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Factors Associated with the Death of Preterm Babies Admitted to Neonatal Intensive Care Units in Ethiopia: A Prospective, Cross-sectional, and Observational Study

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Abstract

Aim. To determine the risk factors for death among preterm neonates. *Methods and materials*. The data set used was derived from a prospective, multi-center, observational clinical study conducted in 5 tertiary hospitals in Ethiopia from July, 2016 to May, 2018. Subjects were infants admitted into neonatal intensive care unit. *Results.* Risk factors were determined using statistical model developed for this study. The mean gestational age was 32.87 (SD ± 2.42) weeks with a range of 20 to 36 weeks. There were 2667 (70.69%) survivors and 1106 (29.31%) deaths. The significant risk factors for preterm death were low gestational age, low birth weight, being female, feeding problem, no antenatal care visits and vaginal delivery among mothers with higher educational level. *Conclusions.* The study identified several risk factors for death among preterm neonates. Most of the risk factors are preventable. Thus, it is important to address neonatal and maternal factors identified in this study through appropriate ANC and optimum infant medical care and feeding practices to decrease the high rate of preterm death.

Keywords

risk factors, survival, preterm

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Introduction

It is estimated that 15 million babies born each year are preterm, of which more than 1 million die as a result of preterm birth and related complications.[1] Neonatal mortality rates have fallen globally between 1990 and 2017.[2] In Ethiopia neonatal mortality has declined by 1.9% per annum for 1995 to 2010.[3] Ethiopia met the Millennium Development Goals (MDG) in 2012 on child mortality and has developed a package of high impact child survival interventions for 2015 to 2020. However, the decline in neonatal mortality has been slow compared to the decline in child mortality rates. About 85% of preterm births world-wide occur in Asia and Africa[2] where health systems are weak and access to and utilization of health services is limited, contributing to the higher risks

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of death and disabilities in preterm babies.[4,5] Preterm infants are at increased risk of dying, especially from neonatal infections[6] with preterm birth estimated to be a risk factor in at least 50% of all neonatal deaths.[7] In Jordan, the neonatal mortality rate was 4/1000 live births among full term infants and 123/1000 live births among preterm babies indicating that being born preterm is a large risk factor for death.[8]

Identification of the risk factors for preterm death is important for developing specific interventions. There are many studies that addressed the risk factors for preterm infant death, however, the findings are varied. In Trinidad and Tobago, birth weight, length of time on the ventilator, and obstetric complications proved to significantly influence the odds of preterm neonatal death.[9] In China, shorter gestation, lower birth weight, and lower income were associated with a higher mortality rate, while use of newborn emergency transport services was associated with a lower preterm infant mortality rate.[10] In Iran, low gestational age, low birth weight, low Apgar scores, need for intensive supports, history of disease in mother, occurrence of pneumothorax, multiple gestation, and preeclampsia predicted occurrence of death in premature infants.[11] In East Africa, moderately preterm babies who were also small for gestational age experienced a considerably increased likelihood of neonatal death.[12] In a study in Ethiopia, having perinatal asphyxia, sepsis, jaundice, low gestational age, respiratory distress syndrome (RDS), and a low initial temperature were factors associated with time to preterm death.[13]

Thus, it can be noted the factors reported to be associated with death in preterm neonates vary from place to place. Therefore, it is relevant to study the factors associated with death among preterm infants born in Ethiopia with its unique socio-economic and cultural factors. Hence, the objectives of this study are to determine the risk factors for death among preterm neonates and the timing of death.

Methodology

Study Setting

The data set used in this study was based on a prospective, multi-center, observational clinical study conducted in neonatal intensive care units (NICU) of 5 tertiary hospitals in Ethiopia over a period of nearly 2 years from July, 2016 to May, 2018.[14] The study was conducted in three locations in Ethiopia, with an intent to obtain geographical representation from several regions across the country. The study hospitals were Gondar University Hospital (GUH), Jimma University Hospital (JUH), Gandhi Memorial Hospital (GMH), St Paul Millennium College hospital (SPH), and Tikur Anbessa Hospital (TAH). The main criteria for selection of hospitals for the study were prior research experience with newborn care, and the expected number of preterm infants that could be enrolled per year. Tikur Anbessa Hospital, Gandhi Memorial Hospital, and St Paul Hospital in Addis Ababa, Gondar University Hospital in the north and Jimma University Hospital in south-west of Ethiopia have significant child health research experience and the largest number of newborn intensive care unit (NICU) admissions in the country.

Study Population

All preterm infants admitted to one of the study hospitals with a gestational age of less than 37 completed weeks and up to the age of 7 days of postnatal life were enrolled. Three methods, that is, ultrasound, LMP, and physical examination using the new Ballard Score were used to estimate gestational age and to be sure that an infant was indeed "preterm". The following criteria were used:

- Mother delivered at or baby transferred to one of the participating study hospitals.
- Gestational age is <37 weeks according to the algorithm with the 3 methods.
- Live born defined as cry, breathing, or movement after delivery or Apgar ≥ 1.
- Infant age is <7 days when screened.
- Consent given for study participation.

Any live born baby that meets the gestational age and age criteria was enrolled in the study regardless of whether the baby dies prior to admission to the NICU or was discharged home without admission.

Exclusion criteria were:

- Delivery is a result of an induced abortion.
- Gestational age cannot be reliably determined using study criteria.

In this study, early preterm was defined as a gestational age of less than 34 weeks gestation whereas late preterm was defined as 34 to less than 37 weeks of gestation. There was a total of 3852 preterm births (<37 weeks of gestation) admitted to the NICUs at the study hospitals. All infants were followed using a standard protocol until 28 days, discharge or death. As shown in the flow diagram, 47 (1.22% of the 3852 preterm births) infants withdrew or were lost to follow-up and data on their survival status were not available. Moreover, to avoid the issue of missed information, complete case observations were considered. Therefore, the total number of complete cases to be considered in the analysis was based on 3773 preterm births (Figure 1).

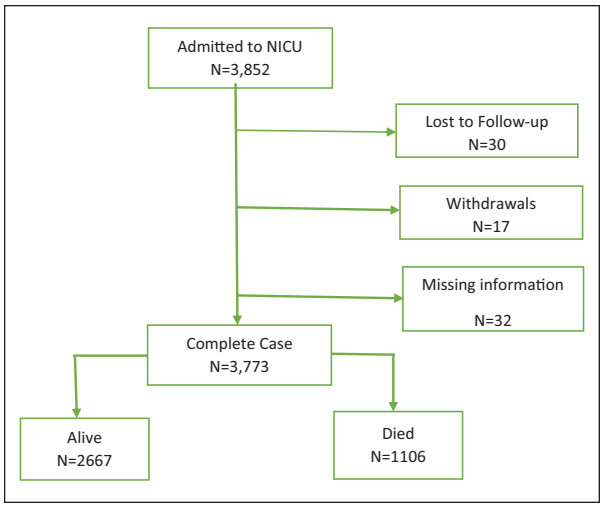

Figure 1. Flow diagram.

Exploratory Data Analysis

As a first step of the analysis, the data were explored in different ways in order to obtain details to help to make decisions regarding subsequent steps of the analysis. The Kaplan–Meier survival curve has been used to show the survival probabilities of infants for each study hospital.

To measure the association between each of the possible determinants and an outcome of interest, we used unadjusted hazard ratios (HR). An unadjusted HR in this analysis was computed by considering survival status of the neonate and one of the potential risk factors at a time. Then, a backward selection procedure based on the Cox proportional-hazards model by considering all the candidate factors and their possible interactions was performed. Finally, the potential risk factors to be included in the final regression model were determined from the backward stepwise selection method.

Statistical Model

Neonates admitted in the same hospital share the same facility, care and other services. However, such facility, care and other services may vary from one hospital to another. In order to consider the homogeneity or correlation usually present between observations within the same cluster/hospital, a semi-parametric frailty model would be more appropriate.[15,16] A frailty in this study context implies an unobservable random effect shared by the patients within a subgroup called hospitals. Hence, to identify the significant risk factors for the survival of neonates, a semi-parametric frailty model was used. The reason behind using this model for this study was due to the fact that infants are clustered within hospitals. This model incorporates cluster/hospital-specific random effects to account for the within cluster homogeneity with respect to the outcome of interests.

Assuming that subjects are nested in one of K clusters (e.g. hospitals in our case), a Cox model with mixed effects can be formulated as:

$$h_i(t) = h_0(t)\exp\left(X_i\beta + \tau_j\right)$$

where τ_j denotes the random effect/ frailty term associated with the j^{th} cluster/hospital. The cluster-specific random effect terms, τ_j, have a relative effect on the baseline hazard function. Thus, the relative effect of a given covariate pattern on the baseline hazard function varies across clusters.

In this study, gamma distribution for the shared frailty term was used as it has been used more frequently in the literature. The Expectation–Maximization algorithm[15,16] was used to fit the suggested model.

Both STATA and R statistical software were used for the data analyses. All tests were performed at 5% of significance level.

Ethical Approval and Informed Consent

The study was approved by the Institutional Review Board of each hospital and the College of Health Sciences, Addis Ababa University (Protocol no. 03/2016/PED). All participants provided written informed consent prior to enrolment in the study. The consent was obtained in Amharic or Oromifa languages, as appropriate. Confidentiality of the information was maintained.

Results

Out of the 3773 preterm births included in the analysis, 2036 (54%) were early preterm (<34 weeks) and 1737 (46%) were late preterm (34–36 weeks). The mean gestational age was 32.87 (SD ± 2.42) weeks with a range of 20 to 36 weeks. The average weight at birth was 1712 (SD ± 462) g. There were 2667 (70.69%) survivors and 1106 (29.31%) deaths of the neonates. The average length of stay in a hospital for those who were discharged alive was 12 days, while the average length of stay among those who died was 6 days.

As shown in Table 1, the overall mortality rate was 29.31%. The highest mortality rate was observed at JUH while the lowest mortality rate was noted in GMH.

To evaluate the discrepancy between the study hospitals in terms of the number of days when death occurred, a plot of the estimated survival probabilities for each hospital using the conventional Kaplan–Meier (KM)

Table 1. Mortality Rates, Mean Birth weights and Mean Gestational Ages across the Study Hospitals.

Hospital	Total admitted	Percent died	Mean birth weight (SD)	Mean gestational age (SD)
GMH	380	24.21	1695.12 (486.50)	32.56 (2.52)
GUH	873	29.21	1715.39 (397.30)	32.73 (2.50)
JUH	485	38.76	1662.31 (419.58)	32.47 (2.32)
SPH	1028	28.89	1646.61 (431.92)	32.96 (2.27)
TAH	1007	27.21	1805.90 (533.28)	33.22 (2.44)
Total	3773	29.31	1711.94 (461.92)	32.87 (2.42)

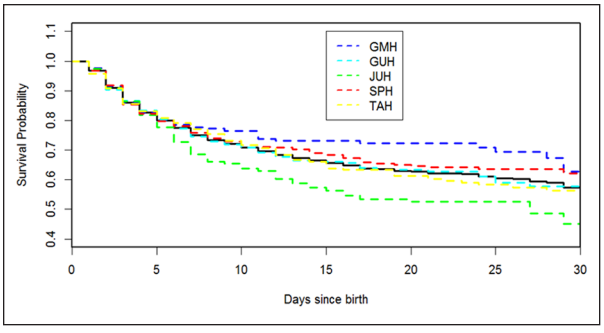

Figure 2. Survival probabilities for each hospital using the conventional (KM) graphical display.

graphical display is shown in Figure 2. The survival probabilities of preterm infants in all hospitals were nearly the same during the first 5 days from birth. However, a substantial difference in survival probability was observed after 5 days.

As shown in Table 2, low gestational age, low birth weight, single births, no formal education of mothers and very low and high maternal ages were found to be significant risk factors for the mortality of preterm infants. However, this analysis was done based on pairwise analysis without adjusting for the other possible risk factors. Table 3 also shows the obstetric risk factors for mortality of preterm infants. Receipt of any antenatal care (ANC) and antepartum hemorrhage (APH) were statistically significant in determining the risk of preterm mortality. However, we believe the results made using a semi-parametric frailty model are more informative since it adjusts for the effect of the other risk factors. Using the backward selection procedure, most of the basic characteristics listed in Tables 2 and 3 were considered as candidate risk factors for the final statistical model. Based on these candidate risk factors, the final semi-parametric frailty model was assessed. The proportional hazards (PH) assumption was checked for each selected covariates using the cox.zph function in the "*survival*" R package based on the *scaled Schoenfeld residuals*. The result suggested as none of the covariates violates the proportionality assumption of the Cox model. The proportional hazard assumption supported when we observe a non-significant relationship between residuals and time, and refuted by a significant relationship.

The adjusted hazard ratios and their 95% confidence intervals and *P*-values resulting from the semi-parametric frailty analyses are presented in Table 4. The significant risk factors for preterm deaths were low gestational age, low birth weight, being female, feeding problem of the neonate, and not ANC received. The interaction effects birth weight with feeding problem, feeding problem with first pregnancy, mother's formal education with C-section deliveries and mother's formal education with first pregnancy were also found to be significant risk factors. Thus, the relative risk of dying for early preterm infants relative to late preterm infant was 2.186, implying that an infant who is early preterm is 2.179 times more likely to die than a late preterm infant. In the same way, being low birth weight significantly increases the risk of dying. Moreover, not receiving ANC also increases the risk of dying for preterm infants. The risk of death for preterm births that have feeding problems is higher than those preterm births that are free from feeding difficulties. However, the magnitude of this risk depends on birth weight of the preterm infants. That is, the effect becomes relatively very high in preterm babies with lower birth weight. Among preterm infants who have feeding difficulties, being the first pregnancy increases the risk of death as compared to other births.

Female preterm infants are more likely to die than male preterm infants. The risk of death for preterm infants delivered with C-section depends on the maternal level of education. For the infants delivered from mothers with high level of education, C-section becomes more protective than vaginal deliveries. However, C-section increases the risk of death for the rest of preterm baby groups.

Discussions

This study has demonstrated that preterm mortality is quite high in NICUs with variations among the study

Table 2. Socio-Demographic Factors and Preterm Mortality in Ethiopia.

Characteristics		Survived	Died	Percent Died	Unadjusted HR (95% CI)	*P*-value
Gestational age	Early preterm	1165	871	42.78	Ref	
	Late preterm	1502	235	13.53	0.318 (0.275, 0.367)	.000
Birth weight (gms)	<1000	28	136	82.93	Ref	
	1000-1499	489	490	50.05	0.416 (0.344, 0.503)	.000
	1500-2500	1963	451	18.68	0.155 (0.128, 0.188)	.000
	>2500	187	29	13.43	0.125 (0.083,0.186)	.000
Sex of neonate	Male	1403	604	30.09	1.107 (0.983,1.245)	.094
	Female	1264	502	28.43	Ref	
Mode of delivery	C-section	1032	403	28.08	0.903 (0.799, 1.020)	.103
	Vaginal	1635	703	30.07	Ref	
Multiple births	Yes	932	324	25.80	0.796 (0.699, 0.906)	.001
	No	1735	782	31.07	Ref	
Formal education	No education	760	354	31.78	Ref	
	Primary	877	365	29.39	0.959 (0.829, 1.110)	.578
	Secondary	608	259	29.87	0.961 (0.818, 1.127)	.622
	Higher	422	128	23.27	0.702 (0.573, 0.859)	.001
Maternal age (years)	<19	107	62	36.69	Ref	
	19-35	2426	982	28.81	0.768 (0.595, 0.993)	.044
	>35	134	62	31.63	0.899 (0.633, 1.280)	.557

Table 3. Obstetric Factors and Preterm Neonatal Mortality.

Maternal clinical characteristics	Survived	Died	Percent died	Unadjusted HR (95% CI)	*P*-value
Antenatal care received	2532	1009	28.49	0.555 (0.515, 0.781)	.000
First pregnancy	994	435	30.44	1.054 (0.934, 1.189)	.393
HIV positive	70	23	24.73	0.852 (0.564, 1.287)	.446
History of tuberculosis	26	10	27.78	0.954 (0.512, 1.778)	.882
Infection	115	56	32.75	1.229 (0.939, 1.609)	.132
Malaria	121	52	30.06	1.035 (0.783, 1.367)	.810
Cardiac disease	33	9	21.43	0.667 (0.346, 1.285)	.226
Diabetes mellitus	36	11	23.4	0.855 (0.472, 1.548)	.604
Thyroid disease	28	6	17.65	0.548 (0.246, 1.223)	.142
Hypertensive disease	683	309	31.15	1.053 (0.923, 1.200)	.444
APH	237	127	34.89	1.201 (0.998, 1.445)	.052

hospitals. Similar to this study, in a previous study at TAH, the mortality rate among preterm neonates was 31.6%.[17] Furthermore, studies in other Addis Ababa hospitals, the mortality rate among preterm neonates was similar to this study.[18,19] Reports from Trinidad and Tobago and Iran indicate lower mortality rates among preterm infants of 18.7% and 12%, respectively.[9,11] In another study from Iran, the mortality rate concords to our study.[20] In a high income country like Norway high survival rate of 59% was reported among preterm neonates 22 to 27 weeks of gestation.[21] It can be noted that survival rates among hospital admitted preterm varies across institutions even in the same country as shown in Iran.[11,20] Helenius[22] reported outcomes of neonates from 10 national and regional networks with variation in survival and time of death among the network countries. This variation may be due to the health care delivery system and it may also depend on the referral system in the health care delivery of the country. In our study the high mortality could also be due to weak treatment facilities and referral system. In an earlier report the main cause of death among preterm neonates was respiratory distress syndrome accounting for 45% where the optimum treatment modality is not available in the study hospitals.[23]

In this study, the average length of stay among the neonates who died was 6 days. The study hospitals varied with timing of death after 5 days of age. In a community-based study in Ethiopia, 51.3% of neonates who died did so in less than 24 hours and 75.6% died within 6 days of life.[24] In another Ethiopian study among

Table 4. Adjusted Hazard Ratios Along with Their 95% Confidence Intervals for the Risk of Death.

Factors		HR	95% CI	*P*-value
Gestational age (Ref: Late Preterm)	Early preterm	2.186	(1.864, 2.563)	<.001
Birth weight (Ref: >2500)	<1000	5.577	(3.449, 9.017)	<.001
	1000-1499	2.463	(1.573, 3.858)	<.001
	1500-2500	1.093	(0.704, 1.696)	.693
Sex of neonate (Ref: Male)	Female	1.285	(1.139, 1.450)	.000
Mother's formal education (Ref: Higher Education)	No education	0.946	(0.698, 1.281)	.718
	Primary	1.211	(0.889, 1.648)	.225
	Secondary	0.882	(0.623, 1.249)	.480
Delivery (Ref: Normal)	C-section	0.623	(0.434, 0.894)	.010
Multiple birth (Ref: No)	Yes	0.791	(0.692, 0.905)	.001
Feeding problem		3.474	(1.454, 8.299)	.005
ANC		0.641	(0.511, 0.803)	.000
First pregnancy		0.896	(0.623, 1.288)	.553
Maternal infection		1.073	(0.752, 1.531)	.697
Cardiac disease		0.573	(0.295, 1.112)	.100
APH		0.574	(0.297, 1.109)	.099
Birth weight(<1000): Feeding problem		0.310	(0.120, 0.802)	.016
Birth weight (1000-1499): Feeding problem		0.401	(0.166, 0.969)	.042
Birth weight (1500-2500): Feeding problem		0.433	(0.179, 1.049)	.064
Mother's formal education (No education): First pregnancy		1.292	(0.844, 1.979)	.238
Mother's formal education (Primary): First pregnancy		1.178	(0.780, 1.780)	.435
Mother's formal education (Secondary): First pregnancy		1.724	(1.118, 2.660)	.014
Mother's formal education (No education): C-Section		1.901	(1.242, 2.910)	.003
Mother's formal education (Primary): C-Section		1.165	(0.764, 1.777)	.478
Mother's formal education (Secondary) : C-Section		1.735	(1.118, 2.692)	.014
Feeding problem: First pregnancy		0.657	(0.496, 0.869)	.003
ANC: APH		1.812	(0.914, 3.593)	.089
First pregnancy: Maternal Infection		1.685	(0.970, 2.926)	.064

preterm neonates admitted to a NICU, 11.4% died in the first 24 hours and 85.27% died in the first 7 days.[25] In a systematic review, it was noted that 83% of prematurity-related deaths occurred in the first week of life.[26] Thus, these findings indicate that the first few days are the most important period for the survival of preterm neonates when intensive care is required.

The primary aim of this study was to identify the risk factors for death among the preterm neonates. Neonatal factors including low gestational age, low birth weight, having feeding problem, and female sex were found to be risk factors for death among preterm infants.

Low gestational age was a risk factor for death among preterm neonates similar to a local[25] and studies from elsewhere.[10,20] It has been shown that as the gestational age increased the survival of the preterm infants significantly increased.[19]

It is a biological truth that neonates born too early will have difficulties to adapt to the external environment. It has also been demonstrated that the rate of complications decreases with progression of gestational age through the LP period.[27]

In this study low birth weight was found a risk factor for death among the study subjects. Other studies have shown that rate of mortality is in an inverse relationship with birth weight.[9,10,12,20,28] Low birth weight may be due to born too soon or it may be due growth failure in utero; both of which are not favorable for survival.

Gender differences in the rates of mortality vary in different age groups and medical conditions. In this study female gender was found as a risk factor for death among preterm neonates. Studies among preterm deaths have shown varied results with regard to gender as a factor for death. In an Ethiopian study gender was not a risk factor for death,[18] but in another Ethiopian study more deaths occurred in males,[3] so also in studies from other countries.[29,30] With the current knowledge we could not explain for these differences, suggesting for further studies with a larger sample size and different settings.

Mortality was higher among late (>24 hours) compared with early (<24 hours) breastfeeding initiators after adjustment for low birth weight, preterm birth, and other covariates.[31] Feeding problem is a risk factor for death in this study in agreement with earlier evidences

which showed that either predominately or exclusively breast-fed infants are at substantially lower risk for infant mortality than non-breast-fed infants.[32] That is, the effect becomes relatively very high in preterm babies with lower birth weight. Among preterm infants who have feeding difficulties, being the first pregnancy increases the risk of death as compared to other births.

In this study, no ANC visit was found as a significant risk factor for death among preterm neonates. A systematic in sub-Saharan African countries indicated that utilization of at least one antenatal care visit by a skilled provider during pregnancy reduces the risk of neonatal mortality by 39%.[33]

Among mothers with higher level of education vaginal delivery was a risk factor than C-section. However, a population-based data support the view that Caesarean section does not enhance the neonatal survival of VLBW babies when obstetric complications are absent.[34] In the multivariate analysis, adjusting for the other risk factors associated with mortality, delivery mode had no effect on infant survival among very low birth weight neonates.[35]

Our study showed that common diseases did not have effect on survival of preterm neonates. Yego et al[36] found that HIV and malaria had no significant effect on neonatal mortality but in another Nigerian study maternal febrile illness affected survival of preterm neonates.[37] In multi-country findings the risks of perinatal mortality was significantly increased with obstetric complications, systemic infections and severe anemia.[38] The differences in these studies is probably is that the severity of maternal illnesses have not been similar. In Vogel et al[38] pyelonephritis was not a significant risk factor but severe infections were risk factors for neonatal and fetal deaths. In the same study HIV was mixed with sever forms of HIV infection. Therefore, the limitation of our study is that we have not classified the maternal diseases by severity.

Conclusions

This study has identified risk factors for preterm deaths in Ethiopia. Some of the risk factors for death are easily preventable such as neonatal feeding problems and no ANC through essential newborn care and availing appropriate ANC service respectively. Thus, it is important to address neonatal and maternal factors identified in this study through appropriate ANC and optimum infant feeding practices to decrease the high rate of preterm death.

Appendix

Table. Testing the proportional hazards assumption for each covariate included in a Cox regression model fit using the R function *cox.zph*.

Factors	Chi-square	DF	*P*-value
Best GA	1.250	1	.264
Birth weight	3.590	3	.309
Infant sex	1.380	1	.240
Formal education	1.530	3	.216
C-section	0.120	1	.729
Multiple pregnancy	0.021	1	.884
Maternal age	0.173	2	.917
Feeding problem	0.283	1	.595
ANC	1.130	1	.288
First pregnancy	0.054	1	.816
Maternal infection	0.128	1	.721
Cardiac disease	0.992	1	.319
Thyroid disease	0.839	1	.360
APH	0.275	1	.600
Birth weight: Feeding problem	0.968	3	.809
Formal education: First pregnancy	9.960	3	.019
Feeding problem: First pregnancy	0.025	1	.874
Formal education: C-Section	2.450	3	.484
ANC: APH	0.591	1	.442
First pregnancy: Maternal Infection	0.000	1	.989
GLOBAL	43.500	31	.067

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Author Contributions

AM: Proposed the research idea, designed the study, contributed to data collection, analysis, interpretation, wrote the manuscript, and is accountable for all the research work.
ZT: Dealt with study design, data collection,analysis and interpretation, responsible for most of statistical analysis; involved in manuscript writing, responsible for all the research work.
LM: Participated in study design, data collection, analysis, interpretation, study follow-up and contributed in the write up of the manuscript.
EM: Particpated in study design, study follow-up and supervision and critically reviewed the manuscript.
RG: Participated in study design, study follow-up and supervision and critically reviewed the manuscript.
AK: Participated in study design, study follow-up and supervision and reviwed the manuscript.
MA: Prticpated in study design, data collection and site supervision and contributed to manuscript writing.
AG: Particpated in the design, data collection and site supervision and cpntributed to writing of the manuscript.
GG: Particpated in the design, data collection and site supervision and contributed to writing of the manuscript.
MB: Particpated in the design, data collection and site suervision and contributed to write up of the manuscript.

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