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Correlation between Cadmium and Lead Levels in Maternal Blood Samples with Preterm Labor

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Abstract: **Background:** Globally, an estimated one million children under the age of five die every year as a direct result of preterm birth and its associated consequences. Preterm birth has a complicated and multi-factored etiology. Prenatal exposure to heavy metals is widely believed to have a significant role in the genesis of preterm birth.

Aim of study: To estimate the association between maternal blood lead and cadmium on one hand, and preterm labor on the other hand.

Study design and setting: This is a case-control study that included 100 patients (50 cases and 50 controls) and was conducted in Baghdad Teaching Hospital/ Medical city, Baghdad in the period from the 1st of January 2022 to the 30th of November 2022.

Methodology:

Preterm birth was defined as birth at gestational age less than 37 weeks and term pregnancy≥37 completed weeks. Testing for blood lead and cadmium levels was conducted in the Iraqi Poisoning Consultation Center of Baghdad Medical City.

Results:

The mean blood lead of the studied sample was 20.8 µg/dl ± 5.4. The mean cadmium lead was 0.26 µg/dl ± 0.08, which was significantly higher than the level considered acceptable by the World Health Organization. For blood lead, using cut-off value of 0.3 µg/dl for blood lead as accepted by the Iraqi center of toxicity), the women with preterm labor had significantly higher levels of blood lead than women with term labor. A cut-off value of 0.3 µg/dl had a sensitivity of 48%, specificity of 100%, postivie predictive value of 100%, negative predictive value of 65.7%, and accuracy of 74%.

As for blood Cd, using cut-off value of 0.3 µg/dl for blood cadmium as accepted by the Iraqi center of toxicity), the women with preterm labor had significantly higher levels of blood Cadmium than women with term labor. a sensitivity of 68%, specificity of 100%, postivie predictive value of 100%, negative predictive value of 75.7%, and accuracy of 84%.

Conclusion:

1. Maternal blood lead and cadmium levels were extremely higher than the level considered acceptable by the World Health Organization and considerably higher than other studies.
2. Moreover, the present study found that both studied heavy metals may contribute as risk factors of preterm labor.

CHAPTER ONE

INTRODUCTION

1.1. General overview:

Preterm birth is one of the most challenging and critical issues in obstetrics [1]. Despite decades of study and therapeutic progress, roughly one out of every ten infants in the United States are born prematurely. These babies are responsible for almost three-quarters of prenatal death and more than half of long-term neonatal morbidity, at a huge social and economic cost[1]. Prematurity complications are the major cause of newborn mortality and the second greatest cause of death among children under the age of five[2].

Morbidity associated with preterm birth often persists throughout adulthood, resulting in tremendous physical, psychological, and economic expenses[3].

Although the etiology of preterm delivery is assumed to be multifaceted, the events leading up to it are still not totally understood. However, it is unclear whether preterm birth is caused by the combination of many pathways or by the independent influence of each pathway. Medical disorders of the mother or fetus, genetic effects, environmental exposure, infertility therapies, behavioral and socioeconomic factors, and iatrogenic prematurity are all risk factors for premature delivery[4].

Toxic metalcontaminants in the environment, including lead and cadmium, are well-known confounding factors for preterm birth. Worldwide, according to a new study, these hazardous heavy metals produce oxidative stress in the trophoblastic placental tissue by creating reactive oxygen species that damage the antioxidant system, perhaps resulting in preterm delivery[5].

1.2. Definition

Preterm is defined by the World Health Organization (WHO) as babies born alive before 37 weeks of pregnancy are completed. Preterm birth is divided into subcategories depending on gestational age: extremely preterm (less than 28 weeks), very preterm (28 to 32 weeks) and moderate to late preterm (32 to 37 weeks).[6]

The Infant Life Preservation Act was amended to set the viability limit at 24 weeks. The mortality rate of preterm newborns delivered after 32 weeks of gestation is identical to that of term babies. The risk of neonatal death or handicapped survival increases in very preterm newborns (those born between the ages of 28 and 32 weeks), but it is particularly severe in extremely preterm newborns (defined as those born before 28 weeks)[7].

1.3. Epidemiology

Every year, about 15 million infants are born too early. That is more than one in every ten infants. Each year, around 1 million children die as a result of preterm delivery problems. Although Africa and South Asia account for more than 60% of premature births, preterm birth is truly a worldwide issue. In lower-income nations, 12% of newborns are born prematurely, compared to 9% in higher-income ones. Within countries, poorer families are more vulnerable.[6]

Some developed countries have recorded preterm birth rates between 5% and 7% of live births, but the percentage is likely much higher in developing countries.[8]

Preterm births are most common in India, China, Nigeria, Pakistan, Indonesia, and the United States. preterm birth rates that surpass 15% are found in Malawi, Congo, Comoros, Zimbabwe, Equatorial Guinea, Mozambique, Gabon, and Pakistan.[6]

In the United States, roughly one out of every ten newborns are born prematurely.[9]

Premature birth occurred in 1 in 8 U.S. births in 2005, whereas it occurred in 1 in 18 births in both Ireland and Finland. Irish infant mortality in 2010 was 3.89 per 1000 live births, whereas the US average was 6.8 per 1000.[10]

In Iraq, between the years 2016 and 2017, a study conducted in Thi-Qar city in three hospitals found that preterm birth was found to be 2.48%.[11]

Another study conducted in three hospitals in Al-Basra city between 2014 and 2015 found that the Incidence of preterm birth was 2.42%.[12]

Preterm birth has stayed at roughly 5-10% of live births in most nations over the last two decades, despite significant preventative measures.[13] According to the research, the rates of PTB were greatest in Africa (11.9%) and North America (10.6%) and lowest in Europe (6.2%).[3]

Medical records and demographic statistics seldom reflect the true state of health in developing countries. Estimation of the prevalence of preterm birth in developing nations is further complicated by factors such as the diversity of gestational age determination methods, the diversity of birth registration practices across countries, the diversity of preterm birth definitions, the diversity of opinions on the viability of preterm infants, and the diversity of religious practices. As a result, it is challenging to estimate the prevalence of preterm birth among developing nations and to establish meaningful comparisons between them.[3]

1.4. Causes and risk factors

1.4.1. Infection.. At least 40% of preterm births are associated with intrauterine infection. UTI (according to a study, about 28.4% of cases had UTI), vaginal infections like bacterial vaginosis and trichomoniasis[14].

In individual cases it is often difficult to determine whether infection is the cause or consequence of the processes leading to pretermdelivery. The amniotic fluid of patients with preterm labor has higher rates of microbial colonization and levels of inflammatory cytokines than preterm patients not in labor and term patients in labor. Extrauterine maternal infections such as pyelonephritis, pneumonia and periodontal disease have been associated with premature parturition.[15]

1.4.2. Psychological causes.. Stress, anxiety and other psychological disturbances have been suspected as risk factors for PTB. It has been claimed that stress and anxiety increases corticotrophin-releasing hormones and may ultimately result in increased uterine contractility. Stress also increases cytokine production, which may independently lead to PTB or increase susceptibility to infection and subsequent PTB.[13]

1.4.3 Malnutrition.. Pregnancy-related malnutrition. For instance, a greater risk of spontaneous preterm birth is shown in women with a low body mass index before pregnancy[16]. Preterm birth rates are higher among women whose blood iron, folate, or zinc levels are below the normal range[17]. Maternal nutritional status may influence preterm birth via several different processes, including lower blood volume and uterine blood flow in thin mothers (which may lead to spontaneous premature delivery)[18]. Low vitamin and mineral intake are linked to impaired blood flow and an increased risk of maternal infection, both of which may be more common in thin women. [17] In other hand, obesity increase the risk of preterm labor through obesity-related maternal diseases such as preeclampsia. In addition, obesity may be linked to infection and inflammation, which are more strongly connected with very preterm birth than moderately preterm birth[14].

1.4.4. Multiple pregnancies.. Premature birth is common in multiple pregnancies, accounting for 20-30% of all preterm births; about 60% of twins are born prematurely. The probability of twins experiencing spontaneous labor or preterm premature rupture of membranes is around 40%[17].

Increased uterine distension may have unintended consequences, including the development of spontaneous preterm labor in multifetal pregnancies. Superovulation and many pregnancies may have a role because they create a unique endocrine environment. Multifetal pregnancies, for instance, result in higher levels of estrogen, progesterone, and sex hormones than do singleton pregnancies. Potentially contributing to the start of labor is an increase in steroid production.)[19].

1.4.5. Demographic variables.. include low socioeconomic status in 82.5%, housewives 99%, and illiterate 64% had PTB[12], inadequate prenatal care, mother age extremes, or malnutrition (iron deficiency anemia has been identified as a risk factor for PTB).[20]

1.4.6. Behavioral factors.. such as smoking (smoking is linked to spontaneous preterm birth regardless of the number of cigarettes consumed. Women who smoke during the first trimester have a 20% greater chance of extremely preterm birth before 28 weeks of gestation).[21]

Family history (a research found that the presence of a maternal family history of preterm birth among female relatives within three generations, most particularly sisters, was shown to be strongly linked with a spontaneous preterm delivery occurring in the present pregnancy)[22].

1.4.7. Uterine deformity (unicornuate, bicornuate, and didelphys individuals, for example, only have one horn for pregnancy because of a significant fusion defect, whereas people with arcuate, septate, and t-shaped uteruses have just a partial alteration of their cavity, these anomalies have a reported prevalence of approximately up to 5–25% in women with adverse reproductive outcomes including preterm labor [23]).

1.4.8. Previous history of PTL.. Women who have once given birth prematurely have a 17% to 40% chance of giving birth prematurely again. This risk seems to rise with each additional premature birth, those who have once had a premature birth have a 2.5-fold higher chance of having another premature birth spontaneously.[24]

1.4.9. Previous cervical surgery or cone biopsy (loss of cervical stroma, which provides tensile strength, loss of cervical glands, which increases vulnerability to infection, and loss of cervical elasticity, due to scarring, are all potential explanations[19].

1.5. Neonatal outcomes after preterm birth

Worldwide, more than one million of the 15 million kids born prematurely each year in the globe die before the age of five owing to preterm delivery and its complications[25]. Many survivors will be disabled for the rest of their lives, including learning difficulties and vision and hearing issues[26].

Bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) and serious brain injury (e.g., intraventricular haemorrhage) are neonatal morbidities with a significant negative influence on the neurodevelopmental outcome of preterm infants[27].

The outcome of preterm labour has changed over the last decade, especially among those born at 22–24 weeks of gestation.[27]

Many studies showed that preterm infants overall academic achievement is lower than for their term counterparts.[28]

Advances in antenatal medicine and neonatal intensive care have successfully resulted in improved survival rates of preterm infants. These improvements have been most dramatic in infants born with extremely low birth weight (ELBW, <or=1000g) and at the limits of viability (22 to 25 weeks). There is increasing evidence of sustained adverse outcomes into school age and adolescence, not only for ELBW infants but infants born late preterm.[29]

Surviving infants' outcomes are defined by various neurodevelopmental impairments and by general measures of health including chronic respiratory diseases, growth parameters and recurrent infections.[30]

1.6. Prediction of Preterm Labour

There are now three broad kinds of screening tests used to predict preterm birth due to spontaneous causes: risk factor evaluations, cervical length measurements, and biochemical indicators [31].

1.6.1. Fetal fibronectin

Glycoprotein fibronectin is made by amniocytes and cytotrophoblasts in the developing fetus. It is not uncommon for it to be detected in cervicovaginal secretions before 22 weeks of pregnancy, but its presence between weeks 24 and 34 of pregnancy is associated with an increased risk for preterm labor[32].

1.6.2. Cervical length

Screening for preterm labor risk by measuring cervical length with transvaginal ultrasonography is effective. With a sensitivity of 37.3% and specificity of 92.2%, the cutoff for preterm labor risk at 24 weeks of pregnancy was determined to be 25mm (10^{th} percentile) of cervical length[32].

1.7. Diagnosis of preterm labor

- Recognize labor signs and symptoms, including regular or frequent contractions, a constant low, dull backache, a sense of pelvic or lower abdominal pressure, and mucus or bloody vaginal discharge.[33]
- Vaginal examination: to evaluate the cervical status (bishop score), do a cervical smear for microbiology to look for infection and fibronectin test (Biochemical marker of the cervical stage).[34]
- Transvaginal ultrasonography for measurement of cervix length.[34]

1.8. The effect of some heavy metals on pregnancy

Researchers suggest that exposure to environmental pollutants and heavy metals in the air, water, soil, and consumer and home items has a significant role in the development of unfavorable pregnancy outcomes[35].

1.8.1. Cadmium

1.8.1.1. Cadmium chemical structure

Cadmium is a chemical substance with atomic number 48(which suggests it has 48 protons and 48 electrons) and the symbol Cd. [36]

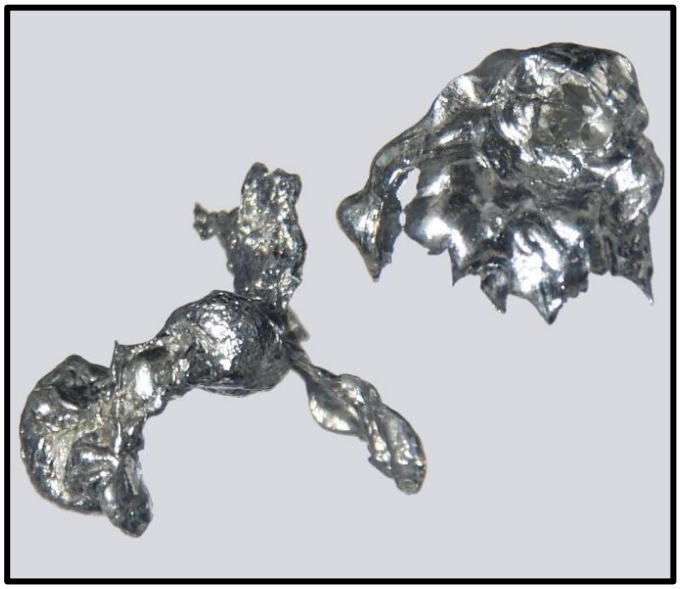

Figure (1.1): Cadmium element[37].

1.8.1.2. Physical properties

Cadmium is a transition metal that is whitish blue in color. It is soft and flexible, having the ability to be sliced with a knife. Cadmium is a divalent metal that is water insoluble. Cadmium is fire resistant and inflammable, however it is flammable in powdered form. Cadmium is an excellent electrical conductor. It is corrosion resistant. Cadmium metal does not react with water.[38]

1.8.1.3. Sources

Cadmium is an uncommon metal. Cadmium content on Earth is around 0.5 ppm (parts per million). It is mostly found in the form of zinc and sulfide ores. Greenockite is the name given to the cadmium sulfide ore(CdS). Cadmium is now derived by the mining, smelting, and purifying of zinc sulfide and copper sulfide ores. Cadmium in its elemental state has been discovered in Siberia. Japan, China, South Korea, and North America are the world's largest cadmium producers.[38]

1.8.1.4. Common reactions with cadmium

Cadmium may be found in a variety of significant compounds in nature, including Cadmium Hydroxide (Cd(OH)2): This chemical is found in nickel-cadmium batteries and forms precipitate in the presence of a Nitric Acid solution. [39]

Cadmium Oxide (CdO): This substance is utilized as a catalyst in a range of processes, including redox reactions, hydrogenation reactions, polymerization, and cleavage. Cadmium Oxide is heat resistant, therefore it may be used in heat-resistant polymers as well as other plastic coatings. This chemical is found in several enamels and batteries. [39]

Cadmium Sulfate (CdSO4): Like many other Cadmium compounds, this substance is utilized in electroplating, pigments, fluorescents, and batteries, notably the Weston Cell.[39]

1.8.1.5. The effect of cadmium on human body

Cadmium exposure in humans may occur via water, food, and cigarette inhalation[40]. When humans are subjected to cadmium, they run the risk of experiencing a number of adverse consequences, some of which include malfunction in the renal and hepatic systems, osteomalacia, pulmonary edema, and damage to the adrenal and hematological systems.[41].

The reference values for cadmium in whole blood (0.5 microg/l) and for cadmium in urine (0.5 microg/l) were confirmed.[42]

1.8.1.6. Cadmium and pregnancy

A special physiological state that could affect and alter essential pathways involved in the handling of Cd is pregnancy. Epidemiological research has shown that prenatal exposure to cadmium has significant effects on human development and public health. Therefore, Cd exposure during pregnancy is linked to negative birth outcomes including lower Apgar scores, lower birth weights, and an increased likelihood of being born small for gestational age, as well as associations with worse cognitive development and epigenetic alterations[43]. During pregnancy, according to research, cadmium may harm the placenta and diminish the weight of a newborn infant [44]. According to other research, high levels of cadmium in the placenta may disrupt hormone balance and affect placental activities including calcium and zinc transport[5]. Furthermore, Toxic levels of cadmium disrupt normal fetal development and pregnancy outcomes by decreasing blood flow and nutrient transfer in the placental tissue[5]. Many studies showed that the concentration of cadmium in the placenta was associated with a high risk of preterm birth[5].

Other researches in recent years have indicated that female body cadmium contents is greater than male body cadmium enrichment. It disrupts the normal process of embryonic development and, in the long term, leads to a number of systemic disorders in adults. Cadmium may be released into the milk during nursing and enters the offspring's body and damages their capacity to learn and remember[45].

1.8.1. Lead

1.8.2.1. Lead chemical structure

Lead is a chemical element with the atomic number 82, which indicates it has 82 protons and 82 electrons in its atomic structure. Lead's chemical symbol is Pb, with an atomic mass of 207.2 u. [46].

Figure (1.2): Lead element[47].

1.8.2.2. Physical properties

Lead is a heavy metal with a higher density than most other materials with a density of lead of 11.34g/cm^3. The melting point of lead is 327.5 °C and the boiling point is 1740 °C.[46] Lead is soft and a highly malleable white shiny metal with a soft texture. In addition to not being a bad electrical conductor, the metal is also very resistant to corrosion[48].

1.8.2.3. Sources

Lead (Pb) is widely used by humans[49]. Although it has unknown physiological functions, it is found almost everywhere in nature[50]. Since Roman times, this metal has been utilized in paints and pipes, also Used in car batteries and as electrodes in electrolysis processes[48] and radiation shielding[51].

1.8.2.4. Common reactions with lead

Characteristic reactions of Pb2+: The +2 oxidation state is the more stable state.[52] Lead has a slow reaction with hydrochloric and nitric acid. In the presence of moisture and carbon dioxide, lead interacts with air to generate a passivating layer. Lead hydroxy carbonate is most likely the layer. Lead slowly dissolves in cold alkalis to generate plumbites. Under acidic circumstances, chromate precipitates lead(II). In the absence of air, lead does not react with water. Lead(II) hydroxide is produced in the presence of air [53].

1.8.2.5 The effect of lead on human body

Lead and its compounds are poisonous, and the body stores them, building over time until a deadly amount is reached; this is known as cumulative poisoning [54].

Lead is toxic to the neurological and renal systems in particular, but may harm other organs as well. Low amounts of lead exposure may also have negative effects on human health, and there is no safe limit to exposure[50].

It may be consumed via food cooked with water transported through lead pipes or from processing companies that use lead-containing equipment or painted walls[44]. Whether it enters the body

through the lungs or the digestive tract, after it has been absorbed it is deposited in the various soft tissues and bones[50]

Small quantities of lead are not known to be dangerous in adults. Even low quantities of lead, however, may be harmful to newborns and children. In adult, Less than 10 micrograms per deciliter (µg/dL) or 0.48 micromoles per liter (µmol/L) of lead in the blood and Less than 5 µg/dL or 0.24 µmol/L of lead in the blood in children are considered normal. There may be some variation in normal value ranges among labs [55].

1.8.2.6 Lead and pregnancy

Calcium transporters are responsible for moving lead and other metals through the cell membranes of living organisms. Heavy metals are known to affect calcium homeostasis in a variety of ways, including the disruption of calcium channels and pumps, interference with protein kinase C and calcium binding protein. It is believed that the transportation of calcium ions through the syncytiotrophoblast is strongly connected to the process of lead transport. Calcium transport into the syncytiotrophroblast may be altered when there is lead present in the blood of the mother and the umbilical cord [56].

When pregnant women are exposed to lead, it might result in a miscarriage or early delivery. Low birth weight has an impact on the development of the brain as well as the growth of newborn infants[44]. Lead passively diffuses through the placenta during pregnancy, resulting in an increased concentration in the cord blood of the newborn. Therefore, there is some evidence from the few studies that have been conducted that maternal exposure to Pb during pregnancy may lead to poor pregnancy outcomes such as premature births[5].

There are studies suggest that up to 0.5% of reproductive-aged women had elevated blood lead levels (10 µg/dL or above). Since lead readily crosses the placenta, neonatal lead poisoning is always to be anticipated when a pregnant woman is exposed to lead[57].

There are data also shows that whole blood lead levels in a pregnant woman may not be the best predictor of lead concentrations in the baby's brain. Over 99% of lead in whole blood is attached to red cells and so is not accessible to cross the placenta, instead, the 1% of lead in the plasma compartment of blood is of most concern in terms of prenatal exposure [58].

There is significant evidence that young children are most at risk of IQ impairment from lead exposure, particularly during the first three years of life, when fundamental cognitive functions develop. Cognitive impairments caused by lead exposure during the first three years of life tend to be most visible on IQ tests performed years later, at the age of ten or older [59].

Table (1.1): Different sources of toxic metals (Cd, Pb) in environment and its impact on reproductive system of women, infants and neonates [60]

Toxic metals	Possible source of exposure	Effects of metals on reproductive system	Effects on infants	Neonatal effects
Cadmium	Food chain Mining, tap water, auto exhaust, earth's crust, forest fires galvanized pipes, volcanic activity Cigarette smoking, Air pollution, Bio mass fuel combustion Flame retarders and stabilizers used in plastics	Sperm quality alterations, progesterone production and gonadic Sexual potency reduction, Interference with the placental dysfunction,	IUGR (Intrauterine growth restriction)	Reduced QI (Intelligence quotient) Low birth weight and SGA (Small gestational age) Reduced neonatal length, Reduced APGAR Score
Lead	Tobacco smoking Pb compounds (e.g., lead-sulfide, lead carbonate) Petrol additives Air pollution Paints, enamels Bio mass fuel, firearms with lead bullets, batteries, radiators of vehicles, Tap water	Oxidative damage, Decreased sex drive, Impotence alterations, Hormonal changes, Menstrual disorders due to oxidative stress in placental tissue	Preterm delivery, IUGR, miscarriage/stillbirth, Low-birth weight, Mental restriction, Congenital malformations	Hematological IUGR changes (WBCs development alteration) Poorer mental Development Index Reduced QI impairment in hearing and motor development Learning disabilities Attention deficit disorders

1.9. Measurement of lead and cadmium levels in human samples

In the context of environmental monitoring, the identification of tiny levels of lead is of utmost importance; nevertheless, a significant number of spectrometric techniques for determination of lead are known to experience interference owing to the presence of various other metal ions.

As an analytical reagent, 5-methylthiophene–2-carboxaldehyde ethylenediamine (MTCED) was used in the development of a spectrophotometric approach that is easy, quick, and sensitive for the detection of lead. At a pH of 3.0, sodium acetate-hydrochloric acid buffer solution, a bright yellow colored complex may be formed by the metal ion in an aqueous medium with MTCED, and this complex shows maximum absorbance at 380 nm.

The color reactions take place instantaneously, and the absorbance values do not change for a period of twenty-four hours. Through the use of job's continuous variation and the molar ratio approach, researchers were able to investigate the composition of the lead complex that was formed using MTCED. Because of its greater sensitivity, the MTCED technique was used to assess lead levels in both medicinal leaves and environmental samples.[61]

Schiff's bases are one of the best chelating agents for determining metal ions spectrophotometrically. At 620 nm, 1, 3-benzenediamine, N,N'-bis(2-furanylmethylene) (BDFM) produced a brown-colored complex with lead. In an acidic medium at pH = 3.5, lead was chelated using Schiff's base in the presence of sodium laureth sulfate (SLS) as a surfactant using acetate buffer.[62]

The task-specific Ionic Liquid Dispersive Liquid-Liquid Microextraction (TSIL-DLLME) technique is a simple and fast preconcentration method for determining cadmium levels in human serum. Trioctylmethyl ammonium thiosalicylate (TOMATS), a new task-specific ionic liquid, was shown to be effective as both a chelating agent and an extractive solvent when combined with other chemicals such as diluents Triton X114 etc., at ideal pH, temperature, and incubation time values. Following enrichment studies, an acidic solution was successfully used to back-extract metal ions from the ionic liquid-rich phase, followed by accurate measurement by electrothermal atomic absorption spectrometry.[63]

Another method of separation of cadmium in human blood and urine samples was accomplished via micro solid phase extraction, which included the use of a combination of captopril nanoparticles and ionic liquid paste on a micro graphite rod.[64]

In atomic absorption spectrometry (AAS), the sample used is heated up to the point when the element atomizes. Light is taken in by the atoms just at the resonance line. It is possible to measure the degree to which the intensity of the light beam has been attenuated. Graphite furnace atomic absorption spectrometry (GF-AAS), also known as electrothermal atomic absorption spectrometry (ET-AAS)., is the method predominantly used for determining the concentration of cadmium in bodily fluids such as blood, urine, hair, and saliva, as well as human milk. In most cases, the preparation of samples involves digestion with nitric acid.[65]

1.10. Aim of study

To estimate the association between maternal blood lead and cadmium on one hand, and preterm labor on the other hand.

CHAPTER TWO

PATIENTS AND METHODS

Study place and time:

The study has been conducted in Baghdad Teaching Hospital/ Medical city, Baghdad. The data was collected from the 1st of January 2022 to the 30th of November 2022.

Study design:

An analytic case control design has been chosen for this study.

Patients and method:

A total number of 100 pregnant women at labor were included in the present study:

1. Case group: include 50 women with spontaneous preterm labor.
2. Control group: include 50 women, term, in labor.

The Gestational age was calculated depending on the mother's LMP and first trimester ultrasound scan. Preterm birth was defined as birth at gestational age less than 37 weeks and term pregnancy ≥ 37 completed weeks.

Full history and thorough general and obstetrical examination were done for all pregnant women. Basic sociodemographic and obstetric data were collected (age, parity, gestational age, past medical history, pre-pregnancy BMI, and birth weight).

An amount of 10 cc of blood was collected from pregnant women for general investigations:(CBC, RFT, LVT, TFT, Blood group and RH) and for test for blood lead and cadmium levels.

Testing for blood lead and cadmium levels was conducted in the Iraqi poisoning consultation center (P.C.C) in Medical City/ Baghdad. Blood samples were put in shaker for 1 hour, after which 2.5 ml of trichloroacetic acid was added to 2.5 ml of blood. The mixture was applied in a centrifuge rotating in a speed of 3000 rounds/minute for a total of 10 minutes. For serum cadmium levels, flameless atomic absorption spectrometer was used (novAA 300, Analytik Jena GmbH); shown in figure (**2.1**). While for blood lead levels, flame atopic absorption spectrometer was used (210 VGP, Buck scientific); shown in figure (**2.2**).

Maternal blood cadmium concentration was classified as the following: acceptable (≤ 0.12 µg/dl) and un-acceptable (>0.12 µg/dl). While maternal lead levels were classified as: acceptable (<10 µg/dl), and un-acceptable (≥10 µg/dl) (according to the WHO).

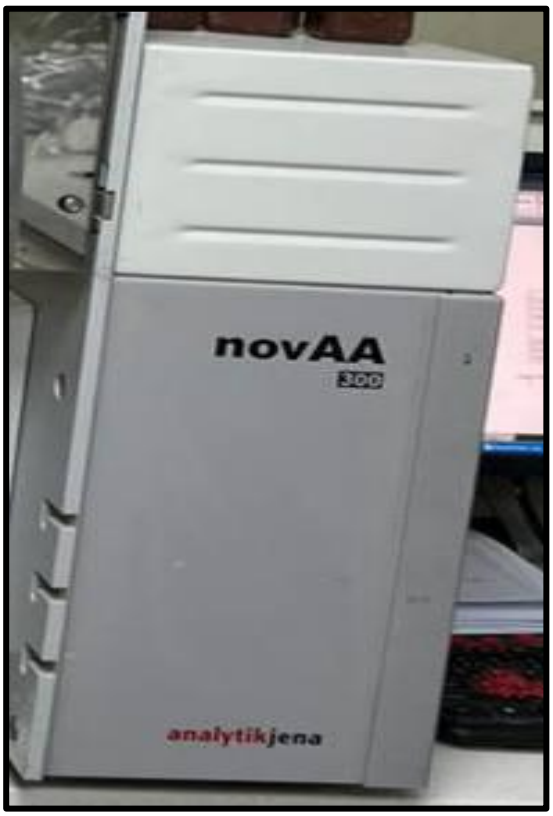

Figure (2.1): novAA 300, Analytik Jena GmbH.

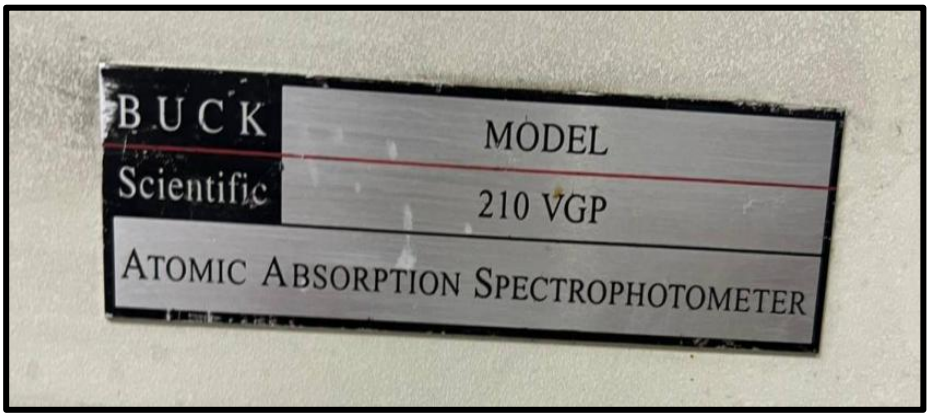

Figure (2.2): 210 VGP, Buck scientific.

Exclusion criteria

Mothers with the following conditions were excluded:

a) Pregnancy-induced hypertension.
b) Preeclampsia.
c) Gestational DM.
d) Heart disease.
e) Thyroid related diseases.
f) Twin pregnancy.
g) Stillbirth.
h) History of previous preterm labor.
i) Alcoholism
j) Smokers
k) Mental disorders.

Participants consent

Verbal consent has been obtained from all participants before data collection.

Approval and official permission

An official letter of approval has been obtained from the scientific committee of the scientific council of Obstetrics and Gynecology – Iraqi Board for Health Specializations.

Data entry and analysis

Data entry was done using Microsoft Excel 2019. Data was recorded into different quantitative and qualitative variables for the purpose of analysis.

Analysis was done using statistical package for social sciences (SPSS version 26).

Data was summarized using measures of frequency (mean), dispersion (standard deviation), tables and graphs. A two-tailed p value of less than or equal to 0.05 was assigned as a criterion for declaring statistical significance.

CHAPTER THREE

Results

3.1. The study sample

A total number of 100 patients were included in the study sample.

3.2. Age and parity distribution of the studied sample

The age distribution of the studied sample ranged from (16-40 years) with a mean of (28.1 years ± 5.7 SD) in the cases group and (28.2 years ± 5.0 SD) in the control group. No significant difference was detected in age between cases and controls. Regarding age group distribution, most of the studied sample were in the age group (20-29 years). Concerning parity, the majority of the studied sample were multiparous. No significant difference was detected in parity between the cases and control group; as illustrated in table (**3.1**).

Table (3.1): Age and parity distribution of the studied sample.

Parameter	Cases (N=50)	Controls (N=50)	P value
Age			
<20 years	4	0	0.941
	8.0%	0.0%	
20-29 years	28	28	
	56.0%	56.0%	
30-39 years	16	22	
	32.0%	44.0%	
40 years	2	0	
	4.0%	0.0%	
Mean ± SD	28.1 years ± 5.7	28.2 years ± 5.0	
Parity			
Primiparous	4	6	0.937
	8.0%	12.0%	
Multiparous	46	44	
	92.0%	88.0%	

3.3. BMI of the studied sample

The pregnancy BMI of the studied sample ranged from (24.3-32.5 kg/m^2) with a mean of (29.63kg/m^2 ±2.3 SD). Concerning pre-pregnancy BMI, (32.0%) were of normal weight, while (68.0%) were overweight. The BMI of the controls group was significantly higher than that of the cases group; as illustrated in table (**3.2**).

Table (3.2): pre-pregnancy BMI of cases and controls

Pre-pregnancy BMI	Cases (N=50)	Controls (N=50)	P value
Normal weight (BMI=18.5-24.9kg/m^2)	32	0	<0.001
	64.0%	0.0%	
Overweight (BMI=25.0-29.9kg/m$^{2)}$	18	50	
	36.0%	100.0%	
Mean ± SD	24.5kg/m^2±1.6	26.9kg/m^2±1.0	

3.4. Gestational age of patients with preterm labor (cases)

Regarding gestational age of 50 patients with preterm labor, 2 cases (4.0%) had very preterm labor (gestational age 28-32 weeks), while the rest of cases (96.0%) had moderate to late preterm labor (gestational age 32-37 weeks); as illustrated in table (**3.3**).

Table (3.3): Subcategories of preterm labor of the cases group for gestational age (categorized according to the WHO).

Gestational age of cases	Frequency	Percentage
Very preterm (28-32 weeks)	2	4.0
Moderate to late preterm (32-37 weeks)	48	96.0
Total	50	100.0

3.5. Blood lead and Cadmium levels of the studied groups (according to WHO)

The lead levels of the studied sample ranged from 11-31 µg/dl with a mean of 20.8 µg/dl ± 5.4; and thus, all the studied sample had blood lead levels higher than that considered acceptable by the WHO (<10 µg/dl). The blood cadmium levels ranged from 0.11-0.42 µg/dl with a mean of 0.26 µg/dl ± 0.08; hence, the vast majority of the studied sample (98.0%) had blood Cd levels higher than that considered acceptable by the WHO (<0.12 µg/dl); as illustrated in table (**3.4**).

Table (3.4): Blood lead and cadmium levels in the studied sample according to WHO

Blood Lead and Cadmium levels	Frequency	Percentage
Blood Pb		
<10 µg/dl	0	0.0
≥10 µg/dl	100	100.0
Total	100	100.0
Blood Cd		
≤ 0.12 µg/dl	2	2.0
>0.12 µg/dl	98	98.0
Total	100	100.0

3.6. Distribution of cases and control groups of lead according to level considered acceptable by Iraqi poisoning consultation center (P.C.C)

Using cut-off value of 25 µg/dl for blood lead as accepted by the Iraqi Poisoning Consultation Center), the women with preterm labor (24 women) were significantly higher than women with term labor (0 women), (P-value <0.001) with a sensitivity of 48%, specificity of 100%, PPV of 100%, NPV of 65.7%, and accuracy of 74%; as illustrated in table (**3.5**) and figure (**3.1**).

Table (3.5): blood lead level in studied groups according to the Iraqi poisoning consultation center (PCC)

Blood lead level	Labor		Total	P value
	Preterm	Term		
≥25 µg/dl	24	0	24	<0.001
<25 µg/dl	26	50	76	
Total	50	50	100	

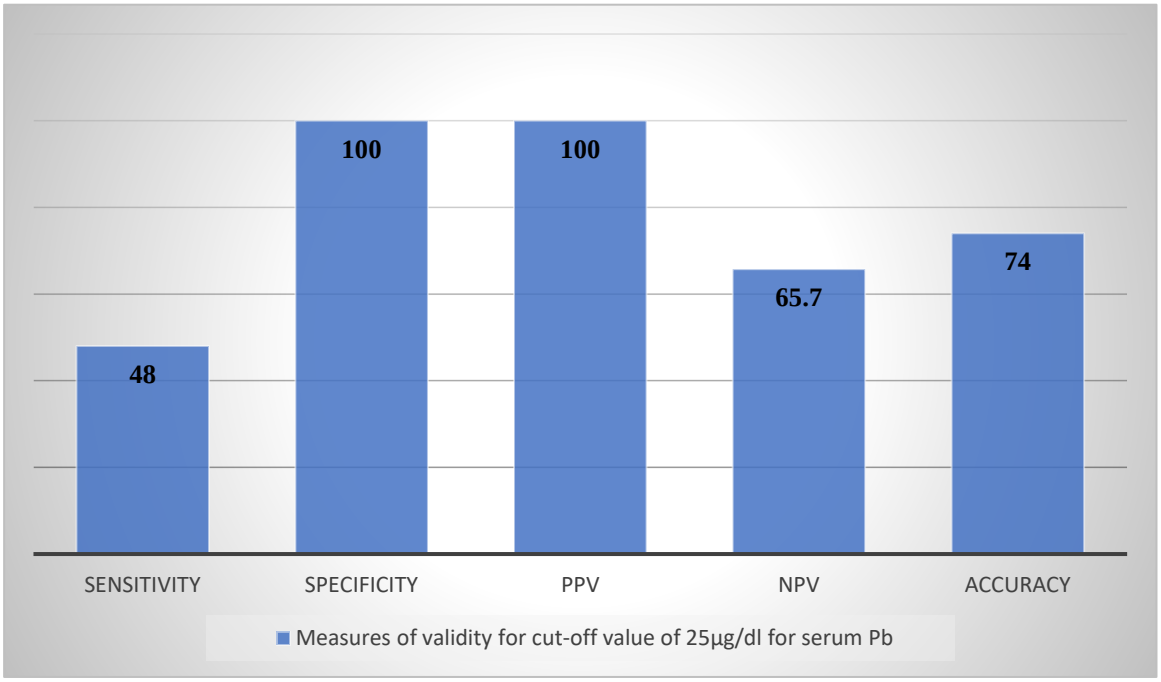

Figure (3.1): Measures of validity for cut-off value of 25µg/dl for blood lead.

3.7. Distribution of cases and control groups of cadmium level according to the Iraqi poisoning consultation center (P.C.C)

Using cut-off value of 0.3 µg\dl for blood cadmium as accepted by the Iraqi Poisoning Consultation Center), the women with preterm labor (34 women) were significantly higher than women with term labor (0 women),(P-value <0.001) with a sensitivity of 68%, specificity of 100%, PPV of 100%, NPV of 75.7%, and accuracy of 84%; as illustrated in table (**3.6**) and figure (**3.2**).

Table (3.6): Blood level of cadmium in the studied groups as accepted by the Iraqi poisoning consultation center (PCC)

Blood cadmium level	Labor		Total	P value
	Preterm	Term		
≥0.3 µg/dl	34	0	34	<0.001
<0.3 µg/dl	16	50	66	
Total	50	50	100	

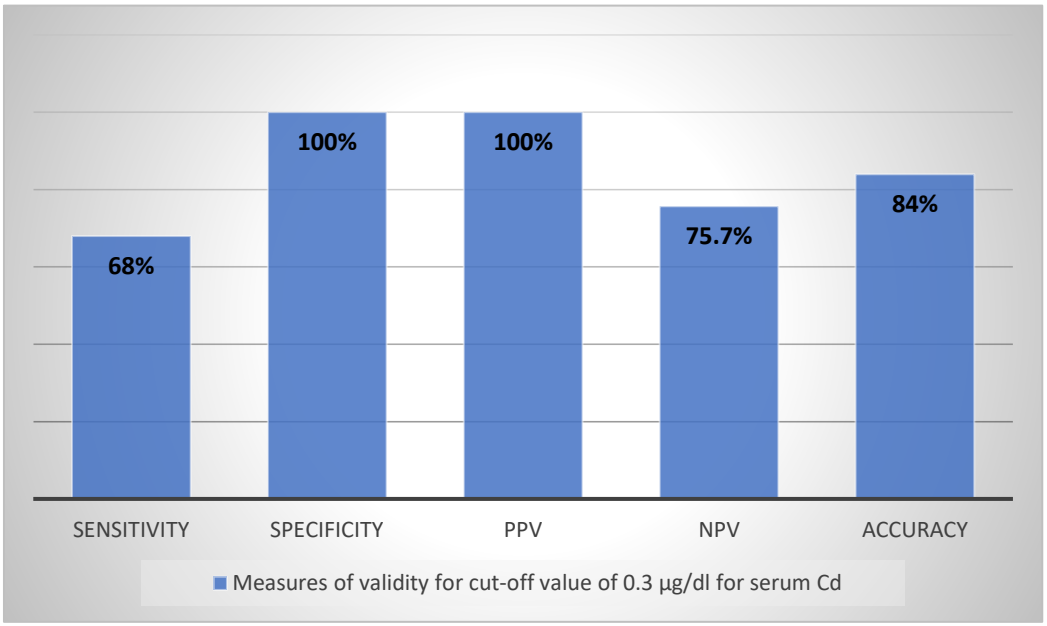

Figure (3.2): Measures of validity for cut-off value of 0.3 µg/dl for blood Cd.

3.8. Lead and Cadmium levels in cases and controls

Blood lead and cadmium levels in cases and controls are illustrated in table (**3.7**). The cases group had significantly higher blood Pb levels (p value <0.001) and blood Cd levels (p value < 0.001) than the control group.

Table (3.7): Blood Lead and Cadmium levels in cases and controls

	Cases (N=50)	Controls (N=50)	P value
Blood Pb			
Mean ± SD	25.60 µg/dl ± 2.6	16.08 µg/dl ± 2.7	<0.001
Blood Cd			
Mean ± SD	0.33 µg/dl ± 0.05	0.19 µg/dl ± 0.03	<0.001

CHAPTER FOUR

DISCUSSION:

In the present study, 100 women were assessed (50 cases and 50 controls) of which the majority were (20-29 years old), multiparous, and in the last trimester of pregnancy. This goes with study done in Japan, (Tsuji et al.) included 14,847 women (of whom the mean age was 31.4 and the majority were multiparous) to evaluate their blood Pb and Cd levels women in the pregnancy weeks (14-39).[66]

In the current study, the mean maternal blood Pb level was **20.84 µg/dl**. This figure is much higher than 10µg/dL that considered acceptable by the WHO.[67]

Although up to this moment; no similar statements has been released by the CDC, as the CDC has not identified an allowable exposure level, level of concern, or any other bright line intended to connote a safe or unsafe level of exposure for either mother or fetus. Instead, CDC is applying public health principles of prevention to intervene when prudent. Cohort studies suggest that prenatal lead exposure, even with maternal blood lead levels below 10 µg/dL, is inversely related to fetal growth and neurodevelopment.[68]

The mean level of current study was higher than other studies like: In Mexico City, (Cantonwine et al.) reported an average baseline blood lead of **7.07 µg/dL**.[69] In China, (Li et al.) reported mean blood Pb level of **1.50 µg/dL** with a range from 0.020 to 5.46 µg/dL.[70] While in Iran, the study by (Vigeh et al.) reported that the mean was **3.5 µg/dl**.[71] In the United States, (Rabito et al.) reported that the average lead typically found in pregnant women is **<1µg/dL**.[72]

The reason for the outstandingly higher blood lead levels in Iraqi women can be attributed to the fact that Iraq is one of just six countries that still use leaded gasoline, despite its worldwide ban.[73] (Angrand et al.) examined worldwide blood lead levels after the implementation of gasoline ban, and found that removal of lead from gasoline is associated with declines in blood Pb in all countries examined. In some countries, blood Pb continues to fall after lead has been eliminated from gasoline. Following elimination of lead from gasoline, blood Pb less than 1 µg/dL was observed in several European and North American countries, and blood Pb less than 3 µg/dL have been documented in several studies from South America. The authors concluded that the removal of lead from gasoline has been a public health success, as the elimination of lead from gasoline has enabled many countries to achieve population mean blood Pb levels of 1 µg/dL or lower.[74]

Although this research found that blood lead levels were elevated in both cases and controls, blood lead levels in the cases group were significantly higher than their control counterparts. As 24 (48.0%) women with preterm labor had blood Pb levels ≥25 µg/dl, while no such levels were detected in any of the control group. This finding is in concordance with the case control study by (Vigeh et al.) in Iran that included 348 women (44 cases and 304 controls) and reported a

significantly higher Pb level in mothers who delivered preterm babies compared to women who delivered at term.[71]

The cohort study conducted by (Li J et al.) assessed 3125 patients and found that maternal blood lead levels in the range of (1.18–1.70 µg/dL) were associated with two-fold increased risk of preterm birth, and Pb levels (>1.70 µg/dL) were linked to three-fold increased risk.[70] A similar conclusion was reached in the study by (Li Z et al.) that included 408 subjects (102 cases and 306 matched controls).[10]

In the USA, (Jelliffe-Pawlowski et al.) conducted a cross sectional study that included 262 pregnant women reported that the blood Pb levels ≥10 µg/dL during pregnancy was associated with 3.2 higher risk of preterm birth.[76]

In Mexico, (Cantonwine et al.) examined the association of blood Pb in different trimesters with the risk of preterm birth in 235 women (22 with preterm birth and 213 with term birth). They concluded that maternal Pb exposure during the second trimester carried the highest risk of preterm labor.[77]

An important finding of the current study is that is that blood lead levels ≥25 µg/dl had a PPV of 100.0% for preterm labor. In the UK, the study by (Taylor et al.) used a cut-off value of ≥ 5 µg/dL for blood Pb level.[78] They justified their choice of this value by citing the ACOG committee opinion No. 533, which states that a blood Pb level of ≥5 µg/dL in pregnant women should initiate lead monitoring.[79]

Contrary to the findings of the current research, the study by (Perkins et al.) assessed blood lead in 949 mother-child pairs and found that maternal RBC lead was not associated with preterm birth. However, it should be taken into consideration that their study was conducted in a society with low exposure level to lead (mean blood lead level in their study was 1.2 µg/dL).[80]

The underlying pathophysiology and molecular processes by which lead is linked to premature labor are not well known, possible mechanism are:

1. Lead exposure may induce hormonal changes (a higher estrogen-to-progesterone ratio), which is linked to higher contractility of the uterus during the final weeks of pregnancy.
2. Lead might shorten the duration of contraction by inducing uterine contractility through calcium mediated control.[71]

As for blood cadmium, maternal levels were shown to have mean of **0.26 µg/dl**, which is also higher than the level considered acceptable by the WHO.[81] This level is also higher than other studies, such as The study by (Hua Wang et al.) obtained a value of **0.089 µg/dl**.[82] The study by (Johnston et al.) found that the median Cd concentration was **0.046 µg/dl**.[83]

It is reasonable to assume that leaded fuel is also the main culprit of the disproportionately high levels of blood Cd in the present study, since leaded gasoline is also a source of cadmium exposure.[84] Smoking can also be blamed (including passive smoking), as the tobacco plant naturally accumulates relatively high concentrations of cadmium in its leaves.[85]

The current study found that Cadmium levels in the cases group were significantly higher than the control group, as 34 (68%) women with preterm labor had blood Cd levels ≥0.12 µg/dl, whereas no such levels were detected in any of the control group. This findings is in concordance with other studied, such as the cross sectional study that included 3254 women by (Wang et al.) who measured Cd in maternal blood of 3254 pregnant mothers and showed that preterm labor was around three times more common in women with high Cd levels (>0.95 mg/L) compared to those with low levels (<0.65 mg/L). [86]

(Huang et al.) in China measured urine Cd levels of 408 pregnant women in a case-control study and reported increased risk of preterm low birth weight (PLBW) among women with a Cd level of ≥0.70 µg/g.[87]

In Turkey, (Ozsoy et al.) conducted a cross sectional study that included 810 mothers. The authors measured meconium Cd levels and found a significant association between meconium Cd level and preterm delivery of unknown etiology.[88]

As for the mechanism by which Cd exposure may lead to preterm labor, several theories are proposed:

1. Cadmium may induce zinc deficiency,[89] which is in turn associated with increased risk of preterm birth.[90]
2. Cadmium may induce preterm labor by increasing reactive oxygen species (ROS) or inflammatory cytokines.[86]

CHAPTER FIVE

CONCLUSIONS AND RECOMMENDATION

5.1. CONCLUSION

1. Maternal blood lead and cadmium levels were extremely higher than the level considered acceptable by the WHO and considerably higher than other studies.
2. Moreover, the present study found that both studied heavy metals may contribute as risk factors of preterm labor.

5.2. RECOMMENDATION

1. Measurement of lead and cadmium level in pregnant women with high risk of preterm labour from early pregnancy.
2. To counteracts the harmful effect of lead and cadmium, we should advice pregnant women for increasing milk consumption which acts as a chelating agent.

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