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1:4 matched case-control study on influential factor of early onset neonatal sepsis

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Abstract. – BACKGROUND: Bacteria, funghi, viruses and protozoa can lead to neonatal sepsis. Neonatal sepsis is the leading cause of infectious disease onset and death in many neonates.

AIM: To explore the major risk factors of early-onset neonatal sepsis and provide a scientific basis for strategies of early-onset neonatal sepsis prevention.

SUBJECTS AND METHODS: A 1:4 matched case-control study was adopted and 147 cases of early-onset neonatal sepsis were enrolled. Conditional logistic regression model was used to analyze the univariate and multivariate data to estimate the odds ratio (OR) and the 95% confidence interval (95% CI).

RESULTS: Univariate analysis shows that the impact factors on the occurrence of early-onset neonatal sepsis include the following: Maternal age > 35, mother having fixed occupation, mother of urban residence, abnormal fetal position, fetal times, parity, caesarean section, premature rupture of membranes, amniotic fluid volume abnormalities, pregnancy-induced hypertension, placental abnormalities, fetal distress, newborn gender, low birth weight infants, neonatal Apgar scoring at one and five minutes, neonatal jaundice, wet lung, anemia, IVH, and premature infant. Multivariate logistic regression analysis showed that maternal age > 35 (OR = 4.835, OR 95% CI = 1.170-19.981), cesarean section (OR = 0.103, OR 95% CI = 0.041-0.258), premature rupture of membranes (OR = 0.207, OR 95% CI = 0.078-0.547), premature infants (OR = 0.059, OR 95% CI = 0.010-0.329) and newborn jaundice (OR = 0.092, OR 95% CI = 0.021-0.404) were the factors of early-onset neonatal sepsis.

CONCLUSIONS: Early-onset neonatal sepsis could be affected by multi-factors, and targeted prevention may reduce the incidence of early-onset neonatal sepsis rates.

Key Words:
Neonatal sepsis, Case-control study, Factors.

Introduction

The conventional pathogens that lead to neonatal sepsis are bacteria, fungi, viruses or protozoa. But in the case of neonatal sepsis, the culprit is bacterial sepsis. With the discovery of new medications, treatments have improved in recent years and a variety of new disinfectants and antibiotics are continuously emerging. The morbidity and mortality of neonatal sepsis has dropped significantly, but its current level is still high. Neonatal sepsis is the leading cause of infectious disease onset and death in newborns[1]. Research shows that the appearance rate of sepsis accounted for 0.1% to 1.0% of living neonate[2], and 5% to 6% of neonatal death[3-5]. Also reported, was that the lower the birth weight, the higher the prevalence rate of neonatal sepsis. Neonatal sepsis in infants with very low birth weight can reach up to 16.4%, which indicates that it is the leading cause of death in premature infants.

The incidence of neonatal sepsis is an important benchmark for measuring a national and regional socio-economic development of maternal and child health care. Exploring the factors influencing the occurrence of neonatal sepsis will help to improve prevention.

For this study, neonatal and maternal medical data from the Women's Hospital, School of Medicine, Zhejiang University, were used to conduct a 1:4 matched case-control study. The objective was to analyze the factors influencing early-onset neonatal sepsis.

Subjects and Methods

Research Subjects

Case Selection

At the Women's Hospital, School of Medicine, Zhejiang University, during the period of January 2010 and 31th May 2011, newborns diagnosed within seven days, with early onset neonatal sepsis were chosen as research subjects. The diagnosis was based on the "Diagnostic and Treatment

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Program of Neonatal Sepsis" enacted in 2003 by the Neonatology Group of the Paediatric Society, of the Chinese Medical Association, and included bacterial blood culture and clinical manifestations. The specific diagnostic criteria were as follows:

Confirmed diagnosis: clinical manifestations in accordance with any of the following: (1) blood culture or pathogenic culture within sterile body cavity. (2) If the blood culture specimens can cultivate opportunistic pathogens, and it will culture the same species of bacteria within another (copy) blood, in a sterile body cavity or catheter tip.

Clinical diagnosis: clinical manifestations in accordance with any of the following: (1) non-specific inspection ≥ 2. (2) The pathogen antigens of blood specimens or DNA testing positive.

The clinical manifestations of neonatal sepsis include:

Systemic manifestations: (1) Body temperature changes: having a fever or low body temperature. (2) Eat, cry, or move less, pale, coolness of extremities, weight unchanged or slow growth. (3) Jaundice: sometimes the only manifestation of sepsis, severe cases may develop into bilirubin encephalopathy. (4) Shock: coolness of extremities, decrease of femoral pulse, prolonged capillary refill time, reduced blood pressure, and severe cases can have disseminated intravascular coagulation (DIC).

Manifestations of the body: (1) Skin and mucous membranes: Scleredema, subcutaneous gangrene, impetigo, periumbilical cellulitis or other sites, nail bed infections, skin burns, bruising, petechia, oral mucosa picking cut injury. (2) Digestive system: anorexia, abdominal distension, vomiting, diarrhea, severe toxic intestinal paralysis or necrotizing enterocolitis (NEC), hepatosplenomegaly in the later stage. (3) Respiratory system: shortness of breath, cyanosis, irregular respiration or apnea. (4) Central nervous system: purulent meningitis, appearing as somnolence and irritability, convulsions, increasing fore fontanel tension and hypermyotonia of limb, etc. (5) Cardiovascular system: infective endocarditis, septic shock. (6) Circulation system: combined with thrombocytopenia, bleeding tendency. (7) Urinary tract infections. (8) Others: purulent osteoarthritis, osteomyelitis and deep abscess.

Control Selection

Study was designed according to 1:4 matched case-control study, and four non-sepsis in neonates were chosen as control subjects from each case with the same date of birth at the same hospital.

Determination of Factors

Data on the factors influencing early-onset neonatal sepsis on the control subjects was obtained from the hospital medical records. This included background information on the pregnant women and their spouses: maternal age >35, mother having fixed occupation, mother of urban residence, abnormal fetal position, fetal times, parity, cesarean section, premature rupture of membranes, amniotic fluid volume abnormalities, pregnancy-induced hypertension, placental abnormalities, and fetal distress. Neonatal factors: newborn gender, low birth weight infant, neonatal Apgar scoring at one and five minutes, neonatal jaundice, wet lung, anemia, IVH and premature infant.

Definition and Assignment of Major Research variables

Dependent Variable

The cases were assigned to 1, and the assignment of controls for 0.

Independent Variable

The variables were defined as follows: Elderly pregnancy: maternal age > 35 years old. Abnormal placenta: placental abruption, previa, and battledore placenta. Abnormal fetal position: fetus head position abnormality, breech presentation, shoulders presentation. Low birth weight infants: birth weight < 2500 g. Preterm infants: gestational age < 37 weeks, abnormal character of amniotic fluid, amniotic fluid volume abnormality, wet lung. Specific assignments are shown in Table I.

Data Statistical Analysis

For collating of raw data, EpiData 3.1 was used to establish the database and input data, and then converted into a recognizable format by

Table I. Influencing factors on early-onset neonatal sepsis.

Variable	Indicator	Content	Assignment	Variable	Indicator	Content	Assignment
Mother	Maternal age > 35	Yes	0	Neonate			
		No	1				
	Having fixed	Yes	0		Low birth	Yes	0
	occupation	No	1		weight	No	1
	Urban residents	Yes	0		Gender	Yes	0
		No	1			No	1
	Abnormal fetal	Yes	0		Jaundice	Yes	0
	position	No	1		performance	No	1
	Fetal times	Yes	0		Wet lung	Yes	0
		No	1			No	1
	Cesarean section	Yes	0		Anemia	Yes	0
		No	1			No	1
	Premature rupture	Yes	0		IVH	Yes	0
	of membranes	No	1			No	1
	Abnormalities of	Yes	0				
	amniotic fluid	No	1				
	Amniotic fluid	Yes	0				
	volume abnormalities	No	1				
	Pregnancy-induced	Yes	0				
	hypertension	No	1				
	Placental	Yes	0				
	abnormalities	No	1				
	Hepatitis B	Yes	0				
		No	1				
	Fetal distress	Yes	0				
		No	1				

SPSS, with SPSS16.0 software (SPSS Inc., Chicago, IL, USA) as a statistical analysis platform for statistical processing. Statistical methods: univariate and multivariate conditional logistic regression analysis (utilizing Cox model in survival analysis for fitting), calculating the odds ratio (OR) and 95% confidence interval of OR (95% CI). OR 95% CI value does not include one, which indicates statistical significance.

Results

General Condition

The sample size was a total of 735 cases, including 147 cases diagnosed as early-onset neonatal sepsis and 588 cases of the control subjects. The median day of early-onset neonatal sepsis diagnosis of the case objects were about two days, with the specific distribution as shown in Figure 1.

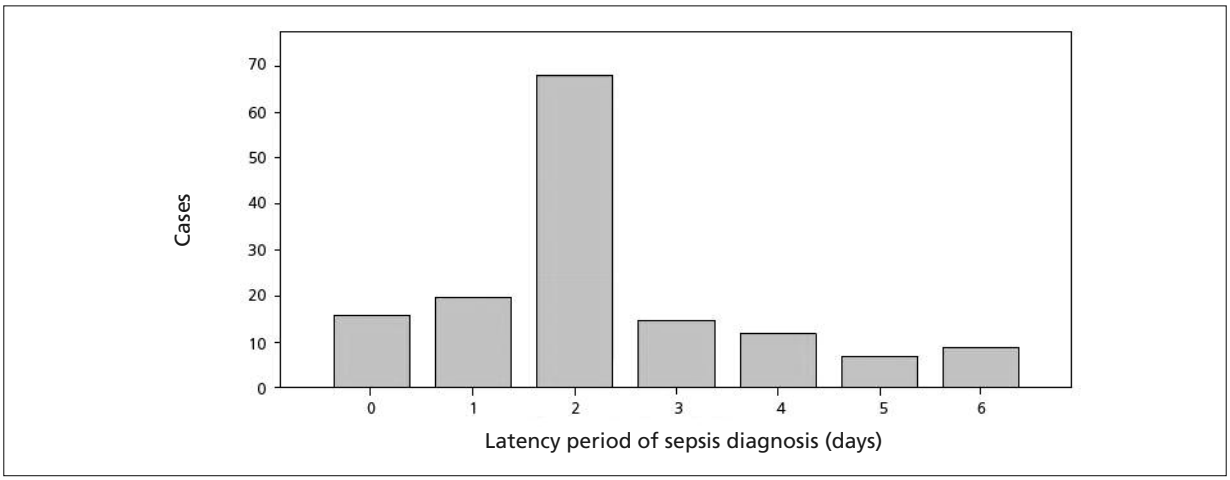

Figure 1. Latency period distribution of early-onset neonatal sepsis diagnosis.

Univariate Analysis on the General Condition of Pregnant Women

Univariate analysis shows that the impact factors on the occurrence of early-onset neonatal sepsis include the following (Table II):

Maternal age > 35 (OR = 2.420, OR 95% CI = 1.396-3.174), mother having fixed occupation (OR = 0.439, OR 95% CI = 0.289-0.668), mother of urban residence (OR = 5.079, OR 95% CI = 2.899-8.990), abnormal fetal position (OR = 1.621, OR 95% CI = 1.340-1.962), fetal times (OR = 1.212, OR 95% CI = 1.041-1.412), parity (OR = 1.859, OR 95 % CI = 1.188-2.908), caesarean section (OR = 0.168, OR 95% CI = 0.107-0.264), premature rupture of membranes (OR = 0.251, OR 95% CI = 0.159-0.397), amniotic fluid volume abnormalities (OR = 0.200, OR 95% CI = 0.054-0.745), pregnancy-induced hypertension (OR = 0.297, OR 95% CI = 0.122-0.726), placental abnormalities (OR = 0.050, OR 95% CI = 0.006-0.428), fetal distress (OR = 0.100, OR 95% CI = 0.019-0.515), newborn gender (OR = 0.620, OR 95% CI = 0.427-0.899), low birth weight children (OR = 0.027, OR 95% CI = 0.013-0.056), neonatal Apgar scoring at one minute (OR = 0.480, OR 95% CI = 0.399-0.577), and at five minutes (OR = 0.267, OR 95% CI = 0.179-0.398), neonatal jaundice (OR = 0.244, OR 95% CI = 0.113-0.526), wet lung (OR = 0.039, OR 95% CI = 0.013-0.112), anemia (OR = 0.012, OR 95% CI = 0.003-0.051), IVH (OR = 0.008, OR 95% CI = 0.001-0.059), premature infant (OR = 0.016, OR 95% CI = 0.006-0.039).

There was no significant statistical correlation between the early-onset neonatal sepsis and the following factors: abnormalities of amniotic fluid (OR = 0.987, OR 95% CI = 0.463-2.104) and mother with hepatitis B (OR = 30.593, OR 95% CI = 0.915-1.039), as shown in Table I.

Multivariate Conditional Logistic Regression Analysis

The 23 variables of statistical significance in the univariate analysis were as follows: maternal age > 35, mother having fixed occupation, mother of urban residence, abnormal fetal position, fetal times, parity, cesarean section, premature rupture of membranes, amniotic fluid volume abnormalities, pregnancy-induced hypertension, placental abnormalities, fetal distress, newborn gender, low birth weight infants, neonatal Apgar scoring at one and five minutes, neonatal jaundice, wet lung, anemia, and IVH, premature infants. In addition, taking into account whether early-onset neonatal sepsis occurs as a dependent variable, a multivariate conditional logistic regression analysis was carried on by stepwise forward algorithm. As a result, maternal age > 35

Table II. Univariate analysis of early-onset neonatal sepsis.

	Factor	*p* value	OR	OR 95% CI
Pregnant women	Maternal age >35	0.002	2.420	1.396-3.174
	Having fixed occupation	0.000	0.439	0.289-0.668
	Urban residents	0.000	5.079	2.899-8.990
	Abnormal fetal position	0.000	1.621	1.340-1.962
	Fetal times	0.013	1.212	1.041-1.412
	Parity	0.007	1.859	1.188-2.908
	Cesarean section	0.000	0.168	0.107-0.264
	Premature rupture of membranes	0.000	0.251	0.159-0.397
	Abnormalities of amniotic fluid	0.973	0.987	0.463-2.104
	Amniotic fluid volume abnormalities	0.0160	0.200	0.054-0.745
	Pregnancy-induced hypertension	0.008	0.297	0.122-0.726
	Placental abnormalities	0.006	0.050	0.006-0.428
	Hepatitis B	0.056	30.593	0.915-1.023E3
	Fetal distress	0.006	0.100	0.019-0.515
Neonate	Low birth weight	0.000	0.027	0.013-0.056
	Gender	0.012	0.620	0.427-0.899
	Apgar scoring for 1 min	0.000	0.480	0.399-0.577
	Apgar scoring for 5 min	0.000	0.267	0.179-0.398
	Jaundice performance	0.000	0.244	0.113-0.526
	Wet lung	0.000	0.039	0.013-0.112
	Anemia	0.000	0.012	0.003-0.051
	IVH	0.000	0.008	0.001-0.059
	Premature infant	0.000	0.016	0.006-0.039

(OR = 4.835, OR 95% CI = 1.170-19.981), cesarean section (OR = 0.103, OR 95% CI = 0.041-0.258), premature rupture of membranes (OR = 0.207, OR 95% CI = 0.078-0.547), premature infants (OR = 0.059, OR 95% CI = 0.010-0.329) and newborn jaundice (OR = 0.092, OR 95% CI = 0.021-0.404) performance eventually entered the model, as shown in Table III.

Discussion

Neonatal sepsis is an infectious disease caused by the invasion of pathogens into the organism. The development of sepsis is related to two factors: infection and neonatal immunity. Infection may include the number of pathogen invasions, virulence, timing and pathway of invasion, and can be summed up in three categories: (1) prenatal infection, (2) infection at birth, (3) postnatal infection. The neonatal immune function is divided into two major categories of non-specific and specific immune function. Therefore, any factors that can affect infection and immune function may have an impact on the occurrence of neonatal sepsis.

In this study, univariate analysis shows that the mother's occupation, education level, prenatal examination, premature rupture of membranes, curettage operation, abnormal fetal position, twin pregnancy, gestational age of newborn, birth weight, appearance, umbilical cord abnormalities, jaundice and Apgar scoring, may be the factors influencing early-onset neonatal sepsis. The multivariate analysis showed that maternal age, premature rupture of membranes, cesarean section, gestational age, and jaundice were factors influencing early-onset neonatal sepsis.

Along with the economic development and increasing openness of society, premarital sex has become widespread. At present, many domestic and foreign literature reports that the induced abortion rate increased gradually while the maternal age was getting younger. However, women's childbearing age is postponed, mainly due to social and economic pressures after marriage. So, with extended periods between the sexually mature phase and childbirth, and an increasing proportion of unplanned pregnancies, many women have induced abortions. This can lead to adhesions or implantation of the placenta and bring adverse effect on pregnant women and their newborn during delivery and following childbirth, thus increasing the risk factors for neonatal sepsis. The studies of Mannan et al[6] (2012) pointed out that an advanced maternal age or one that is too young, is one of the factors that affect neonatal mortality, especially in premature infants with very low birth weight (VLBWI). As reported by Soman et al (Am J Epidemiol 1985; 121: 712-719), maternal age that is advanced or too young are all high risk factors of the early-onset neonatal sepsis. Salem et al[7] (2006) also reported that the early-onset neonatal sepsis was related to advanced maternal age, which is one of the risk factors for early-onset neonatal sepsis. The literature supports the conclusion of this study, i.e., if the maternal age is over 35 years old during delivery, the OR value of early-onset neonatal sepsis is 4.835 (95% CI = 1.170-19.981).

A premature rupture of the membranes refers to the full-thickness natural rupture of fetal membranes (chorion and amnion) before labor, and one should not launch labor one hour after the rupture of the membranes. Its adverse effects on pregnancy and delivery include the elevated rates of preterm birth, increased mortality of perinatal infant, higher rates of intrauterine and puerperal infection. Premature rupture of membranes will

Table III. Conditional logistic regression analysis of risk factors on early-onset neonatal sepsis.

Factor	Regression coefficient	Standard error	Wald χ^2 value	*p* value	OR	OR 95% CI
Pregnant women						
Maternal age > 35	1.576	0.724	4.740	0.029	4.835	1.170-19.981
Cesarean section	-2.275	0.469	23.484	0.000	0.103	0.041-0.258
Premature rupture of membranes	-1.575	0.496	10.089	0.001	0.207	0.078-0.547
Neonate						
Premature infant	-2.835	0.880	10.379	0.001	0.059	0.010-0.329
Jaundice performance	-2.385	0.755	9.988	0.002	0.092	0.021-0.404

lead to prolonged labor, puerperal, decreased appetite, physical exertion and decreased resistance. The degree of infection is related to the rupture time, and if the rupture time is more than 18 hours, the infection rate will increase by five to ten times. Prolonged rupture of the membranes and the draining of the amniotic fluid will result in a fetal pressure that is close to the uterine wall, and would affect the fetal placental circulation, which can cause intrauterine infection, a dead fetus, as well as vaginal infections. Moreover, neonatal pneumonia, sepsis and other serious complications will occur after birth. The results of this study, shows that the odd ratio (OR) of the premature rupture of the membranes on neonatal early-onset sepsis is 0.207 (95% CI 0.078-0.547). More than 18 hours are recommended to conduct the necessary blood culture, while paying close attention to the clinical signs and symptoms of infection. Newborns with a gestational age of less than 35 weeks and/or weight of less than 2500 g are proposed to undergo the necessary anti-infective examination and must be monitored for the clinical signs and symptoms of infection[8].

As early as in 1996, Agrawal et al[9] studied and compared IgG antibody content in the blood of cesarean newborns and neonates by natural labor. He discovered that the blood IgG antibody levels in newborns delivered by cesarean section is significantly lower than that of newborns delivered by natural labor. Boutsikou et al[10] also mentioned that the cesarean section is one of the risk factors of early neonatal sepsis. Wilmink et al[11] conducted a retrospective study on 20973 newborns by selective cesarean section during seven years, and found that there was a higher proportion of neonatal sepsis for newborns delivered by selective cesarean section with a gestational age of less than 39 weeks. The logistic regression analysis showed that the OR value of cesarean section in early-onset sepsis is 0.103 (95% CI 0.041-0.258), and equally revealing is that cesarean section is one of the risk factors causing neonatal early-onset sepsis. The relationship between premature birth and early-onset sepsis mainly consists of the following: Firstly, due to immature function and development of various organs, poor developmental of skin and mucous membranes, lung function, and digestive tract, coupled with less protective antibodies, IgG transferred through maternal placental, and less self-generated IgA and IgM. The premature infants cannot effectively resist the invasion of exotic microorganism, which leads to the occurrence of sepsis. Secondly, many preterm births may have intrauterine infections. Premature rupture of the membranes and amnionitis are factors leading to premature birth with some infants developing intrauterine infection and sepsis in the uterus. The appearance of sepsis in preterm infants is higher than in full-term infants of normal weight. The OR value for premature birth of neonatal early-onset sepsis is 0.059 (95% CI = 0.010-0.329).

Conclusions

Neonatal jaundice is a common global problem, and the reason is very complex. Each year, in the United States, about 60-70% of newborns have clinical jaundice[12]. Neonatal jaundice in Asians is significantly higher than that in Caucasians. Neonatal jaundice occurs earlier, rises quickly with dissipated delay and highly conjugated bilirubin. Hemolytic diseases in neonates with ABO blood group incompatibility, G6PD, low birth weight and sepsis are considered as the main reason that lead to pathologic jaundice[13,14]. Shamir et al[15] reported that gram-negative bacilli can cause elevated liver enzymes and cholestasis of premature infant. Tiker et al (2006) also reported that in neonates with early-onset elevated conjugated bilirubin, the blood cultures are positive in 35.7% of patients[16]. Recently, Shahian et al[17] conducted urine test on 120 neonates with jaundice and pointed out that, in 12.5% of these newborns, had urinary tract infections, but none of newborns in the control group without jaundice had urinary tract infection. The neonatal jaundice diagnosis and the interventions in this study refer to the following: at gestational age greater than or equal to 35 weeks with weight greater than or equal to 2500 g, reference indicators were based on the guideline of neonatal jaundice and intervention published in 2004 by the American Academy of Pediatrics[18]. For the newborns with gestational age less than 35 weeks and birth weight less than 2500 g, it refers to the guidelines of jaundice diagnosis and intervention of premature birth and low birth weight infants for treatment [19]. Data were processed by logistic regression analysis and a conclusion was drawn. The OR value of jaundice performance of neonatal early onset sepsis was 0.092 (95% CI 0.021-0.404), indicating that jaundice is one of the major clinical manifestations of early-onset sepsis in newborns. It was recommended that caregivers

should be highly vigilant when testing for neonatal jaundice associated with risk factors, while blood samples were cultured.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Lee SY, Park KH, Jeong EH, Oh KJ, Ryu A, Park KU. Relationship between maternal serum C-reactive protein, funisitis and early-onset neonatal sepsis. J Korean Med Sci 2012; 6: 674-680.
2) Neonatology Group of Paediatrics Society, Chinese Medical Association. Diagnostic and treated program of neonatal sepsis. Chinese J Pediatr 2003; 41: 897-899.
3) Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, Jha P, Campbell H, Walker CF, Cibulskis R, Eisele T, Liu L, Mathers C; Child Health Epidemiology Reference Group of WHO and UNICEF. Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet 2010; 375: 1969-1987.
4) Hyde FB, Hilger TM, Reingold A, Farley MM, O'Brien KL, Schuchat A; Active Bacterial Core surveillance (ABCs) of the Emerging Infections Program Network. Trends in incidence and antimicrobial resistance of early-onset sepsis: population-based surveillance in San Francisco and Atlanta. Pediatrics 2002; 110: 690-695.
5) Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, Lemons JA, Donovan EF, Stark AR, Tyson JE, Oh W, Bauer CR, Korones SB, Shankaran S, Laptook AR, Stevenson DK, Papile LA, Poole WK. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics 2002; 110(2 Pt 1): 285-291.
6) Mannan MA, Jahan N, Dey SK, Uddin MF, Ahmed S. Maternal and foetal risk factor and complication with immediate outcome during hospital stay of very low birth weight babies. Mymensingh Med J 2012; 4: 639-647.
7) Salem SY, Sheiner E, Zmora E, Vardi H, Shoham-Vardi I, Mazor M. Risk factors for early neonatal sepsis. Arch Gynecol Obstet 2006; 274: 198-202.
8) WHO. Managing newborn problems: a guide for doctors, nurses, and midwives. WHO Library Cataloguing-in-Publication Data 2003.
9) Agrawal S, Agrawal BM, Khurana K, Gupta K, Ansari KH. Comparative study of immunoglobulin G and immunoglobulin M among neonates in caesarean section and vaginal delivery. J Indian Med Assoc 1996; 94: 43-44.
10) Boutsikou T, Malamitsi-Puchner A. Caesarean section: impact on mother and child. Acta Paediatr 2011; 100: 1518-1522.
11) Wilmink FA, Hukkelhoven CW, Lunshof S, Mol BW, van der Post JA, Papatsonis DN. Neonatal outcome following elective cesarean section beyond 37 weeks of gestation: a 7-year retrospective analysis of a national registry. Am J Obstet Gynecol 2010; 202: 250.e1-8.
12) Dennery PA, Rhine WD, Stevenson DK. Neonatal jaundice--what now? Clin Pediatr (Phila) 1995; 34: 103-107.
13) Ho NK. Neonatal jaundice in Asia. Baillieres Clin Haematol 1992; 5: 131-142.
14) Setia S, Villaveces A, Dhillon P, Mueller BA. Neonatal jaundice in Asian, white, and mixed-race infants. Arch Pediatr Adolesc Med 2002; 156: 276-279.
15) Shamir R, Maayan-Metzger A, Bujanover Y, Ashkenazi S, Dinari G, Sirota L. Liver enzyme abnormalities in gram-negative bacteremia of premature infants. Pediatr Infect Dis J 2000; 19: 495-498.
16) Tiker F, Tarcan A, Kilicdag H, Gurakan B. Early onset conjugated hyperbilirubinemia in newborn infants. Indian J Pediatr 2006; 73: 409-412.
17) Shahian M, Rashtian P, Kalani M. Unexplained neonatal jaundice as an early diagnostic sign of urinary tract infection. Int J Infect Dis 2012; 16: e487-490.
18) Mehl AL. Intervention recommendations for neonatal hyperbilirubinemia. Pediatrics 2004; 114: 322-323.
19) Martin RJ, Fanaroff AA. Neonatal-Perinatal Medicine: diseases of the fetus and infat. 8th Edition. Oversea Publishing House, 2005.