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Determinants of neonatal jaundice in neonates delivered at five referral hospitals in Amhara Region, Northern Ethiopia: an unmatched case-control study

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Abstract

Background: Neonatal jaundice is a major cause of hospital neonatal intensive care unit admission and readmissions during the neonatal period and is associated with a significant risk of neonatal morbidity and mortality. Hence, the aimed of this study was to identify the determinant factors of neonatal jaundice in neonates delivered at five referral hospitals in Amhara Region, Northern Ethiopia.

Method: An institution-based unmatched case-control study design was employed, on 447 neonates (149 cases and 298 controls) at referral hospitals in Amhara region, Northern Ethiopia, from March 1st to July 30th/2019. Consecutive sampling method was used to select both the cases and controls. The collected data were entered into Epi data version 4.2 and then exported into SPSS window version 24 for analysis. Bivariate and multivariable analysis were carried out by using binary logistic regression.

Results: The mean (±SD) age of neonate at the time of admission and gestational age were 2.96±2.48 days ranging from 1 to 24 days and 38.22 (±2.53) weeks respectively. Prolonged duration of labor (AOR=2.45, 95% CI =1.34-4.47), being male sex (AOR= 3.54, 95% CI=1.99-6.29), low birth weight (AOR=5.06, 95% CI =2.61-9.82), birth asphyxia (AOR= 2.88, 95% CI=1.38-5.99), sepsis/infection (AOR=2.49, 95% CI =1.22-5.11) and hypothermia (AOR= 2.88, 95% CI=2.63-14.02) were the risk factors for neonatal jaundice.

Conclusions: Prolonged duration of labor, hypothermia, sepsis, birth asphyxia, low birth weight and sex of neonate were independent determinants of neonatal jaundice. Early recognition and treatment of identified modifiable determinants are the recommended interventions.

Keywords: *neonatal jaundice, neonates, referral hospital*

What is known about this topics

- Jaundice is a common clinical problem in neonates that occur due to bilirubin disposition
- Previous studies done on determinant of neonatal jaundice identified some determinant factors but there was no consistency across the study.
- Research data on determinant of neonatal jaundice in prospective study are not done in Ethiopia.

What this study adds

- Prolonged duration of labor, hypothermia, sepsis, birth asphyxia, low birth weight and sex of neonate were the identified determinant factor for neonatal jaundice in Ethiopia.
- Prevention, early recognition and treatment of those identified modifiable risk factors should be considered to reduce neonatal jaundice

Background

Neonatal jaundice (NNJ) is a yellow-orange discoloration of the skin and sclera of neonates because of excessive bilirubin in the skin and mucous membranes [1]. In newborns, jaundice appears when total bilirubin (TB) is more than 7 mg /dl [2, 3]. Hyperbilirubinemia with a TB >25 to 30 mg/dL (428 to 513 µmol/L) is associated with an increased risk for bilirubin-induced neurologic dysfunction (BIND) with a significant risk of neonatal mortality and long-term neurodevelopmental sequelae such as cerebral palsy, sensor neural hearing loss, intellectual difficulties or gross developmental delays [4-7].

Jaundice can be severe when it is seen anywhere on the body on the first day or on the hands and feet in addition to the arms and legs on the next day. It can be managed by therapeutic interventions which include phototherapy, exchange transfusion and improving the frequency and efficacy of breastfeeding or supplementing inadequate formula breastfeeding [2, 8, 9].

Globally, 2.6 million newborns died in 2016, out of this half of all these deaths occurred in India, Pakistan, Nigeria, the Democratic Republic of Congo and Ethiopia. More than 22% neonatal deaths were associated with Rh disease and bilirubin encephalopathy in which Sub-Saharan Africa and South Asia account for 35%, and 39% of the deaths [10, 11]. Severe neonatal jaundice accounted for 2.8% of neonatal deaths in the UK, 30.8% in India, 34% in Nigeria, 14% in Kenya and 6.7% in Egypt [12]. Neonatal jaundice (NNJ) is a major cause of hospital NICU admission and accounts for 75% of hospital readmissions in the first week of life, and is associated with significant mortality [13-15]. It is a common condition worldwide occurring in up to 50% to 60% of full-term newborn babies and 80% of preterm newborn babies in the first week of life and it has been recognized as a condition which deserves more global health attention [16, 17]. Around three fourth, of affected neonates reside in Sub-Saharan Africa and South Asia [18-20] and surviving infants after severe neonatal jaundice may acquire long-term neurodevelopmental sequelae such as cerebral palsy, sensorinueral hearing loss, intellectual difficulties, upward gaze palsy, seizure, gross dental dysplasia and developmental delays in the survivors and death [21, 22]. Different studies done reported that in developed countries feto-maternal blood group incompatibilities are the leading cause of neonatal jaundice, but in developing countries, the case is different as it is mostly prematurity, low birth weight, birth trauma, ABO incompatibility, sepsis as well as effects of herbal medications in pregnancy and application of dusting powder on baby may result in G6PD deficiency which is one of the most important causes of neonatal jaundice in Africa and Asia [23,

24]. Despite a remarkable reduction in the under-five mortality in the past few years following important interventions like immunization, early detection and treatment of infections and diarrhea control programs, the neonatal mortality in sub-Saharan Africa including Ethiopia is still alarmingly high which is 30/1000 [25].

The early identification of neonates who are at a greater risk of developing severe neonatal jaundice is of paramount importance to prevent brain damage [26]. Therefore, this study aimed to identify the determinants of sever neonatal jaundice among neonates at referral hospitals in Amhara region, Northern Ethiopia, 2019.

Methods

Study setting, design and period

A hospital-based unmatched case-control study design was conducted from March 1st to July 30th at Amhara regional state referral hospitals. According to 2019 Amhara region, health bureau reports the region has a total of six referral hospitals. Namely: Felegehiwot referral hospital, University of Gondar referral hospital, Debre Markos referral hospital, Debre Birhan referral hospital, Dessie referral hospital and Tibebe Gion referral hospital.

Inclusion criteria: All neonates who were present to the pediatric/NICU ward of the hospital with neonatal jaundice (pathological), were included as cases and neonates without neonatal jaundice, healthy babies not on any medication, except Nevirapine for the prevention of mother to child transmission (PMTCT) with volunteer mothers were included as controls in the study.

Exclusion criteria: Babies with or without neonatal jaundice and whose mothers did not consent to be enrolled were excluded from the study.

Operational Definitions

Neonatal Jaundice: Neonates diagnosed as jaundiced through clinical signs and symptoms and/or laboratory investigations (total bilirubin value more than 12mg/100ml in term babies and more than 15mg/100ml in preterm babies) by physicians (General practitioners, Pediatricians and Neonatologists) [39].

Physiological Jaundice: Neonates in the presence of one more of the established IMNCI criteria (only skin on the face or eyes yellow and infant aged 2-13 days old) along with total bilirubin value under 12mg/100ml in term babies and under 15mg/100ml in preterm babies.

Hyperthermia: an axillary temperature of >37.5^{0}C

Hypothermia: an axillary temperature of less than 36.5^{0}C

Hyperglycemia: blood glucose level greater than 125mg/dl.

Hypoglycemia: blood glucose level less than 40mg/dl.

Neonatal sepsis: a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first 4 weeks of life.

Sample size determination and sampling procedures

Sample size was calculated using Open EPI INFO version 7 software with double population formula by assuming; confidence interval: 95%, power: 80%, case to control ratio: 1:2, P1: percent

of outcome with exposed group (neonates with jaundice) = 80.6%, P2: percent of outcome in unexposed group (neonates without jaundice) = 14.5% (33). In consideration of 10% of the non-response rate, the final sample was adjusted to 453(151 cases and 302 controls).

Data Collection tool and procedures

Data were collected by interview with the mothers and review of case records of neonates in the hospital. A checklist consisting of demographic, neonatal, and maternal information were used for data collection. The questions are both open and close-ended. The questionnaire addressed the women's socio-demographic characteristics, obstetrics and health-related characteristics and neonatal related characteristics.

Data quality control

Two days training was given for data collectors and supervisors on how to ask and fill the questions, and how to approach the respondents. The questionnaires were pre-tested in 5% of the total sample size at Woldia general hospital before the actual data collection time to see the accuracy of responses, language clarity and appropriateness of the tools. Double data entry was done for its validity and compared to the original data.

Data processing and analysis

The data was coded, cleaned, edited and entered into Epi data version 4.2.0.0 to minimize logical errors and design skipping patterns. Then, the data was exported to SPSS window version 24 for analysis. Bivariate analysis was used to see the association between each determinant and the outcome variable by using binary logistic regression. Adjusted odds ratio along with 95% CI was estimated and P-value < 0.05 was set as a cut-off point for the significant determinants of neonatal jaundice.

Patient and public involvement

In this study neither patient nor public were involved in study proposal development, design and analysis of the study.

Results

Socio-demographic characteristics

In this study, a total of 447 neonates with their mother (149 cases and 298 controls) were included making the overall response rate of 98.68%. The mean age of the study participant was 26.79 (± 5.05 SD) years which ranged from 18 to 43 years. About 85% of cases and more than four-fifths of controls were between the age group of 20-35 years. One hundred one (67.8%) of cases and 213(71.5%) of controls were orthodox religion followers (**Table 1**).

Obstetric characteristics

The mean gestational age of the baby at birth (±SD) was 38.22 (±2.53) weeks. Regarding parity, 100(67.1%) of cases and 244(81.9%) controls were primiparous. Regarding utilization of antenatal care, almost all 145 (97.3%) of cases and 272(91.3%) of controls had ANC follow-up, of them 116(77.9%) of cases and 204(68.5%) controls had 2-4 ANC visit during their recent pregnancy. One hundred forty-six (98.0%) of cases and 287(96.3%) of controls haven't a history of using traditional medicine (**Table 2**).

Neonatal related characteristics

In this study, 87(58.4%) of cases and 170(57.0%) of controls were males. The mean (±SD) of age at the time of admission was 2.96±2.48 days ranging from 1 to 24 days of whom 100(67.1%) of cases and 199(66.8%) of controls of neonates age lies within 2-7 days. Fifty-eight (38.9%) of cases and 8(2.7%) of controls were hypothermic whereas 27(18.1%) of cases and 4(1.3%) of controls were hypoglycemic (**Table 3**).

Determinants of neonatal jaundice

In bivariate binary logistic regression the covariates mothers education level, duration of labor, sex of neonates, birth weight, neonatal sepsis, APGAR score, gestational age, PROM, birth asphyxia, parity, hypothermia, feed breast milk, MSAF, Obstetrics complication and history of jaundice were candidate for multivariable binary logistic regression model. Multivariable binary logistic regression analysis was done by taking variables showing significant association on bivariate analysis at a p-value of ≤0.25 to control (adjust) the possible confounding. Prolonged duration of labor, hypothermia, sex of neonate, sepsis, birth asphyxia and birth weight had a significant association with neonatal jaundice at p-value <0.05 in multivariate analysis.

The odds of neonatal jaundice among mothers whose labor was prolonged were 2.45 times higher than neonates delivered from mothers whose labor was normal(AOR=2.45, 95% CI =1.34-4.47, P-value=0.004). The chance of developing neonatal jaundice among male neonates was 3.54 times higher than female neonates (AOR= 3.54, 95% CI=1.99-6.29, P-value<0.001). The odds of neonatal jaundice among neonates whose birth weight less than 2500 gram were 5.06 times higher than that of neonates whose birth weight were greater than 2500 grams(AOR=5.06, 95% CI =2.61-9.82; P-value<0.001).

Neonates with birth asphyxia had a risk of neonatal jaundice 2.88 times higher than neonates without birth asphyxia (AOR= 2.88, 95% CI=1.38-5.99, P-value=0.012). Similarly, neonates with sepsis/infection had a risk of neonatal jaundice 2.49 times higher than neonates without sepsis (AOR=2.49, 95% CI =1.22-5.11, P-value=0.005). The odds of neonatal jaundice among neonates with hypothermia were 6.07 times higher than neonates without hypothermia (AOR= 2.88, 95% CI=2.63-14.02, P-value<0.001) (**Table 4**).

Discussion

This study was employed using institution-based unmatched case-control study design among neonates in Amhara region referral hospitals, Northern Ethiopia to investigate the main determinants of Neonatal jaundice. Thus, from the adjusted analysis, we found that prolonged duration of labor, hypothermia, parity, sex of neonate, birth asphyxia, sepsis, and birth weight were independent determinants of neonatal jaundice.

This study revealed that prolonged duration of labor was found to be a determinant factor for neonatal jaundice. This finding was consistent with studies conducted in the USA [27], Tehran Iran [28], Nepal [29], Ghana [30] and Mekelle Ethiopia [31]. This might be attributed to bruising and swelling of the scalp of newborns due to the excessive pressure applied by birth attendants as management for prolonged labor which in turn increases risk of jaundice by increasing bilirubin level in the blood. It may also be due to the clinical relationship between longer labor and cephalohaematoma, a known risk factor for neonatal jaundice and/or severe Hyperbilirubinemia.

This study shows the sex of neonate was an important determinant factor for neonatal jaundice. This finding is consistent with a study conducted in Nepal [29], Iran [32], Addis Ababa Ethiopia [33] and Mekelle Ethiopia [31]. This might be due to male newborns have relatively immature liver which may not be able to process all the bilirubin formed from red blood cells in normal condition.

This study revealed that the birth weight of newborns was a determinant factor for neonatal jaundice. The odds of neonatal jaundice among neonates with birth weight less than 2500 gram were 5.06 times higher than neonates with normal birth weight. This finding was in line with studies conducted in Tehran Iran [28], Kerala India [34], North India [35], Nepal [29], South Nigeria [46], and Ghana [30]. This might be due to the fact that most of the time low birth weight is common in newborns with prematurity the presents with immature organs particularly immature liver which fails to conjugate normally produced bilirubin from red blood cell which results in jaundices.

Birth asphyxia was also an important determinant of neonatal jaundice. The odds of neonatal jaundice among neonates with birth asphyxia were 2.88 times higher than neonates without birth asphyxia. Different studies conducted in Hyderabad India [37], Kerala India [34], Southern Nigeria [36] and Southeastern Nigeria [38] supported that neonatal jaundices are influenced by birth

asphyxia. This might be due to the fact that asphyxia is an insult to the newborn due to lack of oxygen, lack of perfusion to various organs which results in multiorgan system dysfunction due to hypoxic damage mainly on brain, lung, liver and intraventricullar hemorrhage which affect the bilirubin conjugation ability of the liver that results in jaundice.

This study revealed that neonatal sepsis was another determinant factor for neonatal jaundice. The odds of neonatal jaundice among neonates with neonatal sepsis were 2.49 times that of neonates without neonatal sepsis. This finding is in line with a study conducted in North India [35], Kerala India [34], Southeastern Nigeria [38], Addis Ababa Ethiopia [33] and Mekelle Ethiopia [31]. This might be due to the fact that sepsis might cause hemolysis of red blood cells and hepatic dysfunction that leads to accumulation of serum bilirubin in the body.

This study revealed that hypothermia was an important determinant of neonatal jaundice. The odds of neonatal jaundice among neonates with hypothermia were 6.07 times that of neonates without hypothermia. This might be due to the fact that prolonged cold injury leads to edema, general hemorrhage (especially pulmonary hemorrhage) which produces excess bilirubin that increases unconjugated serum bilirubin level [39].

Conclusion

This study showed that maternal/obstetrics and neonatal characteristics were risk factors for neonatal jaundices in the study area. Prolonged duration of labor, hypothermia, low birth weight sepsis, birth asphyxia and sex of neonate were independent determinants of neonatal jaundice. Early recognition and treatment of identified modifiable determinants are the recommended interventions.

Abbreviations

AOR: Adjusted Odd Ratio, NICU: Neonatal Intensive Care Unit, NNJ: Neonatal Jaundice, SPSS: Statistical Package for Social Sciences, TSB: Total Serum Bilirubin, WHO: World Health Organizations

Declarations

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Author's Contributions

AD was the principal investigator who initiated the research, wrote the research proposal, conducted the fieldwork, supervised data entry, analyzed the data and wrote the manuscript. All authors (AD, AW, BA, GG, and AG) critically reviewed, provided substantive feedback and contributed to the intellectual content of this paper and made substantial contributions to the conception, conceptualization and manuscript preparation of this study. All authors read and approved the final manuscript.

Availability of data and materials

The dataset supporting the conclusions of this article is available from the authors on request.

Ethical approval and consent to participant

Ethical clearance was obtained from Woldia University, institutional health research ethics review committee (wdu/rcs/aca/fhs/34/2019).

Consent for publication

Not applicable.

Competing interest

The authors declared that they have no competing interests.

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Table 1: Socio-demographic characteristics of mothers in five referral hospitals of Amhara region, Northern Ethiopia, 2019 (Cases=149, Controls=298).

Characteristics	Category	Neonatal jaundice	
		Yes (%)	No (%)
Mothers age (Years)	<20	14(9.4)	39(13.1)
	20-35	127(85.2)	244(81.9)
	>35	8(5.4)	15(5.0)
Marital status	Married	142(95.3)	281(94.3)
	Divorced	4(2.7)	14(4.7)
	Others*	3(2.0)	3(1.0)
Religion	Orthodox	101(67.8)	213(71.5)
	Muslim	46(30.9)	82(27.5)
	Others**	2(1.3)	3(1.0)
Ethnicity	Amhara	135(90.6)	280(94.0)
	Oromo	13(8.7)	16(5.4)
	Others***	1(0.7)	2(0.6)
Mothers education	No formal education	41(27.5)	48(16.1)
	Read and write	23(15.4)	39(13.1)
	Primary education	35(23.5)	68(22.8)
	Secondary education	29(19.5)	77(25.8)
	College and above	21(14.1)	66(22.1)
Occupation of the mother	Government employee	19(12.8)	57(19.1)
	Housewife	96(64.4)	137(46.0)
	Merchant	10(6.7)	21(7.0)
	Student	2(1.3)	31(10.4)
	Farmer	13(8.7)	22(7.4)
	Daily workers	3(2.0)	20(6.7)
	Others****	6(4.0)	10(3.4)
Residence	Urban	98(65.8)	215(72.1)
	Rural	51(34.2)	83(27.9)

Others*: Divorced. Single, **others****: protestant, catholic, **others*****: Southern nation nationalities and peoples of Ethiopia, Tigray, **Others******: private employee.*

Table 2: Obstetrics characteristics of mothers in five referral hospitals of Amhara region, Northern Ethiopia, 2019(Cases=149, Controls=298).

Characteristics	Category	Neonatal jaundice	
		Yes (%)	No (%)
Number of delivery (Parity)	Primiparous	100(67.1)	244(81.9)
	Multiparous	49(32.9)	54(18.1)
Previous child Hx of Neonatal jaundice	Yes	21(14.1)	19(6.4)
	No	128(85.9)	279(93.6)
Antenatal care follow-up	Yes	145(97.3)	272(91.3)
	No	4(2.7)	26(8.7)
Number of antenatal care visit(n=417)	1	10(6.7)	31(10.4)
	2-4	116(77.9)	204(68.5)
	>4	23(15.4)	63(21.1)
Hx of using traditional medicine	Yes	3(2.0)	11(3.7)
	No	146(98.0)	287(96.3)
Obstetrics complication during pregnancy	Yes	56(37.6)	83(27.9)
	No	93(62.4)	215(72.1)
Type of obstetrics complication	HTN	24(46.2)	28(53.8)
	Obstructed labor	3(37.5)	5(62.5)
	Antepartum hemorrhage	12(36.4)	21(63.6)
	Anemia	8(47.1)	9(52.9)
	Multiple pregnancy	6(54.5)	5(45.5)
	Gestational DM	3(60.0)	2(40.0)
	Intrauterine growth restriction	3(50.0)	3(50.0)
	Oligohaydraminous	7(36.8)	12(63.2)
Rh status	Positive	128(85.9)	250(83.9)
	Negative	21(14.1)	48(16.1)
Blood group	A	35(23.5)	60(20.1)
	B	33(22.1)	61(20.5)
	AB	19(12.8)	44(14.8)
	O	62(41.6)	133(44.6)
Gestational age at birth (in weeks)	Preterm(<37 weeks)	57(38.3)	64(21.5)
	Term(37-42)weeks	72(48.3)	177(59.4)
	Post-term (≥42weeks)	9(6.0)	19(6.4)
	Unknown	11(7.4)	38(12.8)
Onset of labor	Spontaneous	132(88.6)	240(80.5)
	Induced	15(10.1)	40(13.4)
	Not in labor	2(1.3)	18(6.0)
Method of induction (n=55)	Oxytocin	13(86.7)	40(100)
	Others	2(13.3)	-
Presentation	Normal presentation	136(91.3)	282(94.6)
	Malpresentation	13(8.7)	16(5.4)
Premature rupture of membrane	Yes	53(35.6)	54(18.1)
	No	96(64.4)	244(81.9)

Meconium stained amniotic fluid(n=107)	Yes	15(28.3)	17(31.5)
	No	38(71.7)	37(68.5)
Meconium stained amniotic fluid Grade(n=32)	Grade I	4(26.7)	7(41.2)
	Grade II	8(53.3)	8(47.1)
	Grade III	3(20.0)	2(11.8)
Duration of labor	Normal	96(64.4)	214(71.8)
	Prolonged	53(35.6)	84(28.2)
Mode of delivery	Spontaneous vaginal delivery	99(66.4)	207(69.5)
	Cesarean section	39(26.2)	63(21.1)
	Instrumental delivery	11(7.4)	28(9.4)

Table 3: Neonatal characteristics distribution among Neonates in five referral Hospitals of Amhara Region, Northern Ethiopia, 2019(Cases=149, Controls=298).

Characteristics	Category	Neonatal jaundice	
		Yes (%)	No(%)
Sex of neonates	Male	87(58.4)	170(57.0)
	Female	62(41.6)	128(43.0)
Age of neonates at admission (in days)	<2 days	30(20.1)	83(27.9)
	2-7 days	100(67.1)	199(66.8)
	>7 days	19(12.8)	16(5.4)
Birth weight (gram)	<2500	59(39.6)	46(15.4)
	2500-4000	88(59.1)	246(82.6)
	≥4000	2(1.3)	6(2.0)
Five minute APGAR score	≤6	13(8.7)	10(3.4)
	7-10	136(91.3)	288(96.6)
Birth asphyxia	Yes	42(28.2)	33(11.1)
	No	107(71.8)	265(88.9)
Feed breast milk	Yes	138(92.6)	283(94.9)
	No	11(7.4)	15(5.1)
Use formula feeding	Yes	14(9.4)	12(4.0)
	No	135(90.6)	286(96.0)
MAS	Yes	20(13.4)	16(5.4)
	No	129(86.6)	282(94.6)
Hypothermia	Yes	58(38.9)	8(2.7)
	No	91(61.1)	290(97.3)
Hypoglycemia	Yes	27(18.1)	4(1.3)
	No	122(81.9)	294(98.7)
Neonatal sepsis/ infections	Yes	81(54.4)	10(3.4)
	No	68(45.6)	288(96.6)
Birth trauma	Yes	13(8.7)	4(1.3)
	No	136(91.3)	294(98.7)

Table 4: Association of socio-demographic, obstetric and neonatal risk factors with neonatal jaundice in referral hospitals of Amhara region, Northern Ethiopia, 2019 (Cases=149, Controls=298).

Characteristics	Neonatal jaundice		COR (95%CI)	AOR (95%CI)
	Yes (%)	No (%)		
Mothers education				
No formal education	41(27.5)	48(16.1)	2.68(1.41-5.11)	0.83(0.35-1.97)
Read and write	23(15.4)	39(13.1)	1.85(0.91-3.77)	1.05(0.41-2.67)
Primary education	35(23.5)	68(22.8)	1.61(0.85-3.06)	1.22(0.53-2.80)
Secondary education	29(19.5)	77(25.8)	1.18(0.61-2.26)	0.72(0.31-1.66)
College and above	21(14.1)	66(22.1)	1	1
Parity				
Primiparous	100(67.1)	244(81.9)	1	1
Multiparous	49(32.9)	54(18.1)	2.21(1.41-3.47)	2.89(0.86-5.59)
Hx of Neonatal jaundice				
Yes	21(14.1)	19(6.4)	2.29(1.18-4.44)	2.06(0.84-5.06)
No	128(85.9)	279(93.6)	1	1
Obstetrics complication				
Yes	56(37.6)	83(27.9)	1.56(1.03-2.36)	0.79(0.44-1.44)
No	93(62.4)	215(72.1)	1	1
Gestational age at birth				
Preterm	57(38.3)	64(21.5)	2.19(1.39-3.43)	1.08(0.54-2.13)
Term	72(48.3)	177(59.4)	1	1
Postterm	9(6.0)	19(6.4)	1.16(0.50-2.69)	1.07(0.35-3.22)
Unknown	11(7.4)	38(12.8)	0.712(0.34-1.46)	0.98(0.41-2.34)
PROM				
Yes	53(35.6)	54(18.1)	2.49(1.59-3.89)	1.43(0.73-2.77)
No	96(64.4)	244(81.9)	1	1
Duration of labor				
≤24 hour	96(64.4)	214(71.8)	1	1
>24 hour	53(35.6)	84(28.2)	1.96(1.29-2.99)	**2.45(1.34-4.47)***
Sex of neonates				
Male	87(58.4)	170(57.0)	2.4(1.57-3.65)	**3.54(1.99-6.29)****
Female	62(41.6)	128(43.0)	1	1
Birth weight (gram)				
<2500	59(39.6)	46(15.4)	6.67(4.13-10.77)	**5.06(2.61-9.82)****
2500-4000	88(59.1)	246(82.6)	1	1
≥4000	2(1.3)	6(2.0)	1.11(0.22-5.62)	1.69(0.25-11.30)
Five minute APGAR score				
≤6	13(8.7)	10(3.4)	2.75(1.17-6.43)	1.48(0.41-5.28)
7-10	136(91.3)	288(96.6)	1	1
Birth asphyxia				
Yes	42(28.2)	33(11.1)	4.14(2.47-6.95)	**2.88(1.38-5.99)*****

No	107(71.8)	265(88.9)	1	1
Feed breast milk				
Yes	138(92.6)	283(94.9)	1	1
No	11(7.4)	15(5.1)	3.09(1.94-4.92)	1.46(0.73-2.89)
Neonatal sepsis				
Yes	81(54.4)	10(3.4)	8.09(4.83-13.56)	**2.49(1.22-5.11)****
No	68(45.6)	288(96.6)	1	1
MSAF				
Yes	20(13.4)	16(5.4)	2.73(1.37-5.44)	2.39(0.88-6.48)
No	129(86.6)	282(94.6)	1	1
Hypothermia				
Yes	58(38.9)	8(2.7)	6.76(3.79-12.07)	**6.07(2.63-14.02)****
No	91(61.1)	290(97.3)	1	1

Significant at: *P=004, **P<0.001, ***P=012, ****P=0.005, 1= constant

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Determinants of neonatal jaundice among neonates admitted to five referral hospitals in Amhara Region, Northern Ethiopia: an unmatched case-control study

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Abstract

Background: Neonatal jaundice is associated with a significant risk of neonatal morbidity and mortality' It is a major cause of hospital neonatal intensive care unit admission and readmissions during the neonatal period. Hence, the study aimed to identify the determinant factors of neonatal jaundice among neonates admitted at five referral hospitals in Amhara Region, Northern Ethiopia.

Method: A hospital-based unmatched case-control study design was employed, on 447 neonates (149 cases and 298 controls) at referral hospitals in Amhara region, Northern Ethiopia, from March 1st to July 30th/2019. Consecutive sampling method was used to select both the cases and controls. The collected data were entered into Epi data version 4.2 and then exported into SPSS window version 24 for analysis. Bivariable and multivariable analysis were carried out by using binary logistic regression. A p-value of < 0.05 was considered as significant difference between cases and controls for the exposure variable of interest.

Results: The median (±IQR) age of neonate at the time of admission and gestational age were 3±2 days and 38 (±3) weeks respectively. Prolonged duration of labor (AOR=2.45, 95% CI =1.34-4.47), being male sex (AOR= 3.54, 95% CI=1.99-6.29), low birth weight (AOR=5.06, 95% CI =2.61-9.82), birth asphyxia (AOR= 2.88, 95% CI=1.38-5.99), sepsis (AOR=2.49, 95% CI =1.22-5.11) and hypothermia (AOR= 2.88, 95% CI=2.63-14.02) were the determinant factors for neonatal jaundice.

Conclusions: Prolonged duration of labour, hypothermia, sepsis, birth asphyxia, low birth weight and sex of neonate were independent determinants of neonatal jaundice. Early recognition and management of identified modifiable determinants are the recommended interventions.

Keywords: *neonatal jaundice, neonates, referral hospital*

What is known about these topics

- Jaundice is a common clinical problem in neonates that occur due to bilirubin disposition
- Previous studies done on the determinant of neonatal jaundice in Ethiopia were done using chart review identified the prevalence of neonatal jaundice using cross-sectional study design.
- Research data on the determinant of neonatal jaundice in the prospective study are not done in Ethiopia.

What this study adds

- Prolonged duration of labour, hypothermia, sepsis, birth asphyxia, low birth weight and sex of neonate was the identified determinant factor for neonatal jaundice in Ethiopia.
- Prevention, early recognition and treatment of those identified modifiable risk factors should be considered to reduce neonatal jaundice

Background

Neonatal jaundice (NNJ) is a yellow-orange discolouration of the skin and sclera of neonates because of excessive bilirubin in the skin and mucous membranes [1]. In newborns, jaundice appears when total bilirubin (TB) is more than 120 µmol/L [2, 3]. Hyperbilirubinemia with a TB 428 to 513 µmol/L is associated with an increased risk for bilirubin-induced neurologic dysfunction (BIND) with a significant risk of neonatal mortality and long-term neurodevelopmental sequelae [4-7]. Around three fourth, of affected neonates, reside in Sub-Saharan Africa and South Asia [8-10] and surviving infants after severe neonatal jaundice may acquire long-term neurodevelopmental sequelae such as cerebral palsy, sensorineural hearing loss, intellectual difficulties, upward gaze palsy, seizure, gross dental dysplasia and developmental delays in the survivors and death [7, 11, 12]. Hyperbilirubinemia can be described in the form of pathological, physiological, jaundice secondary to breast milk or breastfeeding failure, and hemolytic jaundice due to Glucose-6-phosphate dehydrogenase deficiency (GDPD), ABO and Rh incompatibility[12-14].

Jaundice can be severe when it is seen anywhere on the body on the first day or the hands and feet in addition to the arms and legs on the next day. It can be managed by therapeutic interventions which include phototherapy, exchange transfusion and improving the frequency and efficacy of breastfeeding or supplementing inadequate formula breastfeeding [2, 14, 15].

Globally, 2.6 million newborns died in 2016, out of this half of all these deaths occurred in India, Pakistan, Nigeria, the Democratic Republic of Congo and Ethiopia. More than 22% of neonatal deaths were associated with Rh disease and bilirubin encephalopathy in which Sub-Saharan Africa and South Asia account for 35%, and 39% of the deaths [8, 16]. Severe neonatal jaundice accounted for 2.8% of neonatal deaths in the UK, 30.8% in India, 34% in Nigeria, 14% in Kenya and 6.7% in Egypt [17]. Neonatal jaundice (NNJ) is a major cause of hospital NICU admission and accounts for 75% of hospital readmissions in the first week of life, and is associated with significant mortality [18-20]. It is a common condition worldwide occurring in up to 50% to 60% of full-term newborn babies and 80% of preterm newborn babies in the first week of life and it has been recognized as a condition which deserves more global health attention [21, 22]. Different studies done reported that in developed countries feto-maternal blood group incompatibilities are the leading cause of neonatal jaundice, but in developing countries, the case is different as it is mostly prematurity, low birth weight, birth trauma, ABO incompatibility, sepsis as well as effects

of herbal medications in pregnancy and application of dusting powder on the baby may result in G6PD deficiency which is one of the most important causes of neonatal jaundice in Africa and Asia [23, 24]. In studies conducted in Tikur Anbessa Specialized Hospital and Mekelle, Ethiopia showed that prolonged labour, maternal "O" blood group, and sepsis were identified determinant factors for neonatal jaundices [25, 26]. Despite a remarkable reduction in the under-five mortality in the past few years following important interventions like immunization, early detection and treatment of infections and diarrhoea control programs, the neonatal mortality in sub-Saharan Africa including Ethiopia is still alarmingly high which is 30/1000 [27].

The early identification of neonates who are at a greater risk of developing severe neonatal jaundice is of paramount importance to prevent brain damage [28]. Therefore, this study aimed to identify the determinants of neonatal jaundice among neonates admitted at referral hospitals in Amhara region, Northern Ethiopia, 2019.

Methods

Study setting, design and period

A hospital-based unmatched case-control study design was conducted from March 1st to July 30th at Amhara regional state referral hospitals. According to 2019 Amhara region, health bureau reports the region has a total of six referral hospitals. Namely: Felegehiwot referral hospital, University of Gondar referral hospital, Debre Markos referral hospital, Debre Birhan referral hospital, Dessie referral hospital and Tibebe Gion referral hospital. Of the total six hospitals, five of them except Tibebe Gion referral hospital (newly opened referral hospital) have had level-III (subspecialty) NICU rendering services with continuously available personnel (paediatricians and/or neonatologists, general practitioners and neonatal nurses) and equipment to provide life support for as long as needed. All referral hospitals provide general and specialized treatment, known to be open 24 hours for emergency services and each of them assumed to serve more than 5 million peoples.

Inclusion criteria: All neonates who were present to the NICU ward of the hospital with neonatal jaundice (pathological), were included as cases and neonates without neonatal jaundice, healthy babies not on any medication, except Nevirapine for the prevention of mother to child transmission (PMTCT) with volunteer mothers were included as controls in the study.

Exclusion criteria: Babies with or without neonatal jaundice, abandoned neonates, critically ill and mentally incompetent mothers were excluded from the study. Additionally, neonates with incomplete chart were excluded from the study.

Operational Definitions

Neonatal Jaundice: Neonates diagnosed as jaundiced through history, clinical signs and symptoms and/or laboratory investigations (total bilirubin value more than 205 µmol/L in term babies and more than 257 µmol/L in preterm babies) by physicians (General practitioners, Pediatricians and Neonatologists) [29].

Physiological Jaundice: Neonates in the presence of one more of the established IMNCI criteria (only skin on the face or eyes yellow and infant aged 2-13 days old) along with total bilirubin value under 205 µmol/L in term babies and under 257 µmol/L in preterm babies.

Hyperthermia: an axillary temperature of >37.5^{0}C

Hypothermia: an axillary temperature of less than 36.5^{0}C

Hyperglycemia: blood glucose level greater than 125mg/dl.

Hypoglycemia: blood glucose level less than 40mg/dl.

Neonatal sepsis: a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first 4 weeks of life.

Meconium aspiration syndrome: is a breathing problem that a newborn baby may have due to the aspiration of stained amniotic fluid, which can occur before, during, or immediately after birth.

Traditional medicine: taking any herbal traditional medicine during pregnancy to treat nausea and vomiting, reduce the risk of preeclampsia, shorten labour and treat the common cold and urinary tract infections.

Sample size determination and sampling procedures

The sample size was calculated using Open EPI INFO version 7 software with double population formula by assuming; confidence interval: 95%, power: 80%, case to control ratio: 1:2, P1: percent of outcome with an exposed group (neonates with jaundice) = 80.6%, P2: percent of outcome in the unexposed group (neonates without jaundice) = 14.5% [26]. In consideration of 10% of the non-response rate, the final sample was adjusted to 453(151 cases and 302 controls).

Data collection tool and procedures

The data were collected after admission by diploma nurses and midwives working in the labor ward and NICU ward under the supervision of BSc holder neonatal nurses. Data were collected by interview with the mothers and review of case records of neonates in the hospital. A checklist consisting of demographic, neonatal, and maternal information were used for data collection. The questions are both open and close-ended. The questionnaire addressed the women's socio-demographic characteristics, obstetrics and health-related characteristics and neonatal related characteristics.

Data quality control

Two days training was given for data collectors and supervisors on how to ask and fill the questions, and how to approach the respondents. The questionnaires were pre-tested in 5% of the total sample size at Woldia general hospital before the actual data collection time to see the accuracy of responses, language clarity and appropriateness of the tools. The necessary amendment was done based on the findings of the pretest and the amended tool was used for actual

data collection at the selected public health facilities. Double data entry was done by two data clerks and compared to the original data to check the consistency.

Data processing and analysis

The data were coded, cleaned, edited and entered into Epi data version 4.2.0 to minimize logical errors and design skipping patterns. Then, the data were exported to SPSS window version 24 for analysis. The bivariable analysis was used to see the association between each determinant and the outcome variable by using binary logistic regression. All variables with $P \leq 0.25$ in the bivariable analysis was included in the final model of multivariable analysis. Adjusted odds ratio along with 95% CI was estimated and P-value < 0.05 was set as a cut-off point for the significant determinants of neonatal jaundice.

Ethical considerations

The ethical clearance was obtained from Woldia University, College of Health Sciences, institutional health research ethics review committee (IHRERC) with Ref No. (Wdu/rcs/aca/fhs/34/2019). A formal letter for permission and support from Woldia University wrote to Amhara regional health bureau (ARHB) and finally to selected health facilities. All the study participants were informed about the purpose of the study, their right to refuse. Written and signed voluntary consent was obtained from mothers before distributing the questionnaire. The respondents were also be told that the information obtained from them was treated with complete confidentiality and do not cause any harm to them.

Patient and public involvement

In this study, neither patient nor public was involved in study proposal development, design and analysis of the study.

Results

Socio-demographic characteristics

In this study, a total of 447 neonates with their mother (149 cases and 298 controls) were included making the overall response rate of 98.68%. The median ((± IQ range) age of the mother was 26±7 years which ranged from 18 to 43 years. About 85% of mothers who have neonates with jaundice and more than four-fifths (81.9%) of mothers with neonates without jaundice were between the age group of 20-35 years (**Table 1**).

Obstetric characteristics

The median (±IQR) gestational age of the baby at birth were 38 (±3) weeks. Regarding parity, 100(67.1%) of cases and 244(81.9%) controls were primiparous. Regarding utilization of antenatal care, almost all 145 (97.3%) of cases and 272(91.3%) of controls had ANC follow-up, of them 116(77.9%) of cases and 204(68.5%) controls had 2-4 ANC visit during their recent pregnancy. One hundred forty-six (98.0%) of cases and 287(96.3%) of controls haven't a history of using traditional medicine. Concerning the mode of delivery, 99(66.4%) of cases and 207(69.5%) of controls were delivered through spontaneous vaginal delivery. A total of 39 (11 cases and 28 controls) were delivered through instrumental deliveries. Of these 4 cases and 8 controls were through forceps whereas 7 cases and 20 controls were delivered via vacuum (**Table 2**).

Neonatal related characteristics

In this study, 87(58.4%) of cases and 170(57.0%) of controls were males. The median (±IQR) age of neonate at the time of admission were 3±2 days ranging from less than 1 day to 24 days of whom 100(67.1%) of cases and 199(66.8%) of controls of neonates age lies within 2-7 days. Fifty-eight (38.9%) of cases and 8(2.7%) of controls were hypothermic whereas 27(18.1%) of cases and 4(1.3%) of controls were hypoglycemic (**Table 3**).

Determinants of neonatal jaundice

In bivariable binary logistic regression the covariates mothers education level, duration of labour, sex of neonates, birth weight, neonatal sepsis, APGAR score, gestational age, PROM, birth asphyxia, parity, hypothermia, feed breast milk, MSAF, obstetrics complication and history of jaundice were candidates for the multivariable binary logistic regression model. Multivariable binary logistic regression analysis was done by taking variables showing significant association

on bivariable analysis at a p-value of ≤0.25 to control (adjust) the possible confounding factors. Prolonged duration of labour, hypothermia, sex of neonate, sepsis, birth asphyxia and birth weight had a significant association with neonatal jaundice at p-value <0.05 in multivariate analysis.

The odds of neonatal jaundice were 2.45 times higher among neonates born from mothers whose labour was prolonged than neonates delivered from mothers whose labour was normal (AOR=2.45, 95% CI =1.34-4.47, P-value=0.004). The chance of developing neonatal jaundice among male neonates was 3.54 times higher than female neonates (AOR= 3.54, 95% CI=1.99-6.29, P-value<0.001). The odds of neonatal jaundice were 5.06 times more likely among neonates with birth weight less than 2500 gram than neonates with normal birth weight (AOR=5.06, 95% CI =2.61-9.82; P-value<0.001).

The odds of neonatal jaundice were 2.88 times more likely among neonates with birth asphyxia than neonates without birth asphyxia (AOR= 2.88, 95% CI=1.38-5.99, P-value=0.012). Similarly, the odds of neonatal jaundice were 2.49 times more likely among neonates with neonatal sepsis than neonates without neonatal sepsis. (AOR=2.49, 95% CI =1.22-5.11, P-value=0.005). The odds of neonatal jaundice were 6.07 times higher among neonates with hypothermia than neonates without hypothermia (AOR= 2.88, 95% CI=2.63-14.02, P-value<0.001) (**Table 4**).

Discussion

This study was employed using institution-based unmatched case-control study design among neonates in Amhara region referral hospitals, Northern Ethiopia to investigate the main determinants of Neonatal jaundice. Thus, from the adjusted analysis, we found that prolonged duration of labour, hypothermia, parity, sex of neonate, birth asphyxia, sepsis, and birth weight were independent determinants of neonatal jaundice.

This study revealed that prolonged duration of labour was found to be a determinant factor for neonatal jaundice. This finding was consistent with studies conducted in the USA [30], Tehran Iran [31], Nepal [32], Ghana [33] and Mekelle Ethiopia [25]. This might be attributed to bruising and swelling of the scalp of newborns due to the excessive pressure applied by birth attendants as management for prolonged labour which in turn increases the risk of jaundice by increasing bilirubin level in the blood. It may also be due to the clinical relationship between longer labour with cephalohaematoma and subgaleal hemorrhage which is a known determinant factor for neonatal jaundice and/or severe Hyperbilirubinemia.

This study shows the sex of neonate was an important determinant factor for neonatal jaundice. Male sex was a determinant factor for neonatal jaundice. This finding is consistent with a study conducted in Nepal [32], Iran [24], Pasir Malaysia [34], Addis Ababa Ethiopia [26] and Mekelle Ethiopia [25]. This might be due to male newborns have relatively immature liver which may not be able to process all the bilirubin formed from red blood cells in normal condition. Besides, a male has a higher concentration of bilirubin and hige risk of acute bilirubin encephalopathy as compared with females [12, 35].

This study revealed that the birth weight of newborns was a determinant factor for neonatal jaundice. The odds of neonatal jaundice were 5.06 times more likely among neonates with birth weight less than 2500 gram than neonates with normal birth weight. This finding was in line with studies conducted in Tehran Iran [31], Kerala India [36], North India [37], Nepal [32], South Nigeria [38], and Ghana [33]. This might be due to the fact that most of the time low birth weight is common in newborns with prematurity the presents with immature organs particularly immature liver which fails to conjugate normally produced bilirubin from red blood cell which results in jaundices [35, 39].

Birth asphyxia was also an important determinant of neonatal jaundice. The odds of neonatal jaundice were 2.88 times more likely among neonates with birth asphyxia than neonates without birth asphyxia. Different studies conducted in Kerala India [36], Southern Nigeria [38] and Southeastern Nigeria [40] supported that neonatal jaundices are influenced by birth asphyxia. This might be due to the fact that asphyxia is an insult to the newborn due to lack of oxygen, lack of perfusion to various organs which results in multiorgan system dysfunction due to hypoxic damage mainly on brain, lung, liver and intraventricular hemorrhage which affect the bilirubin conjugation ability of the liver that results in jaundice [41]. Also, perinatal asphyxia with hypoxic-ischemic encephalopathy (HIE) can lead to disruption of the blood-brain barrier (BBB), thereby allowing free entry of the unconjugated bilirubin to the neurons resulting in acute bilirubin encephalopathy. Besides, kidney damage from PNA can lead to less excretion of the conjugated bilirubin, thereby causing conjugated Hyperbilirubinemia and jaundice [42].

This study revealed that neonatal sepsis was another determinant factor for neonatal jaundice. The odds of neonatal jaundice were 2.49 times more likely among neonates with neonatal sepsis than neonates without neonatal sepsis. This finding is in line with a study conducted in North India

[37], Kerala India [36], Southeastern Nigeria [40], Addis Ababa Ethiopia [26] and Mekelle Ethiopia [25]. This might be due to the fact that sepsis might cause hemolysis of red blood cells and hepatic dysfunction that leads to accumulation of serum bilirubin in the body [43].

This study revealed that hypothermia was an important determinant of neonatal jaundice. The odds of neonatal jaundice were 6.07 times more likely among neonates with hypothermia than neonates without hypothermia. This might be due to the fact that prolonged cold injury mainly moderate and severe hypothermia leads to oedema, general haemorrhage (especially pulmonary haemorrhage) which produces excess bilirubin that increases unconjugated serum bilirubin level [29].

Conclusion

This study showed that maternal/obstetrics and neonatal characteristics were risk factors for neonatal jaundices in the study area. Prolonged duration of labour, hypothermia, low birth weight sepsis, birth asphyxia and sex of neonate were independent determinants of neonatal jaundice. Therefore, health providers should provide client-centered and meticulous antenatal care for high-risk pregnancies and intrapartum and post-partum care which help to identify high-risk newborns before discharge during routine postnatal care that would reduce the short and long-term complication that arise from late diagnosis. Furthermore, the ministry of health should formulate and evolve strategies to identify high-risk cases and optimize early recognition and management strategies for the identified modifiable determinants to reduce the incidence of neonatal jaundice.

Abbreviations

AOR: Adjusted Odd Ratio, NICU: Neonatal Intensive Care Unit, NNJ: Neonatal Jaundice, SPSS: Statistical Package for Social Sciences, TSB: Total Serum Bilirubin, WHO: World Health Organizations

Declarations

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Author's Contributions

AD was the principal investigator who initiated the research, wrote the research proposal, conducted the fieldwork, supervised data entry, analyzed the data and wrote the manuscript. All authors (AD, AW, BA, GG, and AG) critically reviewed, provided substantive feedback and contributed to the intellectual content of this paper and made substantial contributions to the conception, conceptualization and manuscript preparation of this study. All authors read and approved the final manuscript.

Availability of data and materials

The dataset supporting the conclusions of this article is available from the authors on request.

Ethical approval and consent to participant

Ethical clearance was obtained from Woldia University, institutional health research ethics review committee (wdu/rcs/aca/fhs/34/2019).

Consent for publication

Not applicable.

Competing interest

The authors declared that they have no competing interests.

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Table 1: Socio-demographic characteristics of mothers in five referral hospitals of Amhara region, Northern Ethiopia, 2019 (Cases=149, Controls=298).

Characteristics	Category	Neonatal jaundice	
		Yes (%)	No (%)
Mothers age (Years)	<20	14(9.4)	39(13.1)
	20-35	127(85.2)	244(81.9)
	>35	8(5.4)	15(5.0)
Marital status	Married	142(95.3)	281(94.3)
	Divorced	4(2.7)	14(4.7)
	Others*	3(2.0)	3(1.0)
Mothers education	No formal education	41(27.5)	48(16.1)
	Read and write	23(15.4)	39(13.1)
	Primary education	35(23.5)	68(22.8)
	Secondary education	29(19.5)	77(25.8)
	College and above	21(14.1)	66(22.1)
Occupation of the mother	Government employee	19(12.8)	57(19.1)
	Housewife	96(64.4)	137(46.0)
	Merchant	10(6.7)	21(7.0)
	Student	2(1.3)	31(10.4)
	Farmer	13(8.7)	22(7.4)
	Daily workers	3(2.0)	20(6.7)
	Others**	6(4.0)	10(3.4)
Residence	Urban	98(65.8)	215(72.1)
	Rural	51(34.2)	83(27.9)

Others*: Divorced. Single, ***Others*****: private employee.*

Table 2: Obstetrics characteristics of mothers in five referral hospitals of Amhara region, Northern Ethiopia, 2019(Cases=149, Controls=298).

Characteristics	Category	Neonatal jaundice	
		Yes (%)	No (%)
Health institutions	University of Gondar referral hospital	31(20.8)	71(23.8)
	Debre Markos referral hospital	14(9.4)	31(10.4)
	Felege Hiwot referral hospital	53(35.6)	67(22.5)
	Debre Birhan referral hospital	28(18.8)	65(21.8)
	Dessie referral hospital	23(15.4)	64(21.5)
Number of delivery (parity)	Primiparous	100(67.1)	244(81.9)
	Multiparous	49(32.9)	54(18.1)
Previous child Hx of Neonatal jaundice	Yes	21(14.1)	19(6.4)
	No	128(85.9)	279(93.6)
Antenatal care follow-up	Yes	145(97.3)	272(91.3)
	No	4(2.7)	26(8.7)
Number of antenatal care visit(n=417)	1	10(6.7)	31(10.4)
	2-4	116(77.9)	204(68.5)
	>4	23(15.4)	63(21.1)
Hx of using traditional medicine	Yes	3(2.0)	11(3.7)
	No	146(98.0)	287(96.3)
Obstetrics complication during pregnancy	Yes	56(37.6)	83(27.9)
	No	93(62.4)	215(72.1)
Type of obstetrics complication	HTN	24(46.2)	28(53.8)
	Obstructed labor	3(37.5)	5(62.5)
	Antepartum haemorrhage	12(36.4)	21(63.6)
	Anemia	8(47.1)	9(52.9)
	Multiple pregnancy	6(54.5)	5(45.5)
	Gestational DM	3(60.0)	2(40.0)
	Intrauterine growth restriction	3(50.0)	3(50.0)
	Oligohaydraminous	7(36.8)	12(63.2)
Rh status	Positive	128(85.9)	250(83.9)
	Negative	21(14.1)	48(16.1)
Blood group	A	35(23.5)	60(20.1)
	B	33(22.1)	61(20.5)
	AB	19(12.8)	44(14.8)
	O	62(41.6)	133(44.6)
Gestational age at birth (in weeks)	Preterm	57(38.3)	64(21.5)
	Term	72(48.3)	177(59.4)
	Post-term	9(6.0)	19(6.4)
	Unknown	11(7.4)	38(12.8)
Onset of labour	Spontaneous	132(88.6)	240(80.5)
	Induced	15(10.1)	40(13.4)
	Not in labor	2(1.3)	18(6.0)
Method of induction (n=55)	Oxytocin	13(86.7)	40(100)
	Others	2(13.3)	-

Presentation	Normal presentation	136(91.3)	282(94.6)
	Malpresentation	13(8.7)	16(5.4)
Premature rupture of membrane	Yes	53(35.6)	54(18.1)
	No	96(64.4)	244(81.9)
Meconium stained amniotic fluid(n=107)	Yes	15(28.3)	17(31.5)
	No	38(71.7)	37(68.5)
Meconium stained amniotic fluid Grade(n=32)	Grade I	4(26.7)	7(41.2)
	Grade II	8(53.3)	8(47.1)
	Grade III	3(20.0)	2(11.8)
Duration of labour	Normal	96(64.4)	214(71.8)
	Prolonged	53(35.6)	84(28.2)
Mode of delivery	Spontaneous vaginal delivery	99(66.4)	207(69.5)
	Cesarean section	39(26.2)	63(21.1)
	Instrumental delivery	11(7.4)	28(9.4)

Table 3: Neonatal characteristics distribution among Neonates in five referral Hospitals of Amhara Region, Northern Ethiopia, 2019 (Cases=149, Controls=298).

Characteristics	Category	Neonatal jaundice	
		Yes (%)	No(%)
Sex of neonates	Male	87(58.4)	170(57.0)
	Female	62(41.6)	128(43.0)
Age of neonates at admission (in days)	<2 days	30(20.1)	83(27.9)
	2-7 days	100(67.1)	199(66.8)
	>7 days	19(12.8)	16(5.4)
Birth weight (gram)	<2500	59(39.6)	46(15.4)
	2500-4000	88(59.1)	246(82.6)
	≥4000	2(1.3)	6(2.0)
Five minute APGAR score	≤6	13(8.7)	10(3.4)
	7-10	136(91.3)	288(96.6)
Birth asphyxia	Yes	42(28.2)	33(11.1)
	No	107(71.8)	265(88.9)
Feed breast milk	Yes	138(92.6)	283(94.9)
	No	11(7.4)	15(5.1)
Use formula feeding	Yes	14(9.4)	12(4.0)
	No	135(90.6)	286(96.0)
MAS	Yes	20(13.4)	16(5.4)
	No	129(86.6)	282(94.6)
Hypothermia	Yes	58(38.9)	8(2.7)
	No	91(61.1)	290(97.3)
Hypoglycemia	Yes	27(18.1)	4(1.3)
	No	122(81.9)	294(98.7)
Neonatal sepsis/ infections	Yes	81(54.4)	10(3.4)
	No	68(45.6)	288(96.6)
Birth trauma	Yes	13(8.7)	4(1.3)
	No	136(91.3)	294(98.7)

Table 4: Association of socio-demographic, obstetric and neonatal risk factors with neonatal jaundice in referral hospitals of Amhara region, Northern Ethiopia, 2019 (Cases=149, Controls=298).

Characteristics	Neonatal jaundice		COR (95%CI)	AOR (95%CI)
	Yes (%)	No (%)		
Mothers education				
No formal education	41(27.5)	48(16.1)	2.68(1.41-5.11)	0.83(0.35-1.97)
Read and write	23(15.4)	39(13.1)	1.85(0.91-3.77)	1.05(0.41-2.67)
Primary education	35(23.5)	68(22.8)	1.61(0.85-3.06)	1.22(0.53-2.80)
Secondary education	29(19.5)	77(25.8)	1.18(0.61-2.26)	0.72(0.31-1.66)
College and above	21(14.1)	66(22.1)	1	1
Parity				
Primiparous	100(67.1)	244(81.9)	1	1
Multiparous	49(32.9)	54(18.1)	2.21(1.41-3.47)	2.89(0.86-5.59)
Hx of Neonatal jaundice				
Yes	21(14.1)	19(6.4)	2.29(1.18-4.44)	2.06(0.84-5.06)
No	128(85.9)	279(93.6)	1	1
Obstetrics complication				
Yes	56(37.6)	83(27.9)	1.56(1.03-2.36)	0.79(0.44-1.44)
No	93(62.4)	215(72.1)	1	1
Gestational age at birth				
Preterm	57(38.3)	64(21.5)	2.19(1.39-3.43)	1.08(0.54-2.13)
Term	72(48.3)	177(59.4)	1	1
Postterm	9(6.0)	19(6.4)	1.16(0.50-2.69)	1.07(0.35-3.22)
Unknown	11(7.4)	38(12.8)	0.712(0.34-1.46)	0.98(0.41-2.34)
PROM				
Yes	53(35.6)	54(18.1)	2.49(1.59-3.89)	1.43(0.73-2.77)
No	96(64.4)	244(81.9)	1	1
Duration of labor				
≤24 hour	96(64.4)	214(71.8)	1	1
>24 hour	53(35.6)	84(28.2)	1.96(1.29-2.99)	**2.45(1.34-4.47)***
Sex of neonates				
Male	87(58.4)	170(57.0)	2.4(1.57-3.65)	**3.54(1.99-6.29)****
Female	62(41.6)	128(43.0)	1	1
Birth weight (gram)				
<2500	59(39.6)	46(15.4)	6.67(4.13-10.77)	**5.06(2.61-9.82)****
2500-4000	88(59.1)	246(82.6)	1	1
≥4000	2(1.3)	6(2.0)	1.11(0.22-5.62)	1.69(0.25-11.30)
Five minute APGAR score				
≤6	13(8.7)	10(3.4)	2.75(1.17-6.43)	1.48(0.41-5.28)
7-10	136(91.3)	288(96.6)	1	1
Birth asphyxia				
Yes	42(28.2)	33(11.1)	4.14(2.47-6.95)	**2.88(1.38-5.99)*****

No	107(71.8)	265(88.9)	1	1
Feed breast milk				
Yes	138(92.6)	283(94.9)	1	1
No	11(7.4)	15(5.1)	3.09(1.94-4.92)	1.46(0.73-2.89)
Neonatal sepsis				
Yes	81(54.4)	10(3.4)	8.09(4.83-13.56)	**2.49(1.22-5.11)****
No	68(45.6)	288(96.6)	1	1
MAS				
Yes	20(13.4)	16(5.4)	2.73(1.37-5.44)	2.39(0.88-6.48)
No	129(86.6)	282(94.6)	1	1
Hypothermia				
Yes	58(38.9)	8(2.7)	6.76(3.79-12.07)	**6.07(2.63-14.02)****
No	91(61.1)	290(97.3)	1	1

Significant at: *P=004, **P<0.001, ***P=012, ****P=0.005, 1= constant