

Is Maternal Hypertension a Reducing Factor for Intraventricular Hemorrhage in Iranian Preterm Newborns?

Mandana Kashaki¹; Maryam Saboute¹; Maryam Esmaeili Allafi², *Elahe Norouzi³

¹ Shahid Akbarabadi Clinical Research Development Unit (ShACRDU), School of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran.

² Department of Pediatrics, School of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran.

³ Department of Pediatrics, Pediatric growth and development research center, School of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran.

Abstract

Background: Hypertensive disorders of pregnancy including preeclampsia can be associated with preterm birth and infant mortality and morbidity. It seems that intraventricular hemorrhage (IVH) in preterm neonates born to hypertensive mothers is less common compared to the other ones. In this study, we assessed the relationship between hypertensive disorders of pregnant mothers and the incidence of intraventricular hemorrhage in preterm neonates weighing less than 1500 grams.

Methods: In this case-control study, 305 singleton preterm neonates with a birth weight less than 1500 g were entered. The presence of IVH in all preterm neonates was assessed using brain ultrasonography and its correlation to hypertensive disorders of their mothers were evaluated.

Results: The prevalence of preeclampsia in mothers with and without pre pregnancy hypertension was 40%, and 15.09% respectively. The prevalence of IVH in preterm neonates was 26.9% (n=82). The incidence of IVH in preterm neonates of mothers with and without preeclampsia was 16.07%, and 29.31%, respectively (p=0.028). The prevalence of IVH in preterm neonates of mothers with hypertension and without hypertension was 12.5% and 29.05%, respectively (p=0.018). Preterm neonates with IVH had a lower mean birth weight, smaller gestational age and lower Apgar scores compared to preterm neonates without IVH with p values of <0.001, <0.001 and <0.01, respectively.

Conclusion: Hypertensive disorders of pregnancy increase the risk of preterm delivery, but the incidence of IVH in preterm neonates weighing less than 1500 gr is lower in infants born to mothers with hypertension including preeclampsia compared to those born to non-hypertensive mothers. And also lower gestational age, birth weight, and Apgar scores were important predicting factors for IVH in preterm neonates.

Key Words: Infant, Intraventricular hemorrhage, Hypertension, Low apgar score, Low birth weight, Low gestational age, Newborn, Pediatrics, Preeclampsia, Prematurity, Preterm Neonates.

* Please cite this article as: Kashaki M; Saboute M; Esmaeili Allafi M, Norouzi E Is Maternal Hypertension a Reducing Factor for Intraventricular Hemorrhage in Iranian Preterm Newborns? Int J Pediatr 2022; 10 (8):16469-16476. DOI: **10.22038/ijp. 2022.63523.4840**

*Corresponding Author:

Elahe Norouzi, Department of Pediatrics, Pediatric growth and development research center, School of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran. Email: elahenorouziimd@gmail.com

Received date: Feb.06,2022; Accepted date:Aug.05,2022

1- INTRODUCTION

Intraventricular hemorrhage (IVH) is one of the most common complications and life-threatening events which are associated with high morbidity and mortality in premature infants (1). Since the blood vessels of the brain in preterm neonates are primitive immature ones, they are very fragile and may easily rupture and cause severe damages to the brain (1, 2). The incidence of IVH in premature infants weighing less than 1500 g is approximately 25% (3), but as for extremely preterm neonates weighing 500 to 750 g it occurs in nearly 45% of infants (4). IVH can be associated with adverse neurologic sequelae in premature infants, including cerebral palsy, mental retardation, seizures, behavioral or cognitive disabilities (5, 6). Some studies have reported that premature infants with IVH have significantly lower survival rates compared to those without IVH (2, 7). Therefore, identification of predicting factors for IVH is very important for the diagnosis and treatment of the disease. Several factors including genetic and thrombophilic disorders, intrapartum factors, premature infants with respiratory distress syndrome (RDS), cardiovascular factors such as fluctuations in blood pressure are considered as the possible risk factors for IVH (8-10). Some studies have demonstrated that very low birth weight infants, lower gestational age, low Apgar scores, long-term mechanical ventilation, pneumothorax, type of delivery, presence of seizures, thrombocytopenia, RDS and infection are important predicting risk factors for IVH in preterm neonates; however, debatable results are available (1, 9, 10).

Hypertensive disorders of pregnancy including preeclampsia are among the leading causes of maternal mortality and morbidity and subsequently premature births and perinatal morbidity and mortality (11). Elevated blood pressure in

pregnancy may represent chronic hypertension which is occurring before 20 weeks of gestation or persisting more than 12 weeks after delivery, gestational hypertension (occurring after 20 gestation weeks), preeclampsia, or preeclampsia superimposed on chronic hypertension. Preeclampsia is characterized by hypertension (a systolic BP of at least 140 mm Hg or a diastolic BP of at least 90 mm Hg on at least two occasions, taken at least four hours apart), and proteinuria or one of the following features, which are diagnostic when they develop in the setting of new-onset hypertension after 20 gestation weeks: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, cerebral or visual symptoms (12, 13)

Several lines of studies have considered preeclampsia as a preventive factor for IVH, but the exact mechanism remains unclear. It may be partly related to magnesium sulfate treatment in mothers with preeclampsia, which acts as a neuroprotective agent in their neonates (7). However, it is not obvious that whether preeclampsia itself has protective effects against IVH or not; and there are few studies considering the effect of pregnancy-induced hypertension and preeclampsia on IVH incidence in premature infants; and we found no such work in Iran, thus, this study was designed to find any relationship between maternal preeclampsia and IVH in preterm infants weighing less than 1500 grams.

2- MATERIALS AND METHODS

2-1. Study design and population

In this observational case-control study, all singleton preterm newborns with a birth weight less than 1500 g and gestational age of 34 weeks or lower born at Akbar-Abadi Hospital, Tehran, Iran during 2016-2017 entered the study.

2-2. Inclusion and exclusion criteria

Singleton preterm newborns with a birth weight less than 1500 g and gestational age of 34 weeks or lower were included in the study. Neonates with perinatal asphyxia, pneumothorax, major congenital anomalies, symmetric IUGR, thrombocytopenia and coagulation disorders; and neonates died within the first 72 hours of life before undergoing brain ultrasonography were excluded from the study.

2-3. Clinical interventions

Demographic data of all newborns including gestational age, sex, and birth weight, as well as type of delivery, and Apgar scores of 1 and 5 minutes were recorded. Brain ultrasonography was performed by an expert sonographers as the screening evaluation of the seventh day of life according to AAP protocol for all singleton premature newborns with a birth weight less than 1500 g; and reports were recorded. The history of hypertension prior to pregnancy or during an earlier pregnancy and the presence of preeclampsia in mothers were recorded. Eventually, the relationship between a previous hypertension with the occurrence of preeclampsia in mothers and the incidence of IVH in preterm neonates was evaluated.

2-4. Data analysis

Demographic and clinical characteristics of patients were reported as means \pm standard deviation for quantitative variables and as percentage for categorical qualitative ones. An independent student t-test was also considered to compare the means of parametric data between IVH and non-IVH groups. Chi-square test was applied to compare the qualitative variables. The data was analyzed using SPSS software (version 19) and p-values less than 0.05 were assumed to be statistically meaningful.

2-5. Ethical considerations

The research was approved primarily by the ethics committee of Iran University of Medical Sciences with the code number of IR.IUMS.REC.1397.1018. The objectives of the study were explained to the parents of all participants and written informed consent was obtained. They were also clarified that the data would be kept confidential and analyzed anonymously.

3- RESULTS

3-1. Demographic information

A total of 305 preterm neonates enrolled in the study. Demographic characteristics of all patients are shown in **Table 1**. Among 305 preterm newborn infants (51% boys and 49% girls), mean \pm SD gestational age was 29.26 ± 2.53 weeks, and mean \pm SD of neonates' birth weight was 1157.09 ± 256.24 g. From among the preterm neonates, 78.6% were born by cesarean section method, while 21.4% (n=62) were born by vaginal delivery. Apgar scores of 1 and 5 minutes were 6.46 ± 1.97 and 8.13 ± 1.51 , respectively (**Table 1**).

In total, 46 (18.4%) mothers had preeclampsia. Demographic and clinical data of neonates born from mothers with and without preeclampsia are presented in **Table 2**. The neonates of mothers with preeclampsia had significantly lower mean birth weight compared to the others (1083.18 ± 255.33 g vs 1173.48 ± 254.05 g; $p=0.018$). None of the mothers with preeclampsia had vaginal delivery ($p<0.001$). There were no significant difference in neonatal sex and gestational age and Apgar scores between neonates of mothers affected with preeclampsia and the others (**Table 2**).

3-2. Maternal hypertension and IVH

Overall, 40 (13.1%) out of 305 mothers had high blood pressure. Comparison of the demographic and basic clinical characteristics of neonates from mothers

with and without preeclampsia is presented in **Table 2**. Neonates born from mothers with preeclampsia had significantly lower birth weights compared to others (1083.18 ± 255.33 g vs 1173.48 ± 254.05 g; $p=0.018$). The mean Apgar score of 5 minute of the Hypertensive group was significantly higher than that of the others (8.62 ± 0.77 g vs 8.05 ± 1.59 g; $p=0.026$).

None of the mothers with preeclampsia underwent normal vaginal delivery, while 23.4% of normotensive mothers had vaginal delivery ($p<0.001$). There was no significant difference in sex, gestational age, and Apgar score of 1 and 5 minutes between neonates of hypertensive and normotensive mother groups.

Table-1: Clinical and basic demographic characteristics of preterm neonates

Parameters		Results
Sex	Boys	153 (51%)
	Girls	147 (49%)
Gestational age (weeks)		29.26 ± 2.53
Birth weight (g)		1157.09 ± 256.24
Delivery type	Cesarean	228 (78.6%)
	Vaginal delivery	62 (21.4%)
	Apgar 1	6.64 ± 1.97
	Apgar 5	8.13 ± 1.51
Preeclampsia	Yes	56 (18.4%)
	No	249 (81.6%)
IVH	Yes	82 (26.9%)
	No	223 (73.1%)
Hypertension	Yes	40 (13.1%)
	No	265 (86.9%)

Table-2: Clinical characteristics of preterm neonates born to mothers with and without preeclampsia

Parameters		Preeclampsia		p-value
HTN		Yes (56)	No (249)	
Previous HTN		16 (40%)	24 (60%)	<0.001
No previous HTN		40 (15.09%)	225 (84.9%)	
Sex	Boys	21 (39.62%)	132 (53.44%)	0.068
	Girls	32 (60.37%)	115 (46.55%)	
Delivery type	Cesarean	55 (23.4%)	173 (73.61%)	<0.001
	Vaginal delivery	0	62 (100%)	
	Gestational age (Weeks)	29.37 ± 2.45	29.24 ± 2.56	0.72
	Birth weight (g)	1083.18 ± 255.33	1173.48 ± 254.05	0.018
	Apgar 1	6.47 ± 1.78	6.45 ± 2.02	0.94
	Apgar 5	8.27 ± 1.16	8.1 ± 1.57	0.48

The prevalence of intraventricular hemorrhage in preterm neonates was 26.9% ($n=82$). Comparison of the clinical

and basic demographic characteristics between preterm neonates with IVH and without IVH is summarized in **Table 3**.

Table-3: Comparison of the clinical and basic demographic characteristics between preterm neonates with and without IVH

Parameters		Value		p-value
IVH		Yes (n=82)	No (n=223)	-
Sex	Boys	43 (52.43%)	110 (49.32%)	0.43
	Girls	39 (47.56%)	108 (48.43%)	
Delivery type	Cesarean	61 (78.2%)	167 (78.77%)	0.51
	Vaginal delivery	17 (20.73%)	45 (21.22%)	
	Gestational age (Weeks)	28.12 ± 2.46	29.69 ± 2.43	<0.001
	Birth weight (g)	1011.64 ± 245.38	1211.06 ± 239.06	<0.001
	Apgar 1	5.81 ± 2.11	6.68 ± 1.88	0.001
	Apgar 5	7.57 ± 1.74	8.33 ± 1.37	<0.001
Preeclampsia	Yes	9 (16.07%)	47 (83.92%)	0.028
	No	73 (29.31%)	176 (70.68%)	
HTN	Previous HTN	5 (12.5%)	35 (87.5%)	0.018
	No previous HTN	77 (29.05%)	188 (70.94%)	

There was no significant difference in the frequency of sex and delivery type between the two groups. Significant differences were observed in the mean of gestational age, birth weight, Apgar 1 and 5, as well as the prevalence of preeclampsia between the two groups. The mean gestational age of preterm neonates with IVH was significantly lower than that of the non-IVH group (28.12 ± 2.46 vs 29.69 ± 2.43 weeks; $p < 0.001$). Preterm neonates with IVH had lower mean birth weights compared to non-IVH cases (1011.64 ± 245.38 vs 1211.06 ± 239.06 g; $p < 0.001$). Non-IVH cases had a significantly higher Apgar score mean scores at one and 5 minutes (6.68 ± 1.88 and 8.33 ± 1.37, respectively) compared to IVH group (5.81 ± 2.11 and 7.57 ± 1.74, respectively) ($p < 0.01$).

The incidence of IVH in preterm neonates of mothers with preeclampsia was 16.07%, while it was estimated as 29.31% in preterm neonates of mothers without preeclampsia ($p = 0.028$). There was a significant difference in the prevalence of IVH in preterm neonates of mothers with a history of previous hypertension and without hypertension ($p = 0.018$). The prevalence of IVH in preterm neonates of

mothers with and without preeclampsia were 16.07% and 29.31%, respectively. Accordingly, the prevalence of IVH in preterm neonates of mothers with and without previous hypertension were 12.5% and 29.05%, respectively.

4- DISCUSSION

In this study, we assessed the relationship between maternal hypertension and the incidence of IVH in preterm neonates weighing less than 1500 grams. Our data revealed that the prevalence of preeclampsia in mothers with previous hypertension was 40%, while its prevalence in mothers without previous hypertension was 15.09%. Recently, Gudeta et al., (14) have demonstrated that the prevalence of pregnancy induced hypertension was 7.9%; of which 15.2% were gestational hypertension, 36.4% were mild preeclampsia, and 45.5% were severe preeclampsia. In another cohort study, Subki et al., (15) found that the incidence of preeclampsia in mothers with previous hypertension is 54.9%. Therefore, these data indicate that previous hypertension is a major risk factor for the possibility of preeclampsia in pregnant mothers.

Our data also revealed that the overall incidence of IVH in preterm neonates was 26.88%. Further analyses demonstrated that the incidence of IVH in preterm neonates of mothers with preeclampsia was 16.07%, whereas it was 29.31% in mothers without preeclampsia. Nine (10.97%) out of 82 neonates with IVH were born from mothers with preeclampsia. This data suggests that the incidence of neonatal IVH in mothers without preeclampsia is higher than that in mothers with preeclampsia; however, the underlying mechanism is not known. More recently, Morsing et al., (11) have demonstrated that maternal preeclampsia is associated with lower rates of IVH in preterm neonates (2% vs 11%). Likewise, we found that the mean of birth weight in neonates of mothers with preeclampsia was significantly lower than that of those in mothers without preeclampsia (1083.18 g vs 1173.48 g). In the same line, Morsing et al., (11) reported that the preeclampsia group had a lower median birth weight than the background group (795 g vs 890 g). In another study, Mendola et al., (16) showed that the incidence of IVH in preterm infants of mothers with preeclampsia and normal blood pressure was 4.7% and 4.4%, respectively. Paul et al., (7) didn't find any significant difference in IVH incidence and mortality rate between infants born to mothers with preeclampsia as compared to infants born to mothers without preeclampsia. It may be partly due to magnesium sulfate treatment in mothers with preeclampsia, which acts as a neuroprotective agent in their neonates (7, 17).

Our data have demonstrated that the prevalence of IVH in neonates of mothers without pregnancy hypertension is significantly higher than that in mothers with pregnancy hypertension. As noted in **Table 3**, 12.5% of neonates with pre-pregnancy maternal hypertension (5 out of 40), had IVH; which compared to 29.05% (77 out of 265) neonates without pre-

pregnancy maternal hypertension, and considering the statistically significant p-value of 0.018, previous hypertension may be a reducing factor in IVH occurrence in preterm neonates. In support of this finding, Perlman et al. (18) reported that the incidence of IVH in neonates of mothers with pregnancy-induced hypertension is lower than that in mothers without hypertension (16% vs 30%). A previous study revealed that IVH is less frequent in infants of mothers with preeclampsia compared with the controls (4.8% vs 20.5%) (19). Therefore, these findings indicate a significantly lower incidence of IVH in approximately 50% of preterm neonates from mothers with pregnancy-induced hypertension as compared with its incidence in infants born from mothers without hypertension.

We also found that IVH was significantly associated with decreased gestational age, birth weight, and Apgar scores. Preterm neonates with IVH had significantly lower gestational age, birth weight and Apgar scores compared to preterm neonates without IVH. Therefore, these parameters can be considered as a significant predicting factor for IVH. Some studies considered the gestational age, birth weight and Apgar scores as important risk factors for the prediction of IVH in preterm neonates. For example, Perlman et al., (18) identified that gestational age and birth weight are significant predicting factors of IVH. Jodeiry et al., (20) reported that cases with IVH had significantly lower gestational age and Apgar scores than cases without IVH. They also found that vaginal delivery was significantly higher in cases with IVH, while in our study there was no significant difference in the frequency of vaginal delivery between the two groups. In another study, Khalessi et al., (21) identified that gestational age, birth weight, mode of delivery, maternal hypertension and preeclampsia, pneumothorax, and ventilator therapy are important risk factors for the prediction of

IVH in preterm neonates. In another study, Lee et al., (22) reported that metabolic acidosis and inotrope use increase the risk of IVH in neonates by 6.94 and 3.70 folds, respectively. Yet another study showed that lower gestational age and birth weight increase the risk of IVH by 3.72 and 3.42 times, respectively (23). Therefore, according to the accomplished studies and current research, pregnancy hypertension is significantly associated with preeclampsia, which can substantially increase the risk of preterm delivery.

Surprisingly, none of the mothers with pre-eclampsia in the study had vaginal delivery. It may be due to supererogatory indications for cesarean section delivery in our maternity hospitals, which should be taken under consideration in revising related regional protocols. Although the center, which the study was performed in, was a referral one with a high rate of emergent and premature delivery.

4-1. Limitations of the study

This study mainly assessed the effects of maternal hypertension and pre-eclampsia on reducing IVH, and the influence of drugs used for mothers before, during and after delivery was not assessed; this may be subject of further studies.

5- CONCLUSION

Hypertensive disorders of pregnancy increase the risk of preterm delivery, but incidence of IVH in preterm neonates weighing less than 1500 gr was lower in infants born to mothers with hypertension including preeclampsia compared to non-hypertensive mothers. And also preterm neonates with IVH had significantly lower gestational age, birth weight and Apgar scores compared with preterm cases without IVH.

6- ACKNOWLEDGEMENTS

The authors would like to express their gratitude to Shahid Akbarabadi Clinical Research Development Unit (ShACRDU), Iran University of Medical Sciences (IUMS), Tehran, Iran for their cooperation in this study.

7- CONFLICT OF INTEREST

None.

8- REFERENCES

1. Ballabh P. Intraventricular Hemorrhage in Premature Infants: Mechanism of Disease. *Pediatr Res.* 2010; 67:1–8.
2. Whitelaw A. Intraventricular hemorrhage and post haemorrhagic hydrocephalus: pathogenesis, prevention and future interventions. *Semin Neonatol.* 2001; 6:135-46.
3. Szpecht D, Szymankiewicz M, Nowak M, Gadzinowski J. Intraventricular hemorrhage in neonates born before 32 weeks of gestation—retrospective analysis of risk factors. *Childs Nerv Syst.* 2016; 32:1399–404.
4. Wilson-Costello D, Friedman H, Minich N, Fanaroff AA, M H. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. *Pediatrics.* 2005; 115:997-1003.
5. Murphy BP, Inder TE, Rooks V, Taylor GA, Anderson NJ, Mogridge N, Horwood LJ, Volpe JJ. Post Haemorrhagic ventricular dilatation in the premature infant: natural history and predictors of outcome. *Arch Dis Child Fetal Neonatal Ed.* 2002; 87:F37–F41.
6. Pinto-Martin JA, Whitaker AH, Feldman JF, Van Rossem R, Paneth N. Relation of cranial ultrasound abnormalities in low-birthweight infants to motor or cognitive performance at ages 2, 6, and 9 years. *Dev Med Child Neurol.* 1991; 41:826–33.
7. Paul DA, Kepler J, Leef KH, Siscione A, Palmer C, Stefano JL. Effect of

- preeclampsia on mortality, intraventricular hemorrhage, and need for mechanical ventilation in very low-birth-weight infants. *Am J Perinatol.* 1998; 15:381-6.
8. Volpe JJ. Intraventricular hemorrhage in the premature infant--current concepts. Part I. *Ann Neurol.* 1989; 25:3-11.
9. Antoniuk S, da Silva RV. Periventricular and intraventricular hemorrhage in the premature infants. *Rev Neurol.* 2000; 31:238-43.
10. Ballabh P, Braun A, Nedergaard M. Anatomic analysis of blood vessels in the germinal matrix, cerebral cortex, and white matter in developing infants. *Pediatr Res.* 2004; 56:117-24.
11. Morsing E, Maršál K, Ley D. Reduced Prevalence of Severe Intraventricular Hemorrhage in Very Preterm Infants Delivered after Maternal Preeclampsia. *Neonatology* 2018; 114:205-11.
12. American College of Obstetricians and Gynecologists. Hypertension in pregnancy. <http://www.acog.org/Resources-And-Publications/TaskForce-and-Work-Group-Reports/Hypertension-in-Pregnancy>. Accessed November 23, 2015.
13. Leeman L, Dresang LT, Fontaine P. Hypertensive Disorders of Pregnancy. *Am Fam Physician.* 2016; 93(2):121-127.
14. Gudeta TA, Regassa TM. Pregnancy Induced Hypertension and Associated Factors among Women Attending Delivery Service at Mizan-Tepi University Teaching Hospital, Tepi General Hospital and Gebretsadik Shawo Hospital, Southwest, Ethiopia. *Ethiop J Health Sci.* 2019; 29:831-40.
15. Subki AH, Algethami MR, Baabdullah WM, Alnefaie MN, Azan Bagi MA, Alsolami RM, et al. Prevalence, Risk Factors, and Fetal and Maternal Outcomes of Hypertensive Disorders of Pregnancy: A Retrospective Study in Western Saudi Arabia. *Oman Med J.* 2018; 33:409-15.
16. Mendola P, Mumford SL, Männistö TI, Holston A, Reddy UM, Laughon SK. Controlled Direct Effects of Preeclampsia on Neonatal Health after Accounting for Mediation by Preterm Birth. *Epidemiology.* 2015; 26:17-26.
17. Ehsanipour F, Norouzi E, Khosravi N, Mirfakhraee H. Serum Magnesium Levels in Neonatal Jaundice: Is There any Correlation Between Hypermagnesemia and Moderate to Severe Hyperbilirubinemia in Term Newborns? *J Compr Ped.* 2020 May; 11(2):e94278.
18. Perlman JM, Risser RC, Gee JB. Pregnancy-induced hypertension and reduced intraventricular hemorrhage in preterm infants. *Pediatr Neurol.* 1997; 17:29-33.
19. Shah DM, Shenai JP, Vaughn WK. Neonatal outcome of premature infants of mothers with preeclampsia. *J Perinatol.* 1995; 15:264-7.
20. Jodeiry B, Heidarzadeh M, Sahmani-Asl S, Hoseini M, Jawaheri Zadeh H, Eliasi S, Abedini K. Study of intraventricular hemorrhage in VLBW neonates admitted in Al-Zahra Hospital, Tabriz, Iran. *Niger J Med.* 2012; 21:92-7.
21. Khaleesi N, Farahani Z, Shariat M, Rezaeizadeh G. Risk factors of intracranial hemorrhage in premature neonates. *Acta Med Iran.* 2014; 52:687-9.
22. Lee JY, Kim HS, Jung E, Shim GH, Lee HJ, Lee JA, Choi CW, Kim EK, Kim BI, Choi JH. Risk Factors for Periventricular-Intraventricular Hemorrhage in Premature Infants. *J Korean Med Sci.* 2010; 25:418-24.
23. Khodapanahandeh F, Khosravi N, Larijani T. Risk factors for intraventricular hemorrhage in very low birth weight infants in Tehran, Iran. *Turk J Pediatr.* 2008; 50:247-52.