

Original Article

Effects of Maternal Coagulation disorder on Birth Weight and Post-Natal Non-Coagulation Problems of Neonates

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Abstract

Background: To evaluate the birth weight and post-natal non-coagulation problems of infants of mothers with coagulopathies versus normal mothers. **Materials and Methods:** In a retrospective cohort study, 100 women with coagulation problems attended the Iranian Haemophilia Comprehensive Care Center, and 200 normal women attending two health centers in Tehran and Karaj, with a history of at least one pregnancy were studied. A questionnaire about mothers' and neonates' condition was filled out by an interview, and the data were analyzed using SPSS software, version 16. **Results:** Using linear regression, the maternal coagulation problem had a negative effect on birth weight ($p < 0.001$, $\beta = -0.31$). The prevalence of early and prolonged jaundice in newborns of mothers with coagulopathy was higher than that in newborns of normal mothers (12% vs. 2%, and 7% vs. 3%, respectively), the difference between the two groups in terms of incidence of early jaundice was statistically significant (chi square- $p < 0.001$). The frequency of using phototherapy and blood exchange for treating neonatal jaundice, in neonates of mothers with coagulopathy was higher than in neonates of normal mothers (31% vs. 21% and 8% vs. 21%, respectively) ($p < 0.001$). Furthermore, the duration of hospitalization, hospitalization in NICU, and re-hospitalization during the first month of life in neonates of mothers with coagulation problems was higher than in neonates of normal mothers ($p < 0.001$). **Conclusion:** Considering the high prevalence of neonatal problems in newborns of mothers with coagulation problems and their lower birth weight, further care measures should be provided for them.

Keywords: Coagulation disorder, Birth weight, Neonatal problems, Neonatal jaundice

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Introduction

Coagulopathies are a group of diseases in which the ability of the body in controlling blood coagulation is decreased or lost. Most coagulopathies are congenital, and if one of the parents is affected, the baby has a higher risk for the disorder. For instance, if the mother is affected by hemophilia A or B, all her sons will have the disease, and all her

daughters will be carriers for the disease. If a mother is a carrier of the disease, half of her sons will inherit the disease, and half of her daughters will be carriers of the disease [1, 2]. Hemorrhage in infants with congenital coagulopathy disorders can be life-threatening. Early diagnosis of the disorders in neonates and being sure of the appropriate treatment including the administration of coagulation factors and

early prophylaxis is very hard [3].

In a study on the relationship of pre- and post-partum periods on the one hand and hemophilia A and B on the other hand, Arthur reported the prevalence of pre-term labor in mothers with coagulation disorders, was not significantly different from the rate in the general population. Moreover, the rate of blood exchange in their neonates was not higher than the general population [4].

In the evaluation of iron deficiency in women, Kulkarni et al. showed that bleeding disorders in women resulted in anemia, which in turn would cause pre-term labor and low birth weight in their babies [5].

The study evaluated the effect of low birth weight on school performance and behavioral outcomes of elementary school children and demonstrated that the children with low birth weight had more problems in fulfillment of their school tasks and they have more health problems even until their adulthood [6].

In another study, Indredavik et al. studied the psychiatric symptoms and disorders in adolescents with low birth weight and concluded that adolescents, who were born with low and very low birth weights, will more frequently experience psychiatric disorders including anxiety in adulthood [7].

Furthermore, a study on the approaches in diagnosis and treatment of neonatal coagulopathies, stated that neonatal coagulation disorders will lead to different diseases including hepatic disorders, and the levels of hepatic enzymes would fluctuate [8]. Therefore, increased levels of bilirubin in newborns and coagulation disorders in their mothers may lead to jaundice in these neonates. The complications of jaundice are kernicterus, cerebral palsy, and auditory problems [9].

So, children born to mothers with coagulopathy may have bleeding complications as well as non-bleeding and many other problems at birth. In the current study, we have tried to identify these problems and their prevalence to help parents and physicians provide better care for these neonates.

Methods

This historical cohort study was carried out from July 2010 to June 2011 in the Iranian Haemophilia Comprehensive Care Center, two health centers in Tehran district 6, and Shahid Torkian health center in Karaj. The inclusion criteria were as follows: a history of at least one pregnancy and being in the age range of 20-45.

The study population consisted of two groups: a coagulopathy group that consisted of 100 women with a coagulation disorder. Diagnosis of their disease was previously performed according to the results of laboratory tests, and they were registered in the Iranian Haemophilia Comprehensive Care Center. These women referred to the center from around the country to receive services. The normal group consisted of 200 normal women who were referred to the above-mentioned centers to receive services.

Considering the very low prevalence rate of coagulation disorders in women, the sampling was carried out using an easy sampling method. To this end, until reaching the population size of the study, all women who referred to the centers and had the inclusion criteria were included in the study. For all participants, the data related to their last pregnancy and delivery was collected using a questionnaire. At the beginning of the study, using the viewpoints of obstetricians and internal medicine specialists, a questionnaire was prepared. It consisted of 80 items on demographic information, obstetric history, and delivery report, different aspects of delivery, neonates, post-partum complications, and neonate's hospitalization. For a pilot study, the questionnaire was handed out to 40 participants. The questionnaire pitfalls in data collection and interview were identified and modified (CVR= 0.73, CVI= 0.85, N= 10).

The questionnaire contained items on characteristics of the baby and his/her problems at birth, which were asked from their mothers. The data was also obtained from the files and growth monitoring cards of the infants.

Statistical analysis. The data were analyzed using SPSS software, version 15, with chi-square, and

logistic regression. Chi-square was used to compare the differences in bleeding complications in women with coagulation disorders and normal mothers. A logistic regression test was used to investigate the relationship between bleeding complications and coagulation disorders in women with coagulation disorders, along with the study of factors affecting bleeding complications.

Results

In the current study, 100 women with coagulation disorders and 200 normal women were evaluated. The anthropometric characteristics of participants including height and weight, last child's birth weight, and socioeconomic state Tables 1 and 2.

The prevalence of neonates' problems in different groups is presented in Table 4. The frequency of the types of coagulopathy in the case group are as follow: Hemophilia (3%), hemophilia carrier (44%), von Willebrand (28%), factor VII deficiency (6%), factor X deficiency (3%), factor XI deficiency (2%), factor XII deficiency (2%), factor XIII deficiency (3%), hypofibrinogenemia(3%), Bernard-Soulier syndrome(1%), Glanzmann's syndrome(3%), factors V and VIII deficiency(2%).

Among the newborns of women studied, in the coagulopathy group, 56% of infants were male while the rate in normal women was 38%.

Table1. Physical and socioeconomic characteristics of women participated in the study (N= 300).

		Normal mothers; n (%)	Mothers with coagulation disorders;n (%)	p-value
Blood group	A	54(27)	34(34)	0.537
	B	53(26.5)	24(24)	
	AB	33(16.5)	12(12)	
	O	60(30)	30(30)	
Rh	+	186(93)	94(94)	0.743
	-	14(7)	6(6)	
Education level of mothers	Illiterate	4(2)	4(4)	0.190
	Primary school	3(1.5)	7(7)	
	Secondary school	16(8)	7(7)	
	High school	10(5)	7(7)	
	Diploma	67(33.5)	33(33)	
	Advanced Diploma	52(26)	20(20)	
	Bachelor's Degree or higher	48(24)	22(22)	
Mothers' job	Household	106(53)	66(66)	0.051
	Clerk	85(42.5)	33(33)	
	Worker	9(4.5)	1(1)	

Table2. Evaluation of physical characteristics of women participated in the study by T-test (N= 300).

	Normal mothers		Mothers with coagulation disorders		p-value
	Mean	Standard deviation	Male	Standard deviation	
Mother's age (year)	32.42	7.31	32.61	7.07	0.74
Mother's weight (kg)	61.61	9.14	64.06	10.61	0.54
Mother's height (cm)	161.01	6.05	161.06	6.64	0.98
Mother's age at the last pregnancy (year)	25.99	4.35	25.46	4.36	0.67
Neonate's birth weight (g)	3299.49	456.89	3018.26	546.95	0.71

The mean birth weight of infants in coagulopathy and normal groups was 3018.2 ± 546.95 , and 3299.4 ± 456.89 gram, respectively. The difference in the birth weights of the two groups was not statistically significant. For more accurate comparison of the two groups, we used linear regression test and evaluated the effect of coagulopathy disorder of mothers and factors such as maternal age during pregnancy, occupation and education level, history of taking supplements,

medications, and coagulation factors during pregnancy; hypertension, gestational diabetes, hyperemesis gravidarum, infection during pregnancy, multiple gestations, infants' sex, infants' coagulation disorders, gestational age at the time of delivery on infant birth weight. According to the results obtained, maternal coagulopathy causes neonates' low birth weight ($p < 0.001$, $\beta = -0.17$). Moreover, newborn sex had a significant effect on newborns' birth weight (Table 3).

Table3. Factors effective on birth weight using linear regression analysis (N= 300).

Factors effective on birth weight	Beta	p-value
Mother's Coagulation Disorder	-0.31	<0.001
Mother's Age During Pregnancy	-0.10	0.08
Mother's Job	-0.06	0.92
Mother's Education Level	-0.02	0.63
Drug Used During Pregnancy	-0.08	0.15
Administration Of Coagulation Factor During Pregnancy	0.01	0.76
Multiple Gestation	-0.03	0.58
Hyperemesis	0.000	0.86
Infection During Pregnancy	-0.05	0.31
Gestational Diabetes	-0.07	0.21
Hypertension	0.07	0.19
Neonate's Sex	-0.17	<0.001
Gestational Age at Delivery	-0.01	0.83
Neonate's Coagulation Disorder	0.06	0.28

Table4. Sex and problems of the last baby born to women participated in the study (chi-square test; N= 300).

		Normal mothers	Mothers With Coagulation Disorders	Total	P-value
		n (%)	n(%)		
Neonate’s sex	Male	77(38.5)	56(56)	133	<0.001
	Female	122(61)	41(41)	163	<0.001
Gestational age	<36wk+6d	9(4.5)	8(8)	17	0.16
	37wk+0 to 40wk+6d	185(92.5)	84(84)	269	0.21
	>41 wk	5(2.5)	5(5)	10	0.21
Need for Resuscitation		3(1.5)	4(4)	7	0.222
Abnormal Fetal Position		7(3.5)	3(3)	10	1
Neonate’s disorder	Hemophilia	0(0)	30(30)	30	<0.001
	Hemophilia carrier	0(0)	6(6)	6	<0.001
	Von Willebrand	0(0)	4(4)	4	<0.001
	Factor VII deficiency	0(0)	1(1)	1	<0.001
	Factor XI deficiency	0(0)	1(1)	1	<0.001
	Bernard-Soulier syndrome	0(0)	1(1)	1	<0.001
Abnormal Thyroid Function Test		2(1)	1(1)	3	1
Abnormal Auditory Tests		4(2)	2(2)	6	1
Respiratory Problems		4(2)	3(3)	7	0.687
Congenital Abnormalities		4(2)	3(3)	7	0.687
Breastfeeding In The First 24 Hours After Birth		197(98.8)	92(92)	289	0.04
Baby Feeding	Exclusive breastfeeding	72(36)	48(48)	120	0.031
	Breastfeeding + formula	107(53.5)	35(35)	142	<0.001
	Exclusive formula	18(9)	14(14)	32	0.13
	Pre-term formula	2(1)	0(0)	2	0.44
Neonatal jaundice	Did not happen	96(48)	34(34)	130	0.014
	Physiological jaundice	93(46.5)	44(44)	137	0.38
	Early jaundice	4(2)	12(12)	16	<0.001
	Prolonged jaundice	6(3)	7(7)	13	0.09
Jaundice treatment	Was not required	154(77)	58(58)	212	<0.001
	Phototherapy	42(21)	31(31)	73	0.04
	Blood exchange	3(1.5)	8(8)	11	<0.001
Duration of hospitalization	One day after delivery	178(89)	60(60)	238	<0.001
	One week after delivery	9(4.5)	15(15)	24	<0.001
	More than one week	6(3)	9(9)	15	<0.001
	Non-specified	6(3)	13(13)	19	0.001
NCU hospitalization		5(2.5)	9(9)	14	0.013
Re-hospitalization in the first month of life after the first hospital discharge		1(0.5)	4(4)	5	0.041

In the comparison of babies born to the two groups of mothers, the following rate was obtained; the need for resuscitation (5% versus 3%), abnormal presentation of the fetus (3% versus 3.5%), abnormal respiration problems at birth (3% versus 2%), and congenital abnormalities (3% versus 2%) for coagulopathy and normal groups, respectively. Moreover, the rates of abnormal thyroid function test (1%) and abnormal auditory test (2%) were similar for both groups. The rates were not statistically significant using the chi-square test (Table 4).

Breastfeeding rate in the first 24 hours after birth was lower in newborns of the coagulopathy groups. However, exclusive breastfeeding was more frequent in the babies of the coagulopathy group, and the two groups were significantly different in this respect (p=0.03) (Table 4).

In the coagulopathy and normal groups, the rates for early and prolonged jaundice were 12% versus 2%, and 7% versus 3%, respectively. The difference between the two groups in the prevalence of prolonged jaundice was statistically significant according to the results of the chi-square test (p<0.001). For jaundice treatment in the coagulopathy group, 31% and 8% of infants with jaundice received phototherapy and blood exchange, respectively (compared with 21% and 1.5% in the normal group) (p<0.001). According to the results of the logistic regression test, the effect of maternal coagulopathy disorder together with factors such as Rh, drugs, and administered coagulation factors during pregnancy, newborn’s birth weight and sex, gestational age at the time of delivery, neonate’s coagulation disorder, neonate’s feeding in the first 24 hours after delivery on the incidence of neonatal jaundice were evaluated. According to the results, maternal coagulation disorder led to a two-fold increase in the risk of neonatal jaundice (p= 0.01, odds ratio= 2.10, 9.3 < CI < 11) (Table 5).

The duration of the neonate’s hospital stay in the coagulopathy group was higher than that in the normal group (p<0.001). Furthermore, the rate of

hospitalization in NICU and re-hospitalization after the first hospital discharge in the first month of life was higher in neonates of the coagulopathy group (p<0.001).

Table5. Factors effective on neonatal jaundice (logistic regression test, N= 300).

Effective factors	Odds ratio	p-value
Mother’s coagulation disorder	2.10	0.01
Mother’s Rh	0.5	0.18
Administration of coagulation factors during pregnancy	1.13	0.86
Use of drugs during pregnancy	0.31	0.06
Neonate’s sex	1.08	0.74
Gestational age at the time of delivery	0.78	0.42
Baby feeding in the first 24 hours after birth	0.44	0.38
Neonate’s coagulation disorder	0.83	0.20

Discussion

Coagulation disorders are classified as bleeding disorders, which are mostly congenital and the infected should deal with the disease during all his life. Pregnant women with coagulation disorders encounter two challenges; bleeding complications and the occurrence of the disorder in their baby [4]. As it was observed in the current study, many babies

born to these mothers were affected by coagulation disorders.

It was observed that the coagulation disorder of the mother negatively affects the birth weight. In general, the problem can be the result of taking some drugs or administration of coagulation factors during pregnancy. In different studies, it was demonstrated that using desmopressin increases the risk of pre-term labor [10]. In a study on neonatal coagulation defects, Turner stated that most neonates with severe coagulation disorders were pre-term and had birth weight under 2000 g. [11]. In the current study, it was observed that neonate's coagulation disorder did not affect birth weight. If the current study was performed on a larger sample size, such a relationship could probably be found. However, in the study by Turner, the role of maternal coagulation disorder was not considered. Coagulation disorders are mostly congenital and newborns with such disorders and low birth weight are probably born to mothers who have coagulation disorders or at least they are carriers of the disease, and such conditions may affect neonate's birth weight. In a study on pregnancy and rare bleeding disorders, Kadir et al. reported cases of pre-term labor and very low birth weight in neonates born to mothers with coagulation disorders [12]. Nevertheless, in the current study, we did not observe cases of low birth weight (LBW) or very low birth weight (VLBW). If the study was carried out on a larger population size, the effect of maternal coagulation disorders on birth weight or LBW and VLBT could be evaluated with higher confidence.

Physiological jaundice begins at the second and third days of life, usually peaks at days third to fifth and sometimes seventh, and then within two to three days, the bilirubin level declines to normal. The phenomenon is considered to be pathological if the time of occurrence, duration, or serum bilirubin levels in serial measurements are significantly different from those of physiological jaundice. The pathological jaundice is associated with maternal or neonatal factors (perinatal problems; or underlying genetic, hematologic, or metabolic diseases) [13].

In the current study, it was demonstrated that maternal coagulation disorder increases the risk of pathologic jaundice occurrence (early and prolonged

jaundice) and the need for its treatment (phototherapy and blood exchange). The risk of occurrence of jaundice in babies born to mothers with coagulation disorders is almost two times of babies having normal mothers. Jaundice can be caused by hepatic failure associated with hemostatic abnormalities.

The underlying mechanisms of hepatic failure associated with hemostatic disorders are decreased synthesis of coagulation factors, decreased activity of coagulation and fibrinolytic systems, ineffective clearance of active hemostatic complexes, coagulation protein deficiency, thrombocytopenia, platelet dysfunction, and abnormal vitamin K intake [14]. Hyperbilirubinemia occurs in pre-term neonates, or neonates with neonatal intraventricular hemorrhages, concealed hemorrhages, and hemolysis [11]. Furthermore, in babies born to mothers with coagulation disorders, the level of coagulation factor is decreased and the risk of neonatal hemorrhages including cephalhematoma, intraventricular hemorrhages, and concealed hemorrhages is higher. This can be a predisposing factor for the occurrence of hyperbilirubinemia and jaundice in these newborns [15].

A higher rate of blood exchange in the treatment of neonatal jaundice for babies of mothers with coagulation disorders can be the result higher prevalence of bleeding disorders and hemorrhage and thus a higher prevalence of hyperbilirubinemia in these newborns. This would convince the physicians to employ blood exchange for the treatment of hyperbilirubinemia. Furthermore, since the data of the current study were collected using interviews with mothers, mothers may mistake blood exchange with any cause for blood exchange as a treatment of jaundice [13].

The values obtained for the duration of hospitalization, hospitalization in NICU, and re-hospitalization after the first hospital discharge in the first month of life were higher for babies of mothers with coagulation problems [16]. In the current study, the neonates were evaluated for coagulation disorders. Moreover, babies of mothers who were aware of their disease were observed, and re-hospitalization because of circumcision or other neonatal hemorrhages were recorded. A major cause

of re-admission in neonates of mothers with coagulation problems was the occurrence of jaundice.

We have classified the mothers' coagulation disorders according to the disorder type. However, since the number of cases for each disease was low, the effect of each disease on other factors was not evaluated. Thus, the classification of disorders was used only for the description of mothers' condition, and regardless of the disease type, coagulation disorders, in general, were considered in the study.

The neonates' sex in the two groups was expected to be similar or because of the higher rate of abortion of affected male fetuses, the number of the female newborns in mothers with coagulation disorders be higher. Nevertheless, the number of male newborns in the coagulopathy group was higher, and the difference between the two groups in this respect was statistically significant. In some cases, sampling in the group of mothers with coagulation disorders performed by identification of boys with hemophilia, and as their mothers were carriers for hemophilia, they were included in the study. This can explain the sex difference observed between the babies of the two groups. Thus, the difference originates from the sampling method.

The prevalence of coagulation disorders among babies of mothers with coagulation disorder was determined to be 97%. The rate was higher than that reported by others [17-19]. This is also the result of the sampling method, as in some cases after identification of the affected child; his mother was included in the study. Considering the results of previous studies, it was expected that mothers who feed their babies with their milk in the first 24 hours of life would follow exclusive breastfeeding more frequently. However, it was observed that the rate of breastfeeding in the first 24 hours was lower in the coagulopathy group, while the rate of exclusive breastfeeding was higher in this group. Many mothers with coagulation disorders lived in towns other than Tehran, and many have experienced delivery in hospitals, which were not mother-friendly, and did not insist on early breastfeeding. This can explain the observation of the study. Moreover, considering the lifestyle in Iranian towns and not prescribing a formula for pre-term neonates

by midwives and physicians, such difference is expected. For instance, none of the mothers with coagulation disorders used formula for their pre-term babies.

As maternal coagulation disorder leads to some problems for neonates, these women should be prepared for dealing with the problems. For instance, during pregnancy, they should receive consultation from obstetricians and pediatricians. Besides, by receiving complete pregnancy care, preterm labor and LBW should be prevented; the delivery should be performed in centers with units such as NICU that is required for providing care and treatment to these newborns. The neonates should also be examined for coagulation diseases at birth to prevent the occurrence of future problems. If jaundice occurred, the pediatrician should be aware of the mothers' history of the disease, and the treatment with minimal harm to the child be provided. Considering the problems that occurred for the newborn and their longer hospitalization, health care providers should concern the risk of nosocomial infections.

Conclusion

In general, concerning the lower birth weight and higher prevalence of jaundice in neonates of mothers with coagulation disorders as well as the longer duration and higher frequency of their hospitalization, they should be treated more carefully and the neonatologist should be aware of mothers' disease history.

Conflicts of Interest

The authors declared no competing of interest.

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