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SCREENING THE TODDLERS BORN PRETERM FOR RISK OF NEURODEVELOPMENTAL DELAY

Pediatrics

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ABSTRACT

The present study aimed at identifying the proportion of preterm toddlers at risk of NDD who attended a tertiary care hospital using a screening tool ASQ 3 and comparing the risk of NDD among moderate to late preterm, very preterm and extreme preterms. **Materials and Method:** The present study was conducted in the Paediatric OPD of a tertiary care hospital. The study calculated the risk of neurodevelopmental delay among toddlers born preterm using a validated Marathi-translated version of ASQ 3.The ASQ 3 was completed by parents, mainly the mothers. The study included 111 preterm toddlers with chronological ages ranging from 12 to 24 months, with a mean of 17.63 ± 3.73 months and a male-to-female ratio 0f 1.4 :1. The toddlers under the black zone are considered at high risk of NDD and referred to the Child Development and Guidance Clinic for further evaluation. **Results:** Overall, 22 (19.8%) preterm toddlers failed ASQ, with single-domain failure (63.63%) being the most common, followed by 2-domain (22.72%) failure. Among those 22, more than two third (77.2%) failed in the gross motor domain, followed by 31.8% in fine motor, 22.7% in personal-social, and 13.63% each in communication and problem-solving. Additionally, 39 (35.13%) toddlers were in the grey zone, with 25.64% in fine motor, 20.51% each in the domain of communication, problem-solving and personal-social and 12.82 % in the gross motor domain. A decrease in gestational age was associated with a statistically significant increase in the risk of NDD. the multivariate analysis identified the chronological age of ≤ 18 months, being underweight and receipt of mechanical ventilation during the neonatal period as independent risk factors for being at risk of NDD. **Conclusion:** ASQ is a reliable screening tool that can be easily used in pediatric office practice.

KEYWORDS

INTRODUCTION

Preterm birth is a leading cause of under-five mortality and morbidity worldwide.(1) India was one of the five countries, along with China, Nigeria, Bangladesh, and Indonesia, contributing to 6·6 million (44·6%) of these preterm births. (2,3) The preterm neonates who survive are at a greater risk of short-term and long-term morbidities like respiratory distress syndrome, sepsis, bronchopulmonary dysplasia, periventricular leucomalacia, seizures, intraventricular hemorrhage, hypoxic-ischaemic encephalopathy, cerebral palsy, and visual and hearing problems.(4,5). Several international studies have found that preterm infants are at higher risk of adverse neurodevelopmental outcomes, poor academic performance and psychiatric problems like autism spectrum disorder (ASD), attention deficit hyperactivity disorder, anxiety, and depression.(6,7)

Besides prematurity, many biological and environmental factors positively and negatively influence neurodevelopmental trajectories. Low birth weight, intrauterine growth retardation, sepsis, perinatal brain injuries, and hyperbilirubinemia are examples of biological factors, whereas nutrition, poverty, environmental stimulation, and maternal education are included as the environmental factors influencing neurodevelopment.(8,9).Early detection of non-optimal neurodevelopment is essential for timely intervention to correct or attenuate problems.(10) Standardized tests such as the Bayley scale or Developmental Activities Screening Inventory provide efficient measures of functional outcomes. Various international and national developmental screening tools are available for screening children of different ages.

Ages and Stages Questionnaire (ASQ) is a parent-completed questionnaire used as a general developmental screening tool which assesses five domains: communication, gross motor, fine motor, problem-solving and personal-social. The tool is translated into many languages and is used worldwide as a developmental screening tool.(11)[14] ASQ is also validated for use in children born preterm and advised to be included in the follow-up programs.(12,13)

The recent guidelines on Early Child Development by the Indian Academy of Pediatrics recommend developmental screening of all children at 9, 18, 24 and 30 months.(14) Given the higher risk for preterm infants, screening such toddlers is crucial for appropriate referrals for early intervention. ASQ can be administered from 2-66 months. Many toddlers usually visit the immunization clinic for MMR and DPT booster doses between 12 to 24 months, making it feasible to assess these children using these screening tools during that visit. Therefore a prospective observational study was planned in the tertiary care hospital where toddlers of 12-24 months born preterm will be assessed for the neurodevelopmental delay. ASQ 3 will be administered for toddlers of 12-24 months. This will provide information about the proportion of children at risk of neurodevelopmental delay in toddlers born preterm and the feasibility of screening using parent-administered questionnaires. If found useful and feasible, this can be used routinely for all children, including other high-risk groups in Indian settings.

MATERIALS AND METHODS

The present Cross-Sectional Study was conducted in the Paediatric OPD of a tertiary care hospital from 18 Months (August 2020 to February 2022). A total of 111 participants were included. Any toddler born preterm with chronological age between 12 – 24 Months. Inclusion Criteria was: any toddler with chronological age between 12 – 24 months, born preterm, i.e. delivered before completion of 37 weeks of gestation and exclusion Criteria was :Toddlers having sensory impairments like hearing or visual impairments, known neurological or developmental disorder, known major congenital anomaly, the child having a chronic systemic illness. The eligible subjects visiting the study hospital were enrolled. The Screening Tool Used was: Ages and Stages Questionnaires Version 3 (ASQ 3).

Study Procedures: The study was started after receiving approval from Institutional Ethics Committee. Toddlers of chronological age 12-24 months who were born preterm visiting pediatric OPD or IPD were screened for the study. Written informed consent was obtained from either of the parents of such children in the local language. Inclusion and exclusion criteria were checked, and the eligible children were enrolled in the study. Demographic and baseline characteristics of the participants were recorded in the pre-designed proforma, e.g. name of the child, PRN number, age, gender, date of enrolment, area of residence (urban/rural), education of parents, type of family and socioeconomic status etc. were captured as mentioned in the case report form. The Modified Kuppuswami scale was used for socioeconomic status.(15)Detailed antenatal, natal, and postnatal history, etc., were noted. The corrected gestational age (CGA) of the child was calculated, and appropriate ASQ 3 for that age was given to the parent for self-administration. The questionnaire in the preferred language, i.e., Marathi or English, was used. Anthropometry (weight, length, and head circumference) was measured. Weight was recorded on the calibrated electronic weighing machine (Kidlee Company, lowest weighing 10 gms). These machines were calibrated every six months. The length was measured using a calibrated infantometer. (Abbott Company with lowest measuring 0.1cm) .Method of measuring length: The child was placed supine on a rigid measuring table or infantometer, the head was held firmly in position against a fixed upright headboard by one person, and the legs were straightened, keeping feet at a right angle to the leg with toes pointing upwards. The free footboard is brought into firm contact with the child's heels.

Length is measured from a scale which is set in the measuring table. Head circumference was measured using a non-stretchable measuring tape by encircling the most prominent parts of the occiput and supraorbital ridges, with a minimum measurable length of 0.1 cm. Nutritional status was assessed using WHO Growth Charts and classified as underweight, stunting and wasting. ASQ scores for each domain and overall were calculated. Children with a positive screen, i.e. score of < 2 SD below the mean in any domain or overall on ASQ 3, were referred to the Child Development Guidance Clinic for further evaluation. Parents were observed to see if they could complete the questionnaire easily or need any assistance.

OBSERVATIONS AND RESULTS

The present study was conducted in the pediatric OPD unit of a tertiary care hospital in Pune. A total of 111 toddlers between the age group 12 to 24 months, who were born preterm, were enrolled in the study. Table 1 shows the sociodemographic characteristics and nutrition status of the participant children. The participants' chronological age ranged from 12.0 to 24.0 months, with a mean of 17.63 ± 3.73 months and a median of 17 (IQR- 15-21). Of these 111 children, 65 (58.6%)

Nutrition was also assessed in all enrolled children. Of those 111 children, 38.7% were underweight, 37.8 % were stunted, and 18.0 % were wasted.

Table 2 summarises the frequency of proposed antenatal risk factors for NDD among toddlers. Of those 111 enrolled participants, only 6 (5.4%) toddlers were in vitro fertilized (IVF), and 19 (17.1%) were part of multiple gestations. More than half of mothers (58.6%) had received antenatal steroids, and 27.9 % had received MgSO4. Among them, 5.4 % of the mothers had antepartum hemorrhage (APH), and 26.1 % had Pregnancy induced hypertension (PIH).

Of those 111, almost two–thirds of babies were delivered by caesarian section. Table 3 shows the frequency of perinatal risk factors among the study participants.

Of the 111 preterm toddlers studied, 22 were identified as failing in one or more domains. Refer to table 4. Among those 22, more than two-thirds, i.e. 17 (77.27%) toddlers failed in the gross motor domain, followed by 7 (31.81%) failed in fine motor, 5 (22.72%) failed in personal social, and 3 (13.63 %) each failed in communication and problem-solving.

Overall, 14 (63.63%) children failed in a single domain, followed by 5 (22.72%) who failed in 2 domains, and the rest failed in more than 2 domains.

The questionnaire covers 5 domains, with a score ranging from 0 to 60 for each domain. The means and standard deviation for the total score and the five individual domains are summarized in Table 5. For the 111 assessed children, the overall ASQ score ranged from 135 to 300 with a mean of 257 ± 41.66 and a median of 265 (IQR 235-290). For the subscales, the mean scores ranged from the lowest of 50.14 for personal social to the highest of 53.24 for problem-solving.

For the 22 participants who failed ASQ 3, the mean total ASQ 3 score was 201.36 ± 41.75, ranging from a minimum of 135 to a maximum of 265. Table 6 gives score details of the individual domain in children who failed ASQ. For the subscales, the lowest mean score of 29.77 ± 17.56 was observed for the gross motor domain, and the highest was 46.14 ± 14.05 for fine motor.

The ASQ failure was significantly more in boys (p=0.047). The ASQ performance of participants from rural areas was poor; all were at risk of NDD (p<0.001).

Maternal education > 12th standard and socioeconomic status were also significantly associated with the risk of NDD. As per the nutritional status, underweight toddlers were noticed to be at risk of NDD (p=0.03). However, type of family, maternal age and employment status, stunting and wasting were not associated with ASQ failure.

Perinatal factors like gestational age, birth weight, the requirement of resuscitation at the time of Birth, NICU stay, neonatal sepsis, seizures, IVH, hyperbilirubinemia and the requirement of mechanical ventilation were assessed to see any association with risk of NDD using ASQ 3.

A decrease in gestational age is associated with the risk of NDD (p<0.001). Those who required NICU stay or had neonatal sepsis or neonatal seizures and IVH were significantly associated with ASQ failure (all p<0.05). Similarly, those who needed mechanical ventilation were also associated with ASQ failure (p<0.001), denoting that they were at high risk of developmental delay. Low birth weight was not associated with the risk of NDD.

Univariate logistic regression was conducted separately for these socio-demographic, maternal, antenatal and perinatal factors to assess the strength of association with the risk of NDD. The Odds ratio was calculated for the same and presented in Tables 10 and 11

Although the proportion of males was more among the ASQ failures, it did not show significant strength of association on the univariate analysis. Similarly, the urban area of residence was also not significant in univariate analysis. Only maternal education above 12 standard and underweight children were found significant in univariate analysis.

None of the antenatal factors was found to be a significant risk factor for ASQ failure on univariate analysis. Among the perinatal factors, Gestational age at birth, neonatal sepsis, IVH and mechanical ventilation were identified as risk factors for NDD.

Multivariate logistic regression analysis was conducted to find the strength of the association between various variables simultaneously with the risk of NDD. The results of the same are presented in Table 12. Only mechanical ventilation during the neonatal period was identified as an independent risk factor for ASQ failure, i.e. at risk of NDD on the multivariate analysis.

All the mothers/parents could complete the ASQ 3 independently without assistance. They found it very easy to administer.

DISCUSSION

Over the past several decades, perinatal and neonatal care management advances have led to increased survival rates among premature infants worldwide; among the survivors, short and long-term morbidities are common, and neurodevelopmental delay is one of the most common long-term morbidity.

The present study aimed at identifying the proportion of preterm toddlers at risk of NDD who attended a tertiary care hospital using a screening tool ASQ 3 and comparing the risk of NDD among moderate to late preterm, very preterm and extreme preterms. It also tried to find demographic, maternal, antenatal, and perinatal factors related to the risk of NDD using ASQ 3. ASQ is a validated tool for both term and preterms and is used worldwide. The ASQ 3 was locally adapted, translated into the Marathi language and validated at this tertiary care centre before this study.

The study included 111 preterm toddlers with chronological ages ranging from 12 to 24 months. The mean age of the toddlers was 17.63 ± 3.73 months, and the median was 17 (IQR 15-21) months. A total of 58.6% of children were from the age group ≤ 18 months, and it was identified as an independent risk factor for ASQ failure.

Among these toddlers, 58.6% were male and statistically significant male preponderance was observed among the toddlers at-risk of NDD, i.e. those who failed on ASQ. Flamant et al.(13), Limbos M M et al.(16) and Shahshahani et al.(17) observed significant male preponderance; however, Kerstjens JM et al.(18) and Sumandeep Kaur et al.(19) did not find the same

Various authors have conducted studies to find developmental delay using ASQ, but the age group and settings differ. Ly-Mee Yu et al.,(20) in their large International multicenter study, reported ASQ failure in 19.8%, whereas Limbos MM et al.(16)reported ASQ failure in 28.7%. Juneja et al.(21) observed ASQ failure in 82.5% among high-risk and 30% in low-risk children, whereas Torabi F et al.,(22) had 80% of mothers as high-risk; the overall ASQ failure was only 18.7%..

In the present study, more than two-thirds of toddlers were from the moderate to late preterm group, with only 8.1 % extreme preterm. This being a tertiary care centre, the parents of the high-risk newborns are taught to take special care of the child's development which involves information about tummy time, its advantages of it, methods of giving it, use of black and white flashcards for vision improvement, one to one

communication of mother/parents with the baby etc. These babies are followed up in the specific high-risk OPDs where their growth and development are closely monitored.

Those who failed on ASQ are considered to have a risk of developmental delay and are sent for a thorough evaluation. Still, it is also important to pay attention to those in the grey zone, as parental counselling and home stimulation practices might help them improve. Limbos MM et al.(16) Flamant et al.(13), and the present study observed single-domain failure as more common than multiple-domain failure. In contrast, Bajalan Z et al.(23) reported that two-domain failure was more common than single-domain.

Kerstjens M et al.(18) also reported a rising trend of 22% failure in very preterm to 41% in extreme preterms. A similar rising trend was observed in the present study, which was statistically significant.

Like the present study, Kerstjens et al.(18), Pratibha Agarwal et al.(24), Sumandeep et al.(19) and Soltani M et al.(25) observed the gross motor domain was the most common domain that failed. However, in the present study, it was one of the less common. Motor skills, especially gross motor skills, are visible and easily identified both by the parents and the clinicians. Thus it can be easily picked up at an earlier age on screening.

The overall domain score of these preterm toddlers ranged from 135 to 300 in the present study, whereas other authors who studied the preterms reported it to range from 30 (Kvestad et al.)(26), 40(Flamant et al.)(13), 60 (Halbwatch et al.)(27) to 300. The mean score was also higher in the present study compared to Flamant et al. (13). and Kvestad et al.(26)

The study aimed to identify risk factors for NDD using a simple screening tool, i.e. ASQ 3. It included sociodemographic factors, antenatal and perinatal factors. Prevention, Early identification of such potential risk factors, or appropriate management of the potential risk factors during that specified period, like the perinatal period, is essential. It may help provide close monitoring during early childhood and prevent NDD or identify the NDD at the earliest.

In the present study, chronological age $\leq$ 18 months, extreme preterm, maternal education above 12th standard, neonatal sepsis, IVH, mechanical ventilation, and underweight were identified as risk factors on univariate analysis; however, on multivariate logistic regression, chronological age $\leq$ 18 months, mechanical ventilation during NICU stay and being underweight were identified as independent risk factors. In the present study, toddlers from chronological age 12 to 24 months were enrolled, and the age group $\leq$ 18 months was identified as an independent risk factor. This tells that the risk of NDD is more at a younger age. Delays at an early age, if not identified or intervened properly, may affect the child's development to a greater extent. Early identification is crucial as appropriate interventions can eliminate or minimize the severity of the delay.

Family socioeconomic status (SES) is associated with various health outcomes and cognitive and socio-emotional development outcomes. SES of the lower and middle class and rural areas of residency was associated with at risk of NDD; however, they were not identified as risk factors on univariate analysis. Limbos M et al.(16) and Kerstjens JM 2009 (18) low income as a risk factor for ASQ failure; however, Flamant et al.(13) did not find the same.

The present study identified underweight as an independent risk factor for NDD risk. Shaahmadi F et al.(28) 2015 reported a significant correlation between gross motor skills with child nutrition. As per the review by Suryawan A et al., both stunting and being underweight are negatively associated with various elements of cognitive functioning (attention span, mathematical and language abilities).(29)

In the current study, children of mothers educated above 12th standard were at increased risk of developmental delay on univariate analysis; however, it was not so on the multivariate analysis. Kersjens et al.,(18) also reported that the mothers of a significant number of children who failed on ASQ were highly educated. In contrast, Shaahmadi F et al.(28) and Lamsal R et al.(30) reported children of less educated mothers were at increased risk of developmental delay.

We considered various antenatal factors like IVF, multiple pregnancy, APH, PIH, receiving antenatal steroids, presence of maternal medical illness and Chorioamnionitis as the risk for ASQ failure, i.e. at-risk of NDD, receiving antenatal steroids was identified as a risk factor.

In the current study, only 5.4 % of children were in vitro fertilized, and no NDD was detected using ASQ 3.

Preeclampsia was associated with DD primarily in severe presentations that involved placental insufficiency. Placental insufficiency appeared responsible for the increased DD risk associated with severe preeclampsia (adjusted odds ratio, 5.49; 95% CI, 2.06-14.64). Walker CK et al. (California)(31) and Bajalan Z et al.(23) reported preeclamptic mothers had shown 5 times more risk of NDD in their children. In the current study, 26.1% of mothers of preterm toddlers had a history of preeclampsia and no significant risk of NDD on ASQ 3 was observed.

In the present study, only one mother had GDM mother, and thus the risk could not be assessed. In the current study, 77.3% of toddlers who failed ASQ had a history of exposure to steroids in utero, which marginally missed the statistical significance on univariate analysis ($p=0.053$).We evaluated the strength of the association of a few potential perinatal risk factors with the risk of NDD using ASQ. Among these extreme preterms, neonatal sepsis, IVH and mechanical ventilation were significant on univariate analysis; however, multivariate analysis identified only mechanical ventilation as an independent risk factor.

In the present study, a decrease in gestational age, i.e. from late preterm to very preterm and extreme preterm, was associated with the rising trend of NDD; however, it was not identified as a significant factor for at-risk of NDD. The toddlers born very preterm showed statistically significant decreased risk for ASQ failure on multivariate regression; however, its clinical relevance is not clear.

In this study, 84.7% of children were LBW; among them, 21.3% were at risk of NDD on ASQ 3. However, no statistical significance to NDD was observed. Ali Akbari SA et al.(32) reported that LBW was four times at risk of NDD, whereas Bajalan z et al.(23) could not find a significant association between preterm labor and low birth weight with NDD.

NICU stay was more in children at risk of NDD. However, it marginally missed the significance ($p=0.051$). Kerstjens M et al.(18) reported no association between neonatal sepsis and NDD, similarly in the current study, although neonatal sepsis was significant in univariate but could not be identified as an independent risk factor in multivariate analysis.

Soltani et al.(25) reported no association with the duration of hospital stay and mechanical ventilation. In the present study, 31.5% of children required mechanical ventilation during their NICU stay. Among them, 42.9% of children failed ASQ. The current study identified mechanical ventilation as an independent risk factor for the risk of NDD.

In this study, only 2 toddlers had a history of neonatal seizures, and both failed on ASQ. It showed an association with ASQ failure but could not show any significant strength of association.ASQ was mainly completed by the mothers. They found it easy to complete and did not require any assistance.

Although the estimated sample size was 145, the sample size could not be achieved during the study period. The study enrolled 111 preterm toddlers. As a single-centre study conducted in a tertiary care centre, the results may not represent preterm toddlers. Although we tried to identify the risk factors associated with ASQ failure, the sample size estimation was not done for this as they were secondary objectives.

CONCLUSION

The ASQ was easy to administer, and mothers/parents did not need assistance. Mothers/parents of any socioeconomic status and even with lower education can complete it. ASQ is a reliable screening tool that can be easily used in pediatric office practice. As early identification and intervention are crucial in managing neuro-developmental delay, paediatricians should routinely use ASQ in their office practice, especially for young children born preterm.

Table 1 – Socio-demographic Details Of The Children

Socio-demographic characteristics		Number of Children n=111	
		Frequency (n)	Percentage
Chronological age in months	≤ 18	65	58.6
	>18	46	41.4
Gender	Male	65	58.6
	Female	46	41.4
Area of Residence	Urban	106	95.5
	Rural	5	4.5
Type of Family	Joint	34	30.6
	Nuclear	77	69.4
Maternal age	20-29	61	55.0
	30-39	48	43.2
	≥ 40	2	1.8
Mother Education	≤ 12 standard	50	45.0
	> 12 standard	61	55.0
Maternal Employment Status	Employed	21	18.9
	Unemployed	90	81.1
Social Economic Status	Upper	7	6.3
	Upper Middle	46	41.4
	Lower Middle	31	27.9
	Upper Lower	26	23.4
	Lower	1	0.9
Child Nutrition Status	Stunting	42	37.8
	Wasting	20	18.0
	Underweight	43	38.7

Table 2 Frequency Of Proposed Antenatal Risk Factors For NDD Among The Study Participants

Proposed Antenatal Risk Factor		Number of children N=111	
		Frequency(n)	Percentage (%)
IVF	Yes	6	5.4
	No	105	94.6
Multiple Pregnancy	Yes	19	17.1
	No	92	82.9
APH	Yes	6	5.4
	No	105	94.6
PIH	Yes	29	26.1
	No	82	73.9
Chorioamnionitis	Yes	1	0.9
	No	110	99.1
Antenatal Steroids	Yes	65	58.6
	No	46	41.4
Maternal medical Illness	Yes	1	0.9
	No	110	99.1

Table 3. Distribution Of Proposed Perinatal Risk Factors For NDD Among The Study Participants

Proposed Perinatal risk factors		Number of Toddlers, n=111	
		Frequency(n)	Percentage (%)
Mode of Delivery	Vaginal	30	27.0
	LSCS	81	73.0
GA at Birth	Moderate to Late preterm	76	68.5
	Very Preterm	26	23.4
	Extreme preterm	9	8.1
LBW	Yes	94	84.7
	No	17	15.3
Need of Resuscitation	Yes	28	25.2
	No	83	74.8
NICU stay	Yes	8(	77.5
	No	25	22.5
Mechanical Ventilation	Yes	35	31.5
	No	76	68.5
Neonatal sepsis	Yes	49	44.1
	No	62	55.9
Neonatal seizures	Yes	2	1.8
	No	109	98.2
IVH	Yes	22	19.8
	No	89	80.2
Hyper bilirubinemia	Yes	63	56.8
	No	48	43.2

Table 4. Performance Of Children On Asq 3

	Result of ASQ N= 111 (%)	
Domain	Domain passed	Domain failed
Communication	108 (97.3)	3 (2.7)
Gross motor	94 (84.7)	17 (15.3)
Fine motor	104 (93.7)	7 (6.3)
Problem-solving	108 (97.3)	3 (2.7)
Personal Social	106 (95.5)	5 (4.5)

Table 5. Overall And Individual Domain Scores For The Toddlers

(n=111)	Minimum	Maximum	Mean	SD	Median	Q1	Q3
Overall ASQ score	135	300	257.43	41.66	265	235	290
Communication	10	60	50.86	11.26	55.00	45.00	60.00
Gross motor	10	60	51.62	14.37	60.00	50.00	60.00
Fine motor	20	60	52.16	9.71	55.00	45.00	60.00
Problem-solving	15	60	53.24	10.44	60.00	50.00	60.00
Personal-Social	10	60	50.14	11.37	50.00	40.00	60.00

Table 6. Individual domain score for those who failed on ASQ

(n=22)	Minimum	Maximum	Mean	SD
Overall ASQ score	135	265	201.36	41.75
Communication	10	60	42.05	15.25
Gross motor	10	60	**29.77**	17.56
Fine motor	20	60	**46.14**	14.05
Problem-solving	15	60	42.73	13.86
Personal Social	10	60	38.64	15.13

Table 7. Association Of Socio-demographic And Maternal Factors With At Risk Of NDD

		High risk for NDD on ASQ (n=111)		Total n (%)	Chi-square value	p-value
		Yes, n (%)	No, n (%)			
Gender	Male	17 (26.6)	48(73.4)	65(100)	3.96	**0.047***
	Female	5 (10.9)	41 (89.1)	46 (100)		
Chronological age in months	≤ 18	18(27.7)	47(72.3)	65(100)	6.11	**0.013**
	>18	4(8.7)	42(91.3)	46(100)		
Area of residence	Urban	17 (16.0)	89 (84.0)	106 (100)	21.81	**<0.001 ***
	Rural	5 (100)	0	5 (100)		
Type of Family	Joint	8 (23.5)	26 (76.5)	34 (100)	0.42	0.52
	Nuclear	14 (18.2)	63 (81.8)	77 (100)		
Maternal age	≥35	2 (11.8)	15 (88.2)	17 (100)	0.82	0.67*
	<35	20 (21.3)	74(78.7)	94 (10)		
Mother Education	≤12	5 (10.0)	45 (90.0)	50 (100)	5.52	**0.02***
	>12	17 (27.9)	44 (72.1)	61 (100)		
Employment status of Mother	Employed	3 (14.3)	18 (85.7)	21 (100)	0.50	0.48*
	Unemployed	19 (21.1)	71 (78.9)	90 (100)		
Socioeconomic status	Upper	3 (42.9)	4 (57.1)	7 (100)	9.54	**0.049***
	Upper Middle	11 (23.9)	35 (76.1)	46 (100)		
	Lower Middle	5 (16.1)	26 (83.9)	31 (100)		
	Upper Lower	2 (07.7)	24 (92.3)	26 (100)		
	Lower	1 (100%)	0	1 (100)		
Under Weight	Yes	13 (30.2)	30 (69.8)	43 (100)	4.78	**0.03**
	No	9 (13.2)	59 (86.8)	68 (100)		
Stunting	Yes	9 (21.4)	33 (78.6)	42 (100)	0.11	0.74
	No	13 (18.8)	56 (81.2)	69 (100)		
Wasting	Yes	6 (30.0)	14 (70.0)	20 (100)	1.59	0.21
	No	16 (17.6)	75 (82.4)	91 (100)		

* Indicate Fischer's exact test

Table 8.association Of Antenatal Factors With At Risk Of NDD Using ASQ

Antenatal factors		High risk on ASQ Yes n (%)	High risk on ASQ No n (%)	Total n (%)	Chi-square value	p-value
IVF	Yes	0	6 (100)	6 (100)	-	0.01*
	No	22 (21.0)	83 (79 .0)	105 (100)		
Multiple Pregnancy	Yes	3 (15.8)	16 (84.2)	19 (100)	-	0.76*
	No	19 (20.7)	73 (79.3)	92 (100)		
APH	Yes	1 (16.7)	5(83.3)	6 (100)	-	0.99*
	No	21 (20.0)	84 (80.0)	105 (100)		
PIH	Yes	3 (10.3)	26 (89.7)	29(100)	2.22	0.14
	No	19 (23.2)	63 (76.8)	82(100)		
Chorioamnionitis	Yes	0	1 (100)	1(100)	-	0.99*
	No	22(20.0)	88 (80.0)	110(100)		
Antenatal Steroids	Yes	17 (26.2)	48 (73.8)	65(100)	3.95	**0.047**
	No	5 (10.9)	41 (89.1)	46(100)		
Maternal Medical Illness	Yes	0	1(100)	1(100)	-	0.99*
	No	22 (20.0)	88 (80.0)	110(100)		

* Indicate Fisher Exact Test

Table 9.association Of Perinatal Factors With Risk Of NDD On ASQ

Perinatal risk factors		High risk on ASQ Yes n (%)	High risk on ASQ No n (%)	Total N (%)	Chi-square value	p-value
Resuscitation needed at Birth	Yes	9 (32.1)	19 (67.9)	28(100)	3.58	0.06
	No	13 (15.7)	70 (84.3)	83(100)		
GA at Birth	Moderate to Late preterm	11 (14.5)	65 (85.5)	76(100)	20.71	**<0.001**
	Very Preterm	4 (15.4)	22 (84.6)	26(100)		
	Extremely Preterm	7 (77.8)	2 (22.2)	9 (100)		
LBW	Yes	20 (21.3)	74 (78.7)	94(100)	0.82	0.37
	No	2 (11.8)	15 (88.2)	17(100)		
NICU stay	Yes	21(24.4)	65 (75.6)	86(100)	-	**0.02***
	No	1(04.0)	24 (96.0)	25(100)		
Neonatal sepsis	Yes	15 (30.6)	34 (69.4)	49(100)	6.43	**0.04**
	No	7 (11.3)	55 (88.7)	62(100)		
Neonatal seizures	Yes	2((100)	0	2(100)	8.23	**0.02**
	No	20 (18.3)	89 (81.7)	109(100)		
IVH	Yes	8 (36.4)	14(63.6)	22(100)	4.72	**0.039**
	No	14(15.7)	75(84.3)	89(100)		
Mechanical Ventilation	Yes	15 (42.9)	20 (57.1)	35(100)	17.07	**<0.001**
	No	7(09.2)	69(90.8)	76(100)		
Hyperbilirubinemia	Yes	16 (25.4)	47 (74.6)	63(100)	2.85	0.09
	No	6 (12.5)	42 (87.5)	48(100)		

* Indicate Fisher Exact Test

Table 10. Socio-demographic Factors For Risk Of NDD-Univariate Analysis

		High risk on ASQ Yes	High risk on ASQ No	Total	OR(95%CI)	p-value
Gender	Male	17	48	65	2.90(0.99-8.56)	0.053
	Female	5	41	46	1	
Chronological age in months	≤18	18	47	65	4.02(1.06-12.84)	**0.02**
	>18	4	42	46	1	
Type of Family	Joint	8	26	34	1.38(0.52-3.69)	0.52
	Nuclear	14	63	77	1	
Maternal Age	≥35	2	15	17	0.49(0.10-2.33)	0.37
	<35	20	74	94	1	
Maternal Education	>12	17	44	61	3.48(1.18-10.24)	**0.02**
	≤12	5	45	50	1	
Maternal Employment Status	Employed	3	18	21	0.62(0.17-2.34)	0.48
	Unemployed	19	71	90	1	
Stunting	Yes	9	33	42	1.17(0.45-3.05)	0.74
	No	13	56	69	1	
Wasting	Yes	6	14	20	2.00(0.67-6.02)	0.21
	No	16	75	91	1	
Underweight	Yes	13	30	43	2.84(1.09-7.40)	**0.03**
	No	9	59	68	1	

Table 11. Antenatal And Perinatal Factors For Risk Of NDD-Univariate Analysis

		High risk on ASQ Yes	High risk on ASQ No	Total	OR (95%CI)	p-value
Multiple Pregnancy	Yes	3	16	19	0.72(0.19-2.73)	0.63
	No	19	73	92	1	
APH	Yes	1	5	6	0.80(0.09-7.21)	0.84
	No	21	84	105	1	
PIH	Yes	3	26	29	0.38(0.10-1.40)	0.15
	No	19	63	82	1	
Antenatal Steroids	Yes	17	48	65	2.90 (0.99-8.56)	0.053
	No	5	41	46	1	
Resuscitation needed at Birth	Yes	9	19	28	0.39 (0.15-1.05)	0.06
	No	13	70	83	1	
GA at Birth	Extremely Preterm	7	2	9	20.68(3.79-112.81)	**0.001**
	Very Preterm	4	22	26	1.07(0.31-3.72)	0.91
	Moderate to Late preterm	11	65	76	1	
LBW	Yes	20	74	94	2.02(0.42-9.61)	0.37
	No	2	15	17	1	
NICU stay	Yes	21	65	86	7.75(0.99-60.83)	0.051
	No	1	24	25	1	
Neonatal sepsis	Yes	15	34	49	3.47(1.28-9.36)	**0.01**
	No	7	55	62	1	
IVH	Yes	8	14	22	3.06 (1.08-8.66)	**0.03**
	No	14	75	89	1	
Mechanical Ventilation	Yes	15	20	35	7.39(2.65-20.62)	**0.001**
	No	7	69	76	1	
Hyperbilirubinemia	Yes	16	47	63	2.38(0.85-6.65)	0.10
	No	6	42	48	1	

Table 12.multivariate Logistic Regression Analysis Of Socio-demographic, Antenatal And Perinatal Factors For Risk Of NDD

		High risk on ASQ Yes	High risk on ASQ No	Total	Adj OR(95%CI)	p-value
Chronological age in months	≤18	18	47	65	5.37(1.06-27.19)	**0.04**
	>18	4	42	46	1	
Maternal Education	>12	17	44	61	1.26(0.33-4.78)	0.73
	≤12	5	45	50	1	
GA at Birth	Extremely Preterm	7	2	9	3.58(0.22-57.42)	0.37
	Very Preterm	4	22	26	0.10 (0.01-0.87)	0.04
	Moderate to Late preterm	11	65	76	1	
Neonatal sepsis	Yes	15	34	49	0.98(0.21-4.69)	0.98
	No	7	55	62	1	
Mechanical Ventilation	Yes	15	20	35	12.78(1.44-113.53)	**0.02**
	No	7	69	76	1	
IVH	Yes	8	14	22	0.32(0.05-2.09)	0.23
	No	14	75	89	1	
Underweight	Yes	13	30	43	3.95(1.05-14.84)	**0.04**
	No	9	59	68	1	

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