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Maternal serum levels of selected trace elements and heavy metals in pregnancies complicated by preterm prelabor rupture of membranes: A prospective and case-controlled study

Preterm erken membran rüptürü ile komplike olan gebeliklerde eser elementler ve ağır metallerin maternal serumdaki seviyeleri: Prospektif, vaka-kontrollü çalışma

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ÖZ

Amaç: Alüminyum (Al), antimon (Sb), arsenik (As), kadmiyum (Cd), krom (Cr), kobalt (Co), bakır (Cu), manganez (Mn), civa (Hg), molibden (Mo), nikel (Ni), kurşun (Pb), kalay (Sn) ve çinko (Zn) isimli eser element ve ağır metallerin maternal serumdaki seviyelerini, preterm erken membran rüptürü (pP-ROM) ile komplike olmuş gebelerde ve sağlıklı gebelerde karşılaştırmaktır.

Gereçler ve Yöntemler: pP-ROM ile komplike 55 gebeden oluşan çalışma grubu ile, anne yaşı ve gebelik haftası açısından benzer olan 60 sağlıklı gebenin (kontrol grubu) Al, As, Cd, Co, Cu, Cr, Hg, Mn, Mo, Ni, Pb, Sb, Sn and Zn serum düzeyleri ölçüldü. Her iki gruptaki eser elementlerin ve ağır metallerin maternal serumdaki seviyeleri, indüktif olarak eşleşmiş plazma kütle spektrometrisi kullanılarak ölçülmüş ve karşılaştırılmıştır.

Bulgular: Anne yaşı, vücut kitle indeksi, gebelik sayısı, doğum sayısı ve gebelik haftası ortalamaları iki grupta anlamlı bir fark göstermedi (p≥0.05). Ortalama serum beyaz kan hücresi seviyesi, pP-ROM grubunda sağlıklı kontrollerden daha yüksekti (sırasıyla, 12.2±3.5 µL/mL, 10.1±2.6 µL/mL; p: 0.001). Ortalama serum C-reaktif protein düzeyi, pP-ROM grubunda sağlıklı kontrollerden daha yüksekti (sırasıyla, 0.99±1.47 mg/L, 0.40±0.27 mg/L; p: 0.003). Ayrıca, ortalama doğum ağırlığı pP-ROM grubunda sağlıklı kontrollere göre anlamlı derecede düşüktü (sırasıyla 1859±567 gram, 3209±471 gram; p: 0.001). Gruplar arasında Al, As, Cd, Co, Cu, Cr, Hg, Mn, Mo, Ni, Pb, Sb, Sn and Zn'nın ortalama maternal serum düzeyleri açısından anlamlı fark yoktu (p≥0.05).

Sonuç: Maternal serumda ölçülen bu seçilmiş eser elementler ve ağır metaller, pP-ROM'un patogenezinde önemli gözükmemektedir.

Anahtar Kelimeler: amniyokoryon; fetal membranlar; metal maruziyeti; gebelik; erken doğum

ABSTRACT

Aim: To measure maternal blood elements namely, aluminium (Al), antimony (Sb), arsenic (As), cadmium (Cd), chromium (Cr), cobalt (Co), copper (Cu), manganese (Mn), mercury (Hg), molybdenum (Mo), nickel (Ni), lead (Pb), tin (Sn), and zinc (Zn) in pregnant women complicated by preterm prelabor rupture of the membranes (pP-ROM) and to compare the results with healthy controls.

Materials and Methods: Maternal blood levels of Al, As, Cd, Co, Cu, Cr, Hg, Mn, Mo, Ni, Pb, Sb, Sn, and Zn were evaluated in the pP-ROM group, which included 55 pregnant women complicated by pP-ROM and 60 healthy participants (control group) with respect to gestational weeks and maternal age. The maternal serum levels of trace elements and heavy metals in both groups were measured using inductively coupled plasma-mass spectrometry (ICP-MS) and compared.

Results: No significant differences regarding gestational week, body mass index, gravidity, parity, and maternal age were observed (p≥0.05). The mean serum white blood cell level was higher in the pP-ROM group compared with the healthy controls (12.2±3.5 µL/mL vs. 10.1±2.6 µL/mL, respectively; p=0.001). The mean serum C-reactive protein level was higher in the pP-ROM group than in the healthy group (0.99±1.47 mg/L vs. 0.40±0.27 mg/L, respectively; p=0.003). There were no differences in terms of mean maternal serum levels of Al, As, Cd, Co, Cu, Cr, Hg, Mn, Mo, Ni, Pb, Sb, Sn, and Zn between the study and control group (p≥0.05).

Conclusion: The selected trace elements and heavy metals in maternal serum are not involved in the pathogenesis of pP-ROM.

Keywords: Amniochorion; fetal membranes; metal exposure; pregnancy; premature birth; white blood cells

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INTRODUCTION

Preterm prelabor rupture of the membranes (pP-ROM) is described as rupture of the amniotic membranes prior to 37 weeks of completed gestation. pP-ROM is still a significant obstetric problem worldwide that can affect 3% of all pregnancies and predates 40-50% of all preterm births (1). pP-ROM is an important factor that contributes to maternal morbidity/mortality, perinatal morbidity/mortality, and neonatal morbidity/mortality in the world to date. (2). Amniotic membranes are fetal tissues that play major roles in maintaining the pregnancy by protecting the fetus. Fetal membranes accommodate constant challenges (mechanical-structural-immune-endocrine) during pregnancy. The presence of stem cells in fetal membranes and the division of fetal membrane cells, which needs DNA replication, continue throughout pregnancy. pP-ROM is complex and composed of many different mechanisms, which can be affected by trace elements (TEs) and heavy metals (HMs) acting individually or in concert.

The main reasons include inflammation and/or oxidative stress, collagenolysis and extracellular matrix degradation, apoptosis of amniotic membranes, reduction of telomeres, and microfractures of fetal membranes (1). In their research using electron microscopy, Eroglu et al. presented that the amount and changes in the content of collagen played a vital role in the pathophysiology of pregnancies with premature rupture of membranes (3). In normal pregnancies, there are microfractures in fetal membranes and these usually improve with tissue remodeling. The increase in the number and density of these microfractures in pP-ROM may be accompanied by decreased remodeling capacity of membranes. pP-ROM cases are associated with an intra-amniotic bacterial infection, but it has been debated whether infection is a consequence or cause of pP-ROM. Further, some authors reported that pP-ROM might also be associated with a sterile inflammation in the amniotic membranes, and perhaps infection in pP-ROM was likely a secondary situation rather than a causal factor (1).

TEs and HMs, including both essential minerals and toxic metals, have various effects on the development of the fetus. In the early and late pregnancy periods where rapid growth occurs, TEs are particularly important. Some TEs [such as calcium, copper (Cu), nickel (Ni) and selenium] in amniotic fluid (AF) promotes in-utero fetal growth. Therefore, many TEs and HMs can pass to the fetus. They are high in maternal blood and can be detoxifying [such as folic acid supplementation might alleviate arsenic (As) toxicity]. TEs and HMs may be prevented from passing to the fetus by the placenta and may even accumulate in the placenta. Even if some are given as diet or supplements, their amounts in AF may not change (such as iron), or they may fall [such as chromium (Cr)]. TEs and HMs may also change the absorption of each other, blood levels, and metabolisms (4). Studies have shown that some TE deficiencies such as zinc (Zn) cause pP-ROM (5), and in fact, has even been demonstrated by the current pathological examinations in a recent study. For example, in Zn deficiency, the amniotic membrane has sparse and weak collagen and elastin, which results in pP-ROM (6).

In this study, we aimed to measure the maternal serum levels of 14 different TEs and HMs including aluminium (Al), antimony (Sb), As, cadmium (Cd), cobalt (Co), Cr, Cu, lead (Pb), manganese (Mn), mercury (Hg), molybdenum (Mo), Ni, tin (Sn), and Zn. We also aimed to investigate these elements' probable association with the occurrence of pP-ROM.

MATERIALS AND METHODS

Study Population

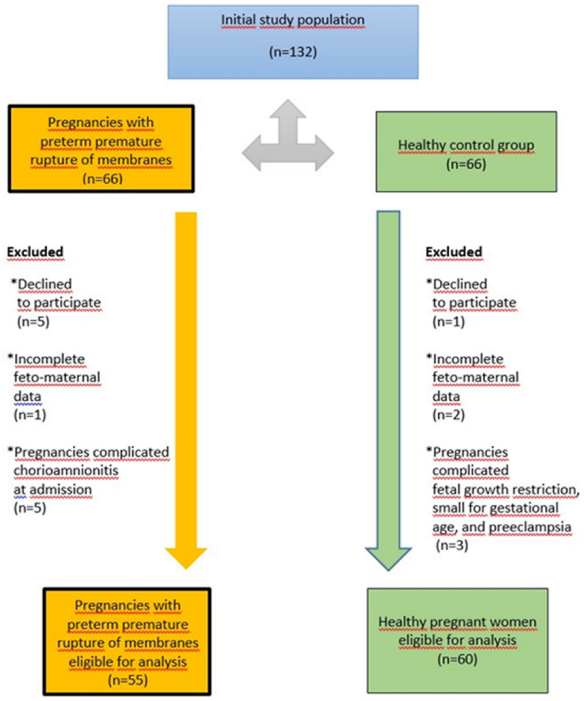
This current observational study was conducted at Cengiz Gokcek Public Hospital Gaziantep, Turkey, in the Department of Obstetrics and Gynecology between August 2018 and March 2019. The experiment was conducted according to the Declaration of Helsinki. All subjects included in the study gave oral and written informed consent. The study population consisted of 55 women with a singleton pregnancy who were diagnosed as having pP-ROM between 24+0 and 36+6 weeks of gestation. The controls were recruited from among healthy pregnant women with a gestational age-matched cohort who were admitted for routine obstetric care to our outpatient clinic. Sixty healthy pregnant women who delivered at term were included in the study as the control group.

The diagnosis of pP-ROM was made in the event of apparent spontaneous leakage of AF from the cervical canal during sterile speculum inspection before the onset of active labor at 37 weeks of pregnancy. The Amnisure test (AmniSure International LLC, Boston, MA) was used when there were inconclusive results to confirm the final diagnosis. The gestational age was determined by calculation from the last menstrual period and supported by the ultrasonography measurements at the first trimester of gestation.

The exclusion criteria for both groups were as follows: women with chronic medical diseases, gestational diabetes mellitus,

drug users, pregnant women who had received any treatment for pP-ROM at the time of admission, pregnancies complicated by fetal congenital abnormalities, genetic syndromes, fetal hypoxia, fetal growth restriction or active labor. Multiparous pregnant women who had a pP-ROM history in their previous pregnancies in both groups were excluded from the study. In addition, pregnant women who had a diagnosis of chorioamnionitis at the time of the first admission were not included in the study. Healthy subjects who had a normal pregnancy period and outcomes without any fetal-neonatal complications were accepted as the control group. All healthy subjects who served as controls were followed up until delivery. One participant in the control group and five participants in the pP-ROM group were excluded from the study because they declined to participate. Incomplete feto-maternal data were seen in two patients in the control group and one patient in the pP-ROM group. Five patients in the pP-ROM group had clinical chorioamnionitis at admission. Three participants in the control group were excluded from the study because of pregnancies complicated by fetal growth restriction, small for gestational age, and preeclampsia. These patients were also excluded from the study (Figure 1).

Figure 1: Flow chart of the pregnant women recruited in the study



Every woman in the study population underwent ultrasound examinations and maternal-fetal assessments were performed by one of the authors. Obstetric anamnesis was obtained from all subjects. The demographic data such as age, gravidity, parity, body mass index (BMI), and gestational age were recorded. The protocol for patients with pP-ROM in our hospital was as follows: women with pP-ROM were hospitalized. Then, the expectant protocol was applied to patients with pP-ROM. After hospitalization until the birth, all women with pP-ROM received prophylactic antibiotics, betamethasone injections for lung maturation (<34 weeks), and magnesium sulfate (<32 weeks) according to the current American Congress of Obstetricians and Gynecologists Guidelines for pP-ROM (2). The non-stress test and fetal movement determined by the mother were used for the detection of fetal well-being. Signs of clinical chorioamnionitis such as uterine tenderness, fever, purulent discharges from the cervical canal, and inflammatory markers such as white blood cell count (WBC) and C-reactive protein (CRP) levels were monitored carefully during hospitalization.

Collection of Biologic Samples

Maternal venous blood samples were taken for measurement of selected TE and HM levels following the diagnosis of pP-ROM in the outpatient clinic. The control group's samples were obtained during routine obstetric care examinations in the third trimester of the pregnancy. These samples were quickly centrifuged at 1500 g for 10 min, serum samples were separated, and stored at -20°C until the day of measurement.

Metal Analyses

The method developed by Aliyev et al. (2012) was used for preparing the samples for analysis (7). One milliliter of the serum sample was placed into high-temperature resistant Teflon tubes in a microwave oven, and 5 mL HNO3 (65%) and 5 mL deionized water was added. A total volume of 20 mL was completed with deionized water in a 50 mL polypropylene tube. All serum samples were digested using the Microwave Digestion System (Milestone, Start D). Nitric acid (Suprapur®, 65%, Merck) was used for sample and standard reference material digestion. Ultra-pure water (Direct-Q®, Millipore) was used for dilution in the standard (Multi-Element Standard - Chem-Lab) and sample preparation.

The TEs and HMs were measured using inductively coupled plasma-mass spectrometry (ICP-MS) (Thermo Scientific ICAPQc, USA). The operating parameters were set as follows: RF power 1550 W, nebulizer gas 0.96 L min-1, plasma gas 0.88 L min-1, nebulizer pressure 3.01 bar, dwell time 0.01 milliseconds and spray chamber temperature 3.7°C. The sampler probe was washed between injections by rinsing with ultrapure water

for 30 s, followed by washing with 2% HNO3 for 45 s, and then rinsing with ultrapure water for 45 s. After the wash steps, the instrument automatically ran the next sample. An 11-point calibration curve (0.5 µg/L to 500 µg/L) was used to measure each element level. The r2 values of the calibration curves of all TEs and HMs calculated a minimum of 0.9994. For the accuracy test of the results, each measurement of the samples and standards was repeated three times. As a result of these measurements, the relative standard deviation (RSD) did not exceed 5%. Certified Reference Material (CRM-Seronorm™ Trace Elements Whole Blood L-2) was used for the validation method. To check the stability and sensitivity of the instrument, a mixture of internal standard (Hf) was used and the mean and RSD values of TEs and HMs were also calculated. The variations of each measurement of the quality controls were <15%. Relative percent differences for replicate analyses were <5% as in the samples and standards.

Statistical Analyses

Descriptive statistics for continuous variables are represented as mean, standard deviation, minimum and maximum. Categorical variables are represented as number (n) and percentage (%). The Chi-square test was used to assess the relationship between categorical variables. Student's t-test was used for the comparison of continuous variables. The Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 22.0. IBM Corp. NY, USA) statistical program was used for all statistical calculations. P<0.05 indicated statistical significance.

Ethical Approval

The institutional ethical review board of Gaziantep University approved the study (Reference number: 2018/226).

RESULTS

The clinical and biochemical parameters of the patients from the study and healthy control groups are shown in Table 1. WBC and CRP levels were found to be statistically significantly higher in the pP-ROM group (p<0.001). The birth weight, gestational week at delivery, and Apgar scores were significantly lower in the study group compared with the healthy controls (p<0.001).

Table 1. Clinical and biochemical parameters of pP-ROM and control groups

Variables†	pP-ROM Group (n=55)	Control Group (n=60)	p
Body mass index (kg/m²)	26.4±4.4	27.7±4.5	0.130
Age (years)	25.7±6.5	25.3±5.4	0.714
Gestational age at venous blood sampling (weeks)	32.1±3.0	32.6±2.6	0.346
Number of pregnancies (min–max)	3.0±2.0	2.7 ± 1.6	0.438
Parity (min–max)	1.5 ± 1.3	1.9 ± 1.1	0.943
Hemoglobin (g/dL)	11.1±1.2	11.0±1.3	0.681
Hematocrit (%)	33.9±3.1	33.8±3.2	0.894
Platelets (x10³/µL)	244±57	236±59	0.448
White blood cells (µL/mL)	12.2±3.5	10.1±2.6	**0.001***
C-reactive protein (mg/L)	0.99±1.47	0.40±0.27	**0.003***
Birth weight (gram)	1859±567	3209±471	**0.001***
Gestational age at delivery (weeks)	32.6±2.3	38.1±1.5	**0.001***
Apgar 1 min	5.7±1,8	7.5±2.2	**0.001***
Apgar 5 min	7.8±2.3	8.4±0.7	**0.001***

pP-ROM Group: Pregnant women with preterm prelabor rupture of the membranes, Control Group: Healthy pregnant women, †Mean±SD, ‡Student's t-test, *Significant at 0.05 level.

The frequency and percentage of sociodemographic variables in both groups are shown in Table 2. The number of patients with dental amalgam was higher in the study group (n = 15) than in the control group (n = 5) (p<0.05). None of the pregnant women with amalgam said they received dental examinations/ treatment during pregnancy.

Table 2. Frequency and percentage of sociodemographic variables in both groups

Sociodemographic variables†		Groups		p
		pP-ROM Group	Control Group	
		n (%)	n (%)	
Smokes	No	50(45.9)	59(54.1)	0.074
	Yes	5(83.3)	1(16.7)	
Passive smoking	No	28(50.9)	27(49.1)	0.526
	Yes	27(45.0)	33(55.0)	
Dental amalgam	None	40(42.1)	55(57.9)	**0.007***
	Have	15(75.0)	5(25.0)	
Sea food consumption	1-2 per week	0(0.0)	4(100.0)	0.148
	1-2 per month	13(48.1)	14(51.9)	
	Rare	42(50.0)	42(50.0)	

pP-ROM Group: Pregnant women with preterm prelabor rupture of the membranes, Control Group: Healthy pregnant women, n: Number, %: Percentage, †Chi-square test. * Significant at 0.05 level.

Table 3 shows the maternal serum levels of these TEs and HMs in both groups. There were no significant differences in terms of the mean TE and HM levels between the groups (p>0.05).

Table 3: Maternal serum levels of selected trace elements and heavy metals in both groups

Variables†	pP-ROM Group (n=55)	Control Group (n=60)	p
Aluminum (Al)	3.05±2.94	2.97±2.34	0.886
Chromium (Cr)	124.41±86.81	130.50±88.85	0.711
Manganese (Mn)	21.38±28.73	23.31±24.83	0.700
Cobalt (Co)	5.45±6.32	4.88±4.34	0.574
Nickel (Ni)	53.64±104.70	32.77±50.52	0.171
Cupper (Cu)	2692.22±781.57	2547.30±700.48	0.297
Zinc (Zn)	764.28±560.61	691.71±259.11	0.368
Arsenic (As)	13.45±3.55	13.99±4.17	0.460
Molybdenum (Mo)	6.50±4.31	5.92±4.22	0.465
Cadmium (Cd)	0.63±1.41	0.46±0.41	0.371
Tin (Sn)	9.57±17.41	7.25±15.45	0.452
Antimony (Sb)	2.38±1.14	2.73±1.20	0.111
Mercury (Hg)	1.84±0.99	1.85±1.00	0.943
Lead (Pb)	7.91±9.04	8.85±10.41	0.610

pP-ROM Group: Pregnant women with preterm prelabor rupture of the membranes, Control Group: Healthy pregnant women, Measurement values†: µg/L (mean±standard deviation), ‡Student's t-test, * Significant at 0.05 level.

DISCUSSION

In the present study, only the maternal serum levels of 14 different TEs and HMs were evaluated to examine the association between the occurrence of pP-ROM and these elements. We found that the maternal serum levels of these TEs and HMs were not significantly different between the study and control groups. The present findings do not support our hypothesis that there might be an association between maternal serum levels of some TEs and HMs and the occurrence of pP-ROM.

The placenta acts as a barrier between the fetus and the mother, except in the mother/fetal metabolic exchange, preventing the arrival of harmful agents that could affect its normal development (8). On the other hand, TEs and HMs may be at different blood levels in different communities and different geographies, and their effects on the placenta/fetus may differ (9). pP-ROM risk factors are mainly low or high BMI, infection, behavioural factors (cigarette smoking, drug and alcohol abuse), low socioeconomic status, and nutrient insufficiency (specifical antioxidants). However, studies have shown that most patients do not have these risk factors (10). pP-ROM is a disease of the amniotic membranes in which inflammation and/or oxidative stress has an important role, and can lead to membrane weakening (11). Therefore, it can also be thought that TEs and HMs that can cause inflammation and/or oxidative stress may cause pP-ROM (12). Menon et al. postulated that the number of microfractures and their dimensions in amniotic membranes was significantly greater in pP-ROM. Furthermore, in these areas with microfractures, tissue remodeling could be insufficient or ineffective. These regions are also associated with large amounts of collagen and extracellular matrix degradation in pP-ROM. Remodeling continues in the amniotic membrane, where DNA synthesis and cell division are important. Many TEs can function in cell division and DNA synthesis, and some HMs may have negative effects (5, 13). In short, pP-ROM remains a difficult obstetric disease with its etiology, diagnosis, prevention, and treatment, and the relationship of TEs and HMs with pP-ROM has not yet been made clear.

We are constantly exposed to TEs and HMs at very low/high levels in our environment. Exposure to TEs and HMs can occur through food, air, house dust, water, medical treatment and smoking/passive smoking (14). HMs can be essential (such as Cu, Zn) and non-essential (such as Hg, Pb). In recent years, numerous authors have examined the impact of TEs and HMs on human health, reproduction, and pregnancy. Many TEs and HMs are known for their relationship with industry and seafood consumption. Many international organizations, such as the World Health Organization (WHO), have released standard limits for TEs and HMs (15). However, Gaziantep, the city in which the study was performed, is far from the coast. The participants' seafood consumption was very low or absent because of the low socioeconomic levels in both groups. Dental amalgam is known for its relationship with TEs and HMs. The relationship between amalgam, preterm birth, pP-ROM and low birth weight was examined by Radnai et al. (16). In our results, the levels of maternal serum TEs and HMs did not differ between the groups, even though those with amalgam in the pP-ROM group were higher than in the control group. In addition, heavy cigarette smoking increases the risk of pP-ROM, more so at early gestational age than at term (17). However, in our study, few women smoked and there was no difference between the groups. Based on our findings, we thought that smoking/passive smoking was not a prominent feature.

Some investigations speculated that pregnancy could be a time of enhanced susceptibility to Al toxicity and competition for transport with TEs (such as calcium, Cu and Zn) as one of the possible mechanisms that might explain Al toxicity. In a study conducted in pregnant rats, it was shown that giving intrape-

ritoneal to maternal rat HMs, such as Al, created a change in the metabolism of TEs and HMs in both the mother and fetus (18). Cr, triggering apoptosis in the placenta, has been shown to cause abortion, preeclampsia, and fetal growth restriction. Furthermore, some TEs and HMs have been reported to cause lesions in the placenta such as Cr, Cd, and Pb (19). Huang et al. showed that maternal exposure to Cr was associated with pP-ROM (20). Kucukaydin et al. reported that the maternal Cd and Pb serum levels did not differ in pP-ROM (9). By contrast, in a study conducted with a high number of patients, the urinary Pb levels in women with pP-ROM were examined and the authors concluded that pP-ROM was associated with elevated levels of Pb in maternal urine. Further, higher levels of maternal Pb exposure were linked with an increased risk of pP-ROM (21). Minerals such as Zn, Mn, and Cu are key components of important complex enzyme systems responsible for antioxidant protection of the organism, immune function, digestion, glucose metabolism and cellular energy, bone growth, blood coagulation/hemostasis, and reproduction (22, 23).

In a few studies, lower serum Cu levels in pregnant women were associated with pP-ROM; however, other studies reported no difference (6). Rahmanian et al. found that there was no difference in serum Zn levels between pregnancies complicated by pP-ROM and normal pregnancies in Iranian pregnant women (24). In a current study in Turkey, Kucukaydın et al. found that maternal serum Zn levels were not statistically significant in pP-ROM. In the literature, different mean Zn levels have been reported, and authors speculated that serum Zn levels in Turkish maternal blood samples were higher than in other countries. The mean maternal serum Zn levels that we found were lower than the values given by Kucukaydın et al.. However, in accordance with their findings, there was no difference between the pP-ROM and control group in our study (9).

Co has a biologically necessary role for vitamin B12. Co exposure can have a systemic oxidative effect and has negative effects on mitochondrial function (14). As primarily exists in its inorganic form in drinking water. Although many adverse pregnancy outcomes of As were shown in the researches, the relationship with pP-ROM was not demonstrated (25). Unlike others, Hg exposure has been investigated in the presence of dental amalgam. Hg placental pass was shown in a study on sheep related to dental amalgam. Hg has been associated with both pregnancy complications and developmental problems in infants (26). Ni exposure can cause DNA oxidative damage (27). Therefore, it can be thought that the oxidative stress effect of Ni can be caused to pP-ROM. Mo is an essential trace metal, exhibits biologic activity as a cofactor for some enzymes that catalyze redox reactions in the body, and deficiency of human Mo-enzyme activities is linked to in early childhood death (28). Sn has a negative effect on the fetal head circumference (29). Sb, an HM, is found in the environment at very low levels and is used in drugs (30). Chromosomes and reproductive systems are sensitive to Sb. Chronic Sb exposure can also lead to an increased risk of preeclampsia (31). To the best of our knowledge, this is the first study in the literature to investigate maternal serum levels of Al, Co, Ni, As, Mo, Sn, Sb, and Hg in maternal blood in pP-ROM.

To summarize, Al (4), Cr (20), Mn (22), Co (30), Ni (27), Cu (22), Zn (24), As (25), Mo (32), Cd (15), Sn (30), Sb (30), Hg (26), and Pb (19) placental accumulation/pass or measurements in AF were shown in studies. Therefore, it could be thought that they could cause pP-ROM by affecting amniotic membranes. However, in this study, we found no differing maternal serum levels in the pP-ROM group. We may not have seen their toxic effects, probably due to none of them being at high levels in either group.

Measurements of cord blood and AF are difficult, laborious, costly, time-consuming, and re-sampling is troublesome. In addition, placental transfer of TEs and HMs varies among individuals. Therefore, the measurements of cord blood, amniotic membranes, and AF may result in different results from the serum (30). In addition, placental measurement is not preventive because it is not usually preferred before delivery, it can be measured after delivery. In maternal urine, TE and HM levels can be influenced by many factors, mainly the interaction between each other and changes in maternal metabolism. Measurements in urine may exhibit differences between the same person or persons (20). Maternal blood measurements are more suitable for a preventive approach. In fact, if toxic levels of TEs and HMs can be detected before pregnancy, preventive arrangements can be made. If a substance is high in the maternal blood initially, it may be thought that it could go to the amniotic membranes and placenta. Therefore, in our study, we thought that if TEs and HMs were low/high in maternal blood, the study of other specimens could be a meaningful basis for future studies. On the other hand, preterm birth and pP-ROM are intertwined with each other (2). Therefore, active labor was not selected in our study, and this is a strength of our study. A limitation in our study is that the inflammatory and oxidant/antioxidant substances accused of pP-ROM were not added.

CONCLUSION

Based on the outcomes of the study, we believe that non-toxic levels of the TEs and HMs we chose are not related to pPROM. However, although a certain amount of TEs and HMs are needed by the body, it is important to avoid toxic levels. To avoid adverse pregnancy outcomes, it is important to take care of the diet of pregnant women and replenish TEs. Studies on the effects of TEs and HMs on pregnancy have difficulties, but it is also obvious that the current literature is insufficient. For these reasons, larger basic and clinical studies are required to investigate the effects of TEs and HMs in pregnancies and the fetus.

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