"EVALUATION OF SERUM MAGNISIUM LEVEL IN PRETERM LABOUR"

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M.S. IN OBSTETRICS AND GYNAECOLOGY

BY

DR. PHURAILATPAM. PRIYADARSHINI MBBS

UNDER THE GUIDANCE OF

DR.GOMATHY.E

&

Under the Co-Guidance of

Dr.Sumathi M.E

Associate Professor, Department of Biochemistry

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY
SRI DEVARAJ URS MEDICAL COLLEGE,
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SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, KOLAR, KARNATAKA.

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Date:

Place

Signature of the guide

DR. GOMATHY.E, MD

Professor,Dept. of Obstetrics and Gynaecology

Sri Devaraj Urs Medical College,Tamaka,Kolar

CERTIFICATE BY THE CO-GUIDE

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DR. PHURAILATPAM.PRIYADARSHINI in partial fulfillment of the requirement for the degree of M.S. Obstetrics & Gynaecology.

DATE

PLACE:

Signature of the Co-guide

DR.SUMATHI. M.E

Associate professor, Department of Biochemistry

Sri Devaraj Urs Medical College Tamaka , Kolar.

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This is to certify, the ethical committee of Sri Devaraj Urs medical college, Tamaka, Kolar has unanimously approved **DR. PHURAILATPAM. PRIYADARSHINI** post graduate resident in the subject of obstetrics and gynaecology at Sri Devaraj Urs medical college, Tamaka, Kolar to take up the dissertation work titled **"EVALUATION OF SERUM MAGNISIUM LEVEL IN PRETERM LABOUR**" to be submitted to Sri Devaraj Urs Academy Of Higher education and Research, Kolar.

Signature of Member Secretary

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Date : Signature of the candidate

Place: (DR.PHURAILATPAM.PRIYADARSHINI)

ABBREVATIONS

AFI	Amniotic Fluid Index
ART	Assisted Reproductive Technology
UTI	Urinary Tract Infection
BPP	Bio Physical profile
USG	Ultrasonography
TVU	Transvaginal ultrasonography
CTG	Cardio tocogram
CRH	Corticotrophin Releasing hormone
LDH	Lactate Dehydrogenase
HCG	Human chorionic Gonadotrophin
ICH	Intra Cranial Hemorrhage
PROM	Premature rupture of membranes
PPROM	Preterm premature rupture of membranes
PTB	Preterm birth
SMFM	Society for Maternal- Fetal Medicine
SGA	Small for gestational age
LGA	Large for gestational age
LLETZ	Large loop excision of transformation zone

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ABSTRACT

INTRODUCTION:

Preterm labour followed by preterm delivery is a major issue for perinatal morbidity and mortality [1]. Preterm infants are at a greater risk of short term and long term complications including disabilities and impediments in growth and mental development. Incidence of preterm labour in India between 1980 -2000 is 5-10% leading to 70-80% of perinatal deaths[1]. The aim of this study is to determine the relationship between serum magnesium level and preterm delivery, so that the high morbidity and mortality related to prematurity could be reduced by early diagnosis of this deficiency and its correction

STUDY DESIGN: Prospective case control study.

DURATION OF STUDY: October 2015 to October 2017.

PLACE OF STUDY: R.L.Jalappa Hospital and Research Centre Tamaka, Kolar.

METHODOLOGY: The study consisted of 50 pregnant women with preterm onset of labour (between 28 and 37 weeks of gestation) and 50 pregnant women with comparable gestational age (28 -37 weeks) attending the OPD for routine ANC and they are followed up till delivery. Venous blood sample of 2 ml is collected and the serum magnesium is estimated by Fusion 5.1 FS magnesium Micro slide method.

RESULTS: The mean age of the patients in the study group was 22.4 ± 3.084 while that in the control group was 22.4 ± 3.064. Majority of the patients in both the age groups were in the age group of 21 to 25 years. Primigravida are more common in both

study group and control group constituting 55% of cases. In study group most cases is in between 34 weeks to 36 weeks 6days contributing of 80%. Most of the cases in study group falls in lower middle class of BG Prasad socioeconomic status constituting of 28%, however, in control group most of the cases falls in middle class (52%) followed by upper middle class (42%).

Most (62%) of the women had preterm vaginal delivery in study group, and in control group most (66%) of the women delivered by full term vaginal delivery. Majority of the baby in both study (58%) and control (52%) were male baby. The mean birth weight of the baby in study population is 2.1 kg with SD of 0.34 and in control group is 3.09 kg with SD of 3.09.

The p-value being <0.001, which is highly statistically significant. The mean APGAR score of the baby in study population is 6.58 with SD of 0.54 at 1 min and 8.56 with SD of 0.54 at 5 min, and in control group is 7 at 1 min and 9 at 8 min. The p-value being <0.001, which is highly statistically significant. In study group 38 % of the baby was admitted to NICU, however in control group none of the baby had required NICU admission. The mean serum magnesium level (mEq/L)in study population is 1.39 mEq/L with SD of 0.2 and in control group is 2.08 mEq/L with SD of 0.2 . The p-value being <0.001, which is highly statistically significant. The low level of mean serum magnesium is observed in lower middle class which is 1.29 with SD of 0.14 and in lower class is 1.28 with SD of 0.1. The p-value being 0.003 and 0.004 respectively which is statistically significant. The value of serum magnesium levels decrease with the increase in gestational age in both study and control group.

CONCLUSION: Serum magnesium levels in our study were significantly lower in those who delivered preterm when compared with those who delivered at term,

suggesting a possible role of hypomagnesemia in initiation of preterm labour. Larger studies are required to conclusively prove the role of hypomagnesemia in preterm labour.

INTRODUCTION

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INTRODUCTION

Preterm labour is defined as labour occurs with regular and frequent uterine contractions causing progressive cervical changes before 37 completed weeks of gestation.[1] For the last 50 years, extensive research has been conducted with the objective of preventing, predicting and optimizing the outcome of patient with preterm labor.

WHO defines preterm labour as one where the labour starts before the 37 completed week (259 days) of gestation, counting from the first day of last menstrual period [1]. Incidence of preterm labour in India is about 5-10 % [2] . This leads to about 70- 80% of perinatal deaths[2]. Late preterm (between 34 weeks and 0 days and 36 weeks and 6 days) accounts for about 74% of all preterm births, while the severe preterm birth (< 32 weeks) rate has remained relatively constant during the last two decades[2].

The causes of preterm labour is not yet completely known; in 50 % cases it is spontaneous and idiopathic [3]. Some of the causes of preterm labour are PROM , multiple pregnancies, polyhydramnios, hypertensive disorders of pregnancy, infections, cervical incompetence, antepartum haemorrhage, fetal and uterine anomalies, anaemia, heavy work, smoking etc. it is also related to socioeconomic status and geographic location [4]. To prevent preterm labour successfully the therapeutic approach should be to focus on the initial event of labour instead of attempting to inhibit the cascade of events culminating in preterm labour**.**

Besides varied etiology, preterm labour may be due to an alteration in basic biochemical function of body at cellular levels stating emphasis to trace elements of which magnesium, being one of them is a subject of interest now a days. Magnesium is the

second most plentiful positively charged ion found within the cells of body signifying its importance in various physiological cellular functions .

Serum levels of magnesium ranges from 1.6 to 2.6 mEq/dl in adults [4]. Hypomagnesaemia leads to neuromuscular hyperexcitability resulting in muscle cramps and uterine hyperactivity. The hyperexcitability of uterine musculature induced by hypomagnesemia leads to increased cervical dilatation which in turn facilitates approach of vaginal microorganisms into cervical canal and changes quality and quantity of vaginal discharge while uterine passage is being colonised by pathogenic micro organisms[5].

It is known that serum magnesium levels fall during pregnancy with gestational age[6]. This decrease serum magnesium play an important role in the physiology of parturition. Decrease of magnesium level in plasma may be responsible for decrease of same in myometrium leading to initiation of uterine contraction and labour[7,8].

The aim of this study is to determine the relationship between serum magnesium level and preterm delivery, so that the high morbidity and mortality related to prematurity could be reduced by early diagnosis of this deficiency and its correction.

AIMS AND OBJECTIVES OF THE STUDY

- 1.To estimate the serum magnesium levels in women with preterm labour.
- 2. To compare the value of serum magnesium levels in women with preterm labour with those women in the same gestational age who delivered at term.

REWIEW OF LITARATURE

A) CONCEPT OF PRETERM LABOUR:

The average duration of normal pregnancy is 267 days, counted after conception, or 280 days (40 weeks) from the first day of the last normal period. Infants born at 39 and 40 weeks of gestation have the lowest rates of adverse outcomes.

In the past, birth weight was taken as the parameter to differentiate between preterm and term infants. It is now understood that many factors beside gestational age affect birth weight.

Hence, gestational age is the only parameter used for diagnosis of preterm labor.[9]

Preterm labor is defined by WHO in 1969 that it is the initiation of regular painful uterine contractions that occurs usually with increasing frequency and intensity associated with progressive cervical changes of effacement and dilatation of cervix before 37 completed weeks of gestation from the first day of the last normal menstrual period.[10,11] This definition, which has now been in use for almost 40 years, was first promulgated in 1969 by World Health Organisation (WHO) and International Federation of Gynecology and Obstetrics (FIGO).

Preterm birth (PTB) may be defined as birth between the age of viability and before 37 completed weeks of gestation [5]. In the Unitedkingdom, PTB includes deliveries between 24 weeks and 36 weeks and 6 days gestation and many developed and developing countries officially records all births with birth weight above 500g.The lower limit of this definition is less clearly defined it will be that gestational age though to correlate with fetal viability.[12] In USA, this is often taken as 20wks.

In Singapore, for legal purposes viability is defined as any gestation carried beyond 28

weeks, but fundamental to the issue of viability is the gestation at which the fetus isthought to be capable of being born alive and the capacity to sustain such life without undue morbidity and mortality.[13]

Threatened preterm labour is defined as pregnancies complicated by episodes of clinically significant uterine activity but without cervical change.[14]

Those born before 34 completed weeks of gestation are labeled as early preterm and those occurring between 34 completed weeks and 36 completed weeks are labeled as late preterm. Late preterm comprises of 74% of all the preterm births[15].

Preterm can be categorise based on gestational age as :

1. Extremely preterm (<28 weeks)
2. Very preterm (28 to <32 weeks)
3. Moderate to late preterm (32 to <37 weeks)

Most recently, Spong (2013) observed[16], "it has become apparent that infants born between 37 weeks 0 days and 38 weeks 6 days gestation experience morbidities that are associated with prematurity compared to births at 39 weeks 0 days through 40 weeks 6 days when infant mortality is lower than at any other time in human gestation." Those births 37weeks 6 days through 38 weeks 6 days are now defined as *early term* and those 39 weeks 0 days through 40 weeks 6 days are defined as *term*.

The American College of Obstetricians and Gynecologists (ACOG) [17]and Society for Maternal-Fetal Medicine (SMFM) have adopted the nomenclature later preterm (34 weeks to 36 weeks 6 days of gestation) and early term (37 weeks to 38 weeks 6 days of

gestation) to acknowledge the contribution of gestational age in these ranges to neonatal risks.

Olsen IE, et al, (2013)[18] defined "small for gestational age" (SGA), defined as weight less than 10th percentile at a given fetal gestational age. By this definition, less than 2,500 grams at birth is considered SGA. "Large for gestational age" (LGA) is defined as weight greater than the 90th percentile for duration of gestation. Infants greater than 4,500 grams at term birth are LGA. Low birth weight infants can be further classified into very low birth weight (VLBW) which includes infants less than 1500 grams and extremely low birth weight infants (ELBW) which are infants less than 1000 grams.

WHO (2013) [19] Viability is often defined as the gestational age at which there is a 50% chance of survival with or without medical care; therefore, under current conditions, viability in developed, high income countries of the world is somewhere between 22–24 weeks, whereas viability is closer to 34 weeks gestational age in low- and middle-income countries.

INCIDENCE:

Every year, an estimated 15 million babies are born preterm (before 37 completed weeks of gestation), and this number is rising. That is more than 1 in 10 babies.

Almost 1 million children die each year due to complications of preterm birth. Many survivors face a lifetime of disability, including learning disabilities and visual and hearing problems[20].

Globally, prematurity is the leading cause of death in children under the age of 5. And in

almost all countries with reliable data, preterm birth rates are increasing.Inequalities in survival rates around the world are stark. In low income settings, half of the babies born at or below 32 weeks (2 months early) die due to a lack of feasible, cost-effective care, such as warmth, breastfeeding support, and basic care for infections and breathing difficulties. In high-income countries, almost all of these babies survive[20].

The incidence of preterm birth range from 5% to 8% in most developed and developing countries but the incidence is increasing worldwide due to rise in multiple gestations from assisted reproductive techniques, better dating scans and iatrogenic deliveries .[6]

Incidence of preterm labour in India is about 5-10 % leading to 70-80% of perinatal deaths.[2]

About 0.75 million neonates die every year in India, the highest for any country in the world.

The neonatal mortality rate (NMR) declined from 52 per 1000 live births in 1990 to 28 per 1000 live births in 2013, but the rate of decline has been slow and lags behind that of infant and under-five child mortality rates[21].

A systematic analysis of global, regional and national causes of child mortality in 2013 identified preterm birth complications and infections to be the two major causes of neonatal deaths in India.

A systematic analysis of global, regional and national causes of child mortality in 2013 identified preterm birth complications and infections to be the two major causes of neonatal deaths in India.[22](figure no.1)

The review, which included the data from the Million Death Study from India, found perinatal asphyxia and malformations to be the other two significant causes of neonatal

mortality. These findings are very similar to the overall global pattern[22].

The data from three studies on the timing of neonatal deaths indicates that about three-fourths of total neonatal deaths occur in the first week of life.[23,24,25.]The first 24 hours account for more than one-third (36.9%) of the deaths that occur in the entire neonatal period.

The prospective study by Baqui et al.[23] provided data on the timing of cause-specific neonatal deaths: almost all deaths (97.8%) due to asphyxia occur in the first week of life, with 70% of them occurring within the first 24h (day 0).

About three-fourth of deaths due to prematurity (74.8%) occur in the first week of life, with 30% in the first 24h (day 0) to 50% of neonatal deaths secondary to sepsis occur in the first week of life. About 30% of sepsis-related deaths occur in the second week, whereas around one-fifth in weeks 3–4. Three-fourth of the deaths due to malformations occur in the first week of life, with day 0 alone contributing to nearly half of these deaths. [23]

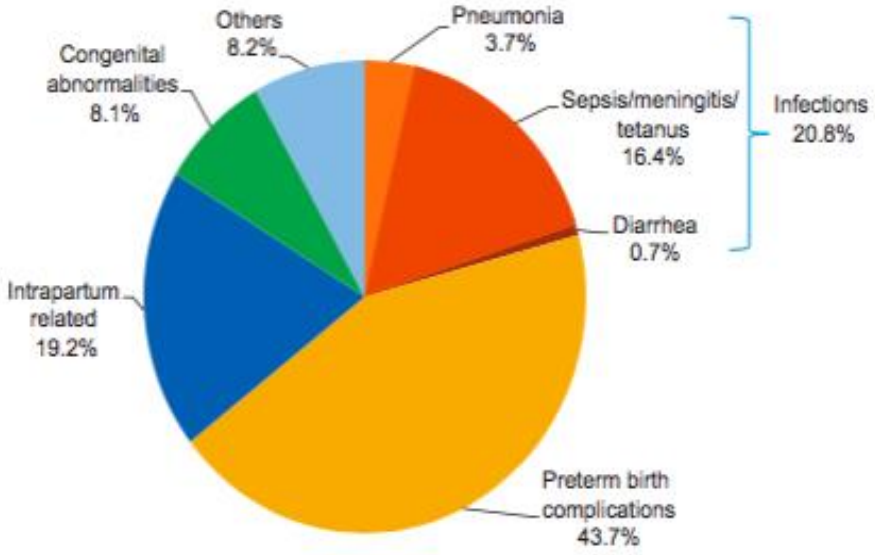


FIGURE NO.1. CAUSES OF NEONATAL DEATH IN INDIA.

The percentage of preterm births increased 36 percent from 9.4 percent in 1984 to a high of 12.8 percent in 2006 (Mathews, 2013)[26]. Since 2006, however, the trend has reversed, and the percentage of preterm births declined to 11.7 percent in 2011 is decline in the percentage of preterm births occurred for both the early—less than 34 weeks—and later preterm periods (Hamilton, 2012)[27]. Although the lowest level in more than a decade, the 2011 preterm birth rate is still higher than rates reported during the 1980s and most of the 1990s.

PATHOPHYSIOLOGY OF PRETERM LABOUR:

Term parturition and preterm parturition share anatomic, physiologic and biochemical features that are considered a common pathway of parturition. The pathway includes 1) cervical changes (softening and ripening), 2) membrane/ decidual activation, and 3) increased uterine contractility.Spontaneous labor at term results from physiologic activation of the common

pathway of parturitionWhereas preterm labor is the result of a pathologic activation of this pathway.

Asynchrony can be clinically recognized as 1) cervical insufficiency when the process affects cervix predominantly; 2) preterm uterine contractions when the process affects the myometrium; or 3) preterm premature rupture of membrane (PPROM) if the insult acts on the chorioamniotic membrane.

Cervical changes occur over weeks, myometrial contractibility is increased before the onset of labor,and appearance of fetal fibronectin (FFN) in the cervicovaginal mucus can be considered to reflect extracellular matrix (ECM) degradation, which indicates activation of the decidua and membranes.

A fetal maturity- based signal for labor originates in the fetal hypothalamus and leads to increased Secretion of corticotropin releasing hormone (CRH), which in turn stimulates adrenocorticotropic Hormone (ACTH) and cortisol production by the fetal adrenals, which ultimately leads to activation of the common pathway of parturition. The fetus may contribute to spontaneous onset of preterm labor in the context of fetal inflammatory response syndrome.

Spontaneous PTB may be defined as a syndrome in which the clinical presentation of preterm labor, Preterm ruptured membrane and preterm cervical effacement and dilatation without labor occur as a result of multiple etiologies that can occur alone or in combination.

CERVICAL CHANGES: SOFTENING AND RIPENING:

The cervix is the main structure in pregnancy and parturition; it must maintain structural Integrity and acts as a physical barrier during pregnancy and subsequently transition to allow passage of the fetus during delivery. The change is not acute; physiological parturition occurs over the course of gestation and requires evolving biochemical and biomechanical changes in the cervix that manifest as cervical ripening.[28,29.]

The 3 main structural components in the cervix of women are smooth muscle, collagen and the connective tissue ground substance containing glycosaminoglycans (GAGs). Smooth muscle content in the cervix is about 25%, 16% and 6% in the upper, middle and lower segments respectively.[30]

Although collagen is the main contributor to the tensile strength of the cervix, GAGs are critical to determining the viscoelastic properties of the tissue. The GAGs are long, unbranched polysaccharides- vital components of the extracellular matrix(ECM).

Changes in ECM during cervical ripening includes an influx of inflammatory cells- macrophages, neutrophils, mast cells, eosinophils and so on- into the cervical stroma in a process similar to an inflammatory response. These cells produce cytokines and prostaglandins that affect ECM metabolism. Prostaglandins effect cervical ripening physiologically.

The primary factor for cervical ripening is the changes that take place in collagen and in connective tissue. The collagen fibrils which was previously arranged in an orderly fashion breaks up and the ground substances becomes prominent.

The cervical distensibility increase, while protein and collagen concentrations decline. This lost of collagen results in proteolytic digestion and subsequent elimination of the soluble collagen fragments.

Cervical changes normally precede the onset of labor, are gradual and develop over several weeks. PTB is often preceded by cervical ripening over a period of weeks in the second andthird trimesters, evidenced on clinical examination by softening and thinning of the cervix.

ACTIN-MYOSIN INTERACTION:

Interaction of myosin and actin is essential to muscle contraction. This interaction requires that actin be converted from a globular to a filamentous form. Moreover, actin must be attached to the cytoskeleton at focal points in the cell membrane to allow development of tension.

Actin must partner with myosin, which is composed of multiple light and heavy chains. The interaction of myosin and actin activates adenosine triphosphatase (ATPase), hydrolyzes adenosine triphosphate, and generates force. This interaction is brought about by enzymatic phosphorylation of the 20-kDa light chain of myosin. This is catalyzed by the enzyme myosin light-chain kinase, which is activated by calcium. Calcium binds to calmodulin, a calcium- binding regulatory protein, which in turn binds to and activates myosin light-chain kinase.

Agents that promote contraction act on myometrial cells to increase intracellular cytosolic calcium concentration—$[Ca^{2+}]_i$. They allow an influx of extracellular calcium through ligand- or voltage-regulated calcium channels. For example, prostaglandin $F_{2\alpha}$ and oxytocin bind their respective receptors during labor to open ligand-activated calcium channels.

Activation of these receptors also releases calcium from the sarcoplasmic reticulum to cause decreased electronegativity within the cell. Voltage-gated ion channels open, additional calcium ions move into the cell, and cellular depolarization follows. This increase in [Ca^{2+}] is often transient, but contractions can be prolonged through the inhibition of myosin phosphatase activity (Woodcock, 2004)[31].

Conditions that decrease [Ca]$_i$ and increase intracellular concentrations of cyclic denosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP) ordinarily promote uterine relaxation.

In addition to myocyte contractility, myocyte excitability is also regulated by changes in the electrochemical potential gradient across the plasma membrane. Before labor, myocytes maintain a relatively high interior electronegativity. This state is maintained by the combined actions of the ATPase-driven sodium potassium pump and the large conductance voltage- and Ca^{2+}-sensitive K channel—maxi-K channel (Parkington, 2001)[32].

During uterine quiescence, the maxi-K channel is open and allows potassium to leave the cell to maintain interior electronegativity. At the time of labor, changes in electronegativity lead to depolarization and contraction (Brainard, 2005; Chanrachakul, 2003)[33,34]. And, as parturition progresses, there is increased synchronization of electrical uterine activity.

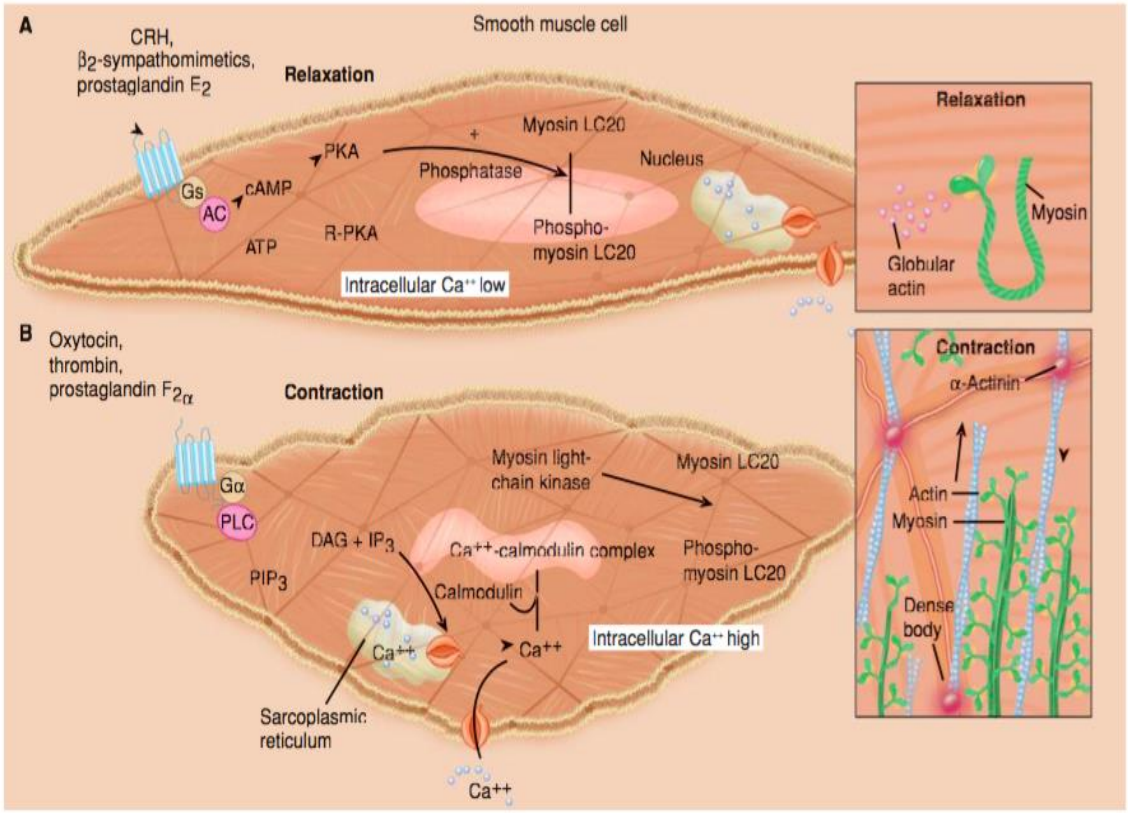


FIGURE NO. 2 . Uterine myocyte relaxation and contraction

A. Uterine relaxation is maintained by factors that increase myocyte cyclic adenosine monophosphate (cAMP). This activates protein kinase A (PKA) to promote phosphodiesterase activity with dephosphorylation of myosin light-chain kinase (MLCK). There are also processes that serve to maintain actin in a globular form, and thus to prevent fibril formation necessary for contractions.

B. Uterine contractions result from reversal of these sequences. Actin now assumes a fibrillar form, and calcium enters the cell to combine with calmodulin to form complexes. These complexes activate MLCK to bring about phosphorylation of the myosin light chains. This generates ATPase activity to cause sliding of myosin over the actin fibrils, which is a uterine contractor. AC = adenylyl cyclase; Ca^{++} = calcium; DAG = diacylglycerol; Gs and Gα = G-receptor proteins; IP_3 = inositol triphosphate; LC20 = light chain 20; PIP_3 = phosphatidylinositol 3,4,5–triphosphate; PLC = phospholipase C; R-

PKA = inactive protein kinase. (Redrawn from Smith, 2007.)

RISK FACTORS ASSOCIATED WITH PRETERM LABOR:[30]

MATERNAL CHARACTERISTICS NOT MODIFIABLE DURING PREGNANCY	RELATIVE RISK
Age<18yrs	1.5-3.4
Age>35yrs	1.3-1.8
Unmarried	2.2
Unemployed	2.3
Primigravida	1.9
Black women	-
MATERNAL CHARACTERISTICS MODIFIABLE DURING PREGNANCY	RELATIVE RISK
Low BMI(<20)	1.5-1.8
Cigarette smoking(>20/day)	1.3
Heavy work	2.1-3.3`
Stress(perceived)	1.2-1.8
Substance abuse	2.5-6.0
PAST REPRODUCTIVE HISTORY	RELATIVE RISK
2 Previous first trimester loss	2.9
2 Previous therapeutic terminations	2.5
Second trimester loss	4.2
One previous preterm delivery	2-5
Two previous preterm deliveries	4-7.6

The risk of preterm labor birth before 32 weeks was 1 in 10 if the previous preterm birth

was before 28wks, 1 in 15 if the previous preterm birth was 28 to 34weeks and 1 in 28 if it was between 35 to 36 weeks of gestation.

PREGNANCY COMPLICATIONS NOT AMENABLE TO INTERVENTION	**RELATIVE RISK**
Multiple pregnancies	-
Pre-existing maternal illness	-
Fetal malformation	-
Preeclampsia	-
First or second trimester bleeding	1.6-2.0

Assisted reproductive techniques like IVF and ovulation inducers increases multiple pregnancies, contributing 50% of twins being born preterm.

The acute maternal illness, especially systemic infection can precipitate labor. Fetal malformations like multiple anomalies, renal anomalies and anterior abdominal wall defect deliver preterm.

PREGNANCY COMPLICATIONS AMENABLE TO INTERVENTION	**RELATIVE RISK**
Asymptomatic bacteriuria	2-4
Bacterial vaginosis	1.4-1.8
Cervical incompetence	-
Uterine anomalies	-
STD's	-
SCREENING TESTS DURING PREGNANCY IN SELECTED PREGNANCIES	**RELATIVE RISK**
Cervical length<1st centile	1.4
Cervical length5th centile	9.5
Fetal fibronectin	7.5
Maternal plasma CRH in second trimester	3.5

EITIOLOGY OF PRETERM LABOR:

CERVICAL INSUFFICIENCY:

The cervix is a unique and complex structure with has a central role in maintaining the growing and developing embryo until term inside the uterine cavity.

The objective is achieved by remaining closed and non-compliant until the onset of labor at term. The cervix is therefore likely to play a very significant role in the etiology, prevention and treatment of preterm labor. In the non-pregnant state, the cervix consists of an extracellular connective tissue matrix made up of collagen, elastin, proteoglycans, a thin layer of smooth muscle and fibroblasts, which penetrate the connective tissue matrix. During pregnancy, the cervix increases in water content, in mass and vascularity with a

reduction in collagen content as pregnancy advances which leads to cervical softening. If these changes occurred in early pregnancy, an 'insufficient cervix' will result.

'Cervical insufficiency' is defined as painless cervical effacement and dilatation leading to second trimester pregnancy loss or preterm delivery.[35] Cervical insufficiency occurs in upto 2% of all pregnancies, but responsible for only 8-9% of all preterm births compared to 40-50% from spontaneous preterm labor and 20-30% from preterm prelabor rupture ofmembranes (PPROM). [36,37.]

Preterm labor has many causes which include:

1)Previous history:

There is a strong relationship between a history of prior preterm labor and short cervical length. Studies have reported that a strong correlation between cervical length in index pregnancy and previous obstretric history in a study which includes women with a history of cervical insufficiency (32 women) previous preterm delivery < 26 weeks (98 women), 27- 32 weeks(98 women), 33-35 weeks (127 women) and a control group of women with previous term delivery (106 women) [38]

The gestational age of the first preterm delivery was significantly correlated with cervical length in the present pregnancy at each gestational interval between 20 weeks and 30 weeks in a continouous manner[38].

Guzman studies also found a strong relationship between previous obstetric history and cervical length in the subsequent pregnancy[39]. Similarly, Andrews and coworkers found that those women who had history of spontaneous second-trimester miscarriage and preterm delivery due to cervical insufficiency had an increased risk of recurrence in a subsequent pregnancy[40,41,42..]

Preterm delivery rates increases as the gestational age of the prior preterm decreased (David F Colombo, 2000 [43])

BIRTH OUTCOME	**SECOND BIRTH <34WKS(%)**
First birth>35wks	5
First birth<34wks	16
First and second births<34wks	41

2) Congenital abnormalities:

Female offspring's of women who took diethylstilbestrol (DES) were at increased risk of uterine anomalies with approximately 30% of these affecting the cervix[44].

3) Obstetrics trauma:

Cervical laceration or injury may occur during labour or delivery, that might includes spontaneous labour, forceps and vacuum delivery or caesarean section[45].

These factors may weaken the cervix and contribute to cervical insufficiency.

4) Cervical surgery:

Pregnant women giving history of cone biopsy, large loop excision of transformation zone (LLETZ) or laser ablation of the cervix are at increased risk of preterm birth[46]. It is said that the risk was greater if the depth of excision was >10 mm compared to excision depths of <10mm.[47]

Laser vaporization, cryotherapy and punch biopsy are associated with preterm birth [48]

5) Uterine over-distension:

Multiple pregnancies and polyhydramious also carry an increased risk of preterm labor. About 40% of twin pregnancies will have spontaneous preterm labour or pPROM. Women with multiple gestations has been shown to be more likely to have short cervix at 24 weeks,which is probably due to a rapidily expanding uterus putting extra pressure on the cervix.[49]

In Multiple pregnancy and in polyhydramnios it is likely that early uterine distension acts to initiate expression of contraction associated proteins (CAPS) in the myometrium. The CAP genes influenced by stretch include those coding for gap junction proteins such as connexin 43, for oxytocin receptors and for prostaglandin synthesis resulting of excessive uterine stretch is the premature loss of myometrial quiescence.[50]
Uterine stretch also exhibits an early activation of the placental fetal endocrine cascade resulting in an early rise in maternal CRH and oestrogen levels, which can further enhance the expression of myometrial CAP genes.[51]

6) Multiple dilatation and evacualtion:

The Aggressive and forceful dilatation of the cervix during surgical termination of pregnancy may in some women leads to cervical damage. Studies have shown that two or more prior dilatation and evacuation especially for late termination of pregnancy is associated with increased risk of cervical insufficiency and preterm labour[52].
Therefore RCOG recommends the use of cervical ripening agents such as vaginal misoprostol prior to the procedure[53].

7) Infection:

Infection may have a casual or effect relationship with cervical insufficiency. Some proportion of women with cervical insufficiency in the second trimester have microbial invasion of amniotic cavity (MIAC)[54,55].

It is caused by premature cervical dilatation with exposure of chorioamniotic membranes to the microbial flora of lower genital tract.

Intrauterine infection can either be from the ascending or haematogenous route in the second trimester of pregnancy may produce cervical ripening and dilatation, and uterine contractions[56]. These contractions are usually silent in the mid-trimester and the clinical conditions may be indistinguishable from that of an incompetent cervix.[57]

The presence of abnormal vaginal flora such as bacterial vaginosis or intermediate flora is associated with an increases risk of late miscarriages and early preterm delivery and in women with a short cervix[58,59]. Other infections which can implicate in preterm births includes chlamydia, Group B streptococcus, mycoplasma and gonorrhea.

Sources of intrauterine infection:

Bacteria can gain access to the intrauterine tissues through

. 1) Trans placental transfer of maternal systemic infection.

. 2) Retrograde flow of infection from the peritoneal cavity via the fallopian tubes.

. 3) Ascending infection from the vagina and cervix is considered the most common.

. Intra uterine infection is categorized into 4 stages of microbial invasion that includes

1) Bacterial vaginosis (stage 1)

2) Decidual infection (stage 2)

3) Amniotic infection (stage 3)

4) Fetal systemic infection(stage 4)

Progression of these stages is throughout to increase the effects on preterm birth as well as neonatal morbidity.[60]

MECHANISM CAUSING INFECTION INDUCED PRETERM LABOR

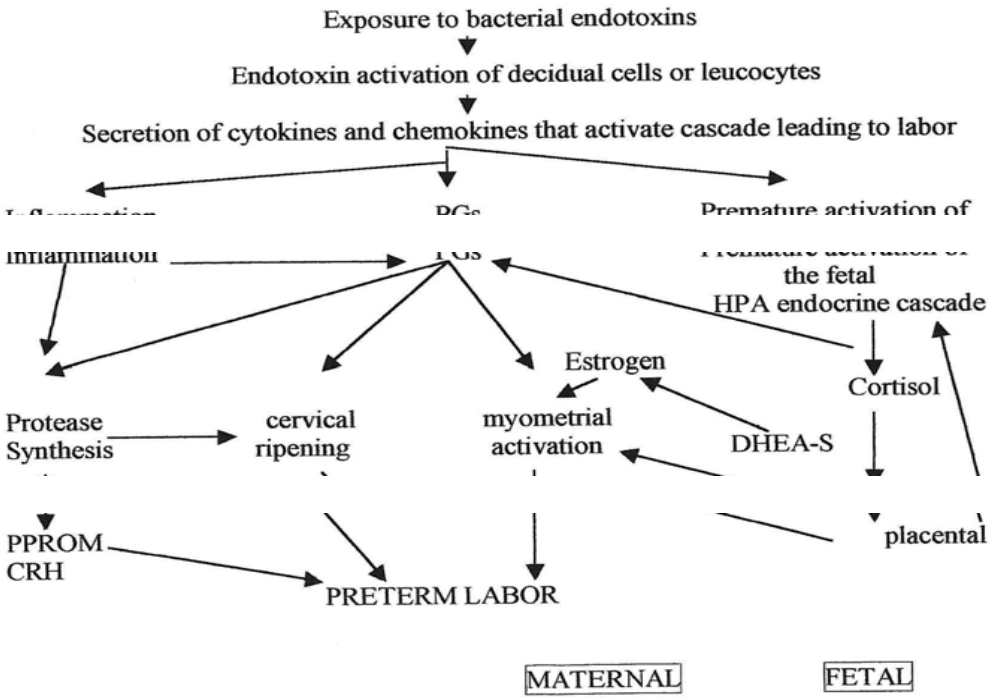


FIGURE NO. 3. MECHANISM OF INFECTION INDUCED PRETERM LABOR.

TESTS TO DETECT THE INFECTION:

No tests are available to diagnose the earlier stage of infection, but test to detect the advanced stages of infection are available.

1) Amniotic fluid gram stain has got 100% positive predictive value.[61]
2) Limulus gametocyte lysate assay: This test is used for the detection of gram-negative endotoxin and also certain gram positive intra amniotic infection. The sensitivity of this test when combined with gram stain is 95%.[62]
3) Gas liquid chromatography: This test identifies fatty acid chains elaborated by icrobial metabolism. The sensitivity is high. The test is very expensive.[63]
4) Bacterial cultures: This provides definite evidence of the presence of amniotic fluid infection.[64]
5) Presence of leucocytes in the amniotic fluid is a relatively insensitive test. Leucocytosis in the absence of bacteria may suggests the possibility of Mycoplasma infection.
6) Acridine orange stain allows visualization of Mycoplasma in the amniotic fluid with leucocytosis and without bacteria seen in the gram stain.
7) Histologic examination of the placenta which can be done post partum.

Extra Uterine Infection:

5 to 10% of patients in preterm labor have an infection outside the uterus, most common is culture proven UTI, other like pyelonephritis, Malaria, pneumonia, tuberculosis and periodontal infection.

8) Preterm prelabour rupture of membranes(pPROM):pPROM is defined as the spontaneous rupture of fetal membranes prior to the onset of labour and before 37 weeks of gestation. pPROM complicates about 2% of pregnancies and occurs

in 14,000 pregnancies in UK and 150,000 pregnancies in the US, which accounts for 30% of preterm deliveries [65].

It is also associated with significant materials risks including chorioamnionitis with serious systemic infection and neonatal morbidity and mortality including prematurity, sepsis and pulmonary hypoplasia[66,67].

Studies have shown that women with pPROM have positive amniotic fluid culture in a third of pregnancies following amniocentesis[68,69]. Women with intrauterine infection have a shorter latency period than non-infected women and babies usually born with sepsis leading to four-fold increase in mortality rate compared with babies without sepsis.[70]

9) Connective tissue disorders:

Certain connective tissue disorders such as Ehlers-Danlos Marfans syndrome have been implicated in the aetiology of preterm birth [71]. It is characterized by disorganization of collagen fibrils in the cervix causing cervical incompetence and preterm labour [72].

10) Placental abnormalities:

Battledore placenta, circumvallate placenta and Marginal insertion of the Umbilical cord, placenta previa, abruptio placenta and placental vascular insufficiency all lead to preterm labor.

11) Fetal pathology:

Neural tube defects and inborn errors of metabolism like; Hyperalaninemia and potters

syndrome are found to be associated with preterm labor.

12) Assisted reproductive technique:

Preterm labor delivery occurs more commonly in pregnancies conceived after ovulation inducers and assisted reproductive technologies such as IVF, GIFT.ART pregnancies contributed 22% of all high order multiple gestation and 40% following super ovulation.

IMPLICATIONS OF PRETERM BIRTH:

Preterm birth is the leading cause of neonatal morbidity and mortality worldwide and accounting for 75% of neonatal deaths and 50% of long term morbidity, including respiratory diseases and neurodevelopment impairement [73].

The risk of morbidity and mortality are inversely related to the gestational age at birth. The EPICure study in the United Kingdom and Ireland [74] assessed survival trends and health outcomes in infants who are borned in less than or equals to 26 completed weeks (20 weeks to 25 weeks and 6 days) over a period of 10 months in 1995. This study showed increased survival and reduced rate of severe disability with each additional week of intrauterine gestation.

They have also reported that 50% of survivors at 23-25 weeks gestation were impared, half with severe disability[74].

In another study the Epipage study also recruited babies born in nine French regions during 1997 and Trent health region study also produced similar results on rates of survival and Discharge[75,76].

The EPICure two study has been collected data on all babies born in England in 2006 between 22 and 26 weeks 6 days gestation[77]. There was an improved survival of these babies by 13 % (40-53%) and was more at 24 weeks and 25 weeks. They also found that the care which has provided to these mothers have improved but the number of babies discharge from hospital with disabilities such as abnormal brain scans, lung, bowel and eye problems are very similar to the findings of EPICure in 1995.

Studies show that preterm birth carries significant social and economic burden which is estimated to cost the public sector of 2.9 billion euro a year [54]. The total cost of preterm birth estimated by Khan and coworkers was 15,688 euro for upto 34 weeks and 12,104 euro for upto 37 weeks [78].

Severe morbidity such as intraventricular hemorrhage (IVH), Respiratory Distress syndrome (RDS), bronchopulmonary dysplasia (BPD), Necrotising Enterocolitis (NEC) is common before 28 weeks and extends into 30-32 weeks Range.

Tracy A. MANUCK , et al, studied a secondary analysis of an obstetric cohort of 115,502 women and their neonates who were born in 25 hospitals nationwide, 2008–2011[79]. All live born non-anomalous singleton preterm (23.0–36.9 weeks of gestation) neonates were included in this analysis. The frequency of neonatal death, major neonatal morbidity (intraventricular hemorrhage grade III/IV, seizures, hypoxic-ischemic encephalopathy, necrotizing enterocolitis stageII/III, bronchopulmonary dysplasia, persistent pulmonary hypertension), and minor neonatal morbidity (hypotension requiring treatment, intraventricular hemorrhage grade 1/2, necrotizing enterocolitis stage 1, respiratory distress syndrome, hyperbilirubinemia requiring treatment) were calculated by deliver

gestational age; each neonate was classified once by the worst outcome they met criteria for. Major morbidity includes persistent pulmonary hypertension, intraventricular hemorrhage grade 3/4, seizures, hypoxic-ischemic encephalopathy, necrotizing enterocolitis stage II/III, bronchopulmonary dysplasia minor morbidity includes intraventricular hemorrhage grade 1/2, necrotizing enterocolitis stage 1, RDS, hyperbilirubinemia requiring treatment, hypotension requiring treatment.

Table.1. Frequency of death and major, intermediate and minor morbidity. Data are n(%)[79].

Delivery gestational age	death	Major morbidity	Minor morbidity	Survival without any of the above morbidities
All (n=83334)	119(1.4)	657(7.9)	3136(37.6)	4422(53.1)
23(n=43)	19(42.2)	19(42.2)	4(9.3)	1(2.3)
24(n=114)	36(31.6)	60(52.6)	18(15.8)	0(0.0)
25(n=124)	15(12.1)	68(54.8)	39(31.5)	2(1.6)
26(n=169)	19(11.2)	88(52.1)	59(34.9)	3(1.8)
27(n=159)	13(8.2)	64(40.3)	77()48.4	5(3.1)
28(n=196)	4(2.0)	43(21.9)	144(733.5)	5(2.6)
29(n=213)	4(1.9)	48(22.5)	147(69.0)	14(6.6)
30(n=262)	4(1.5)	36(13.7)	206(78.6)	16(6.1)
31(n=312)	3(1.0)	22(7.1)	255(81.7)	32(10.3)
32(n=451)	1(0.2)	39(8.7)	344(76.3)	67(14.9)
33(n=639)	1(0.2)	27(4.2)	406(63.5)	205(32.1)
34(n=1058)	0	46(4.4)	540(51.0)	472(44.6)
35(n=1477)	0	42(2.8)	402(27.2)	1033(69.9)
36(n=3117)	0	55(1.8)	495(15.9)	2567(82.4)
P for trend	<0.001	<0.001	<0.001	

Threshold of Viability

Births *before* 26 weeks are generally considered the current threshold of viability. The preterm infants pose various complex medical, social, and ethical considerations. Infants now considered to be at the threshold of viability are those born at 22, 23, 24, or 25 weeks (American College of Obstetricians and Gynecologists, 2012) [80].

The infants have been described as fragile and vulnerable because of their immature organ systems. Moreover, they are at high risk for brain injury from hypoxic-ischemic injury and sepsis. In this setting, hypoxia and sepsis start a cascade of events that lead to brain hemorrhage, white-matter injury that causes periventricular leukomalacia, and poor subsequent brain growth eventuating in neurodevelopmental impairment.

Because active brain development normally occurs throughout the second and third trimesters, those infants born at 22 to 25 weeks are believed especially vulnerable to brain injury [81].

The most recent report from the United States concerning survival and morbidity rates for births at 22 to 26 weeks is from the National Institute of Child Health and Human Development (NICHD) Neonatal Network [82].

This dataset includes 5736 live births delivered between 2003 and 2007 at 20 medical centers across the United States[82]. Rates of survival and survival without morbidity in the neonatal period are shown in the table below.

outcome	22 weeks	23 weeks	24 weeks	25 weeks	26 weeks
Live infants	**421**	**871**	**1370**	**1498**	**1576**
Survived to discharge(%)	**6**	**26**	**55**	**72**	**84**
Percentage with no chronic morbidity	**0**	**8**	**9**	**20**	**34**

TABLE NO. 2. SURVIVAL AND DISABILITY RATES FOR 5736 LIVE BIRTHS BORN BETWEEN 22 WEEKS AND 26 WEEKS GEATATION AT 20 MEDICAL CENTRES IN THE UNTED STATES DURING 2003 TO 2007.

PREDICTION OF PRETERMBIRTH:

The three main lines of research in the prediction of the preterm labor.

1) Risk scoring system
2) Biochemical methods
3) Biophysical methods

RISK SCORING SYSTEM:

In 1984 Papiernik organized several factors associated with preterm labour into a high risk scoring system and this was slightly modified by **Gonik and Creasy in** 1986.

Point	**Socio-economic Factors**	**Previous medical and Obstetric History**	**Daily habits**	**Aspects of Current Pregnancy**
1.	Two children at home low socio- economic status	Abortion x 1 Less than 1 year Since last birth	Works outside	Unusual fatigue
2.	Maternal age<20 Years or>40years Single parent	Abortion x2	Smokes>10 Cigarettes/day More than 3 flights of stairs without elevator	Gain of <5k by 32 weeks
3.	Very low Socioeconomic status Height < 150 cms Weight < 45 kg	Abortion x 3	Heavy or stressful Work that is long and tiring Long daily commuting extensive travelling	Breech at 32 weeks Weight loss Head engaged at 32
4.	Maternal age<18 Years			Bleeding after 12 weeks Short cervix Opened internal os Uterine irritability

5.		Uterine anomaly Second-trimester Abortion DES exposure Cone biopsy		Placenta previa Hydramnios
6.		Preterm delivery Repeated second Trimester abortions		Twins Abdominal surgical Procedure

The patient with score of 10 or more in the papiernik scoring system is classified as being at high risk for preterm labor.

It gives a sensitivity of only 40% and a false positive rate of almost 80% reason may be multifactorial nature of disease and these mostly rely on past obstetric history and are inappropriate in nulliparous women.[83]

BIOCHEMICAL MARKERS:

Cervical length screening and various biochemical markers like cervico vaginal cytokines (IL 1, TNF) and proteases, fibronectin, serum CRH and Estriol have been primarily investigated as potential predictive or diagnostic markers of preterm labor. They are

1) Fetal fibronectin (FFN)
2) Salivary Estriol

1) Fetal fibronectin:

It is a glycoprotein that is secreted by fetal membrane and help attach the chorion to the decidua. Fetal fibronection thus acts like a 'glue' binding the choriodecidual membranes. Its presence in the cervicovaginal secretion, placenta and amniotic fluid is normal up to the 20^{th} week.

It is rarely present in vaginal secretions between 23 weeks to 34 weeks of gestation. The test is performed at bedside and proper technique is required for the correct results.

Digital examination of the cervix should not be performed prior to this test and no lubricating gel should be used. The test is considered to be positive when fetal fibronectin is greater than 50ng/ml[84].

Studies have evaluated the role of fetal fibronectin test both in asymptomatic high- risk women and women in preterm labor. A positive test is associated with an increased likelihood of birth before 34 weeks gestation with14 days of the test with the positive predictive value of 16% [85].

In the negative test the risk of preterm delivery is < 1% within 14 days of the test.

There are two mechanisms may explain the presence of FFN in vaginal secretions in cases of spontaneous preterm labor. [86]

1. Separation of the chorion from the deciduous membrane of the lower uterine segment may allow its release.
2. FFN may be secreted in the cervical canal in response to chorionic inflammation.

50 ng/ml is used as a cut off value for a positive determination. Disadvantage is that the results are not availavle for serveral hours. Positive fetal fibronectin yields 90% sensitivity and 72% specificity. Negative fetal fibronectin has 94% negative predictive. Factors which increase the false positive are PROM, vaginal bleeding and where as vaginal lubricants and disinfectants increases the false negatives. There is a significant data to support the use of fetal fibronectin in evaluating preterm labor.

2) Estriol

Estriol begins to appear during the 9^{th} week of pregnancy and its plasma concentration to increase through out the course. It have been shown to directly affect myometrial contractility, modulate the excitability of myometrial cells and increase uterine sensitivity to oxytocin.

There is surge in estradiol level within 2-4 weeks prior to the onset of labour[87]. The estriol concentration in saliva very precisely reflects the free estriol concentration in plasma.

Cut off value 2 – 3ng/ml for predicting those women at risk of preterm labor and delivery with a sensitivity of 71% and specificity 77%, positive predictive value of 23%.

Administration of corticosteroids and dietary factors, which increases the false negatives.

This test can be used in asymptomatic population because it is a simple, reliable and stable test.[88]

	SINGLE POSITIVE TEST	**SECOND POSITIVE TEST**
with in a week	23%	70%
with in 2weeks	54%	90%
with in 3weeks	85%	100

Others Biochemical markers:

Several biochemical markers have been evaluated for association with preterm labour like activin, inihibin and relaxin[89], but they all require further evaluation.

Elevated levels of b hCG and AFP have been noted, either individually or in combination to be associated with a increased risk of preterm delivery and also adverse pregnancy outcomes.[90]

1) **OTHER BIOCHEMICAL MARKERS: Mediators of inflammatory process** have not shown any promise as screening tests.

Amniotic fluid cytokines predicted preterm birth; IL 8 shows a sensitivity of 91% and a specificity of 87%. The high level of IL 18 in the cord blood of preterm infants is associated with neonatal development of periventricular leukomalacia and cerebral palsy.[91]

Ideally screening and treating lower genital tract and sexually transmitted infection is recommended prior to and in the first trimester of pregnancy.

Bacterial vaginosis is caused by anaerobic bacterial like Gardeneralla vaginalis, Mobiluncus species and Mycoplasma hominis. It is associated with spontaneous abortion, preterm labor and premature rupture of membrane, chrioamnionitis and amniotic fluid infection [92].

Bacterial vaginosis is the only infectious marker that are being used as primary predictor in an unselected population. The higher risks of bacterial vaginosis are reported when

screening has been performed seven fold before 16wks and fourfold before 20wks of gestation. The use of inflammatory markers in current practice is limited because of lack of simplicity, medicare reproducibility and high cost, all issue as fundamental in daily practice as their capacity to identify preterm birth due to infection.

Some studies have found the association between Trichomonas infection and preterm birth [93]. But there are certain others studies which could not provide such association and hence currently the screening and treatment for chlamydia or trichomonas to prevent preterm birth in women is not recommended[94].

Asymptomatic bacteriuria has been linked to preterm birth. Screening and treatment of asymptomatic bacteriuria in pregnancy have become standard practice in obstretrics care. Group B streptococcal (GBS) has been linked with preterm births, therefore it is recommended to the women at risk of preterm delivery to screen for GBS antenatally which allows intravenous antibiotics at the time of labor. Screening can be done by combined lower vaginal and rectal swab.

2) Plasma CRH:

Plasma CRH is a peptide produced by the syncitiotrophoblast and the fetal membranes is implicated in the initiation of labor. Its highest production of CRH levels is seen during the 3rd trimester.

PGE2 and F2 production from placenta and fetal membranes are regulated by CRH, and it potentiates the action of oxytocin. Sensitivity of the test is 24-73% Women at high risk for preterm labour have higher CRH levels when compared with women at low risk[95]. The clinical use of CRH is doubtful in those cases which are associated with infections

and in cases of recurrent preterm labor.

3) HCG:

When there is abnormal placentation or disruption in the integrity of the choriodecidual interface shows the increased level of HCG in the maternal serum.

If > 32miu/ml to predict the delivery within 7 days it has positive predictive of 89% and negative predictive value of 95%.[96]

4) Serum AFP has been suggested but sensitivity is poor.

5) Plasma granulocyte stimulating factors levels with odds ratio between 4-10 for delivery within a 4 weeks period after the test.

6) Cervical lactoferrin and sialidase values are related to preterm labor but sensitivities are low.

7) Role Of Thrombin: The presence of thrombin anithrombin levels of 8ng/ml had a positive predictive value of 80% for delivery within 3wks of positive test.[97]

8) Recent markers include maternal serum collagenase, serum ferritin, and placental alkaline phosphatase. However, the routine use of these markers cannot be considered until convincing studies are available.

BIOPHYSICAL METHODS:

1) Uterine activity monitoring

2) Cervical assessment.

Uterine activity monitoring for the early diagnosis of preterm labor has been explain by four study methodology.

1) Maternal self-detection of uterine activity is significantly less likely to identify the crescendo in uterine activity.
2) Perinatal nurses support the educational compartment by systematically questioning the patients regarding signs and symptoms of preterm labor and their subjective uterine contraction frequency based on self-palpation and to assess the patient's compliance with physician directed therapies or restrictions.
3) HUAM: This is a devise which was first used by katz and colleagues in 1986 at Sanfrancisco in a woman who are at high risk for preterm labor. When there is Persistent uterine contractions at a frequency of >3/hr between 26-28 weeks, >4/hr between 28 30wks,>5/hr between 30 -32 weeks predicted 80% of preterm births.
4) The simultaneous assessment of an individual patient's signs and symptoms during the daily perinatal nursing telephone call along with objective uterine activity monitoring complemented by 24hrs/day, 7days/week availability of obstetrician are believed to be critical factors in the early diagnosis of preterm labor.[98]

5) UTERINE ELECTROMYOGRAPHY (EMG): The amounts to the acquistion of uterine electrical signals can be taken noninvasively from the abdominal surface could benefit obstetriticians when utilized as an everyday tool in the antenatal and labor wards to monitor uterine electrical recording in normal pregnancies and to diagnose or even predict abnormal conditions like preterm labor, in sufficient labor progress and dystocia.[99]

CEVICAL ASSESSMENT:

The precocious cervical ripening and dilatation of the internal os of the cervix increase the risk of preterm delivery.

Papiernik in France has observed early cervical ripening was noted in 30% of pregnancies.

There was dilatation of the internal os was associated with fourfold increased risk of preterm delivery. The positive value for abnormal cervical findings are disappointingly low at 25 – 30% for high risk group and 4% for the low risk group and cervical dilatation of more than 2 cm predicts preterm delivery with a sensitivity of 60%.[100]

Cervical length is a good predictor of PTB particularly in high risk women like those who had prior PTB[101]. It has been observed a positive predictive value of 70% and a sensitivity of 60-80% with a transcervical ultrasound cervical length (TVS CL) of less than 25mm between 14 and 18 weeks gestation[47].

There was only 4% risk of delivering preterm in high-risk women with normal cervical measurement between 14 and 18 weeks[65]. It has been found that TVS CL is a positive predictive of PTB in other high risk women including women with prior cone biopsy, prior multiple dilatation and evacuation and mullerian anomalies [102].

Women with uterine anomaly and short cervix on TVS have 13 fold increase in spontaneous PTB and those who have unicornuate uterus have the highest rate of PTB.

Skentou and coworkers found a TVS CL less than 2cm to have a 100% predictive value for PTB before 28 weeks gestation[103]. Similarly other studies have also found cervical

length of less than 2.5cm at 24 weeks gestation to be a strong predictive factor for preterm labour[49].

Guzman and co-workers have found TVS CL to be a positive predictive factor of PTB in triplet pregnancies[49].Women with multiple gestations have been shown to be more likely to have short cervix at 24 weeks which may be due to rapidly expanding uterus exerting extra pressure on the cervix and not particularly due to cervical incompetent.

The cervical length measured at mean gestational age 28-31wks, optimal cut off value varies from 1.8-3 cm. Cut off value of 30 mm has sufficient sensitivity of 70-100%, if>30mm, negative predictive value of 100% in between 34-37wks.

Only cervical length (CL) has significant predictive accuracy but not the funneling (>5mm) because measurement incorporating funnel length to be less responsible and so less clinically useful.

Translabial ultrasound has recently been advocated for evaluation of cervix with the advantage of avoiding vaginal instrumentation compared to transvaginal ultrasound.

FLUORESCENCE SPECTROSCOPY:

It is a widely used research tool in biosciences to examine the collagen content of a variety of tissues including some cancers, now they are using this to evaluate the cervix.

The Cervical light induced fluorescence (LIF) is obtained noninvasively using an instrument **collascope.** Cervical LIF values decrease significantly as gestational age increases and are predictive of delivery within 24 hrs.[104]

PREDICTORS OF RISK OF PRETERM LABOUR:[105]

IN NULLIPAROUS WOMEN

	Delivery<32 wks	**Delivery <35wks**	**Delivery <37wks**
Both tests negative	**0.6%**	1.7%	6.0%
CL <25mm	**3.7%**	**9.2%**	**18.4%**
FFN positive	**3.9%**	**5.8%**	**11.5%**
Both tests positive	**35.3%**	**58.8%**	**64.7%**

IN MULITIPAROUS WOMEN ALONG WITH OR WITHOUT SPONTANEOUS PRETERM BIRTH (SPB).[105]

	Delivery<32wks	**Delivery<35wks**	**Delivery<37wks**
All narjers are negative	**0.5%**	**1.5%**	**7.3%**
Previous SPB alone	**1.8%**	**8.6%**	**17.6%**
Previous SPB&CL <25mm	**8.3%**	**29.2%**	**35.4%**
Previous SPB&FFN Positive	**24.0%**	**40.0%**	**48.0%**
All markers are positive	**50.0%**	**60.0%**	**60.0%**

THE DAIGNOSIS OF PRETERM LABOUR

1) Uterine Contractions

The main symptom of preterm labor is uterine contractions. They should occur regularly, four or more in 20 minutes or eight or more in 1 hour, and each should last more than 40 seconds.

The perception of the frequency, intensity, and duration of contractions by different health care providers is frequently inaccurate and the best objective way to determine the frequency and duration of the contractions is by external monitoring with a tocodynamometer.

2) Digital Pelvic Examination

This examination the obstetrician should assess the position, length, consistency, and dilatation of the cervix, as well as the development of the lower uterine segment. The two more important variables to assess clinically are the length (effacement) and the dilatation of the cervix.

An important part of the digital examination of the women in preterm labor is the assessment of the lower uterine segment. All pregnant women regardless of their parity or gestational age stretch or develop their lower uterine segment before parturition. When the lower uterine segment is not developed, it is possible to introduce easily the fingers into the vaginal fornices. In contrast, when the lower uterine segment is developed, the examiner finds that the upper third of the vagina is filled with the thinned lower uterine segment.

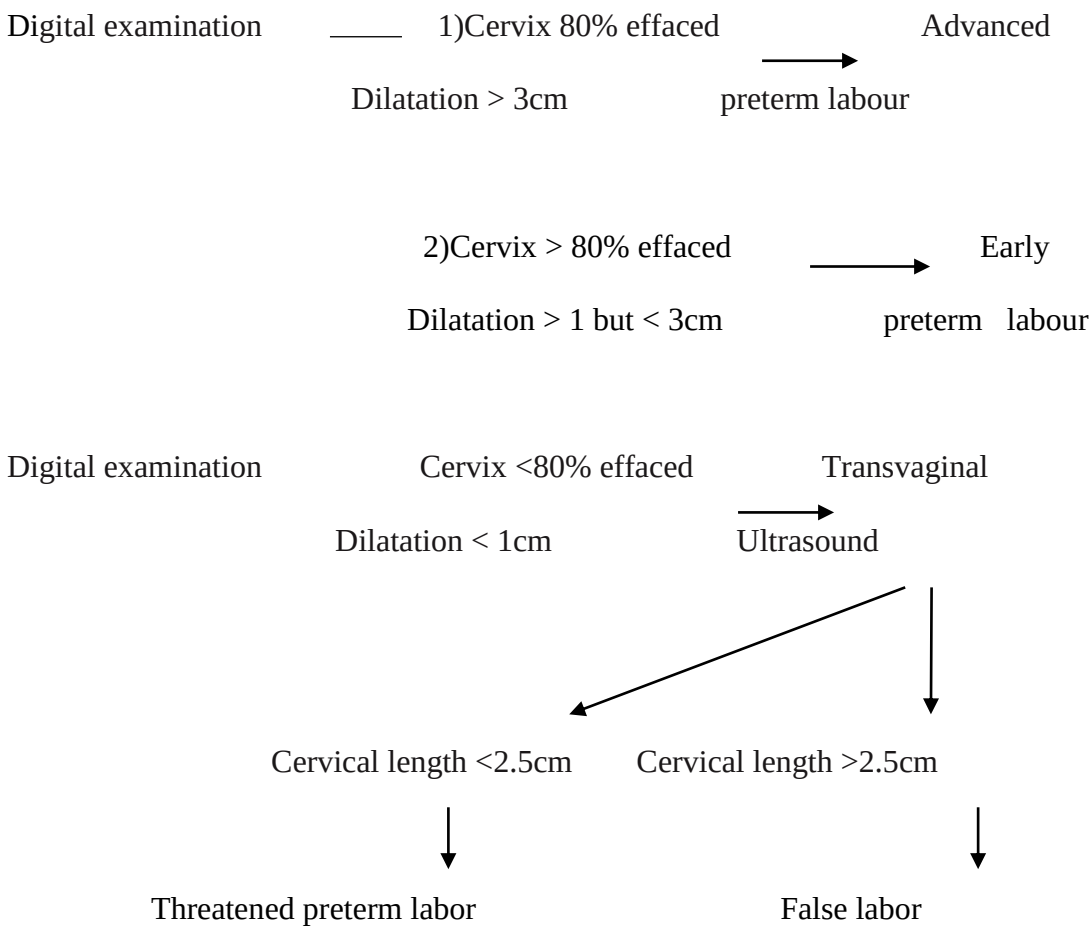


FIGURE NO. 4 . DIAGNOSIS OF PRETERM LABOR

B) MAGNESIUM

Magnesium is the fourth most abundant cation in the body and the second most prevalent intracellular cation. The total body magnesium content is approximately 25 gms (1.03 mol), of which about 55% resides in the skeletal magnesium is exchangeable and is thought to serve as a reservoir for maintaining extracellular magnesium concentration. About 45% of magnesium is intracellular.

Drug was first used by Steer and Petrie as a tocolytic and later refined by Elliot in early 1970. It ranks as the tocolytic of choice by most of obstetricians in United States.

BIOCHEMISTRY AND PHYSIOLOGY:

The concentration of magnesium in cells is approximately 1 to 3 mmol/L (2.4 to 7.3 mg/dl). In general higher the metabolic activity of the cell, higher is its magnesium content. Within the cells most of the magnesium is bound to proteins and negatively charged molecules; 80% of cytosolic magnesium is bound to ATP and Mg ATP is the substrate for numerous enzymes.

The nucleus, mitochondria and endoplasmic reticulum content significant amount of magnesium. Approximately 0.5% to 5.0% of the total cellular membrane is regulated by a specific magnesium transport system. Extracellular magnesium accounts for about 1% of the total body content.

About 55% of magnesium is free, 30% is associated with proteins (primarily albumin), and 15% is complexed with phosphate, citrate and other anions.

Magnesium is the cofactor for more than 300 enzymes in the body. It is required for enzymes formation (for example, MgATP). In addition, magnesium is an allosteric

activator of many enzymes systems.

Examples of enzymes that require magnesium for action includes ademylate cyclase, Na K adenosine triphosphate (ATPase), Ca ATPase,phosphofructokinase , and creatine kinase.

The guanine nucleotide regulatory proteins Gs and Gi require magnesium for activity. Magnesium is important in oxidative phosphorylation, glycolysis, cell replication, nucleotide metabolism and protein biosynthesis.

Serum levels between 5-8 ng/dl of MgSO4 are needed to attain myometrial inhibition. Magnesium is excreted by kidneys at a very high rate (90%) is cleared with in 24hrs. [106]

Reducing the serum magnesium concentration decreases the threshold of axonal stimulation and increases the release of neurotransmitter at the neuromuscular junction by competively inhibiting the entry of calcium in the presynaptic nerve terminal. Reducing the serum magnesium concentration results in increased neuromuscular excitability.

Assessment of magnesium levels:

The most common test done is the estimation of serum magnesium concentration. The other available test are estimation of ultrafiltrable Mg, Mg content of RBC's, mononuclear cells, metabolic tests like 24 hours urinary excretion of magnesium, Mg loading test, estimation of intracellular free magnesium ion concentration, etc. Serum magnesium can be measured by a variety of techniques. Serum magnesium is preferable to plasma as the anticoagulant in the vacuette could be contaminated with magnesium or

can directly interfere with assay. For instance, citrate binds not only calcium but also magnesium and affects fluorometric and colorimetric procedures.

Haemolysis, bilirubin, lipaemia, high phosphate concentration and delay in Separating serum can affect the measurement.

In adult serum magnesium concentration is not affected by sex or age except in the very elderly where it may be slightly higher. Serum magnesium concentration is lower during the third trimester of pregnancy.

The total serum magnesium concentration is not the best method to evaluate magnesium status as changes in serum protein concentrations may affect the total concentration without necessarily affecting the ionized fraction or total body magnesium status. The correlation between total magnesium and total body magnesium status is poor.

Serum magnesium is measured by different methods; viz;

1. Photometric methods
2. Atomic absorption spectrometry
3. Flame emission
4. Fluorometric methods

CAUSES OF HYPOMAGNESEMIA:

1) Redistribution of magnesium
    a) Insulin therapy
    b) Hungry bone syndrome

c) Correction of acidosis

d) Catecholamine excess

e) Massive blood transfusion

2) Gastrointestinal causes

a) Reduced intake

Mg free intravenous fluids

Dietary deficiency

Low oxalate diet

Cellulose phosphate

b) Reduced absorption

Malabsorption syndrome

Chronic diarrhoea

Intestinal resection

Primary infantile hypomagnesaemia

3) Renal loss

Reduced sodium reabsorption

Saline infusion

Diuretics

4) Renal disease

Post obstructive nephropathy

Post renal transplantation

Dialysis

Diuretic phase of acute renal failure

Inherited disorders

Bartter's syndrome

Gitelman's syndrome

5) Endocrine causes

   a) Hypercalcaemia

      Primary

      Malignant

   b) Hyperthyroidism

   c) Hyperaldosteronism

6) Diabetes mellitus

7) Alcocholism

8) Drugs

   Diuretics

   Cytotoxic drugs; cisplatin, carboplatin, gallium nitrate

   Antimicrobial agents

   Aminoglycosides; gentamycin, tobramycin, amikacin

   Antituberculous drugs; viomycin, capreomycin

   Immunosuppressants; cyclosporine, ritrodrine

   Beta adrenergic agonist: theophylline, salbutamol, reniterol

   Others drugs; amphotericin B, pentamidine, Foscarne

   pamidronate, anascrine.

HYPOMAGNESEMIA IN PREGNANCY

Pregnancy is a state if marked hypomagnesemia. Kruzel RB and co-workers have shown that the serum magnesium level has no gestational dependence (mean 1.79+/- 0.44mg/dl) until 33 weeks of gestation, at which point it continuously declines[107].

In another study which was conducted in India with 150 patients by Agarwal U et al showed that the mean serum magnesium level in non-pregnant group, 1st trimester, 2nd trimester, 3rd trimester were found to be 2.31+/- 0.39 mg/dl, 2.20 +/- 0.26 mg/dl, 1.49+/- 0.63 mg/dl and 1.07+/- 0.39 mg/dl respectively[108].

Therefore, the study have observed that magnesium level is lower in pregnancy and in pregnancy there was a significant fall in serum magnesium level in third trimester.

Kamal S et al have shown that the mean magnesium level is 2.2mg% +/- 0.33 S.D. in non pregnant women and 1.9mg % +/- 0.3 S.D in normal pregnant women[109].

Other study have concluded that pregnancy is a state of extracellular magnesium depletion and diabetes in pregnancy exaggerates this deficiency[110].

Hypomagnesemia in pregnancy can be due to hemodilution associated with pregnancy. The increase in renal clearance during pregnancy may contribute to reduction in serum magnesium. The other factors leading to hypomagnesemia in pregnancy may be poor dietary intake and consumption of minerals by growing fetal skeletal system[111].

Studies have found that another important cause for markedly increased magnesium in

pregnancy loss is due to routine calcium supplementation at 1.5g/day[112].

Cunze T et al conclude that magnesium level in the plasma correlates with magnesium in the myometrium and hence hypomagnesemia during pregnancy decrease the magnesium in the myometrium[113].

HYPOMAGNESEMIA AND PRETERM LABOUR

The pathophysiology of the labor have described a central role of calcium in initiation of uterine contraction. Phillippe M have conducted a study to test the hypothesis that magnesium inhibits extracellular calcium entry[114]. He performed in vitro studies using uterotonic agents like oxytocin, which produced cystolic calcium oscillations and simultaneous phasic contractions, both of which inhibited by magnesium. The study concluded that magnesium inhibited extracellular calcium entry, intracellular release, cystolic calcium oscillaions and phasic contractions of the myometrial smooth muscle.

Both magnesium and calcium acts as cofactors in the synthetic activity of variety of enzymes and in the secretory process. They bind to the fatal membrane and diffuse through the membrane which play a role in the synthesis or action of prostaglandins and generation of NO which are believed to regulate the myometrial activity. Nitric oxide is generated by nitric oxide synthase (NOS) from argenine. It has a relaxant effect on the myometrium and its relaxation is specially blocked by inhibitors of NOS[115].

The presence of NOS has been demonstrated in myometrium, placenta and fetal membrane[84].

The activity of the NOS is dependent on calcium[116]and this activity is inhibited by reduction in the concentration of magnesium [117].

Adam et al showed that the diffusion of calcium and Mg across the fetal membranes was much lower in preterm than compared with the term[118]. The reduction in the availability of calcium in the myometrium and the placenta would result in down regulation of nitric oxide synthase activity and thereby reduction in the NO production. This mechanism along with an effect on intracellular calcium transport resulting from a reduced availability of magnesium would lead to increased myometrial activity in preterm labor.

Magnesium has a membrane stabilizing action which contributes in stabilization of highly ordered organization of macro-cellular structures DNA, RNA and ribosome. Magnesium also has a local anesthetic activity and depresses myoneural transmission which acts by reducing quantal release of acetylcholine and by antagonizing its depolarizing effect at the motor end plate and by reducing the excitability of muscle cell membrane[109].

Shaheena Kamel et al[109] and Deo P et al[119] have found out that the serum magnesium level was significantly lower in preterm labour cases (1.47mg% +/- 0.22 SD) as compared to the normal pregnant women (1.9 mg% +/- 0.3 SD).

They have also demonstrated that lower the socioeconomic status, lower is the magnesium level. But they could not relate any significant findings with the age and parity on magnesium levels. Hypomagnesemia seems to be associated with vegetarian diet also.

In another study by Agrawal U et al there was hypomagnesemia in habitual abortion and premature labour were significantly lower in third trimester of pregnancy[120]. They have concluded that serum magnesium level should be within the range of 1.5 to 3.5 mg%.

Kurzel RB found that women with preterm labor have significantly depressed magnesium level which was independent to the etiology of preterm labour. He has defines hypomagnenesemia of less than 1.4 mg% as a marker for preterm labour[107].

Smorlarczyk. R, et al, in their study have compared the calcium, phosphorous and magnesium of women with threatened preterm delivery between 29 weeks to 36 weeks of gestation with those of uncomplicated pregnancy of the same duration. There was hypomagnesemia in patients with threatened preterm delivery and also low levels of calcium and phosphorous. They have explained that it might be due to premature uterine contractility, but did not predict premature labor after 36 weeks of gestation [120].

Caroline A Crowthe, et al, (2014) have searched the Cochrane Pregnancy and Childbirth Group's Trials Register (last searched 31 January 2014)[121]. They conducted a Randomised controlled trials of magnesium sulphate as the only tocolytic, administered by any route, compared with either placebo, no treatment or alternative tocolytic therapy (not magnesium sulphate) to women considered to be in preterm labour. Magnesium sulphate is ineffective at delaying birth or preventing preterm birth, has no apparent advantages for a range of neonatal and maternal outcomes as a tocolytic agent and its use for this indication may be associated with an increased risk of total fetal, neonatal or infant mortality.

Helen C McNamara, et al (2015) searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2015) and reference lists of retrieved studies [122]. Randomised trials was done, comparing different magnesium sulphate treatment regimens when used as single agent tocolytic therapy during pregnancy in women in

preterm labour. There is some evidence from a single study suggesting a reduction in the length of stay in the neonatal intensive care unit and a reduced risk of respiratory distress syndrome where a high-dose regimen of magnesium sulphate has been used compared with a low-dose regimen. However, given that evidence has been drawn from a single study (with a small sample size), these data should be interpreted with caution. Magnesium sulphate has been shown to be of benefit in a wide range of obstetric settings, although it has not been recommended for tocolysis. In clinical settings where health benefits are established, further trials are needed to address the lack of evidence regarding the optimal dose (loading dose and maintenance dose), duration of therapy, timing of therapy and role for repeat dosing in terms of efficacy and safety for mothers and their children. Ongoing examination of different regimens with respect to important health outcomes is required.

Shatha A et al, (2016), one hundred patients who admitted into the labour room of the hospital due to preterm labour (28 to 36+6 weeks of gestation)[123] whose etiology could not be explained by etiological factors were enrolled in this prospective case-control study during the period from June 2013 to June 2014. And another 80 women of comparable gestational age who were referred to the consultation clinic of their hospital for achieving prenatal care or for causes other than preterm labour, provided only those whose birth occurred after 37th week considered as a control group. Serum magnesium level was measured in both groups. In their study they have concluded that serum magnesium level can be used as a predicting tool for idiopathic preterm labour.

Jenabi et al, (2017) conducted an observational study was conducted at the Social Security Hospital in Hamadan City, the west of Iran, from October 2014 to January

2015[124]. The case group included 32 preterm labour women (28 to less than 37 weeks pregnant women) and the control group included 32 term pregnant women. The maternal serum magnesium level, the duration of the first and second stage of labor were measured in both the groups.

They concluded that low level of maternal serum magnesium is associated with poor pregnancy outcomes, including preterm labor and low birth weight.

DOSAGE AND ADMINISTRATION:

HIGH DOSE: loading dose of 6gms intravenously over 15-30 mins followed by IV infusion at the rate of 2-6 gms/hr for maintenance with success rate of 88.7%.

LOW DOSE: loading dose of 4gms intravenously over 15-30 mins followed by IV infusion at the rate of 2gms/hr for maintenance therapy with success rate of 70.7%.

Drug is then titrated to levels of 5-8 mg/dl or until adequate tocolysis is achieved. Magnesium levels should be checked every 4-6 hrs.

Monitor vitals, intake output chart, deep tendon reflexes, respiratory rate every 2 hours to evaluate the evidence of drug toxicity.

Decreased or absent DTR represents an initial sign of toxicity (>10 mg/dl), respiratory depression (>15mg/dl) and myocardial depression at very high doses.

ANTIDOTE: 1gm of calcium gluconate intravenously.

CONTRAINDICATIONS;

ABSOLUTE: Myasthenia gravis.

RELATIVE:

1) Cardiac disease

2) Renal impairment

3) Concomitant use of calcium channel blockers.

SIDE EFFECTS: [106]

SHORT TERM	**LONG TERM**	**TOXICITY**
MATERNAL Lethargy, nausea, vomiting, constipation, dry mouth, hypocalcemia,	Osteoporosis, tetany, renal stones, paralytic ileus, pulmonary edema, hypothermia, rhabdomyolysis.	absent DTR, respiratory depression, cardiac arrest, death.
FETAL Decreased fetal movements, absent fetal breathing, decreased short term variability of heart rate, altered uterine blood flow, blunted fetal response.	Decalcification of Bone	
NEONATAL Hypomagnesemia, hypocalcemia, lethargy, depressed APGAR, hypotonia, decalcifiaction of bone.	**HIGH DOSES** Neonatal death	**LOW DOSES** Neuro protective (decreased incidence of cerebral palsy and IVH)

Magnesium sulfate as neuroprotection for preterm neonates:

Despite significant improvements in survival for infants born preterm, the rate of major neurodevelopmental impairment in survivors has not diminished. As a result, strategies designed to reduce adverse neurological outcomes have been a major perinatal research focus. Antenatal magnesium sulfate ($MgSO_4$) is one such strategy. Following the rst report of an association between perinatal administration of $MgSO_4$ and a reduction in the risk of peri/intraventricular hemorrhage (P/IVH), its use as a neuro-protective therapy when given to women at risk of preterm birth has become established practice . While $MgSO_4$ has been shown to decrease the risk of P/IVH, cerebral palsy and the rate of substantial gross motor dysfunction, the mechanismsunderlying these effects remain poorly understood.

Pamela Borja-Del-Rosario et al (2014) [125], conducted a retrospective study on 289 mothers who received antenatal magnesium for neuroprotection as a loading dose of 4–6 g infused over 30 min, followed by a maintenance infusion of 1–2 g/h. Total magnesium dose infused to the mother and maternal serum magnesium concentrations were correlated with neonatal serum magnesium concentrations. They have concluded that the total dose of magnesium infused to the mother correlates with neonatal serum magnesiumconcentrations. To keep neonatal serum magnesium concentrations within a range that is effective for neuroprotection and safe for the neonates, the total dose received by the mother needs to be monitored and limited.

Michael J. Stark et al (2015) [126]in their study of CBF and tissue oxygenation index were measured, and oxygen delivery, consumption, and cFTOE calculated within 24□h of birth and at 48 and 72□h of life in 36 infants ≤ 30□wk gestation exposed to $MgSO_4$ and 29 unexposed infants. The total internal carotid blood ow and cerebral oxygen delivery did not differ between the groups at the three study time-points. Cerebral oxygen consumption and cFTOE were lower in infants exposed to antenatal $MgSO_4$ (P = 0.012) compared to unexposed infants within 24□h of delivery. This difference was not evident by 48□h of age. Fewer infants in the $MgSO_4$ group developed P/IVH by 72□h of age (P = 0.03). They have concluded that infants exposed to $MgSO_4$ had similar systemic and cerebral hemodynamics but lower cFTOE compared to nonexposed. These findings suggest reduced cerebral metabolism maybe a component of the neuro-protective actions of antenatal $MgSO_4$.

However, Betsy Ostrander, et al (2016)[127] performed a retrospective cohort analysis in infants born <37 weeks gestation over a 10-year period. Prenatal, perinatal, and postnatal clinical and demographic information was collected. Crude and adjusted odds ratios were estimated under generalized linear models with generalized estimating equations to examine the association of the neonatal serum magnesium level between 24 and 48 hours following birth with the risk of epilepsy and/or motor impairment. The final cohort included 5,461 infants born <37 weeks gestation from 2002–2011. This study shows that the neonatal magnesium level between 24 and 48 hours of life in premature infants is not significantly associated

with the risk for developing epilepsy or motor impairment.

Another study by Sajjad Ur Rahman et al (2017)[128], a multicenter double-blind randomized controlled trial in which the term and near-term newborn infants (≥35 weeks) with a clinical diagnosis of moderate or severe HIE were randomized to either Arm A (therapeutic hypothermia plus $MgSO_4$) or Arm B (therapeutic hypothermia plus placebo) using a net-based randomization system. Both groups received, within 6 h of birth, standard hypothermia therapy (72 h of cooling to 33.5°C followed by slow rewarming over a period of 8 h) plus either $MgSO_4$ (250 mg/kg/dose ×3 doses) or placebo (normal saline). The groups were compared for short-term predischarge adverse outcomes. They have concluded that the combined use of therapeutic hypothermia and $MgSO_4$ appears to be safe particularly with respect to maintaining normal blood pressure and coagulopathy. Long-term survival and neurodevelopmental outcomes remain to be evaluated.

METHODS AND MATERIALS

SOURCE OF DATA: All patients who present to Dept. of Obstretics and Gynaecology R.L.Jalappa Hospital and Research Centre Tamaka, Kolar with preterm labour and uncomplicated pregnancies of the same gestational age who meet the inclusion/exclusion criteria were included in the study. The duration of the study was from October 2015 to October 2017. A minimum of 100 subjects were proposed to be included in this study. Serum magnesium levels was estimated by Fusion 5.1 FS Micro slide method.

INCLUSION CRITERIA:

All pregnant women of any age group attending as out patient or in patient to R L JALAPPA Hospital, Tamaka, kolar with 28 weeks to 36 weeks 6 days of gestational age in preterm labour or not in labour. And the patient was followed up till delivery.

EXCLUSION CRITERIA:

1. Previous history of recurrent abortions or preterm delivery.

2. Patients with recurrent urinary tract infections.

3.Patients with preeclampsia, polyhydramnios, antepartum haemorrhage, fetal congenital malformations, intrauterine death.

4. Patient with preterm premature rupture of membranes.

6 . Patients with cervical incompetence or any uterine malformations.

7. Patients with multiple gestation.

Prospective case control study.

Study group: Consisted of 50 pregnant women with preterm onset of labour (between 28 weeks to 36 weeks 6 days of gestation) and had preterm deliveries.

Control group: Consisted of 50 pregnant women with comparable gestational age (between 28 weeks to 36 weeks 6 days of gestation) attending the OPD for routine ANC and they were followed up till delivery

Method of collection of samples.

Patients were selected using the above criteria. After institutional clearance and informed consent blood samples was being collected as follows:

Group 1(study group): Blood samples was collected at the time of admission to labor room.

Group 2(control group): Blood samples was collected in out patients department. They were followed up till delivery.

Methods: 2ml of venous blood was collected in a plain tube from 28 weeks onwards of gestation and patients are followed up till delivery.

METHODOLOGY:

Demographic details of women like socioeconomic status, gravidity, gestational age as well as obstetric factors like history pain abdomen, frequency of uterine contraction, past obstetric history and any medical or obstetric complications were noted.

Gestational age was based on LMP, if LMP and first trimester scan was corresponding. If notearlier ultrasound measurement was used to determine the gestational age. Those who did not have a dating scan where gestational age could not be determined accurately were excluded.

Women were classified to different socioeconomic status which we used BG Prasad classification (2014) based on the husband occupation.

The frequency of uterine contraction was assessed by abdominal examination. Per speculum examination was done to look for dilatation. Per vaginal examination was done to feel the effacement of cervix and diagnosis of preterm labor was made.

Serum venous sample were collected for the estimation of magnesium before any parenteral therapy as describe above. Serum magnesium was estimated by Fusion 5.1 FS magnesium Micro slide method.

The neonatal outcomes were assessed by noting birth weight, APGAR scores at 1 minute and 5 minute, any neonatal morbidity and NICU admission.

SAMPLE SIZE CALCULATION

Sample Size For Comparing Two Means

Input Data

Confidence Interval (2-sided)	95%		
Power	90%		
Ratio of sample size (Group 2/Group 1)	1		
	Group 1	**Group 2**	**Difference***
Mean			0.23
Standard deviation	0.3	0.4	
Variance	0.09	0.16	
Sample size of Group 1	50		
Sample size of Group 2	50		
Total sample size	100		

STATISTICAL ANALYSIS

The collected information was coded and entered to an excel data sheet. The quantitative measured are presented by mean and standard deviation and the qualitative measured are presented by proportions and confidence interval.

The significance of the difference in the quantitative measure stands by using student ‘t’ test. The difference is qualitative measure between the group by using chi square test.

p-value less than or equal to 0.05 was considered as statistically significance

Analysis of serum magnesium levels:

After collecting serum samples was separated by centrifugation and used for analysis.

Serum magnesium is measured by Fusion 5.1 FS magnesium Micro slide method.

Magnesium reacts with formazam dye derivatives in the reagent layer; the high magnesium affinity of the dye dissociated magnesium from binding proteins. The resulting magnesium dye complex cause a shift in the dye absorption maximum. The amount of dye complex form is proportional to the magnesium concentration present in the samples and measured by reflection density.

$Mg^{+2} + Ca^{+2} \xrightarrow{\text{chelator}} Mg^{+2} + Ca^{+2}$ chelator complex.

Mg^{+2} + formazam dye derivative $\xrightarrow{\text{ph 9.76}}$ Mg^{+2} dye complex .

(this complex is measured)

REFERENCE VALUE:

Serum magnesium 1.6 to 2.6 mEq / l. [4]

RESULTS

This was a prospective study where serum magnesium levels were estimated in a group of 50 women who was presented with preterm labor and delivered preterm (study group) and compared with a group of 50 women who delivered at term (control group) to determine the possible role of magnesium in initiation of preterm labor.

The following are the results of the analysis:

1) The comparison of age in years in study and control group:

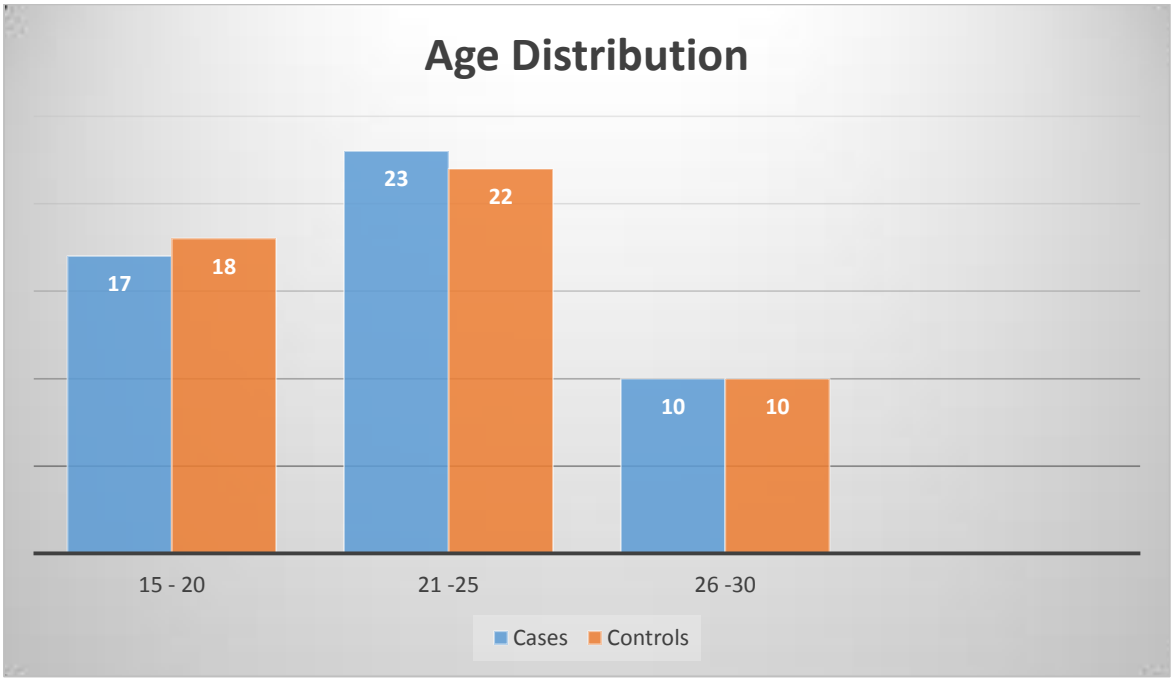
The mean age of the patients in the study group was 22.4 ± 3.084 while that in the control group was 22.4 ± 3.064.

Majority of the patients in both the age groups were in the age group of 21 to 25 years.

Table.no.3. Comparison of age in years in Study and Control group.

Age in years	Study group NO. (N=50)	Study group in percentage(%)	Control group NO. (N=50)	Control group percentage (%)
18 to 20	17	34	18	36
21 to 25	23	46	22	44
26 to 30	20	20	10	20
TOTAL	50	100	50	100
Mean SD	22.4 ± 3.084		22.4 ± 3.064	

Figure. No. 5. Bar chart of Age distribution among study and control group.



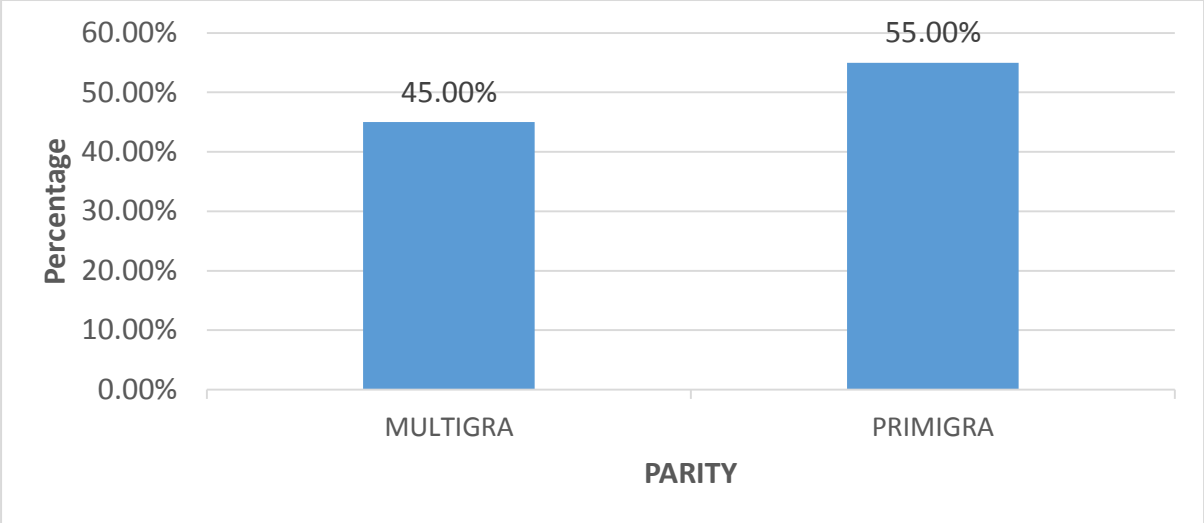
2) The distribution of parity in study and control group:

Primigravida are more common in both study group and control group constituting 55% of Cases.

Table. No. 4. Distribution of parity in study and control group.

PARITY	Frequency	Percentage
Multigravida	45	45.00%
Primigravida	55	55.00%

Figure.6. Bar chart of PARITY distribution in study population (N=50) and control population (N=50).



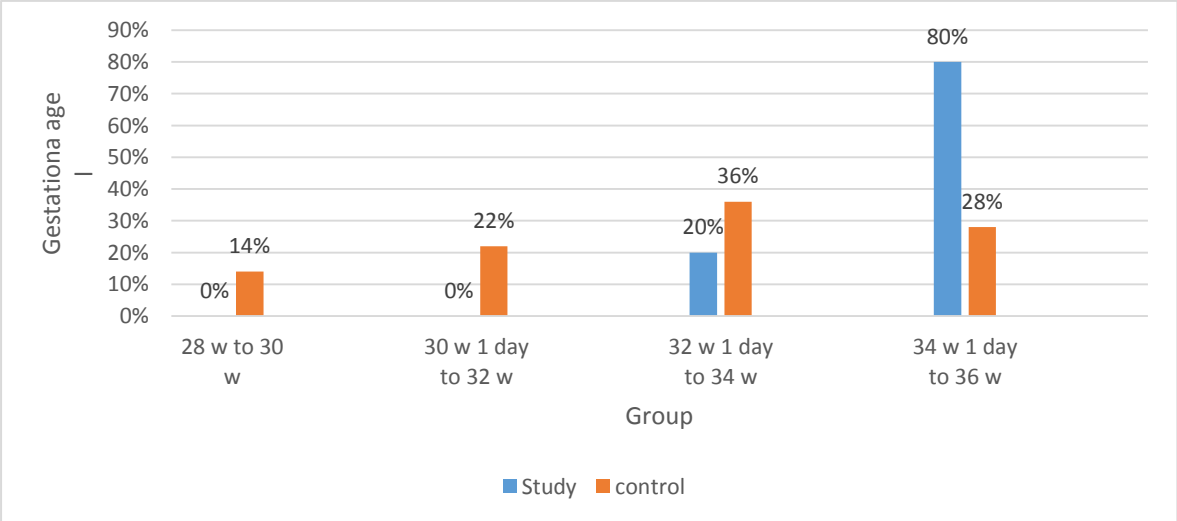
3) The comparison of gestational age in study and control group:

In study group most cases is in between 34 weeks to 36 weeks 6days contributing of 80%

Table.no. 5. The comparison of gestational age in study and control group.

Gestational age	Group	
	Study (N=50)	Control (N=50)
28 weeks to 30 weeks	0 (0%)	7 (14%)
30 weeks 1 day to 32 weeks	0 (0%)	11 (22%)
32 weeks 1 day to 34 weeks	10 (20%)	18 (36%)
34 weeks 1 day to 36 weeks 6 days	40 (80%)	14 (28%)

Figure.no.7. Bar chart of Gestational age distribution in study population (N=50) and control population (N=50).



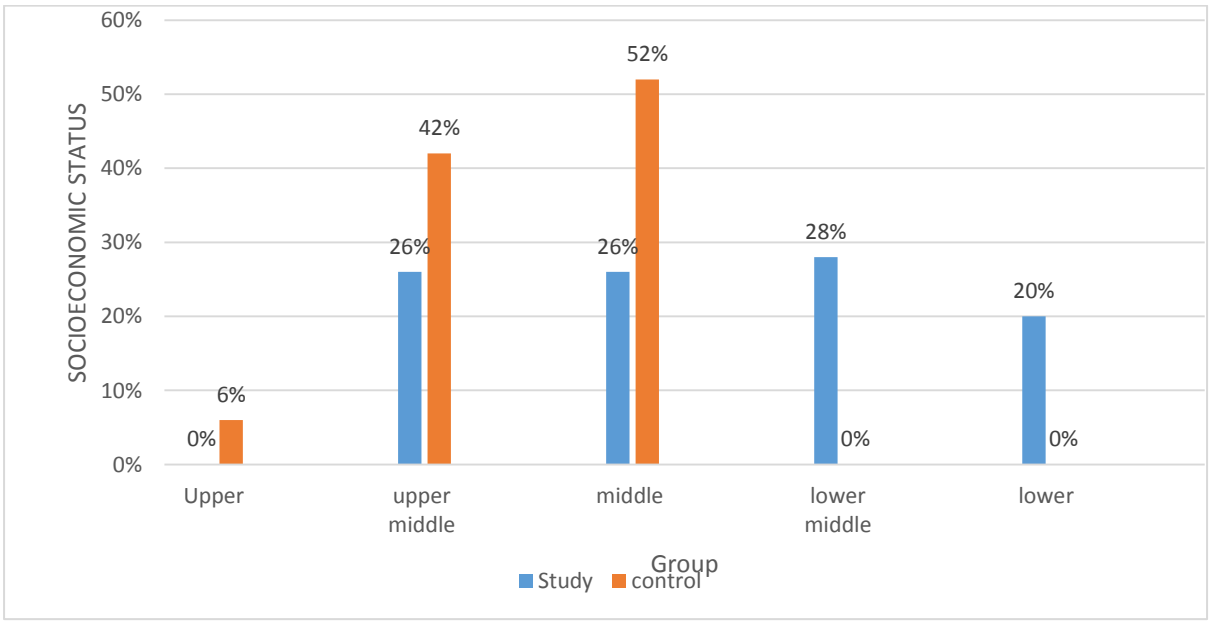
4) The comparison of Socioeconomic status in study and control group:

In the study group most of the cases falls in lower middle class of BG Prasad socioeconomic status constituting of 28%, however, in control group most of the cases falls in middle class (52%) followed by upper middle class (42%).

Table. No. 6. The comparison of Socioeconomic status in study and control group.

Socioeconomic status	Group	
	Study (N=50)	Control (N=50)
Upper class	0 (0%)	3 (6%)
upper middle class	13 (26%)	21 (42%)
middle class	13 (26%)	26 (52%)
lower middle class	14 (28%)	0 (0%)
lower class	10 (20%)	0 (0%)

Figure.no.8. Bar chart of Socioeconomic status distribution in study population (N=50) and control population (N=50).



5) Distribution of mode of delivery in study and control group:

Most (62%) of the women had preterm vaginal delivery in study group,and in control group most (66%) of the women delivered by full term vaginal delivery.

Table. No. 7. Distribution of mode of delivery in study and control group:

MOD	Group	
	Study (N=50)	Control (N=50)
asst breech	1 (2%)	0 (0%)
ftvd	0 (0%)	33 (66%)
lscs	14 (28%)	12 (24%)
out force	0 (0%)	4 (8%)
out forcep	4 (8%)	0 (0%)
ptvd	31 (62%)	0 (0%)
vacuum	0 (0%)	1 (2%)

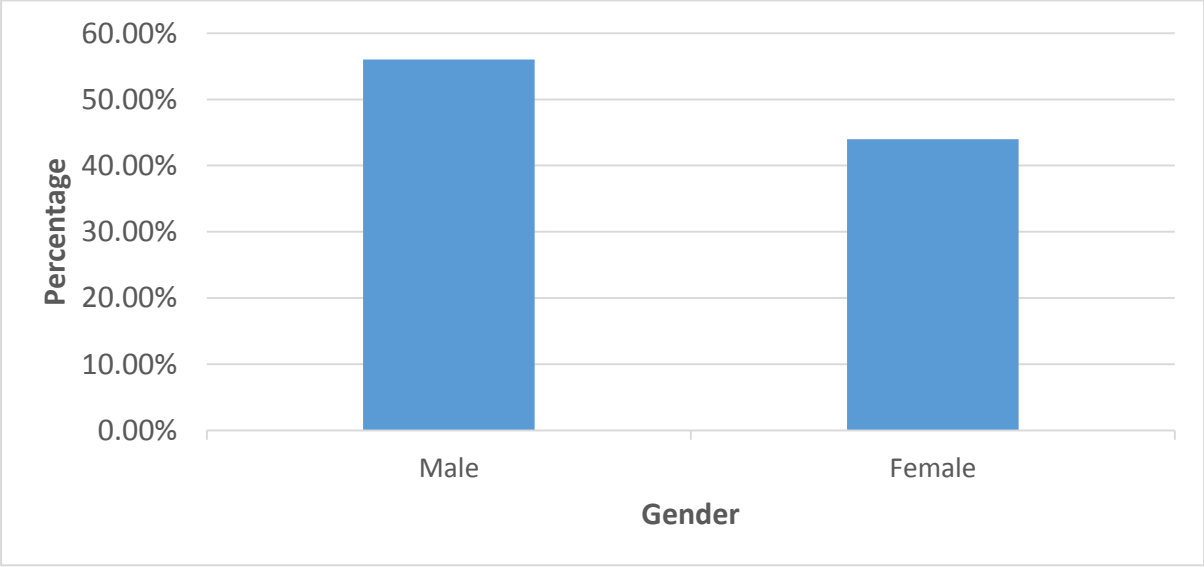
6) The comparison of sex of baby in study and control group:

Majority of the baby in both study (58%) and control (52%) were male baby.

Table.no. 8. The comparison of sex of baby in study and control group:

Sex of baby	Study group NO. (N=50)	Study group in percentage(%)	Control group NO. (N=50)	Control group percentage (%)
Male	29	58	26	52
Female	21	42	24	48

Figure.no.9. Bar chart of sex of baby in study population (N=50)



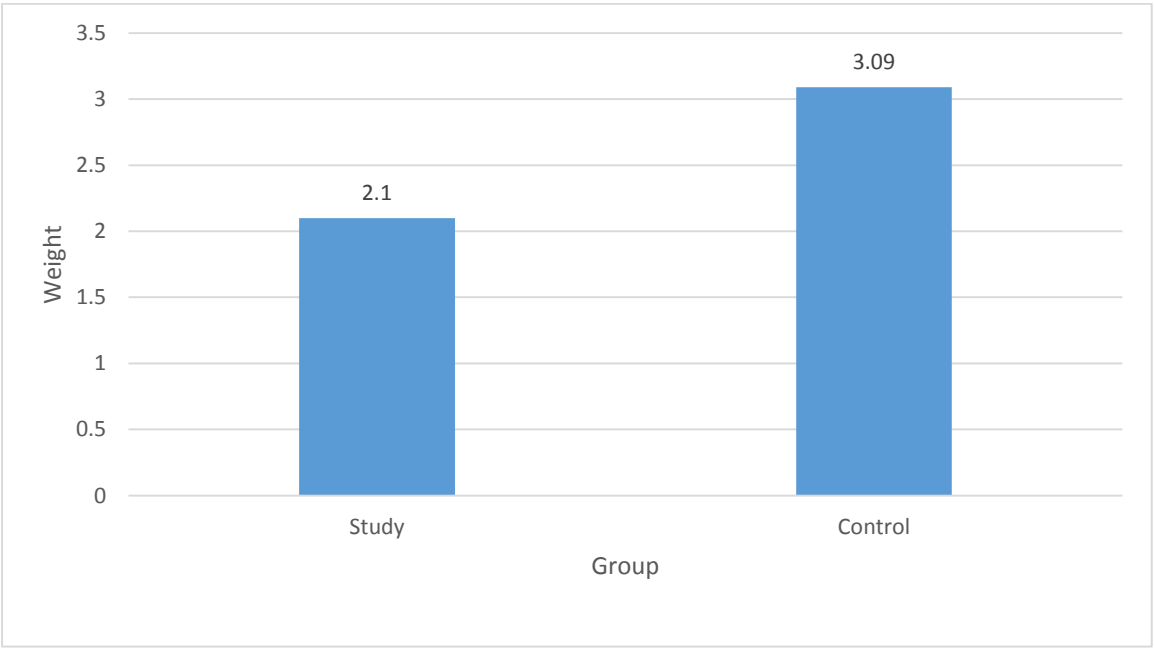
7) **The comparison of birth weight of baby (Kg) in study and control group:**

The mean birth weight of the baby in study population is 2.1 kg with SD of 0.34 and in control group is 3.09 kg with SD of 3.09. The p-value being <0.001, which is highly statistically significant.

Table. No. 9. The comparison of birth weight of baby (Kg) in study and control group.

Group	WEIGHT Mean± STD	Mean difference	95% CI		P value
			Lower	Upper	
Study (N=50)	2.1 ± 0.34	-0.98	-1.11	-0.86	**<0.001**
Control (N=50)	3.09 ± 0.29				

Figure.no. 10. Bar chart of weight of baby (Kg) in study population (N=50) and control population (N=50).



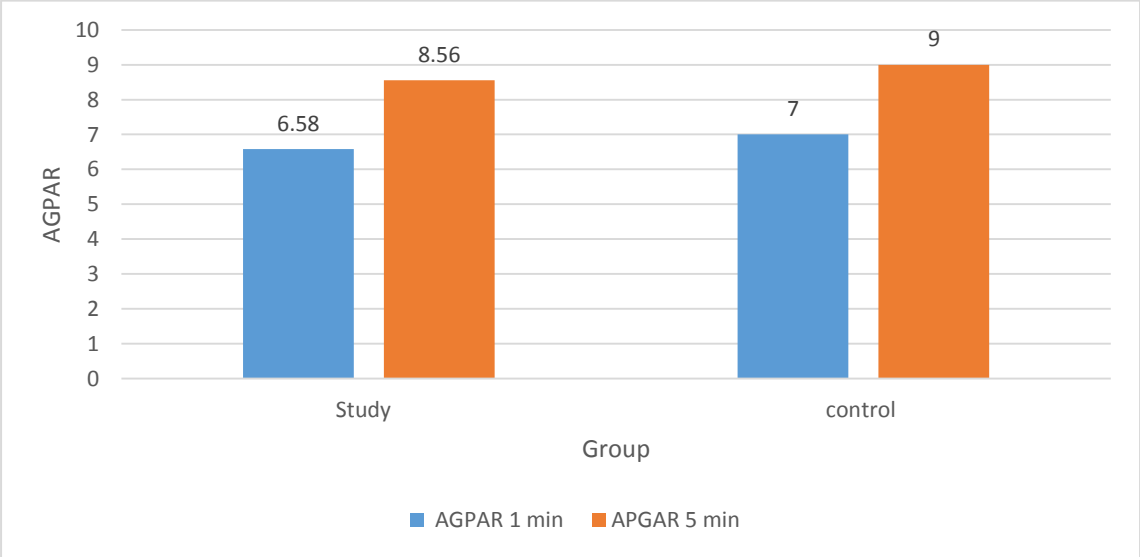
8)The comparison of APGAR SCORE in study (N=50) and control (N=50) group:

The mean APGAR score of the baby in study population is 6.58 with SD of 0.54 at 1 min and 8.56 with SD of 0.54 at 5 min, and in control group is 7 at 1 min and 9 at 8 min. The p-value being <0.001, which is highly statistically significant.

Table.no. 10.The comparison of APGAR SCORE in study (N=50) and control (N=50) group:

Parameter	Mean ±SD		P value
	Study (N=50)	control (N=50)	
AGPAR 1 min	6.58 ± 0.54	7 ± 0	<0.001
APGAR 5 min	8.56 ± 0.54	9 ± 0	<0.001

Figure.no. 11. Bar chart of AGPAR **between study group (N=50) and control group (N=50).**



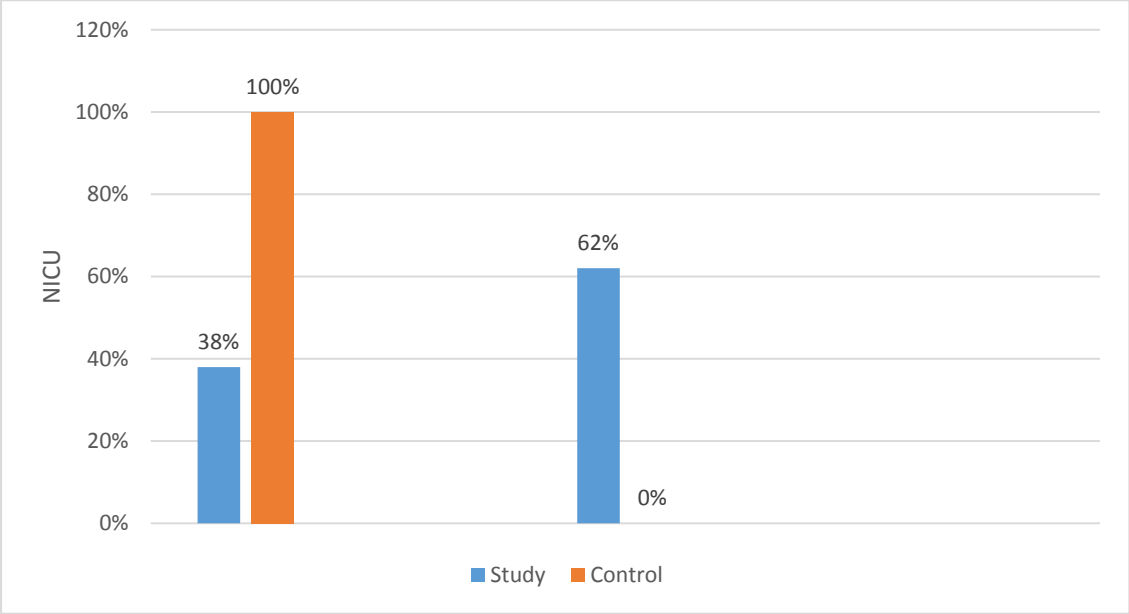
9) Comparison of neonatal outcome in study (N=50) and control (N=50) group.

In study group 38 % of the baby was admitted to NICU, however in control group none of the baby had required NICU admission.

Table.no. 11. Comparison of neonatal outcome in study (N=50) and control (N=50) group.

NICU	Group	
	Study (N=50)	Control (N=50)
yes	19 (38%)	50 (100%)
No	31 (62%)	0 (0%)

Figure.no. 12. Bar chart of NEONATAL OUTCOME between study group (N=50) and control group (N=50).



10) Comparison of mean Serum Mg mEq/L across study groups (N=50) and control group (N=50).

The mean serum magnesium level (mEq/L)in study population is 1.39 mEq/L with SD of 0.2 and in control group is 2.08 mEq/L with SD of 0.2 . The p-value being <0.001, which is highly statistically significant.

Table.no. 12. Comparison of mean Serum Mg mEq/L across study groups (N=50) and control group (N=50).

Group	Mg (mEq/L) Mean± STD	Mean difference	95% CI		P value
			Lower	Upper	
Study (N=50)	1.39 ± 0.2	-0.69	-0.77	-0.61	**<0.001**
Control (N=50)	2.08 ± 0.2				

Figure.no. 13. Bar chart distribution of Serum Mg in study group (N=50) and control group.

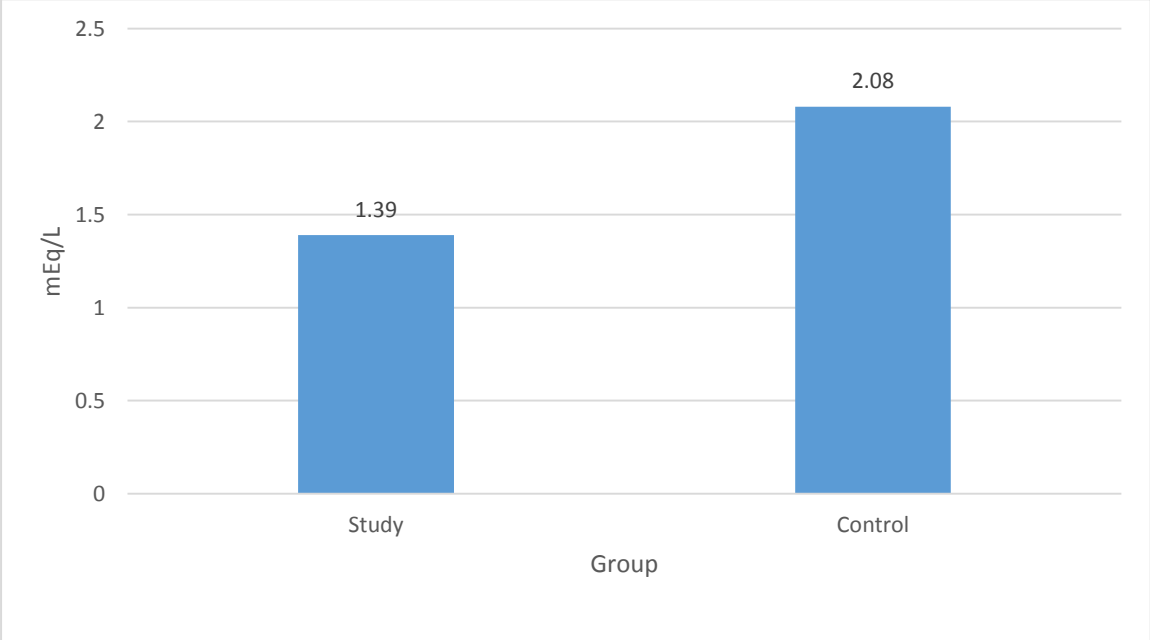
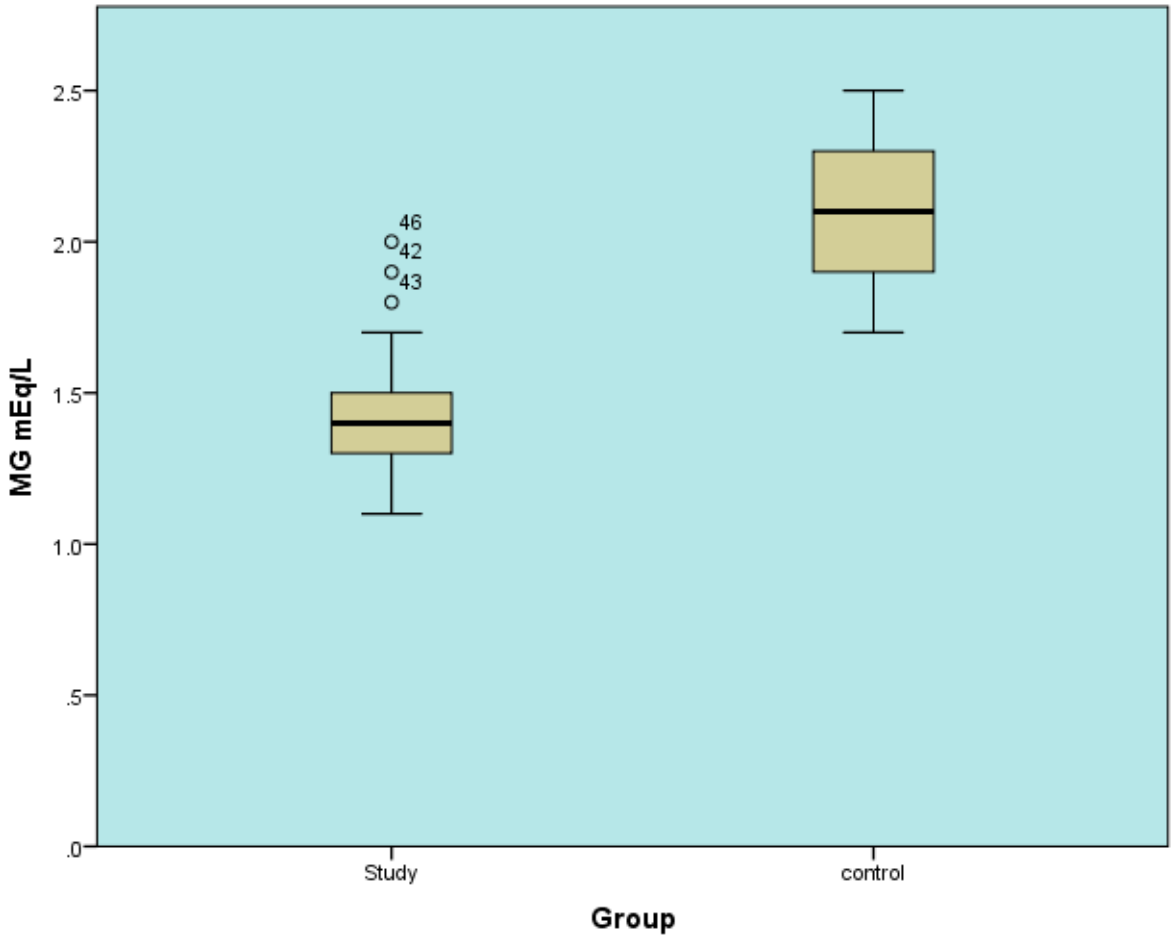


Figure.no. 14. Box and whisker plot of distribution of Mg level in mEq/L in study group (N=50) and control group(N=50)



11) Distribution of mean magnesium(mEq/L) in different Socioeconomic status in study and control group.

The low level of mean serum magnesium is observed in lower middle class which is 1.29 with SD of 0.14 and in lower class is 1.28 with SD of 0.1. The p-value being 0.003 and 0.004 respectively which is statistically significant.

Table.no. 13. Distribution of mean magnesium (mEq/L) in different Socioeconomic status in study and control group.

SOCIOECONOMIC STATUS	Mean ± Std. Dev	Mean difference	95% Confidence Interval for Mean		P value
			Lower Bound	Upper Bound	
Upper class	1.9 ± 0.1				
upper middle class	1.9 ± 0.32	0.00	-0.38	0.38	1.000
middle class	1.85 ± 0.39	0.05	-0.32	0.43	0.787
lower middle class	1.29 ± 0.14	.6071	0.21	1.01	***0.003***
lower class	1.28 ± 0.1	.6200	0.21	1.03	***0.004***

Figure.no. 15 : Bar chart of Socioeconomic Status distribution in study and control group.

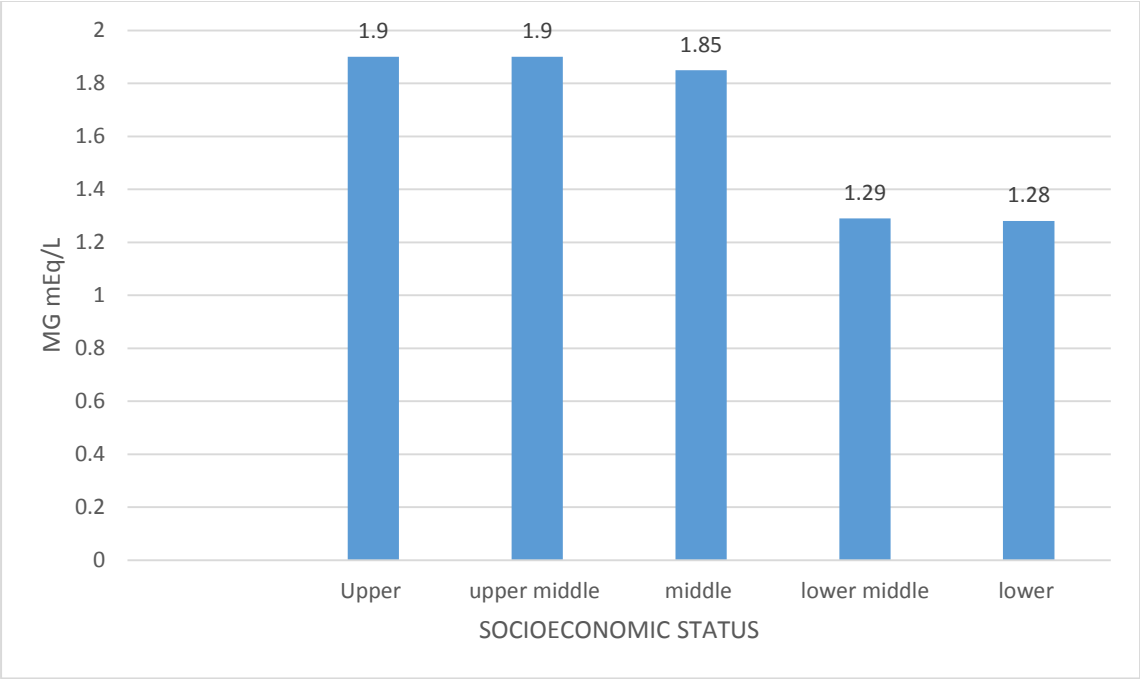


Figure.no. 16. Box and whisker plot of Serum Mg level (mEq/L) in different Socioeconomic Status between study and control group.

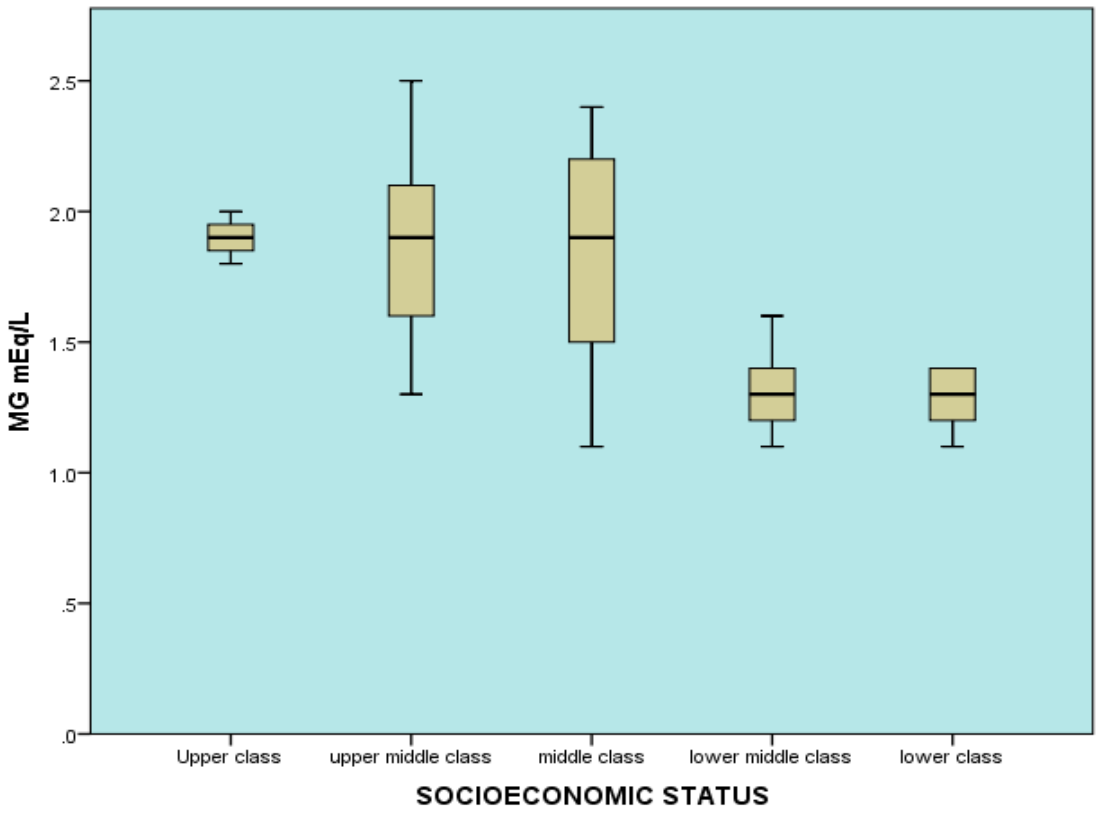
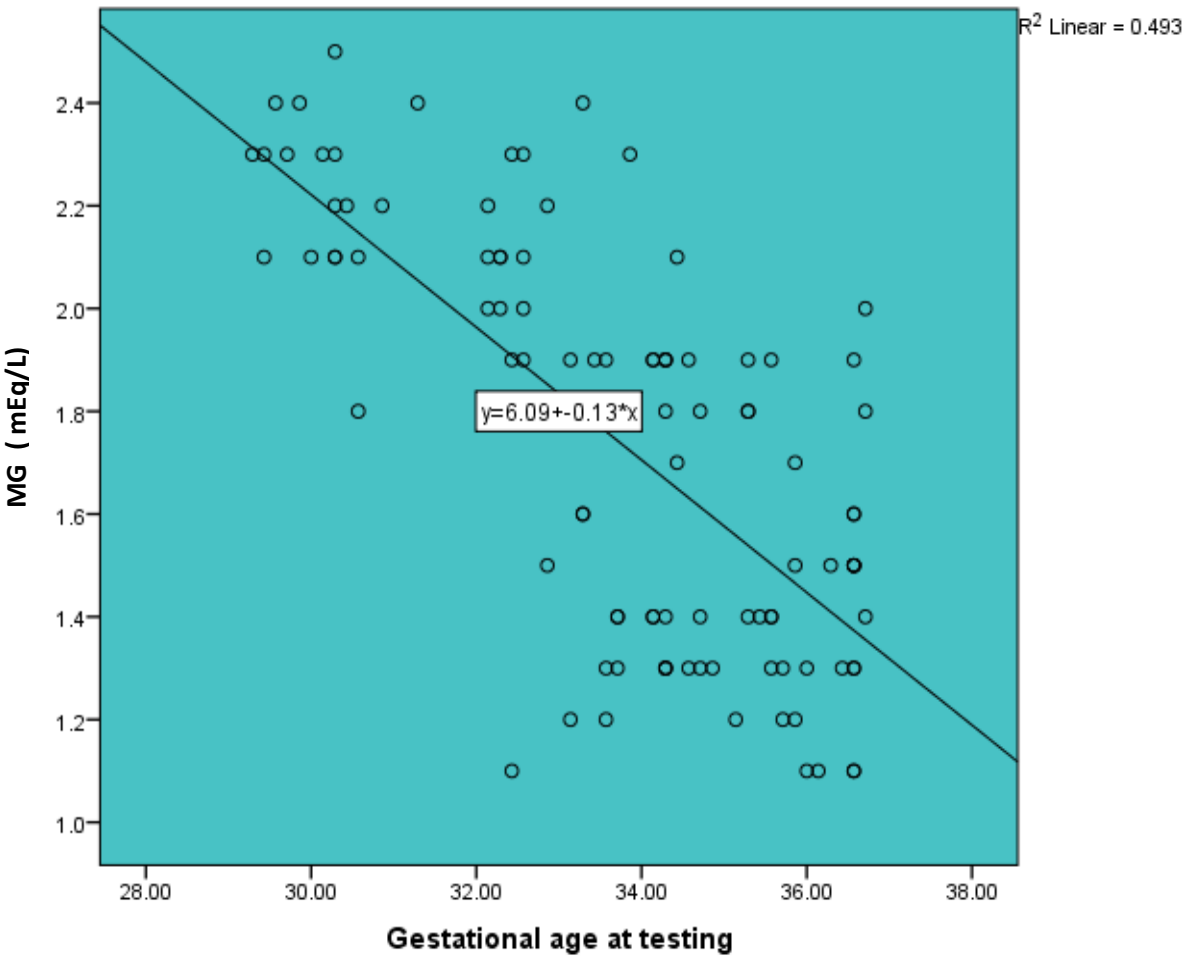


Figure.no.17: Correlation between Gestational age at time of testing and serum Mg (mEq/L) in the study group (N=50) and control Group (N=50).



The value of serum magnesium levels decrease with the increase in gestational age in both study and control group.

DISCUSSION

The main focus in the current study to compare the serum magnesium level in preterm birth and in those who had a term delivery, many records findings have augmented measuring magnesium level as a predictor for preterm birth. The exact cause of hypomagnesaemia in patient of preterm birth is unknown but individualized and socioeconomic factors have been considered.

Based on the results of a case-control study conducted by Bhat et al[1] in 2012, serum magnesium level in women with preterm labor was significantly lower than women with term labor (1.343 ±0.09 mg/dl versus 1.875 ±0.013 mg/dl, respectively). In addition, Hantoushzadeh et al [5] reported that serum magnesium level in preterm pregnant women was lower than term pregnant women (1.7 ±0.38 versus 2 ±0.184).

STUDIES	Preterm labour	Normal pregnancy
Present study	1..39 ± 0.2 mEq/L	2.08 ± 0.2 mEq/ L
Bhat et al [1]	1.343 ±0.09 mg/dl	1.875 ±0.013 mg/dl
Hantoushzadeh et al [5]	1.7 ±0.38 mg/dl	2 ±0.184 mg/dl
Ensiyeh Jenabi et al [130]	1.95 ± 0.16 mg/dl	2.12± 0.27 mg/dl
Kamal et al[109]	1.47 ±0.22 mg/dl	1.75 ±0.21 mg/dl

Kurzel [107] investigated the effect of serum magnesium levels in pregnancy on preterm labor and indicated that hypomagnesaemia (magnesium equal to or less than 1.4 mg/dl) can be considered as a marker for true preterm labor. A proposed hypothesis suggests that magnesium has an immediate effect on placenta vascular flow and its depletion can have

an adverse effect on the placenta vascular dilation leading to placenta insufficiency.

Jenabi et al, (2017)[129] conducted an observational study concluded that low level of maternal serum magnesium is associated with poor pregnancy outcomes, including preterm labor and low birth weight. In addition, there was a direct correlation between maternal serum magnesium level, gestational age and neonatal weight.

Durlach J,et al [130]. concluded that exact cause of hypomagnesemia in patients of preterm labour is not known but nutritional and socio-economic factors have been suggested for it.

Neuromuscular hyperexcitability is an initial problem cited in individuals who have or are developing magnesium deficiency. Neuromuscular hyperexcitability in turn leads to uterine hyperactivity resulting in premature onset of labour

In present study a number of preterm labour cases belong to lower middle class and lowerclass of BG Prasad socioeconomic status and it is similar as Sharma A et al [131]findings.

On the contrary Khani et al[132] demonstrated non-significant increase in preterm labour among low socioeconomic class women may be due to the smaller sample size in his study when he took only 40 pregnant women.

This increase in preterm labour in low socioeconomic class may be attributed to poor prenatal care, stressful life style and nutritional deficiency of trace elements includingmagnesium.

Kamal S et al [109], (I*ndian J Pathol Microbiol* 2003) also observed in their study that low Level of serum magnesium is detected in lower socioecomonic status than compared to higher socioeconomic status.

Regarding magnesium level at different gestational age, we observed that there was a decrease in serum magnesium with progression of pregnancy in both groups, and the same is observed in Bhat S, et al [1].

Gestational age	Serum Magnesium in mg/dl (Group 1)	Serum Magnesium in mg/dl (Group 2)	Statistical analysis (p-value)	Remarks
(28-30) weeks	1.37+- 0.055	1.97+- 0.073	<0.001	HS
(31-33) weeks	1.35+- 0.63	1.89 +- 0.84	< 0.001	HS
(34- 36) weeks	1.31+- 0.060	1.77 +- 0.111	< 0.001	HS

*HS – highly significant.

Shatha A, et al[133]. also concluded that as the gestational age of the pregnancy increase the serum magnesium level is observed to be decreased ,which may due to increased demand with the advance of pregnancy.

Watson et al,[134] performed a prospective cohort study on 504 pregnant women in New Zealand in 2010 and investigated the association between infant birth weight and maternal diet and supplement intake. They reported a positive correlation between magnesium intake during pregnancy and neonatal birth weight.

In the present study the mean birth weight of the baby in study population is 2.1 kg with SD of 0.34 and in control group is 3.09 kg with SD of 3.09. The p-value being <0.001, which is highly statistically significant. Elezabeth Kh et al[135], in their study showed that serum magnesium to be lowest in preterm low birth weight newborns, then term low birth weight (including IUGR) infants, and then term normal control.

On the other hand, Pourarian et al[136] conducted a case-control study on 180 pregnant women in 2014 and reported no significant association between maternal magnesium level and infant birth weight and gestational age.

Moreover, the mean APGAR score of the baby in study population is 6.58 with SD of 0.54 at 1 min and 8.56 with SD of 0.54 at 5 min, and in control group is 7 at 1 min and 9 at 8 min.

The p-value being <0.001, which is n also highly statistically significant. Also, in study group 38 % of the baby was admitted to NICU, however in control group none of the baby had required NICU admission.

A study conducted by Cunze et al [113]. on magnesium and calcium concentration in the pregnant and non-pregnant myometrium concluded that low magnesium concentration in the pregnant human myometrium could be a cause of preterm labour.

Further studies have demonstrated that prophylactic oral magnesium supplementation to patient at risk of preterm labour was successful in lowering the

preterm delivery rate and intake should be sufficient to maintain serum magnesium level at the range of 2.0 - 3.5 mg/dl [137].

However, larger studies need to be initiated to conclusively prove the role of hypomagnesemiain the initiation of preterm labour. If proved so, estimation of magnesium levels in early pregnancy could be simple and easy to perform and cost effective test to detect women at risk for preterm delivery. Availability of a marker for preterm labour would initiate more research in the direction of interventions for prevention and would ultimatelygives the way for primary prevention, thereby reducing the morbidity and mortality associated.

Magnesium supplementation itself could be simple and inexpensive interventiontowards prevention of preterm labour.

SUMMARY

The magnitude of preterm labour and subsequent neonatal morbidity and mortality provoked our study to investigate the possible role of serum magnesium deficiency in triggering the onset of preterm labour.

We compared the serum magnesium levels of 50 women who delivered at 28 weeks to 36 weeks and 6 days of gestation with serum magnesium levels of women between weeks to 36 weeks and 6 days but delivered after 37 completed weeks of gestation.

1. The mean serum magnesium levels in the study group was 1.39 ± 0.2 mEq/L which was significantly lower than the control group 2.08 ± 0.2 mEq/L.
2. Serum magnesium levels were also lower in lower socioeconomic status in both study and control group.
3. The birth weight of the baby in study group is 2.1 ± 0.34 kg and in control group is 3.09 ± 0.29 kg, which is statistically significant.
4. The mean APGAR score of the baby in study population is 6.58 with SD of 0.54 at 1 min and 8.56 with SD of 0.54 at 5 min, and in control group is 7 at 1 min and 9 at 8 min. The p-value being <0.001, which is highly statistically significant.
5. In study group 38 % of the baby was admitted to NICU, however in control group none of the baby had required NICU admission.
6. The value of serum magnesium levels decrease with the increase in gestational age in both study and control group

CONCLUSION

Serum magnesium levels in our study were significantly lower in those who delivered preterm when compared with those who delivered at term, this suggest a possible role of hypomagnesemia in initiation of preterm labour.

Pregnant women should be counseled to include good sources of magnesium in their diets, such as nuts, seeds, green leafy vegetables and fish.

Identifying deficiency is the safest and most effective way to determine supplement requirements. In the absence of this, a low dose magnesium could be safely recommended to prevent women in general, eg. 100- 200 mg/day.

Larger studies are required to conclusively prove the role of hypomagnesemia in preterm labour.

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PERFORMA: (STUDY GROUP)

1 .Name of the patient:

2. Age:

3. Hospital no:

4. Marital status:

5. Husband name:

6. Occupation:

7. Husband's occupation:

8. Socioeconomic status:

9. H/o amenorrhoea:

10. Chief complaints

11. H/o presenting illness:

12. H/o present pregnancy:

1st trimester:

2nd trimester:

3rd trimester:

13. H/o presence of muscle cramps during pregnancy

14. Any changes in the quality and quantity of vaginal discharge.

15. H/o pre eclampsia and imminent signs

16. H/o bleeding pv

17. H/o pv leak

18. H/o fever

19. H/o burning micturition

20. H/o previous surgery

21. H/o medical illness like HTN, DM, BA, thyroid or cardiac anomalies.

22. H/o abortions

23. H/o preterm delivery

25. H/o multiple pregnancy

26. Patients with uterine malformations

27. married life - marriage-

28. Gravida -

Para- Living- Abortion- Dead-

Last child birth

29. Outcome of pregnancy:

30. H/o contraception:

31. Menstrual history:

PMC a. age of menarche

b. duration

c. cycle

d. no. of pads used per day

e. associated with dysmenorrhoea or clots

LMP-

EDD-

POG-

32. GENERAL PHYSICAL EXAMINAION:

Built a. poor

b. moderate

c. obese

Febrile/ afebrile

Pallor Icterus Clubbing Cyanosis Koilonychia Lymphadenopathy Edema

BP- PR-

CVS:

RES:

CNS:

P/A: uterus size

Acting / relaxed

Lie

Presentation

FHR

P/S:

P/V:

33. INVESTIGATION:

a. CBC

hb Plt Tlc- Dlc-

b. urine routine:

c Hbsag HIV VDRL

d. OGCT with 75mg glucose :

e. Serum magnesium (study group) :

f. USG:

34. CONTROL GROUP :

Outcome of labour:

a. Date of delivery:
b. Time of delivery:
c. Type of delivery :
    1. Spontaneous vaginal delivery
    2. Forceps
    3. Ventouse
    4. LSCS (along with indication)

BABY NOTES :

a. Male / female
b. Live / still birth
c. Birth weight
d. Apgar score
    1' - 5' –
e. NICU admission:
f. Follow up in NICU:

Take home baby :

PERFORMA: (CONTROL GROUP)

1 .Name of the patient:

2. Age:

3. Hospital no:

4. Marital status:

5. Husband name:

6. Occupation:

7. Husband's occupation:

8. Socioeconomic status:

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11. H/o presenting illness:

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15. H/o pre eclampsia and imminent signs

16. H/o bleeding pv

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18. H/o fever

19. H/o burning micturition

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22. H/o abortions

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26. Patients with uterine malformations

27. married life - marriage-

28. Gravida -

Para- Living- Abortion- Dead-

Last child birth

29. Outcome of pregnancy:

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31. Menstrual history:

PMC a. age of menarche

b. duration

c. cycle

d. no. of pads used per day

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Built a. poor

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Febrile/ afebrile

Pallor Icterus Clubbing Cyanosis Koilonychia Lymphadenopathy Edema

BP- PR-

CVS:

RES:

CNS:

P/A: uterus size

Acting / relaxed

Lie

Presentation

FHR

P/S:

P/V:

33. INVESTIGATION:

a. CBC

hb Plt Tlc- Dlc-

b. urine routine:

c Hbsag HIV VDRL

d. OGCT with 75mg glucose :

e. Serum magnesium (control group) :

f. USG:

34. CONTROL GROUP :

Outcome of labour:

d. Date of delivery:
e. Time of delivery:
f. Type of delivery :
    5. Spontaneous vaginal delivery
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    8. LSCS (along with indication)

BABY NOTES :

g. Male / female
h. Live / still birth
i. Birth weight
j. Apgar score
    1' - 5' –
k. NICU admission:
l. Follow up in NICU:
m. Take home baby :

SRI DEVARAJ URS MEDICAL COLLEGE & RESEARCH CENTRE, TAMAKA, KOLAR

PATIENT CONSENT FORM

Case no:

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I have understood that I have the right to refuse consent or withdraw it at any time during the study and this will not affect my treatment in any way. I consent voluntarily to participate in this study " **EVALUATION OF SERUM MAGNISIUM LEVEL IN PRETERM LABOUR"**

Name of Participant_____

Signature/ thumb print of Participant _____

Date _____

Statement by the researcher/person taking consent:

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. Blood sample will be taken from the patient for serum MAGNISIUM analysis.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____

Name and Address of Principal Investigator: Dr.Phurailatpam. Priyadarshini.
R.L Jalappa Hospital
Tamaka, Kolar.

ಒಪ್ಪಿಗೆ ಪತ್ರ / ರೂಪ

ಮಾನ್ಯರೆ,

ನಾವು ನಡೆಸಿತ್ತಿರುವ ಸಂಶೋಧನಾ ವಿಷಯ ವಾದ " EVALUATION OF SERUM MAGNISIUM LEVEL IN

PRETERM LABOUR " ದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಅನುಮತಿಯನ್ನು ಕೋರುತ್ತಿದೇವೆ.

ನಿಮ್ಮ ಭಾಗವಹಿಸುವಿಕೆಯ ಸಂಪೂರ್ಣವಾಗಿ ನಿಮ್ಮ ಇಚ್ಚಾನುಸಾರವಾಗಿದ್ದು ಇದರಲ್ಲಿ ಬಗೆಗೆ ನಿಮ್ಮ ನಿರ್ಧಾರವು ನಿಮ್ಮ ಮತ್ತು ಆಸ್ಪತ್ರೆಯ ನಡುವಿರುವ ಸಂಬಂಧದ ಮೇಲೆ ಯಾವುದೇ ರೀತಿಯ ಪರಿಣಾಮವನ್ನು ಬೀರುವುದಿಲ್ಲ ಮತ್ತು ಭಾಗವಹಿಸಲು ನಿಮ್ಮ ಒಪ್ಪಿಗೆಯಿದ್ದರೆ ಈ ಸಂಶೋಧನಾ ಕಾರ್ಯಕ್ರಮದಿಂದ ಯಾವುದೇ ಕ್ಷಣದಲ್ಲಿ ಹಿಂಜರಿಯ ಬಹುದಾದ ಅವಕಾಶ ಇರುತ್ತದೆ.

ಈ ಸಂಶೋಧನೆಯಿಂದಾಗಿ ನಿಮ್ಮ ದೇಹದ ಮೇಲೆ ಯಾವುದೇ ದುಷ್ಪರಿಣಾಮವಾಗುವುದಿಲ್ಲ.

ನಿಮ್ಮ ಭಾವಹಿಸುವಿಕೆಯ ಬಗೆಗೆ ಗೌಪಾತ್ಯಯನ್ನು ಕಾಪಾಡಲಾಗುತ್ತದೆ ಹಾಗೂ ಮಾಹಿತಿಯ ಬಾರಿ ನಮ್ಮ ಸಂಶೋಧನಾ ತಂಡದವರಿಗೆ ಮಾತ್ರ ತಿಳಿದಿರುತ್ತೆದೆ.

ಇದರ ಬಗೆಗಿರುವ ಎಲ್ಲಾ ಅನುಮಾನಗಳನ್ನು ಹಾಗೂ ಪ್ರಶ್ನೆಗಳ್ಳನ್ನು ಯಾವುದೇ ನಿರ್ಭಂದವಿಲ್ಲದೆ, ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ನೀವು ನಿಮ್ಮ ತಂಡದೊಂದಿಗೆ ಚರ್ಚಿಸಬಹುದು.

ಇದರಲ್ಲಿ ಭಾಗವಹಿಸಲು ತಾವು ಮನಸ್ಪೂರ್ಪಕವಗಿ ಇಚ್ಚೆವಿದ್ದರೆ ದಯವಿಟ್ಟು ಇಲ್ಲಿ ಸಹಿ ಮಾಡಿ.

ಭಾಗವಹಿಸುವ ಮಹಿಳೆಯರ ಸಹಿ

ದಿನಾಂಕ :

ಸಾಕ್ಷಿಗಾರರ ಸಹಿ:

PATIENT INFORMATION SHEET

Study title: EVALUATION OF SERUM MAGNISIUM LEVEL IN PRETERM LABOUR.

Study location: R L Jallappa Hospital and Research Centre attached to Sri DevrajUrs Medical College. Tamaka, Kolar

Details-

The study will be taken up in the patients presenting between 28 to 37 weeks of gestation. The blood sample will be evaluated for serum magnesium level.

Patients in this study will have to undergo routine blood investigations such as complete blood count, viral serology, urine routine and random blood sugar levels. To assess the fetal wellbeing and an obstetric ultrasound with biophysical profile will also be done.

Please read the following information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in the study we will collect information (as per proforma) from you or a person responsible for you or both. Relevant history will be taken. This information collected will be used only for dissertation and publication.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. This study has been reviewed by the Institutional Ethics Committee and you are free to

contact the member of the Institutional Ethics Committee. There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

For further information contact

Dr.Phurailatpam. Priyadarshini.

Post graduate . phone no. 9612169373

Department of obstetrics and gynecology, SDUMC , Kolar.

PATIENT INFORMATION SHEET (KANNADA

ಅಧ್ಯಾನಹೆಸರು

-. EVALUATION OF SERUM MAGNISIUM LEVEL IN PRETERM LABOUR.
ಕೆಳಗಿನಮಾಹಿತಿಯನ್ನುಓದಲುಮತ್ತುನಿಮ್ಮಕುಟುಂಬಸದಸ್ಯರುಚರ್ಚಿಸಬೇಕುದಯವಿಟ್ಟು.ನೀವುಅಧ್ಯಯನಬಗ್ಗೆಯಾವುದೇ ಪ್ರಶ್ನೆಕೇಳಬಹುದು.ನೀವುಅಧ್ಯಯನದಲ್ಲಿಭಾಗವಹಿಸಲುಒಪ್ಪಿದಲ್ಲಿನಾವುನೀವುಅಥವಾನೀವುಅಥವಾಎರಡೂನಿರ್ವಹಿಸುವ ವ್ಯಕ್ತಿರಿಂದ (Proforma ಪ್ರಕಾರ)

ಮಾಹಿತಿಸಂಗ್ರಹಿಸುತ್ತದೆ.ಸಂಬಂಧಿತಇತಿಹಾಸತೆಗೆದುಕೊಳ್ಳಲಾಗುವುದು.ಸಂಗ್ರಹಿಸಿದಈಮಾಹಿತಿಯನ್ನುಪ್ರೌಢಪ್ರಬಂಧ ದಲ್ಲಿಮತ್ತುಪ್ರಕಟಣೆಗೆಬಳಸಲಾಗುತ್ತದೆ.

ನೀವುಸಂಗ್ರಹಿಸಿದಎಲ್ಲಾಮಾಹಿತಿಯನ್ನುಗೌಪ್ಯವಾಗಿಇಡಲಾಗುತ್ತದೆಮತ್ತುಯಾವುದೇಹೊರಗಿನವರಬಹಿರಂಗಮಾಡಲಾ ಗುವುದಿಲ್ಲ. ನಿಮ್ಮಗುರುತನ್ನುತೋರಿಸಲಾಗುವುದಿಲ್ಲ.
ಈಅಧ್ಯಯನವುನೈತಿಕಸಮಿತಿಯವಿಮರ್ಶೆಮತ್ತುನೀವುನೈತಿಕಸಮಿತಿಯಸದಸ್ಯಸಂಪರ್ಕಿಸಲುಉಚಿತ.
ಈಅಧ್ಯಯನದಲ್ಲಿಒಪ್ಪಿಕೊಳ್ಳಲುಯಾವುದೇಕಡ್ಡಾಯಇಲ್ಲ.
ನೀವುಭಾಗವಹಿಸಲುಇಚ್ಛಿಸದಿದ್ದರೆನೀವುಪಡೆಯುತ್ತಾನೆರಕ್ಷಣೆಬದಲಾಗುವುದಿಲ್ಲ. ನೀವು / ಸೈನ್ನೀವುಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದಈಅಧ್ಯಯನದಲ್ಲಿಭಾಗವಹಿಸಲುಒಪ್ಪುತ್ತೀರಿಮಾತ್ರಹೆಬ್ಬೆಟ್ಟಿನಗುರುತುಒದಗಿಸುವಅಗತ್ಯ ವಿದೆ.

ಹೆಚ್ಚಿನಮಾಹಿತಿಗಾಗಿಸಂಪರ್ಕಕ್ಕೆ

Dr. priyadarshini.

ಸ್ನಾತಕೋತ್ತರ

ಪ್ರಸೂತಿಮತ್ತುಸ್ತ್ರೀರೋಗಶಾಸ್ತ್ರಇಲಾಖೆ

* SDUMC, ಕೋಲಾರ

NAME	IP.NO.	AGE	DOA	BOOKED	PARITY	GA	SE STATUS	ANC	RELIGION	S.MG mg/dl	DOD	MOD	SEX	WEIGHT	APGAR 1min	APGAR 5min	NICU
Roopa	286627	26	5/11/2016	unbooked	primi	36+1	low middle	nil	hindu	1.1	5/11/2016	ptvd	male	2.1 kg	6-Jan	8-Jan	yes
chaitra	284323	20	5/5/2016	unbooked	primi	35+1	low middle	nil	hindu	1.2	5/5/2016	ptvd	female	1.9 kg	6-Jan	8	yes
gyathri	229270	26	12/6/2015	booked	primi	35+6	middle	nil	hindu	1.2	12/7/2015	lscs	femlae	2 kg	7	9	yes
shabana	256914	19	12/15/2016	booked	primi	36+4	low middle	nil	islam	1.1	12/15/2016	lscs	male	2.4kg	7	9	mother side
tabassum	229277	25	12/6/2015	unbooked	G2P1	34+6	low middle	nil	islam	1.3	12/6/2015	ptvd	male	i.8kg	6	8	yes
mounika	299697	21	2/6/2016	unbooked	G2P1	35+4	low middle	rh negative	hindu	1.4	2/6/2016	ptvd	female	2kg	7	9	yes
kalavathi	281327	30	5/7/2016	unbooked	G3P2L2	33+2	low middle	nil	hindu	1.6	5/7/2016	ptvd	male	1.7kg	6	8	yes
satya	300021	20	3/10/2016	unbooked	primi	32+3	low	nil	hindu	1.1	3/10/2016	ptvd	male	1.5kg	5	7	yes
preeti	256899	19	2/17/2016	unbooked	primi	33+4	low	nil	hindu	1.2	2/17/2016	ptvd	female	1.76kg	6	8	yes
baby rani	293711	22	3/4/2016	unbooked	G2P1	34+2	low middle	nil	hindu	1.3	3/4/2016	ptvd	male	2kg	6	8	yes
shantama	194322	19	9/11/2015	booked	primi	36	middle	cont pelvis	hindu	1.1	9/12/2015	lscs	male	2.4kg	7	9	mother side
rathnama	197130	22	9/20/2015	unbooked	G2P1	36	middle	nil	hindu	1.3	9/20/2015	ptvd	female	2.3kg	7	9	mother side
anitha	202342	29	10/5/2015	unbooked	G3P2L2	34+1	low	nil	hindu	1.4	10/6/2015	ptvd	male	1.67kg	6	8	yes
pravabathi	206715	20	10/11/2015	unbooked	primi	33+4	low	breech	hindu	1.3	10/11/2015	asst breech	male	1.8kg	6	8	yes
renuka	203038	24	10/14/2015	booked	primi	36+4	low middle	rh negative	hindu	1.1	10/15/2015	ptvd	female	2.5kg	7	8	mother side
radha	214642	25	10/29/2015	unbooked	G3P2L2	35+5	middle	nil	hindu	1.3	10/29/2015	out forcep	male	2.3kg	7	9	mother side
gulzar begum 119591		23	10/31/2015	booked	primi	36+4	upper mid	transvere lie	islam	1.5	10/31/2015	lscs	male	2.5kg	7	9	mother side
sujatha	208502	26	11/10/2015	unbooked	G4P3L2D1	33+2	upper mid	nil	hindu	1.6	11/11/2015	ptvd	female	1.3kg	6	8	yes
archana	226579	19	12/8/2015	booked	primi	35+6	middle	rh negative	hindu	1.5	12/9/2015	lscs	male	2.2kg	7	9	yes
ambika	231037	20	12/9/2015	unbooked	G2P1	34+5	low middle	nil	hindu	1.4	12/10/2015	ptvd	female	2.2kg	6	8	yes
tasmeen	224129	21	11/23/2015	booked	primi	36+4	low middle	rh negative	islam	1.3	11/24/2015	out forcep	male	2.4kg	7	9	mother side
radha bai	229338	27	12/22/2015	unbooked	G4P3L2D1	34+1	low middle	nil	hindu	1.4	12/23/2015	ptvd	female	1.87kg	6	8	yes
asha	237650	22	12/28/2015	unbooked	primi	36+3	middle	transvere lie	islam	1.3	12/29/2015	lscs	male	2.47kg	7	9	mother side
jayama	257226	26	2/19/2016	unbooked	g3P2L2	36+4	middle	nil	hindu	1.5	2/20/2016	ptvd	female	2.5kg	7	9	mother side
rathnama	256911	24	2/29/2016	booked	primi	36+2	upper mid	rh negative	hindu	1.5	6/29/2016	lscs	male	2.48kg	7	9	mother side
bhavya	265900	22	3/25/2016	unbooked	G2P1	33+5	low	nil	hindu	1.4	3/25/2016	ptvd	male	1.79kg	6	8	yes
shobha	280100	23	4/24/2016	booked	primi	36+4	upper mid	breech	hindu	1.5	4/25/2026	lscs	male	2.6kg	7	9	mother side
shashikala	281892	24	5/11/2016	unbooked	G2P1	35+4	middle	nil	hindu	1.4	5/12/2016	ptvd	female	2 kg	7	9	yes
lakshmama	285752	22	5/23/2016	booked	G3P2L2	34+2	middle	nil	hindu	1.3	5/23/2026	ptvd	male	1.9 kg	7	9	yes
gyathri	295280	22	5/30/2016	booked	primi	36+4	low middle	nil	hindu	1.3	5/31/2016	lscs	female	2.3kg	7	9	mother side
shabren taj	250583	19	2/10/2016	unbooked	primi	35+5	low	nil	islam	1.2	2/10/2016	ptvd	male	1.88kg	6	8	yes
ashma	266876	18	3/19/2016	unbooked	primi	35+3	upper mid	nil	islam	1.4	3/20/2016	ptvd	female	2.1kg	7	9	yes
pravavathi	300958	20	6/21/2016	unbooked	G2P1	32+6	upper mid	nil	hindu	1.5	6/22/2016	ptvd	male	1.76kg	6	8	yes
ayesha	281851	18	4/26/2016	unbooked	primi	33+5	low	rh negative	islam	1.4	4/27/2016	out forcep	male	1.8kg	6	8	yes
subha	305359	25	6/29/2016	booked	G2P1	36+5	middle	breech	hindu	1.4	6/29/2016	lscs	female	2.5kg	7	9	mother side
shanta	307018	28	7/7/2016	booked	G3P2L2	36+4	middle	nil	hindu	1.6	7/8/2016	ptvd	male	2.6kg	7	9	mother side
pravathi	308378	24	7/16/2016	unbooked	primi	35+6	upper mid	nil	hindu	1.7	7/16/2016	lscs	female	2.63kg	7	9	mother side
nazma	295345	20	6/2/2016	unbooked	G3P2L2	34+4	low middle	rh negative	islam	1.3	6/2/2016	ptvd	male	1.79kg	6	8	yes
ayesha	405580	19	3/3/2017	unbooked	primi	35+2	upper mid	breech	islam	1.4	3/3/2017	lscs	female	2.1kg	7	9	yes
sulochana	359484	22	11/14/2016	booked	primi	36+4	upper mid	nil	hindu	1.6	11/15/2016	ptvd	male	2.5kg	7	9	mother side
shanaz	322920	21	8/18/2016	unbooked	primi	33+1	low	nil	islam	1.2	8/19/2016	ptvd	female	1.62kg	6	8	yes
baby	451913	26	7/10/2017	booked	G2P1	36+4	upper mid	nil	hindu	1.9	7/11/2017	ptvd	male	2.6kg	7	9	mother side
arfa katum	317756	22	8/4/2016	booked	primi	36+5	upper mid	cont pelvis	islam	1.8	8/5/2016	lscs	female	2.5kg	7	9	mother side
niha begum	343158	18	9/22/2016	unbooked	primi	33+5	low	nil	islam	1.3	9/23/2016	ptvd	male	1.86kg	6	8	yes
savitha	455516	26	7/17/2017	unbooked	G2P1	34+5	upper mid	nil	hindu	1.3	7/17/2017	ptvd	female	1.98kg	7	9	yes
prabhavati	456773	23	7/26/2017	booked	primi	36+5	upper mid	nil	hindu	2	7/26/2017	lscs	female	2.4kg	7	9	mother side
manjula	448823	18	6/29/2017	unbooked	primi	34+2	middle	nil	hindu	1.4	6/29/2017	ptvd	male	1.69kg	7	9	yes
husnna	373123	19	8/12/2016	unbooked	primi	35+4	low middle	nil	islam	1.3	8/12/2016	out forcep	male	2.1kg	6	8	yes
salma	378047	24	12/22/2016	unbooked	G2P1	34+2	low	nil	islam	1.3	12/23/2016	ptvd	female	2kg	7	9	yes
manasa	455516	22	7/10/2017	unbooked	primi	36+4	middle	nil	hindu	1.5	7/10/2017	ptvd	male	2.1kg	7	9	yes

NAME	IP.NO	AGE	BOOKED	PARITY	GA TEST	GA delivery		ANC complications		RELIGION	SE STATUS	MG mg/dl	MOD	SEX	WEIGHT	AGPAR 1min		APGAR 5 min		OUTCOME	
chaitra	456127	24	booked	primi	32+3	38+6		nil		hindu	middle	2.3	ftvd	male	2.7kg	7		9		mother's side	
nithiya	452357	22	booked	G2P1L1	34+2	40+2		nil		hindu	upper mid	1.9	ftvd	female	2.8kg	7		9		mother's side	
rajamma	194920	26	booked	G3P2L2	29+6	38+1		previous lscs		hindu	upper mid	2.4	lscs	male	2.87kg	7		9		mother's side	
swathi	196191	19	booked	primi	30	37+6		nil		hindu	upper mid	2.1	out force	male	3.01kg	7		9		mother's side	
farzana	203407	20	booked	G2P1L1	32+2	38+2		previous lscs		islam	upper mid	2.1	lscs	male	3.15kg	7		9		mother's side	
padmavathi	202121	22	booked	primi	32+6	40+2		nil		hindu	middle	2.2	ftvd	female	2.7kg	7		9		mother's side	
kousalya	203407	21	booked	G2P1L1	34+2	38+4		rh negative		hindu	upper mid	1.9	ftvd	female	2.89kg	7		9		mother's side	
suhail taj	224650	23	booked	primi	30+1	39+5		nil		islam	middle	2.3	ftvd	male	2.97kg	7		9		mother's side	
zaith unisa	209663	19	booked	primi	34+3	38+5		nil		islam	upper mid	2.1	ftvd	female	2.98kg	7		9		mother's side	
kousalya	203407	24	booked	G3P2L2	34+1	39+4		nil		hindu	upper mid	1.9	ftvd	male	3.34kg	7		9		mother's side	
bhavya	205623	28	booked	G2P1L1	33+2	38+6		nil		hindu	middle	2.4	ftvd	female	2.97kg	7		9		mother's side	
aruna	212011	25	booked	G3p2L1D1	30+2	39+1		nil		hindu	upper mid	2.5	ftvd	male	2.79kg	7		9		mother's side	
dilshad	274744	29	booked	G2A1	30+4	37+4		nil		islam	middle	2.1	ftvd	male	3.06kg	7		9		mother's side	
shanta	218852	30	booked	G4P2L2A1	32+3	38+6		nil		hindu	middle	1.9	ftvd	female	3.05kg	7		9		mother's side	
pavithra	211174	22	booked	primi	34+1	39+5		nil		hindu	upper mid	1.9	out force	male	3.4Kg	7		9		mother's side	
lalitha	223759	24	booked	G2A1	35+2	40+1		nil		hindu	middle	1.9	ftvd	female	3.45Kg	7		9		mother's side	
usha	224571	19	booked	primi	29+3	37+6		nil		islam	middle	2.1	lscs	male	2.8kg	7		9		mother's side	
suhasani	221264	26	booked	G3P1L1A1	30+2	38+1		previous lscs		hindu	upper mid	2.1	lscs	female	2.97kg	7		9		mother's side	
somya	195172	22	booked	primi	34+4	38+2		nil		islam	upper mid	1.9	ftvd	male	3.2kg	7		9		mother's side	
ashwini	226544	25	booked	G2P1L1	31+2	38+1		previous lscs		hindu	upper mid	2.4	lscs	female	3.46kg	7		9		mother's side	
pramella	235527	19	booked	primi	32+2	39+3		nil		hindu	middle	2.1	ftvd	male	3.2kg	7		9		mother's side	
manjula	257226	24	booked	G2A1	35+2	40+1		nil		hindu	middle	1.8	ftvd	female	3.1kg	7		9		mother's side	
suma	258143	21	booked	primi	32+1	38+4		rh negative		hindu	middle	2.1	ftvd	male	3.2kg	7		9		mother's side	
usha	256911	19	booked	primi	33+4	39+1		nil		hindu	low mid	1.9	lscs	female	2.8kg	7		9		mother's side	
shashikala	260624	22	booked	primi	32+4	40+1		nil		hindu	middle	2.3	out force	male	3.5kg	7		9		mother's side	
roopa	266097	20	booked	G2A1	35+2	37+5		nil		islam	low mid	1.8	ftvd	female	2.6kg	7		9		mother's side	
muniyama	236773	26	booked	G3P2L2	32+1	38+3		nil		hindu	middle	2.2	ftvd	male	2.8Kg	7		9		mother's side	
shoba	282430	23	booked	primi	33+6	38+4		nil		hindu	upper mid	2.3	vacum	male	3.46kg	7		9		mother's side	
heena kouser 229756	229757	18	booked	primi	34+5	37+6		rh negative		islam	middle	1.8	ftvd	male	2.7kg	7		9		mother's side	

shilpa	257436	23	booked	G2P1L1	29+4	38+5		nil		hindu	middle	2.4	ftvd	female	2.98kg	7		9		mother's side	
farah	231213	27	booked	G3P1L1A1	33+3	38+2		previous lscs		islam	upper mid	1.9	lscs	female	3.3kg	7		9		mother's side	
fathima	233173	19	booked	primi	34+2	37+4		nil		islam	middle	1.8	ftvd	male	2.68kg	7		9		mother's side	
shavama	217736	20	booked	primi	30+2	38+5		nil		hindu	upper mid	2.3	ftvd	female	3.5Kg	7		9		mother's side	
safiya	287402	19	booked	primi	29+5	38+6		nil		hindu	middle	2.3	lsca	male	3.03kg	7		9		mother's side	
amravathi	286537	24	booked	G2A1	30+4	40+3		nil		hindu	upper mid	1.8	ftvd	female	3.4kg	7		9		mother's side	
tasmiya	287437	19	booked	primi	34+3	39+3		nil		islam	middle	1.7	out force	male	2.98kg	7		9		mother's side	
asha	294144	22	booked	G2P1L1	32+4	39+6		rh negative		hindu	middle	1.9	ftvd	female	3.07kg	7		9		mother's side	
sumitra	290011	23	booked	primi	29+2	38+4		nil		hindu	upper mid	2.3	ftvd	male	3.5kg	7		9		mother's side	
radha	300487	26	booked	G3P2L2	30+3	39+6		nil		hindu	middle	2.2	ftvd	female	3.47kg	7		9		mother's side	
somya	300837	20	booked	primi	33+1	40+2		nil		hindu	upper mid	1.9	lscs	male	3.6g	7		9		mother's side	
swetha	302727	26	booked	G3P1L1A1	32+4	38+2		nil		hindu	middle	2.1	ftvd	female	2.98kg	7		9		mother's side	
pavithra	304164	19	booked	primi	30+2	38+5		nil		hindu	middle	2.2	ftvd	male	3.04kg	7		9		mother's side	
asma	308402	19	booked	primi	32+1	39+1		nil		islam	low mid	2	ftvd	female	2.6kg	7		9		mother's side	
gyatri	301239	21	booked	G2P1L1	34+2	38+2		previous lscs		hindu	middle	1.9	lscs	male	3.4kg	7		9		mother's side	
ramya	303576	25	booked	primi	32+2	38+6		nil		hindu	middle	2	lscs	male	2.87kg	7		9		mother's side	
fouziya	386589	19	booked	G2A1	35+4	37+5		nil		islam	upper mid	1.9	ftvd	female	2.58kg	7		9		mother's side	
nandini	339482	26	booked	G2P1L1	32+4	38+1		previous lscs		hindu	upper mid	2	lscs	male	3.5kg	7		9		mother's side	
anitha	384687	20	booked	primi	30+6	39+4		nil		hindu	middle	2.2	ftvd	female	3.3kg	7		9		mother's side	
lakshimi	355455	22	booked	primi	29+3	38+4		nil		hindu	upper mid	2.3	ftvd	male	3.45kg	7		9		mother's side	
sabeena	455675	19	booked	primi	30+2	38+4		nil		islam	middle	2.1	ftvd	female	3.2kg	7		9		mother's side	