

Original Research Article

Outcome of moderate preterm and term babies at tertiary care centre

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Received: 27 July 2018

Accepted: 27 September 2018

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ABSTRACT

Background: To study the maternal risk factors, morbidity, mortality of moderate preterm in comparison to term neonates.

Methods: This Cohort study involved two hundred fifty consecutively born moderate preterm and equal number of term newborns delivered in a tertiary care hospital. They were followed till discharge for morbidities and mortality. Detailed maternal and neonatal factors were studied and compared between the two groups.

Results: Moderate preterm babies constituted 55% of all live preterm births during the study period. The odds of babies developing major morbidity was significantly more in those whose mothers had hypertension and infections (OR 2.69 95% CI: 1.55, 4.68 and 2.08, 95% CI: 1.6, 2.71 respectively). In the study group, 42.4% and 20.8% babies suffered major and minor morbidity compared to 8.4% and 6.8% of term controls respectively. Moderate preterm neonates had significantly higher odds of developing morbidity like respiratory distress (12.4% vs. 5.6%, OR 2.21, 95% CI 1.21, 4.11), need for non-invasive (17.3% vs. 5.7%, OR 3.05 95% CI 1.69, 5.47) and invasive ventilation (14.6% vs. 1.7%, OR 8.62, 95% CI 3.09, 24.04), sepsis (20.8% vs. 5.2%, OR 5.20, 95% CI 2.71, 9.99), seizures (22.8% vs. 4.8%, OR 4.75 95% CI 2.61, 8.63), shock (17.6% vs. 4.4%, OR 4.00 95% CI 2.12, 7.56), and jaundice (26% vs. 6%, OR 4.33 95% CI 2.54, 7.39). By logistic regression, the odds of developing major morbidity decreased with increasing gestational age (aOR 0.28 95% CI 0.18, 0.45; $p < 0.001$) and increased with hypertensive disease of pregnancy (aOR 2.16 95% CI 1.09, 4.260; $p = 0.026$).

Conclusions: Moderate preterm neonates have significantly more mortality and morbidity compared to term controls. Maternal hypertension and lower gestational age are the strongest predictors of morbidity.

Keywords: Moderate preterm, Morbidity, Outcome

INTRODUCTION

There has been an upsurge in the interest in moderate preterm neonates recently, depicting their high-risk status. In 2005, the NICHD proposed the definition of moderate preterm infants as those born between 32 (224 d) to 36 weeks (238 d) of gestation.¹ The advocacy for this subgroup of preterm babies began with the complacent attitude of child physicians towards these infants. Moreover, this gestational age marks the obstetrical landmark after which most centers do not

administer antenatal prophylactic steroids, and after which expectant management of preterm labour for maternal morbidity are abandoned.^{2,3} There has also been an increase in the proportion of babies born moderate preterm due to earlier termination of high risk pregnancies to prevent sudden and unexpected fetal loss, and of course the rising number of multifetal gestations partly explained by increasing success of artificial reproductive techniques.⁴ Till date many retrospective studies have been conducted in the western hemisphere, which prove the vulnerability of moderate preterm infants

to short term morbidity as well as high rates of re-admission to hospital.⁵⁻⁸ A recent Indian study has analyzed the differences in morbidity but the relationship with maternal risk factors has not been studied.⁹ Data from India is otherwise limited. This is relevant because racial and demographic variations have been found to have impact on outcome.¹⁰ It is also important to anticipate problems in this category as majority of the time minimal infrastructure; monitoring and support would suffice to stabilize them. Even in resource poor countries a large difference can probably be made to neonatal morbidity and infant mortality by giving adequate attention to moderate preterm babies compared to small preterm who need more specialized care. The authors, thus, designed and conducted this prospective cohort study to compare the morbidity and mortality between moderate preterm and term babies; and evaluate the relationship of maternal risk factors with morbidity in these groups.

METHODS

The study approved by the institute ethics committee was conducted in the authors' hospital between the period of September 2017 to March 2018. A sample size of 250 was calculated. Hence, the authors included 250 moderate preterm newborns and one term baby of the same sex as control. Maternal details were collected including the presence of complicating illnesses during pregnancy and birth details. The gestational age at birth was collected by records. They were further classified based on week of gestation into sub groups at weekly intervals. Morbidity was subdivided into minor and major.

Minor morbidity included (i) Transient tachypnea of newborn (concomitant with clinical findings and chest roentgenogram) which did not require invasive ventilation, (ii) Jaundice requiring phototherapy and (iii) Suspect sepsis based on a positive sepsis screen of any

two of CRP or hematological changes with a negative blood culture in an asymptomatic baby.

Major morbidity included (i) Septicemia or clinical sepsis with positive sepsis screen, including congenital pneumonia (ii) Respiratory distress syndrome, as evidenced by clinical features, Chest radiograph and respiratory support requirements, (iii) Apnea of prematurity requiring bag and mask ventilation or intubation, having ruled out other usual causes (iv) Birth asphyxia proven Apgar score ≤ 5 at 5 min and a cord blood pH of less than 7.1, (v) Jaundice requiring double volume exchange transfusion, (vi) Hypoglycemia <40 mg% requiring iv dextrose infusions, (vii) Shock requiring inotropes and (viii) Seizures.

Statistical Analysis

To compare association between outcomes and groups, chi-square test was used. Significant differences between means of continuous variables among various groups was tested using the Student 't' independent test. The One-way ANOVA was used to compare the means between subgroups. To determine the strongest predictive factors/the effect of various risk factors on occurrence of morbidity, multivariate logistic regression analysis was done. All these analyses were carried out using SPSS statistical software SPSS version 13.0. Epical 2000 programme was used to compute odds ratio, risk ratio and 95% confidence interval for individual risk factors. P value of <0.05 was taken as significant

RESULTS

It was observed that the need for operative deliveries was far higher in the moderate preterm gestation. There was a significant difference ($t=23.13$; $P < 0.001$) in the mean (\pm SD) birth weights between study (1973.04 $g \pm 410.98$) and control group (2778.72 $g \pm 366.67$) (Table 1).

Table 1: Baseline characteristics of neonates in two groups.

Characteristic	Moderate preterm		Term		P value
	Mean* /n	SD* /%	Mean* /n	SD* /%	
Maternal age*	24.81	4.151	24.05	4.187	0.51
Normal vaginal delivery	137	54.8	203	81.2	0.01
Operative vaginal delivery	32	12.8	29	11.6	0.91
Cesarian section	81	32.4	18	7.2	0.01
Birth weight*	1973.04 g	410.98	2778.72	366.675	0.001
IUGR	17	6.8	5	2.0	0.02
AGA	202	80.8	209	83.6	0.48
APGAR at 1 min*	6.50	2.038	7.54	1.305	<0.001
APGAR at 5 min*	7.38	1.798	8.54	1.176	<0.001
Needed NICU admission	124	49.6	36	14.4	<0.001

*Mean and SD

The weights also rise significantly ($F=0.95$; $df=2,24$; $P < 0.001$) with each week of increasing gestation. The

incidences of hypertensive disease including eclampsia, diabetes, urinary tract infection, chorioamnionitis, severe

anemia, oligohydramnios, previous preterm delivery and fetal distress were significantly higher in the study group. Moreover, after correcting for possible covariates, the

odds of babies developing major morbidity was significantly more in those whose mothers had hypertension and infections (Table 2).

Table 2: Maternal risk factor and neonatal morbidity in moderate preterm.

No. of mothers with risk factor	Babies with Morbidity n (%)	OR* (95% CI)
Hypertensive disease of pregnancy(n=76)	45(59.2)	2.689 (1.546-4.677)
Eclampsia (n=25)	17(68.0)	3.247(1.344-7.843)
Infection (n=21)	17(80.9)	2.083 (1.6-2.711)
Rh isoimmunisation (n=6)	4(66.7)	2.784 (0.5-15.492)
Seizure disorder (n=9)	4(44.4)	1.090 (0.286-4.161)
Hepatitis b+(n=6)	5(83.3)	7.079 (0.815-61.513)
HIV + (n=2)	1(50)	1.362 (0.084-22.024)
Multifetal (n=60)	15(25)	0.504 (0.126-2.017)
Fetal distress (n=60)	37(61.7)	1.698 (1.291-2.234)
Premature rupture of membrane (n=44)	21(47.7)	1.157 (0.815-1.641)
Previous preterm (n=21)	13(61.9)	1.524 (1.053-2.207)

*Compared to those babies whose mothers did not have that risk factor.

The mean birth weight of babies in the study group who developed major morbidity (1838.49±437.92) was

significantly lower than those who had a smooth course (2060±392.93); 2 tailed p value<0.001.

Table 3: Comparison of specific morbidity and mortality in the study groups.

Morbidity	Moderate preterm no. (%)				Term no. (%) (n=250)	RR (95%CI)	RD%	P value
	32-33 Week (n=80)	33-34 week (n=83)	34-36 week (n=87)	Total (n=250)				
Overall major morbidity	58 (72.5)	31 (37.3)	17 (19.5)	106 (42.4)	21 (8.4)	5.048 (3.27-7.791)	34	<0.001
Clinical sepsis	28 (35)	16 (19.3)	8 (9.2)	52 (20.8)	10 (4)	5.2 (2.70-9.99)	16.8	<0.001
TTN	7 (8.8)	11 (13.3)	13 (14.9)	31 (12.4)	14 (5.6)	2.21 (1.20-4.06)	6.8	0.012
RDS	11 (13.8)	3 (3.6)	0	14 (5.6)	0	-	5.6	<0.001
Surfactant use	6 (7.5)	1 (1.2)	0	8 (3.226)	0	-	3.226	0.012
NIV	21 (26.2)	12 (14.5)	5 (5.7)	38 (17.35)	14 (5.69)	3.049 (1.7-5.47)	11.66	<0.001
MV	16 (20)	11 (13.3)	4 (4.6)	31 (14.62)	4 (1.7)	8.62 (3.1-24.04)	12.93	<0.001
Hypoglycemia	21 (26.2)	9 (10.8)	7 (8)	37 (14.8)	2 (0.8)	18.5(4.50-75.98)	14	<0.001
Hypocalcemia	6 (7.5)	10 (12)	6 (6.9)	22 (8.8)	5 (2)	4.4 (1.69-11.43)	6.8	<0.001
Seizures	30 (37)	19 (22.9)	8 (9.2)	57 (22.8)	12 (4.8)	4.75 (2.61-8.63)	18	<0.001
IVH	10 (12.5)	4 (4)	0	14 (5.6)	0	-	5.6	<0.001
Meningitis	5 (6.2)	8 (9.6)	2 (2.3)	15 (6)	0	-	6	<0.001
Shock	23 (28.8)	14 (16.9)	7 (8)	44 (17.6)	11 (4.4)	4 (2.12-7.56)	13.2	<0.001
NEC	18 (22)	11 (12)	5 (5.7)	34 (13.6)	1 (0.4)	34 (4.69-246.4)	13.2	<0.001
Jaundice	21 (26.2)	30 (37)	14 (16.1)	65 (26.0)	15 (6)	4.3 (2.54-7.38)	20	<0.001
Malformati-ons	9 (11.3)	14 (16.8)	11 (12.6)	34 (13.6)	9 (3.6)	3.778 (1.851-7.711)	10	<0.001
Mortality	8 (10%)	8 (9.6%)	4 (4.5%)	20 (8%)	4 (1.6)	5.883(2.498-13.62)	12.4	<0.001

TTN: Transient tachypnea of newborn; RDS: Respiratory distress syndrome; NIV: Non-invasive ventilation; MV: Mandatory ventilation; IVH: Intraventricular hemorrhage; NEC: Necrotizing enterocolitis

As a group, 42.4% of late preterm babies suffered major morbidity compared to 8.4% of term controls. The morbidity rates were 19.5% in the 35-36 week babies, 37.3% in the 34-35 week subgroup, which further doubled to 72.5% in the most immature of subgroups.

The rates were similar among babies in the control group irrespective of gestational age. All the major morbidities defined in the methodology, suffered by the study group were higher than term controls (Table 3). Far higher number of babies in the moderate preterm group were

given antibiotics for suspected sepsis (OR 5.32 95% CI 3.47, 8.13). The authors needed to administer surfactant to 7 moderate preterm babies out of 31 who were diagnosed to have RDS. The requirement for non-invasive and mandatory ventilation was more in the moderate preterm infants. No term babies developed apnea, but 11.6% of pre-term (all between 34 and 35 week) had apnea of prematurity.

Mean duration of hospital stay decreased from 8.81±5.69 d at 34 weeks to 7.28±3.58 d at 35 week and 6.16±3.71 d at 36 week. There was a similar pattern with mean duration of NICU stay (6.32±6.25 d for the 34-week gestation neonates, 4.23±11.16 d for 35 week and 1.77±3.62 d for 36 week). Comparison with term babies revealed a significant difference in the mean NICU and hospital stay (F07.45; df 2; P00.001 and F 7.58; df 2; P00.001 respectively). The overall mortality was 8% in the study group compared to 1.6% among controls.

The main causes for death were congenital malformations in 9 babies (44%) and severe perinatal asphyxia in 3 (14%). Neural tube defects constituted 23.5% (8 babies) of all malformations and heart diseases 17.6% (6 babies). Other malformations were chromosomal trisomies (4 babies), urogenital tract anomalies (3 babies), trachea esophageal fistulas (2 babies) and skeletal dysplasias (3 babies) among others.

Finally, after a logistic regression analysis, having removed congenital malformations, IUGR, effect of birth weight and other potential covariates like asphyxia; lower gestational age and presence of hypertension in the mother emerged as the strongest predictors of morbidity. The odds decreased with increasing gestational age (aOR 0.29; 95% CI 0.18, 0.45; p<0.001) and increased with PIH (aOR 2.16; 95% CI 1.09, 4.26; p00.026). TTN Transient tachypnea of newborn; RDS Respiratory distress syndrome; NIV Noninvasive ventilation; MV Mandatory ventilation; IVH Intraventricular hemorrhage; NEC Necrotizing enterocolitis.

DISCUSSION

Owing to the shifted focus on increasing survival of small preterm babies, the moderate preterm group could potentially be assumed to be “nearly mature”. However, evidence has been contrary to this belief in the recent past. Their proportion has increased significantly in the past decade due to various hypothesized reasons.

However, such data is lacking from our country. The authors observed 55% of all preterm deliveries in the study period were moderate preterm. The author’s hospital being a referral one, it is possible that more preterm deliveries are conducted here. A population-based analysis is required to obtain the true situation. Although, the etiology of preterm births continues to be pregnancy induced hypertension, preterm premature rupture of membranes and multifetal gestation have been

long recognized as the common associations and causes for spontaneous and iatrogenic early delivery.³ Shapiro Mendoza et al. conducted a large population-based study and found that maternal medical conditions are self-determining risk factors for newborn morbidity in the moderate preterm group.⁸

A recent study from Greece reported an intensified independent risk for neonatal morbidity when the mothers suffered antepartum hemorrhage and were subjected to emergency cesarian deliveries.¹¹ However, this study did not have a control group. Khashu et al. established that there was increased prevalence of chorioamnionitis, hypertension and PROM in the study group.⁶ The index study recognized the higher presence of maternal illnesses and fetal distress complicating pregnancies and deliveries in moderate premature births.

The presence of pregnancy induced hypertension and maternal infections in peripartum period are separate and significant risk factors (aOR 2.16; 95% CI 1.09, 4.26; P00.026 and aOR 3.25; 95%CI 1.34–7.84 respectively) for newborn morbidity in the moderate preterm group by logistic regression. Cesarean delivery was conducted in 32.4% of study group vs. 7.2% of controls in the present cohort (P<0.001), but the outcome and morbidity risk were not related to the mode of delivery. However, De Luca et al, concluded that infants delivered by emergency CS had significantly higher mortality (aRR 2.1) and larger risk for morbidity.¹²

Many retrospective cohort studies have reported increased morbidity like temperature instability, apnea, infections, hypoglycemia, respiratory problems and jaundice. These can be explained by decreased brown fat, insulation from heat by white fat; central nervous system immaturity, decreased response to hypercarbia and hypoxic respiratory depression, upper airway muscle hypotonia; lower energy reserves, immature glucose regulatory mechanisms; lung immaturity in the transition phase from terminal sac to alveolar; and underdeveloped bilirubin handling.^{13,14}

These problems and their clinical implications have been extensively reviewed recently.^{3,13,15} A recent Indian study has reported that moderate preterm infants are at significantly higher risk of morbidity.⁹ The present study supports the above findings that moderate preterm newborns are a significantly vulnerable population. The percentage of babies with IUGR was significantly higher in the present study group (6.8% vs. 2% respectively). But the authors did not uncover IUGR to be a significant risk factor for neonatal morbidity by logistic regression.

The findings of Rocha et al, suggest that length of hospitalization and hypoglycemia were significantly higher in the IUGR preterms compared to AGA controls.¹⁶ The mortality in the present cohort was 8% in contrast to 1.6% in the controls. The main cause was congenital malformations, similar to that detailed by

Young et al.¹⁷ He further elucidated that the association of anomalies with moderate preterm births and mortality may indicate that the presence of malformations has probably led to early onset of labor.

Being prospective, many of the drawbacks of previous studies have been avoided. The present observations are not based on case record review and therefore, recording mistakes, misinterpretations of old data and missed information are not error producing factors. The findings add to literature with respect to effect of maternal risks which in the present study has been found to have significant association with major morbidity in moderate preterm infants. There are a few limitations which need to be highlighted.

The etiology of preterm births needs to be determined, especially with respect to percentage of iatrogenic moderate prematurity. This would have relevance in formulating an obstetrical policy for iatrogenic deliveries in the moderate preterm gestation. There may be a need for reevaluating the role of antenatal steroids beyond 34 weeks of maturity.¹⁸

Tomashek et al delineated that 4.3% late preterms vs. 2.7% of term babies who were discharged early required re-admission.¹⁹ The authors' being a free hospital, cost of care analysis was not done. Reports from USA state nearly 3 times the cost in treatment of moderate preterm neonates.^{6,20}

However, the present analysis revealed that moderate preterm babies had significantly lengthier NICU and hospital stay, longer duration of IV fluid requirement and higher mean age at which the first oral feed could be started after stabilization which means that the costs incurred by the hospital were probably higher. More systematic data collection and coordination is required to determine the situation in India.

Most of all, the emphasis of a future study should be to determine if the immediate course and outcome have a bearing on the long-term neurodevelopment and functioning of these infants. The present study further strengthens the evidence for individualizing their management and not complacently placing them under the category of "near term" infants. The findings also suggest that some obstetrical practices may need revision like the use of antenatal steroid for prevention of RDS and expectant management of preterm labor only up to 34-week gestation. Larger population-based studies would be required in future from the developing world.

CONCLUSION

Moderate preterm neonates have significantly more mortality and morbidity compared to term controls. Maternal hypertension and lower gestational age are the strongest predictors of morbidity.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Balai SS, Katara D, Arora V. Outcome of moderate preterm and term babies at tertiary care centre. *Int J Contemp Pediatr* 2018;5:2222-7.