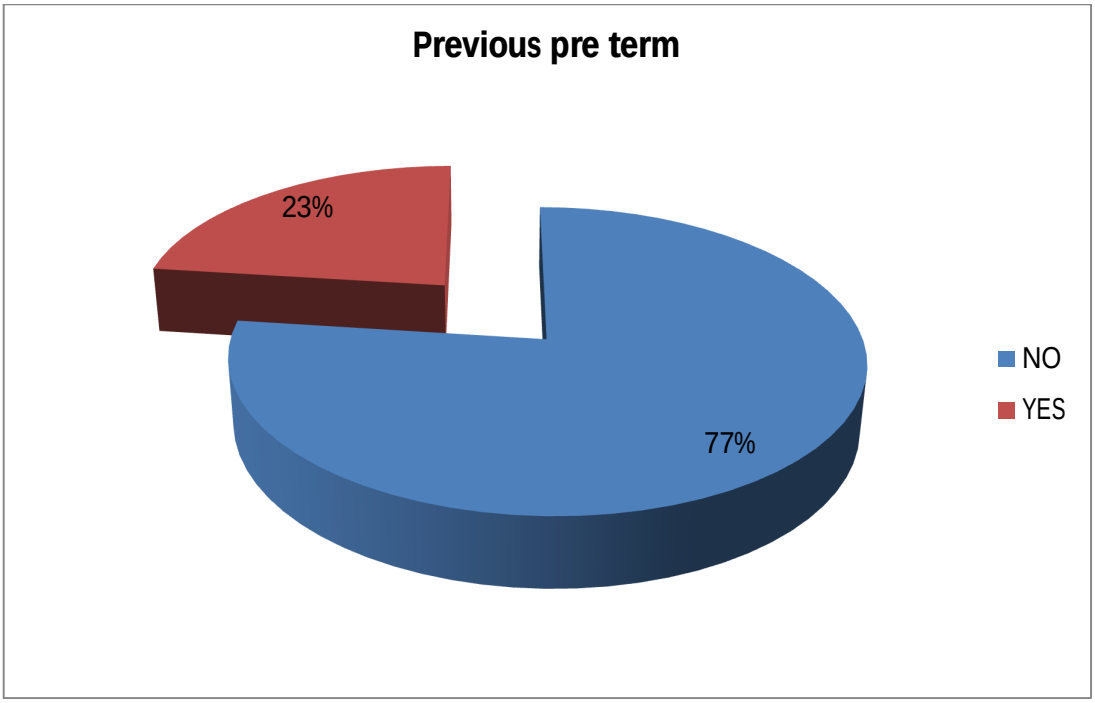
B HCG was measured for 31% of mothers at < 32 weeks and 69% of mothers >32 weeks.



4.PREVIOUS HISTORY OF PRETERM

Previous pre term	Frequency	Percent
NO	77	77.0
YES	23	23.0
Total	100	100.0

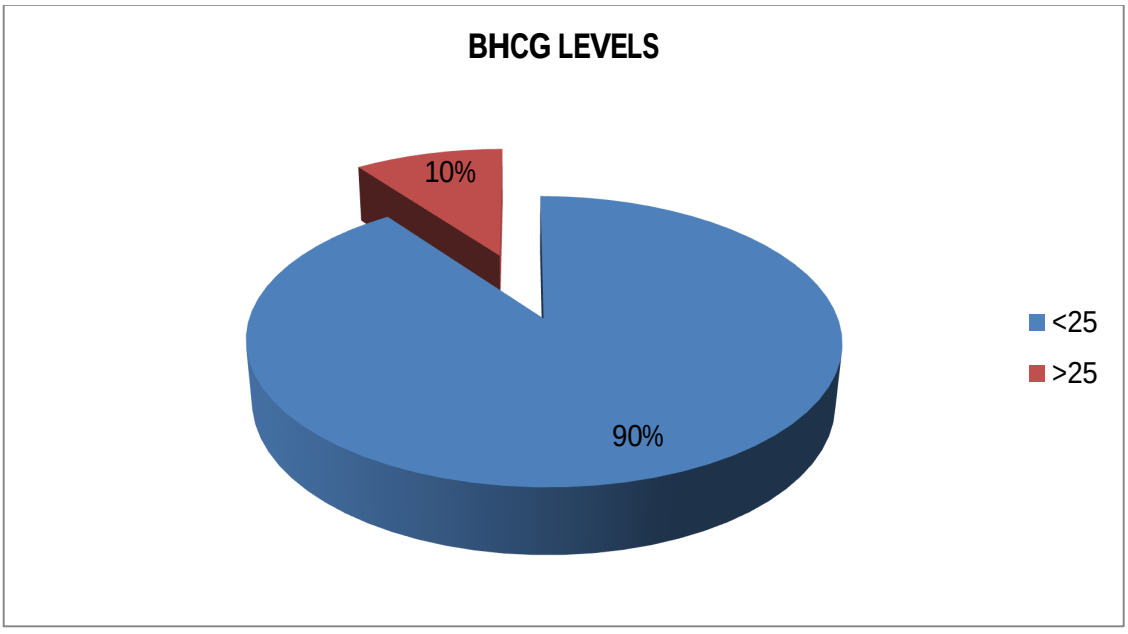
Out of the mothers included in the study 23% had previous history of preterm and 77% presented with symptoms suggestive of preterm labour in present pregnancy.



B.BHCG LEVELS IN CERVICOVAGINAL SECRETIONS

BHCG Levels(in IU/L)	Frequency	Percent
<25	90	90.0
>25	10	10.0
Total	100	100.0

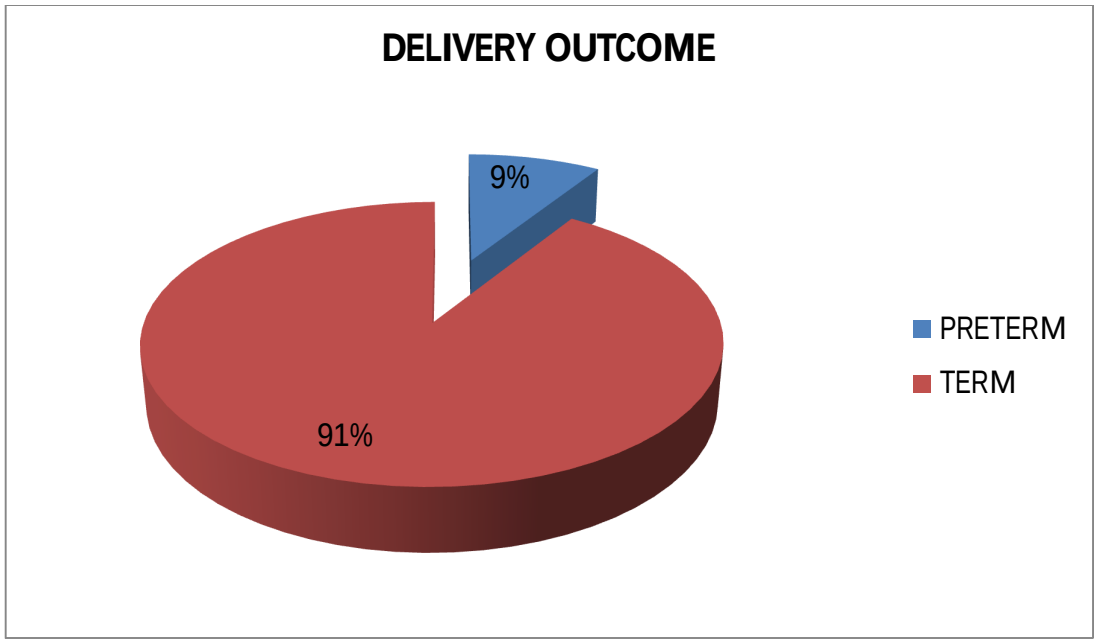
Of the 100 cases taken for the study 10% had B hcg levels above the significant cut off chosen for the study.



C.DELIVERY OUTCOME(TERM Vs PRETERM).

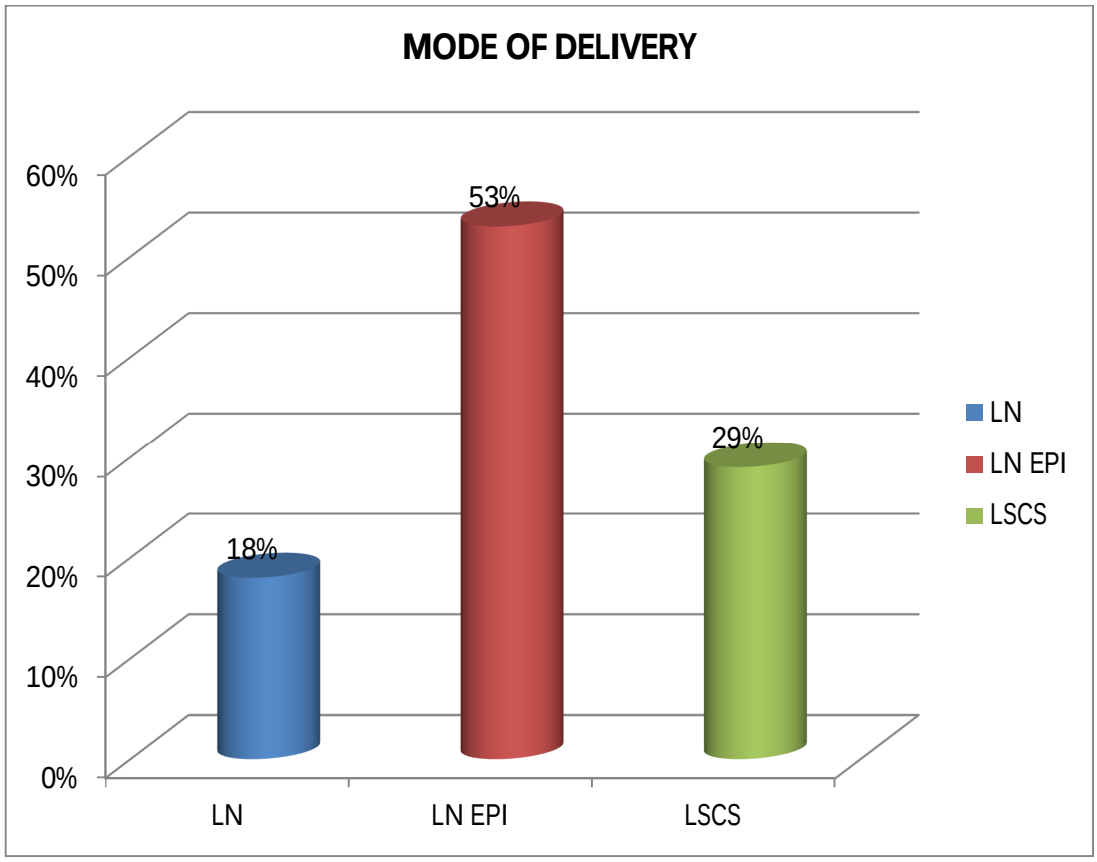
	Frequency	Percent
PRETERM	9	9.0
TERM	91	91.0
Total	100	100.0

The incidence of preterm delivery was 9%.



D.MODE OF DELIVERY

Mode of delivery	Frequency	Percent
LN	18	18.0
LN EPI	53	53.0
LSCS	29	29.0
Total	100	100.0

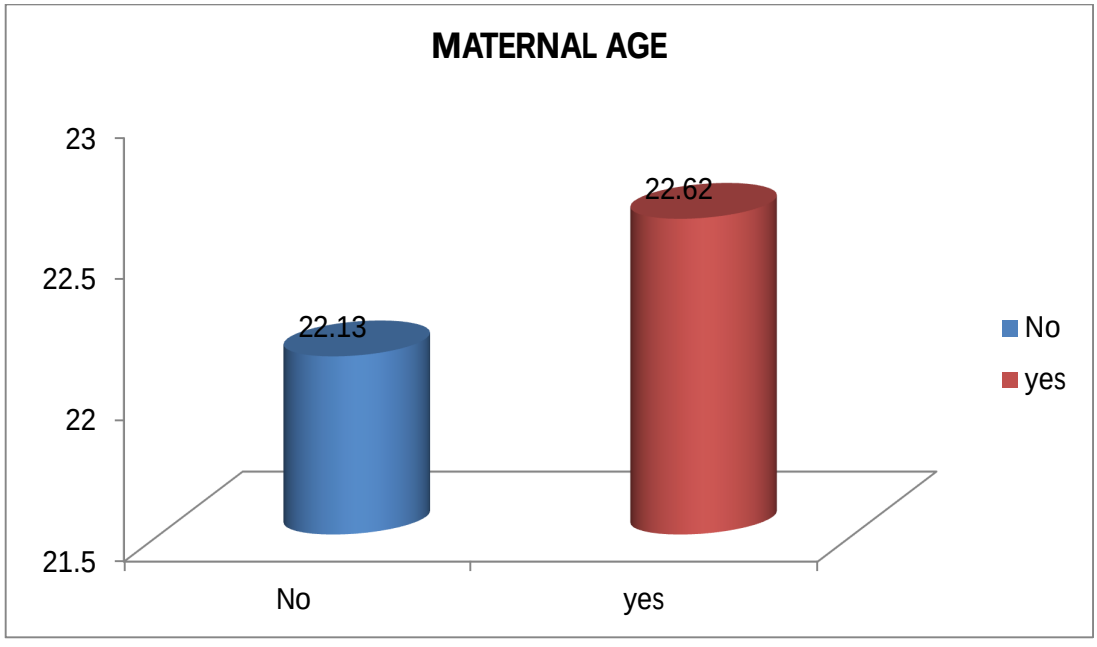


E. RELATIONSHIP BETWEEN OUTCOME OF DELIVERY AND OTHER VARIABLES.

1.MATERNAL AGE

	pre_term	N	Mean	Std. Deviation	Std. Error Mean	T value
age	Pre term	9	22.2222	1.98606	.66202	0.012 P=0.9904
	Term	91	22.2308	1.99487	.20912	

Non Significant p>0.05

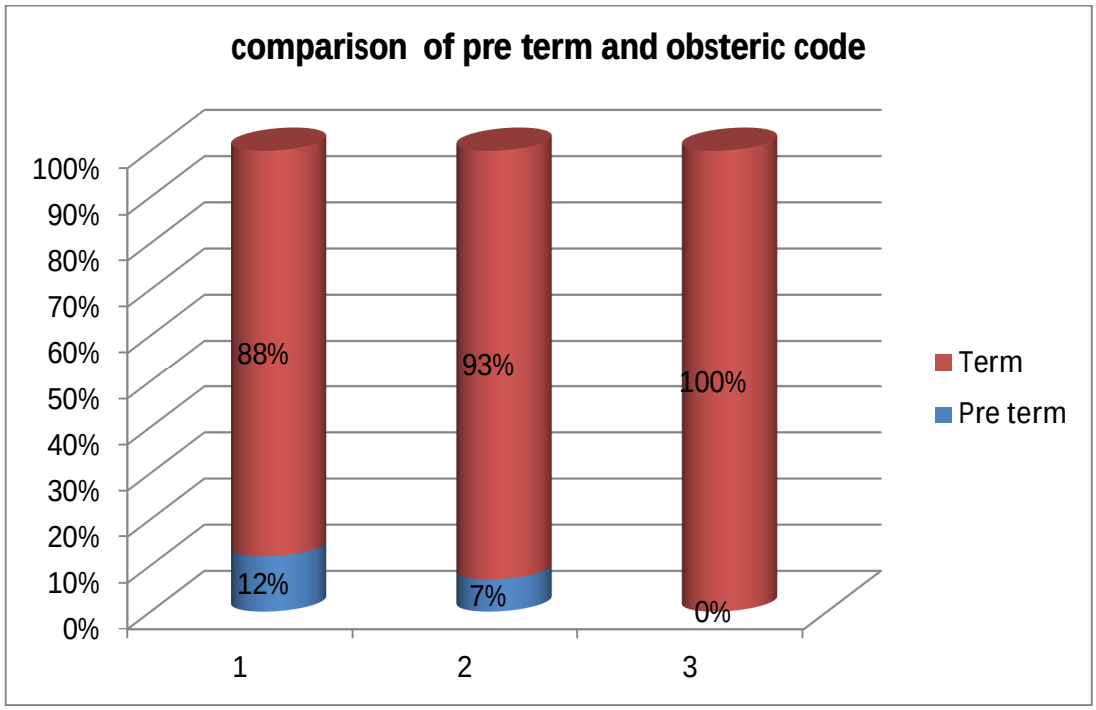


No significant association was found between maternal age and incidence of preterm delivery.

2. OBSTETRIC CODE

RELATIONSHIP BETWEEN OBSTETRIC CODE AND PRETERM DELIVERY					
Outcome		**Obsteric_Code**			**Total**
		1	**2**	**3**	
Pre term	Count	5	4	0	9
	% within obsteric_code	12.2%	7.3%	0.0%	9.0%
Term	Count	36	51	4	91
	% within obsteric_code	87.8%	92.7%	100.0%	91.0%
Total	Count	41	55	4	100
	% within obsteric_code	100.0%	100.0%	100.0%	100.0%

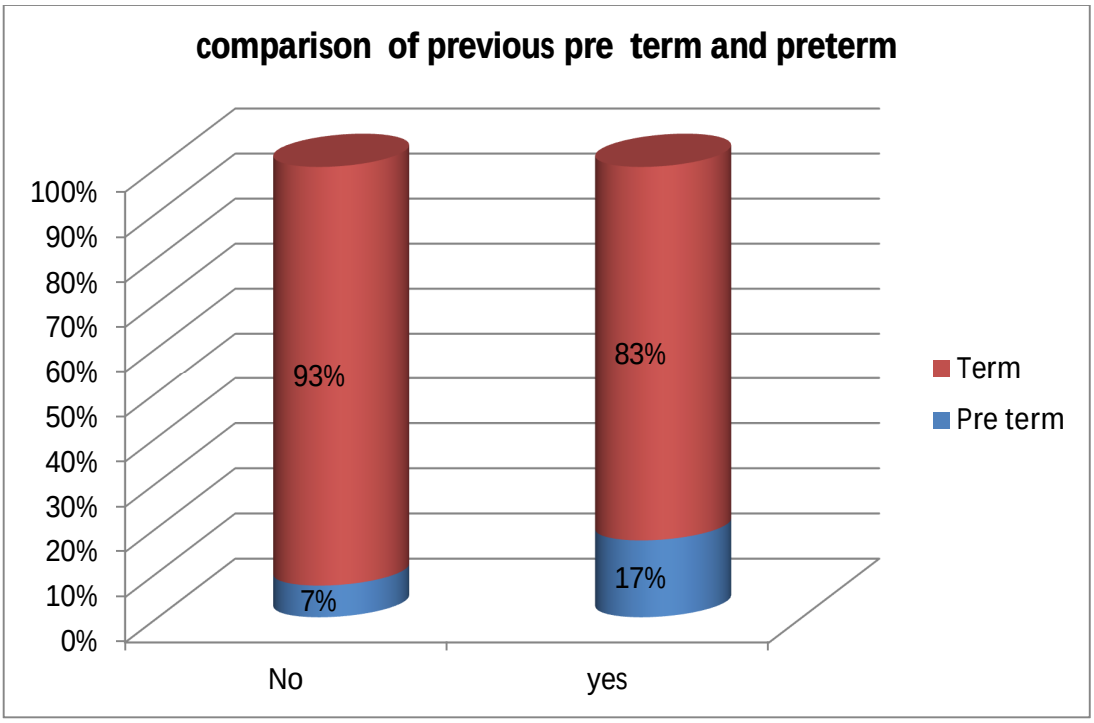
The percentage of preterm deliveries among primi and multigravidas did not have a statistically significant difference (Pearson Chi-Square 1.107 p= 0.575).



3.PREVIOUS PRETERM DELIVERY

outcome * previous_histroy Crosstabulation				
Outcome		previous_histroy		Total
		NO	YES	
Pre term	Count	5	4	9
	% within previous_histroy	6.5%	17.4%	9.0%
Term	Count	72	19	91
	% within previous_histroy	93.5%	82.6%	91.0%
Total	Count	77	23	100
	% within previous_histroy	100.0%	100.0%	100.0%

Though previous h/o preterm delivery was associated with increased incidence of preterm delivery, the association was not statistically significant(Pearson Chi-Square=2.568 p=0.109).

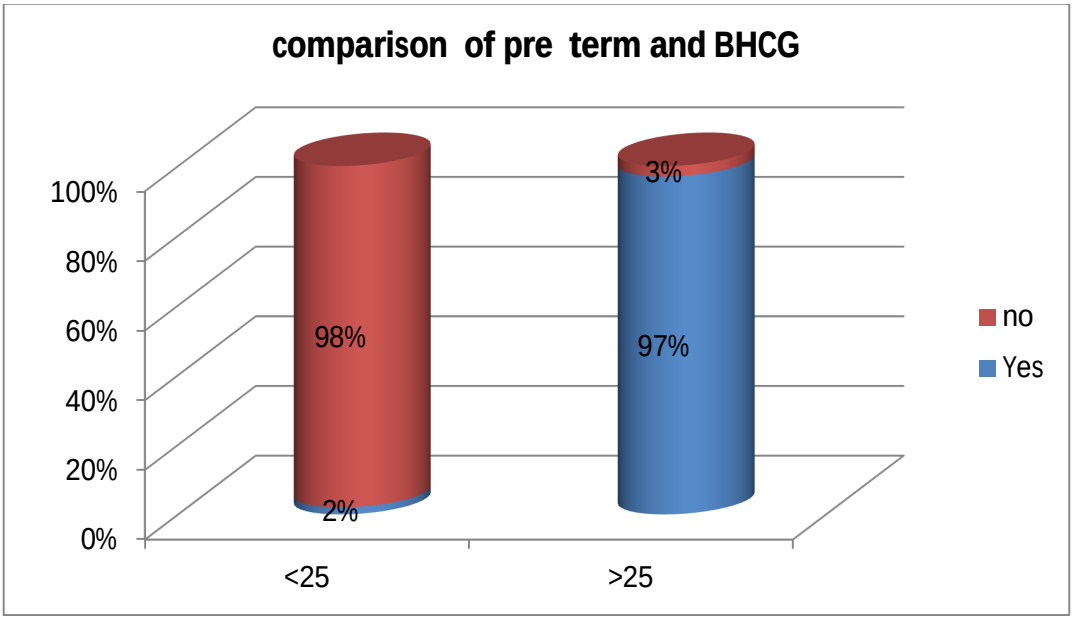


E.BHCG LEVELS AND PRETERM DELIVERY.

Outcome * BCHG Crosstabulation				
Outcome		**BCHG**		**Total**
		<25	**>25**	
Pre term	Count	2	7	9
	% within BCHG	2.2%	97%	9.0%
Term	Count	91	3	91
	% within BCHG	97.8%	3%	91.0%
Total	Count	93	7	100
	% within BCHG	100.0%	100.0%	100.0%

Out of 9 Preterm, 7 preterm were >25.

Out of 9 preterm deliveries 7 mothers had BHCG > 25IU/L ,thus a significant association was found between increased B HCG levels in cervicovaginal secretions and preterm delivery(Pearson Chi-Square=76.105 **P<0.001).

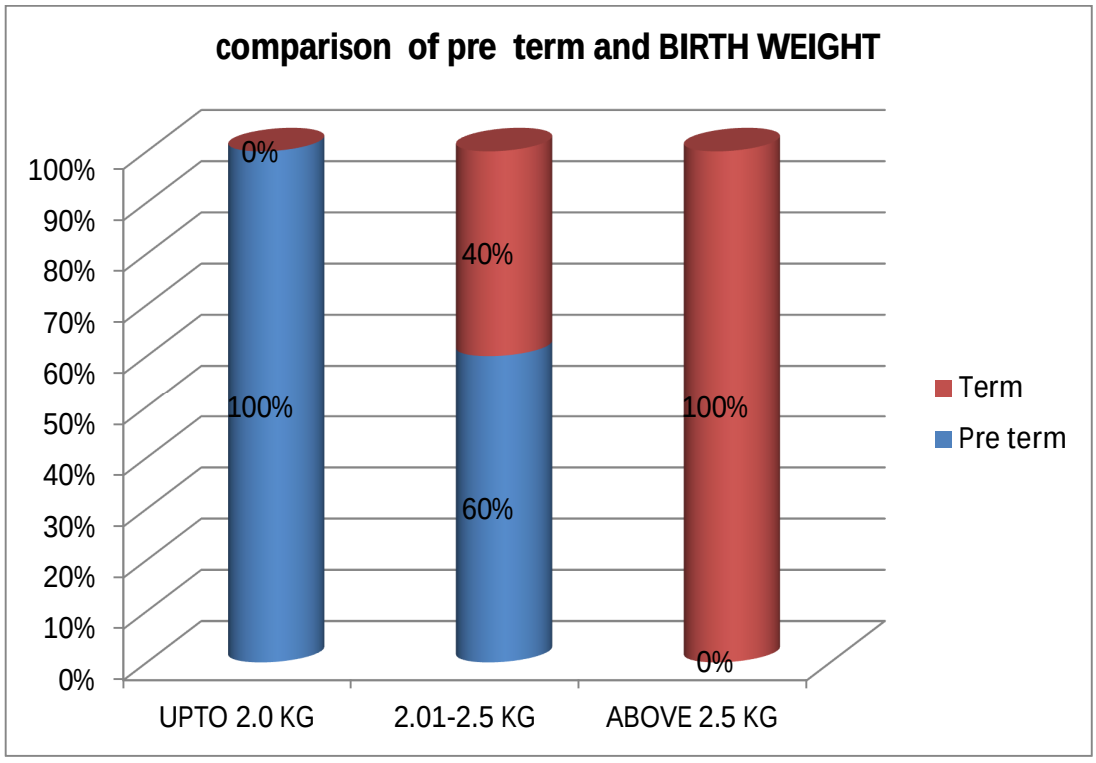


F.OUTCOME OF DELIVERY AND FETAL WEIGHT.

outcome * BIRTH_WEIGHT Crosstabulation					
Outcome		BIRTH_WEIGHT			Total
		Upto 2.00 KG	2.01-2.5 KG	Above 2.5 KG	
Pre term	Count	6	3	0	9
	% within BIRTH_WEIGHT	100.0%	60.0%	0.0%	9.0%
Term	Count	0	2	89	91
	% within BIRTH_WEIGHT	0.0%	40.0%	100.0%	91.0%
Total	Count	6	5	89	100
	% within BIRTH_WEIGHT	100.0%	100.0%	100.0%	100.0%

Pearson Chi-Square=85.348*P<0.001

Among the 9 preterm babies,6 had birth weight less than 2kg while remaining 3 weighed more than 2kg.

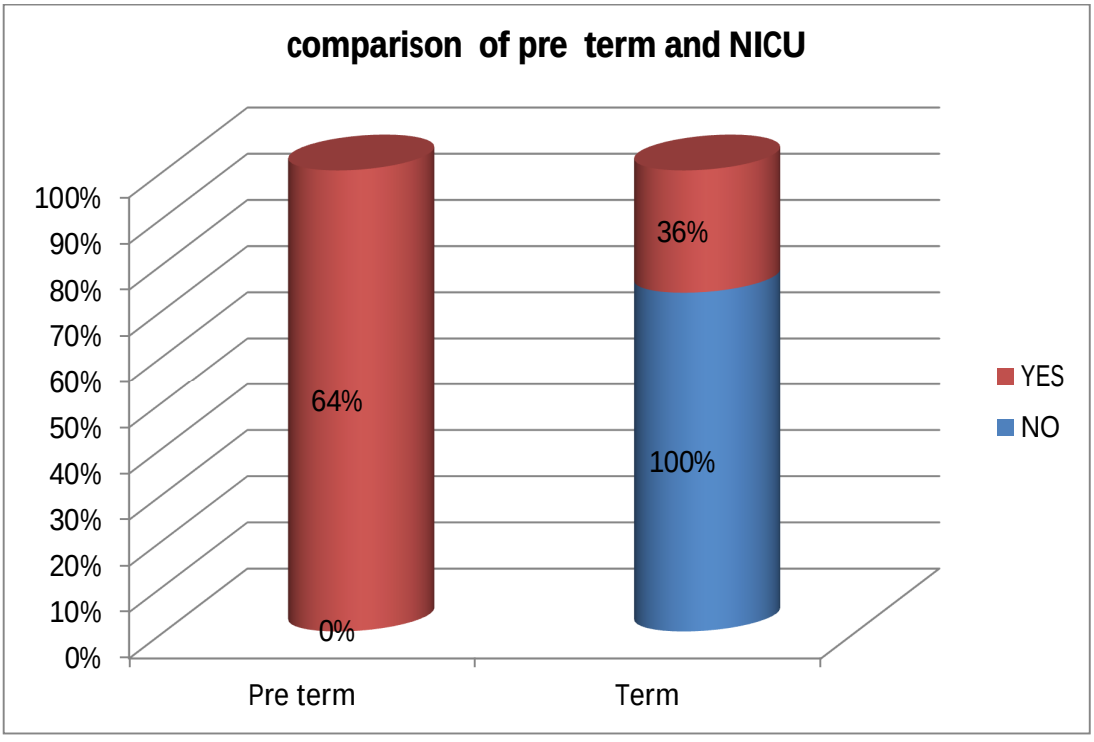


G.OUTCOME OF DELIVERY AND NICU ADMISSION.

outcome * NICU Crosstabulation				
outcome		NICU		Total
		NO	YES	
Pre term	Count	0	9	9
	% within NICU	0.0%	64.3%	9.0%
Term	Count	86	5	91
	% within NICU	100.0%	35.7%	91.0%
Total	Count	86	14	100
	% within NICU	100.0%	100.0%	100.0%

Pearson Chi-Square=60.754*P<0.001

All preterm babies required NICU admission,while among term delivery 36% required NICU admissions for various reasons.



Discussion

DISCUSSION

Preterm delivery is defined as birth occurring prior to 37 completed weeks of gestation..Incidence in India is 10% - 14% and developed countries 5% - 10%.

100 antenatal mothers were included in this study with the incidence of preterm delivery was 9%.Out of whom 7 mothers had cervicovaginal BHCG levels >25 IU/L.

In the study conducted by soghra et al . A total of 83 pregnant women were studied of which Some 43%(n=36) subjects delivered at or before 37 weeks. Cervicovaginal beta hcg showed a range of 0 to 186mIu/ml with an optimal cut-off value of 25, odds ratio for gestational age <37 was 3.016 (CI=1.12-8.06,95%). There was an association between preterm delivery (gestational age<37) and cervicovaginal beta-hcg titre in 28 weeks' gestation.The study showed a sensitivity of 42% with a, specificity of 81%, positive and negative predictive values of the test was 63% and 64% respectively.

Garshasbi et.al studied βhCG levels of cervicovaginal secretions of patients who had a risk factor for preterm delivery, between 24 and 28 gestational weeks. Their study showed the cut-off value of cervicovaginal βhCG was reported to be 77.8 mIu/ml.

According to this cut-off value the sensitivity, specificity and positive and negative predictive values for predicting delivery were 87%, 97%, 88.5% and 98% respectively These researches have concluded that cervicovaginal βhCG measurement in patients with preterm labor may be used as a predictive test.

In Ranjbar et al study, according of ROC curves, the cut-off of cervicovaginal βhCG secretions for predicting preterm labor and delivery and preterm labor & term delivery was 22.5 mIu/ml and the rate of sensitivity, specificity, positive and negative predictive value for cut-off were 97%, 76%, 81% and 96%,respectively (Fig. 2); the cut-off value of cervicovaginal βhCG secretions for predicting preterm labor & preterm delivery and term delivery was 18 mIu/ml and the rate of sensitivity, specificity, positive and negative predictive value for cut-off were 100%, 93%, 94% and 100%,respectively

In our study out of the total 100 participants presenting with preterm labour 9% delivered at <37 weeks..Out of these 7 had a BHCG value of >25mIu/ml ($p<0.001$).chi square 76.105.

Among the total 10 mothers with BHCG > 25 IU/L ,7 delivered preterm rest had term deliveries.

The sensitivity of the test was 77% with 96.7% specivicity indicating that mothers with BHCG <25 IU/L were less likely to have preterm deliveries.

The positive predictive value of our study was 70% with a false positive of 3%.The negative predictive value was 97% .

Of these 100 women 23% had previous history of preterm delivery. Among these 17.4% delivered at <37 weeks.(p=0.109)

Summary & Conclusion

SUMMARY AND CONCLUSION

To evaluate the association between elevated BHCG levels in cervicovaginal secretions and preterm delivery.

Our study group included 100 antenatal mothers without any co existing medical disorders who presented with either H/o preterm delivery in previous pregnancy or with symptoms suggestive of threatened preterm labour in present pregnancy at gestational age >28 weeks between December 2015-august 2016 at Government Kasturba Gandhi Hospital and Institute of Obstetrics and Gynecology, Egmore.

Cervicovaginal secretions were collected from all mothers by swab testing and levels of BHCG were estimated. They were assigned into two groups with BHCG <25IU/L and >25 IU/L respectively. All mothers were followed up outcome of delivery including gestational age and mode of delivery noted.

The following observations were made.

In this study group age of mother and outcome of delivery was not significantly related.

Maternal obstetric code and delivery outcome was not statistically related.

The study group with BHCG >25 IU/L 97% had preterm delivery while the remaining 3% delivered at term.(($p<0.001$).chi square 76.105).

Our study had a sensitivity of 77% and specificity of 96.7% with an Odds ratio of 1.01.

Thus our study showed cervicovaginal BHCG levels to be a predictor preterm delivery.

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Annexures

PROFORMA

DATE:

NAME: AGE: LMP:

IP NO: EDD:

D.O.A: D.O.D

OBSTETRIC CODE:

ADDRESS :

PRESENTING COMPLAINTS:

MENSTRUAL HISTORY : M/S:

OBSTETRIC HISTORY:

PAST HISTORY:

GENERAL EXAMINATION:

HT: WT: TEMP: PR: BP:

PALLOR: PEDAL EDEMA:

CVS: RS:

P/A: CONTRACTIONS:

P/V:

INVESTIGATIONS:

HB: RBS: U/A:

USG:

B-HCG LEVELS IN VAGINAL SECRETION

TREATMENT:

STAY IN HOSPITAL:

OUTCOME:

RESULT:

MASTER CHART

SNO	NAME	AGE	IP NO	G	P	L	A	LMP	EDD	PrPreterm	GA of preterm	GA at sample collection	BHCG	GA AT DELIVERY	MODE	B.WT	APGAR 1	APGAR 5	NICU
1	LAKSHMI	25	13014	2	1	1		2/7/2015	9/4/2016	YES	35	32	14.3	39	LN	2.8	7	9	NO
2	AMBIKA	24	13088	1				10/7/2015	12/4/2016	NO		32	16	38	LN EPI	3	8	8	NO
3	GRACE	22	13725	1				23/05/15	30/02/16	NO		36	12	38	LN	2.7	8	8	NO
4	SHEEBA	27	13645	2	1	1		29/6/15	6/4/2016	NO		32	11	38	LSCS	2.8	6	8	NO
5	LALITHA	23	13212	3	1	1	1	20/8/15	27/5/16	NO		32	18	37	LSCS	2.7	7	8	NO
6	LILY	25	13423	1	0	0		14/7/15	21/4/16	NO		32	26	34	LN	2	5	6	YES
7	JEBA	21	17625	2	0	0	1	24/8/15	31/5/16	NO		34	16	37	LN EPI	2.7	8	9	NO
8	RAMYA	24	13545	1	0	0		18/7/15	26/4/16	NO		35	22	37	LN	2.6	7	8	NO
9	FATIMA	22	13654	2	1	1		11/9/2015	18/6/16	YES	32	28	15	37	LN	2.5	7	8	YES
10	PRIYA	19	13767	1	0	0		22/7/15	29/4/16	NO		36	14	38	LSCS	3.2	7	8	NO
11	DEVI	20	13645	1	0	0		4/5/2015	11/2/2016	NO		36	11	38	LSCS	3.2	8	9	NO
12	ANNIE	22	13256	2	1	1		8/5/2015	15/2/16	YES	34	36	12	38	LN	2.6	8	9	NO
13	VEMBU	23	13897	2	1	1		19/9/15	26/6/16	NO		32	13	39	LN EPI	3	8	9	NO
14	KANIKA	21	13745	1	0	0		24/7/15	31/4/16	NO		32	28	33	LN	2	6	7	YES
15	VANI	25	13264	2	1	1		23/6/15	29/3/16	NO		34	24	38	LN EPI	2.8	8	9	NO
16	NITHYA	26	12546	2	1	1		12/7/2015	19/4/16	NO		32	15	39	LN	2.8	8	9	NO
17	RAJI	20	13612	1				30/6/15	7/4/2016	YES	32	36	14	38	LN EPI	2.9	8	9	NO
18	DIVIYA	22	13765	1				28/7/15	4/5/2016	NO		32	14.5	38	LN EPI	2.7	8	9	NO
19	PUSHPA	23	13243	2	1	1		10/5/2015	17/2/16	YES	34	36	15	39	LN EPI	2.9	8	9	NO
20	USHA	19	13906	1				17/7/15	24/4/16	NO		32	16	38	LN	2.9	8	9	NO
21	MARIYAM	20	13712	1				15/6/15	22/3/16	NO		32	15	39	LSCS	2.9	8	9	NO
22	ANITHA	24	13456	2	1	1		13/6/15	20/3/16	NO		30	16	38	LSCS	3	8	8	NO
23	AMBIKA	25	12434	2	1	1		19/7/15	26/4/16	NO		32	15	38	LSCS	2.9	8	9	NO
24	SATHYA	23	13762	2	1	1		21/5/15	28/2/16	NO		35	13.4	38	LN EPI	2.8	8	8	NO
25	VANITA	22	13154	2	1	1		13/6/15	20/3/16	NO		32	12	39	LN EPI	2.8	7	8	NO
26	MANJU	21	13651	1				3/6/2015	10/3/2016	NO		28	14	38	LN EPI	2.8	8	9	NO
27	RANI	21	13871	1				7/7/2015	14/4/16	NO		30	15	38	LN EPI	2.8	6	7	YES
28	KUMARI	26	13908	2	1	1		5/7/2015	12/4/2016	NO		34	16	38	LSCS	2.7	8	9	NO
29	NATHIYA	20	13710	1				8/5/2015	15/2/16	NO		36	14	37	LN EPI	2.8	8	8	NO
30	KOUSALYA	19	13004	1				11/7/2015	18/4/16	NO		30	15.6	38	LN EPI	3	8	9	NO
31	KALAI	19	13612	1				18/5/15	25/2/16	NO		32	12.5	38	LSCS	2.8	8	9	NO
32	BHARATHI	21	13817	2	1	1		4/6/2015	11/3/2016	NO		30	13.6	39	LN EPI	2.7	8	9	NO
33	THARANI	24	13945	2	1	1		12/6/2015	19/3/16	NO		32	12.5	38	LSCS	2.8	8	9	NO
34	SUKUMARI	20	13732	2	1	1		24/7/15	1/5/2016	NO		28	13.8	38	LSCS	2.8	5	6	YES
35	ANITHA	20	13767	1				22/8/15	29/5/16	NO		34	17	39	LN EPI	2.9	7	8	NO
36	SUJI	25	13634	2	1	1		28/7/15	4/4/2016	YES	34	32	29.7	34	LN	2.2	6	8	YES
37	VALLI	22	13624	1				14/9/15	21/6/16	NO		28	14.8	38	LN EPI	2.9	8	9	NO
38	RAMA	24	13898	2	1	1		11/10/2015	18/7/16	NO		28	16	39	LN EPI	2.8	8	9	NO
39	SHREYA	23	13909	2	1	1		15/11/15	22/8/16	NO		32	14	38	LSCS	2.8	9	9	NO
40	BLESSY	21	13709	2			1	25/10/15	2/8/2016	NO		30	15.2	38	LN EPI	2.9	8	8	NO
41	JAMILA	22	13203	2	1	1		15/10/15	22/8/16	NO		30	23	38	LN EPI	2.8	8	8	NO
42	MALIKA	22	13150	2	1	1		12/8/2015	19/5/16	NO		28	16.8	39	LN EPI	2.9	8	9	NO
43	SHANTHI	20	13265	2	1	1		10/10/2015	17/7/16	YES	32	30	28.5	32	LN	1.6	5	7	YES

44	JEYA	20	14512	3	1	1	1	24/10/15	31/7/16	NO		28	21	40	LN EPI	2.6	8	8	NO
45	MARY	19	12369	1	0	0		22/3/2015	29/12/16	NO		28	22	39	LSCS	2.6	7	8	NO
46	MALI	23	15125	1	0	0		24/4/15	31/1/16	NO		36	20	39	LN EPI	2.8	8	9	NO
47	SHELA	22	12487	2	1	1		12/5/2015	19/7/16	NO		32	14.8	39	LN EPI	2.7	8	9	NO
48	RAGA	21	11265	2	1	1	0	15/11/15	22/8/16	YES	32	28	12.8	40	LN EPI	2.7	8	8	NO
49	RAJI	22	12356	2	1	1	0	25/11/15	1/8/2016	NO		32	12.4	39	LSCS	2.7	7	8	NO
50	AJITHA	23	11478	2	1	1	0	2/10/2015	9/7/2016	YES	35	30	16.2	39	LN EPI	2.8	7	8	NO
51	JEYA	21	12698	2			1	4/6/2015	11/3/2016	NO		32	13.4	40	LN EPI	2.7	8	8	NO
52	ELAVARASI	25	13214	2	1	1		22/5/15	29/2/16	NO		30	12.4	37	LN EPI	2.6	8	9	NO
53	MARIYAMAL	19	12358	1	0	0		8/9/2015	15/6/16	NO		29	13.2	39	LN EPI	2.8	7	8	NO
54	JHANSI	20	11698	1				20/5/15	27/2/16	NO		34	14.6	39	LN EPI	2.8	8	8	NO
55	ALAMELU	26	13985	2	1	1		13/5/15	20/2/16	NO		32	15.2	39	LN EPI	3.2	8	9	NO
56	SHALINI	25	11956	2	1	1		14/11/15	21/8/16	NO		35	14.8	38	LN EPI	2.9	8	9	NO
57	RATHI	24	11265	2	1	1		15/8/15	22/5/16	YES	32	32	27.8	32	LN	1.8	7	7	YES
58	SIVARANJANI	21	11598	1				9/9/2015	16/6/16	NO		32	26.6	38	LSCS	2.9	8	8	NO
59	JANCY	22	12589	2	1	1		5/8/2015	12/5/2016	YES	34	28	28.8	32	LN	1.5	7	7	YES
60	KALAIVANI	19	11325	1				18/10/15	25/7/16	NO		30	15.4	37	LN	2.5	6	7	YES
61	NANDHINI	21	12698	1				21/9/15	28/6/16	NO		35	19	38	LSCS	3.8	7	8	NO
62	KANMANI	20	12698	2			1	11/7/2015	18/4/16	NO		34	15.6	39	LN EPI	2.9	7	8	NO
63	SAROJA	24	11569	2	1	1		8/6/2015	15/3/16	YES	36	32	14.7	38	LN EPI	3.2	8	9	NO
64	GAYATHRI	23	12365	2	1	1		12/6/2015	19/3/16	YES	34	32	16	39	LSCS	3.4	8	9	NO
65	KAVITHA	23	14865	2	1	1		15/10/15	22/7/16	NO		30	12.7	38	LSCS	2.8	8	9	NO
66	KANIKA	23	12314	2	1	1		19/10/15	26/7/16	NO		32	13.7	38	LSCS	2.8	8	9	NO
67	CLARA	26	11856	2	1	1		4/11/2015	11/8/2016	YES	32	34	18	39	lscs	2.9	8	8	NO
68	SHEELA	21	15369	1				18/11/15	25/8/16	NO		32	16	40	LN EPI	2.8	9	9	NO
69	TARA	20	14236	1				20/11/15	27/8/16	NO		30	15.7	38	LSCS	3.2	8	8	NO
70	PUSHPA	24	12657	1				22/11/15	29/8/16	NO		30	13.5	39	LN EPI	2.8	8	9	NO
71	TAMIL	23	12158	2	1	1		8/6/2015	15/3/16	NO		32	15.6	39	LN EPI	2.8	8	9	NO
72	SOBANA	21	13698	2	1	1		3/7/2015	10/4/2016	YES	30	32	26	38	LN	2.8	8	8	NO
73	KAVYA	23	12489	2	1	1		20/5/15	27/2/16	YES	32	31	12.9	39	LN EPI	2.9	9	9	NO
74	KIRUTHIKA	24	12176	2	1	1		24/6/15	31/3/16	YES	35	32	13.8	39	LSCS	2.9	8	8	NO
75	JAYANTHI	22	13125	1				13/4/15	20/1/16	NO		34	17.8	38	LSCS	2.8	8	8	NO
76	SOLAIYAMA	21	13265	1				16/8/15	23/5/16	NO		28	15	39	LN EPI	2.8	8	8	NO
77	SUGANTHI	22	13254	1				12/7/2015	19/4/16	NO		32	15.7	32	LN	1.8	7	8	YES
78	RATHIKA	21	12658	1				16/6/15	25/3/16	NO		30	16.7	32	LN EPI	2.2	8	9	YES
79	SANGEETHA	23	12478	1				2/6/2015	9/3/2016	NO		28	15	38	LN EPI	3	8	8	NO
80	SUGANYA	24	13432	3	1	0	1	9/6/2015	16/3/16	YES	34	32	18	39	LN EPI	2.8	8	8	NO
81	CHANDRA	21	14356	1				24/4/15	31/1/16	NO		34	12	39	LN EPI	2.9	9	9	NO
82	MANGAALAM	23	14347	1				13/8/15	20/5/16	NO		32	15	38	LSCS	3	6	7	YES
83	MANOGARI	24	12435	2	1	1		24/6/15	31/3/16	NO		32	14.8	39	LSCS	3.7	7	8	NO
84	SUBHA	25	13367	2	1	1		10/6/2015	17/3/16	NO		32	13.6	39	LN EPI	3.7	7	8	NO
85	JAYALAXMI	23	13278	2	1	1		8/5/2015	15/2/16	YES	28	34	14	38	LN EPI	2.8	7	8	NO
86	RAJALAXMI	21	14387	2	1	1		19/6/15	26/3/16	NO		32	13	39	LSCS	2.8	8	9	NO
87	NATHIYA	22	12345	1				20/7/15	27/4/16	NO		32	14	38	LN EPI	2.8	8	8	NO
88	DIVIYA	20	13248	1				21/7/15	28/4/16	NO		32	27	38	LN EPI	2.8	8	9	NO
89	KALAIVANI	21	13125	2	1	1		21/8/15	18/5/16	YES		32	14	38	LN EPI	2.8	8	8	NO
90	CHITHRA	23	14685	2	1	1		2/7/2015	9/4/2016	NO		28	15	39	LSCS	2.9	7	8	NO

91	KRISNAVENI	20	12487	1				15/8/15	22/5/16	NO		34	27	36	LN	2.3	7	8	YES
92	PRIYA	20	12698	2	1	1		4/5/2015	11/2/2016	YES	32	32	12	39	LN EPI	2.9	8	9	NO
93	ANUSHYA	21	12148	3	2	2		9/9/2015	16/6/16	NO		34	13	37	LN	2.6	8	8	NO
94	AMMU	21	12985	1				20/5/15	27/2/16	NO		32	11.8	38	LSCS	3.5	8	9	NO
95	ANUJA	20	13248	2	1	0		17/5/15	24/2/16	YES	34	32	21.7	39	LN EPI	2.8	9	9	NO
96	POORNA	23	12145	1				19/7/15	26/4/16	NO		30	13.5	38	LSCS	2.9	9	9	NO
97	SEETHA	27	12985	2	1	1		1/5/2015	8/2/2016	NO		32	15.6	38	LN EPI	3	7	8	NO
98	RABI	23	11698	2	1	1		5/5/2015	12/2/2016	NO		34	17.6	39	LN EPI	2.8	8	9	NO
99	ROSE	24	12678	2	1	1		22/4/15	29/1/16	NO		32	13.5	38	LN EPI	3.2	9	9	NO
100	ANNAPOORANI	23	13456	1				26/11/15	3/9/2016	YES		30	16	38	LN EPI	3	9	9	NO

MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Raghavi.N.
PG in M.S.(O & G)
Madras Medical College/KGH
Chennai 600 003

Dear Dr.Raghavi.N.,

The Institutional Ethics Committee has considered your request and approved your study titled **"MEASUREMENT OF BEATA HCG IN CERVICOVAGINAL SECRETIONS AS A PREDICTOR OF PRETERM DELIVERY" - NO.22012016.**

The following members of Ethics Committee were present in the meeting hold on **12.01.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.R.Vimala,MD.,Dean,MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD.,Inst.of Pharmacology,MMC,Ch-3	: Member
5.Prof.P.Raghumani,MS, Dept.of Surgery,RGGGH,Ch-3	: Member
6.Prof.M.Saraswathi,MD.,Director, Inst.of Path,MMC,Ch-3	: Member
7.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
8.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
9.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary - Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

MADRAS MEDICAL COLLEGE
21 JAN 2016
CHENNAI-600 003

INFORMATION SHEET

- We are conducting a study on **"MEASUREMENT OF Beta HCG IN CERVICOVAGINAL SECRETIONS AS A PREDICTOR OF PRETERM DELIVERY"** among patients attending Government Kasturba Gandhi Hospital, Chennai and for that your clinical details may be valuable to us.

- We are selecting certain patients and if you are found eligible, we may be using your clinical details in such a way so as to not affect your final report or management.

- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator Signature of participant

Date: . .2015

ஆராய்ச்சி தகவல் தாள்

"குறைமாத பிரசவம் ஏற்பட வாய்ப்பு உள்ளதா என்பதை யோனிப்பாதை திரவங்களில் B-HCG -இன் அளவீட்டை கொண்டு கண்டறிதல்" பற்றிய ஆய்வு.

ஆய்வின் நோக்கம்:

குறைமாத பிரசவம் ஏற்பட வாய்ப்பு உள்ளதா என்று அறிய 24-28 வார கர்ப்பிணி பெண்களின் யோனி பாதை திரவங்களை பரிசோதித்தல், அதில் B-HCG -இன் அளவீட்டை கொண்டு குறை மாத பிரசவதிற்கான வாய்ப்பினை கண்டறிதல்.

ஆய்வின் செயல்முறை:

ஆய்வில் பங்கேற்கும் கர்ப்பிணி பெண்கள் அனைவருக்கும், அடிவழி பரிசோதனை மூலம் யோனி திரவங்கள் சேகரிக்கப்படும். அதில் B-HCG இன் அளவீடு கணக்கிடப்படும். B-HCG இன் அளவீடு அதிகமாக உள்ளவர்கள் குறைமாத பிரசவம் ஏற்படுகிறதா என்று கணக்கிடப்படுவர்.

ஆய்வினால் ஏற்படும் நன்மைகள்:

வருங்காலத்தில் குறைமாத பிரசவம் ஏற்பட வாய்ப்புள்ள கர்ப்பிணி பெண்கள் முன்னதாக கண்டறியப்பட்டு அதை தடுப்பதற்கான சிகிச்சை முறைகள் அளிக்க வாய்ப்பு அமையும்.

மருத்துவ சிகிச்சையின் தகவல்கள் குறித்த விபரங்கள்:

உங்கள் மருத்துவ சிகிச்சை பற்றிய தகவல்கள் இரகசியமாக பாதுகாக்கப்படும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களுக்கு பரிசோதனைகள் செய்து அதன் தகவல்களை ஆராய்வோம். அதனால் தங்கள் நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக் கொள்கிறோம். முடிவுகள் அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்கள் பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதை தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களது விருப்பத்தின் பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு சிகிச்சையின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சி முடிவின்போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி:
இடம்:

CONSENT FORM

STUDY TITLE : "MEASUREMENT OF Beta HCG IN CERVICOVAGINAL SECRETIONS AS A PREDICTOR OF PRETERM DELIVERY"

STUDY CENTRE : Institute of Social Obstetrics,
Govt. Kasturba Gandhi Hospital,
Chennai-5.

PARTICIPANT NAME : AGE: SEX: MRD.NO:

I confirm that I have understood the purpose of procedure for the above study, I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the possible complications that may occur during the procedure, I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason.

I understand that investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties of published, unless as required under the law. I agree not to restrict the use of any or results that arise from the study.

I hereby consent to participate in this study of ""MEASUREMENT OF Beta HCG IN CERVICOVAGINAL SECRETIONS AS A PREDICTOR OF PRETERM DELIVERY"

Signature of Investigator:

Place : Chennai
Date : . .2015

Study Investigators Name

Institution

Signature / Thumb Impression of patient

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு:

"குறைமாத பிரசவம் ஏற்பட வாய்ப்பு உள்ளதா என்பதை யோனிப்பாதை திரவங்களில் B-HCG -இன் அளவீட்டை கொண்டு கண்டறிதல்" பற்றிய ஆய்வு.

ஆய்வு நடத்தப்படும் இடம்:

அரசு கஸ்தூரி பாய் கர்ந்தி தாய் சேய் நல மருத்துவமனை மற்றும் சமூக மகப்பேறுயியல் மையம்

பங்கு பெறுபவரின் பெயர்: பங்கு பெறுபவரின் வயது:

பங்கு பெறுபவரின் எண்:

இந்த ஆய்வில் குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. நான் இவ்வாய்வில் தன்னிச்சையாக பங்கேற்கிறேன் எந்த காரணத்தினாலோ எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக் கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ அதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என்பதை அறிந்து கொள்கிறேன். இந்த ஆய்வின் மூலம் கிடைக்கும் முடிவை பயன்படுத்திக் கொள்ள மறுக்கமாட்டேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன்.

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தேதி:

சாட்சிகளின் கையொப்பம்
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தேதி:

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Dissertation submitted to

The Tamil Nadu Dr. MGR University

Chennai

In partial fulfillment of the regulations

For the award of the degree of

M.S.

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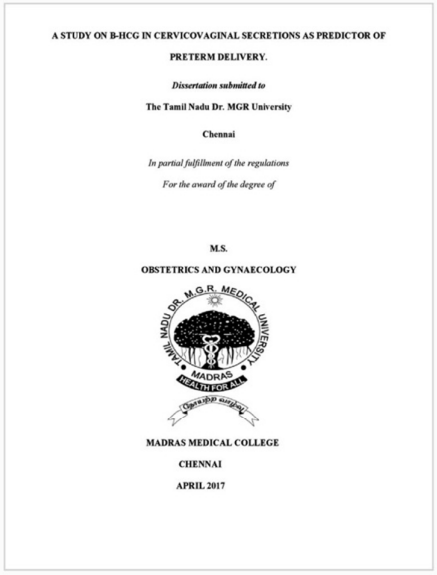

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