

Investigation of the Causes of Prematurity and Neonatal Death Admitted to Hospitals in Ardabil City

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ARTICLE INFO	ABSTRACT
<p>Article type: Original Article</p> <hr/> <p>Article History: Received: 21 Dec 2024 Accepted: 02 Feb 2025</p> <hr/> <p>Keywords: Mortality, Newborns, Premature birth, Premature birth</p>	<p>Introduction: Premature delivery is the delivery of a baby before the completion of 37 weeks of pregnancy. Premature birth is the main cause of infant mortality. Several risk factors and causes for preterm delivery and its mortality have been stated. The aim of this study was to investigate the causes of prematurity and death of neonates hospitalized in Ardabil city hospitals.</p> <p>Materials and Methods: In this cross-sectional study, 500 premature births which selected randomly were evaluated between September 2022 and September 2023. The required information, including the demographic characteristics of the baby and parents, birth weight, cause of preterm delivery and related factors, and the cause of infant death, were collected by examining the patient files in the hospital archive.</p> <p>Results: 273 babies (55.6%) were boys. Preeclampsia and high blood pressure (21.8%), followed by gestational diabetes (10.6%) and overt diabetes (6.2%) were the most common underlying diseases in mothers. The difference in the final outcome of death or life in babies born with different indications and etiologies of preterm delivery was significant.</p> <p>Conclusion: Pulmonary-respiratory causes were the most common causes involved in the death of preterm infants studied. The etiology of preterm delivery was significantly related to the outcome of mortality in the studied preterm infants and its causes.</p>
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Introduction

A baby born before 37 weeks of pregnancy is referred to as a preterm birth. An estimated 15 million premature babies are born each year worldwide (1); 13.4 million preterm births, or 9.9% of all births, were recorded globally in 2020 (2). Preterm birth rates in Iran have been estimated to be around 10%, with Tehran having the highest frequency at 19.8% and Bam having the lowest at 5.4% (3). The rate of preterm birth has risen by 33% in the last 20 years (4). The primary cause of infant mortality is premature delivery; in 2013, problems from preterm birth accounted for 15.4% (about 1 million) of the 3.6 million children under the age of five who died (1). Numerous risk factors for preterm delivery have been proposed, including multiple birth, chorioamnionitis, maternal illnesses, genetic factors, uterine anomalies, and the mother's history of preterm birth. However, there is no known cause for a significant percentage of premature deliveries. Premature rupture of membranes (PROM), pathological inflammation, and the start of preterm labor all contribute to these spontaneous deliveries (5).

The average total cost of healthcare treatments for preterm infants is around twice that of term infants, according to estimates for the first three years of life. Most of this expense is associated with managing and treating preterm problems, infections, hospitalization, and several doctor visits (6). Premature babies are susceptible to respiratory issues, hyperbilirubinemia, hypoglycemia, and other neonatal disorders because of their insufficient physiological maturity. Additionally, they are more than twice as likely to be readmitted as term newborns (8) and are at a higher risk of hospitalization during the first month of life (7). The chance of death for premature babies is also higher than for term babies because of these serious problems. Biological and non-biological reasons are the two main categories into which the causes of death in preterm newborns are typically separated. Non-biological variables are just as significant as biological factors, even though biological factors including infections, asphyxia, and other respiratory abnormalities at birth are

well-known causes of newborn mortality. These factors include socioeconomic status, gender, and maternal education level (9). Perinatal mortality is influenced by conditions and circumstances during labor, as well as prenatal, maternal, and fetal disorders. Numerous factors are linked to perinatal deaths; the main causes of premature infant death include intrauterine growth restriction, conditions that predispose the fetus to asphyxia, such as placental insufficiency, severe maternal anomalies, early and potentially fatal neonatal infections, diseases linked to low birth weight and preterm birth, and fatal congenital anomalies (10). Investigating the causes of preterm and mortality among newborns admitted to Ardabil City hospitals was the goal of the current study.

Materials and Methods

Study design

This was a descriptive cross-sectional study conducted on 500 preterm infants (born under 37 weeks) which selected randomly at Alavi and Bu Ali Hospital in Ardabil city between September 2022 and September 2023. Infants who were stillborn and had informational deficiencies in their records, as well as infants with severe congenital anomalies and chromosomal abnormalities at birth, were excluded from the study. The study was registered with the Ethics Committee of Ardabil University of Medical Sciences, with the ethics code IR.ARUMS.REC.1402.060. Required information includes the baby's gender and weight, gestational age, family's socioeconomic level, mother's place of residence and occupation, mother's and father's education, mother's addiction, mother's age at delivery, type of delivery, history of medication use, number of pregnancies over 3, prenatal factors such as: mother's fertility history (miscarriage, stillbirth, premature or low birth weight, consecutive pregnancies, multiple pregnancies, history of hydrops fetalis) as well as problems in the current pregnancy (maternal preeclampsia, polyhydramnios, oligohydramnios, PPROM, trauma, history of coronavirus disease, first and second trimester bleeding, number of prenatal care visits, interval with previous pregnancies)

and mother's chronic diseases in the current pregnancy (Gestational Diabetes Mellitus (GDM), Infants of diabetic mothers (IDM), heart, neurological and renal disease, malnutrition and obesity), and mother's anatomical problems (bicornuate uterus, cervical insufficiency, etc.), history of maternal infection (urinary tract infection, vaginitis, chorioamnionitis, Pelvic inflammatory disease (PID)) and finally factors during delivery (placenta previa, abruptio placentae) (premature placental abruption) were extracted and recorded by studying and reviewing the records. Also, problems and complications resulting from preterm birth, including hyaline membrane disease, bronchopulmonary dysplasia, pneumothorax, pneumomediastinum, pneumonia, pulmonary hemorrhage, asphyxia, hypoglycemia, apnea, patent ductus arteriosus, meconium aspiration, decreased or increased blood pressure, bradycardia, anemia, disseminated intravascular coagulation, necrotizing enterocolitis (NEC), electrolyte imbalance, intraventricular hemorrhage, seizures, and sepsis, were recorded and collected by the researcher

through a checklist prepared by reviewing the patient records in the hospital archives. Statistical Analysis Data were analyzed using SPSS version 26 software using descriptive statistics in the form of tables and calculation of statistical indices. The normal distribution of data was examined using the Kolmogorov-Smirnov test. The chi-square test was also used to determine the relationship between mortality outcome and its causes with the causes of preterm birth.

Results

Among all preterm infants born, 273 (55.6%) were boys and 218 (44.4%) girls. The median age at birth of the infants was 33 weeks with an interquartile range of 4 weeks and their mean weight was 2071.1 ± 721.1 grams. Also, 100 infants (25%) were the result of multiple pregnancies. The average ± standard deviation of the age of the mothers of the infants studied was 28.3 ± 6.7 years, with a maximum of 49 and a minimum of 15 years. 193 (38.8%) mothers had a diploma and 69 (14.7%) mothers were employed (Table 1).

Table 1. Demographic characteristics of the parents of the infants studied

Demographic Variables		n	%
Mother's education	High school	179	36.0
	Diploma	193	38.8
	University	125	25.1
Mother's job	Housewife	397	84.8
	Employed	69	14.7
Father's education	High School	162	32.6
	Diploma	161	32.4
	University	174	35.0
Place of Residence	Urban	365	73.7
	Rural	127	25.7
Perceived socioeconomic status	Weak	25	5.2
	Medium	350	72.5
	Good	106	21.9

In the study of prenatal risk factors, premature rupture of membranes (PPROM) was the most common cause of preterm

delivery in the prenatal period, with a frequency of 168 cases (33.6%). (Figure 1).

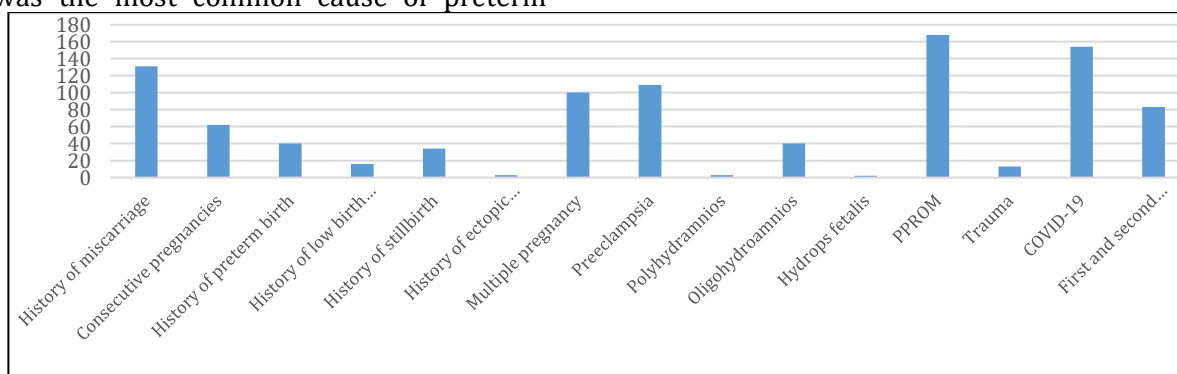


Fig 1. Prenatal risk factors in studied infants

Preeclampsia and high blood pressure were the most common underlying chronic diseases in mothers with a frequency of 109 cases (21.8%), followed by gestational diabetes with a frequency of 53 cases (10.6%), and pre-gestational diabetes with a

frequency of 31 cases (6.2%). Among infectious diseases, urinary tract infection with a frequency of 156 cases (31.2%) and vaginitis with a frequency of 37 cases (7.4%) were the most common diseases during pregnancy (Table 2).

Table 2. Medical history during pregnancy in mothers of the studied infants

Maternal illness		n	%
Diabetes	Gestational diabetes	53	10.6
	Pre-gestational diabetes	31	6.2
Neurological and psychiatric diseases	Seizure	3	0.6
	Psychosis	2	0.4
	Depression	4	0.8
Infectious diseases	Urinary tract infection	156	31.2
	Vaginitis	37	7.4
	PID	11	2.2
	Chorioamnionitis	8	1.6
Maternal anatomical issues	Bicornuate uterus	11	2.2
	Cervical insufficiency	22	4.4
Kidney diseases		3	0.6
Cardiovascular diseases		4	0.8
Anemia		4	0.8
Rheumatic diseases		2	0.4
Thyroid disease		65	13
Obesity		47	9.4
Malnutrition		1	0.2
Addiction		1	0.2

Levothyroxine was the most frequently used drug in the mothers of the infants

studied, with a frequency of 63 (12.6%) during pregnancy (Figure 2).

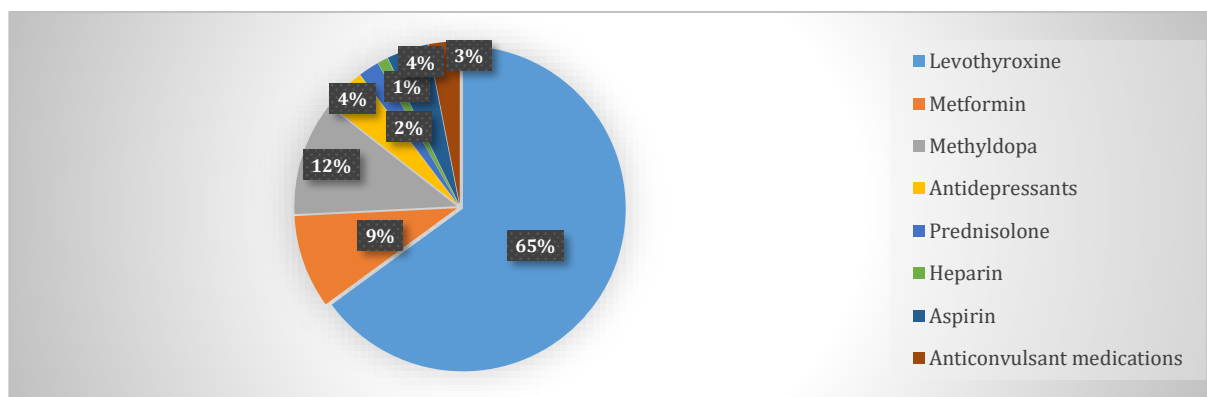


Fig 2. Medication history during pregnancy of mothers of the studied infants

Cases related to supplements and temporary medications, including antibiotics, are not considered. Medication information was available for 314 mothers. In 367 cases (73.4%) they had received care more than seven times and in 65 cases (13.0%) they had received care less than seven times. In 22 infants (4.4%), the risk factor during delivery was related to placenta previa and in 8 cases (1.6%) to premature placental abruption. The etiology of preterm delivery in 412 cases

(82.4%) was related to prenatal causes, 6% to intrapartum causes, and 11.6% to idiopathic preterm delivery. Among the preterm infants studied, 95 births (19%) resulted in neonatal death. Based on the findings of this table, the pulmonary-respiratory causes category was the most common cause of death among the preterm infants studied. Among the pulmonary-respiratory causes, RDS was the most prevalent with a frequency of 72 cases with 75.4% (Table 3).

Table 3. Causes of death of preterm infants studied

Causes of death		n	%
Pulmonary-respiratory	RDS	72	75.4
	BPD	2	2.1
	Pneumothorax	14	14.7
	Pneumomediastinum	1	1.1
	Pulmonary hemorrhage	16	16.8
	Asphyxia	1	1.1
	Apnea	1	1.1
Infectious	Sepsis	8	8.4
	Penymoney	16	16.8
Others	DIC	1	1.1
	IVH	2	2.1
	Severe prematurity	3	4.3

RDS: Respiratory Dstress Syndrome 'BPD: Bronchopulmonary Dysplasia ' IVH: Intraventricular Hemorrha 'DIC: Disseminated Intravascular Coagulation.

There were 57 deaths (13.8%) in infants born with prenatal indications, 2 deaths (6.7%) with intrapartum indications, and 36 deaths (62.1%) following idiopathic preterm delivery. The difference in the final outcome of death or survival in infants born with different causes and etiologies of preterm delivery was significant according to the

results of the chi-square test ($P < 0.001$). Accordingly, the final outcome of death or survival of preterm infants is related to the etiology causing preterm delivery. The most common etiology involved in the death of preterm infants was related to COVID-19 disease with 22.7%, followed by preeclampsia with 20.2% (Table 4).

Table 4. Outcome of death of preterm infants studied, broken down by common etiologies of preterm delivery

		Death(n=95)	Life (n=405)	P-Value
Multiple pregnancy	Yes	4(4.0%)	96(96%)	<0.001
	No	91(22.8%)	309(77.3%)	
Preeclampsia	Yes	22(20.2%)	87(79.8%)	0.783
	No	73(18.3%)	318(81.3%)	
PPROM	Yes	20(11.9%)	148(88.1%)	0.002
	NO	75(22.6%)	257(77.4%)	
Oligohydroamnios	Yes	3(7.5%)	37(92.5%)	0.034
	No	92(20.0%)	368(80.0%)	
COVID-19	Yes	35(22.7%)	119(77.3%)	0.175
	No	60(17.3%)	286(82.7%)	
First and second trimester bleeding	Yes	8(9.6%)	75(90.4%)	0.081
	No	87(20.9%)	330(79.1%)	
Maternal diabetes	Yes	13(15.5%)	71(84.5%)	0.446
	No	82(19.7%)	334(80.3%)	
Maternal infectious diseases	Yes	13(7.0%)	173(93.0%)	0.001
	No	82(26.1%)	232(73.9%)	
Maternal anatomical issues	Yes	1(1.2%)	31(96.9%)	0.013
	No	94(20.1%)	374(79.9%)	

Among the 65 infants who died due to pulmonary respiratory causes, 46 (66.7%) were born due to prenatal causes, 1 (1.4%) due to intrapartum causes, and 22 (31.9%) due to idiopathic preterm birth. In the group of 24 infants who died due to infectious

causes, 18 (81.8%) due to prenatal causes and 4 (18.2%) due to idiopathic causes were born. According to the chi-square test, this difference in the etiologies of preterm birth in infants who died from different causes was significant ($P = 0.009$).

Discussion

Of the total number of infants studied, 273 (55.6%) were boys. Nearly half of the infants were born at 34 to 36 weeks and 6 days of gestation and were late preterm. The average weight of the preterm infants studied was 2071.1 grams, with 65.8% of cases weighing less than 2500 grams. In a study by Sabzei et al. (2019, Hamedan), the mean age of preterm infants was 34.4 weeks and the mean weight was 2475.4 grams (11). In a similar study by Amani et al. in Ardabil province in 2003, 55.6% of preterm infants who died were boys. Among these infants, 19.4% weighed less than 1500 grams and 26.3% weighed between 1500 and 2500 grams (12).

In the study by Mekic et al., consistent with the present study, there were 60% more boys than girls (13). In the study by Tan et al., consistent with the present study, 55.4% were boys and the mean birth weight was 2045 g, indicating a similar demographic composition in preterm infants (14). In a study by Peelen et al., examining the same issue in over 1,700 preterm infants, male gender was shown to be a significant risk factor ($p=0.023$) for spontaneous preterm birth. However, no increased risk of medically indicated preterm birth was observed in the male population compared to the female population (15). According to the results of the present study, 25% of the newborns were the result of multiple pregnancies and 80.5% were born by cesarean section. Also, only 16.5% of the newborns were born following an unwanted pregnancy. In the study of Ebadi et al., consistent with the present study, 83.3% of preterm newborns were the result of cesarean section (16). In the study by Sabzei et al., 90.6% of preterm infants were born by cesarean section, which was slightly higher than in the present study (11). In the study by Gebremedhin et al., only 2.5% of preterm infants were born as a result of unwanted pregnancies, which was about one-third of the present study (17). According to a meta-analysis conducted in the country by Jalali et al., about 27.9% of pregnancies among Iranian women are unintended, which is much lower than the results of the present study (18). In general, unintended pregnancy is considered a social indicator of

women's health. In addition to imposing economic costs on the entire society, unintended pregnancy affects the mother's health and survival. Several factors such as the age of the spouse, age of marriage, age of first intercourse, lack of awareness and use of contraceptive methods, low economic and social status were mentioned. Differences in the studied environments and subsequent differences in the aforementioned cases can lead to this difference in the rate of unwanted pregnancies in preterm and term infants. In the present study, the average age of the mothers of the infants studied was 28.3 years. Also, 74.8% of the mothers had a diploma or less education and 14.7% were employed. Regarding the fathers of the infants studied, 67% had a diploma or less education and generally had a higher level of education than the mothers. In the study by Sabzei et al., consistent with the present study, the mean age of mothers was 28.9 years (11). In the study by Dolatian et al., consistent with the present study, the mean age of mothers was 28.5 years and their mean years of education was 13.03 years. Also, consistent with the present study, only 13.6% of mothers were employed (19). On the other hand, in the study by Ghilichiani et al., 91.5% of mothers had a diploma or less, which indicates a lower level of education of mothers compared to the present study (20). Among foreign studies, in the study by Lopezosa et al. (2019, Spain), in line with the present study, about 70% of mothers had less than academic education (21). In the study by Abdo et al. (2020, Ethiopia), similar to the present study, 76.6% of mothers were in the age group of 20 to 34 years (22). In the study by Umeigbo et al. (2020, Nigeria), similar to the present study, the average age of mothers was 30.4 years. Also, in their study, only 38.1% of patients were unemployed, which is much lower than the similar statistics in the present study (23). Kramer and colleagues believed that, in line with the results of the present study, adverse economic conditions are unlikely to be a direct and independent factor for preterm birth. However, it can cause preterm birth through unhealthy behaviors, stress exposure, and psychological responses to stress (24). In a meta-analysis conducted by Sharifi et al., no significant relationship

between socioeconomic factors and preterm birth was found, contrary to expectations (25). In general, socioeconomic status is a key determinant of health and mortality, which can also affect pregnancy outcomes. Families with low socioeconomic status who suffer from problems such as malnutrition, inadequate prenatal care, addiction, smoking, alcohol consumption, multiple pregnancies, and stress are prone to adverse pregnancy outcomes. Accordingly, the slight differences between the present study and other studies can be explained by differences in the cities studied across the country and people's beliefs in all social, cultural, and religious dimensions, and access to facilities and social welfare.

In examining prenatal risk factors in the studied infants, PPRM (33.6%), COVID-19 infection (30.8%), and history of miscarriage (26.2%) were the most commonly reported, respectively. Regarding the history of maternal diseases during pregnancy, preeclampsia and hypertension (21.8%), followed by gestational diabetes (10.6%) and pre-gestational diabetes (6.2%) were the most common chronic underlying diseases in mothers. In the study by Zulhamdi et al., 37.1% of mothers with preterm infants had a history of miscarriage, and 46% had a history of preeclampsia, which was higher in both cases than in the present study (26). In the study by Abdo et al., 16.6% of mothers had a history of previous preterm birth and 9.9% had a history of miscarriage. A history of preeclampsia was also reported in only 9.2% of cases, which was higher than in the present study (22). In the study by Sabzei et al., PPRM was reported in 19.1 cases, which is lower than the present study (11).

In the study by Zulhamdi et al., PPRM was reported in 33.9% of cases, consistent with the present study. The estimated incidence of bleeding in their study was related to the third trimester and was 75.2% (26). In the study by Abdo et al., 3.6% of mothers had a history of peripartum bleeding and 5.6% had PPRM, which is lower than the present study (22). In the Umeigbo study, PPRM was also reported in 28.1% of preterm deliveries (23). Comparing the present study with other similar studies, it seems that the occurrence of PPRM and maternal factors

prior to delivery are among the most important reasons for preterm delivery, which requires special attention to identify these maternal factors and manage them as much as possible to reduce preterm deliveries. According to the results of the present study, pulmonary-respiratory causes were the most common causes of death in preterm infants studied. Among pulmonary-respiratory causes, RDS was the most prevalent with a frequency of 75.4%. Then, pulmonary hemorrhage and pneumothorax were the most common respiratory causes of death in preterm infants. After that, infectious causes such as pneumonia and neonatal sepsis, and finally, less common causes such as intraventricular hemorrhage and DIC were other causes of death in the studied infants. In the study of Guinsberg et al., consistent with the present study, respiratory disorders were the most common cause of neonatal death (27). In the domestic studies of Babaei et al. in Kermanshah, consistent with the present study, respiratory distress and sepsis after birth below 37 weeks were considered the most common causes of neonatal mortality (28). In the study of Sarrashteh Dari et al. in Qazvin, respiratory distress syndrome, sepsis and its complications, and asphyxia were the three most common causes of neonatal mortality (29).

In the study by Schind et al., respiratory problems and sepsis were the most common causes of neonatal death, followed by IVH. According to the results of this study, the etiology of death was dependent on the age of the infant, such that mortality due to respiratory problems or major IVH was more likely at younger ages compared to NEC and miscellaneous causes (30). One of the reasons for the differences in the results of different studies on the etiology of premature infant death is the difference in the time and period of study.

This issue has been well studied in the Berrington study. In this study, by examining 1504 deaths of preterm infants over a 21-year period, it was shown that from 1998 to 2012, mortality due to respiratory problems was decreasing, while mortality due to infections and fetal malformations was increasing. Despite the downward trend in respiratory causes of infant death, it still

tops the list of etiologies of preterm infant death. This is due to the advancement of medical technology and skills in respiratory management of infants (31). Regional differences and access to health care facilities in different geographical areas of the world can be the basis for these differences in different studies. Comparing the results of different studies with the present study, it was found that pulmonary respiratory problems were among the top causes in all studies conducted and the most common cause of death in preterm infants was constant. However, the pattern of other causes was different in different regions and studies.

According to the results, the etiology of preterm birth, which consisted of 3 categories of prenatal, intrapartum, and idiopathic causes, was significantly associated with mortality in the preterm infants studied; with the highest mortality rates reported in infants born idiopathically (62.1%), due to prenatal causes (13.8%), and due to intrapartum causes (12.2%). In general, according to the results of this study, the underlying cause of preterm birth can be associated with the outcome of death as well as the cause of death in premature infants. In the study by Chen et al., some maternal and fetal parameters were compared in two groups of idiopathic and iatrogenic preterm deliveries. According to the findings of this study, the frequency of maternal causes, including hypertension and diabetes ($P=0.001$), and placental causes, including placental abruption ($P=0.001$), and multiple pregnancy ($P=0.001$) were significantly different in the two groups of spontaneous and iatrogenic preterm deliveries, which in a way confirms the results of the present study regarding the significant relationship between the etiology of preterm delivery and the outcome of death and its causes (32).

The current investigation was carried out as a cross-sectional, descriptive-analytical study, and one of its limitations was the selection of only a few hospital facilities and a certain time frame. The utilization of data from archival files may also be linked to inaccurate reporting of infants' weight and age. Additionally, preterm delivery may have an impact on a number of characteristics

that emerge throughout time and with the child's growth and are linked to neurodevelopmental outcomes. Further research in this area is necessary because the outcome of neonatal mortality may also be influenced by medical care and socioeconomic factors in addition to preterm birth itself and its different causes.

Conclusion

The current study's findings demonstrated that preterm newborns' demographics were consistent across most research, with boys making up the majority. Among the preterm newborns under study, pulmonary-respiratory reasons accounted for the majority of deaths. The findings of the current study suggest that particular steps must be taken to care for premature newborns in their early days of life as well as to control and manage factors associated to the mother and the pregnancy process, given the significance of managing their delivery and mortality. It is suggested that by designing and conducting multicenter studies with a larger sample size, more accurate information can be obtained about the underlying causes of preterm birth and their mortality in the region. Also, by conducting prospective studies with a longer time period, the trend of changes in the pattern of neonatal mortality can be examined. By using information recorded from neonatal deaths in forensic medicine, reporting errors can be reduced to some extent. Also, by considering long follow-up periods and cohort studies, developmental complications in preterm infants during childhood and adolescence can be investigated.

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