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Determinants of neonatal sepsis among neonates admitted to neonatal intensive care unit of public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020. Unmatched case-control study.

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Abstract

Introduction: Reducing neonatal sepsis by improving the quality of care is a global and local priority. Despite the highest burden of neonatal sepsis in the region, determinants of neonatal sepsis in the neonatal intensive care units were not well understood. Therefore, this study was conducted to find out determinants of neonatal sepsis in the neonatal intensive care units in public hospitals of Hawassa city administration, Sidama region, Ethiopia, 2020.

Methods: Institutional based unmatched case-control study was conducted from August 1st to September 30, 2020. Data were collected by using a pretested, interviewer-administered questionnaire and data extraction checklist. After data collection, data were coded and entered into Epi data version 3.1 and exported to SPSS version 20 for analysis. Bivariate and multivariate logistic regression analyses were done to identify the determinants of neonatal sepsis. Finally, the statistically significant association of variables was determined based on a p-value<0.05.

Results: A total of 331(110 cases and 221 controls) neonates with their index mothers were included. Cesarean section [AOR= 2.56; 95% CI (1.3- 5.00)], maternal history of anemia [AOR =2.58; 95% CI (1.45-4.6)] and not vaccinated to Tetanus toxoid [AOR= 3.5 95% CI (2.07-6.19)] were identified variables as determinants of neonatal sepsis.

Conclusions: Cesarean section, maternal history of anemia, and not vaccinated to tetanus were founded to be risk factors of neonatal sepsis. Establishing preconception care practice, strengthening quality of ANC care and standardized infection prevention practice are needed for the improvement of neonatal health.

Keywords: Determinants, Neonatal Sepsis, Neonatal Intensive Care Unit, Ethiopia.

Strengths and limitations of this study

- The study addressed all of public hospitals found in Hawassa city.
- Appropriate statistical methods were used.
- As the association between the exposure and the outcome variables was measured using OR, the true relationship might have been overestimated as OR tends to overestimated the relative risk.
- Cause–effect relationships could not be determined.

Introduction

Neonatal sepsis is a systemic infection occurring in infants ≤28 days of life (1). According to the onset of symptoms, neonatal sepsis can be classified as early- onset neonatal sepsis or late-onset neonatal sepsis (2).

Reducing neonatal sepsis by improving the quality of care is a global and local priority. Worldwide, the neonatal mortality rate is on the way of decrement from 36 deaths per 1,000 live births in 1990 to 19 in 2015, and the number of neonatal deaths also declined from 5.1 to 2.7 in 1990 to 2015 respectively. But when we compare neonatal and post neonatal mortality rates, neonatal mortality declined slower than the decline in the post-neonatal mortality rate (1-59 months) mortality rate, which is 47 % and 58 % respectively (3).

Worldwide, an estimated 750,000 annual neonatal deaths were due to neonatal sepsis with mortality highest in sub-Saharan Africa (4). Though the neonatal deaths are preventable, the problem is highly concentrated in the world's poorest countries and 85% of all the neonatal mortality occurred in low and middle-income countries (5). Studies indicated that neonatal sepsis presents a $10–$469 billion financial burden that could be decreased through successful treatment and prevention in SSA (4).

According to the mini Ethiopian Demographic and Health Survey (EDHS) 2019, neonatal mortality rate have shown decrement from 39 per 1000 live births in 2005 to 30 in 2019. But there is a slight increment of neonatal mortality in 2019 as compared to 29 neonatal death per 1000 live births reported in 2016 EDHS (6).

Regarding the prevalence of neonatal sepsis in Ethiopia, there are studies which shows, prevalence of neonatal sepsis is high like Shashemene (77.9%) and Wolaita Sodo (33.8%) (7, 8). Among factors, maternal intra-partum fever, season of birth and admission, vaginal mode of delivery and preterm gestational age at birth increased the risk having neonatal sepsis (9).

Studies related with neonatal sepsis conducted in Ethiopia are more of prevalence studies and based on secondary data. Studies on determinants of neonatal sepsis would give data to identify high risk neonates; therefore, this study was aimed to identify determinants of neonatal sepsis among neonates admitted to Neonatal Intensive Care Unit (NICU) of public hospitals in Hawassa city administration.

Methods

Study Area

Hawassa city administration is found in Sidama Region, Ethiopia. It is located 275km South of the capital city of Ethiopia, Addis Ababa with a total population of 385,257. From those 191,858 and 193,399 of them are males and females respectively. Among the total population 89,765 of females found in reproductive age and also there are 13,330 pregnant women. The city has 8 sub cites and 32 kebeles from which 21 are urban kebeles and 11 are rural kebeles. In Hawassa city administration totally there are 8 hospitals (3 public and 5 private), 12 Public Health Centers (PHC) and 18 Health Posts (HPs). The three public hospitals are Hawassa University Teaching Hospital (HUCSH), Adare general hospital and Hawela Tula primary hospital all those public hospitals have NICU .

Study Design and period

Institutional based unmatched case-control study was conducted from August 1st to September 30, 2020**.**

Source Population

All neonates who were admitted to NICUs of public hospitals in Hawassa city administration were source population.

Study Population

Cases were neonates with sepsis and controls were neonates without sepsis who were admitted to neonatal ICU of Public Hospitals in Hawassa city administration, during study period.

Sample size determination

Sample size required to the study was determined by using double proportion formula(using Epi info version 7.2), by considering that the proportion of neonates with PROM among the controls of 8.5% and with AOR(2.812), which was estimated from study conducted in Debre markos referral hospital (10), 95% CI, 80% power of the study, case to control ratio of 1:2, which gave a total sample size of 315 (105 case and 210 controls) and by adding 5% for the non-response rate the final sample size became 331(110 cases and 221 controls).

Sampling Technique

All three public hospitals fund Hawassa city administration namely; Hawassa University Comprehensive Specialized Hospital (HUCSH), Adare General Hospital (AGH) and Hawela Tula Primary Hospital (HTPH) were considered in this study. Sample size was proportionally allocated for each hospital by considering the previous six month records of neonatal sepsis. By considering the last six month case flow of each hospitals the two month case flow was determined.

Data collection tools

The data were collected using pretested, interviewer administered questionnaire and data extraction checklist. The questionnaire was adapted from other similar studies with some contextual modification by considering the main objective of the study (5, 9, 11).

Data quality assurance and data quality control

The questionnaire was prepared in English and then translated to Amharic for data collection. Pretest was conducted in 5 %(6 cases and 11 controls) in Leku primary hospital to determine the time needed for interview and consistence of the questionnaire. Based on the pretest appropriate modification was made. Data were collected by three BSc. Midwives and one BSc. Midwife supervised the data collection process. One day training was given for data collectors and

supervisor about the aim of study, questioner, and how they approach case and controls in similar ways by principal investigator. Completeness of collected questionnaires was checked by the supervisor and corrective discussion was taken with data collectors.

Data Processing and Analysis

The collected data were coded and entered into Epi data version 3.1. and then, exported to SPSS version 20 for analysis. Descriptive statistics were carried out and presented with texts and tables. To observe the comparability of variables among cases and controls,x^2 test was computed. Bivariable Logistic regression analyses were performed to select candidate variables for the multi variable Logistic Regression analyses. Variables with p value < 0.25 in the bivariable analysis were considered as candidates for multivariate logistic regression analyses. Multicollinearity was checked out to determine the correlation between the independent variables and Hosmer-Lemeshow goodness of fit statistics was used to assess fitness of model. Variables having a P value <0.05 during multivariable analyses were considered as statistically significant. Finally, crude (COR) and adjusted odds ratio (AOR) with 95% confidence intervals (CI) were used for summarizing the findings of the analysis.

Operational definition

Neonatal sepsis: For the diagnosis of neonatal sepsis, one or more established Integrated Management of Neonatal and Childhood Illness (IMNCI) clinical features of neonatal sepsis (either not feeding well or convulsion or drowsy or unconscious or movement only stimulated or no movement at all or fast breathing>60 breath per min or grunting or severe chest in drawing or raised temperature (>38°C) or hypothermia (<35.5°C) or central cyanosis or severe jaundice or severe abdominal distention or many or severe skin pustules or bulging fontanels along with one or more hematological criteria (total white blood cells <5,000 or >20,000), or c-reactive protein <0.9 or >15.8 or platelet count (<150 or >440 cells/m3) or absolute neutrophil count (<1500 cells/mm^3 or >7500 cells/mm^3), erythrocyte sedimentation rate (ESR) (>15/1 h) (12).

Case definition

Cases: 0-28 day-old neonates, who were admitted to NICU of public hospitals in Hawassa city administration during the study period. Those who fulfill the operational definition of neonatal

sepsis (≥1 IMNCI criteria along with ≥1 hematologic criteria) with their index mother were considered as cases.

Control definition

Controls: 0-28-day old neonates who were admitted in NICU of public hospitals in Hawassa city administration during study period. Those who are not fulfilling case definition with their index mother were controls.

Ethics considerations

Ethical clearance was obtained from Hawassa University College of medicine and health science ethical review committee on the behalf of institutional review board of Hawassa University (Ref. No: IRB/09/12). Letter of cooperation was written for the respective Hospitals and letter of permission was obtained from each hospitals medical directorate (Ref. No.MID/395/12). Both written and verbal consent was taken from each study subjects after explaining the purpose of the study and the right of the study participant. Confidentiality was also assured by keeping the records locked.

Patient and public involvement

Patients and/or the public were not involved in the design, development, analysis and publication of this study.

Result

Socio-demographic characteristics of the mother

A total of 331 (110 cases and 221 controls) study participants participated and making a response rate of 100%. More than half of mothers among cases 70(63.6%) and more than two third of controls 152(68.8%) were aged between 25-34 years. Ninety five (86.4%) of mothers among cases and 194(87.8%) among controls were married. More than half of mothers among cases 67(60.4%) and three fourth of controls 160(72.4%) were urban dwellers. Concerning educational status of mothers among cases 33(30%) and controls 63(28.5%) have attended college and above education. Nearly half of the cases 51(46.4%) and 95(43 %) of controls' earned monthly income

of ≤ 1399 ETB. Regarding occupational status of the respondents 57(51.8%) of cases and 108 (48.9%) of controls were housewives (Table 1).

Table **1:** Socio demographic characteristics of the respondents among neonates admitted to NICU of public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020 (N=331).

Variable	Cases N=110(%)	Control N=221(%)	x^2(p-value)
Maternal age at current birth			
15-24	28(25.5)	49(22.2)	0.64
25-34	70(63.6)	152(68.8)	
≥35	12(10.9)	20(9)	
Marital status			
Single	10(9.1)	10(4.5)	0.72
Married	95(86.4)	194(87.8)	
Others*	5(4.5)	17(7.7)	
Residence			
Urban	67(60.9)	160(72.4)	0.024
Rural	43(39.6)	61(27.6)	
Mother`s educational status			
Cannot read and write	26(23.6)	40(18.1)	0.15
Primary first cycle (1-4)	20(18.2)	31(14)	
Primary second cycle (5-8)	12(10.9)	48(21.7)	
Secondary (9-12)	19(17.3)	39(17.6)	
Collage and above	33(30)	63(28.5)	
Monthly Income			
≤1399	51(46.4)	95(43)	0.55
1400-1999	13(11.8)	21(9.5)	
2000-2599	8(7.3)	10(4.5)	
≥2600	38(34.5)	95(43)	
Occupation of the mother			
Government employee	26(23.6)	42(19)	0.66
Housewife	57(51.8)	108(48.9)	
Merchant	12(10.9)	33(14.9)	
Daily laborer	5(4.5)	19(8.9)	
Others**	10(9.1)	19(8.6)	

Note: Others* widowed, divorced, separated and cohabiting; Others ** private organization and student

Obstetric related factors

Mothers of 85(77.7%) of case's and 161(72.9%) of control's were multiparous. From the collected data, 85(77.3%) of cases and 195(88.2%) of controls, their mode of delivery was vaginal. The proportion of mothers who gave birth before 8 hours of rupture of membrane was higher in controls 42(77.8%) than cases 15 (51.7%) (Table 2).

Table **2:** Obstetric related factors of the respondents among neonates admitted to NICU of public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020 (N=331).

Variable	**Case N=110(%)**	**Control N=221(%)**	x^2**(p-value)**
Gravidity			
≤4	95(86.4)	192(86.9)	0.52
≥5	15(13.6)	29(13.1)	
Parity			
Primiparous	25(22.7)	60(27.1)	0.23
Multiparous	85(77.3)	161(72.9)	
Duration of labor			
<6	7(6.4)	10(4.5)	0.056
6-12	45(40.9)	122(55.2)	
13-23	50(45.5)	70(31.7)	
≥24	8(7.3)	19(8.6)	
Current pregnancy status			
Single	106(96.4)	217(98.2)	
Multiple	4(3.6)	4(1.8)	
Place of delivery			
Home	8(7.3)	10(4.5)	0.5
Hospital	81(73.6)	173(78.3)	
Health center	21(19.1)	38(17.2)	
Mode of delivery			
Vaginal delivery	85(77.3)	195(88.2)	0.008
Cesarean section	25(22.7)	26(11.8)	
Onset of delivery			
Spontaneous	90(81.8)	181(81.9)	0.14
Induced	20(18.2)	40(18.1)	
Place of onset of labor			
Home	90(81.8)	177(80.1)	0.4
Institution	20(18.2)	44(19.9)	

Hypertension			
No	106(96.4)	215(97.3)	
Yes	4(3.6)	6(2.7)	
Antepartum hemorrhage			
No	105(95.5)	218(98.6)	
Yes	5(4.5)	3(1.4)	
Premature rupture of membrane			
No	81(73.6)	167(75.6)	0.4
Yes	29(26.4)	54(24.4)	
Duration of rupture of membrane			
<8	15(51.7)	42(77.8)	0.015
≥8	14(48.3)	12(22.2)	

Maternal medical illness

Urinary tract infections (UTI) were experienced among 15(13.6%) of cases and 20(9 %) of controls during their recent pregnancy. Thirty five (31.8%) of cases and 39(17.6%) of controls had history of anemia during their recent pregnancy. Syphilis were detected among 10(9.1%) of cases and 15(6.8%) of control (Table 3).

Table **3:** Maternal medical illness of the respondents among neonates admitted to NICU of public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020 (N=331).

Variable	Case N=110(%)	Control N=221(%)	x^2(p-value)
Anemia			
No	75(68.2)	182(82.4)	0.03
Yes	35(31.8)	39(17.6)	
Diabetes mellitus			
No	106(96.4)	213(96.4)	
Yes	4(3.6)	8(3.6)	
Urinary Tract Infection (UTI)			
No	95(86.4)	201(91)	0.13
Yes	15(13.6)	20(9)	
Malaria			
No	97(88.2)	195(88.2)	0.56
Yes	13(11.8)	26(11.8)	
HIV			
No	90(81.8)	182(82.4)	
Yes	2(1.8)	9(4.1)	
Unknown	18(16.4)	30(13.6)	
Syphilis			
No	77(70)	164(74.2)	0.66
Yes	10(9.1)	15(6.8)	
Unknown	23(20.9)	42(19)	

Health service utilization

Mothers of nearly half of cases 51(46.4%) and more than half of controls 119(53.8%) utilized ante natal care follow-up more than four times during the recent pregnancy. The proportion of mothers who didn't took anemia prevention and treatment during their recent pregnancy were higher among cases 42(38.2) than controls 66(30%) (Table 4).

Table 4: Health service utilization of the respondents among neonates admitted to NICU of public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020 (N=331).

Variable	Case N=110(%)	Control N=221(%)	x^2(p-value)
Antenatal follow up			
Yes	87(79.1)	188(85.1)	0.11
No	23(20.9)	33(14.9)	
Number of Antenatal follow up			
<4	36(41.4)	69(36.7)	0.13
≥4	51(58.6)	119(63.3)	
Tetanus Toxoid			
Yes	75(68.2)	178(80.5)	0.00
No	35(31.8)	43(19.5)	
Nutrition counseling			
Yes	61(55.5)	143(64.7)	0.06
No	49(44.5)	78(35.3)	
Birth preparedness and complication counseling			
Yes	61(55.5)	138(62.4)	0.13
No	49(44.5)	83(37.6)	
Prevention and treatment of anemia			
Yes	68(61.8)	154(70)	0.08
No	42(38.2)	66(30)	

Neonatal related factors

Of the total neonates included in this study, 61(55.5%) of the cases and 133(60.2%) of controls were found under the age of 7 days. Higher proportions of neonates were male in the controls group 123(55.7%) than cases 57(51.8%). More than half of cases 63(57.3%) and nearly two third 140(63.3%) of controls were born with normal birth weight. Majority of cases 99(90%) and 207(93.7%) of controls had normal presentation during delivery. More than half 60(54.5%) of neonates among cases and more than one third 85(38.5%) of neonates among controls did not have immediate breast feeding within 1hour after birth. Most of neonates among cases 107(97.3%) and controls 215(97.3%) had no congenital anomaly. The proportion of first minute low Apgar score is higher among cases 26(23.6%) than controls 23(10.4%). Seventeen (15.5%) of cases and 21(9.5%) of controls had birth asphyxia (Table 5).

Table 5: Neonatal related factors of respondents among neonates admitted to NICU public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020 (N=331)

Variable	Case N=110(%)	Control N=221(%)	x^2(p-value)
Age of neonate in days			
0-7 days	61(55.5)	133(60.2)	0.24
8-28 days	49(44.5)	88(39.8)	
Sex of neonate			
Male	57(51.8)	123(55.7)	0.29
Female	53(48.2)	98(44.3)	
Neonate presentation			
Normal	99(90)	207(93.7)	0.166
Mal presentation	11(10)	14(6.3)	
Type of mal presentation			
Breach	6(54.5)	7(50)	0.66
Others	5(45.5)	7(50)	
Gestational age			
<37wks	45(40.9)	34(15.4)	0.78
37-40wks	49(44.5)	157(71)	
>40wks	16(14.5)	30(13.6)	
First APGAR score			
≥7	39(35.5)	93(42.1)	0.03
4-6	15(13.6)	53(24)	
<4	26(23.6)	23(10.4)	
Unknown	30(30)	52(23.5)	
Fifth APGAR score			
≥7	53(48.2)	132(59.7)	0.15
4-6	18(16.4)	21(9.5)	
<4	9(8.2)	15(6.8)	
Unknown	30(27.3)	53(24)	
Cried immediately after birth			
Yes	65(59.09)	157(71)	0.02
No	45(40.9)	64(29)	
Neonate resuscitated at birth			
No	67(60.09)	156(70.6)	0.05
Yes	43(39.09)	65(29.4)	
Immediate breastfeeding within 1hour			
Yes	50(45.5)	136(61.5)	0.004
No	60(54.5)	85(38.5)	
Birth asphyxia			
No	93(84.5)	200(90.5)	0.62
Yes	17(15.5)	21(9.5)	
Invasive procedure done			
No	81(73.6)	182(82.4)	0.04

Yes	29(26.4)	39(17.6)

Results of bi-variable and multi-variable Logistic Regression analyses

On bivariable logistic regression analysis residence, mode of delivery, anemia, cried immediately, immediate breast feeding within 1 hour and Tetanus Toxoid (TT) vaccination were candidate for multivariable Logistic regression analyses at p- value less than 0.25. In the multivariable model; maternal TT vaccination, mode of delivery and history of anemia during pregnancy were found to be significant predictors of neonatal sepsis at P-value less than 0.05 and 95% CI.

Accordingly; neonates who were delivered by caesarian section had 2.56 times increased odds of having neonatal sepsis [AOR(95% CI) = 2.56 (1.3 - 5.05)], neonates born from mothers who had history of anemia were 2.58 times at increases chance of having neonatal sepsis [AOR (95% CI) = 2.58(1.45 - 4.6)] and neonates born from mothers who were not TT vaccinated had 3.5 times increased odds of having neonatal sepsis [AOR(95% CI) = 3.5 (2.07-6.19)] (Table 6).

Table 6: Factors associated with neonatal sepsis among neonate admitted to NICU of public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020. (N=331)

Variable	Cases N=110(%)	Control N=221(%)	COR(95%CI)	AOR(95%CI)
Residence				
Urban	67 (60.9)	160(72.4)	1	1
Rural	43 (39.1)	61(27.6)	1.683(1.04-2.7)	1.3(0.7-2.2)
Mode of delivery				
Vaginal delivery	85(77.3)	195(88.2)	1	1
Cesarean section	25(22.7)	26(11.8)	2.206(1.204-4.04)	2.56(1.3-5.00)*
History of anemia				
No	75(68.2)	182(82.4)	1	
Yes	35(31,8)	39(17.6)	2.2(1.28-3.69)	2.58(1.45-4.6)*
Cried Immediately				
Yes	65(59.1)	157(71)	1	1
No	45(40.9)	64(29)	1.698(1.1-2.7)	0.98(0.5-1.9)
Immediate breastfeeding				
Yes	50(45.5)	136(61.5)	1	
No	60(54.5)	85(38.5)	1.92(1.2-3.05)	1.3(0.7-2.5)
TT vaccination				
Yes	75(68.2)	178(80.5	1	
No	35(31.8)	43(19.5)	3.33(2.02-5.4)	3.5(2.07-6.19)*

Note:- TT: tetanus toxoid,* p- value <0.05

Discussion

Neonatal mortality remains an urgent concern and is an indicator of child health, development and wellbeing (13). Neonatal sepsis is a common and fatal condition affecting neonates globally (14), and the major cause of mortality and morbidity particularly in developing countries (15). The current study aimed to identify determinants of neonatal sepsis to decrease burden of neonatal sepsis and to focus on the specific factors on the study area.

The study revealed that mode of delivery, history of anemia and not vaccinated for tetanus toxoid vaccination during recent pregnancy were predictors of neonatal sepsis. From the total of 110 cases, 55.5% of neonates had early onset neonatal sepsis (≤7days) and 44.5% of neonates had late onset neonatal sepsis (≥8 days). The result showed that early onset neonatal sepsis is higher than late onset neonatal sepsis. This could be due to direct contact with causative agents with newborn body during delivery. This result is lower than previous studies conducted in Gondar (59.33%) (9), Shashemene (65%) (7), and Bishoftu (81.4%) (16) this variation might be due to study design difference. Similarly the result is lower than study conducted in Ghana(78.7%) (11) the possible reason could be socio-demographic variation. But higher than study conducted in Egypt (44.2%) this might be due to sample size, socio demographic and study period variation (17).

Based on the finding on this study the odds of neonatal sepsis among neonates delivered by cesarean section were 2.5 higher than the odds of neonatal sepsis among neonates delivered by vaginal delivery. This association might be due to prolonged hospital stay which can increase the risk of hospital acquired infection during cesarean section delivery. Also there is less skin to skin contact and late initiation of breast feeding (18). Since the first milk which is colostrum is considered as a first vaccine, which is important to improve neonatal immunity. This finding is similar with study done in Egypt (17), Ghana (11) and part of Ethiopia in Gondar (19). However, there is finding is contrary with this result done in Gondar (9), this variation occur, probably do to sample size variation.

The odds of neonatal sepsis among neonates who were delivered from mothers who were not vaccinated for TT were 3.5 times higher than the odds their counterparts. The reason could be related the principle of antenatal vaccination, those maternal pathogen specific antibodies used to boosted and provide protection to the infant until the appropriate time for infant vaccinations or

until the period of greatest susceptibility has passed (20-22). Antibodies derived from trans placental and breast milk function as the primary source of protection against infectious disease in neonates (23).

The odds of neonatal sepsis among neonates who were delivered from mothers who had history of anemia during recent pregnancy were 2.5 times higher than the odds of their counterparts. The finding of prospective study conducted in India was in line with this finding, from neonates delivered from anemic mother 9% of neonates developed neonatal sepsis (24). The possible reason might be related with, in anemic mothers, studies showed that there is significant reduction of breast milk micronutrients which in turn can affect immunity status of neonate and increase susceptibility to sepsis (25). Also there is a study which shows cesarean section is high in anemic mothers (26, 27). There is also a study conducted in Nepal revealed that, maternal anemia reduce resistance to infection for both mother and neonate (28).

The following limitations should be considered in the interpretation of the findings of this study. First, as the study was limited to a hospital, the external validity of the study might have been affected. Secondly; some of the variables in findings are prone to subjective bias. And thirdly, as the association between the exposure and the outcome variables was measured using OR, the true relationship might have been overestimated as OR tends to overestimated the relative risk.

Conclusion

Based on the finding of this study, obstetric, health service utilization and maternal medical illness factors were determinants contributed to neonatal sepsis. Specifically, cesarean mode of delivery, history of maternal anemia, and not vaccinated to tetanus were identified risk factors for neonatal sepsis. Proper ANC, intrapartum care, and improving maternal nutritional status during pregnancy through proper counseling and micronutrient supplementation and timely Tetanus Toxoid (TT) vaccination is important for improvement of neonatal health. Finally, further research is recommended on neonatal sepsis rate among mothers with history of anemia and who did not take (TT) vaccination.

Abbreviations

ANC: Antenatal care; APGAR: Appearance, pulse, grimace, activity, and respiration; EDHS: Ethiopian demographic health survey; IMNCI: Integrated management of neonatal and

childhood illness; NICU: Neonatal intensive care unit; SDG: Sustainable Development goal; TT: Tetanus toxoid.

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Competing interests

The authors declare no competing interest.

Contributors

KB conceptualized the study, analyzed and interpreted the data. RF, TA and AZ participated in the designing of the study and supervised the fieldwork and the analysis of the data. All the authors drafted, reviewed and approved the final manuscript.

Data sharing statement: Available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical clearance was obtained from the Institutional Review Board of Hawassa University, College of Medicine and Health Sciences.

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Reference

1. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clin Microbiol Rev. 2014;27(1):21-47.
2. Singh M, Narang A, Bhakoo O. Predictive perinatal score in the diagnosis of neonatal sepsis. Journal of tropical pediatrics. 1994;40(6):365-8.
3. UNICEF. Levels and trends in child mortality. New York: UNICEF. 2015.
4. Ranjeva SL, B.C. Warf, and S.J. Schiff,. Economic burden of neonatal sepsis in sub-Saharan Africa. BMJ global health. 2018;3(1).
5. Gebremedhin D, Berhe H, Gebrekirstos K. Risk Factors for Neonatal Sepsis in Public Hospitals of Mekelle City, North Ethiopia, 2015: Unmatched Case Control Study. PLoS One. 2016;11(5):e0154798.
6. Ethiopian Public Health Institute (EPHI) [Ethiopia] and ICF. Ethiopia Mini Demographic and Health Survey 2019: Key Indicators. Rockville, Maryland, USA: EPHI and ICF, 2019.
7. Getabelew A, Aman M, Fantaye E, Yeheyis T. Prevalence of Neonatal Sepsis and Associated Factors among Neonates in Neonatal Intensive Care Unit at Selected Governmental Hospitals in Shashemene Town, Oromia Regional State, Ethiopia, 2017. International Journal of Pediatrics. 2018;2018:1-7.
8. Mersha A, Worku T, Shibiru S, Bante A, Molla A, Seifu G, et al. Neonatal sepsis and associated factors among newborns in hospitals of Wolaita Sodo Town, Southern Ethiopia. Research and Reports in Neonatology. Research and Reports in Neonatology. 2019;9:1-8.
9. Gudayu TW, Zeleke EG, Lakew AM. The role of the season at admission in neonatal sepsis: a retrospective chart review of a 1-year data at University of Gondar comprehensive specialized hospital. BMC Res Notes. 2019;12(1):643.
10. Alemu M, Ayana M, Abiy H, Minuye B, Alebachew W, Endalamaw A. Determinants of neonatal sepsis among neonates in the northwest part of Ethiopia: case-control study. . Italian Journal of Pediatrics. 2019;45(150):1-8.
11. Adatara P, Afaya A, Salia S, Afaya RA, K.Kuug A, Agbinku E, et al. Risk Factors for Neonatal Sepsis: A Retrospective Case-Control Study among Neonates Who Were Delivered by Caesarean Section at the Trauma and Specialist Hospital, Winneba, Ghana. . BioMed Research International. 2018;Volume 2018.

12. World Health Organization. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses. Geneva: WHO; 2013.

13. Tekelab T, Chojenta C, Smith R, Loxton D. The impact of antenatal care on neonatal mortality in sub-Saharan Africa: A systematic review and meta-analysis. PLoS One. 2019;14(9):e0222566.

14. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. The Lancet Respiratory Medicine. 2018;6(3):223-30.

15. Amare D, M. Mela, and G. Dessie,. Unfinished agenda of the neonates in developing countries: magnitude of neonatal sepsis: systematic review and meta-analysis. . Heliyon. 2019;5(9).

16. Woldu M, Lenjisa J, Tegegne G, Tesfaye G, Dinsa H, Guta M. Assessment of the incidence of neonatal sepsis, its risk factors, antimicrobials use and clinical outcomes in Bishoftu general hospital, neonatal intensive care unit, Debrezeit-Ethiopia. International Journal of Contemporary Pediatrics. 2014:1.

17. Shehab El-Din EM, El-Sokkary MM, Bassiouny MR, Hassan R. Epidemiology of Neonatal Sepsis and Implicated Pathogens: A Study from Egypt. Biomed Res Int. 2015;2015:509484.

18. Prado DS, Mendes RB, Gurgel RQ, Barreto IDdC, Cipolotti R, Gurgel RQ. The influence of mode of delivery on neonatal and maternal short and long-term outcomes. Revista de saude publica. 2018;52:95.

19. G/eyesus T, Moges F, Eshetie S, Yeshitela B, Abate E. Bacterial etiologic agents causing neonatal sepsis and associated risk factors in Gondar, Northwest Ethiopia. BMC Pediatrics. 2017;17(1).

20. Jones C, Heath P. Antenatal immunization. Human Vaccines & Immunotherapeutics. 2014;10(7):2118-22.

21. Vojtek I, Dieussaert I, Doherty TM, Franck V, Hanssens L, Miller J, et al. Maternal immunization: where are we now and how to move forward? Annals of medicine. 2018;50(3):193-208.

22. Calvert A, Jones CE. Placental transfer of antibody and its relationship to vaccination in pregnancy. Current opinion in infectious diseases. 2017;30(3):268-73.

23. Maertens K, Orije MRP, Van Damme P, Leuridan E. Vaccination during pregnancy: current and possible future recommendations. European journal of pediatrics. 2020;179(2):235-42.

24. Shah N, Upadhyay C, Sahota R. Neonatal outcome in anemic mothers: A prospective study. Journal of Evolution of Medical and Dental Sciences. 2013;2(43):8355-60.

25. El-Farrash RA, Ismail EAR, Nada AS. Cord blood iron profile and breast milk micronutrients in maternal iron deficiency anemia. Pediatric Blood & Cancer. 2012;58(2):233-8.

26. Drukker L, Hants Y, Farkash R, Ruchlemer R, Samueloff A, Grisaru-Granovsky S. Iron deficiency anemia at admission for labor and delivery is associated with an increased risk for Cesarean section and adverse maternal and neonatal outcomes. Transfusion. 2015;55(12):2799-806.

27. Smith C, Teng F, Branch E, Chu S, Joseph K. Maternal and perinatal morbidity and mortality associated with anemia in pregnancy. Obstetrics and gynecology. 2019;134(6):1234.

28. Prakash S, Yadav K. Maternal Anemia in Pregnancy: An Overview. Ijppr Human. 2015;4(3):164-79.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	*20*
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	17
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Determinants of neonatal sepsis among neonates admitted to neonatal intensive care unit of public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020. Unmatched case-control study.

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Determinants of neonatal sepsis among neonates admitted to neonatal intensive care unit of public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020. Unmatched case-control study.

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Abstract

Objective: This study was conducted to find out determinants of neonatal sepsis in the neonatal intensive care units in public hospitals of Hawassa city administration, Sidama region, Ethiopia, 2020.

Design: Institutional based unmatched case-control study.

Setting: The study was conducted in three (Hawassa University Teaching Hospital, Adare General Hospital and Hawela Tula Primary Hospital) public hospitals of Hawasa city, Ethiopia.

Participants: A total of 331 (110 cases and 221 controls) neonates with their index mothers were included in the study from August 1st to September 30, 2020.

Outcome measures: A pretested, interviewer-administered questionnaire and data extraction checklist were used to collect data. Data was coded and entered into Epi data version 3.1 before being exported to SPSS version 20 for analysis. The factors associated with neonatal sepsis were assessed using bivariabel and multivariable logistic regression analyses. Finally, a p-value of less than 0.05 was used to establish the statistically significant association of variables.

Results: Cesarean section delivery [AOR= 2.56; 95 % CI (1.3-5.00)], maternal anemia [AOR = 2.58; 95 % CI (1.45-4.6)], and not vaccinated against Tetanus toxoid [AOR= 3.5 95 % CI (2.07-6.19)] were all identified as factors significantly associated with neonatal sepsis.

Conclusions: Cesarean section, maternal history of anemia, and not vaccinated against Tetanus were founded to be risk factors of neonatal sepsis. Establishing preconception care practice, strengthening quality of ANC care and standardized infection prevention practice are needed for the improvement of neonatal health.

Keywords: Determinants, Neonatal Sepsis, Neonatal Intensive Care Unit, Ethiopia.

Strengths and limitations of this study

- The study was a prospective study and addressed all of public hospitals found in Hawassa city.
- Factors associated with neonatal sepsis were explored in this study.
- One of the study's limitations is that it relied on clinical and hematologic criteria to diagnose neonatal sepsis.
- As the association between the exposure and the outcome variables was measured using OR, the true relationship might have been overestimated as OR tends to overestimate the relative risk.
- Cause–effect relationships could not be determined.

Introduction

Neonatal sepsis is a systemic infection occurring in infants ≤28 days of life (1). Neonatal sepsis is a common and fatal condition affecting neonates globally (2), and the major cause of mortality and morbidity particularly in developing countries (3). Neonatal sepsis is characterized as early-onset neonatal sepsis or late-onset neonatal sepsis based on the onset of symptoms (4).

Reducing neonatal sepsis by improving the quality of care is a global and local priority. Worldwide, the neonatal mortality rate is on the way of decrement from 36 deaths per 1,000 live births in 1990 to 19 per 1,000 live births in 2015 (5). Neonatal deaths have decreased as well, from 5.1 million in 1990 to 2.4 million in 2020(6). When comparing neonatal and post-neonatal mortality rates (1-59 months), neonatal mortality decreased at a slower rate than post-neonatal mortality, which was 47 percent and 58 percent, respectively (5, 6). Neonatal mortality remains an urgent concern and is an indicator of child health, development and wellbeing (7).

Neonatal sepsis caused an estimated 750,000 yearly neonatal deaths worldwide, with mortality rates highest in Sub-Saharan Africa (8). Despite the fact that newborn deaths are preventable, the problem is concentrated in the world's poorest countries, with low and middle-income countries accounting for 85 percent of all neonatal deaths (9). Studies indicated that neonatal sepsis presents a $10–$469 billion financial burden that could be reduced through successful treatment and prevention in SSA (8).

The neonatal death rate has also decreased in Ethiopia from 39 per 1000 live births in 2005 to 30 in 2019, according to the Ethiopian Demographic and Health Survey (EDHS). However, compared to the 29 neonatal deaths per 1000 live births reported in the 2016 EDHS, there is a modest increase in neonatal mortality in 2019 (10).

In terms of the prevalence of neonatal sepsis in Ethiopia, studies have found that it is as high as 77.9% in Shashemene and as low as 33.8 percent in Wolaita Sodo, though both studies asserted neonatal sepsis using medical diagnosis of the neonate stated as 'neonatal sepsis' by the physician in the neonate's medical record chart (11, 12). Among factors, maternal intra-partum fever, season of birth and admission, vaginal mode of delivery and preterm gestational age at birth increased the risk having neonatal sepsis (13).

In Ethiopia, investigations on newborn sepsis have primarily been prevalence studies based on secondary data. Studies on determinants of neonatal sepsis would give data to identify high risk neonates; thus, this study was aimed to identify determinants of neonatal sepsis among neonates admitted to Neonatal Intensive Care Unit (NICU) of public hospitals in Hawassa city administration.

Methods

Study Area

Hawassa city administration is located in Ethiopia's Sidama Region. It is located 275 kilometers South of Ethiopia's capital city, Addis Ababa, which has a population of 385,257 people. Males and females account for 191,858 and 193,399 people, respectively. There are 89,765 females of reproductive age in the entire population, as well as 13,330 pregnant women. The city is divided into 8 sub-cities and 32 kebeles, with 21 urban and 11 rural kebeles. There are 8 hospitals (3 public and 5 private) in the Hawassa city government, as well as 12 Public Health Centers (PHC) and 18 Health Posts (HPs). The three public hospitals are Hawassa University Teaching Hospital (HUCSH), Adare general hospital and Hawela Tula primary hospital all those public hospitals have NICU. The NICUs of the three hospitals provide services free of charge. In terms of the types of respiratory assistance available, all three institutions provide oxygen, assisted breathing, and surfactant. Diagnosis of neonatal sepsis depends on clinical decision in all of the three hospitals. The hospitals follow Ethiopia's National Standard Treatment Guideline for Hospitals,

which advises broad-spectrum antibiotics such as penicillin and aminoglycosides for treatment of neonatal sepsis (14).

Study Design and period

Institutional based unmatched case-control study was conducted from August 1st to September 30, 2020**.**

Source Population

The source population included all neonates admitted to NICUs of public hospitals in Hawassa city administration.

.Study Population

Cases were neonates with sepsis and controls were neonates without sepsis who were admitted to NICUs of Public Hospitals in Hawassa city administration, during study period.

Sample size determination

Sample size required for the study was calculated using double population proportion formula (using Epi info version 7.2), taking into account the proportion of neonates with PROM among the controls of 8.5 percent and an Adjusted Odds Ratio (AOR) of 2.812, which was estimated from a study conducted in Debre Markos referral hospital (15), 95% CI, 80% power of the study, and case to control ratio of 1:2, which resulted in a total sample size of 315 (105 case and 210 controls). By adding 5% for the non-response rate the final sample size became 331(110 cases and 221 controls).

Sampling Technique

All three public hospitals fund Hawassa city administration were considered in this study. The calculated final sample size was proportionally allocated for each hospital based on newborn sepsis records from the previous six months. The two-month case flow was calculated using each hospital's previous six-month case flow.

Data collection tools and procedures

The data were collected using a pretested, interviewer administered questionnaire and a data extraction checklist. The questionnaire was adapted from other similar studies with some contextual modification based on the main objective of the study (9, 13, 16). The data were gathered by interviewing the mothers and reviewing the medical records of the neonates.

Data quality assurance and data quality control

The questionnaire was prepared in English and then translated to Amharic. Pretest was conducted in 5 %(6 cases and 11 controls) in Leku primary hospital to determine the amount of time needed for the interview and the consistency of the questionnaire. Appropriate modification was performed based on the results of the pretest. Three BSc. Midwives collected the data while one BSc. Midwife supervised the data collection process. One day training was given for data collectors and supervisor about the aim of study, questioner, and how to approach cases and controls in similar ways. Completeness of collected questionnaires was checked by the supervisor and corrective discussion was made with data collectors.

Data Processing and Analysis

The collected data were coded and entered into Epi data version 3.1. then exported to SPSS version 20 for analysis. Descriptive statistics were carried out and presented using texts and tables. Chi-square (x^2) tests were computed to observe the comparability of variables among cases and controls test. Bivariable Logistic regression analyses were performed to select candidate variables for the multi variable Logistic Regression analyses. Variables with p value < 0.25 in the bivariable analysis were considered as candidates for multivariate logistic regression analyses. Multicollinearity was checked out to determine the correlation between the independent variables and Hosmer-Lemeshow goodness of fit statistics was used to assess fitness of model. Variables having a P value <0.05 during multivariable analyses were considered as having statistically significant association with neonatal sepsis. Finally, the findings of the

analysis were summarized using crude (COR) and adjusted odds ratio (AOR) with 95% confidence intervals (CI).

Operational definition

Case definition (Neonatal sepsis): Newborns aged 0 to 28 days, who were admitted to NICU of public hospitals in Hawassa city administration during the study period. One or more established Integrated Management of Neonatal and Childhood Illness (IMNCI) clinical features of neonatal sepsis (either not feeding well or convulsion or drowsy or unconscious or movement only stimulated or no movement at all or fast breathing>60 breath per min or grunting or severe chest in drawing or raised temperature (>38°C) or hypothermia (<35.5°C) or central cyanosis or severe jaundice or severe abdominal distention or many or severe skin pustules or bulging fontanels along with one or more hematological criteria (total white blood cells <5,000 or >20,000), or c-reactive protein <0.9 or >15.8 or platelet count (<150 or >440 cells/m3) or absolute neutrophil count (<1500 cells/mm^3 or >7500 cells/mm^3), erythrocyte sedimentation rate (ESR) (>15/1 h) were used for the diagnosis of neonatal sepsis (17). Those who fulfill the operational definition of neonatal sepsis (≥1 IMNCI criteria along with ≥1 hematologic criteria) with their index mother were considered as cases.

Control definition

Controls: controls for the study were 0-28-day old neonates with their index mothers who were admitted in NICU of public hospitals in Hawassa city administration during study period and did not meet the case definition (such as neonates admitted in the NICU due to prematurity needing supportive care, Neonatal hyperbilirubinemia needing phototherapy, etc.).

Ethics considerations

On behalf of Hawassa University's institutional review board (Ref. No: IRB/09/12), ethical approval was acquired from the Hawassa University College of Medicine and Health Science ethical review committee. A letter of collaboration was written for each hospital, and permission was acquired from the medical directorate of each hospital (Ref. No.MID/395/12). After describing the goal of the study and the study participant's rights, each study subject/guardian

gave written and verbal concent. The confidentiality of the records was also ensured by keeping them closed.

Patient and public involvement: Patients and/or the public were not involved during the design, development, analysis and publication of this study.

Result

Socio-demographic characteristics of the mother

A total of 331 study participants (110 cases and 221 controls) participated, with a response rate of 100% (50 cases and 101 controls from HUCSH, 42 cases and 84 controls from AGH, and 18 cases and 36 controls from HTPH). More than half of mothers among the cases 70(63.6%) and more than two thirds of the controls 152(68.8%) were between the ages of 25-34 years. Ninety five (86.4%) of mothers among the cases and 194(87.8%) among the controls were married. More than half of mothers in cases 67(60.4%) and three fourth of controls (72.4%), were urban dwellers. In terms of educational attainment, 30% of cases and 28.5% of controls have completed college or higher education. Nearly half of the cases 51(46.4%) and 95(43 %) of controls' earned monthly income of ≤ 39.19 USD. When it came to the respondents' occupations, 57(51.8%) of cases and 108 (48.9%) of controls were housewives (Table 1).

Table **1:** Socio demographic characteristics of the respondents among neonates admitted to NICU of public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020 (N=331).

Variable	Cases N=110(%)	Control N=221(%)	x^2(p-value)
Maternal age at current birth			
15-24	28(25.5)	49(22.2)	0.64
25-34	70(63.6)	152(68.8)	
≥35	12(10.9)	20(9)	
Marital status			
Single	10(9.1)	10(4.5)	0.72
Married	95(86.4)	194(87.8)	
Others*	5(4.5)	17(7.7)	
Residence			
Urban	67(60.9)	160(72.4)	0.024
Rural	43(39.6)	61(27.6)	
Mother`s educational status			
Cannot read and write	26(23.6)	40(18.1)	0.15
Primary first cycle (1-4)	20(18.2)	31(14)	
Primary second cycle (5-8)	12(10.9)	48(21.7)	
Secondary (9-12)	19(17.3)	39(17.6)	
Collage and above	33(30)	63(28.5)	
Monthly Income			
≤39.19 USD	51(46.4)	95(43)	0.55
39.2-55.99 USD	13(11.8)	21(9.5)	
56-72.79 USD	8(7.3)	10(4.5)	
≥72.8 USD	38(34.5)	95(43)	
Occupation of the mother			
Government employee	26(23.6)	42(19)	0.66
Housewife	57(51.8)	108(48.9)	
Merchant	12(10.9)	33(14.9)	
Daily laborer	5(4.5)	19(8.9)	
Others**	10(9.1)	19(8.6)	

Note: Others* widowed, divorced, separated and cohabiting; Others ** private organization and student

Obstetric related factors

Mothers of 85(77.7%) of case's and 161(72.9%) of control's were multiparous. The mode of delivery was vaginal in 85 (77.3%) of cases and 195 (88.2%) of controls, according to the statistics (Table 2).

Table **2:** Obstetric related factors of the respondents among neonates admitted to NICU of public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020 (N=331).

Variable	**Case N=110(%)**	**Control N=221(%)**	x^2**(p-value)**
Gravidity			
≤4	95(86.4)	192(86.9)	0.52
≥5	15(13.6)	29(13.1)	
Parity			
Primiparous	25(22.7)	60(27.1)	0.23
Multiparous	85(77.3)	161(72.9)	
Duration of labor			
<6	7(6.4)	10(4.5)	0.056
6-12	45(40.9)	122(55.2)	
13-23	50(45.5)	70(31.7)	
≥24	8(7.3)	19(8.6)	
Current pregnancy status			
Single	106(96.4)	217(98.2)	
Multiple	4(3.6)	4(1.8)	
Place of delivery			
Home	8(7.3)	10(4.5)	0.5
Hospital	81(73.6)	173(78.3)	
Health center	21(19.1)	38(17.2)	
Mode of delivery			
Vaginal delivery	85(77.3)	195(88.2)	0.008
Cesarean section	25(22.7)	26(11.8)	
Onset of delivery			
Spontaneous	90(81.8)	181(81.9)	0.14
Induced	20(18.2)	40(18.1)	
Place of onset of labor			
Home	90(81.8)	177(80.1)	0.4
Institution	20(18.2)	44(19.9)	

Hypertension			
No	106(96.4)	215(97.3)	
Yes	4(3.6)	6(2.7)	
Antepartum hemorrhage			
No	105(95.5)	218(98.6)	
Yes	5(4.5)	3(1.4)	
Premature rupture of membrane			
No	81(73.6)	167(75.6)	0.4
Yes	29(26.4)	54(24.4)	

Maternal medical illness

During their recent pregnancy, 15 (13.6 percent) of mothers of the cases and 20 (9 percent) of controls had experienced urinary tract infections (UTI). Thirty five (31.8%) of cases and 39(17.6%) of controls had history of anemia during their recent pregnancy. Syphilis were found among 10(9.1%) of cases and 15(6.8%) of control (Table 3).

Table **3:** Maternal medical illness of the respondents among neonates admitted to NICU of public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020 (N=331).

Variable	Case N=110(%)	Control N=221(%)	x^2(p-value)
Anemia			
No	75(68.2)	182(82.4)	0.03
Yes	35(31.8)	39(17.6)	
Diabetes mellitus			
No	106(96.4)	213(96.4)	
Yes	4(3.6)	8(3.6)	
Urinary Tract Infection (UTI)			
No	95(86.4)	201(91)	0.13
Yes	15(13.6)	20(9)	
Malaria			
No	97(88.2)	195(88.2)	0.56
Yes	13(11.8)	26(11.8)	
HIV			
No	90(81.8)	182(82.4)	
Yes	2(1.8)	9(4.1)	
Unknown	18(16.4)	30(13.6)	
Syphilis			
No	77(70)	164(74.2)	0.66
Yes	10(9.1)	15(6.8)	
Unknown	23(20.9)	42(19)	

Health service utilization

Mothers of nearly half of cases 51(46.4%) and more than half of controls 119(53.8%) utilized ante natal care follow-up more than four times during the recent pregnancy. The proportion of mothers who didn't took anemia prevention and treatment during their recent pregnancy were higher in cases 42(38.2) than controls 66(30%) (Table 4).

Table 4: Health service utilization of the respondents among neonates admitted to NICU of public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020 (N=331).

Variable	Case N=110(%)	Control N=221(%)	x^2(p-value)
Antenatal follow up			
Yes	87(79.1)	188(85.1)	0.11
No	23(20.9)	33(14.9)	
Number of Antenatal follow up			
<4	36(41.4)	69(36.7)	0.13
≥4	51(58.6)	119(63.3)	
Tetanus Toxoid			
Yes	75(68.2)	178(80.5)	<0.001
No	35(31.8)	43(19.5)	
Nutrition counseling			
Yes	61(55.5)	143(64.7)	0.06
No	49(44.5)	78(35.3)	
Birth preparedness and complication counseling			
Yes	61(55.5)	138(62.4)	0.13
No	49(44.5)	83(37.6)	
Prevention and treatment of anemia			
Yes	68(61.8)	154(70)	0.08
No	42(38.2)	66(30)	

Neonatal related factors

The majority of the neonates in this study were under the age of seven days, with 61 (55.5%) cases and 133 (60.2%) controls. The controls group had a higher proportion of male newborns, 123 (55.7%) than the cases group 57 (51.8%). More over half of the cases (57.3%) and almost two-thirds of the controls (63.3%) were born with a normal birth weight.

The majority of cases 99(90%) and 207(93.7%) of controls had normal presentation during delivery. More than half 60(54.5%) of neonates among cases and more than one third 85(38.5%) of neonates among controls did not have immediate breast feeding (within 1hour after birth). The proportion of first minute low Apgar score is higher among cases 26(23.6%) than controls 23(10.4%). Seventeen (15.5%) of cases and 21(9.5%) of controls had birth asphyxia (Table 5).

Table 5: Neonatal related factors of respondents among neonates admitted to NICU public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020 (N=331)

Variable	Case N=110(%)	Control N=221(%)	x^2(p-value)
Age of neonate during data collection			
0-7 days	61(55.5)	133(60.2)	0.24
8-28 days	49(44.5)	88(39.8)	
Sex of neonate			
Male	57(51.8)	123(55.7)	0.29
Female	53(48.2)	98(44.3)	
Neonate presentation			
Normal	99(90)	207(93.7)	0.166
Mal presentation	11(10)	14(6.3)	
Type of mal presentation			
Breach	6(54.5)	7(50)	0.66
Others	5(45.5)	7(50)	
Gestational age			
<37wks	45(40.9)	34(15.4)	<0.001
37-40wks	49(44.5)	157(71)	
>40wks	16(14.5)	30(13.6)	
First APGAR score			
≥7	39(35.5)	93(42.1)	0.03
4-6	15(13.6)	53(24)	
<4	26(23.6)	23(10.4)	
Unknown	30(30)	52(23.5)	
Fifth APGAR score			
≥7	53(48.2)	132(59.7)	0.15
4-6	18(16.4)	21(9.5)	
<4	9(8.2)	15(6.8)	
Unknown	30(27.3)	53(24)	
Cried immediately after birth			
Yes	65(59.09)	157(71)	0.02
No	45(40.9)	64(29)	
Neonate resuscitated at birth			
No	67(60.09)	156(70.6)	0.05
Yes	43(39.09)	65(29.4)	
Immediate breastfeeding within 1hour			
Yes	50(45.5)	136(61.5)	0.004
No	60(54.5)	85(38.5)	
Birth asphyxia			
No	93(84.5)	200(90.5)	0.62
Yes	17(15.5)	21(9.5)	
Invasive procedure done*			
No	81(73.6)	182(82.4)	0.04
Yes	29(26.4)	39(17.6)	

* Invasive procedures are Vacuum and forceps deliveries and Artificial Rupture of Membrane (AROM).

Results of bi-variable and multi-variable Logistic Regression analyses

Residence, mode of delivery, anemia, cried immediately, immediate breast feeding within 1 hour and Tetanus Toxoid (TT) vaccination were candidates for multivariable Logistic regression analyses at p- value less than 0.25 on bivariable logistic regression analysis. In the multivariable model; maternal TT vaccination, mode of delivery and history of anemia during pregnancy were found to be significant predictors of neonatal sepsis at P-value less than 0.05 and 95% CI.

Accordingly; neonates who were delivered by caesarian section had 2.56 times increased odds of developing neonatal sepsis [AOR(95% CI) = 2.56 (1.3 - 5.05)], while neonates born to mothers with a history of anemia were 2.58 times at increases chance of developing neonatal sepsis [AOR (95% CI) = 2.58(1.45 - 4.6)] and neonates born to mothers who were not TT vaccinated had 3.5 times increased odds of developing neonatal sepsis [AOR(95% CI) = 3.5 (2.07-6.19)] (Table 6).

Table 6: Factors associated with neonatal sepsis among neonate admitted to NICU of public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020. (N=331)

Variable	Cases N=110(%)	Control N=221(%)	COR(95%CI)	AOR(95%CI)
Residence				
Urban	67 (60.9)	160(72.4)	1	1
Rural	43 (39.1)	61(27.6)	1.683(1.04-2.7)	1.3(0.7-2.2)
Mode of delivery				
Vaginal delivery	85(77.3)	195(88.2)	1	1
Cesarean section	25(22.7)	26(11.8)	2.206(1.204-4.04)	2.56(1.3-5.00)*
History of anemia				
No	75(68.2)	182(82.4)	1	
Yes	35(31,8)	39(17.6)	2.2(1.28-3.69)	2.58(1.45-4.6)*
Cried Immediately				
Yes	65(59.1)	157(71)	1	1
No	45(40.9)	64(29)	1.698(1.1-2.7)	0.98(0.5-1.9)
Immediate breastfeeding				
Yes	50(45.5)	136(61.5)	1	
No	60(54.5)	85(38.5)	1.92(1.2-3.05)	1.3(0.7-2.5)
TT vaccination				
Yes	75(68.2)	178(80.5	1	
No	35(31.8)	43(19.5)	3.33(2.02-5.4)	3.5(2.07-6.19)*

Note:- TT: tetanus toxoid,* p- value <0.05

Discussion

The current study aimed to identify determinants of neonatal sepsis in order to reduce the burden of neonatal sepsis and to focus on the specific factors on the study area. From the total of 110 cases, 55.5% of neonates had early onset neonatal sepsis (≤7days) and 44.5% of neonates had late onset neonatal sepsis (≥8 days). Early onset neonatal sepsis is more common than late onset neonatal sepsis, according to the finding of the study. This could be attributed to maternal factors like adequacy of the maternal immune response, multiple digital vaginal examinations and fetal factors such in-utero swallowing of infected amniotic fluid, prematurity/low birth weight and immaturity of the neonatal immune system.

This finding is lower than previous studies conducted in Gondar (59.33%) (13), Shashemene (65%) (11), and Bishoftu (81.4%) (18). This difference could be owing to differences in research design. Similarly the result is lower than that of a study conducted in Ghana (78.7%) (16), which could be socio-demographic differences. However, it is higher than a study conducted in Egypt (44.2%), which could be attributed to differences in sample size, socio demographics and study period (19).

Mode of delivery, history of anemia, and lack of tetanus toxoid vaccination during recent pregnancy were all found to be predictors of neonatal sepsis in the current study. The odds of neonatal sepsis among neonates delivered by cesarean section were 2.5 times higher than neonates delivered vaginally. Furthermore, early onset neonatal sepsis was higher in proportion among neonates delivered by cesarean section. This link could be related to a longer stay in the hospital, which increases the chance of a hospital-acquired infection during cesarean delivery. There is also less skin-to-skin contact and a later start to breast-feeding (20). Since the initial milk, colostrum, is thought to be the first vaccine, this is crucial for improving newborn immunity (21). This association could also be due to the underlying condition of the mother and lack of asepsis in the OR. This finding is similar with that of an Egyptian study (19) which indicated that the incidence of sepsis was greater in neonates born via cesarean section than in those born vaginally. A study conducted in Ghana reported increased risk of neonatal sepsis among mothers with emergency CS (16) and similarly a study in Gondar, Northern Ethiopia, found a five-fold increased odds of neonatal sepsis in neonates born by caesarian section (22).

However, there is a finding in Gondar (13) that contradicts with this result; this variation occurs, probably do to sample size variation.

The odds of neonatal sepsis were 3.5 times higher in neonates born to mothers who had not been vaccinated against TT than in their counterparts. The rationale could be linked to the principle of antenatal vaccination, in which maternal pathogen specific antibodies are employed to boost and protect the newborn until the appropriate time for infant vaccination or until the period of maximum sensitivity has passed (23-25). In neonates, antibodies generated from the placenta and breast milk serve as the primary source of defense against infectious diseases (21).

The odds of neonatal sepsis were 2.5 times higher in neonates born to women who had a history of anemia during a recent pregnancy than in their counterparts. The findings of a prospective research conducted in India, which found that 9% of neonates born to anemic mothers had neonatal sepsis, were in line with this conclusion (26). The possible reason for this could be due to a considerable loss in micronutrients in breast milk in anemic mothers, which can weaken the newborn's immunity and make them more susceptible to sepsis (27). In addition, a study found that anemic mothers are more likely to have a cesarean section (28, 29). There is also a study conducted in Nepal that found maternal anemia reduces infection resistance in both the mother and the newborn (30).

The following limitations should be taken into account when interpreting the results of this study. First, as the study was limited to hospitals, the external validity of the study might have been compromised. Second, some of the variables in findings are prone to subjective bias. Third, the study relied on clinical and hematologic criteria for diagnosis of neonatal sepsis which may have lead to over estimation of the prevalence of neonatal sepsis. Finally, as the association between the outcome and the exposure variables was measured using OR, the true relationship might have been overestimated, as OR tends to overestimated the relative risk.

Conclusion

According to the findings of this study, obstetric, health service utilization and maternal medical illness factors were determinants contributed to neonatal sepsis. More specifically, cesarean mode of delivery, of maternal history of anemia, and being not vaccinated to tetanus were identified risk factors for neonatal sepsis. Improved infant health requires standard ANC, intrapartum care, and improving maternal nutritional status during pregnancy through proper

counseling and micronutrient supplementation as well as timely Tetanus Toxoid (TT) vaccination. Due to the lack of culture for the identification of neonatal sepsis, neonates may be treated with antibiotics that are unnecessary. Finally, studying the determinants of early onset and late onset neonatal sepsis separately and more investigation into the rate of neonatal sepsis among mothers with a history of anemia and who did not receive the (TT) immunization is recommended.

Abbreviations

ANC: Antenatal care; APGAR: Appearance, pulse, grimace, activity, and respiration; EDHS: Ethiopian demographic health survey; IMNCI: Integrated management of neonatal and childhood illness; NICU: Neonatal intensive care unit; SDG: Sustainable Development goal; TT: Tetanus toxoid.

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Competing interests

The authors declare no competing interest.

Contributors

KB conceptualized the study, analyzed and interpreted the data. RF, TA and AZ participated in the designing of the study and supervised the fieldwork and the analysis of the data. All the authors drafted, reviewed and approved the final manuscript.

Data sharing statement: Available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical clearance was obtained from the Institutional Review Board of Hawassa University, College of Medicine and Health Sciences.

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Reference

1. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clin Microbiol Rev. 2014;27(1):21-47.
2. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. The Lancet Respiratory Medicine. 2018;6(3):223-30.
3. Amare D, M. Mela, and G. Dessie,. Unfinished agenda of the neonates in developing countries: magnitude of neonatal sepsis: systematic review and meta-analysis. . Heliyon. 2019;5(9).
4. Singh M, Narang A, Bhakoo O. Predictive perinatal score in the diagnosis of neonatal sepsis. Journal of tropical pediatrics. 1994;40(6):365-8.
5. UNICEF. Levels and trends in child mortality. New York: UNICEF. 2015.
6. UNICEF. World Bank Group. Levels & trends in child mortality 2020. New York: United Nations Children's Fund; 2020. 2020.
7. Tekelab T, Chojenta C, Smith R, Loxton D. The impact of antenatal care on neonatal mortality in sub-Saharan Africa: A systematic review and meta-analysis. PLoS One. 2019;14(9):e0222566.
8. Ranjeva SL, B.C. Warf, and S.J. Schiff,. Economic burden of neonatal sepsis in sub-Saharan Africa. BMJ global health. 2018;3(1).

9. Gebremedhin D, Berhe H, Gebrekirstos K. Risk Factors for Neonatal Sepsis in Public Hospitals of Mekelle City, North Ethiopia, 2015: Unmatched Case Control Study. PLoS One. 2016;11(5):e0154798.

10. Ethiopian Public Health Institute (EPHI) [Ethiopia] and ICF. Ethiopia Mini Demographic and Health Survey 2019: Key Indicators. Rockville, Maryland, USA: EPHI and ICF, 2019.

11. Getabelew A, Aman M, Fantaye E, Yeheyis T. Prevalence of Neonatal Sepsis and Associated Factors among Neonates in Neonatal Intensive Care Unit at Selected Governmental Hospitals in Shashemene Town, Oromia Regional State, Ethiopia, 2017. International Journal of Pediatrics. 2018;2018:1-7.

12. Mersha A, Worku T, Shibiru S, Bante A, Molla A, Seifu G, et al. Neonatal sepsis and associated factors among newborns in hospitals of Wolaita Sodo Town, Southern Ethiopia. Research and Reports in Neonatology. Research and Reports in Neonatology. 2019;9:1-8.

13. Gudayu TW, Zeleke EG, Lakew AM. The role of the season at admission in neonatal sepsis: a retrospective chart review of a 1-year data at University of Gondar comprehensive specialized hospital. BMC Res Notes. 2019;12(1):643.

14. FMHACA. Standard Treatment Guidelines for General Hospital. Food, Medicine and Healthcare Administration and Control Authority of Ethiopia; 2014.

15. Alemu M, Ayana M, Abiy H, Minuye B, Alebachew W, Endalamaw A. Determinants of neonatal sepsis among neonates in the northwest part of Ethiopia: case-control study. . Italian Journal of Pediatrics. 2019;45(150):1-8.

16. Adatara P, Afaya A, Salia S, Afaya RA, K.Kuug A, Agbinku E, et al. Risk Factors for Neonatal Sepsis: A Retrospective Case-Control Study among Neonates Who Were Delivered by Caesarean Section at the Trauma and Specialist Hospital, Winneba, Ghana. . BioMed Research International. 2018;Volume 2018.

17. World Health Organization. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses. Geneva: WHO; 2013.

18. Woldu M, Lenjisa J, Tegegne G, Tesfaye G, Dinsa H, Guta M. Assessment of the incidence of neonatal sepsis, its risk factors, antimicrobials use and clinical outcomes in Bishoftu general hospital, neonatal intensive care unit, Debrezeit-Ethiopia. International Journal of Contemporary Pediatrics. 2014:1.

19. Shehab El-Din EM, El-Sokkary MM, Bassiouny MR, Hassan R. Epidemiology of Neonatal Sepsis and Implicated Pathogens: A Study from Egypt. Biomed Res Int. 2015;2015:509484.

20. Prado DS, Mendes RB, Gurgel RQ, Barreto IDdC, Cipolotti R, Gurgel RQ. The influence of mode of delivery on neonatal and maternal short and long-term outcomes. Revista de saude publica. 2018;52:95.

21. Maertens K, Orije MRP, Van Damme P, Leuridan E. Vaccination during pregnancy: current and possible future recommendations. European journal of pediatrics. 2020;179(2):235-42.

22. G/eyesus T, Moges F, Eshetie S, Yeshitela B, Abate E. Bacterial etiologic agents causing neonatal sepsis and associated risk factors in Gondar, Northwest Ethiopia. BMC Pediatrics. 2017;17(1).

23. Jones C, Heath P. Antenatal immunization. Human Vaccines & Immunotherapeutics. 2014;10(7):2118-22.

24. Vojtek I, Dieussaert I, Doherty TM, Franck V, Hanssens L, Miller J, et al. Maternal immunization: where are we now and how to move forward? Annals of medicine. 2018;50(3):193-208.

25. Calvert A, Jones CE. Placental transfer of antibody and its relationship to vaccination in pregnancy. Current opinion in infectious diseases. 2017;30(3):268-73.

26. Shah N, Upadhyay C, Sahota R. Neonatal outcome in anemic mothers: A prospective study. Journal of Evolution of Medical and Dental Sciences. 2013;2(43):8355-60.

27. El-Farrash RA, Ismail EAR, Nada AS. Cord blood iron profile and breast milk micronutrients in maternal iron deficiency anemia. Pediatric Blood & Cancer. 2012;58(2):233-8.

28. Drukker L, Hants Y, Farkash R, Ruchlemer R, Samueloff A, Grisaru-Granovsky S. Iron deficiency anemia at admission for labor and delivery is associated with an increased risk for Cesarean section and adverse maternal and neonatal outcomes. Transfusion. 2015;55(12):2799-806.

29. Smith C, Teng F, Branch E, Chu S, Joseph K. Maternal and perinatal morbidity and mortality associated with anemia in pregnancy. Obstetrics and gynecology. 2019;134(6):1234.

30. Prakash S, Yadav K. Maternal Anemia in Pregnancy: An Overview. Ijppr Human. 2015;4(3):164-79.

Strengthening Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI) Checklist: An extension of the STROBE statement for neonatal infection research

Section	Item No.	Recommendation	Reported in Page#
		TITLE AND ABSTRACT	
	STROBE 1(a)	Indicate the study's design with a commonly used term in the title or abstract	1
	STROBE1(b)	Provide in the abstract an informative and balanced summary of what was done and what was found	2
		INTRODUCTION	
Background/ rationale Objectives	STROBE2	Explain the scientific background and rationale for the investigation being reported	3
	STROBE3	State specific objectives, including any pre-specified hypotheses	4
		METHODS	
Study design	STROBE 4	Present key elements of study design early in the paper	5
	STROBE-NI 4.1	Clearly state case ascertainment methods (eg. physician diagnosis, clinical algorithm), documenting individual clinical signs used for diagnosis of possible serious bacterial infection. Give microbiological and/or laboratory and/or radiological criteria for other infectious syndromes (eg. meningitis, sepsis, pneumonia). Include indications for clinical investigations (eg. lumbar puncture)	7
	STROBE-NI4.2	Give criteria used to differentiate between new infection episodes and relapses	-
	STROBE-NI 4.3	For facility-based studies, indicate if the study is of community and/or hospital acquired infections (HAI), defining HAI using an international standard and presenting specific HAIclinical syndromes separately	-
	STROBE-NI4.4	State whether this is an outbreak study, and if so define an outbreak, with reference to an international standard	NA
	STROBE-NI4.5	Describe sampling strategy (eg. clinical indication vs. routine surveillance) and sampling details, (eg. minimum volumes; timing in relation to antimicrobial administration)	NA
	STROBE-NI4.6	Describe conventional and/or molecular microbiological methods used, with details (eg. automation, enrichment steps), and the use of controls	NA
	STROBE-NI4.7	List pathogens that are likely to be identified by microbiological methods used, and criteria used to determine clinical significance	NA
	STROBE-NI4.8	Describe antimicrobial susceptibility tests and thresholds used with reference to an international standard (eg. CLSI or EUCAST)	NA
Setting	STROBE 5	Describe the setting, locations, and relevant dates, including periods of recruitment,	5

		exposure, follow-up, and data collection	
	STROBE-NI 5.1	Describe the study context in terms of incidence of neonatal mortality, stillbirth and preterm birth.	4-5
	STROBE-NI 5.2	Describe the population included eg. facility live births, referrals from home, referrals from another facility	5
	STROBE-NI 5.3	For community-based studies, describe care-seeking and adherence and time to referral	NA
	STROBE-NI 5.4	For facility-based studies, describe obstetric care (basic or comprehensive), including proportion of births by caesarean section. Report annual number of live births per facility and state proportion of births in the study area that occur in hospital (vs. community)	
	STROBE-NI 5.5	For facility-based studies, indicate if the facility is public or private, and give the number of healthcare staff and their training. Indicate the level of neonatal care available (eg. ventilatory support, indwelling catheters) and investigations available (eg. biochemistry, radiology). Report antimicrobial guidelines used for the empiric management of neonatal sepsis.	4-5
	STROBE-NI 5.6	State the laboratory location and capacity to process different sample types, and give quality control and assurance measures in place.	NA
Participants	STROBE 6(a)	Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	7
	STROBE 6(b)	Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	NA
	STROBE-NI 6.1	State age of participants (eg. 0-27 days defines neonates; 'day 0' as day of birth). Disaggregate neonatal data from that of older infants and from stillbirths	7
Variables	STROBE 7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
	STROBE-NI 7.1	State criteria used to define clinically significant organisms for each sample type	
Data sources measurement	STROBE 8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	STROBE 9	Describe any efforts to address potential sources of bias	6

Study size	STROBE 10	Explain how the study size was arrived at	
Quantitative variables	STROBE 11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	STROBE 12(a)	Describe all statistical methods, including those used to control for confounding	6
	STROBE 12(b)	Describe any methods used to examine subgroups and interactions	
	STROBE 12(c)	Explain how missing data were addressed	
	STROBE 12(d)	Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	NA
	STROBE 12(e)	Describe any sensitivity analyses	
RESULTS			
Participants	STROBE 13(a)	Report numbers of individuals at each stage of study—eg. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
	STROBE 13(b)	Give reasons for non-participation at each stage	-
	STROBE 13(c)	Consider use of a flow diagram	-
	STROBE-NI 13.1	See Figure 3 for suggested components of a flow diagram for neonatal infections	_
Descriptive data	STROBE-NI 14.1	Describe maternal infections (clinical or on screening, eg. GBS or HIV) or risk factors for infection (eg. PROM, peripartum fever).	10-12
	STROBE-NI 14.2	Describe key neonatal characteristics, including sex, postnatal and gestational age categories (range and median), birth weight categories (range and median), birth place, feeding (breast milk or other) and comorbidities	15
	STROBE-NI 14.3	Report data on occurrence of individual signs (eg. fast breathing) according to case definitions	
	STROBE-NI 14.4	Give proportion of mothers and neonates with peripartum antibiotic exposure (+/- pre-admission exposure for neonates). Report details of antimicrobials (or supportive care) given during the study	
	STROBE 14(b)	Indicate number of participants with missing data for each variable of interest	-
	STROBE 14(c)	Cohort study—Summarise follow-up time (eg. average and total amount)	NA
Outcome data	STROBE 15	Cohort study—Report numbers of outcome events or summary measures over time Case-control study—Report numbers in each exposure category, or summary measures of exposure Cross-sectional study—Report numbers of outcome events or summary measures	
	STROBE-NI 15.1	Report the number (+/- proportion) of samples microbiologically tested (including lumbar	NA

		punctures for meningitis cases); the number (+/-proportion) that were positive (including thresholds for detection, where applicable); all isolates obtained (including clinically significant and non-significant); and antimicrobial susceptibilities of pathogens, where done.	
	STROBE-NI 15.2	Report number (+/- proportion) of babies with microbiologically proven infection (and number of infections per baby), and include this in the flow chart.	NA
	STROBE-NI 15.3	Report infections by day, for days 0-6. State age categories, if used, defining 'early-onset' and 'late-onset' infection (eg. <72 hours and ≥ 72 hours respectively)	15
	STROBE-NI 15.4	Report deaths and any sub-analyses by risk groups	
Main results	STROBE 16(a)	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17
	STROBE 16(b)	Report category boundaries when continuous variables were categorized	
	STROBE 16(c)	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
	STROBE-NI 16.1	For incidence, give risk per 1000 live births, or if alternative denominator used (eg. total births or bed days), define this clearly	NA
Other analyses	STROBE 17	Report other analyses done—eg. analyses of subgroups and interactions, and sensitivity analyses	NA
DISCUSSION			
Key results	STROBE 18	Summarize key results with reference to study objectives	19
Limitations	STROBE 19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20
	STROBE-NI 19.1	Discuss sources of recruitment bias, particularly regarding the period of time shortly after birth. State source of denominator data and discuss possible related biases	-
Interpretation	STROBE 20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	STROBE 21	Discuss the generalisability (external validity) of the study results	20
OTHER INFORMATION			
Funding	STROBE 22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA
Ethics	STROBE-NI 23.1	Report any ethical considerations, including the recruitment of young mothers (minors), and the consent process for early recruitment of neonates after delivery. Provide details of research ethics approval.	7 & 21

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Determinants of neonatal sepsis among neonates admitted to neonatal intensive care unit of public hospitals in Hawassa city administration, Sidama Region, Ethiopia, 2020. An unmatched case-control study.

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Abstract

Objective: This study was conducted to assess the determinants of neonatal sepsis in the neonatal intensive care units in public hospitals of Hawassa city administration, Sidama region, Ethiopia, 2020.

Design: Institutional-based unmatched case-control study.

Setting: The study was conducted in three (Hawassa University Teaching Hospital, Adare General Hospital, and Hawela Tula Primary Hospital) public hospitals of Hawasa city, Ethiopia.

Participants: A total of 331 (110 cases and 221 controls) neonates with their index mothers were included in the study from August 1st to September 30, 2020.

Outcome measures: A pretested, interviewer-administered questionnaire and data extraction checklist were used to collect data. Data were coded and entered into Epi data version 3.1 before being exported to SPSS version 20 for analysis. The factors associated with neonatal sepsis were assessed using bivariable and multivariable logistic regression analyses. P-value of less than 0.05 was used to establish the statistically significant association of variables.

Results: Cesarean section delivery [AOR= 2.56; 95 % CI (1.3-5.00)], maternal anemia [AOR = 2.58; 95 % CI (1.45-4.6)], and lack of vaccination with tetanus toxoid [AOR= 3.5 95 % CI (2.07-6.19)] were all identified as factors significantly associated with neonatal sepsis.

Conclusions: Cesarean section delivery, maternal history of anemia, and lack of vaccination with tetanus toxoid were founded to be risk factors of neonatal sepsis. Establishing preconception care practice, strengthening the quality of ANC care and standardized infection prevention practice are needed for the improvement of neonatal health.

Keywords: Neonatal sepsis, Sepsis neonatorum, Neonatal infection, Neonatal Intensive Care Unit, Ethiopia.

Strengths and limitations of this study

Strengths

- The study was a prospective study and addressed all of the public hospitals found in Hawassa city.
- The study used both primary and secondary data sources.

Limitations

- The study relied on clinical and hematologic criteria to diagnose neonatal sepsis.
- As the associations between the exposure and the outcome variables were measured using OR, the true relationship might have been overestimated as OR tends to overestimate the relative risk.
- No matching was applied which would have strengthened the findings of this study

Introduction

Neonatal sepsis is a systemic infection occurring in infants ≤28 days of life (1). Neonatal sepsis is a common and fatal condition affecting neonates globally (2), and the major cause of mortality and morbidity particularly in developing countries (3). Neonatal sepsis is characterized as early-onset neonatal sepsis or late-onset neonatal sepsis based on the onset of symptoms (4).

Reducing neonatal sepsis by improving the quality of care is a global and local priority. Worldwide, the neonatal mortality rate is on the way of decrement from 36 deaths per 1,000 live births in 1990 to 19 per 1,000 live births in 2015 (5). Neonatal deaths have decreased as well, from 5.1 million in 1990 to 2.4 million in 2020(6). When comparing neonatal and post-neonatal mortality rates (1-59 months), neonatal mortality decreased at a slower rate than post-neonatal mortality, which was 47 percent and 58 percent, respectively (5, 6). Neonatal mortality remains an urgent concern and is an indicator of child health, development and wellbeing (7).

Neonatal sepsis caused an estimated 750,000 yearly neonatal deaths worldwide, with mortality rates highest in Sub-Saharan Africa (8). Despite the fact that newborn deaths are preventable, the problem is concentrated in the world's poorest countries, with low and middle-income countries accounting for 85 percent of all neonatal deaths (9). Studies indicated that neonatal sepsis presents a $10–$469 billion financial burden that could be reduced through successful treatment and prevention in SSA (8).

The neonatal death rate has also decreased in Ethiopia from 39 per 1000 live births in 2005 to 30 in 2019, according to the Ethiopian Demographic and Health Survey (EDHS). However, compared to the 29 neonatal deaths per 1000 live births reported in the 2016 EDHS, there is a modest increase in neonatal mortality in 2019 (10).

In terms of the prevalence of neonatal sepsis in Ethiopia, studies have found that it is as high as 77.9% in Shashemene and as low as 33.8 percent in Wolaita Sodo, though both studies asserted neonatal sepsis using a medical diagnosis of the neonate stated as 'neonatal sepsis' by the physician in the neonate's medical record chart (11, 12). Among factors; maternal intrapartum fever, the season of birth, and admission, vaginal mode of delivery and preterm gestational age at birth increased the risk of having neonatal sepsis (13).

Recognition of the determinants of neonatal sepsis is important for public health advocacy to reduce risks of exposure. In Ethiopia, few investigations were available on neonatal sepsis and have primarily been prevalence studies based on secondary data. Studies on determinants of neonatal sepsis would give data to identify high-risk neonates; thus, this study was aimed to identify determinants of neonatal sepsis among neonates admitted to Neonatal Intensive Care Unit (NICU) of public hospitals in Hawassa city administration.

Methods

Study area

Hawassa city administration is located in Ethiopia's Sidama Region. It is located 275 kilometers south of Ethiopia's capital city, Addis Ababa, which has a population of 385,257 people. Males and females account for 191,858 and 193,399 people, respectively. There are 89,765 females of reproductive age in the entire population, as well as 13,330 pregnant women (14). The city is divided into 8 sub-cities and 32 kebeles, with 21 urban and 11 rural kebeles. There are 8 hospitals (3 public and 5 private) in the Hawassa city government, as well as 12 Public Health Centers and 18 Health Posts. The three public hospitals are Hawassa University Comprehensive Specialized Hospital (HUCSH), Adare General Hospital (AGH), and Hawela Tula Primary Hospital (HTPH) in which all those public hospitals have NICUs. The NICUs of the three hospitals provide services free of charge. In terms of the types of respiratory assistance available, all three institutions provide oxygen, assisted breathing (non-invasive assisted ventilation), and

surfactant. Diagnosis of neonatal sepsis depends on a clinical decision in all of the three hospitals. The hospitals follow Ethiopia's National Standard Treatment Guideline for Hospitals, which advises broad-spectrum antibiotics such as penicillin and aminoglycosides for treatment the of neonatal sepsis (15).

Study design and period

Institutional based unmatched case-control study was conducted from August 1st to September 30, 2020**.**

Source population

The source population included all neonates admitted to NICUs of public hospitals in Hawassa city administration.

Study population

Cases were neonates with sepsis and controls were neonates without sepsis who were admitted to NICUs of Public Hospitals in Hawassa city administration, during study period.

Sample size determination

The sample size required for the study was calculated using double population proportion formula (using Epi info version 7.2), taking into account the proportion of neonates with PROM among the controls of 8.5 percent and an Adjusted Odds Ratio (AOR) of 2.812, which was estimated from a study conducted in Debre Markos referral hospital (16), 95% CI, 80% power of the study, and case to control ratio of 1:2, which resulted in a total sample size of 315 (105 case and 210 controls). By adding 5% for the non-response rate the final sample size became 331(110 cases and 221 controls).

Sampling technique

All three public hospitals fund in Hawassa city administration were considered in this study. The calculated final sample size was proportionally allocated for each hospital based on newborn

sepsis records from the previous six months. The two-month case flow was calculated using each hospital's previous six-month case flow.

Data collection tools and procedures

The data were collected using a pretested, interviewer-administered questionnaire and a data extraction checklist. The questionnaire was adapted from other similar studies with some contextual modification based on the main objective of the study (9, 13, 17). The data were gathered by interviewing the mothers and reviewing the medical records of the neonates.

Data quality assurance and data quality control

The questionnaire was prepared in English and then translated into Amharic language for data collection. Pretest was conducted in 5 % (6 cases and 11 controls) in Leku primary hospital to determine the amount of time needed for the interview and the consistency of the questionnaire. Appropriate modifications were made based on the results of the pretest. Three BSc. Midwives collected the data while one BSc. Midwife supervised the data collection process. One-day training was given for data collectors and supervisor about the aim of the study, questioner, and how to approach cases and controls in similar ways. Completeness of collected questionnaires was checked by the supervisor and corrective discussion was made with data collectors.

Data processing and analysis

The collected data were coded and entered into Epi data version 3.1. then exported to SPSS version 20 for analysis. Descriptive statistics were carried out and presented using texts and tables. Chi-square (x^2) tests were computed to observe the comparability of variables among cases and controls test. Bivariable Logistic regression analyses were performed to select candidate variables for the Multivariable Logistic Regression analyses. Variables with a p-value < 0.25 in the bivariable analysis were considered as candidates for multivariate logistic regression analyses. Multicollinearity was checked out to determine the correlation between the independent variables and Hosmer-Lemeshow goodness of fit statistics was used to assess the fitness of the model. Variables having a p-value <0.05 during multivariable analyses were considered as having a statistically significant association with neonatal sepsis. Finally, the

findings of the analysis were summarized using crude (COR) and adjusted odds ratio (AOR) with 95% confidence intervals (CI).

Operational definition

Case definition (Neonatal sepsis): Newborns aged 0 to 28 days, who were admitted to NICU of public hospitals in Hawassa city administration during the study period. One or more established Integrated Management of Neonatal and Childhood Illness (IMNCI) clinical features of neonatal sepsis (either not feeding well or convulsion or drowsy or unconscious or movement only stimulated or no movement at all or fast breathing>60 breath per min or grunting or severe chest indrawing or raised temperature (>38°C) or hypothermia (<35.5°C) or central cyanosis or severe jaundice or severe abdominal distention or many or severe skin pustules or bulging fontanels along with one or more hematological criteria (total white blood cells <5,000 or >20,000), or c-reactive protein <0.9 or >15.8 or platelet count (<150 or >440 cells/m3) or absolute neutrophil count (<1500 cells/mm^3 or >7500 cells/mm^3), erythrocyte sedimentation rate (ESR) (>15/1 h) were used for the diagnosis of neonatal sepsis (18). Those who fulfill the operational definition of neonatal sepsis (≥1 IMNCI criteria along with ≥1 hematologic criteria) with their index mother were considered as cases.

Control definition

Controls: Controls for the study were 0-28-day old neonates with their index mothers who were admitted in NICU of public hospitals in Hawassa city administration during the study period and did not meet the case definition (such as neonates admitted in the NICU due to prematurity needing supportive care, Neonatal hyperbilirubinemia needing phototherapy, etc.).

Ethics considerations

On behalf of Hawassa University's institutional review board (Ref. No: IRB/09/12), ethical approval was acquired from the Hawassa University College of Medicine and Health Science ethical review committee. A letter of collaboration was written for each hospital, and permission was acquired from the medical directorate of each hospital (Ref. No.MID/395/12). After describing the goal of the study and the study participant's rights, each study subject/guardian gave written and verbal consent. The confidentiality of the records was also ensured by keeping them closed.

Patient and public involvement: Patients and/or the public were not involved during the design, development, analysis and publication of this study.

Result

Socio-demographic characteristics of the mother

A total of 331 study participants (110 cases and 221 controls) participated, with a response rate of 100% (50 cases and 101 controls from HUCSH, 42 cases and 84 controls from AGH, and 18 cases and 36 controls from HTPH). More than half of mothers among the cases 70(63.6%) and more than two-thirds of the controls 152(68.8%) were between the ages of 25-34 years. A higher proportion (60.4%) of mothers in cases and three fourth (72.4%) of controls, were urban dwellers ($p = 0.024$). No significant differences were found between the other basic characteristics of the two groups (Table 1).

Table **1:** Socio demographic characteristics of the respondents among neonates admitted to NICU of public hospitals in Hawassa city, Sidama Region, Ethiopia, 2020 (N=331).

Variable	Cases N=110(%)	Control N=221(%)	x^2(p-value)
Maternal age at current birth			
15-24	28(25.5)	49(22.2)	0.64
25-34	70(63.6)	152(68.8)	
≥35	12(10.9)	20(9)	
Marital status			
Single	10(9.1)	10(4.5)	0.72
Married	95(86.4)	194(87.8)	
Others*	5(4.5)	17(7.7)	
Residence			
Urban	67(60.9)	160(72.4)	0.024
Rural	43(39.6)	61(27.6)	
Mother`s educational status			
Cannot read and write	26(23.6)	40(18.1)	0.15
Primary first cycle (1-4)	20(18.2)	31(14)	
Primary second cycle (5-8)	12(10.9)	48(21.7)	
Secondary (9-12)	19(17.3)	39(17.6)	
Collage and above	33(30)	63(28.5)	
Monthly Income			
≤39.19 USD	51(46.4)	95(43)	0.55
39.2-55.99 USD	13(11.8)	21(9.5)	
56-72.79 USD	8(7.3)	10(4.5)	
≥72.8 USD	38(34.5)	95(43)	
Occupation of the mother			
Government employee	26(23.6)	42(19)	0.66
Housewife	57(51.8)	108(48.9)	
Merchant	12(10.9)	33(14.9)	
Daily laborer	5(4.5)	19(8.9)	
Others**	10(9.1)	19(8.6)	

Note: Others* widowed, divorced, separated and cohabiting; Others ** private organization and student

Obstetric related factors

Mothers of 85(77.7%) of the cases and 161(72.9%) of the controls were multiparous. The mode of delivery was vaginal in 85 (77.3%) of the cases and 195 (88.2%) of the controls, according to the statistics (Table 2).

Table **2:** Obstetric related factors of the respondents among neonates admitted to NICU of public hospitals in Hawassa city, Sidama Region, Ethiopia, 2020 (N=331).

Variable	**Case N=110(%)**	**Control N=221(%)**	x^2**(p-value)**
Gravidity			
≤4	95(86.4)	192(86.9)	0.52
≥5	15(13.6)	29(13.1)	
Parity			
Primiparous	25(22.7)	60(27.1)	0.23
Multiparous	85(77.3)	161(72.9)	
Duration of labor			
<6	7(6.4)	10(4.5)	0.056
6-12	45(40.9)	122(55.2)	
13-23	50(45.5)	70(31.7)	
≥24	8(7.3)	19(8.6)	
Current pregnancy status			
Single	106(96.4)	217(98.2)	
Multiple	4(3.6)	4(1.8)	
Place of delivery			
Home	8(7.3)	10(4.5)	0.5
Hospital	81(73.6)	173(78.3)	
Health center	21(19.1)	38(17.2)	
Mode of delivery			
Vaginal delivery	85(77.3)	195(88.2)	0.008
Cesarean section	25(22.7)	26(11.8)	
Onset of delivery			
Spontaneous	90(81.8)	181(81.9)	0.14
Induced	20(18.2)	40(18.1)	
Place of onset of labor			
Home	90(81.8)	177(80.1)	0.4
Institution	20(18.2)	44(19.9)	

Hypertension			
No	106(96.4)	215(97.3)	
Yes	4(3.6)	6(2.7)	
Antepartum hemorrhage			
No	105(95.5)	218(98.6)	
Yes	5(4.5)	3(1.4)	
Premature rupture of membrane			
No	81(73.6)	167(75.6)	0.4
Yes	29(26.4)	54(24.4)	
Interventions during delivery *			
No	81(73.6)	182(82.4)	0.04
Yes	29(26.4)	39(17.6)	

* Interventions during delivery include Vacuum and forceps deliveries and Artificial Rupture of Membrane (AROM).

Maternal medical illness

During their recent pregnancy, 15 (13.6 percent) of mothers of the cases and 20 (9 percent) of the controls had experienced urinary tract infections (UTI). Thirty-five (31.8%) of the cases and 39(17.6%) of the controls had a history of anemia during their recent pregnancy. Syphilis was found among 10(9.1%) of the cases and 15(6.8%) of the controls (Table 3).

Table **3:** Maternal medical illness of the respondents among neonates admitted to NICU of public hospitals in Hawassa city, Sidama Region, Ethiopia, 2020 (N=331).

Variable	Case N=110(%)	Control N=221(%)	x^2(p-value)
Anemia			
No	75(68.2)	182(82.4)	0.03
Yes	35(31.8)	39(17.6)	
Diabetes mellitus			
No	106(96.4)	213(96.4)	
Yes	4(3.6)	8(3.6)	
Urinary Tract Infection (UTI)			
No	95(86.4)	201(91)	0.13
Yes	15(13.6)	20(9)	
Malaria			
No	97(88.2)	195(88.2)	0.56
Yes	13(11.8)	26(11.8)	
HIV			
No	90(81.8)	182(82.4)	
Yes	2(1.8)	9(4.1)	
Unknown	18(16.4)	30(13.6)	
Syphilis			
No	77(70)	164(74.2)	0.66
Yes	10(9.1)	15(6.8)	
Unknown	23(20.9)	42(19)	

Health service utilization

The proportion of mothers who were not vaccinated with tetanus toxoid during their recent pregnancy was significantly higher in controls 42(80.5%) than cases (68.2%) (p<0.001) (Table 4).

Table 4: Health service utilization of the respondents among neonates admitted to NICU of public hospitals in Hawassa city, Sidama Region, Ethiopia, 2020 (N=331).

Variable	Case N=110(%)	Control N=221(%)	x^2(p-value)
Antenatal follow up			
Yes	87(79.1)	188(85.1)	0.11
No	23(20.9)	33(14.9)	
Number of Antenatal follow up			
<4	36(41.4)	69(36.7)	0.13
≥4	51(58.6)	119(63.3)	
Tetanus Toxoid vaccine			
Yes	75(68.2)	178(80.5)	<0.001
No	35(31.8)	43(19.5)	
Nutrition counseling			
Yes	61(55.5)	143(64.7)	0.06
No	49(44.5)	78(35.3)	
Birth preparedness and complication counseling			
Yes	61(55.5)	138(62.4)	0.13
No	49(44.5)	83(37.6)	
Prevention and treatment of anemia			
Yes	68(61.8)	154(70)	0.08
No	42(38.2)	66(30)	

Neonatal related factors

The majority of the neonates in this study were under the age of seven days, with 61 (55.5%) cases and 133 (60.2%) controls. The majority 99(90%) of the cases and 207(93.7%) of the controls had normal presentation during delivery. Moreover, a significantly higher (71%) proportion of controls cried immediately after birth as compared to the cases (p=0.02). Similarly, a higher proportion (54.5%) of cases were not immediately breastfed within 1hour of delivery as compared to the controls (38.5%) (p=0.004). The proportion of first minute low Apgar score is higher among cases 26(23.6%) than controls 23(10.4%). Seventeen (15.5%) of cases and 21(9.5%) of controls had birth asphyxia (Table 5).

Table 5: Neonatal related factors of respondents among neonates admitted to NICU public hospitals in Hawassa city, Sidama Region, Ethiopia, 2020 (N=331)

Variable	Case N=110(%)	Control N=221(%)	x^2(p-value)
Age of neonate during data collection			
0-7 days	61(55.5)	133(60.2)	0.24
8-28 days	49(44.5)	88(39.8)	
Sex of neonate			
Male	57(51.8)	123(55.7)	0.29
Female	53(48.2)	98(44.3)	
Neonate presentation			
Normal	99(90)	207(93.7)	0.166
Mal presentation	11(10)	14(6.3)	
Type of mal presentation			
Breach	6(54.5)	7(50)	0.66
Others	5(45.5)	7(50)	
Gestational age			
Preterm	45(40.9)	34(15.4)	<0.001
Term	65(59.1)	187(84.6)	
Birthweight			
Low birth weight	43(39.1)	74(33.5)	0.331
Normal birth weight	67(60.9)	147(66.5)	
First APGAR score			
≥7	39(35.5)	93(42.1)	0.03
4-6	15(13.6)	53(24)	
<4	26(23.6)	23(10.4)	
Unknown	30(30)	52(23.5)	
Fifth APGAR score			
≥7	53(48.2)	132(59.7)	0.15
4-6	18(16.4)	21(9.5)	
<4	9(8.2)	15(6.8)	
Unknown	30(27.3)	53(24)	
Cried immediately after birth			
Yes	65(59.09)	157(71)	0.02
No	45(40.9)	64(29)	
Neonate resuscitated at birth			
No	67(60.09)	156(70.6)	0.05
Yes	43(39.09)	65(29.4)	
Immediate breastfeeding within 1hour			
Yes	50(45.5)	136(61.5)	0.004
No	60(54.5)	85(38.5)	
Birth asphyxia			
No	93(84.5)	200(90.5)	0.62
Yes	17(15.5)	21(9.5)	

Results of bi-variable and multi-variable Logistic Regression analyses

Residence, mode of delivery, anemia, cried immediately, immediate breastfeeding within 1 hour and Tetanus Toxoid (TT) vaccination were candidates for multivariable Logistic regression analyses at a p-value less than 0.25 on bivariable logistic regression analysis. In the multivariable model; maternal TT vaccination, mode of delivery and history of anemia during pregnancy were found to be significant predictors of neonatal sepsis at a p-value less than 0.05 and 95% CI.

Accordingly; neonates who were delivered by caesarian section had 2.56 times increased odds of developing neonatal sepsis [AOR(95% CI) = 2.56 (1.3 - 5.05)], while neonates born to mothers with a history of anemia were 2.58 times at increased chance of developing neonatal sepsis [AOR (95% CI) = 2.58(1.45 - 4.6)] and neonates born to mothers with lack of vaccination with tetanus toxoid had 3.5 times increased odds of developing neonatal sepsis [AOR(95% CI) = 3.5 (2.07-6.19)] (Table 6).

Table 6: Factors associated with neonatal sepsis among neonate admitted to NICU of public hospitals in Hawassa city, Sidama Region, Ethiopia, 2020. (N=331)

Variable	Cases N=110(%)	Control N=221(%)	COR(95%CI)	AOR(95%CI)
Residence				
Urban	67 (60.9)	160(72.4)	1	1
Rural	43 (39.1)	61(27.6)	1.683(1.04-2.7)	1.3(0.7-2.2)
Mode of delivery				
Vaginal delivery	85(77.3)	195(88.2)	1	1
Cesarean section	25(22.7)	26(11.8)	2.206(1.204-4.04)	2.56(1.3-5.00)*
History of anemia				
No	75(68.2)	182(82.4)	1	
Yes	35(31,8)	39(17.6)	2.2(1.28-3.69)	2.58(1.45-4.6)*
Cried Immediately				
Yes	65(59.1)	157(71)	1	1
No	45(40.9)	64(29)	1.698(1.1-2.7)	0.98(0.5-1.9)
Immediate breastfeeding				
Yes	50(45.5)	136(61.5)	1	
No	60(54.5)	85(38.5)	1.92(1.2-3.05)	1.3(0.7-2.5)
TT vaccination				
Yes	75(68.2)	178(80.5	1	
No	35(31.8)	43(19.5)	3.33(2.02-5.4)	3.5(2.07-6.19)*

Note: - TT: tetanus toxoid,* p- value <0.05

Discussion

The current study aimed to identify determinants of neonatal sepsis in order to reduce the burden of neonatal sepsis and to focus on the specific factors in the study area. Thus, mode of delivery, history of anemia, and lack of vaccination with tetanus toxoid during recent pregnancy were all found to be predictors of neonatal sepsis in the current study.

The odds of neonatal sepsis among neonates delivered by cesarean section were 2.5 times higher than neonates delivered vaginally. Furthermore, early-onset neonatal sepsis was higher in proportion among neonates delivered by cesarean section. This link could be related to a longer stay in the hospital, which increases the chance of a hospital-acquired infection during cesarean delivery. There is also less skin-to-skin contact and a later start to breastfeeding (19). Since the initial milk, colostrum, is thought to be the first vaccine, this is crucial for improving newborn immunity (20). This association could also be due to the underlying condition of the mother and lack of asepsis in the OR. This finding is similar to that of an Egyptian study (21) which indicated that the incidence of sepsis was greater in neonates born via cesarean section than in those born vaginally. A study conducted in Ghana reported an increased risk of neonatal sepsis among mothers with emergency CS (17) and similarly a study in Gondar, Northern Ethiopia, found a five-fold increased odds of neonatal sepsis in neonates born by caesarian section (22). However, there is a finding in Gondar (13) that contradicts this result. The contradiction to these results may be due to factors that differ between the cohorts like asepsis, the indications of cesarean section and the timing of cesarean section.

The odds of neonatal sepsis were 3.5 times higher in neonates born to mothers with a lack of vaccination with tetanus toxoid than in their counterparts. The rationale could be linked to the principle of antenatal vaccination, in which maternal pathogen-specific antibodies are employed to boost and protect the newborn until the appropriate time for infant vaccination or until the period of maximum sensitivity has passed (23-25). In neonates, antibodies generated from the placenta and breast milk serve as the primary source of defense against infectious diseases (20).

The odds of neonatal sepsis were 2.5 times higher in neonates born to women who had a history of anemia during a recent pregnancy than in their counterparts. The findings of a prospective research conducted in India, which found that 9% of neonates born to anemic mothers had neonatal sepsis, were in line with this conclusion (26). The possible reason for this could be due

to a considerable loss in micronutrients in breast milk in anemic mothers, which can weaken the newborn's immunity and make them more susceptible to sepsis (27). In addition, a study found that anemic mothers are more likely to have a cesarean section (28, 29). There is also a study conducted in Nepal that found maternal anemia reduces infection resistance in both the mother and the newborn (30).

As a strength, this study was a prospective study and addressed all of the public hospitals found in the study area. The study used both primary and secondary data sources. The following limitations should be taken into account when interpreting the results of this study. First, as the study was limited to hospitals, the external validity of the study might have been compromised. Second, some of the variables in the findings are prone to subjective bias. Third, the study relied on clinical and hematologic criteria for diagnosis of neonatal sepsis which may have led to overestimation of the prevalence of neonatal sepsis. Fourth, unmatched design was applied. Finally, as the association between the outcome and the exposure variables was measured using OR, the true relationship might have been overestimate, as OR tends to overestimated the relative risk.

Conclusion

According to the findings of this study, obstetric, health service utilization and maternal medical illness factors were determinants that contributed to neonatal sepsis. More specifically, cesarean mode of delivery, maternal history of anemia, and being not vaccinated to tetanus were identified risk factors for neonatal sepsis. Improved infant health requires standard ANC, intrapartum care, and improving maternal nutritional status during pregnancy through proper counseling and micronutrient supplementation as well as timely Tetanus Toxoid (TT) vaccination. Due to the lack of culture for the identification of neonatal sepsis, neonates may be treated with antibiotics that are unnecessary. So, the government and other stakeholders should work towards incorporating bacterial cultures in hospitals in order to reduce antibiotic utilization. Finally, studying the determinants of early-onset and late-onset neonatal sepsis separately and more investigation into the rate of neonatal sepsis among mothers with a history of anemia and who did not receive the (TT) immunization is recommended.

Abbreviations

ANC: Antenatal care; APGAR: Appearance, pulse, grimace, activity, and respiration; EDHS: Ethiopian demographic health survey; IMNCI: Integrated management of neonatal and childhood illness; NICU: Neonatal intensive care unit; SDG: Sustainable Development goal; TT: Tetanus toxoid.

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Competing interests

The authors declare no competing interest.

Contributors

KB conceptualized the study, analyzed and interpreted the data. RF, TA and AZ participated in the designing of the study and supervised the fieldwork and the analysis of the data. All the authors drafted, reviewed and approved the final manuscript.

Data sharing statement: Available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical clearance was obtained from the Institutional Review Board of Hawassa University, College of Medicine and Health Sciences. Permission was acquired from the medical directorate of each hospital and written consent was also secured each mother/guardian after describing the goal of the study and the study participant's right.

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Reference

1. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clin Microbiol Rev. 2014;27(1):21-47.
2. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. The Lancet Respiratory Medicine. 2018;6(3):223-30.
3. Amare D, M. Mela, and G. Dessie,. Unfinished agenda of the neonates in developing countries: magnitude of neonatal sepsis: systematic review and meta-analysis. . Heliyon. 2019;5(9).
4. Singh M, Narang A, Bhakoo O. Predictive perinatal score in the diagnosis of neonatal sepsis. Journal of tropical pediatrics. 1994;40(6):365-8.
5. UNICEF. Levels and trends in child mortality. New York: UNICEF. 2015.
6. UNICEF. World Bank Group. Levels & trends in child mortality 2020. New York: United Nations Children's Fund; 2020. 2020.
7. Tekelab T, Chojenta C, Smith R, Loxton D. The impact of antenatal care on neonatal mortality in sub-Saharan Africa: A systematic review and meta-analysis. PLoS One. 2019;14(9):e0222566.
8. Ranjeva SL, B.C. Warf, and S.J. Schiff,. Economic burden of neonatal sepsis in sub-Saharan Africa. BMJ global health. 2018;3(1).
9. Gebremedhin D, Berhe H, Gebrekirstos K. Risk Factors for Neonatal Sepsis in Public Hospitals of Mekelle City, North Ethiopia, 2015: Unmatched Case Control Study. PLoS One. 2016;11(5):e0154798.
10. Ethiopian Public Health Institute (EPHI) [Ethiopia] and ICF. Ethiopia Mini Demographic and Health Survey 2019: Key Indicators. Rockville, Maryland, USA: EPHI and ICF; 2019.
11. Getabelew A, Aman M, Fantaye E, Yeheyis T. Prevalence of Neonatal Sepsis and Associated Factors among Neonates in Neonatal Intensive Care Unit at Selected Governmental Hospitals in Shashemene Town, Oromia Regional State, Ethiopia, 2017. International Journal of Pediatrics. 2018;2018:1-7.

12. Mersha A, Worku T, Shibiru S, Bante A, Molla A, Seifu G, et al. Neonatal sepsis and associated factors among newborns in hospitals of Wolaita Sodo Town, Southern Ethiopia. Research and Reports in Neonatology. Research and Reports in Neonatology. 2019;9:1-8.

13. Gudayu TW, Zeleke EG, Lakew AM. The role of the season at admission in neonatal sepsis: a retrospective chart review of a 1-year data at University of Gondar comprehensive specialized hospital. BMC Res Notes. 2019;12(1):643.

14. Sidama Region Health Bureau. Sidama Region Health Report. Hawassa, Ethiopia: SRHB; 2020.

15. FMHACA. Standard Treatment Guidelines for General Hospital. Food, Medicine and Healthcare Administration and Control Authority of Ethiopia; 2014.

16. Alemu M, Ayana M, Abiy H, Minuye B, Alebachew W, Endalamaw A. Determinants of neonatal sepsis among neonates in the northwest part of Ethiopia: case-control study. . Italian Journal of Pediatrics. 2019;45(150):1-8.

17. Adatara P, Afaya A, Salia S, Afaya RA, K.Kuug A, Agbinku E, et al. Risk Factors for Neonatal Sepsis: A Retrospective Case-Control Study among Neonates Who Were Delivered by Caesarean Section at the Trauma and Specialist Hospital, Winneba, Ghana. . BioMed Research International. 2018;Volume 2018.

18. World Health Organization. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses. Geneva: WHO; 2013.

19. Prado DS, Mendes RB, Gurgel RQ, Barreto IDdC, Cipolotti R, Gurgel RQ. The influence of mode of delivery on neonatal and maternal short and long-term outcomes. Revista de saude publica. 2018;52:95.

20. Maertens K, Orije MRP, Van Damme P, Leuridan E. Vaccination during pregnancy: current and possible future recommendations. European journal of pediatrics. 2020;179(2):235-42.

21. Shehab El-Din EM, El-Sokkary MM, Bassiouny MR, Hassan R. Epidemiology of Neonatal Sepsis and Implicated Pathogens: A Study from Egypt. Biomed Res Int. 2015;2015:509484.

22. G/eyesus T, Moges F, Eshetie S, Yeshitela B, Abate E. Bacterial etiologic agents causing neonatal sepsis and associated risk factors in Gondar, Northwest Ethiopia. BMC Pediatrics. 2017;17(1).

23. Jones C, Heath P. Antenatal immunization. Human Vaccines & Immunotherapeutics. 2014;10(7):2118-22.

24. Vojtek I, Dieussaert I, Doherty TM, Franck V, Hanssens L, Miller J, et al. Maternal immunization: where are we now and how to move forward? Annals of medicine. 2018;50(3):193-208.

25. Calvert A, Jones CE. Placental transfer of antibody and its relationship to vaccination in pregnancy. Current opinion in infectious diseases. 2017;30(3):268-73.

26. Shah N, Upadhyay C, Sahota R. Neonatal outcome in anemic mothers: A prospective study. Journal of Evolution of Medical and Dental Sciences. 2013;2(43):8355-60.

27. El-Farrash RA, Ismail EAR, Nada AS. Cord blood iron profile and breast milk micronutrients in maternal iron deficiency anemia. Pediatric Blood & Cancer. 2012;58(2):233-8.

28. Drukker L, Hants Y, Farkash R, Ruchlemer R, Samueloff A, Grisaru-Granovsky S. Iron deficiency anemia at admission for labor and delivery is associated with an increased risk for Cesarean section and adverse maternal and neonatal outcomes. Transfusion. 2015;55(12):2799-806.

29. Smith C, Teng F, Branch E, Chu S, Joseph K. Maternal and perinatal morbidity and mortality associated with anemia in pregnancy. Obstetrics and gynecology. 2019;134(6):1234.

30. Prakash S, Yadav K. Maternal Anemia in Pregnancy: An Overview. Ijppr Human. 2015;4(3):164-79.

Strengthening Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI) Checklist: An extension of the STROBE statement for neonatal infection research

Section	Item No.	Recommendation	Reported in Page#
		TITLE AND ABSTRACT	
	STROBE 1(a)	Indicate the study's design with a commonly used term in the title or abstract	1
	STROBE1(b)	Provide in the abstract an informative and balanced summary of what was done and what was found	2
		INTRODUCTION	
Background/ rationale Objectives	STROBE2	Explain the scientific background and rationale for the investigation being reported	3
	STROBE3	State specific objectives, including any pre-specified hypotheses	4
		METHODS	
Study design	STROBE 4	Present key elements of study design early in the paper	5
	STROBE-NI 4.1	Clearly state case ascertainment methods (eg. physician diagnosis, clinical algorithm), documenting individual clinical signs used for diagnosis of possible serious bacterial infection. Give microbiological and/or laboratory and/or radiological criteria for other infectious syndromes (eg. meningitis, sepsis, pneumonia). Include indications for clinical investigations (eg. lumbar puncture)	7
	STROBE-NI4.2	Give criteria used to differentiate between new infection episodes and relapses	-
	STROBE-NI 4.3	For facility-based studies, indicate if the study is of community and/or hospital acquired infections (HAI), defining HAI using an international standard and presenting specific HAIclinical syndromes separately	7
	STROBE-NI4.4	State whether this is an outbreak study, and if so define an outbreak, with reference to an international standard	NA
	STROBE-NI4.5	Describe sampling strategy (eg. clinical indication vs. routine surveillance) and sampling details, (eg. minimum volumes; timing in relation to antimicrobial administration)	6
	STROBE-NI4.6	Describe conventional and/or molecular microbiological methods used, with details (eg. automation, enrichment steps), and the use of controls	7
	STROBE-NI4.7	List pathogens that are likely to be identified by microbiological methods used, and criteria used to determine clinical significance	NA
	STROBE-NI4.8	Describe antimicrobial susceptibility tests and thresholds used with reference to an international standard (eg. CLSI or EUCAST)	NA
Setting	STROBE 5	Describe the setting, locations, and relevant dates, including periods of recruitment,	5

		exposure, follow-up, and data collection	
	STROBE-NI 5.1	Describe the study context in terms of incidence of neonatal mortality, stillbirth and preterm birth.	4-5
	STROBE-NI 5.2	Describe the population included eg. facility live births, referrals from home, referrals from another facility	5
	STROBE-NI 5.3	For community-based studies, describe care-seeking and adherence and time to referral	NA
	STROBE-NI 5.4	For facility-based studies, describe obstetric care (basic or comprehensive), including proportion of births by caesarean section. Report annual number of live births per facility and state proportion of births in the study area that occur in hospital (vs. community)	4
	STROBE-NI 5.5	For facility-based studies, indicate if the facility is public or private, and give the number of healthcare staff and their training. Indicate the level of neonatal care available (eg. ventilatory support, indwelling catheters) and investigations available (eg. biochemistry, radiology). Report antimicrobial guidelines used for the empiric management of neonatal sepsis.	4-5
	STROBE-NI 5.6	State the laboratory location and capacity to process different sample types, and give quality control and assurance measures in place.	NA
Participants	STROBE 6(a)	Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	7
	STROBE 6(b)	Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	NA
	STROBE-NI 6.1	State age of participants (eg. 0-27 days defines neonates; 'day 0' as day of birth). Disaggregate neonatal data from that of older infants and from stillbirths	7
Variables	STROBE 7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
	STROBE-NI 7.1	State criteria used to define clinically significant organisms for each sample type	
Data sources measurement	STROBE 8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	STROBE 9	Describe any efforts to address potential sources of bias	6

Study size	STROBE 10	Explain how the study size was arrived at	
Quantitative variables	STROBE 11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	STROBE 12(a)	Describe all statistical methods, including those used to control for confounding	6
	STROBE 12(b)	Describe any methods used to examine subgroups and interactions	
	STROBE 12(c)	Explain how missing data were addressed	
	STROBE 12(d)	Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	NA
	STROBE 12(e)	Describe any sensitivity analyses	
RESULTS			
Participants	STROBE 13(a)	Report numbers of individuals at each stage of study—eg. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
	STROBE 13(b)	Give reasons for non-participation at each stage	-
	STROBE 13(c)	Consider use of a flow diagram	-
	STROBE-NI 13.1	See Figure 3 for suggested components of a flow diagram for neonatal infections	_
Descriptive data	STROBE-NI 14.1	Describe maternal infections (clinical or on screening, eg. GBS or HIV) or risk factors for infection (eg. PROM, peripartum fever).	10-12
	STROBE-NI 14.2	Describe key neonatal characteristics, including sex, postnatal and gestational age categories (range and median), birth weight categories (range and median), birth place, feeding (breast milk or other) and comorbidities	15
	STROBE-NI 14.3	Report data on occurrence of individual signs (eg. fast breathing) according to case definitions	
	STROBE-NI 14.4	Give proportion of mothers and neonates with peripartum antibiotic exposure (+/- pre-admission exposure for neonates). Report details of antimicrobials (or supportive care) given during the study	
	STROBE 14(b)	Indicate number of participants with missing data for each variable of interest	-
	STROBE 14(c)	Cohort study—Summarise follow-up time (eg. average and total amount)	NA
Outcome data	STROBE 15	Cohort study—Report numbers of outcome events or summary measures over time Case-control study—Report numbers in each exposure category, or summary measures of exposure Cross-sectional study—Report numbers of outcome events or summary measures	
	STROBE-NI 15.1	Report the number (+/- proportion) of samples microbiologically tested (including lumbar	NA

		punctures for meningitis cases); the number (+/-proportion) that were positive (including thresholds for detection, where applicable); all isolates obtained (including clinically significant and non-significant); and antimicrobial susceptibilities of pathogens, where done.	
	STROBE-NI 15.2	Report number (+/- proportion) of babies with microbiologically proven infection (and number of infections per baby), and include this in the flow chart.	NA
	STROBE-NI 15.3	Report infections by day, for days 0-6. State age categories, if used, defining 'early-onset' and 'late-onset' infection (eg. <72 hours and ≥ 72 hours respectively)	15
	STROBE-NI 15.4	Report deaths and any sub-analyses by risk groups	
Main results	STROBE 16(a)	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17
	STROBE 16(b)	Report category boundaries when continuous variables were categorized	
	STROBE 16(c)	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
	STROBE-NI 16.1	For incidence, give risk per 1000 live births, or if alternative denominator used (eg. total births or bed days), define this clearly	NA
Other analyses	STROBE 17	Report other analyses done—eg. analyses of subgroups and interactions, and sensitivity analyses	NA
DISCUSSION			
Key results	STROBE 18	Summarize key results with reference to study objectives	19
Limitations	STROBE 19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20
	STROBE-NI 19.1	Discuss sources of recruitment bias, particularly regarding the period of time shortly after birth. State source of denominator data and discuss possible related biases	-
Interpretation	STROBE 20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	STROBE 21	Discuss the generalisability (external validity) of the study results	20
OTHER INFORMATION			
Funding	STROBE 22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA
Ethics	STROBE-NI 23.1	Report any ethical considerations, including the recruitment of young mothers (minors), and the consent process for early recruitment of neonates after delivery. Provide details of research ethics approval.	7 & 21