Perinatal factors related to premature neonate's mortality in the NICU, Ghaem Hospital, Mashhad

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Abstract: Prematurity is the major cause of neonatal mortality, so this study aimed to determine the perinatal factors related to the premature infant's mortality. Sample of records of this historical cohort study, was premature infants hospitalized since 1386 to 1389. 200 cases were randomly selected. After sample loss, 172 files precisely were studied from admission to discharge. Data were collected using a validated questionnaire. Finally, patients were allocated into case and control groups, respectively, based on death or alive until 28_{th} day after birth. Data were analyzed with SPSS19th, and presented with descriptive statistics, Fisher's exact test, chi-square, T tests and multivariate regression analysis. From 172 neonates, 54 were included in the case group and 118 in the control group. Birth weight and gestational age of the subjects, respectively were 1549.54(±635.42) g and 31.46 (±3.35) weeks. Antenatal antibiotics (OR: 0.3) had a protective effect. Maternal diabetes, preeclampsia, maternal RH and blood group, were the most effective maternal factors. Birth characteristics, such as crying, breathing, cyanosis, tonicity, cord status, and neonatal resuscitation in the delivery room and neonatal clinical findings at the time of admission including apnea, bradycardia, gasping ,hydrops , ascites , and IUGR were the most influential factors ($p<0.05$). Gestational age ($r=0.718$), height ($r=0.673$), head circumference ($r=0.608$), and 5_{th} minutes Apgar score ($r=0.662$) had the highest correlation with the final prognosis. According to the multivariate regression analysis bradycardia at admission time, maternal diabetes, maternal Rh, gasping at the admission time, tonicity in the delivery room, at birth crying, birth length, gestational age, birth weight remained in the premature neonates mortality estimation equation. The results of this study addressed increasing and protective perinatal factors against premature infant's mortality.

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Introduction

Regarding to its importance, the neonatal mortality rate is used as a standard indicator of a country's health care, educational and social development (1). Currently almost two-thirds of annual deaths of under one year old, and almost 40% of all deaths of under 5 years old, allocated to that. And certainly the first step in reducing mortality is identifying the causes and risk factors of that (2). According to the previous studies prematurity and low birth weight have been the most common causes of neonatal mortality (3-6). On the other hand, Beck and colleagues (2010) reported the global statistics of premature births as 9.6%. About 13 million premature births have occurred only in 2005 (7).

Regarding that prematurity is one the most common causes of neonatal mortality, while a significant percentage of live births are allocated to that, identification of risk factors and underlying causes of mortality in this population can be helpful in identifying at risk premature infants, shifting health care services, designing the models of illness severity, health care management and finally reducing the chance of mortality. But most studies of infant mortality considered the neonatal period as a whole. And the issue of premature neonate's mortality, that is the most common form of neonatal mortality, has received less attention. In addition, some of the results about neonatal mortality are very different in the term and premature neonates. For example, Fallahian and colleagues (1378) have shown that in the mothers with gestational hypertension, neonatal mortality is higher by 7.5

fold (6), whereas Chen and colleagues (2006) have shown that gestational hypertension is associated with reduction in premature neonate's mortality (8). Thus this study aimed to identify the factors associated with premature neonates' mortality. Since early prevention could be achieved by early recognition, attention has been concentrated on the perinatal factors.

Method

In this historical cohort study, after receiving permission from the Research Department of Mashhad medical University, by project No. 88415, sampling was conducted by the simple –random method, among preterm infants who were hospitalized in the neonatal intensive care unit (NICU) of Ghaem hospital between 1386 and 1389. The purpose of this time period was assessing the recent cases and easy access to subjects. Inclusion criteria included infants with gestational age less than 37 weeks, admitted to the Ghaem NICU between 1386 and 1389. Exclusion criteria were referring from other centers, home delivery and personal satisfaction discharge before than 28_{th} day after birth. Two hundred cases (in order to meet the estimated sample size) among totally 800 neonates were extracted, from which 28 cases were excluded. Exclusions mostly included referring from other centers and discharge with personal satisfaction before than 28_{th} day after birth.

The patient records were studied carefully from the time of admission until discharge, in terms of maternal history, clinical progression, physician order sheet, vital signs chart sheet, labor room history, and hospital discharge abstracts . Perinatal data were collected using a researcher-made, content validated instrument, in three categories including maternal perinatal history, delivery room history of neonates, and neonatal history during NICU admission. Maternal data included age, previous parity number, maternal drug history including chronic drug use (history of any durable and regular drug use during pregnancy) and antenatal drug history (recent drug use during hospitalization period for childbirth and especially before delivery), history of an special disease according to an specialist physician diagnosis, history of chronic or gestational hypertension, multiple pregnancy (according to ultrasound or based on what has been observed in the labor room and recorded in the delivery room history sheet), eclampsia or pre-eclampsia (according to the gynecologist's diagnosis which was recorded in the labor history sheet), maternal blood group and Rh (according to the test result print), maternal premature rupture of membrane (PROM) (according to the gynecologist's diagnosis), the type of pregnancy (natural or induced pregnancy IUI or IVF procedure according to the gynecologist's history note), time of delivery and type of delivery (vaginal or cesarean).

The second category of data or delivery room history of neonates, included neonate's status in terms of after birth cry (no cry, weak or delayed cry, and normal active cry), after birth breathing(artificial respiration, breathing with ambo-bag, delayed spontaneous breathing, and normal spontaneous breathing), cyanosis at 5_{th} minute after birth (whole body cyanosis, acrocyanosis, without cyanosis), pallor in delivery room (having or not), after birth in delivery room tonicity (very loose, a little loose and normal tonicity [flexion of extremities]), gender, congenital major abnormality (visible in the delivery room), cardiopulmonary resuscitation in delivery room, weight (gram), height and head circumference (centimeter) and 1_{th} and 5_{th} minute Apgar scores. Neonate's status in terms of the above criteria was identified by a delivery room nurse or midwife, and confirmed by a neonatologist and were recorded in the delivery room history sheet.

The third category of data included the neonatal finding at the NICU admission time. This section of the questionnaire was open answer. Such that all of the clinical findings on the NICU admission time were entered to the questionnaire, and at the end, these items were categorized and analyzed. All subjected files were studied from admission until discharge, with the purpose of extracting all perinatal data and minimizing data loss. Finally the neonatal outcome was determined. Neonatal outcome was accessible in the physician order sheet, file summary sheet, clinical progression sheet or cardio-pulmonary resuscitation report sheet. Subjects were allocated in two groups based on the outcome. The case group included the neonates whose had been died in the NICU until 28_{th} days after birth; the control group included neonates who had been discharged as directed by physician, or still were in the NICU and under treatment, until 28_{th} days after birth. Finally from the 172 remaining patient records, 54 were placed in the case and 118 were placed in the control group.

Data analyzed with SPSS19th and presented with descriptive statistics (mean, standard deviation and ratio), deductive statistics (t test, Fisher exact test, and chi-square test). Spearman correlation and the Odds ratio index also were used. P value less than 0.05 was considered statistically significant. At the end multivariate regression analysis was used to determine the relationship between the risk factors and premature neonate's mortality. Thus the risk factors that had a significant correlation at a confidence level of about 90% ($P < 0.1$) in the assessing individual variables were entered into the equation.

Ethical considerations

During this study, 26-fold ethical codes were considered. And to prevent releasing confidential data, data collected from the patient records was done without patient name and using numerical codes.

Results

From 200 neonates, 172 ones had the inclusion criteria, 54 neonates in the case group and 118 neonates in the control group. Mean ± SD birth weight and gestational age of the subjects were respectively, 1549.5±635.4g and 31.4±3.3 weeks. The chronic and antenatal maternal drug history is listed in Table I. The most common chronic and antenatal drug was antibiotics and betamethasone, respectively.

According to the Fisher exact test, two groups were not significantly different in term of the drug history. Odds ratios of the drugs are given in Table I.

Delivery time during the day (morning, afternoon, night) (p=0.408), type of delivery (p=0.479), multiple pregnancies (p=0.588), pregnancy type of the mother (0.053), chronic antibiotic use during pregnancy (p=0.075), chronic insulin use during pregnancy and antenetal hydralazine (p=0.299) were not significantly different in the case and control group. Cesarean delivery had a protective effect against mortality in the premature neonates (Odds ratio=0.792, CI=0.293-1.511). Multiple pregnancies (odds ratio=2.017,CI=1.019-3.992), pregnancies resulting from induced fertilization (odds ratio=2.137, CI=0.981-4.655), chronic insulin use and antenetal hydralazine (Odd ratio=1.905, CI=0.555-6.539) had a increasing effect on premature neonates' mortality. Chronic antibiotics use during pregnancy (Odds ratio=1.125. CI=0.536-2.362) had a slightly increasing effect on the premature neonates' mortality.

Table I.Distribution of the neonates according to maternal perinatal history separately in the case and control groups

Factor		frequency	Case group	Control group	p-value	Odds ratio	95% confidence interval for odds ratio
			Number(percent)	Number(percent)			
Antenatal Betamethasone	No	82	28(34.1)	54(65.9)	0.458	0.783	(0.411-1.493)
	Yes	90	26(28.9)	64(71.1)			
Antenatal Magnesium sulfate	No	146	42(28.8)	104(71.2)	0.078	2.122	(0.907-4.967)
	Yes	26	12(46.2)	14(53.8)			
Antenatal Methyldopa	No	157	47(29.9)	110(70.1)	0.182	2.048	(0.702-5.972)
	Yes	15	7(46.7)	8(53.3)			
Antenatal Antibiotics	No	158	52(32.9)	106(67.1)	0.150	0.340	(0.073-1.574)
	Yes	14	2(14.3)	12(85.7)			
Diabetes	No	153	43(28.1)	110(71.9)	0.008	3.517	(1.325-9.340)
	Yes	19	11(57.9)	8(42.1)			
Preeclampsia	No	120	32(26.7)	88(73.3)	0.042	2.017	(1.019-3.992)
	Yes	52	22(42.3)	30(57.5)			
Maternal blood group	A	44	8(18.2)	36(81.8)	0.003		
	B	44	8(18.2)	36(81.8)			
	AB	24	12(50.0)	12(50.0)			
	O	36	16(44.4)	20(55.6)			
PROM	No	96	36(37.5)	60(62.5)	0.015		
	≤18 hours	26	2(7.7)	24(92.3)			
	>18 hours	50	16(32.0)	34(68.0)			
Maternal Rh	Negative	24	12(50)	12(50)	0.018	0.348	(0.142-0.852)
	Positive						

The case and control groups were compared in term of the after birth history. And the results are summarized in Table II. In this Regard, two groups had not a statistically significant difference in terms of gender (p=0.201) and after birth pallor (p=0.309). But the male gender had a protective (Odds ratio=0.647, CI=0.331-1.264), and after birth pallor had an increasing (Odds ratio=1.467, CI=0.600-3.682) effect against neonatal mortality. The case and control groups had a significantly deference in term of after birth quality of cry (p<0.001), quality of immediately after birth respiration (p<0.001), quality of cyanosis (p<0.001), quality of after birth tonicity (p<0.001), umbilical cord status (p = 0.007) and CPR in the delivery room (P≤0.001). Delivery room history profile of the case and control group are summarized in Table II

Table II. Distribution of the neonates according to neonatal delivery room history characters separately in the case and control groups

Factor		frequency	Case group	Control group	p-value	Odds ratio	95% confidence interval for odds ratio
			Number(percent)	Number(percent)			
Crying	No	24	18(33.3)	6(5.1)	≤0.001		
	Delayed or Weak	93	27(50.0)	66(56.0)			
	Active and normal	55	9(16.7)	46(39.0)			
Breathing	Artificial respiration	16	14(26.0)	2(1.7)	≤0.001		
	With ambo bag	17	7(13.0)	10(8.5)			
	Delayed and irregular	35	11(20.4)	24(20.4)			
	Spontaneous and natural	104	22(40.1)	82(69.5)			
Cyanosis at 5th minute	severe cyanosis of the body	46	26(48.2)	20(17.0)	≤0.001		
	acrocyanosis	109	21(39.0)	88(74.6)			
	No	17	7(13.0)	10(8.5)			
Tonicity	severe Hypotony	82	42(77.8)	40(33.9)	≤0.001		
	mild hypotonia	43	7(13.0)	36(30.5)			
	With tonicity	47	5(9.3)	42(35.6)			
Resuscitation	yes	44	34(63.0)	10(8.5)	≤0.001	18.360	(7.837-43.013)
	No	126	20(37.0)	106(89.9)			

On the admission time clinical findings of the neonates in the two groups, are summarized in Table III;bruising, cyanosis, poor Moro reflex, poor grasping reflex, nasal flaring and retraction were not significantly different in the two groups. In terms of these parameters case and control groups were compared with Fisher exact test.

Table III. Distribution of the neonates according to the NICU admission time clinical findings separately in the case and control groups

Factor		frequency	Case group	Control group	p-value	Odds ratio	95% confidence interval for odds ratio
			Number(percent)	Number(percent)			
Hypotonia	Yes	23	3(5.6)	20(17.0)	0.052	0.282	(0.08-0.996)
	No	147	51(94.4)	96(81.4)			
poor sucking	Yes	53	11(20.4)	42(35.6)	0.05	0.451	(0.210-0.967)
	No	117	43(79.6)	74(62.7)			
Tachypnea	Yes	48	4(7.4)	44(37.3)	≤0.001	0.131	(0.044-0.388)
	No	122	50(92.6)	72(61.0)			
IUGR	Yes	28	14(26.0)	14(11.9)	0.028	2.55	(1.116-5.852)
	No	142	40(74.0)	102(86.5)			
Granting	Yes	71	12(22.3)	59(50.0)	≤0.001	0.286	(0.137-0.597)
	No	101	42(77.8)	59(50.0)			
Apnea	Yes	34	26(48.2)	8(6.8)	≤0.001	12.536	(5.123-30.673)
	No	136	28(51.9)	108(91.5)			
Bradycardia	Yes	18	18(33.4)	0(0.0)	≤0.001		
	No	154	36(66.7)	118(100.0)			
Gasping	Yes	8	8(14.8)	0(0.0)	≤0.001		
	No	164	46(85.1)	118(100.0)			

The quantitative results of the study are given in Table IV. According to the Independent-Sample T test, two groups had significant difference in terms of all quantitative variables.

Table IV. Mean and standard deviation of the quantitative maternal and neonatal factors separately in the case and control groups

			mean± SD case group	control group	P_{value} (Independent Sample T test)
Maternal results	Quantitative	mother age (year)	29.9±5.3	27.2±6.1	0.007
		maternal PROM (hour)	314.8±1079	36.5±71	0.006
neonatal results	Quantitative	Gestational age (week)	27.9±3.1	33.08±1.9	≤0.001
		Birth weight (gram)	1042±611	1781±498	≤0.001
		birth Stature (centimeter)	35.2±4.7	43.24±3.85	≤0.001
		birth Head circumference (centimeter)	25.8±2.9	30.2±2.6	≤0.001
		APGAR- minute 1	4.5±2.3	7±1.3	≤0.001
		APGAR- minute 5	5.43±2.0	8±0.9	≤0.001

Correlations between quantitative maternal and neonatal factors and neonatal prognosis are given in Table V.

Table V. correlation between quantitative maternal and neonatal factors with neonatal outcome (mortality)

Factor	r*	Spearman P value
Gestational age (week)	-0.718	≤0.001
birth Stature (centimeter)	-0.673	≤0.001
birth Head circumference (centimeter)	-0.608	≤0.001
Birth weight (gram)	-0.514	≤0.001
APGAR- minute 1	-0.581	≤0.001
APGAR- minute 5	-0.662	≤0.001
maternal PROM (hour)	0.210	0.006
mother age (year)	0.206	0.007

*At significant level 0.01

Finally, multivariate regression analysis was used to determine the interaction between the risk factors and premature neonate's mortality. So the risk factors that were significant at a confidence level of 90% (P <0.1) in the assessing individual variables, were entered into the equation of regression analysis; which included 30 variables. There was a significant multiple correlation between bradycardia at admission time, maternal diabetes, maternal Rh, gasping at the admission time, tonicity in the delivery room, at birth crying, birth length, gestational age, birth weight and premature neonates mortality(R= 0.915, P <0.001). Totally, these variables explained more than 83 percent of the premature neonate's mortality risk. In the regression model maternal age (p=0.381), antenatal magnesium sulfate (p=0.724), pre-Eclampsia (p=0.725), the type of pregnancy (p=0.228), birth head circumference (p=0.626), hypotonia at the admission time (p=0.213), poor sucking at the admission time (p=0.094), tackypnea at the admission time (p=0.900), intra uterin growth restriction (p=0.826), grunting at the admission time (p=0.736), pnea at the admission time (p=0.161), after birth breathing (p=0.990), cyanosis at the 5th minute after birth (p=0.249), CPR at the delivery room (p=0.543), 1th minute Apgar (p=0.364), 5th minute Apgar (p=0.565) and maternal blood group (p=0.514) Were excluded from the equation. Bradycardia at the admission time was the most relevant factor (B= 0.397, P= 0.003). The relationship intensity of the other relevant variables with the neonatal mortality is ranked in the Table 6.

Table VI. The correlation intensity between maternal and neonatal factors and premature neonates' outcome (mortality) based on the multivariate correlation analysis

stars	Variable	B	P
1	Bradycardia at the admission time	0.397	0.003
2	Maternal diabetes	0.326	0.000
3	Maternal Rh	0.294	0.000
4	Gasping at the admission time	0.264	0.021
5	Birth time tonicity	0.088	0.017
6	Birth time crying	0.055	0.045
7	Birth length	0.052	0.000
8	Gestational age	0.038	0.009
9	Birth weight	0.0001	0.004
10	Maternal PROM	0.00008	0.048

Discussion

This study showed that some of perinatal factors are related to the premature neonates' mortality. In terms of maternal factors antenatal taking of nitroglycerin, magnesium sulfate, methyldopa, hydralazine, and chronic use of insulin were the strongest drug factors influencing premature neonates' mortality. Antenatal antibiotics had the greatest protective effect against premature neonate's mortality. However, the chronic use of antibiotics has been associated with an increased risk of mortality. Diabetes, preeclampsia, maternal blood group and Rh were significantly different in the two groups and diabetes, abnormal pregnancies, and preeclampsia

respectively, were the strongest maternal factors influencing premature neonate's mortality.

Regarding immediately after birth characters crying, breathing, cyanosis, tonicity, umbilical cord status, and cardio-pulmonary resuscitation in delivery room in the two groups were significantly different, but pallor and major congenital anomalies were not significantly different. The gestational age, birth weight, birth head circumference, birth length, and 1_{th} and 5_{th} minute's low Apgar scores, reversely affected the premature neonate's mortality.

In terms of neonates clinical finding at the NICU admission time poor sucking, tachypnea, IUGR, granting, apnea, bradycardia, gasping and ascites, were significantly different in the case and control groups. Apnea, bradycardia, gasping, hydrops, ascites, and IUGR, respectively were the most influential factors. Poor neonatal reflexes and cyanosis hadn't significant difference in the two groups, but had Odds ratios more than 1.

Considering the importance of neonatal mortality, many studies have been done about underlying causes and risk factors. However most of them, were been done in total population of neonates, and the premature subgroups have been less considered. Forssas et al (1999) have determined the most important maternal risk factors predicting perinatal mortality as in-vitro fertilization, earlier stillbirth, higher maternal age, maternal diabetes, lower socioeconomic status, during pregnancy smoking, single mother and first mothers (9). Basu et al (2008) determined the factors directly responsible for neonatal mortality in the very low birth weight neonates as maternal per vaginal bleeding, failure to administer steroid antenatally, Apgar score less than or equal to 5 at one minute, apnea, gestational age, neonatal septicemia and shock. The survival rate was found to increase with the increase in birth weight and gestational age (10). Chanvitan et al (2010) determined the most important perinatal risk factors of very low birth weight infants as birth weight < 1,000 g, congenital anomalies, and Apgar score at 1 minute < or = 5 (11). Terzic et al (2010) determined the factors affecting mortality in preterm infants with very low birth weight as gestational age, birth weight, Apgar score, Crib score, base excess, presence of respiratory distress syndrome and hemodynamic stability at the birth (12).

Many of these findings are confirmed in our study, too. Although congenital anomalies are the major causes of neonatal mortality both in developed and developing countries (13), and this is confirmed in the study of Chanvitan et al (11) however in our study, congenital malformations were not confirmed as influencing factors of premature neonates' mortality. Similarly Terzic et al did not determine congenital anomalies as leading causes of premature neonates' mortality (12). Since that our study is focused on perinatal factors, focused on the major malformations that were observable in the delivery room, and abnormalities detectable with diagnostic techniques were not included. However, based on the results obtained so far, congenital anomalies were not confirmed as leading cause of mortality in premature infants. Differences in prevalence and type of the congenital anomalies in different countries, and importance of the other causes that could reduce the ranking of congenital abnormalities in the leading causes, could explain this discrepancies. Confirming this result requires more studies with larger sample size and caring process analysis in the various NICUs, aiming to adjust the effects of the caring process on the premature neonate's mortality.

Basu et al have reported septicemia as a major cause of mortality in premature infants (10). Although in this study infection was not investigated, but it was seen that mortality risk of newborns whose mothers had received antibiotics antenatally was 0.3. It means that receiving antibiotics antenatally by mothers had a protective effect against mortality in preterm infants. This finding can be considered consistent with the findings of Basu et al. Based on these findings we can conclude that transmitted antibiotic across the placenta, with prophylactic effects, can reduce the risk of infection and finally the risk of death, in the prematurely born neonate. If these findings be confirmed with prospective and semi-experimental studies, could be effective against preterm neonates' mortality reduction.

The results of this study in terms of birth weight and gestational age are common in nearly all of the above studies. However, in this study, researchers also considered at birth height and head circumference. And the results showed that birth weight, height and head circumference of the neonates in the case group was significantly lower than the control group. As expected, with increasing fetal weight fetal maturation and the maturity of the body systems have increased, and finally ability to adaptation with the extra uterine life promotes (14). Thus increasing the survival chance of the premature neonates due to increasing birth weight, which is a function of gestational age, will be explained. It is expected that birth head circumference and height, which are functions of birth weight, be such. But as shown in Table V the correlation between birth height and head circumference, and neonatal survival were higher than the birth weight. Since fetal weight has more environmental effectiveness than height and head circumference (13), it can be concluded that, in determining the premature neonates at risk of mortality according to the anthropometric criteria, birth height, and head circumference are more reliable than birth weight. Similar findings are also obtained in the study of Sreeramareddy et al (2008). They showed that head circumference and chest circumference are more reliable measurements for determining the neonatal survival chance (15).

In the studies have been obtained so far, the relationship between maternal drug history and premature neonate's mortality has not been assessed widely. In our study, maternal drug history was assessed and significant differences in terms of chronic and antenatal drugs were not found between the case and control groups. However the Odds ratios obtained some interesting data. Antenatal administration of nitroglycerin, magnesium sulfate,

methyldopa and hydralazine and chronic use of insulin have increased mortality risk by2 to 3 times. As expected these drugs, except insulin indicate acute clinical situations that could affect maternal and fetal conditions. And insulin refers to diabetes during gestational period, which is a neonatal mortality risk factor (13). So Judgment regarding the part of the drugs by themselves, or the conditions indicating drug administration in the increased risk of mortality would be difficult.

Although multiple pregnancies are the risk factors of mortality, in the overall neonatal population (5), but similar to the previous studies in the premature neonates (10-12), also in the current study case and control groups were not significantly different in terms of multiple pregnancies. In twin pregnancies, Ananth et al (2004) argue that this phenomenon is due to the increased midwifery interventions (16). Because of technology advancement and the promotion of health services, generally multiple pregnancies could be confirmed early in pregnancy. Eventually these factors added up health care team considerations and maternal follow up, and finally its possible effects on the fetus could be minimized.

Shirvani et al determined more than 18 hours PROM as mortality risk factor in the neonatal general population (5). Also in this study the duration of PROM in the case group was significantly higher than the control group. Also there was a significant correlation (CI = 99%, r = 0.210) between maternal PROM and neonatal mortality. Interpreting this phenomenon it can be said that, PROM increases the risk of ascending infections thorough the vaginal canal, and exposed the fetus to pathogenic microorganisms. Thus it has been confirmed as a risk factor of neonatal mortality (14). Regarding the premature immunity system of the premature neonates (13), this finding would have a special importance. The results of our study have also confirmed this point.

Non-clear amniotic fluid in several studies is determined as neonatal mortality risk factor (5,16), but this is not confirmed in our study. Since meconial amniotic fluid is not a common phenomenon in the premature neonates' population, could be an explanatory factor for this difference. Scott et al (2001) estimated the prevalence of meconial amniotic in the premature infants as 4.8%. In addition to this relatively low prevalence, this phenomenon themselves had no effect on the incidence of neonatal acidosis, only the chance of NICU admission in the affected premature infants was increased (75% vs. 53%). Many of these admissions could be precautionary and prophylactic (17).

Eftichia et al (2005) assessed the neonatal mortality rate according to birth weight discordance. Their study showed that neonatal mortality rate increased with increasing degrees of birth weight discordance regardless of mode of delivery. Cesarean section was associated with decreased neonatal mortality rate when birth weight discordance was between 20% and 40%, but this was significant at birth weight discordance ≥40%; vaginal delivery twins had a 1.6-fold (95% CI 1.1-2.2) increased neonatal mortality rate compared with cesarean (18). Meta analysis studies have not confirmed any of the vaginal or cesarean section as a choice method in premature deliveries. And the results have been controversial (19). However current study supported the protective effect of the cesarean section against premature neonate's mortality.

Ayaz et al (2009) showed that Pre-eclampsia had a large effect on the adverse neonatal outcomes including low Apgar score, intrauterine growth restriction, and increased need for NICU admission (20). Stephen et al (2005) showed that in very low birth weight neonates maternal Pre-eclampsia had a preventive effect against mortality (Odds ratio=0.6). Increased use of seizure prophylaxis such as magnesium sulfate, have been introduced in their study as a possible explanation for this finding. Because several studies have shown that magnesium sulfate can reduce the negative consequences of the premature births (21). However in our study, maternal Pre-eclampsia increased premature neonates' mortality more than 2 times, and two groups were significantly different in term of maternal Pre-eclampsia. In the pathogenesis of Preeclampsia there is abnormal placentation associated with vascular and immunity events; that could affect fetus circulation. The disease also has been associated with an imbalance of angiogenic factors and oxidative stress. But only a limited number of fetal and neonatal studies that suggest that infants born from women who have Preeclampsia are exposed to increased oxidative stress (22). However, the odds ratio of 2 indicates a strong effect of Preeclampsia on the premature neonate's mortality in this population. The high rate of infection in neonatal intensive care units in developing countries (23) and a higher risk of neutropenia in infants born from women who have Preeclampsia (24) could be an explanatory mechanism for this finding in this population.

Unlike acute hypertensive events, according to maternal history, case and control groups had not a significantly difference in term of history of chronic hypertension. And Odds ratio in the group who had a history of hypertension was 1. Therefore maternal history of hypertension had no effect on neonatal mortality. Chen et al (2006) have shown that gestational hypertension is associated with reduced mortality in preterm infants (8). While according to the results of this study, hypertensive crisis, and maternal history of recent treatment for hypertension, including Pre-eclampsia has increased premature neonate's mortality risk. In the explanation it must be said that, in chronic asphyxia neonatal complications increase but mortality does not increase directly, but acute asphyxia especially complete asphyxia, such as decolman placenta, can increase the risk of mortality (14). If we consider chronic hypertension as chronic fetal asphyxia, and hypertensive crisis as acute fetal asphyxia, above findings could be interpreted. Confirming these findings requires subsequent, correlational, observational, large sample size studies.

Fallahi et al (1388) have also shown that in died neonates low Apgar score, was 9 times more than control group (25). Also in our study the 1_{th} and 5_{th} minute Apgar scores in the case

group was significantly lower than the control group. However the 5_{th} minute Apgar score's correlation with neonatal survival was higher. Similar results were obtained in the study of Vahabi et al (26). But the 5^{th} minute Apgar score had a higher correlation with infant survival. As we take away from the birth time, it has been expected that a better physiological adaptation achieved by the newborn, so it is rational that 5^{th} minute Apgar score be a better indicator of the neonate's prognosis. And thus have higher correlation with the neonatal outcome.

One of the interesting results obtained in this study were maternal blood group and RH. While the lowest frequent blood groups in the case group were A and B, and the most frequent blood groups were O and AB, the two groups were significantly different in term of blood group. Also while the commonest maternal Rh in the case group was positive Rh; the two groups were significantly different in term of maternal Rh. Also it has been shown that neonatal mortality odds ratio in the Rh negative mother and Rh positive mothers were respectively, 0.35 and 2.9. It means that maternal negative Rh had a protective effect against neonatal mortality, while maternal positive RH increased neonatal mortality chance by 3 times. If this finding be confirmed in the next studies, a strong mechanism for it should be sought.

Two other interesting findings in this study are related to the neonatal clinical findings at the NICU admission time which include Hypotonia with an odds ratio of 0.282 and poor sucking with an odds ratio of 0.451. Regarding this Odds ratios, at first glance it seems that they had a protective effect against neonatal mortality. But definitely it is not true. It seems that yielding such finding is related to the importance of on admission findings; problems which at the time of admission more attention from the physician directed to themselves have been the priorities. For example, apnea at admission time increased chance of premature mortality by 12.5-folds. And as also confirmed in other studies, this result is acceptable. But accepting that poor sucking at admission time reduced mortality chance couldn't be true. Certainly, with apnea, neonate hasn't sucking or sucking is weak. But the Apnea is so great important that, admitting physician considered apnea as more important, and recorded it, instead poor sucking. But the newborn that is so well at the time of admission that, just the poor sucking draw attention, can have a better prognosis. So we can say that in term of prognosis, admission whit poor sucking is better than apnea! And what is recorded as "at admission time clinical findings", mostly refers to main problems instead all of the results obtained in the physical examination. And it is recommended that this point considered in the next researches. This Explanation is proposed for hypotonia, too.

Although the results of this study in the assessing individual variables were consistent with other studies, but assessing the interaction of the neonatal risk factors with the neonatal prognosis have showed a significant exception. Multivariate regression analysis determined the greatest neonatal mortality risk factors as bradycardia at admission time, maternal diabetes, maternal Rh, gasping at the admission time, tonicity in the delivery room, at birth crying, birth length, gestational age and birth weight. And apnea at the NICU admission time and CPR in the delivery room, while were significantly different in the case and control groups, and had considerable Odds ratios, were not significant in the interaction of the multivariate regression and excluded from the equation. Also the 1th and 5^{th} minute apgar while had a strong correlation whit the neonatal survival, but excluded from the equation. In the study of Basue et al (2008), Logistic regression equation showed maternal bleed, apnea, birth weight, gestational age, hypothermia and shock predicted 65 percent of mortality in VLBW babies (10).

From the clinical point of view conditions such as bradycardia, low Apgar scores, gasping, apnea and CPR indication, are associated with each other. And all of them describe a neonate with unfavorable clinical condition. This point of view was assessed by statistical analysis. Correlational analysis between variables assumed in the regression equation did not show a significant correlation between them. But the four variables including 1th and 5^{th} minute Apgar score, CPR in delivery room, and apnea at the NICU admission time that were excluded from the regression equation had a strong correlation with the equation remained variables. For example, apnea at the NICU admission time had significant correlation with all of the equation remained variables except with maternal Rh and PROM. The reason of excluding from the equation was not their lack of importance in predicting neonatal mortality, but was their high overlap with other factors in the equation; hence influencing them in the equation of premature neonate's mortality probability estimation, was not longer needed. However it could be means that the Odds ratios of CPR in delivery room and apnea at the NICU admission time, coulde be affected by these correlations. Considering that it is desirable that in a logistic regression analysis there were at least 50 observations per each independent variable, repeating this study with a larger sample size could be recommended.

At the end it is added that, the retrospective nature of this study can be presented both as strength and limitation of this study. In the past occurrence of events and data recordation by those who were not involved in the study provided the natural clinical progression and reduced biases. But lack of access to the subjects in the hospitalized period has led to some data loss. However regarding the teaching nature of Ghaem Hospital, records were relatively complete and data loss in the assessed patient files was very little. In the rare case, that, there was not specific finding in a patient file, analysis was conducted based on the available data. Infant transfer from a center to another center can affect infant mortality rate. Assessing this variable can also provide valuable results. However in this study neonates who were referred from other centers were excluded due to defects in the patient files. It is recommended that it be addressed in the next studies. The results of our study provided several suggestions for the next studies. If these findings be

confirmed by the next interventional or semi-experimental studies could be a basic for evidence-based interventions.

Conclusion

The final result of this study indicates that although prematurity is the major cause of neonatal mortality, but premature neonates' mortality, itself is associated with several maternal and neonatal perinatal factors. Some of them increase premature neonates' mortality and some have protective effect. Therefore all premature neonates have not equal mortality risk. And we can also consider maternal and neonatal perinatal factors, for estimating the risk of infant mortality.

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