"UTILITY OF PREBIOTICS AND PROBIOTICS IN PRETERM AND IUGR BABIES ADMITTED TO TERTIARY CARE HOSPITAL-A PROSPECTIVE INTERVENTION STUDY"

BY

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UNDER THE GUIDANCE OF

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LIST IF ABBREVIATIONS USED

AGA	- APPROPRIATE FOR GESTATIONAL AGE
B.Breve	- BIFIDOBACTERIUM BREVE
B.Lctis	- BIFIDOBACTERIUM LACTIS
CFU	- COLONY FORMING UNIT
CRP	- C-REACTIVE PROTIEN
CNS -	- CENTRAL NERVOUS SYSTEM
CVS	- CARDIOVASCULAR SYSTEM
DIC	- DISSEMINATED INTRAVASCULAR COAGULATION
E-coli	- ESCHERICHIA COLI
E.Sp	- ENTEROBACTER SPECIES
ELBW	- EXTREMELY LOW BIRTH WEIGHT
FFP	- FRESH FROZEN PLASMA
GM/D	- GRAM PER DAY
GA	- GESTATIONAL AGE
GI	- GASTROINTASTINAL
GIT	- GASTROINTASTINAL TRACT
HPF	- HIGH POWER FIELD

H2	- HISTADINE
Hrs	- HOURS
IL	- INTERLEUKINS
INF	- INTERFERON
IVIG	- INTRAVENOUS IMMUNOGLOBULIN
Kg/d	- KILOGRAM PER DAY
LAB	- LACTIC ACID BACILLI
LBW	- LOW BIRTH WEIGHT
L.casei	- LACTOBACILLUS CASEI
L.reuteri	- LACTOBACILLUS REUTERI
L.sporgens	-LACTOBACILLUS SPOROGENS
LGA	- LARGE FOR GESTATIONAL AGE
M-ESR	- MICRO ERYTHROCYTE SEDIMENTATION RATE
µ mole/kg	- MICRO MOLE PER KILOGRAM
µg/g	- MICRO GRAM PER GRAM
µl	- MICROLITRE
NICU	- NEONATAL INTENSIVE CARE UNIT
NHSN	- NATIONAL HEALTHCARE SAFETY
NDI	- NEURO DEVELOPMENT IMPAIRMENT

NNPD	- NEONATAL PERINATAL DATA
NF-KB	- NUCLEAR FACTOR KAPPA B
PDA	- PATENT DUCTUS ARTERIOSUS
PROM	- PREMATURE RUPTURE OF MEMBRANE
ROP	- RETINOPATHY OF PREMATURITY
Sp	- SPECIES
SGA	- SMALL FOR GESTATIONAL AGE
TNF	- TUMOUR NECROSIS FACTOR
Yrs.	- YEARS
CSF	- CEREBRO SPINAL FLUID
IVH	- INTRA VENTRICULAR HAEMORRHAGE
FDA	- FOOD AND DRUG ADMINISTRATION
VLBW	-VERY LOW BIRTH WEIGHT

ABSTRACT

Introduction

Preterm infants are those born before 37 weeks of gestational age. Premature infants, especially very low birth weight (<1500gm) are at risk of neonatal morbidity and mortality and amongst the developing countries India has a very high incidence.

Immaturity of the organ systems of preterm infants makes them more susceptible to complications mainly, feed intolerance, NEC, sepsis, poor weight gain. Prebiotic and probiotic have beneficial effect on preventing complication, so our study was carried out to know the effects of probiotic and prebiotics on feeding intolerance, necrotizing enterocolitis, sepsis and weight gain in premature and IUGR babies admitted to Shri B M Patil medical college vijayapur.

Objectives:

A) To study the effect of introduction of prebiotics and probiotics on feeding intolerance, necrotizing enterocolitis, Sepsis, and overall mortality in preterm IUGR babies.

B) To study the weight gain pattern in above children till they reach the term age (37wks).

C) To compare this group with preterm and IUGR babies not on prebiotic and probiotic (control group).

Method of study

1. All the babies fulfilling inclusion criteria and having no exclusion criteria will be recruited in the study.

2. Alternate babies were given prebiotic and probiotic mixture mixed in the feeds, it was introduced only when they reach 50% of their oral feeds or between 2^{nd} to 5^{th}

days of life. Dose selected was $3.5x10^9$ CFU four times in a day in divided doses, till 37week. preparation was one having multiple organism along prebiotics (FLORA SB {mankind} contains *lactobacillus acidophilus, lactobacillus rhamnosus, Bifidobacterium longum, bifido bacterium bifidum, saccharomyces boulardi, fructo oligo saccharides)* and clinical evaluation for feeding intolerance ,necrotizing enterocolitis, sepsis, investigation was done as required by the clinical status of babies till discharge from NICU.

RESULTS-

Total 162 infants were enrolled. 81 in study group and 81 in control group. probiotic supplementation helps significantly in gaining mean weight in study group. There were no significant difference between two groups with regard to sepsis & NEC but incidence of NEC and sepsis, feed intolerance and good weight gain is better in study group compared to control group and weight gain was better even with morbidities in study group.

Conclusion-

Probiotics and prebiotics appear to be useful in prevention of sepsis, NEC, feed intolerance. Though statistically could not be shown. Weight gain is better in babies with probiotics and was statistically significant.

Key words- Preterm, Probiotic, NEC, Sepsis, Feed intolerance

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INTRODUTION

Premature or preterm infants are those born before 37 weeks of gestational age.[1,]The incidence of preterm births (< 37 weeks gestation) is increasing in many countries around the world and has become a global health concern. Amongst the developing countries India has a very high incidence of 22%.[2]

Low birth weight is associated with prematurity and defined as birth weight<2500g, Premature infants, especially very low birth weight (VLBW)(<1500gm) are at risk of neonatal morbidity and mortality, Immaturity of the organ systems of preterm infants makes them more susceptible to many complications including respiratory distress syndrome, feed intolerance, bronchopulmonary dysplasia, necrotizing enterocolitis (NEC), patent ductus arteriosus, sepsis, anemia, retinopathy of prematurity and intraventricular hemorrhage.[3]In order to survive in extra uterine environment, preterm babies often need special care and extensive support in neonatal intensive care unit.

Among all Necrotizing enterocolitis is one of the major causes of morbidity and mortality in neonatal intensive care units (NICU) which involve 7% to 14% of premature babies weighing less than 1500gm.[4]

Prebiotic and probiotic have been identified in many studies to reduce the prevalence of necrotizing enterocolitis; feeding intolerance, sepsis, and improvement in the weight gain and reduce the mortality in preterm IUGR babies. Prebiotic and probiotics are easily available in market apart from; it may used for other condition like diarrhea and allergy.

Probiotics are supplement or foods that contain viable microorganism that alter the microflora of the host.

Prebiotics are supplement or foods that contain non digestible ingredient that selectively stimulate the growth and /or activity of indigenous bacteria.[5]

The combination of probiotics and prebiotics is called symbiotic.

The improvement of neonatal care has increased the survival rate of premature infants and consequently the incidence of problems like NEC, Sepsis, feeding intolerance leading to poor weight gain and increased mortality. The present study was carried out to know the effects of probiotic and prebiotics on feeding intolerance, necrotizing enterocolitis, sepsis and weight gain in premature and IUGR babies in this hospital.

OBJECTIVES OF STUDY

1. To study the effect of introduction of prebiotics and probiotics on feeding intolerance, necrotizing enterocolitis, Sepsis, and overall mortality in preterm IUGR babies
2. To study the weight gain pattern in above children till they reach the term age (37wks).
3. To compare this group with preterm and IUGR babies not on prebiotic and probiotic (control group).

REVIEW OF LITRATURE

Prematurity –Incidence and definition of LBW

Preterm birth is defined as birth prior to 37 completed weeks of gestation.[1] Incidence-approximately 12.7 % all births in United States are preterm .the distribution this group is gradually shifting to relatively older gestational age because of a 25 % increase in late preterm infants (34-36weeks) since 1990 to current rate of 9.1%.[6]

Nearly 30% of neonates—7.5 million—are born with a LBW (<2500 g) in India.[7]this accounts for 42% of the global burden, the largest for any country. About 60% of the LBW infants are born at term after fetal growth restriction, whereas the remaining 40% are born preterm.[8] The prevalence of SGA is 46.9%, higher than all but two countries in the world (Pakistan and Mauritania have a marginally higher prevalence at 47.0%.[7]Each year, ~ 3.5 million preterm (<38 weeks of gestation) neonates are born in India.[7] Community-based studies indicate that the LBW infants are at 11– 13 times increased risk of dying than NBW infants.43 Indeed, 480% of total neonatal deaths occur among LBW/preterm neonates.[9 , 10]

Definitions.[6]

Small for gestational age-(SGA)

Defined as weight below the 10th percentile for the period of gestation.

Large for gestational age-(LGA)

Defined as a weight, length, or head circumference that lies above the 90th percentile for that gestational age.

Appropriate for gestational age-(AGA)

Defined as weight, length, and head circumference that lies in between 10^{th} percentile and 90^{th} percentile for that age.

ETIOLOGY OF PRETERM -

- **Low social economic status-** measured by family income, education status, geographical area, social class and occupation.
- **Non-Hispanic black-Women** are more than three times as likely to deliver an extremely preterm infants (<28 weeks of gestation) (1.9%) compared with non-Hispanic white and Hispanic women (0.6%).
- **Women younger than 16 or older than 35 more** likely to deliver preterm or LBW infants; the association with age is more significant in whites than in African Americans.
- **Maternal activity** requiring long periods of standing or substantial amounts of physical stress maybe associated with IUGR and prematurity.
- **Acute or chronic maternal illness** is associated with early delivery, whether spontaneous or not infrequently, induced.
- **Multiple gestation births** frequently deliver preterm (60% of twins and 94 % of triplets in United States in 2005).in such births higher rate of neonatal mortality is primarily due to prematurity.
- **Prior poor birth outcome** is the single strongest predictor of poor birth outcome. A preterm first birth is the best predictor of second preterm birth.
- **Obstetric factors** such as uterine-malformations, uterine-trauma, placenta Previa, abruptio placentae, hypertensive disorder, preterm cervical shortening, previous cervical surgery , PROM and chorioamnionitis also contribute to maternal factors.

- **Fetal conditions** such as non-reassuring testing of fetal well-being, IUGR, or sever hydrops may require preterm delivery.
- **Inadvertent early delivery** because of in correct estimation of GA is increasingly uncommon.[6]

The common problems associated with prematurity mentioned below

Table no-1

General	Hypothermia, trans epidermal fluid loss
CNS	Apnea, intraventricular bleed, birth asphyxia
Lung	Respiratory distress syndrome, chronic lung disease,
CVS	PDA,
GIT	Feed intolerance, NEC, cholestasis, intraabdominal bleed, and hyperbilirubinemia.
Hematology	Anemia of prematurity
Immune system	Infections(bacterial,viral,fungal)
Eye	Retinopathy of prematurity(ROP)
Metabolic	Hypoglycemia, hyperglycemia, hypocalcemia, hyperkalemia, acidosis

The preterm gastrointestinal system

Aside from its digestive and absorptive functions, the gastrointestinal (GI) tract is an essential immune organ and the largest defense barrier protecting the host from pathogens, toxins and subsequent inflammation while allowing commensal bacteria to grow.

The GI tract begins to develop at four weeks' GA, facilitated by amniotic fluid, and continues to mature throughout childhood under the influence of dietary and environmental factors.[11] The maturity of this system is directly proportional to GA. The preterm infant's gut is immature in multiple functions including motility, digestion, barrier defense function, intestinal permeability, immune defense and anti-

inflammatory control.[12] The immaturity of these functions can lead to significant pathological symptoms and complications such as feeding intolerance due to dysmotility and bacterial translocation – a phenomenon in which bacteria cross the 'leaky gut' of the premature infant and spread into lymph and blood, causing sepsis and multiorgan failure.[13]

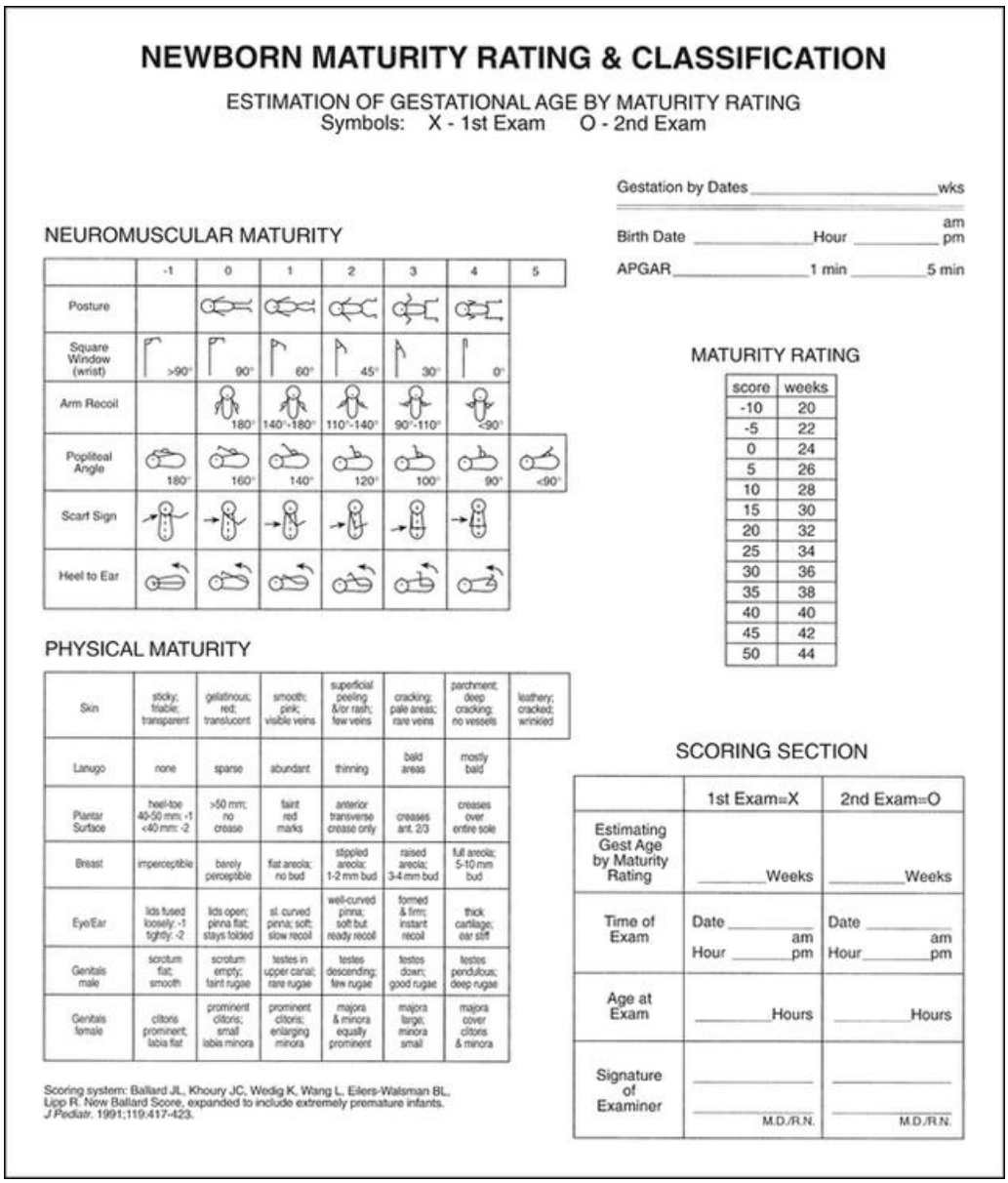
In addition, the production of digestive enzymes, mucus and immunoglobulins is inadequate, which can allow pathogenic invasion and intestinal injury. Furthermore, preterm infants in the neonatal intensive care unit experience delayed initiation of enteral feeding and are exposed to common medications, such as antibiotics and H_2 blockers, all of which cause intestinal atrophy and alter the defense barrier and immunity, allowing epithelial adherence and bacterial translocation.[14]

The micro biome is a complex ecosystem consisting of more than 1000 species of live bacteria that play major roles in nutrition and in the development of the immune system.[15] The development of the neonatal micro biome begins with the exposure of the fetus to microbes in the amniotic fluid.[16] and continues to diversify depending on factors such as GA, mode of delivery, hospitalization, antibiotic use and type of feeding.[17]Unlike the micro biome of the term infant, the preterm infant micro biome is less diverse and is predominated by *Staphylococcus* species, with *Bifido bacterium* species being less well represented.[18]This is due to the fact that preterm infants are primarily treated with a course of broad spectrum antibiotics.[19] Another cause of disequilibrium in the intestinal micro biota is bacterial colonization from the intensive care environment.[20] These changes in the composition of the micro biome of the preterm infant can further alter the development of epithelial barrier mechanisms and gut immune function.

Accumulating evidence has shown that imbalances in intestinal micro biota may enhance certain acute diseases, such as neonatal sepsis and NEC, and may be involved in the initiation of chronic diseases such as type I diabetes, inflammatory bowel disease and obesity.[21-23]

ASSESSMENT OF GESTATIONAL AGE - BASED ON BALLARD SCORING SYSTEM

Table no-2



NEWBORN MATURITY RATING & CLASSIFICATION

ESTIMATION OF GESTATIONAL AGE BY MATURITY RATING
Symbols: X - 1st Exam O - 2nd Exam

Gestation by Dates _____ wks

Birth Date _____ Hour _____ am pm

APGAR _____ 1 min _____ 5 min

NEUROMUSCULAR MATURITY

	-1	0	1	2	3	4	5
Posture							
Square Window (wrist)	>90°	90°	60°	45°	30°	0°	
Arm Recoil		180°	140°-180°	110°-140°	90°-110°	<90°	
Popliteal Angle	180°	160°	140°	120°	100°	90°	<90°
Scarf Sign							
Heel to Ear							

PHYSICAL MATURITY

Skin	sticky; friable; transparent	gelatinous; red; translucent	smooth; pink; visible veins	superficial peeling &/or rash; few veins	cracking; pale areas; rare veins	parchment; deep cracking; no vessels	leathery; cracked; wrinkled
Lanugo	none	sparse	abundant	thinning	bald areas	mostly bald	
Plantar Surface	heel-toe 40-50 mm: -1 <40 mm: -2	>50 mm; no crease	faint red marks	anterior transverse crease only	creases ant. 2/3	creases over entire sole	
Breast	imperceptible	barely perceptible	flat areola; no bud	stippled areola; 1-2 mm bud	raised areola; 3-4 mm bud	full areola; 5-10 mm bud	
Eye/Ear	lids fused loosely: -1 tightly: -2	lids open; pinna flat; stays folded	sl. curved pinna; soft; slow recoil	well-curved pinna; soft but ready recoil	formed & firm; instant recoil	thick cartilage; ear stiff	
Genitals male	scrotum flat; smooth	scrotum empty; faint rugae	testes in upper canal; rare rugae	testes descending; few rugae	testes down; good rugae	testes pendulous; deep rugae	
Genitals female	clitoris prominent; labia flat	prominent clitoris; small labia minora	prominent clitoris; enlarging minora	majora & minora equally prominent	majora large; minora small	majora cover clitoris & minora	

Scoring system: Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr. 1991;119:417-423.

MATURITY RATING

score	weeks
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

SCORING SECTION

	1st Exam=X	2nd Exam=O
Estimating Gest Age by Maturity Rating	_____ Weeks	_____ Weeks
Time of Exam	Date _____ Hour _____ am pm	Date _____ Hour _____ am pm
Age at Exam	_____ Hours	_____ Hours
Signature of Examiner	_____ M.D./R.N.	_____ M.D./R.N.

NECROTIZING ENTEROCOLITIS

Definition –

NEC is an acute inflammatory necrosis of gastrointestinal tract.

Necrotizing enterocolitis is one of the major causes of morbidity and mortality in neonatal intensive care units (NICU) which involve 7% to 14% of premature babies weighing less than 1500g.[4]The National Healthcare Safety Network (NHSN) updated the clinical and surgical criteria for the diagnosis of NEC. These updated criteria stated that for an infant to be diagnosed with NEC based on clinical and radiographic criteria, they must present with bilious aspirate, vomiting, abdominal distension, or occult blood in stool, plus one or more of the following radiographic signs: pneumatosis intestinalis, which is gas in the bowel wall, portal venous gas, or pneumoperitoneum.[24]Furthermore, the surgical criteria for NEC are that the infant must have more than two centimeters of necrotic bowel or surgical evidence of pneumatosis intestinalis, with or without intestinal perforation.[24]

It has been hypothesized that NEC results from the interaction between prematurity and hypoxic ischemic events in the perinatal period, which include low Apgar score, enteral feeding, episodes of apnea and administration of Indomethacin.[25] Although the exact etiology of NEC is not well understood, pathogenesis is believed to be due to a multifactorial process that is related to one or more of the following:

- Hypoxic ischemic events
- Immaturity and dysfunctionality of the GI tract (e.g. impaired peristalsis and disruption of tight junctions)
- Altered micro biota and
- Enteral feeding.[26]

The net result of the interaction among these factors is the invasion of the intestinal wall by bacteria, followed by bacterial translocation and release of inflammatory mediators. Other factors that may contribute to the development of NEC include-

- Insufficient production of epidermal growth factor, an enzyme responsible for cell proliferation and differentiation
- Additional stimulation of platelet-activating factor, a phospholipid inflammatory mediator
- Increased production of nitric oxide, a vasodilator and free radical molecule.[27,28]

During hypoxic ischemic events, it has been postulated that blood is shunted from the bowel to vital organs, such as the brain, and the reperfusion of blood to the intestine provokes a pro-inflammatory cytokine cascade in the gut.[29] The release of pro-inflammatory cytokines further disrupts tight junctions, causing an increase in intestinal permeability and, therefore, bacterial translocation.[29,30] Moreover impaired peristalsis of the preterm intestine may allow more time for the carbohydrate from enteral feeding to serve as bacterial substrate, thereby leading to bacterial invasion of the intestinal wall and inflammation.

Another important factor is the compromise of serum immunoglobulin A production, which eventually eases bacterial translocation.[29,30]The use of antibiotics, in addition to the previously mentioned factors, facilitates the proliferation of pathogenic bacteria, which may then induce a hyper immune inflammatory response in the preterm infant intestine causing intestinal necrosis.[29] The use of breast milk and

probiotics are potential preventive strategies to reduce the incidence of this devastating complication.[28]

DIAGNOSIS AND CLASSIFICATION OF NECROTIZING ENTEROCOLITIS BASED ON BELL'S STAGING.

Table no-3

Stage	Classification	Intestinal Signs	Radiologic Signs	Radiologic Signs
IA	Suspected NEC	Decreased gastric emptying, Abdominal distention, Emesis	Normal or Intestinal obstruction	Temperature instability, apnea, Bradycardia, lethargy
IB	Suspected NEC	Bright red blood from rectum	Same as IA	Same as IA
IIA	Proven NEC-mild	Same as IA plus Absent bowel sound, with or without abdominal tenderness	Intestinal dilatation ,ileus, and, Pneumatosis intestinalis	Same as IA
IIB	Proven NEC-moderate	Same as IIA with Definite abdominal Tenderness and with or without right lower lobe quadrant mass	Same as IIA plus portal venous gas , with or without ascites	Same as IA plus mild metabolic acidosis and thrombocytopenia
IIIA	Advanced NEC bowelintact Requires surgery.	Same as IIB with generalized peritonitis, marked tenderness, and distention of abdomen	Same as IIB with definite ascites	Same as IIB with hypotension, bradycardia, apnea, respiratory and metabolic acidosis and neutropenia
IIIB	Advanced NECbowelperforation Requires Surgery.	Same as IIIA	Same as IIB with pneumoperitoneum	Same as IIIA

Treatment of Necrotizing Enterocolitis-

Treatment of NEC ranges from bowel rest for suspected NEC, the use of antibiotics along with bowel rest for proven but mild NEC, to surgery for advanced NEC. When NEC progresses into the "advanced" stages of NEC and requires surgery, it is termed "surgical NEC" and the Long-term prognosis for the infant decreases. Long-term ramifications of surgical NEC include short bowel syndrome and neurodevelopment impairment (NDI).[31]Due to its costly and deadly nature, an effective preventative strategy needs to be further researched and implemented.[32].

There are multiple proposed strategies for the prevention of NEC. These strategies include antenatal corticosteroids, which have been shown to mature the gut in a manner similar to the mechanism enhancing lung maturation; trophic feedings in which small volumes of enteral feedings are introduced in order to facilitate peristaltic action; oral antibacterial, in an effort to reduce the number of pathogenic bacteria; and prebiotics, used to selectively increase the population of commensal GI bacteria. And lastly, the use of probiotics, thought to be the most promising of therapies, and the focus of this literature review.[33]

Neonatal septicemia

Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms 0f infection in first four weeks of life. Neonatal septicemia is the most important cause of morbidity and mortality especially among LBW and preterm babies in developing countries.

When clinical and laboratory findings are consistent with bacterial infection but blood culture is sterile, infant is labeled to have "probable sepsis" .

According to NNPD (neonatal-perinatal data) the incidence of neonatal sepsis is around 30 per 1000 live births. Neonatal sepsis is divided in to two subtypes based on whether the onset is during first 72 hrs. or later.

Early onset of sepsis is caused by the organism mainly present in the genital tract or in the labor room and maternity operation theater.in west most prevalent organism is Group B streptococci and E coli,while in our setup most cases are due to gram negative organism especially E.coli, Klebsiella,and Enterobacter sp.

When two or more fallowing high risk factors present, the baby is considered to be treated with appropriate antibiotics.

- Presence of foul smelling liquor
- Febrile illness in mother during or within two weeks of delivery
- Prolonged rupture of membrane (>18hrs).
- Single unclean or more than three veginal examinations during labor.
- Prolonged labor (>24hrs both stages) and difficult delivery with instrumentation.
- Birth asphyxia and difficult resuscitation.
- Pathological evidence of funisitis or presence of polymorphs (>5/HPF) in gastric aspirate.

Late onset of sepsis defined as the onset of sepsis is delayed for 72 hrs after birth. Mainly organism acquired from the nursery or postnatal ward.

Most common organism responsible are Gram negative bacilli viz. Klebsiella pneumonia, enterobacteria E. Coli, pseudomonas aeruginosa, Salmonella typhimurium, Proteus SP, Citrobacter and serratia while the rest are contributed by

Gram positive organism including coagulase positive staphylococcus aureus and coagulase negative staphylococci.

The manifestations of neonatal septicemia are often vague and therefore high index of suspicion for early diagnosis (table no).the most common and characteristic manifestation is an alteration established feeding behavior in late onset sepsis and respiratory distress in early onset.

Clinical manifestations

Table no-4

Lethargy	Cyanosis*
Refusal of feed	Tachypnea*
Poor cry	Chest retractions*
Abdominal distention	Grunting*
Diarrhea	Apnea/gasping*
Vomiting	Seizures+
Hypothermia	Blank look+
Poor perfusion	High pitched cry+
Sclerema	Irritability+
Shock	Bulging fontanelle +
Bleeding	Neck retractions+
Renal failure	

*Particularly suggestive of pneumonia.

+particularly suggestive of meningitis.

Diagnosis and screening of neonatal sepsis

Table no-5

Parameter	Abnormal values
Total count	<5000mm3
Absolute neutrophil count	Low count as per Manroe chart for term and Mouzhino chart for VLBW babies
Immature or band cell to total neutrophil ratio	>0.2
Micro-ESR	>10mm 1st hr
C-reactive protein	>1mg/dl
Blood culture	positive

- Sepsis screen is consider to be positive when 2 or more parameters are positive
- When initial screen is negative, it should be repeated after 12-24hrs when clinical suspicion of infections strong. When repeat sepsis screen is also negative, the diagnosis of sepsis can be excluded with reasonable certainty.
- In early onset sepsis , polymorphs in the gastric aspirate as a marker of chorioamnionitis, can be used as an additional parameter of sepsis screen
- Culture should be taken before starting the antibiotic therapy. And blood culture is considered to be gold standard for diagnosis of sepsis but it is positive only in 60% of patients.
- Lumbar puncture should always be done in a suspected case of late onset of sepsis except when the infant is too sick to undergo the procedure.

Management of neonatal sepsis

The rational use of antimicrobial agents in neonatal sepsis is governed by the knowledge of the prevalent bacterial flora of particular newborn NICU and there sensitivity battle against available antibiotics. The initial regimen must cover the most common pathogens. It should be borne in mind that there can be no single universal recommendation for the antimicrobial regimen. Each treating unit should adopt a suitable protocol on the basis of considerations highlighted above. Based on changes in the spectrum of etiologic agents. In the rural setting where antimicrobial resistance is less likely to be a problem, rational choice of antibiotic would include a combination of kanamycin or gentamicin (aminoglycoside) with Benzyl penicillin or ampicillin. Gentamicin 4mg/kg single-dose per day intramuscularly is effective for ambulatory management of neonatal sepsis in the community.

The most common organisms causing Sepsis in most in NICU are E. coli, Klebsiella, Enterobacter and Staphylococcus aureus. The initial antibiotic regimen must cover these pathogens. The logical initial choice would be a combination of an Aminoglycoside and Ampicillin or Cefazolin or Cloxacillin. The new were antibiotic preparation, like Tobramycin, Netilmicin, Vancomycin, cefotaxime, Ceftriaxone, Ceftazidime, Cefeperazone, Cefepime, and Imipenem should be kept in mind for treatment of meningitis and life-threatening infections. In centers with high incidence of resistance to third generation Cephalosporins and emergence of extended spectrum beta lactamase positive organisms, Piperacillin -Tazobactum or Methicillin-Vancomycin are drug of choice. Ciprofloxacin should be used in a last resort in critically sick babies when bacterial isolates are resistance to all other antibiotics.

In desperate situations, newer antibiotics like Azitronam, and Meropenem may be used. Is it true name has excellent activity against gram negative organisms while Meropenem is effective against most bacterial and pathogens except methicillin resistant staph aureus and Enterococcus. Imipenem is generally avoided in newborn baby is due to risk of seizures.

Duration of antibiotic therapy in neonatal sepsis

Table No -6

Diagnosis	duration
Culture and sepsis screen negative but clinical picture is suggestive of sepsis	5-7 days
Sepsis screen is positive blood/CSF culture negative	7-10 days
Blood culture positive but no meningitis	10-14 days
Meningitis (irrespective of culture report)	21 days
Arthritis, osteomyelitis and endocarditis	4-6 weeks
Ventriculitis	6 weeks
*efforts should be made to administer antibiotics intravenously as long as feasible	

Immunotherapy–

Exchange blood transfusion in infected babies can theoretically help to achieve improved peripheral and pulmonary confusion, correction of coagulation abnormalities and removal of toxins; and provide specific antibodies, compliment and phagocytic cells. The procedure is recommended in critical sick babies with Sclerema, DIC and Hyperbilirubinemia. Controlled studies are, however needed to further evaluated the therapeutic utility of exchange blood transfusion.

Granulocyte transfusion ($1X10^9$granulocytes/kg) is recommended as an adjunct to immunologic therapy for septic newborn infants with neutropenia and has been used successfully in a limited number of infected babies to decrease the mortality.

Immunoglobulin preparations containing type-specific monoclonal antibody is to group the Group B Streptococci have been shown to be beneficial. There is evidence to suggest that administration of single dose of non-specific IVIG (750 mg/kg) in critically sick preterm infants (1gm/kg for term) with sepsis is associated with improved survival. In future specific immunoglobulins harnessed in donors or produced by monoclonal antibody technic are likely to be used.

Complication

Table no-7

Meningitis Pneumonia Pyelonephritis DIC	Osteomyelitis and septic arthritis Shock Sclerema NEC

Prognosis-

Outcome depends upon weight and maturity of the infant, type of etiologic agent and it's antibiotic sensitivity pattern; and adequacy of specific and supportive therapy.

Associated congenital malformations light meningomyelocoel, tracheoesophageal fistula and surgical procedure, adversely affecting prognosis. The early onset septicemia due to Group B Streptococcus and nosocomial infections due to Klebsiella and Pseudomonas Aeruginosa are associated with adverse outcome . Early and aggressive therapy is mandatory for improved salvage because extension of infection into various body organs and development of complications such as Endotoxic Shoock, Sclerema, NEC, and DIC is associated with extremely high mortality.

The reported mortality rates in neonatal sepsis in various studies from India range between 15 and 50%. Early institution of specific antimicrobial therapy with the help of sepsis screen, excellent supportive care, close monitoring of vital signs, and judicious use of fresh blood, FFP and immunotherapy is likely to improve their outcome of units with septicemia. [34].

Feed intolerance-

Definition-

The inability to digest enteral feedings presented as gastric residual volume more than 50%, abdominal distention or emesis of both, and the disruption of the patient's feeding plan.[35]

Feeding intolerance is one of the most important factors of growth failure in preterm infants.Establishing and tolerating adequate enteral nutrition is difficult due to the immaturity of the preterm infants' gastrointestinal system; however, it is important for their normal growth, infection resistance, and long-term cognitive and neurologic development.

Clinical evidence of feeding tolerance in the preterm infant was most often described in the literature as the number of days required to reach full-feeding volumes (reported ranges from 100 to 160 millimeters per kilogram per day), the number of episodes of feeding intolerance, the number of days feeds are withheld due to feeding intolerance symptoms, time to regain birth weight, lower leg growth, and increase in weight gain, occipital-frontal head circumference, and length.[36, 37]

Feed intolerance usually associated with fallowing symptoms like gastric residuals, emesis, abdominal distention, visible bowel loops, and blood in stool.

Apnea, bradycardia, and temperature instability are also included as symptoms of feeding intolerance but solely for the purposes of the nursing assessment in order to provide guidance on identification of potential progression to more serious complications such as pneumatosis intestinalis and necrotizing enterocolitis.[35]

There are number of studies which show that prebiotic and probiotic therapy in prevention and treatment of feed intolerance.

Mechanism of action of prebiotic and probiotic in prevention of feed Intolerance –

Probiotic bacteria improve health by affecting the immune system in different ways. It increases cytokine production such as Interleukin-6 (IL-6), Interferon-gamma (IFN-γ), Tissue Necrosis Factor – alpha (TNF-α), Interleukin-1beta (IL-1β) and Interleukin-10 (IL-10).[38]some strains increase phagocytic activity of peripheral blood leukocytes (monocytes, polymorph nuclear cells).

Other strains strengthen the mucosal barrier function by promoting the production of mucosal antibodies and reducing the trans mucosal transfer of antigens. This reduces the intestinal permeability which in turn promotes growth.[39, 40, 41, 42]

Probiotics bacteria also enhance production of low molecular weight antibacterial substances produced by epithelial cells and production of short chain fatty acids, the main energy source for colonocytes. This maintains the integrity of colon mucosa.[39, 43, 44,, 45, 46]

Probiotic

Definition –

Probiotics are supplements or foods that contain viable microorganisms that alter the microflora of the host.

The Greek meaning of the word probiotic is for life. Which are viable live microorganisms when administered in adequate amounts confer a health benefit on the host. Several lactococci, lactobacilli and bifid bacteria are held to be health benefiting bacteria but little is known about the probiotic mechanism of gut microbiota.[47]

Lactic acid bacteria or LAB constitute an integral part of the healthy gastrointestinal microceology and are involved in the host metabolism.[48]Fermentation has been specified as a mechanism of probiotics.[47] Probiotics along with other gut microbiota ferment various substrates like lactose, biogenic amines and allergenic compounds into short chain fatty acids and other organic acids and gases.[47,49,50].LAB synthesizes enzymes, vitamins, antioxidants and bacteriocins.[48,51] With these properties, intestinal LAB constitutes an important mechanism for the metabolism and detoxification of foreign substances entering the body.[52]

Probiotics - properties

Probiotics have been suggested to have the following properties and functions:-

Adherence to host epithelial tissue, acid resistance and bile tolerance, elimination of pathogens or reduction in pathogenic adherence, production of acids, hydrogen peroxide and bacteriocins antagonistic to pathogen growth, safety, nonpathogenic and non-carcinogenic, and Improvement of intestinal microflora.[53]

Influencing factors for the functionality of probiotics-

Several factors are there, which technically support and influencing the function of probiotics. Among them most important are strain characteristics, stability, fermentation technology, target prebiotics, viability and non-viability, microencapsulation etc.

Mechanisms of Action-

In preterm infants, probiotic supplementation can allow acquisition of normal commensal flora in a host where this process has been delayed or support the transition to an intestinal microbiome with beneficial microbes, particularly in hosts where this process has been disrupted. Several mechanisms of probiotic action may explain how their therapeutic use can help prevent NEC. These mechanisms include enhancement of epithelial barrier function, competitive exclusion of pathogens, and direct anti-inflammatory effects on epithelial signaling pathways.[54–56]

At the cellular level, probiotics have a number of important effects (Figure 2)

1) Attenuation of NF-κB activation, a major pro-inflammatory pathway.[57]
2) Up regulation of cytoprotective genes.[58,59]
3) Prevention of apoptosis and cell death.[59,60]

4) Generation of reactive oxygen species important in cell signaling.[61,62]
5) Induction of the expression of tight junction proteins necessary for barrier function.[63, 64]

Whether live microorganisms, instead of killed or inactivated bacteria or bacterial products, are required for these beneficial effects remains an important area of study and recent data suggest that bacterial products, in the absence of viable organisms, may have similar effects on signaling pathways.[65] and barrier function.[63]

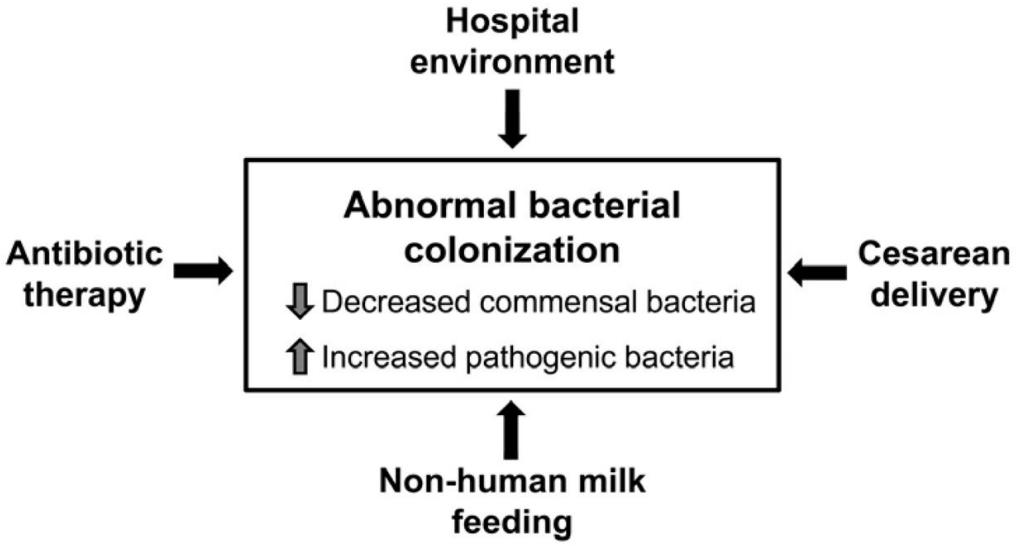


Figure 1 : Factors influencing abnormal intestinal bacterial colonization in preterm infants

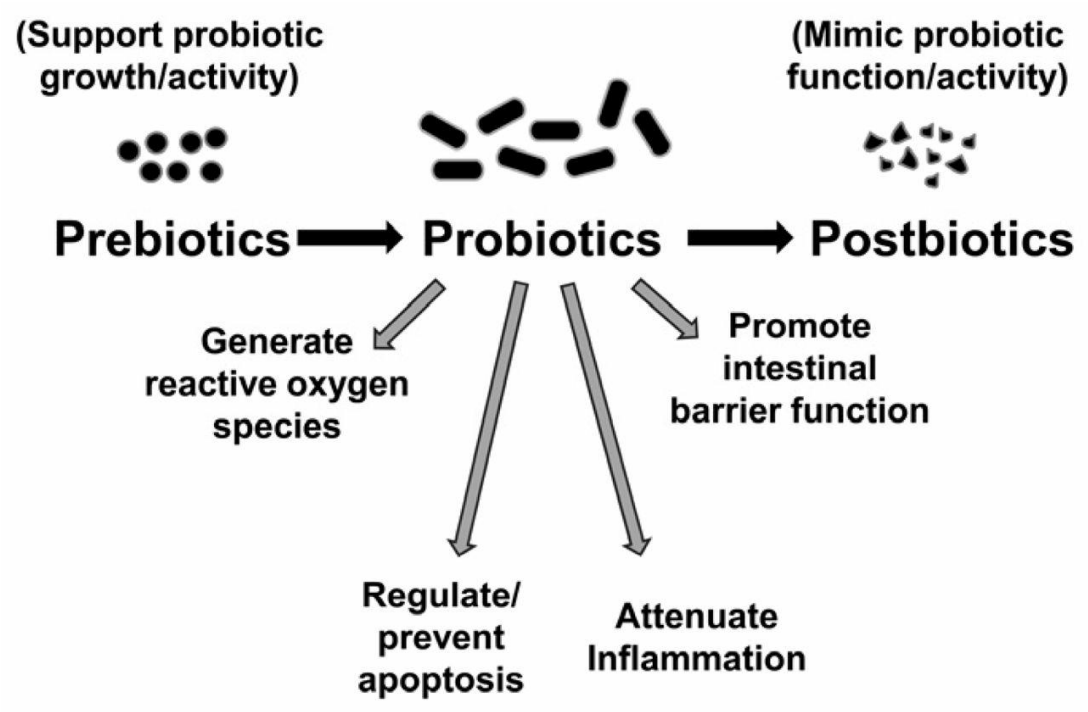
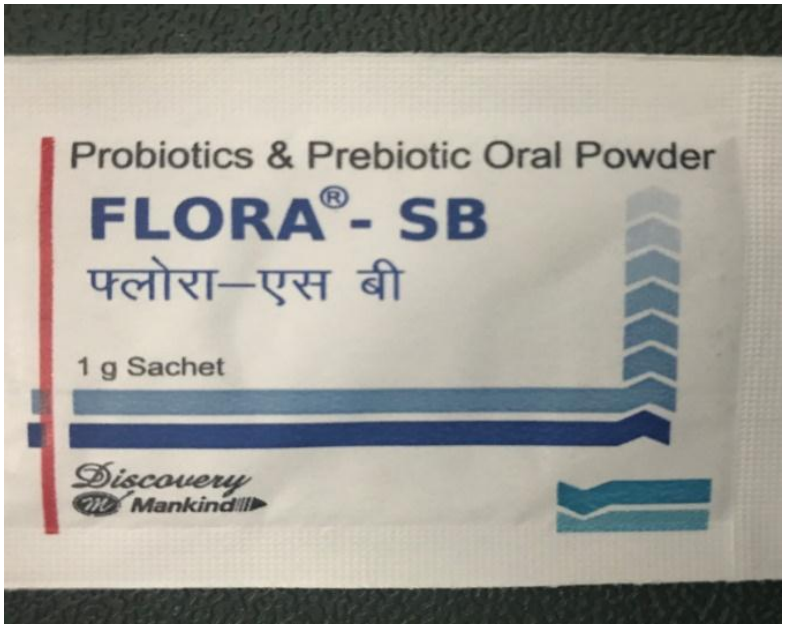


Figure 2 :Mechanisms of action of probiotics at the cellular level in intestinal epithelia.

Figure No 3 :



Probiotic strained in study

Figure No-4 :

Preterm LBW Baby

Prebiotics-

Definition-

Prebiotics are supplements or foods that contain a non-digestible ingredient that selectively stimulates the growth and/or activity of indigenous bacteria.

The concept of prebiotics came to light during mid-nineties of the twentieth century.[66]Prebiotics pass through the digestive system without being broken down by the digestive enzymes *i.e.* reach the large intestine in an intact form. Once these non-digestible carbohydrates pass into the intestines, they serve as a feast for the probiotic bacteria that live there.

Prebiotics of proven efficacy are able to modulate the gut microbiota by stimulating indigenous beneficial flora while inhibiting the growth of pathogenic bacteria therein. Preferred target organisms for prebiotics are species belonging to the *Lactobacillus* and *Bifidobacterium* genera. The most common prebiotics are oligosaccharides, which are found in human milk.

For the food ingredient to be classified as a prebiotic, the following three criteria have been defined:

- The food ingredient must not be hydrolyzed or absorbed in the stomach or small intestine
- It must be selective for beneficial commensal bacteria in the colon by encouraging the growth/metabolism of the organisms;
- It will alter the microflora to a healthy composition by inducing beneficial luminal/systemic effects within the host.

Any food substrate that enters the colon may be a potential prebiotic, however, selective fermentation is a necessary determinant. Much of the early and present work

on prebiotics has been carried out in Japan. The search for bifidobacteria promoting substances began by screening a range of carbon sources for their ability to increase these organisms in pure culture. For example, Yazawa *et al.* (1978) screened a range of dietary carbohydrates for their ability to promote bifidobacteria in comparison to other intestinal isolates.[67]Further studies used mixed culture, animal models and human trials to determine the efficacy of oligosaccharides to modulate the gut flora composition.

Synbiotic-

Symbiotic is a product that contains both probiotics and prebiotics. It is nothing but the synergy between probiotic and prebiotic effect in the GI tract or in other words, synbiotic is the usage of both probiotics and prebiotics in combinations. Indeed synbiotic combinations are considered to have more beneficial effects on human health than probiotics or prebiotics alone.

Recent studies established that synbiotics improve the intestinal microbial environment and activate host immune function, leading to prevention of bacterial translocation.

Different studies regarding probiotic and prebiotic usage in neonates and their results.

Deshpande G, Rao S[68]conducted a study called Updated metanalysis of probiotics for preventing necrotizing enterocolitis in preterm neonates in the year of 2010 showing the result that risk for NEC and death was significantly lower in prebiotic and probiotic group. Risk for sepsis did not differ significantly. No significant adverse effects were reported. Trial sequential analysis showed 30% reduction in the incidence of NEC.

Susan M Garland, Jacinta M Tobin[69]conducted a study multi-center, prospective, randomized, double blind, placebo controlled trial investigating the treatment of very preterm infants with a probiotic combination comprising *Bifidobacterium infantis, Streptococcus thermophilusand Bifidobacterium lactis* In the year 2011 a total of 1100 subjects were included in the study in different centers of Australia and new Zealand showing results from previous studies on the use of probiotics to prevent diseases in preterm infants are promising. However, a large clinical trial is required to address outstanding issues regarding safety and efficacy in this vulnerable population.

Carole Rouge´, Hugues Piloquet[70], conducted a study in the year of 2009 , Oral supplementation with probiotics in very-low-birth-weight preterm infants: a randomized, double-blind, placebo controlled trial supplementation with *Bifidobacterium longum & Lactobacillus rhamnosus* GG (BB536-LGG) may not improve the gastrointestinal tolerance to enteral feeding in very-low-birthweight infants but may improve gastrointestinal tolerance in infants weighing >1000 g.

Taciana Duque Braga, Giselia Alves Pontes da Silva,[71]conducted astudy in 2011 A double-blind, randomized, controlled clinical trial was conducted in 231 preterm infants weighing from 750 to 1499 g at birth showed that oral supplementation of *B. breve* and *L. casei* reduced the occurrence of NEC (Bell's stage >2).

Mary N Mugambi , Alfred Musekiwa[72], conducted a study in the year 2012 named Probiotics, prebiotics infant formula use in preterm or low birth weight infants concluded that there is not enough evidence to suggest that supplementation with probiotics or prebiotics results in improved growth and clinical outcomes in exclusively formula fed preterm infants.

Mihatsch, Vossbeck,Eikmanns,[73]A Randomized Controlled Trial Effect of *Bifidobacterium lactis* on the incidence of nosocomial infections in Very-Low-Birth-Weight Infants. There were 93 infants in the *B. lactis* group and 90 in the placebo group, there was no significant difference between the two groups with regard to the incidence density of nosocomial infections (0.021 vs. 0.016; p = 0.9, x 2 test).There were 2 cases of NEC in the *B. lactis* group and 4 in the placebo group concluded that in the present setting, *B.lactis* at a dosage of 6 ! 2.0 ! 10 9 CFU/kg/day (12 billionCFU/kg/day) did not reduce the incidence density of nosocomial infections in VLBW infants. No adverse effect of *B. lactis.*

Hung-Chih Lin, Bai-Horng Su, An-Chyi Chen[74]conducted a study in 2005 a randomized control trial was conducted to evaluate the beneficial effects of probiotics in reducing the incidence and severity of NEC among VLBW (<1500 g) infant. The strains used in the study (*Lactobacillus acidophilus* and *Bifidobacterium infantis).* A total of 367 infants were enrolled in the study 180 in the study group and 187 in the control group, the incidence of death or NEC (≥ stage 2) was significantly lower in

the study group (9 of 180 vs 24 of 187), the incidence of NEC (≥ stage 2) was also significantly lower in the study when compared with the control group (2 of 180 vs 10 of 187)and there were 6 cases of severe NEC (Bell stage 3) in the control group and none in the study group. None of the positive blood culture grew Lactobacillus or Bifidobacterium species. The overall results showed that probiotics fed enterally with breast milk reduce the incidence and severity of NEC in VLBW infants.

Studies related to prebiotic and probiotic supplementation in preterm infants in related to feed intolerance duration of NICU stay, mean weight gain and mortality -

Carole Rouge´, Hugues Piloquet, Marie-Jose´ Butel[70]conducted a study in preterm infants in 2009 supplementation with Bifidobacterium longum, Lactobacillus rhamnosus GG may not improve the gastrointestinal tolerance to enteral feeding in extremely -low-birth weight infants but may improve gastrointestinal tolerance in infants weighing >1000 g.

Sari FN et al.[75]in the year of 2010 total to 221 babies enrolled in the study group, and this study showed that feed intolerance was significantly lower in the pre-and probiotic group as compared to control group but single strain (L.sporogens)) probiotic was used in this study as compared to our study we have used mixture of multiple strain or organism..

Rojas MA et al[76]in 2009 also found that duration of NICU stay was less in probiotic group than the placebo (p-0.04).

Moni S.C. et all.[77]conducted a study in 2015 also showed that the duration of stay was less in probiotic group compared to placebo group which was statistically significant and weight gain was good in probiotic group which was statistically significant(p-0.000).

Wang Q et al[78] in his trial of probiotic in preterm babies and NEC shows that mortality rate was less in preterm VLBW babies treated with pre and probiotics compared with placebo group

Yang Y. et al [79] as shown that two trials with 205 babies in cases and 199 baby is in control group, studied weight gain in this group and they didn't found any statistical difference between the two groups but there was a significant heterogeneity among these two trials.

METHODOLOGY

MATERIALS AND METHODS-

Prospective interventional study .

SOURCE OF DATA:

Preterm babies less than 37 weeks of gestational age and less than 2000grams of birth weight admitted or referred to NICU, Department of Pediatrics at B.L.D.E.U's Shri. B. M. Patil Medical College Hospital and Research Centre, Vijayapur.

STUDY PERIOD-

November 2015 to August 2017

Sample size calculation : With the incidence of necrotizing enterocolitis (stage >2) in the study group 3.2% and in control group 7.2% @ 99.9% confidence level and at 90% power in the study, the sample size is 81.

$$n = \frac{(z_\alpha + z_\beta)^2 \times 2 \times p \times q}{d^2}$$

z_α = Z value at α level

z_β = Z value at β level

p= incidence ratio

q=1-p

d= difference between two parameters

hence 81 cases and 81 controls will be included in the study.

Statistical analysis:

Data was analyzed using

- Mean ± SD
- Diagrams
- Relative risk
- Odds ratio

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries. Chi-square (χ^2)/ Freeman-Halton Fisher exact test was employed to determine the significance of differences between groups for categorical data. The difference of the means of analysis variables between two independent groups was tested by unpaired t test. The difference of the means of analysis variables between more than two independent groups was tested by ANOVA and F test of testing of equality of Variance. f the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23.0. and Microsoft office.

Selection criteria-

Inclusion Criteria: All preterm babies more than 30 weeks but less than 37weeksof GA and less than 2000gms of birth weight delivered in or referred to Department of Pediatrics at B.L.D.E.U's Shri. B.M. Patil Medical College Hospital and Research Centre and admitted in NICU, Vijayapur.

Exclusion Criteria:

1. Babies having congenital anomalies of gastrointestinal tract or multiple anomalies (except ASD and VSD)

2. Babies with suspected chromosomal anomalies or other syndromes.

Consent and ethical clearance:

Informed and written consent of parents was taken after explaining in detail about the methods and procedure involved in the study in their own vernacular language.

Ethical clearance was obtained from Institutional Ethical committee.

Method of study:

1. Proforma was designed to collect the relevant information regarding the mother(antenatal history birth history) and condition of the baby at the time of admission to NICU till discharge and fallow up till 37 week.
2. All the babies fulfilling inclusion criteria and having no exclusion criteria were recruited in the study.
3. Alternate babies were given prebiotic and probiotic mixture mixed in the feeds, it was introduced only when they reach 50% of their oral feeds or between 2^{nd} to 5^{th}days of life. Dose selected was $3.5x10^9$ CFU four times in a day in a divided doses, till 37week . preparation was one having multiple organism along prebiotics (FLORA SB {mankind} contains lactobacillus acidophilus, lactobacillus rhamnosus, Bifidobacterium longum, bifido bacterium bifidum, saccharomyces boulardi, fructo oligo saccharides) and this

was given till 37 weeks of life then daily weight record and clinical evaluation for feeding intolerance, necrotizing enterocolitis, sepsis, investigation was done as required by the clinical status of babies till discharge from NICU.

4. Patients were fallowed up in HIGH RISK clinic weekly till they reach 37week of life apart complete examination babies, their weight, was measured and recorded. Based on the clinical status of infant further advise was given.
5. Those patients who were lost for fallow up, on one occasion were contacted on phone to improve the fallow up. In case there were defaulters they were asked about the wellbeing or otherwise and details were noted. In case the baby was well if the patient recorded weight anywhere else was noted. In case this information was not available they were not considered in the fallow up list.

Instrument used:

Digital weighing machine–Phoenix e=10gm(minimum 200gm)

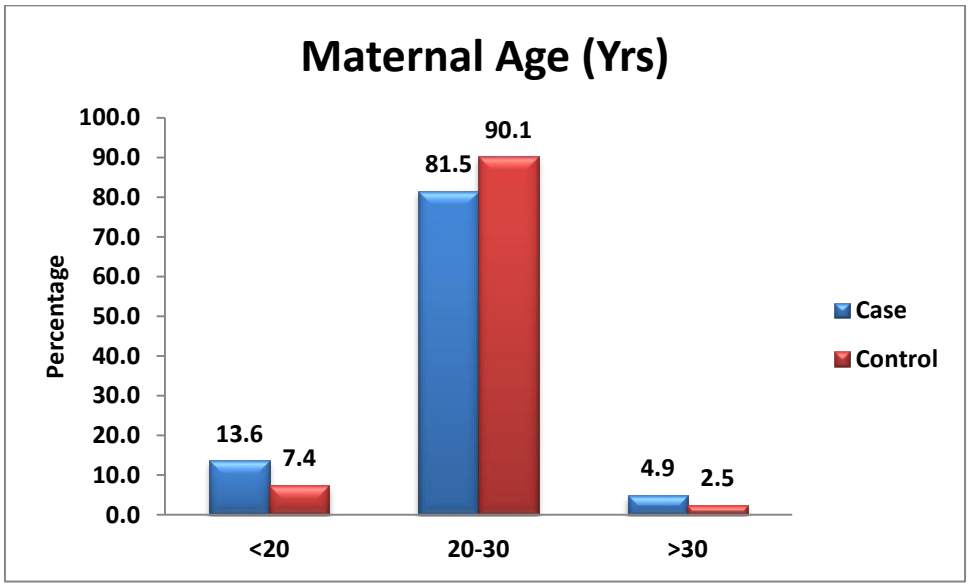
RESULTS

Total of 162 babies patients (81 cases and 81 controls) were recruited .

TABLE NO-8: DISTRIBUTION OF MATERNAL AGE BETWEEN CASES AND CONTROLS

Maternal Age (Yrs)	Case		Control		p value
	N	%	N	%	
<20	11	13.6	6	7.4	0.288
20-30	66	81.5	73	90.1	
>30	4	4.9	2	2.5	
Total	81	100.0	81	100.0	

Graph 1: DISTRIBUTION OF MATERNAL EDUCATION BETWEEN CASES AND CONTROLS



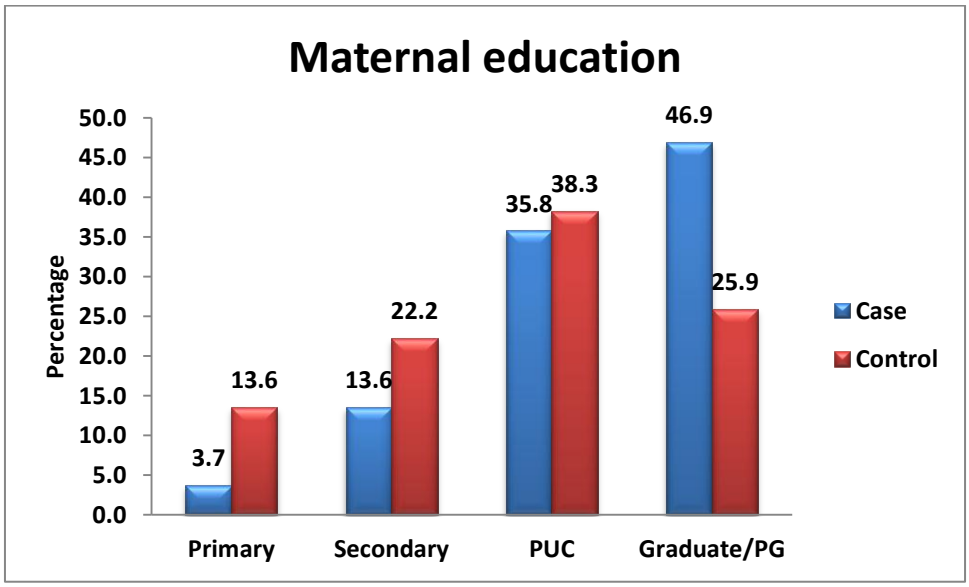
The above table shows that 81% and 90% of the mothers respectively in cases and controls were between 20 to 30 year.

TABLE NO-9: DISTRIBUTION OF MATERNAL EDUCATION BETWEEN CASES AND CONTROLS

Maternal education	Case		Control		p value
	N	%	N	%	
Primary	3	3.7	11	13.6	0.011*
Secondary	11	13.6	18	22.2	
PUC	29	35.8	31	38.3	
Graduate/PG	38	46.9	21	25.9	
Total	81	100.0	81	100.0	

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

Graph 2: DISTRIBUTION OF MATERNAL AGE BETWEEN CASES AND CONTROLS

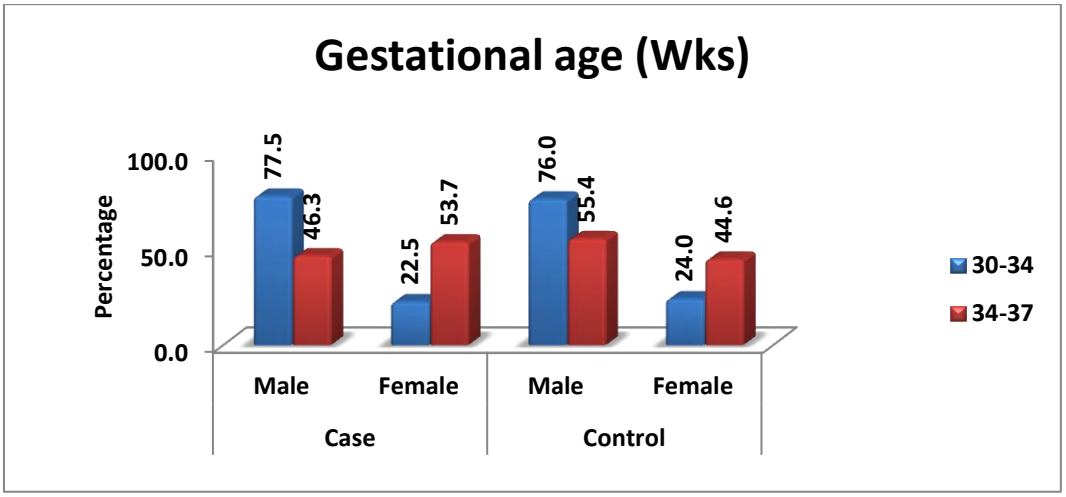


This above table shows distribution of maternal education in case and controls individually. In cases 82 % and in control 64% were PUC or above and there was no illiterate mother.

TABLE NO-10 : Description of our subjects

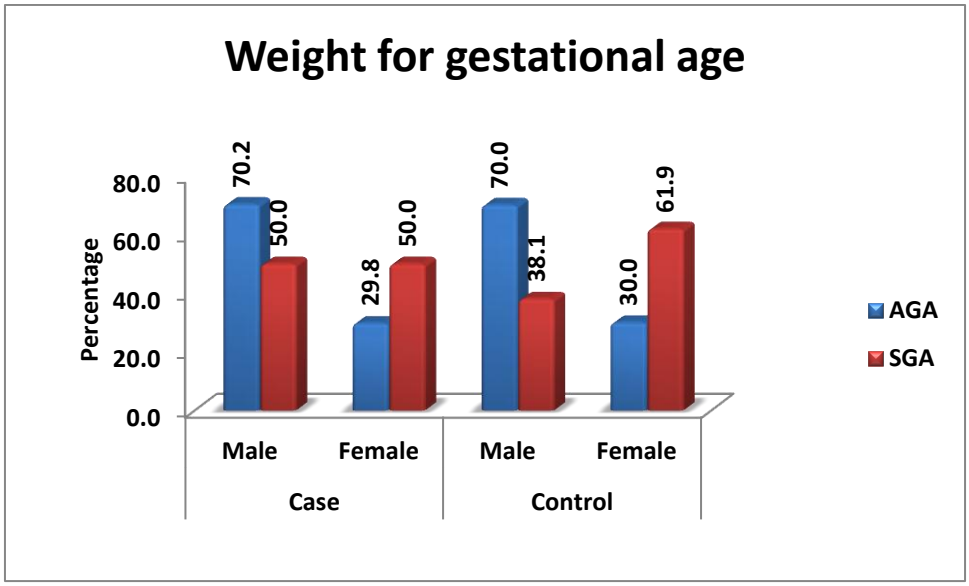
Variables		Case					Control				
		Male		Female			Male		Female		
		N	%	N	%	total	N	%	N	%	total
Gestational age (Wks.)	30-34	31	77.5	9	22.5	40	19	76.0	6	24.0	25
	34-37	19	46.3	22	53.7	41	31	55.4	25	44.6	56
	Total	50	61.7	31	38.3	81	50	61.7	31	38.3	81
Weight for gestational age	AGA	33	70.2	14	29.8	47	42	70.0	18	30.0	60
	SGA	17	50.0	17	50.0	34	8	38.1	13	61.9	21
	Total	50	61.7	31	38.3	81	50	61.7	31	38.3	81
Place of delivery	Inborn	33	62.3	20	37.7	53	30	62.5	18	37.5	48
	Outborn	17	60.7	11	39.3	28	20	60.6	13	39.4	33
	Total	50	61.7	31	38.3	81	50	61.7	31	38.3	81
Weight (grams)	<1000	0	0.0	0	0.0	0	1	100	0	0.0	01
	1000-1500	19	59.4	13	40.6	32	16	50.0	16	50.0	32
	1500-2000	31	63.3	18	36.7	49	33	68.8	15	31.3	48
	Total	50	61.7	31	38.3	81	50	61.7	31	38.3	81

Graph 3: CASES AND CONTROLS BY GESTATIONAL AGE



- The above table and graph depicts that out of 40 babies born between 30 to 34 weeks of gestation in cases group 31 babies are male (77.5%)) and 9 are female (22.5%)%) babies and in control group out of 25 babies 19 babies are male(76%)) and 6 babies(24%) are female.
- The babies born between 34 to 37 weeks of gestation in cases group are 41.Out of 41 babies 19 babies (46.3%) are male and 22 babies are females (53.7%). In control group 31babies are male (55.4%) and 25 babies are female (44.6%).

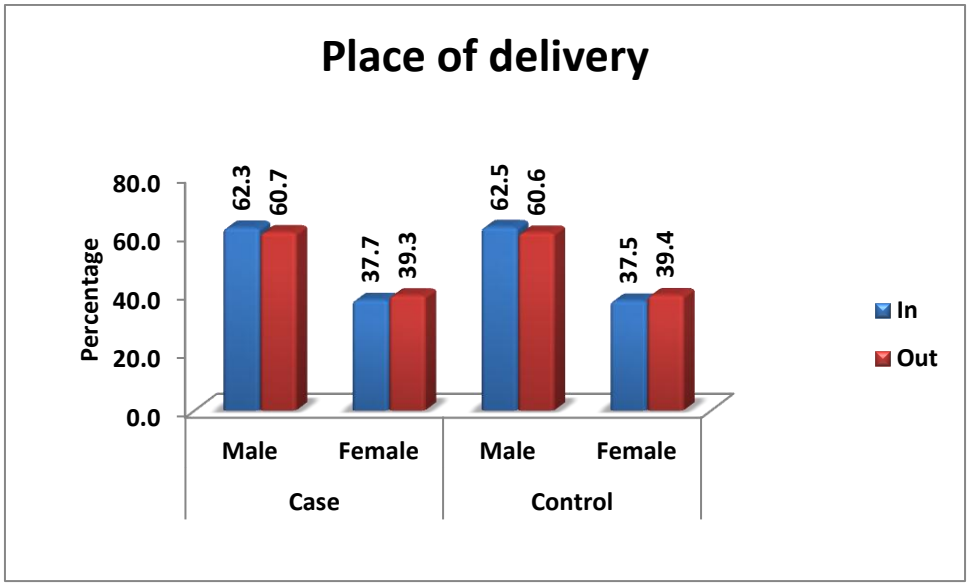
Graph 4: DISTRIBUTION OF CASES ACCORDING TO SEX BETWEEN CASES AND CONTROLS BY WEIGHT FOR GESTATIONAL AGE



- The above table and graph depicts that in cases group out of 47 babies 33(70.2%) were male and 14(29.8%) were female babies belonging to AGA group, In control group out of 60babies 42(70%) were male babies,18(30%) were female belonging to AGA group.

- In SGA babies out of 34 babies 17 (50%) were male and 17(50%) babies were female in cases group and in control group out of 21 babies 8(38.1%) male and 13(61.9%) babies were female.

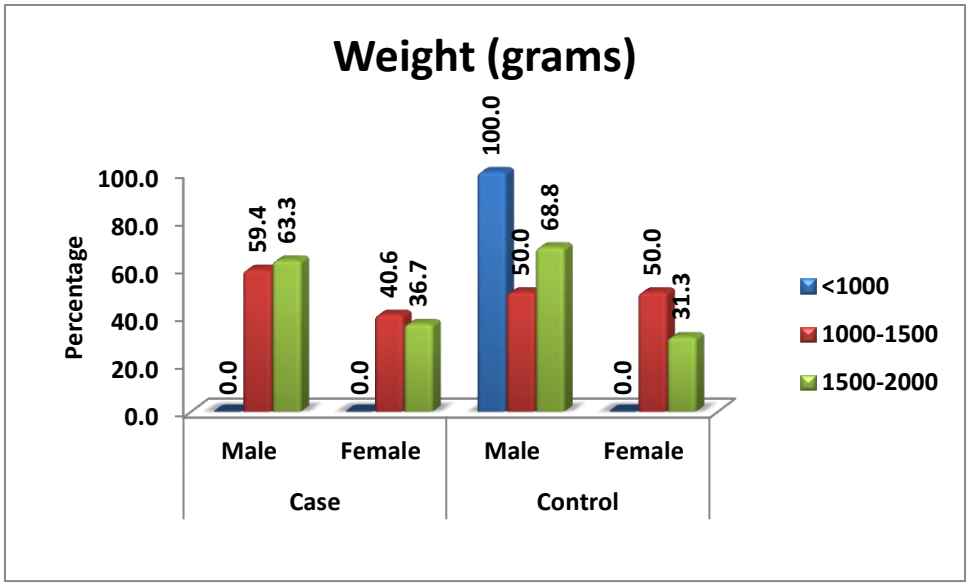
Graph 5: DISTRIBUTION OF CASES ACCORDING TO SEX BETWEEN CASES AND CONTROLS BY PLACE OF DELIVERY



- The above graph and table depicts that 53 inborn babies(65.4%) were in cases group out of which 33(62.3%) were male and 20(37.7%) babies were female. In control group out of 48(59.2) in born babies 30(62.5%) babies were male and 18(37.5%) were female.

- In out born babies group out of 28 babies (34.6%), 17 (60.7%) were males and 11 (39.3%) were females in cases group. In control group out of 33 babies (40.74%)20 (60.6%) were male and 13(39.4%) were female.

Graph 6 : DISTRIBUTION OF CASES ACCORDING TO SEX BETWEEN CASES AND CONTROLS BY WEIGHT



- The above graph depicts that no single babies born < 1000gm in cases group, and only one baby was born <1000gm (924gm) in control group.
- The total babies born between 1000-1500 gm were 64 .In cases group out of 32 babies born between 1000 to 1500 gm 19 (59.4%) babies were male and 13 (40.6%) babies were female. In control group out of 32 babies born between 1000-1500gm 16(50%) babies were male and 16(50%) babies were female.
- The babies born between 1500-2000 gm were 97 in cases group and control group together. In cases group out of 59 babies 31 (63.3%) babies were male and 18 (36.2%) babies were female and in control group out of 48 babies 33 (68.8%) babies were male and 15 (31.3%) babies were female.

TABLE N0-11: MORBIDITY PATTERN BETWEEN CASES AND CONTROLS

Morbidity		Case		Control		p value
		N	%	N	%	
NEC	Stage 1	0	0.0	0	0.0	0.468
	Stage 2	0	0.0	1	1.2	
	Stage 3a	3	3.7	3	3.7	
	Stage 3b	0	0.0	1	1.2	
	total	3	3.7	4	4.9	0.7074
Sepsis	Proved	7	8.6	9	11.1	0.199
	Probable	3	3.7	7	8.6	
	total	10	12.3	16	19.7	0.2003

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

- The above table shows that the number of babies diagnosed with NEC is more in the control group (4.9%) as compared to cases group (3.7%) which is statistically insignificant.

- The number of babies diagnosed with neonatal sepsis (proved and suspected sepsis) in control group is (19.7%) more than the cases group (12.3%). Though the number is high in control group the data showing statistically insignificant.

Graph 7 : MORBIDITY PATTERN BETWEEN CASES AND CONTROLS

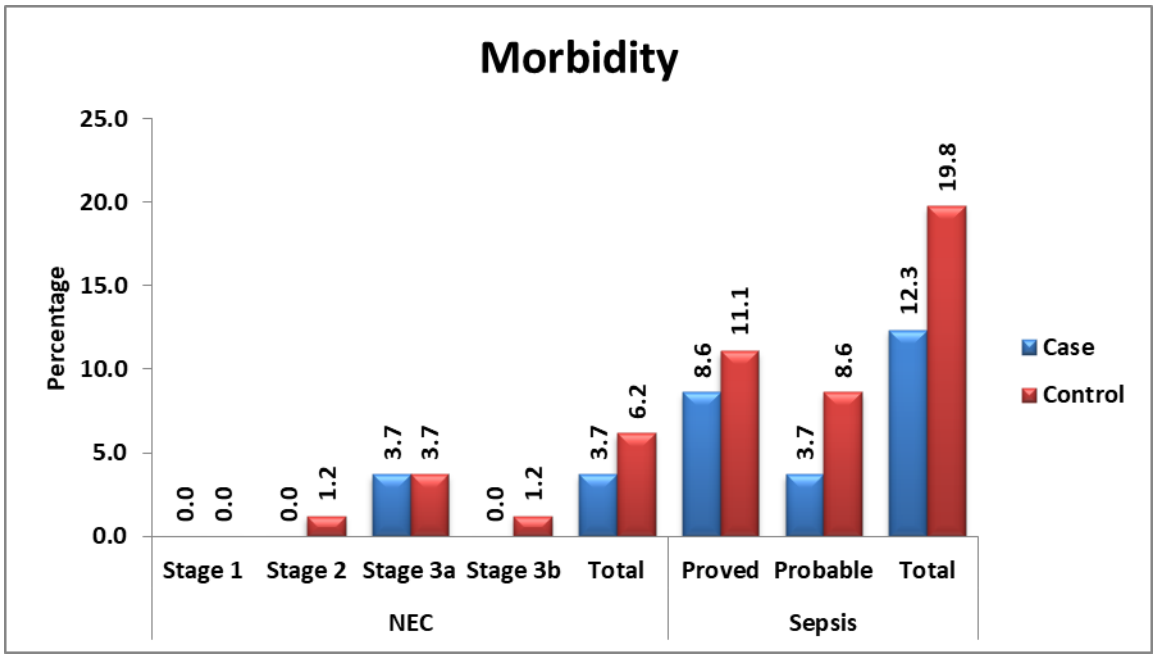
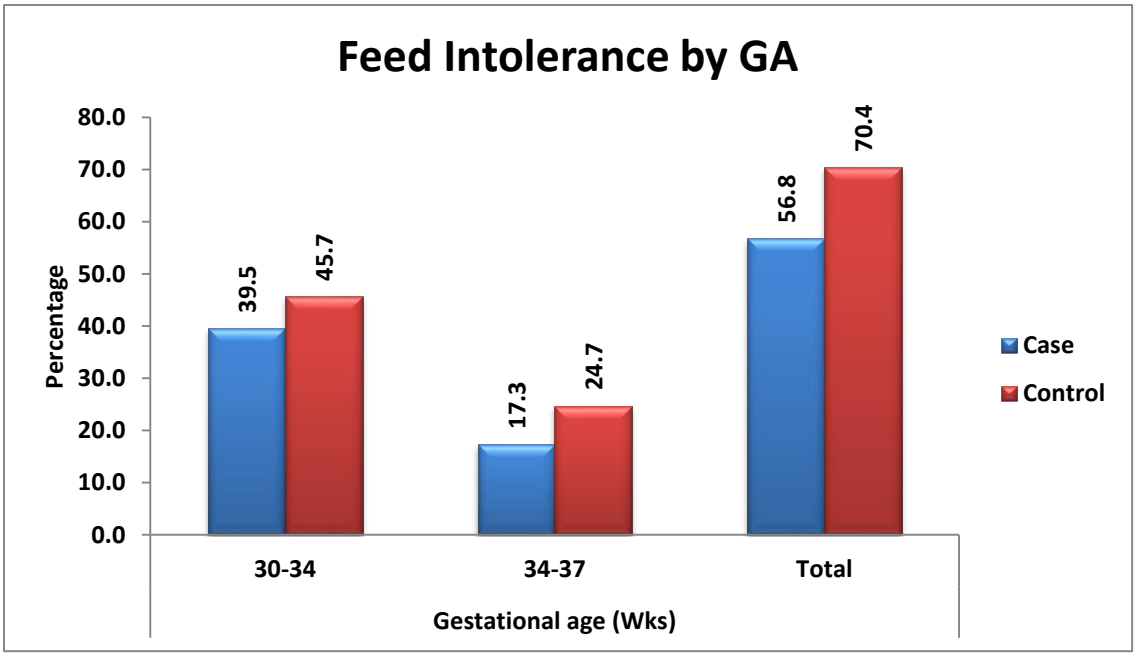


TABLE N0-12: PATTERN OF FEED INTOLERANCE BETWEEN CASES AND CONTROLS BASED ON GESTATIONAL AGE.

Feed intolerance		Case(81)		total	Control(81)		total	p value
		N	%	n	N	%	n	
Gestational age (Wks.)	30-34	27	67.5	40	19	76	25	0.4426
	34-37	7	17.07	41	16	28.5	56	0.2082
	<1000							
	1000-1500	24	75%	32	23	71%	32	0.7207
	1500-2000	09	18.3%	49	13	27%	48	0.2907

Graph 8 : PATTERN OF FEED INTOLERANCE BETWEEN CASES AND CONTROLS BASED ON GA(weeks).

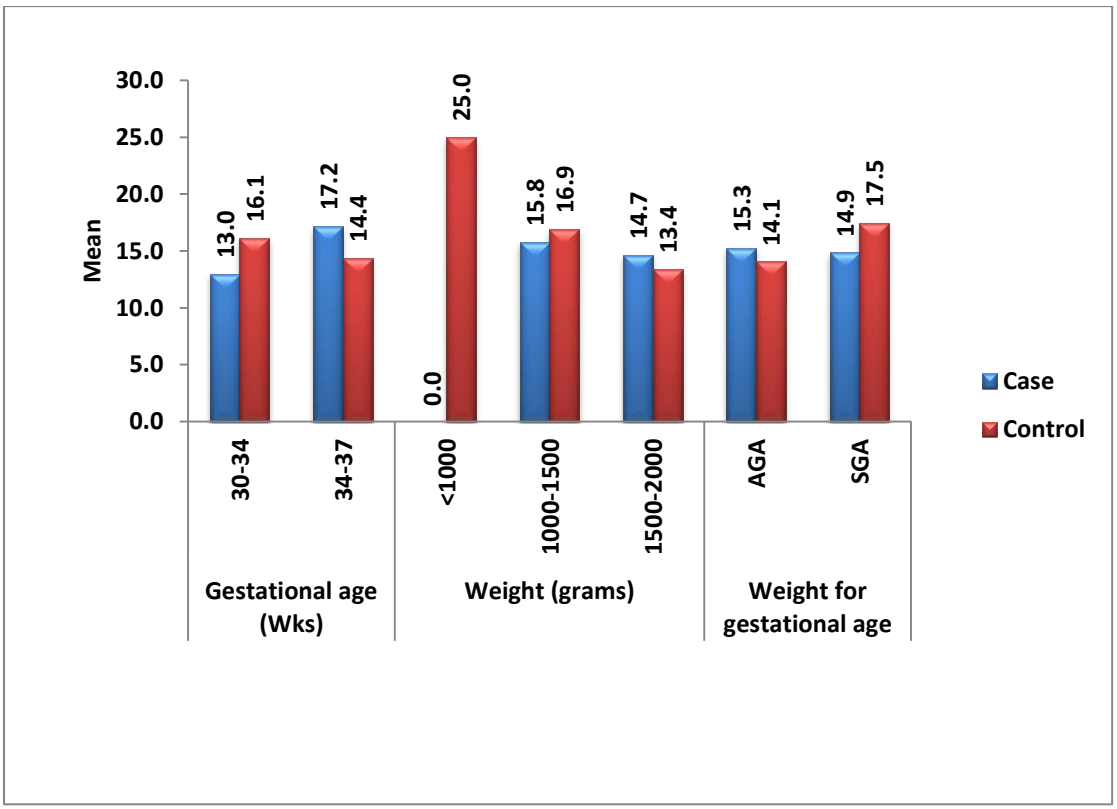


Above table and graph reveals that that feed intolerance was less in cases as compared to controls in all the groups except in babies between 1000-1500gm group but we could not show statistical significance

TABLE NO-13: COMPARISON OF MEAN DURATION OF NICU STAY BETWEEN CASES AND CONTROLS BY (TOTAL NUMBER OF DAYS).

Variables		NICU STAY(days)				p value
		Case		Control		
		Mean	SD	Mean	SD	
Gestational age (Wks)	30-34	13.0	8.7	16.1	7.0	0.132
	34-37	17.2	10.2	14.4	9.7	0.18
Weight (grams)	<1000	0.0	0.0	25.0	0.0	-
	1000-1500	15.8	10.4	16.9	6.4	0.595
	1500-2000	14.7	9.2	13.4	10.1	0.524
Weight for gestational age	AGA	15.3	9.9	14.1	8.4	0.489
	SGA	14.9	9.5	17.5	10.2	0.339
Total		15.1	9.7	14.9	9.0	0.932

Graph 9 : COMPARISON OF NICU STAY BETWEEN CASES AND CONTROLS BY SELECTED FACTORS



- The above table depicts that the babies born between 30-34 weeks of gestation the mean duration of NICU stay is more in the control group(16.1days) as compared to cases group(13) though it is statistically insignificant.

- The babies born between 34-37 weeks of gestation the mean duration of stay is more in the case group (17.2days) as compared to control group (14.4 days).

- Based on the weight of the babies only one baby was <1000gm in control group and the mean duration of stay was 25days.

- The babies born between 1000-1500gm, the mean duration of stay was more in control group (16.9days) as compared to cases group (15.8days) .We could not show statistical significance.

- The babies born between 1500 – 2000gm the mean duration of stay is more in cases group(14.7 days) as compared to control group (13.4 days).

- Based on the weight for gestational age, the duration of NICU stay is more in the cases group (15.3days) as compared to control group which is less (14.1days).but the duration of NICU stay

- In SGA babies is more in the control group (17.5 days) compared to cases group (14.2 days).

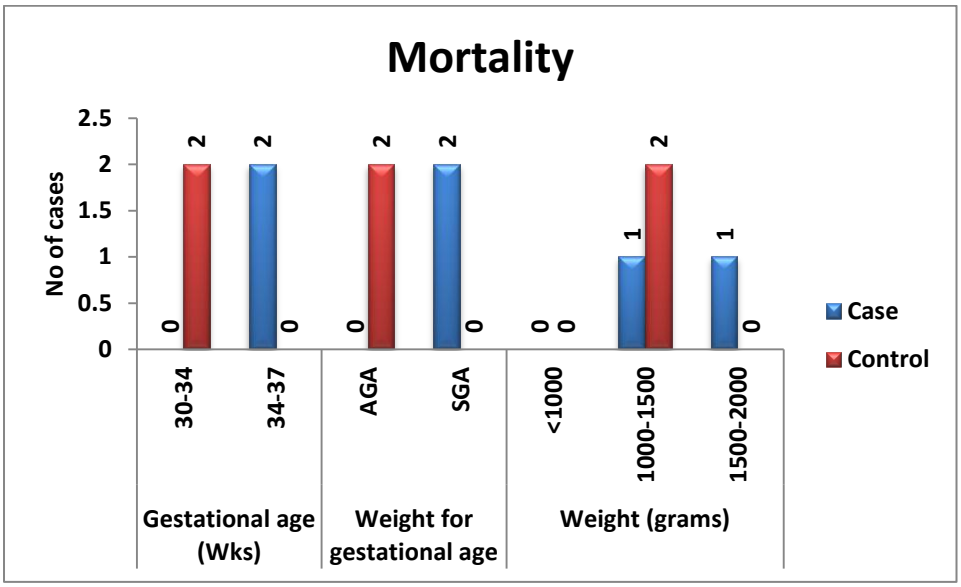
- Probiotic and prebiotic appear useful below 34 weeks of gestation babies , below 1500gm babies and SGA babies.

TABLENO-14 COMPARISON OF MORTALITY BETWEEN CASES AND CONTROLS BY SELECTED FACTORS

Variables		Deaths				p value
		Case		Control		
		N	%	N	%	
Gestational age (Wks)	30-34	0	0	2	100	0.157
	34-37	2	100	0	0	
Weight for gestational age	AGA	0	0	2	100	0.157
	SGA	2	100	0	0	
Weight (grams)	<1000	0	0	0	0	0.361
	1000-1500	1	50	2	100	
	1500-2000	1	50	0	0	
Total		2	100	2	100	

- Total 4 deaths 2 in cases group and 2 in control group.

Graph 10 : COMPARISON OF MORTALITY BETWEEN CASES AND CONTROLS BY SELECTED FACTORS



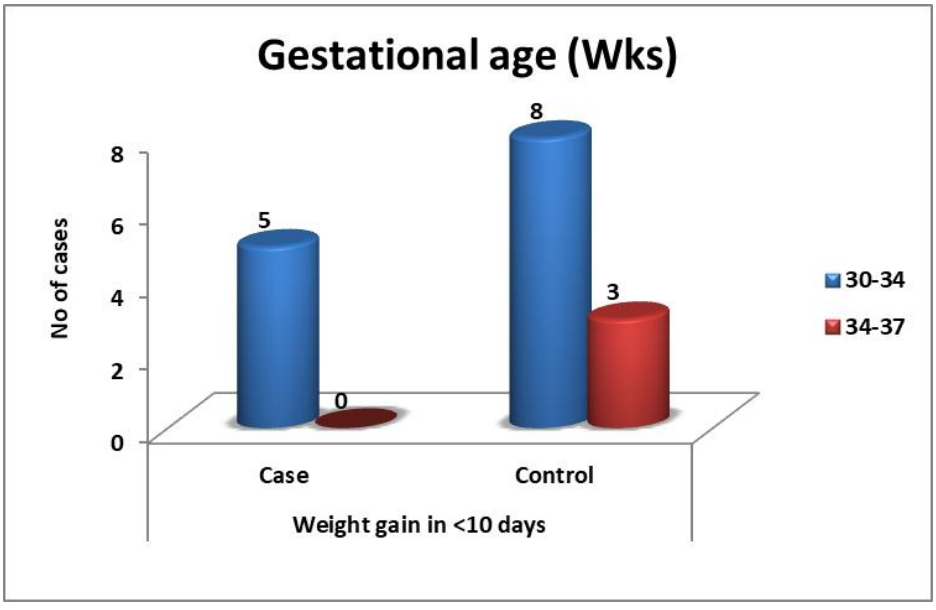
There were only 2 deaths in each group hence mortality could not be compared.

TABLE NO- 15: WEIGHT LOSSBETWEEN CASES AND CONTROLS BY SELECTED FACTORS IN <10 days

Variables		Weight loss in <10 days						
		Case (n=81)		Total	Control (n-81)		Total	p value
		N	%	n	N	%	n	
Gestational age (Wks)	30-34	5	12.5	40	8	32	25	0.0503
	34-37	0	0	41	3	5.35	56	0.1345
Weight (grams)	<1000	0	0.0	00	0	0.0	01	-
	1000-1500	3	9.37	32	4	12.5	32	0.6538
	1500-2000	2	4.08	49	7	14.5	48	0.0779

All preterm lose weight up to 15 % in first 10 days .This table shows proportion of cases and controls losing weight more than 15%. In babies below 34 weeks only 12.5% babies lost more than 15 % weight as compared to controls (32%).This was statistically just significant .In other groups also number of babies who had significant weight loss was less in cases though statistical significance was not seen.

Graph 11 : Weight loss between cases and controls by gestational age in <10 days



Graph 12 : Weight loss between cases and controls by selected factors in <10 days based on gestational age

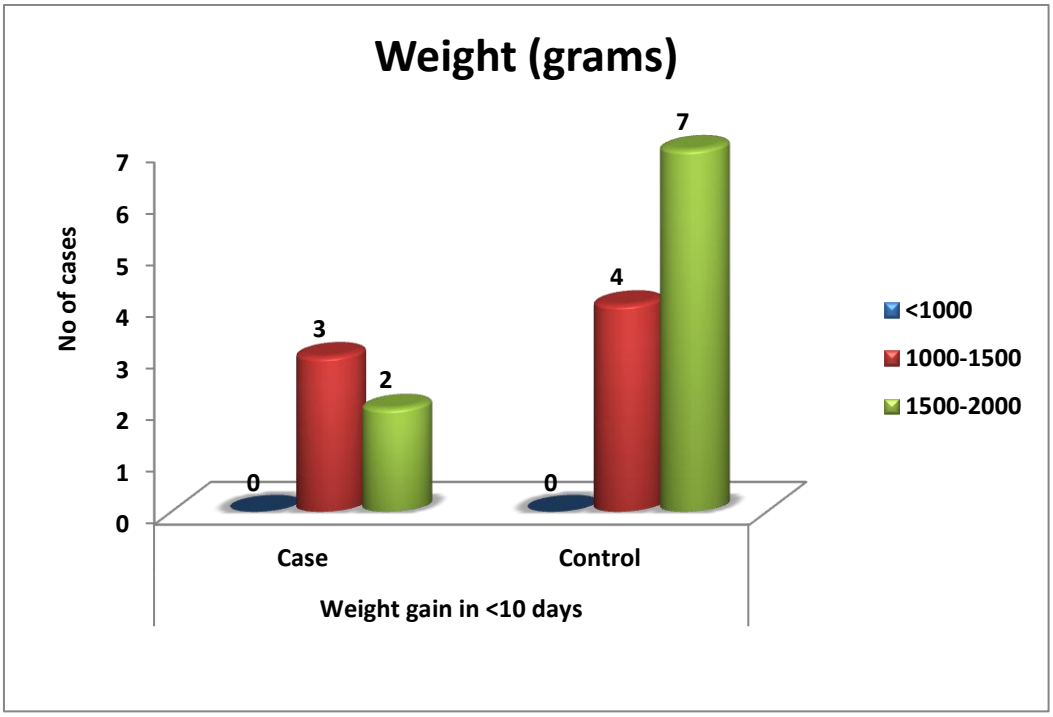
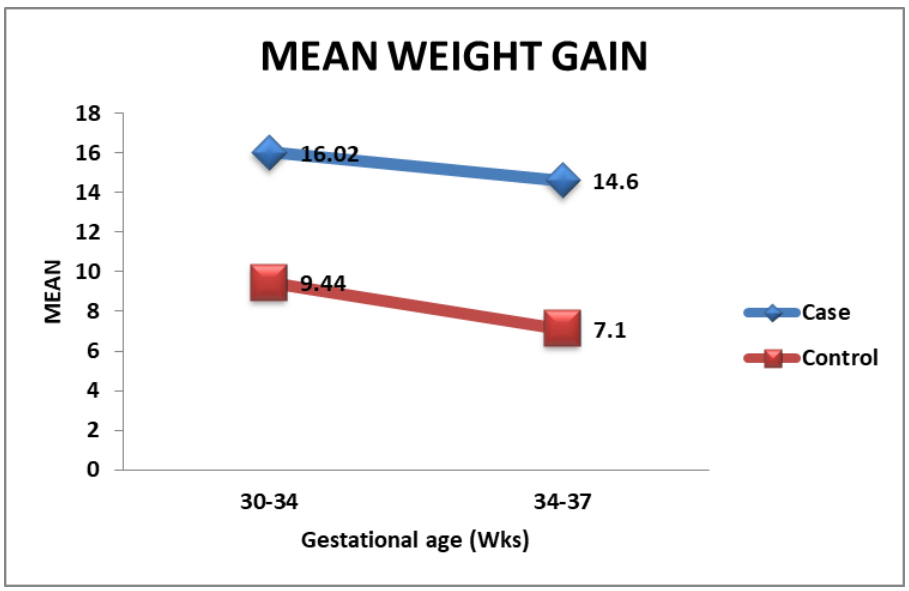


Table no 16-: MEAN WEIGHT GAIN IN CASES AND CONTROLS BY SELECTED FACTORS IN >10 days UP TO 37 WEEKS.

Variables		case		Control		p-value
		Mean weight gain/day	n	Mean weight gain/day	n	
Gestational (age)	30-34	16.02 (SD-6.65)	40	9.44 (6.8)	25	P = 0.0003
	34-37	14.6 (9.45)	41	7.10 (8.1)	56	P = 0.0001
		15.31	81	8.27	81	
Weight (gm)	<1000	0	00	8.3	01	
	1000-1500	14.09 (7.95)	32	8.68 (6.33)	32	P = 0.0038
	1500-2000	16.05 (8.25)	49	7.41 (8.7)	48	P < 0.0001
	total	15.07(mean)	81	8.13(mean)	81	

This table shows weight gain was better in cases in all above groups as compared to controls which is statistically significant.

Graph 13 : MEAN WEIGHT GAIN IN CASES AND CONTROLS BY SELECTED FACTORS IN >10 days UP TO 37 WEEKS BASED ON GESTATIONAL AGE.



Graph 14 : MEAN WEIGHT GAIN IN CASES AND CONTROLS BY SELECTED FACTORS IN >10 days UP TO 37 WEEKS BASED ON WEIGHT OF THE BABY.

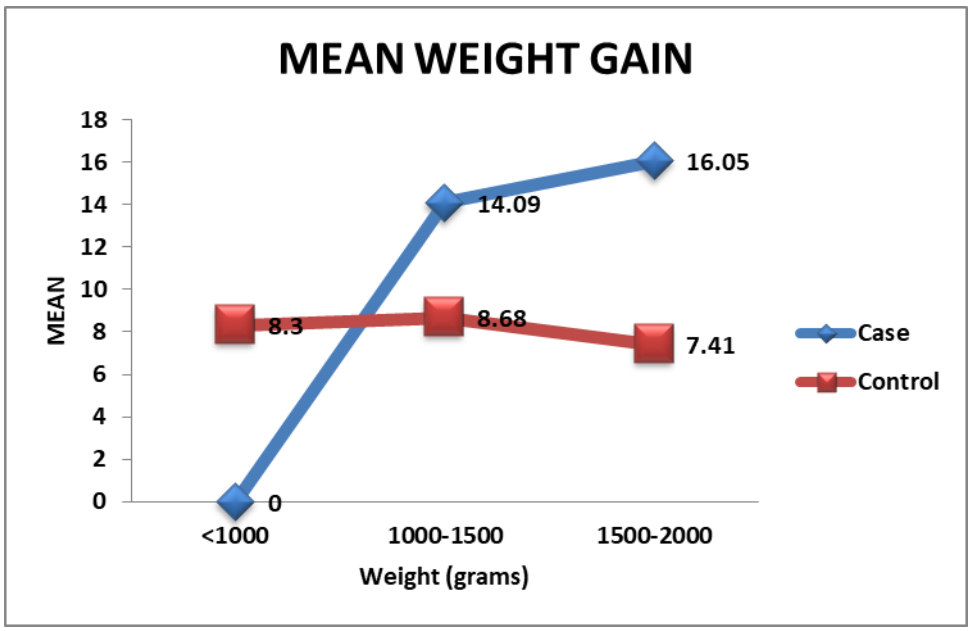
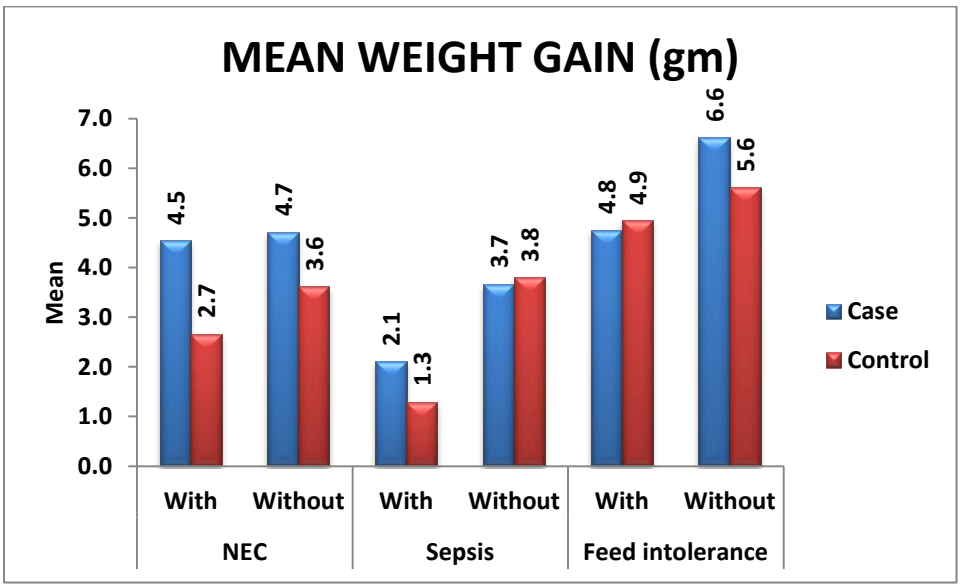


TABLE NO-17: WEIGHT GAIN PATTERN IN CASES AND CONTROLS ACCORDING TO MORBIDITY

Variables		MEAN WEIGHT GAIN (gm)				p value
		Case		Control		
		Mean	SD	Mean	SD	
NEC	With	4.5	5.7	2.7	5.7	0.038*
	Without	4.7	7.0	3.6	6.6	0.306
Sepsis	With	2.1	6.2	1.3	5.9	0.403
	Without	3.7	4.6	3.8	7.2	0.890
Feed intolerance	With	4.8	5.1	4.9	5.7	0.828
	Without	6.6	6.7	5.6	4.9	0.272

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

Graph 15 : WEIGHT GAIN PATTERN IN CASES AND CONTROLS ACCORDING TO MORBIDITY



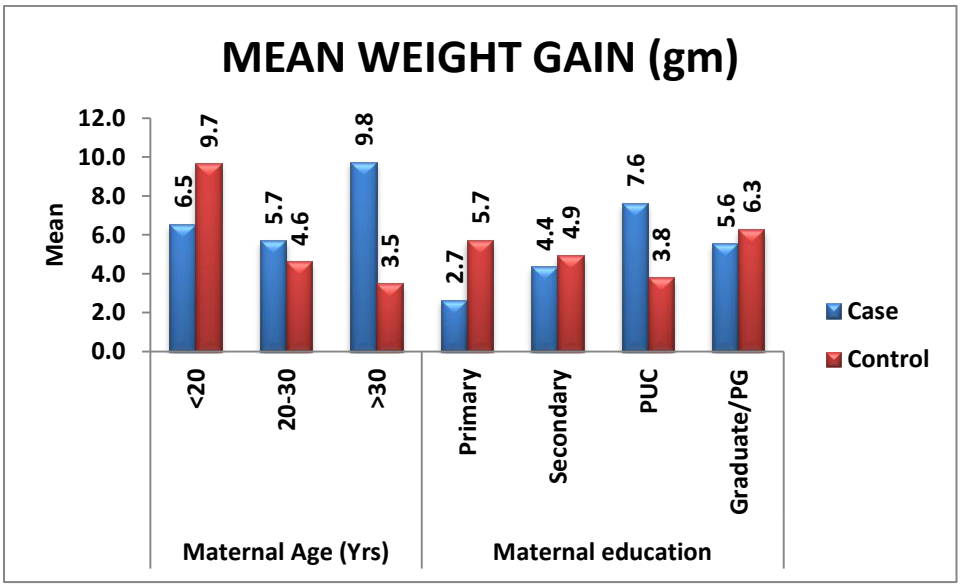
- The above graph and table depicts that weight gain was significantly improved in NEC if probiotics and prebiotics were given.
- Similar observation was there with the sepsis also though statistically insignificant.
- Weight gain pattern remained same if there was feed intolerance.
- Without morbidity weight gain was better in cases.

TABLE NO -18 MEAN WEIGHT GAIN PATTERN IN CASES AND CONTROLS ACCORDING TO MATERNAL FACTORS

Variables		MEAN WEIGHT GAIN (gm)				p value
		Case		Control		
		Mean	SD	Mean	SD	
Maternal Age (Yrs)	<20	6.5	5.7	9.7	5.6	0.295
	20-30	5.7	6.1	4.6	5.6	0.27
	>30	9.8	6.9	3.5	4.9	0.329
Maternal education	Primary	2.7	4.6	5.7	7.3	0.513
	Secondary	4.4	5.0	4.9	5.7	0.784
	PUC	7.6	6.7	3.8	4.9	0.014*
	Graduate/PG	5.6	5.8	6.3	5.8	0.644
Total		6.0	6.0	5.0	5.7	0.252

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

Graph 16 : WEIGHT GAIN PATTERN IN CASES AND CONTROLS ACCORDING TO MATERNAL FACTORS



- The above graph and table shows that the weight gain in cases group improved with mothers increasing age though not statistically significant.
- Maternal education shows significantly increased weight gain in PUC mothers may be bigger sample size will bring better results.

DISCUSSION

Premature infants, especially very low birth weight (VLBW), are at risk of neonatal morbidity and mortality. Immaturity of the organ systems of preterm infants makes them more susceptible to many complications including respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis (NEC), and patent ductus arteriosus, sepsis, and anemia, retinopathy of prematurity and intraventricular hemorrhage.[80] To survive the extra uterine environment, preterm infants often require special care and extensive support in the neonatal intensive care unit. Despite advances in neonatal care and new therapies, these complications remain a concern.[81] In this study, we have concentrated mainly on NEC, Sepsis and feed intolerance along with weight gain pattern in preterm babies.

In the present sample most of the mothers between 20 to 30 years in both cases and control group and majority were educated up to PUC or higher education with no illiterate mothers which makes this sample very useful as effect of immaturity due to mother's age or poor education may not be a factor affecting the use of products(prebiotics & probiotics) or understanding the instruction given by the doctor (table no-1&2).

In our study we have included babies between 30 to 37 weeks of gestation, because the number of babies which were <30 weeks less in our institute, as well as mortality rate is high in that group so is difficult to study the long-term effects.

It also includes both inborn and out born babies. An advantage in Inborn babies was, we could start prebiotic and probiotic earlier but starting of prebiotic and probiotic in out born babies depended on when they were referred to our institution.

Among the cases there were 53 (%) inborn and among the controls 48(%) were inborn so in our sample 2/3 rd. were inborn only. (Table no-10)

The majority of subjects between cases and controls were between 1000 - 2000 g and they were equally distributed in weight cadres in outborn and inborn babies (table no-10).

In our study the number of babies diagnosed with NEC is more in the control group (4) as compared to cases group (3) which is statistically insignificant. Various studies and meta-analysis have shown results varying from significantly useful to not useful table no -.

NEC

Table no-19 Effect of probiotics on NEC, comparison with other studies.

Effect on NEC	A	B	C	D	E	F
Effective and useful	Wanq Q,Dong J,Zhu Y-J Ped Surg 2012[78]	Lin HC, Su BH, Chen AC, Lin TW 2005[74]	Samantac et al; J Trop Pediatr 2009[85]	Braga TD et al. Am J Clin Nutri-2011[71.]	Hunter C, et al BMC Pediatr-2012[86]	Fernandez-Carrocera LA et al-2013[87]
Not effective non useful	Dani C, BiadaioliR Bertini G, Martelli E,2002[88]	Sari FN.et al. Am J Clin Nutri-2011[75]				
*useful but not significant	Rojas MA et al [76]	Our study				

*Statistical significance not found.

Aceti A et al[89], conducted a meta-analysis of study trial in 2015, majority of studies showed prebiotic and probiotic had an overall preventive effect on NEC in preterm infants. In this meta-analysis most of the studies considered NEC stage >2 according to bells staging. Similarly in our study also we had NEC stage >2 .In the

above meta-analysis they showed mainly effect on very low birth weight infants (VLBW), which was similar to our study but there was insufficient data For extremely low birth weight babies (ELBW). As Far as strain of probiotic was concerned bifidobacteria and probiotic mixture shows significant effect in above meta-analysis, our study also used the probiotic mixture which includes bifidobacteria.

Other studies quoted in the above table have shown significant difference between cases and control, but in our Study we could not show statistical significance.

Yangs et al.[79] In their meta-analysis(2014) which included 6665 preterm babies have stidied NEC and found For Bell stage>1 and GA< 37 weeks, risk of NEC was significantly lower in Pre-and probiotic group.(p-value-<0.0001).For Bells stage >2 and GA <34 weeks , again there was significantly low prevalence in Pre-and pro-biotic group as compared to placebo group.

SEPSIS

In our study the number of babies diagnosed with neonatal sepsis (proved and suspected sepsis) in control group is (16) more than the cases group. Though statistically insignificant.

Table NO-20 ;showing effect of probiotics in sepsis in different studies.

In favor	Not in favor	*inconclusive
Zhang .G.Q et al.[90]	Mihatsch W.A et al. In the year 2010[73]	Rojas M A et al-2012[76]
	Yang .Y et al[79]	
	Hunter C et al[86]	
	Jacobs SE et al.2013.[69]	
	Wang Q et al-2012[78]	
	Dani C et al -2002[88]	

*statistically not significant.

Mihatsch W.A et al.[73] In the year 2010 found that probiotic did not reduces the incidence of nosocomial infection . But in this trial they have taken only single strain of organism (B.lactis) and considered only nosocomial infections.

In the meta-analysis by Yang et al,[79] there were total of 6665 preterm babies included in the study and this study also could not show significant difference in the risk of sepsis in cases and control group.

In the meta-analysis by Zhang .G.Q et al.[90] in the prevention of late onset of sepsis in preterm babies they found significant reduction of sepsis both bacterial and fungal in babies <1500gm but not in babies <1000gm.

They have considered only culture positive sepsis but in our study we have considered both proved and suspected sepsis. In our study we did not have fungal sepsis. There were 27trial included in above meta-analysis most studies used multiple strain,. And the analysis also showed lactobacillus and the mixture of 2 to 3 strains is more effective in reduction of late onset of sepsis . In our study we also have used mixture of different organisms.

Hunter C et al.[86] showed that prebiotic and probiotic was not effective in both cases and control group.

As far as harmful effects of pre-and probiotic consider all meta-analysis studies and our study has not shown any adverse effects of pre and probiotic. None of the cultures grew the organisms contained in the mixture of pre-and probiotic.

Feed intolerance

In our study we found that Feed intolerance was more in the control group as compared to cases group but was not statistical significant.

In the year 2012 the study done by Rojas M A et al[76] were found that episodes of Feed intolerance was lower in babies <1500gmsand in this study the probiotic used was L.reuteri DSM17938.

A study done by Sari FN et al.[75]in the year of 2010 in which total to 221 babies were enrolled in the study group, and this study showed that feed intolerance was significantly lower in the pre-and probiotic group as compared to control group but they used single strain (L.sporogens)) probiotic as compared to our study, we have used mixture of multiple strains.

Similarly the study done by Carole Rouge' et al.[70]In the year 2009 shows that supplementation of probiotic mixture Lactobacillus rhomnosusu GG and Bifidobacterium longum BB536 (BB536-LGG) to premature Babies improve the feed intolerance in infants weighing >1000gm, but no improvement was seen in babies who were extremely low birth weight (<1000gm).

This above finding was explained by the fact that probability of gut to be colonized by probiotic strains diminished with decreasing birth weight and it is similar to our study.

In our study there were no patient below <1000gm, so we could not comment on this issue.

Flavio Indrio et al.[91] also conducted the study in 2017 results were similar to our study, i.e feed intolerance were less in probiotic group as compared to control group they also used single strain of probiotic was used (L.reuteriDSM17938).

Durations of NICU stay

Probiotic and prebiotics, because of their effect on NEC, Feed Intolerance and Sepsis is expected to reduce the NICU stay .We studied duration of NICU stay in cases and control, we found that duration of stay was Less in babies <1500 and also in SGA babies but we could not show statistical significant.

Carole Rouge et al[70] in the year 2009 found that the duration of stay was less in cases but they also could not show any statistical significant Like our study.

Rojas MA et al[76] in 2009 also found that duration of NICU stay was less in probiotic group than the placebo (p-0.04).

Moni S.C. et all.[77] conducted a study in 2015 also showed that the duration of stay was less in probiotic group compared to placebo group which was statistically significant.

Mean weight gain

We tried to compare the effect of probiotics on weight in cases and control in the first 10 days of life. Preterm babies normally lose weight in first 10 days .If it is > 15% it becomes pathological, so we studied effect in first 10 days of life. We found that the in babies <34 weeks,12.5% babies lost >15% of birth weight this proportion has 3 times increased in controls group. So the value was just statistically significant. In 34-37 wks none of babies in cases group has lost >15% weight but in control group 5% of babies showed weight loss >15%. Which means that excessive weight loss in first 10 days can be prevented by pre and probiotics this part has not been studied by other authors.

Meta-analysis by Yang Y. et al [79]all as shown that two trials with 205 babies in cases and 199 baby is in control group, studied weight gain in this group and they didn't found any statistical difference between the two groups but there was a significant heterogeneity among these two trials.

Hay's et al [92]in 2016 used Bifidobacterium and their trail did not exhibit better postnatal growth in pre-and probiotic treated group but they used single strain in the study.

Sukanya S et al[93]in the year 2017 showed that average weight gain was better in probiotic group and which was statistical significant, similar to our study which also shows weight gain was significantly better in probiotic group.

Moni S.C et al.[77] in the year of 2015 conducted trial includes 65 preterm infants and found that mean weight gain was good in probiotic group which was statistically significant(p-0.000).

Mortality

In our study there were only 4 deaths2 in each group hence we could not compare the mortality in two groups.

Susan E et al[69] in 2013 conducted a study trial he did not find any reduction in mortality in probiotic group as compared to placebo.

Wang Q et al[78] in his trial of probiotic in preterm babies and NEC shows that mortality rate was less in preterm VLBW babies treated with pre and probiotics compared with placebo group.

Probiotic strain

Effects of probiotics are described to be strain specific but in preterm especially in NEC it may not matter as NEC has many pathogenetic mechanisms so different strains can also act in different ways.[94]

As far today a preparation of different strains and species is preferred specially in preterm so that organisms can act in multiple ways and high dose of single strain is more likely to cause bacteremia and Infection.[95]Multi strain product is more functionally effective than single strain. Lactobacillus GG when tried as single strain did not show any role in NEC prevention.[96] It is safe to use previously tested combinations. We have used a mixture of strains mainly contains lactobacillus acidophilus, lactobacillus rhamnosus, Bifidobacterium longum, bifido bacterium bifidum, saccharomyces boulardi, fructo oligo saccharides and most of the single study used Bifidobacterium.

Safety of probiotic and prebiotic-

We used mixture of probiotic and prebiotic .it was easy to administer ,easy to mix with breast milk and no side effects was noted .None of the lab culture in sepsis babies grew the organism present in the mixture .

CONCLUSION

1. Total 162 babies were recruited, 81 as cases and were given prebiotic and probiotic combination and 81 were controls.
2. Most of the mothers in each group were between 20 – 30 years.
3. Majority of mothers were above secondary level education in both groups. There were no illiterate mothers.
4. Babies were between 30 and 37 weeks, weighing 1000gms to 2000 gms, with male female ratio of 1.16 :1 in each group.
5. NEC and Sepsis were more common in control group though statistically significance could not be seen.
6. Feed intolerance was less in cases as compared to controls in all the groups except in babies between 1000-1500gm group but we could not show statistical significance.
7. Only 2 deaths were in each group so effect on mortality could not be assessed.
8. In babies below 34 weeks only 12.5% babies lost more than 15 % weight as compared to controls (32%) .This was statistically just significant .In other groups also number of babies who had significant weight loss was less though statistical significance was not seen.
9. Mean weight gain was almost double or more in cases as compared to controls and was statistically significant all sub groups.
10. Mean weight gain in cases was always better than controls. Probiotic and prebiotic improved the weight gain in NEC and Sepsis though statistically significant only in NEC.
11. Mean NICU stay was less in cases when gestational age was below 34 weeks, weight below 1500 gm, and SGA babies.

12. While correlating maternal factors, weight gain improved with maternal age especially above 30 years. Weight gain in both groups improved with better maternal education and was still better with prebiotics and probiotics though statistically significance was seen only in PUC group.
13. To conclude probiotics and prebiotics appear to be useful in prevention of Sepsis, NEC, feed intolerance though statistically could not be shown. Weight gain is better in babies receiving probiotics and was statistically significant. A larger sample may help to get statistical significant results.

Limitations of study-

Sample size was adequate as per statistical calculations but larger sample may give better statistical significant results.

SUMMARY

A Prospective interventional study of utility of prebiotics and probiotics in preterm and IUGR babies admitted to Shri B M Patil medical College& Research center hospital. Objectives was to study the effect of introduction of prebiotics and probiotics on feeding intolerance, necrotizing enterocolitis, Sepsis, and overall mortality in preterm IUGR babies and to compare this to control group.

Observations noted in the study were Total 162 babies were recruited, 81 as cases and were given prebiotic and probiotic combination and 81 were controls.

- Most of the mothers in each group were between 20 – 30 years, majority were above secondary level education in both groups and there were no illiterate mothers.

- Babies were between 30 and 37 weeks, weighing 1000gms to 2000 gms, with male female ratio of 1.16 :1 in each group

- NEC and Sepsis and feed intolerance were more common in control except in babies between 1000-1500gm group feed intolerance was more in cases group.

- Mean weight gain was almost double or more in cases as compared to controls and was statistically significant all sub groups and also even better with morbidities in cases group.

- Mean NICU stay was less in cases when gestational age was below 34 weeks, weight below 1500 gm, and SGA babies.

- Weight gain of the babies improved with maternal age especially above 30 years and with better maternal education in both groups and was still better with prebiotics and probiotics though statistically significance was seen only in PUC group.

- Only 2 deaths were in each group so effect on mortality could not be assessed.

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ANNEXURES

ETHICAL CLEARANCE CERTIFICATE

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

No/58/2015
20/11/15

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

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

Title "Utility of prebiotics and probiotics in preterm & IUGR babies admitted to tertiary care Hospital A prospective intervention study"

Name of P.G. Student : Dr Mohammad Ismail Magdalai
Dept of pediatrics

Name of Guide/Co-investigator : Dr. S.V. Patil
Prof & HOD.

DR.TEJASWINI VALLABHA
CHAIRMAN

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

Following documents were placed before E.C. for Scrutinization
1)Copy of Synopsis/Research Project
2)Copy of informed consent form.
3)Any other relevant documents.

INFORMED CONSENT FORM

TITLE OF THE PROJECT : UTILITY OF PREBIOTIC AND PROBIOTIC IN PRETERM AND IUGR BABIES

GUIDE : DR. S.V.PATIL
(PROFESSOR AND HOD DEPT OF PEDIATRICS)

PG STUDENT : DR. MOHAMMAD ISMAIL MOGALAI
(PG IN PEDIATRICS)

PURPOSE OF RESEARCH:

I have been informed Present study will help in assessing the role of prebiotics and probiotics in preterm and IUGR babies in prevention of necrotizing enterocolitis, sepsis, feeding intolerance and also helps in assessing their role in weight gain and reduction in mortality .

PROCEDURE:

I understand that after having obtained a detailed clinical history, thorough clinical examination and relevant investigations, a final work up for the etiological identification and appropriate management is planned.

RISK AND DISCOMFORTS:

I understand that my baby's might may experience some pain and discomforts during the examination or during the treatment. This is mainly the result of my baby's condition and the procedures of this study are not expected to exaggerate these feelings which are associated with the usual course of treatment.

BENEFITS:

I understand that my baby's participation in the study will have no direct benefit to the baby's other than the potential benefit of the treatment.

CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of hospital records and will be subject to the confidentiality. Information of sensitive personal nature will not be part of the medical record, but will be stored in the investigations research file. If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs will be used only with special written permission. I understand that I may see the photograph before giving the permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time and Dr. Mohammad Ismail at the department of pediatrics is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my baby's continued participation. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL FOR WITHDRAWAL OF PARTICIPATION:

I understand that my baby's participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice. I also understand that Dr. Mohammad Ismail may terminate my baby's participation in the study after he has explained the reasons for doing so.

INJURY STATEMENT:

I understand that in the unlikely event of injury to my baby's resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me. But, no further compensation would be provided by the hospital. I understand that by my agreements to participate in this study and not waiving any of my legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks to the best of my ability.

_____ _____

Dr.mohammad ismail Date

(Investigator)

PARENTS / GUARDIAN CONSENT STATEMENT:

We confirm that Dr. MOHAMMAD ISMAIL is doing a study on UTILITY OF PREBIOTIC AND PROBIOTIC IN PRETERM AND IUGR BABIES has explained to us the purpose of research and the study procedure. We are willing to allow our baby to undergo the investigations and the possible discomforts as well as benefits. We have been explained all the above in detail in our own language and we understand the same. Therefore we agree to give consent to participate as a subject in this research project.

_____ _____

(Parents / Guardian) Date

_____ _____

(Witness to signature) Date

PROFORMA

CASE / CONTROL

NAME-

SUBJECT-

AGE-

OP/IPNO-

SEX-

DOB-

ADRESS&PHONE NO-

DOA-

DOF-

MOTHERS AGE-

DOP-

ANTENATAL HISTROY-

GESTATIONAL AGE-

MODE OF DELIVERY -

WEIGHT FOR GEST AGE-SGA/AGA/LGA-

MOTHEREDUCATION

PONDERAL INDEX-

ANTROPOMETRY

BIRTH WEIGHT-

GPE (IF SIGNIFICANT)-

SYSTEMIC EXAMINATION (IF SIGNIFICANT)-

DIAGNOSIS-

INVESTIGATION

DATE	INVESTIGATION REPORT	ACTIVE MEASURES &REMARKS

NICU COURSE

DATE	DOL	FEED	WEIGHT	PROBLEMS	ACTIVE MEASURES	DIAGNOSIS

FALLOW UP

DATE	DOL	WEIGHT	PROBLEMS	REMARKS

OUTCOME-

DISCHARGE-

DEATH/AMA-

OTHERS-F/U

GOOD-

POOR (<2)

ZERO-

RESULT-

KEY TO MASTER CHART

M	-	Male
F	-	Female
G A	-	Gestational Age (in weeks)
S.NO	-	Serial number
OP	-	Out patient
IP	-	in patient date
GA	-	Gestational age
MSAF	-	Meconium Stained Amniotic Fluid
GM -	-	Gram
AGA	-	Appropriate for gestational age
SGA	-	Small for gestational age
LGA	-	Large for gestational age
GPE	-	General physical examination
SCR	-	Sub costal retraction
RDS	-	Respiratory distress syndrome
B WT	-	Birth weight
TC	-	Total count
ANC	-	Absolute neutrophil count

CRP	-	C reactive protein
B/N	-	Band neutrophil
PDA	-	Patent ductus arteriosus
ASD	-	Atrial septal defect
PAH	-	Pulmonary arterial hypertension
IN	-	Inborn
OUT	-	Out born
WT	-	Weight
MN WT GN	-	Mean Weight Gain
PS	-	Peripheral smear
GI	-	Gastrointestinal
HMDN	-	Haemorrhagic diseases of new-born
NVD	-	Normal veginal delivery
NSG	-	Neurosonogram
M ESR	-	Micro Erythrocyte Sedimentation Rate
WK	-	Week