The Effect of Heavy Metals and Trace Elements in the Meconium on Preterm Delivery of Unknown Etiology

Mekonyumdaki Ağır Metallerin ve Eser Elementlerin Etiyolojisi Bilinmeyen Erken Doğuma Etkisi

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ABSTRACT Objective: Prematurity is an important etiologic factor for perinatal mortality and morbidity. In our country, preterm births and complications of prematurity account for 26% of perinatal mortality. There are many maternal, fetal or placental, genetic and environmental etiologic factors that cause prematurity. There have been no studies to show an association between preterm delivery of unknown etiology and exposure to heavy metals and trace elements at toxic levels in meconium. The purpose of this study is to measure the levels of heavy metals (lead, cadmium) and trace elements (zinc, iron, copper) in meconium samples and to understand their associations with preterm delivery of unknown etiology. **Material and Methods:** The levels of heavy metals and trace elements in the meconiums of 810 term or preterm infants with known and unknown etiology for being preterm were measured with a flame atomic absorption spectrophotometer. **Results:** Lead and cadmium were detected in all meconium samples. Heavy metal and trace element levels in meconium were significantly higher in preterms of unknown and known etiology for being preterm compared to term infants (for all $p<0.0001$). Lead levels in meconium were significantly higher in preterm of unknown etiology compared to preterm of known etiology in posthoc analysis with Bonferroni corrected Mann Whitney U test. **Conclusion:** These results may suggest that lead levels in meconium samples are higher in preterm newborns especially with unknown etiology compared to term newborns. Therefore, we suggest that preterm delivery of unknown etiology may be decreased by decreasing air pollution.

Key Words: Cadmium; lead; meconium

ÖZET Amaç: Prematürite perinatal mortalite ve morbidite için önemli bir risk faktörüdür. Ülkemizde erken doğumlar ve prematüritenin komplikasyonları perinatal mortalitenin %26'sından sorumludur. Prematüriteye neden olan çok sayıda maternal, fötal veya plasental, genetik ve çevresel etiyolojik faktör vardır. Etiyolojisi bilinmeyen erken doğumla mekonyumdaki toksik düzeylerde ağır metallere ve eser elemetlere maruziyet arasındaki iliskiyi gösteren hiçbir çalısma yoktur. Bu çalısmanın amacı mekonyum örneklerinde ağır metal (kursun, kadmiyum) ve eser element (çinko, demir, bakır) düzeylerini ölçmek ve etiyolojisi bilinmeyen erken doğumla ilişkilerini anlamaktır. **Gereç ve Yöntemler:** Etiyolojisi bilinen ve bilinmeyen 810 term veya preterm bebeğin mekonyumlarındaki ağır metaller ve eser elementler alevli atomik absorbsiyon spektrofotometresi ile ölçüldü. **Bulgular:** Tüm mekonyum örneklerinde kursun ve kadmiyum saptandı. Mekonyumdaki ağır metal ve eser element düzeyleri etiyolojisi bilinen ve bilinmeyen pretermlerde term bebeklere göre belirgin olarak yüksekti (tümü için $p<0,0001$). Tukey testiyle post-hoc analizde sadece mekonyumdaki kursun düzeyleri etiyolojisi bilinmeyen pretermlerde etiyolojisi bilinen pretermlere göre belirgin olarak yüksekti. **Sonuç:** Bu sonuçlar mekonyum örneklerindeki kursun düzeylerinin preterm yenidoğanlarda özellikle nedeni bilinmeyen preterm doğumlarda term yenidoğanlara göre daha yüksek olduğunu düsündürebilir. Bu yüzden hava kirliliği azaltılarak nedeni belli olmayan premature doğumların azaltılabileceği düşünülebiliriz.

Anahtar Kelimeler: Kadmiyum; kurşun; mekonyum

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Prematurity is an important etiologic factor for perinatal mortality and morbidity.[1] In our country, preterm births and complications of prematurity account for 26% of perinatal mortality.[2] There are many maternal, fetal or placental, genetic and environmental etiologic factors that cause prematurity. In recent years, one of the most frequently discussed etiologic factors for prematurity is environmental pollution. Many studies suggest that environmental pollution, especially air pollution, is closely related to prematurity.[3-8] Two further studies suggest an association between prematurity and maternal blood lead or meconium mercury contents.[9,10]

Nutritional elements and toxic substances are transported from mother to fetus via blood circulation, and excessive levels of toxins and certain toxic metals harm the fetus. The levels of trace elements and toxic metals in fetal blood may not reflect the degree of fetal exposure to toxic metals or actual degrees of excess or deficiency of trace elements. Many substances processed by the fetus accumulate in the fetal intestine, thus meconium analysis may also be used to assess levels of fetal exposure to toxic metals and mineral content.[11-17] It has been suggested that, in dry meconium, concentrations of trace elements higher than 100 μg/g (0.01%) can indicate toxicity.[12] Replacing trace element deficiencies or detoxifying after toxic metal exposure pose significant challenges for the neonatologist in the first few weeks of an infant's life.[15]

Kocaeli is located in Western Anatolia and it is an industrial city that contains 17% of all firms and factories in Turkey. Turkey's largest shipyard and largest tire factory are in Kocaeli. In addition, there are numerous industrial factories, including petroleum, plastic, rubber, dye, chemistry, farming, drugs, iron, steel, copper, automobile spare parts, cable, glass, lime and ceramic factories. These foundations are stationed alongside the highway between Europe and Asia. Moreover, the highway, autobahn, and railroad connecting Europe and Asia are located in this city.

In this study, the levels of toxic metals (lead, cadmium) and trace elements (zinc, iron and copper) of preterm and term newborns were measured in meconium samples.

MATERIAL AND METHODS

The study was approved by the Kocaeli University, Faculty of Medicine Ethics Committee (Ethic Committee number is 108/15/20). Term and premature infants who were born at Kocaeli University Hospital and/or hospitalized in the newborn intensive care unit between November 2006 and February 2009 were included in the study group. Infants whose meconium samples could not be taken because of (1) early discharge (especially in normal spontaneous vaginal birth), (2) lack of parental permission, (3) insufficient meconium (especially in premature infants), and infants with congenital abnormalities were excluded. An approval form was signed by the parents. Risk factors for prematurity (fetal distress, multiple gestations, placental diseases, uterine abnormalities cervical insufficiency, preeclampsia/eclampsia, maternal diseases, drug and cigarette use during pregnancy, infection, close delivery, premature rupture of membranes, polyhydramnios and oligohydramnios) were investigated in the form completed for each infant. General infant characteristics, including gender, gestational age, type of birth and meconium collection time as well as demographic features of parents (age, education and social insurance status, occupation, income, number of people living together in the same house) were recorded.

The infants were divided into three groups:

1- Preterm delivery of unknown etiology,

2- Preterm delivery of known etiology,

3- Term delivery.

Last menstrual period and the new Ballard score were used to determine the gestational age. While evaluating the risk factors for prematurity, all placental diseases (placenta previa, etc.), uterine anomalies and cervical insufficiency were identified as 'gynecological diseases' in the statistics. Medical records of mothers were used for the diagnosis of gynecological diseases, preeclampsia/eclampsia, polyhydramnios, and oligohydramnios. Urinary tract infection and vaginitis history was obtained from the mother for diagnosis of maternal infection. In addition, acute phase reactants (white cell count and levels of C-reactive protein) and the any antibiotic therapy taken were recorded from the mothers' files. If the interval between this gestation and the prior gestation was less than two years, "close delivery" was assumed.

Meconium collection time was recorded. The meconium was usually collected in the first or second postnatal days for term infants while it was collected later for preterm infants. The latest meconium collection time was the sixth postnatal day of a 24-week gestational age infant.

Education levels of the parents were categorized in six groups: (1) illiterate, (2) literate, (3) primary school, (4) secondary school, (5) high school, and (6) university. Social insurance of parents were recorded as follows: (1) no security, (2) health security for the poor, called "green card" in Turkey, (3) social insurance institution, a kind of health security for private firms and workers, (4) pension fund, health security for government employees, (5) social insurance for artisans and the self-employed, and (6) private insurance.

Parent occupations were recorded based on their statements. Maternal occupations were grouped as follows: stay-at-home mom, officer or worker. Paternal and maternal occupations were classified according to their exposure levels to toxic metals as follows: low-risk (government employee, teacher, farmer, cook, doctor, etc.), medium-risk (construction worker, factory worker, engineer, etc.), high-risk (driver, worker in automotive industry or turnery, whitewasher, painter, furnisher, etc.) and very high-risk (metal worker, printer, chemist, scrap dealer, etc.).

In 2007, the Turkish Statistical Institute declared the monthly poverty level for a family of four to be 619 new Turkish liras. In this study, parental economical status was classified into two categories: low income level (fewer than 155 new Turkish liras monthly individual income) and middle or high income level.

Parents were grouped according to socioeconomic status by Barratt score (The Barratt Simplified Measure of Social Status). Tables in the Barratt score were used. The sum of the averaged education level points and occupation points of the parents were accepted as the Barratt score.

MECONIUM ANALYSIS

Meconium samples, which were taken with wooden pipe from diaper, were put in the nonmetal cups, quickly frozen and kept at -20ºC. Meconium levels of Pb, Cd, Zn, Cu, and Fe were determined in a flame atomic absorption spectrophotometer (Shimadzu AA- 680) at the biophysics laboratory of Cerrahpasa Medical Faculty. Measurements were based on a comparison with external standards. The standards were freshly prepared from standard stock metal solutions (Titrisol 1000 8 0.002 mg/l, Merck) immediately prior to analysis, and were used for initial calibration for each substance. These solutions were also used as internal quality standards. Hollow Cathode Lamp and Background Correction (with Deuterium Lamp) modes were selected for element analyses. Each result was corrected for the appropriate reagent used and matrix blanks. For the accuracy of trace element concentrations, each sample was measured twice for each element analysis and differences of <5% between two measurements were accepted. The result for each substance was expressed as nanograms per gram of dry meconium ηg/g).[18] Deionized water was used to clean the chamber and as a zero control for each analysis. The stock standard metal solutions for every metal (Merck, 1,000 mg/l) were used for positive controls and tested for every 25 samples, to ensure measurement reliability. Minimum detectable limits for Pb, Cd, Zn, Cu, and Fe were 0.045, 0.009, 0.037, 0.080 and 0.014 μg/ml, respectively. The recovery of trace elements (Zn, Fe and Cu) spiked in meconium ranged between 94.1% (92.4-96.7%) and 93-101% and the percent variance ranged around 2.6% (2.2-3.1%).[14-16] The recovery of heavy metals (Pb and Cd) spiked in meconium ranged between 100% and 102%. The inter-assay-coefficient of variability ranged between 0.34% and 8.9%; the intra-assay coefficient of variability ranged between 0.44% and 8.44%.[19-21] The precision, as relative standard deviation (RSD), was between 3.9% and 6.7% for Cd.[22]

The values of metal levels in meconium; were divided by birth weight in order to standardize the metal levels and were expressed as (ηg/g/kg).

STATISTICAL ANALYSIS

Statistical analysis was performed with the SPSS-13 program. Continuous variables were given as median (minimum-maximum) and mean + standard deviation; categorical variables were defined as percentages. Continuous variables were compared by Kruskal-Wallis analysis because the data were not normally distributed. Chi-square test was used for the categorical variables among three groups. Post-hoc analysis with Bonferroni corrected Mann-Whitney U test was used for continuous variables of three groups.

RESULTS

GENERAL CHARACTERISTICS AND DEMOGRAPHIC CHARACTERISTICS

The preterm delivery of unknown etiology and known etiology groups and the term birth group had statistically similar gender distributions. Median (min-max) values of gestational weeks in the preterm and term groups were 34 (24-36) and 38 (37-41) weeks, respectively. When prenatal risk factors were compared between the two groups, the rate of multiple gestations, placenta previa, preeclampsia, maternal infection, premature rupture of membranes, and oligohydramnios were higher in the preterm group (Table 1). The rate of Cesarean section was higher in the preterm group than in the term group. First and fifth minute Apgar scores were significantly lower in the preterm groups (Table 1). Two groups had statistically similar parent ages (Table 1). Barratt scores associated with socioeconomic status were found to be significantly lower in the preterm group (Table 1).

TOXIC METAL AND TRACE ELEMENT LEVELS IN MECONIUM

The toxic metals lead and cadmium were detected in all meconium samples. Zinc, iron and copper levels in meconium samples were higher than 100 μg/g in 809 (99.9%), 590 (72.8%) and 408 (50.4%) infants, respectively. The metal levels of both preterm groups were significantly higher than the metal levels of the term infants (for all $p<0.001$). In Post-Hoc analysis with Bonferroni corrected Mann Whitney U test, only lead levels in preterm deliveries of unknown etiology were higher than in preterm deliveries of known etiology ($p <0.0001$). The other heavy metal and trace element levels in preterm deliveries of unknown etiology were not significantly higher than in preterm deliveries of known etiology (for all $p >0.05$) (Table 2).

Corralation of the metal levels with gender of infants was not statistically significant ($p>0.05$).

DISCUSSION

The toxic metals lead and cadmium were detected in all meconium samples. Trace element levels were detected at toxic levels in most of the samples. Multiple gestation rate, placenta previa, preeclampsia, maternal infection, premature rupture of the membranes, and oligohydramnios were found to be higher in the preterm delivery of unknown etiology group, in accordance with previous studies.[1,22,23] Other prenatal risk factors (uterine anomaly, cervical insufficiency, maternal chronic diseases, maternal smoking) were insignificant. The reason for this may be due to a deficiency in their numbers.

Most admissions to the university hospital are risky pregnancies. This factor could explain the increased rate of Cesarean section in this study.

Socioeconomic status is associated with prematurity.[1,24-27] The following findings in this study show that socioeconomic status is also closely associated with prematurity as Barratt scores were lower in the premature groups.

Mean values of toxic metal and trace element levels in meconium were found to be higher in this study compared to other studies.[10,15-17] It is noteworthy that lead levels in meconium that were detected by Li et al. in Guiyu, an electronic waste recycling town in China, were remarkably lower than in our study and previous reports.[10,27]

There have been few studies investigating toxic metal and trace element levels in meconium.

TABLE 1: General characteristics of study groups.

	Preterm delivery of unknown etiology n=131	Preterm deliver of known etiology n= 176	Term n=503	p
Gestational age (week)				
<28	12	0		
28-31	15	28		
32-33	31	53		
34-36	73	95		
Sex F/M	52/79	93/83	266/237	0.022
Number of hospitalization	90	115	63	<0.001
Multiple gestations	0	99	28	<0.001
Fetal distress	3	4	16	>0.005
Placenta previa	0	16	7	<0.001
Uterine anomalies	0	0	1	>0.005
Cervical insufficiency		7	4	0.02
Preeclampsia	0	51	37	<0.001
Maternal chronic disease		41	14	>0.05
Maternal smoking	8	5	14	>0.005
Maternal infection	0	33	17	<0.001
Close delivery	0	16	12	0.014
Premature rupture of membranes	0	41	22	<0.001
Polyhydramnios	0	7	4	>0.005
Oligohydramnios	0	21	17	0.025
Cesarean section	100	155	388	0.006
Apgar (1. minute)*	8 (2-9)	8 (0-9)	8 (3-10)	<0.001
Apgar (5. minute)*	10 (0-10)	10(0-10)	10 (4-10)	<0.001
Birth weight (grams)*	2180 (570-3800)	2000 (870-4800)	3170 (1950-5000)	<0.001
Maternal age (years)*	28 (19-43)	27 (18-42)	28 (17-43)	>0.005
Paternal age (years)*	31(22-46)	31(19-58)	31(18-61)	>0.005
Barratt score*	24+11	23+11	27+14	0.01
Maternal occupation score	29+8	28+9	29+8.7	0.4
Paternal occupation score	16+8	16+8	17.6+9.4	0.8

Chi square test, * median (min-max) Kruskall-Wallis test was used.

TABLE 2: Meconium toxic metal and trace element levels in the preterm and term infants.

	Preterm delivery of unknown etiology	Preterm delivery of known etiology	Term	p[a]	P[b]
Lead	14.5 (5.2-73.8)	15.5 (5.8-43.2)	10.2 (4.6-27.1)	**<0.001**	**<0.0001**
Cadmium	1.08 (0.43-7.92)	1.31 (0.48-5.03)	0.78 (0.28-2.57)	**<0.001**	<0.05
Zinc	88.4 (30.5-498.3)	98.3 (29.1-361.9)	60.6(30.4-241.9)	**<0.001**	<0.05
Iron	50.8 (23-227.7)	59.6 (19.9-159.5)	34.8 (16.6-77.1)	**<0.001**	<0.05
Copper	44.8 (14.3-179.7)	51.6 (19.5-129.9)	31.4(10.2-59.3)	**<0.001**	<0.05

Values are median (min-max), metal levels are (ng/g/Kg). P[a] values are comparisons between term and preterm groups (Kruskal-Wallis H test was used). P[b] values are comparisons between preterm delivery of unknown etiology and preterm delivery of known etiology (Post-Hoc analysis with Bonferroni corrected Mann Whitney U test was used).

In these studies, there were differences in measurement methods, such as using various units for metals and different atomic absorption spectrophotometers (except flame).

As expected, infants' body surface area was distributed in a wide interval in a study group that consisted of term and premature infants. Exposure time to toxic metals in utero is longer in term infants. Because of these reasons, units of metal levels in this study were represented as ng/g/kg in order to standardize metal levels.

When previous reports were examined, it was determined that there were only two studies about toxic metals and prematurity.[9-10] By contrast, there have been a large number of studies showing an association between air pollution and prematurity.[3,6,27-31] Ostrea et al. searched for toxic metals (lead, cadmium, mercury and arsenic) and pesticides in 426 meconium samples from five hospitals.[10] Arsenic was not detected in any sample. Mercury, lead and cadmium were detected in 83.9%, 26.5% and 8.5% of meconium samples, respectively. The prematurity rate was higher in the mercury-positive group ($p<0.05$). It may be that the reason that no relation was detected between prematurity and lead and cadmium levels in this study is due to an insufficient positive sample number. Jelliffe-Pawlowski et al. measured pregnancy blood lead levels in 262 women.[9] They compared women with maximum pregnancy blood lead levels ≥10 mg/dl and those with lower levels, and found a threefold increased risk for preterm delivery (adjusted OR= 3.2, 95% CI 1.2-7.4) in the higher maximum pregnancy blood lead levels group. The risk for preterm delivery in infants who had toxic metals and trace elements detected in their meconium samples was increased one fold in our study.

Despite being from a single hospital, our sample count was thought to be sufficient for demonstrating an association between prematurity and toxic metals and trace elements. Heavy metal levels (lead and cadmium) and toxic levels of trace elements (zinc, iron and copper) in meconium samples were higher in both preterm groups compared to the term group ($p<0.001$). In Post-Hoc analysis, lead in meconium samples was significantly higher in preterm deliveries of unknown etiology compared to preterm deliveries of known etiology. Results of these analyses may suggest that in-utero exposure of lead may cause preterm delivery of unknown etiology. In one study, Kocaeli University Public Health Department showed that toxic metals and trace elements, especially iron, spread uncontrolled to the air and water from factories in all regions of Kocaeli.[31] The risk of toxic metal and trace element exposure is very high in Kocaeli and its periphery, as explained in the results of this and our previous studies.[32] The analysis in this study showed that increased levels of lead in meconium samples were associated especially with preterm deliveries of unknown etiology and may affect gestational age at the fetal stage. Therefore, we suggest that preterm deliveries of unknown etiology may be decreased by decreasing air pollution. Furthermore, the results of this study may potentially serve to investigate the association between neurodevelopmental delay and alteration in the mineral composition of meconium. It is conceivable that analysis of meconium may be used as noninvasive approach to further clarify unanswered questions regarding the effect of environmental pollution to fetus.

CONCLUSION

The results in this study may suggest that lead levels in meconium samples are higher in preterm newborns, especially with unknown etiology, than term newborns. Therefore, we suggest that preterm deliveries of unknown etiology may be decreased by decreasing air pollution.

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