International Journal of Women's Health

Dovepress

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ORIGINAL RESEARCH

Placental Barrier on Cadmium Transfer from Mother to Fetus in Related to Pregnancy Complications

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Purpose: As two of the most severe and common medical disorders during pregnancy, gestational diabetes mellitus (GDM) and hypertensive disorder complicating pregnancy (HDCP) cause adverse effects on placental barrier function and thus may lead to a high risk of intrauterine exposure to toxic metals from mother to fetus. This study investigates the impact of the placental barrier on the transfer of cadmium (Cd) from mother to fetus and the relationship between pregnancy complications.

Methods: A total of 107 pairs of samples were collected in Kunming, China; 29 were from healthy pregnant women, and 78 were from patients with pregnancy complications. Cd was measured in each mother's placenta and maternal and umbilical cord blood. The expressions of MT and Cd-MT complex in blood and placental tissue samples were determined by enzyme-linked immunosorbent assay (ELISA).

Results: The cesarean section rate in the whole pathological group (60.7%) was higher than that in the normal group (20.7%), and the ratio of the effective barrier (ratio of maternal blood to umbilical cord blood>1) in the pathological group (74%) was lower than that in the normal group (79%). In addition, the proportion of practical placental barriers in women aged 20–25 years was 83.3%, 76.3% in women aged 26–30 years, 74.3% in women aged 31–35 years, 70% in women aged 36–40 years, and 71% in women aged 40–45 years. The Cd content in the placenta of the three pathological groups was significantly higher than that in maternal and umbilical cord blood ($P<0.05$), and the distribution of Cd was the same as that in the normal group. However, there was no significant difference between maternal and umbilical cord blood Cd concentrations in the pathological group. The Cd concentration in the normal group's maternal blood was significantly higher than that in cord blood ($P<0.05$). In addition, the expression levels of both metallothionein (MT) and Cd-MT complex in placenta is much higher than in maternal and umbilical blood, and which in normal group are significantly higher than those in pathological group.

Conclusion: Both mothers and fetuses are at increased health risk for pregnancy disorders when maternal age, BMI, or body weight increases. Increased maternal age increases the likelihood of Cd transfer from the mother to the fetus. Pregnancy complications may induce lower expression of MT, thus reducing the Cd-MT complex in the placenta, weakening the placental barrier, and increasing the risk of Cd transfer and exposure to the fetus.

Keywords: gestational diabetes mellitus, gestational hypertension, maternal blood, placenta barrier, pregnancy complication

Introduction

Toxic metals are environmental contaminants known to be harmful to wildlife and humans. They may directly interact with organisms in water, soil, and air and enter mammals through the respiratory tract, skin, and digestive tract.[1] Thus, the widely distributed toxic metals accumulate in organisms, in blood, liver, uterus, placenta, and even bones.[2] Even at low concentrations, toxic metals can affect human activities and threaten human health. Therefore, an increasing number

Received: 11 October 2022
Accepted: 18 January 2023
Published: 10 February 2023

of researchers have provided new evidence on the health hazards of toxic metals, especially in the vulnerable group of pregnant women.[3] Studies have shown that toxic metals can pass through the placental barrier to cause prenatal fetal exposure and trigger various gestational diseases, low neonatal birth weight, intrauterine growth retardation, deformities, and other adverse outcomes.[4–6] Embryos in early fetal development are vulnerable to the influence of toxic elements.[7] Exposure to toxic elements during fetal organ formation leads to irreversible morphological changes and adverse functional consequences.[8] Given the potentially negative impact on fetuses, it is of great importance to illustrate the transfer processes of toxic metals from mother to fetus and understand the operation mechanisms of the placental barrier.

Cadmium(Cd) is an ecotoxic toxic metal of considerable environmental and occupational concern[4] and has been identified as a human carcinogen by the International Agency for Cancer Research.[9] In mammals, Cd accumulates mainly in the kidney, liver, lung, bone, testicles, and brain, where it can cause severe oxidative stress and other harmful effects.[10] It can combine with protein molecules containing hydroxyl (-OH), amino (-NH), and thiol (SH-) groups to form complexes and thus inhibit many enzyme systems (even deactivate enzyme activity). Consequently, the normal physiological functions of the liver and other organs are destroyed, which may influence the body's digestion and absorption of protein, fat, sugar, and other nutrients, causing hypertension and cardiovascular disease.[11] Pregnant women and fetuses are more susceptible to environmental stresses as a high-risk population in a polluted environment.

The incidence of hypertensive disorder complicating pregnancy (HDCP) and gestational diabetes mellitus (GDM), which are unique diseases in human pregnancy, is increasing yearly. These diseases seriously affect maternal and neonatal health and are two major causes of pregnancy-related maternal and perinatal death. In addition, these diseases may disturb normal physiological processes and consequently alter toxic metal transfer in the human body. Hypertension caused by Cd has been extensively studied in animal models, and the results indicate that pregnant animals are more sensitive to the toxicity of Cd than nonpregnant animals. Larsen et al's research[12] showed that Cd exposure during pregnancy could affect the vascular system of the fetus, reducing placental blood flow and the gas and nutrient exchange area between the mother and fetus and increasing the risk of intrauterine growth retardation. Cd concentration in maternal blood, placenta, and umbilical cord blood in human beings has been investigated to assess health risks to the mother or fetus, but only for individual measurements without paired samples.

In this study, regular long-term residents in Kunming were selected as the research subjects. This work aims to explore (I) the concentrations and distribution patterns of Cd in the maternal-fetal system in the Kunming area and (II) the potential for Cd transfer in the maternal-fetal system as affected by pregnancy complications. This line of study will provide vital information for pollution control and healthy pregnancy.

Materials and Methods

Study Population and Sample Collection

The investigation was carried out according to the principles of the Declaration of Helsinki. This project was approved by the Medical Ethics Committee of the First People's Hospital of Yunnan Province. The research population was restricted to pregnant women who attended the antenatal clinic and delivered in the Department of Obstetrics of the First People's Hospital of Yunnan Province from 2019 to 2020. After carefully screening the questionnaire, 107 pregnant women were selected as the research subjects. The inclusion criteria for pregnant women were as follows: (I) being 20–45 years old; (II) have no special or occupational exposure history; (III) no bad habits, such as smoking, alcohol consumption, and drug abuse; (IV) no neonatal death or malformation, stillbirth, twin or multiple births; and (V) non-illiterate, have ability to sign informed consent. Other extra exclusion criteria for women with pregnancy disorders were as follows: (I) pregnancy-induced GDM or HDCP before 26 weeks of pregnancy; (II) pregnant women had prepregnancy disorders (hypertension, diabetes, heart, liver, or kidney disease).

We studied 107 pregnant women as subjects and measured Cd levels in maternal blood, umbilical cord blood, and placenta. Women with no complications and full-term deliveries during pregnancy were considered the normal group (n=29). Pregnant women with pregnancy complications were marked as the pathological group, including the GDM group (n=27), HDCP group (n=32), and HDCP & GDM group (both GDM and HDCP, n=19). After signing the informed

consent form and ethics document, maternal blood, placenta, and umbilical cord blood were collected during childbirth. All the samples were stored at −80 °C until analysis.

The questionnaire used included the following information: educational level, smoking, drug use, alcohol consumption, potential environmental exposures, occupation, and lifestyle. Other information was obtained from the medical records, such as maternal age, height, weight, parity, medical history, gravidity, pregnancy complication diagnosis, place of residence, ethnic group, infant birth date, Apgar scores, and gestational age.

Collection and Preparation of Blood and Placental Samples

Approximately 10–20 g of the placenta, 10 mL of maternal venous blood, and 6 mL of umbilical cord blood were sampled immediately after delivery by well-trained obstetricians or midwives. The maternal and umbilical cord blood was placed in a vacuum blood collection tube, and the placenta was placed in a polyethylene plastic bag. All samples were labeled and transported frozen and stored at −80 °C until used for subsequent experiments. For laboratory analysis, the placenta samples were thawed at 4 °C, and approximately 5 g was taken from the middle point between the edge of the placenta and the cord attachment site on the fetus side. The samples were rinsed three times with deionized water and then dried with clean tissue paper to remove excess water. One gram of placental tissue (wet weight), 5 mL of nitric acid (BV-grade III), and 2 mL of H_2O_2 were mixed for high-pressure microwave digestion. The blood samples (0.5 g), 3 mL of nitric acid (BV-grade III), and 1 mL of H_2O_2 were mixed in a polyethylene tetramethylene bottle for high-pressure microwave digestion.

The power profile used for microwave digestion was as follows: the power of the digestion system was set at 600 W for the first phase, followed by 5 min ramping and 5 min holding. In the second phase, the power was increased to 1400 W, followed by 5 min of ramping and 10 min of holding time. Finally, the power was turned to zero with a holding time of 15 min.[13] After digestion, the samples were diluted to 20 mL with 1% HNO_3.

Instrumental Analyses of Cd

The prepared samples were subjected to the inductively coupled plasma–mass spectrometry (ICP–MS, NexION 350X, USA) for Cd quantification. The ICP–MS measurement conditions were set as follows: power 1050 W, carrier gas flow 0.90 L/min, cooling gas flow 15 L/min, auxiliary gas flow 1.80 L/min, analysis chamber vacuum 1.18×10 Pa, detector pulse voltage 900 V, resolution (10% peak height) 0.8 μ and 0.6 μ, sample lift 1 mL/min, dwell time 100 min, repeat times 3, measurement peak 1, and number of cycles 10.

The Cd standard solution certification standard was 1000 μg/mL, purchased from Aladdin, according to the selection principle of the internal reference standard and literature reference.[14] The ICP–MS system detected ^{114}Cd and selected ^{115}indium (^{115}In) as the internal reference element for calibration. A certain volume of element standard solution and internal standard stock solution were placed in a volumetric flask, diluted with nitric acid solution, and prepared into 0.2, 1, 10, 20, and 50 μg/L calibration series. The internal standard stock solution was directly added to the calibration series. The calibration curve was established with the concentration of metal elements as the abscissa and the ratio of the response value to the internal standard response value as the ordinate. During each analysis, the corresponding value of the internal standard was between 70% and 130% of the calibration curve value. ICP–MS detection was conducted in kinetic energy discrimination (KED) mode. Two blank solutions were prepared for each analysis.

Expression Analysis of Metallothionein (MT) and Cd-MT Complex

The expressions of MT and Cd-MT complex in blood and placental tissue samples were determined by enzyme-linked immunosorbent assay (ELISA).[15,16]

Statistical Analysis

The Statistics Package for Social Science (SPSS) for Windows, version 17.0 was used for the statistical analyses. An independent sample *t*-test was used to evaluate whether there were any significant differences in terms of toxic metal concentrations in different groups (GDM group, HDCP group, GDM & HDCP group). A P value of < 0.05 was considered statistically significant.

Results

Maternal Characteristics and Neonatal Parameters

The maternal characteristics and neonatal parameters for the pathological (n = 78) and normal (n = 29) groups are listed in Table 1. The maternal age, weight, and body mass index (BMI) of the normal group ranged from 21 to 41 years old, 54 to 79 kg, and 20.62 to 30.86 kg/m^2, respectively. The maternal age, weight, height, and BMI of the pathological group ranged from 22 to 44 years old, 55 to 121 kg, 153 to 176 cm, and 21.48 to 33.22kg/m^2, respectively.

The Apgar score provides a general summary of the health of newborn children. As shown in Table 1, the neonatal Apgar scores at 1 minute and 5 minutes were significantly lower in the pathological group than in the normal group ($P < 0.05$). Meanwhile, the cesarean section rate of the pathological group was 60.7%, which was much higher than the 20.7% of the normal group.

The Placental Barrier to Cd Transfer in the Normal Maternal-Fetal System

Table 2 shows the distribution of Cd in maternal venous, placental and umbilical cord blood in this study and elsewhere in the world. According to the recommendation by the WTO expert group, the biological threshold of Cd in the blood of the nonoccupational population was 5 μg/L. Thus in the normal group, 14% of maternal blood samples and 3% of umbilical cord blood samples were collected, and in the pathological groups, 19% of maternal blood samples and 22% of umbilical cord blood samples exceeded the above threshold.

As presented in Figure 1, for the normal group, the concentrations of Cd in the placenta were significantly higher than those in maternal blood and umbilical cord blood, and all the *P* value were <0.005. The results indicated that the placenta can effectively block the entry of Cd from mother to fetus.

Differences Between the Pathological Groups and the Normal Group

The measured Cd concentrations in the maternal-fetal system in the three pathological groups are shown in Figure 1. Cd levels in the placenta was significantly higher than those in maternal blood and umbilical cord blood in the three pathological groups ($P<0.05$), which is similar to the Cd distribution in the normal group. However, no significant difference in Cd concentrations between the maternal blood and umbilical cord blood was observed in the pathological groups. The concentration of Cd in the maternal blood was significantly higher than that in umbilical cord blood ($P<0.05$) in the normal group. This phenomenon indicates that pregnancy complications may reduce but not destroy the function of the placental barrier while increasing the risk of Cd metastasis and exposure to the fetus.

The effectiveness of the placental barrier was shown by a higher Cd concentration in maternal blood than that in umbilical cord blood (eg, a ratio of maternal blood to umbilical cord blood >1). Figure 2 shows the effective placental

Table 1 Comparison of Maternal and Neonatal Characteristics in the Pathological and Normal Groups

	General Characteristics	Normal Group	Pathological Groups							
			GDM	*P* value	HDCP	*P* value	GDM & HDCP	*P* value	Total	*P* value
	Sample numbers	29	27		32		19		107	
Maternal	Age (years)	27.9±4.7	29.9±5.2	>0.05	31.3±5.0	<0.05	33.2±5.7	<0.01	31.5±5.4	<0.01
	BMI (kg/m^2)	25.9±2.6	28.0±2.4	<0.05	27.6±1.8	<0.05	29.7±4.1	<0.01	28.4±3.0	<0.01
	Weight (kg)	67.2±7.4	72.6±9.9	>0.05	71.5±7.4	>0.05	78.7±15.0	<0.05	74.2±11.4	<0.01
	Cesarean rate (%)	20.7	51.9		87.5		89.5		60.7	
Neonatal	Weight (kg)	3.2±0.4	3.3±0.7	>0.05	2.5±0.8	<0.01	3.2±0.6	>0.05	3.0±0.7	>0.05
	Height (cm)	50.1±2.2	49.8±3.0	>0.05	45.9±4.6	<0.01	50.4±2.2	>0.05	48.7±3.9	>0.05
	Apgar score in 1 min	9.00±0.00	9.00±0.00	>0.05	8.86±0.36	>0.05	8.86±0.35	>0.05	8.91±0.30	<0.05
	Apgar score in 5 mins	9.96±0.19	10.00±0.00	>0.05	9.57±0.51	<0.05	9.87±0.35	>0.05	9.81±0.40	<0.05

Notes: The values reported in the table are mean ± standard error. *P* <0.01 and *P* <0.05 indicated a significant difference, while *P* >0.05 indicated no significant difference.

Table 2 Comparison of Toxic Metal Cd Levels in Placenta, Maternal and Umbilical Blood Samples

Sample Type (Unit)	N	Arithmetic Mean ± SD	Median	Range (Min-Max)	Reports from Other Cohorts (Approximate Values)				
					Location	Median	Range	Unit	Reference
Mother blood (μg/kg)	107	5.04 ± 7.6952	2.352	0.228–62.28	Germany (Saudi)	0.983	0.233–3.157	μg/L	[19]
					Spain (Catalonia)	0.4	0.3–2.5	μg/g	[23]
					Sweden	1.4	0.12–18	nmol/L	[20]
					China (Beijing)	0.33	ND-2.69	μg/L	[21]
					Japan	0.037	0.019–0.083	μg/L	[49]
					Slovenia	0.346	0.20–3.084	ng/mL	[18]
					Brazil (Rio de Janeiro)	0.30	0.00–22.43	μg/dL	[24]
					China (Zhejiang)	1.09	0.72–1.31	μg/L	[22]
					South Korea	0.61	0.24–2.80	μg/L	[50]
Placenta (μg/kg wet wt)	107	12.158 ± 9.64976	9.012	1.464–52.584	Germany (Saudi)	0.035	0–4.363	μg/g dry wt	[19]
					South Africa	2.1	0.5–6.9	μg/kg wet wt	[51]
					Sweden	5.2	1.1–19.1	μg/kg wet wt	[20]
					Italy	5.1	2.1–28.6	μg/kg wet wt	[52]
					Spain (Southern)	3.80	0.70–13.60	ng/g wet wt	[53]
					China (Beijing)	0.04	0.01–0.15	μg/g dry wt	[21]
					China (Zhejiang)	3.61	2.19–4.37	μg/kg wet wt	[22]
umbilical cord blood (μg/kg)	107	4.004 ± 6.22236	1.428	0.044–32.976	Germany (Saudi)	0.704	0.245–15.325	μg/L	[19]
					Spain (Catalonia)	0.5	0.2–0.9	μg/g	[23]
					Sweden	0.19	0–0.74	nmol/L	[20]
					China (Beijing)	0.039	ND	μg/L	[21]
					Brazil (Rio de Janeiro)	0.41	0.00–17.41	μg/dL	[24]
					China (Zhejiang)	0.37	0.19–0.46	μg/L	[22]
					South Korea	0.010	0.00–0.22	μg/L	[50]

https://doi.org/10.2147/IJWH.S393067

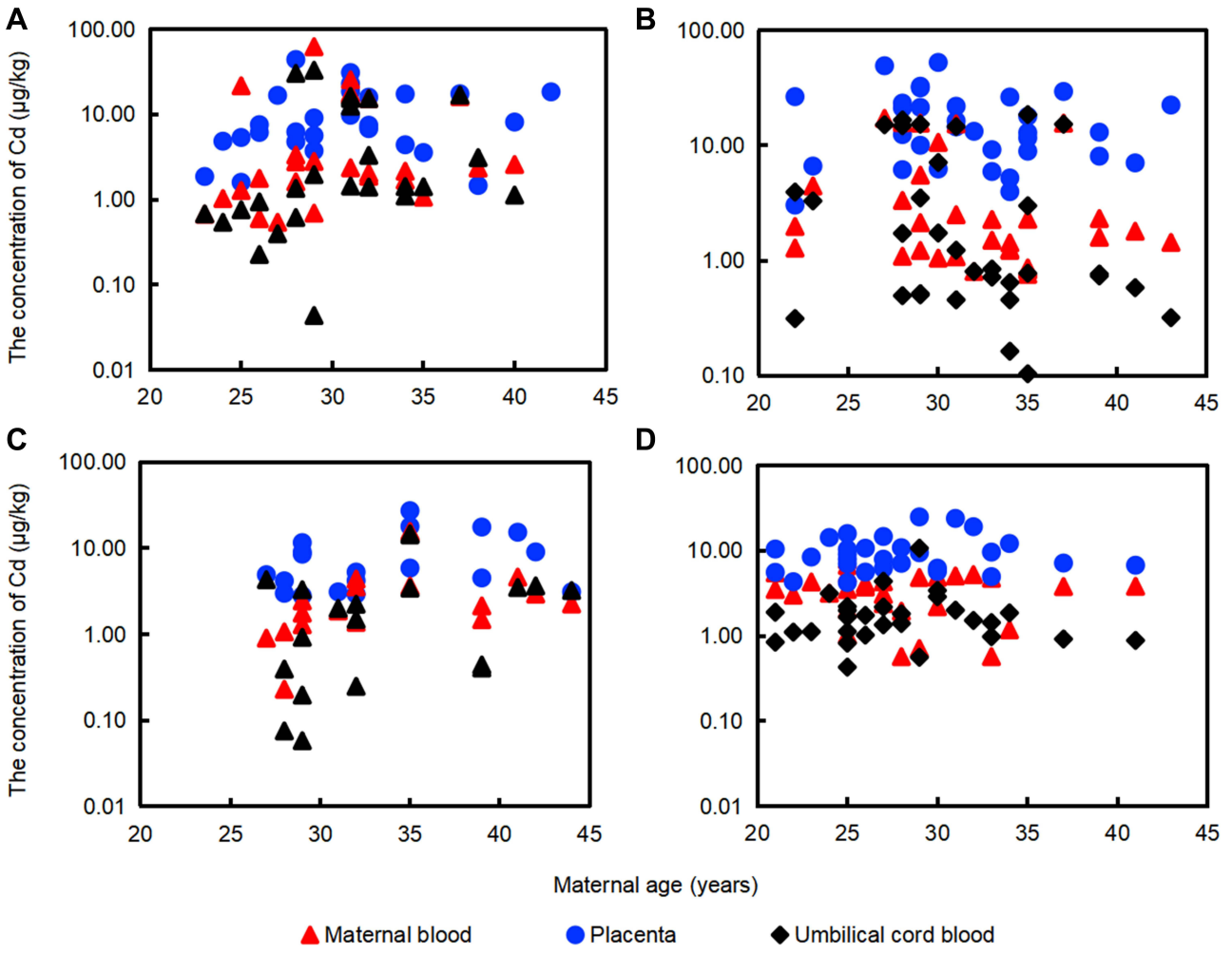

Figure 1 The concentration of Cd in the placenta, maternal blood, and umbilical cord blood in the normal group and pathological groups. (**A**) GDM group; (**B**) HDCP group; (**C**) GDM & HDCP group; (**D**) Normal group.

barrier rate in the normal group and each pathological group. The distribution of this ratio along with maternal age is also shown in Figure 3. As shown in Figure 2, the ratio of the effective placental barrier was 79% in the normal group, slightly higher than 74% in the pathological group. This result suggested that pregnancy complications may weaken the placental barrier. Analyzing the relationship between the age of pregnant women and the placental barrier (Figure 3), it was found that the proportion of effective placental barrier in women aged 20–25 years was 83.3%, 76.3% in women aged 26–30 years, 74.3% in women aged 31–35 years, 70% in women aged 36–40 years, and 71% in women aged 40–45 years. Thus, increased pregnancy age may increase the possibility of Cd transfer from the mother to the fetus.

Comparison of MT and Cd-MT Expression Levels

As discussed above, pregnancy complications fractionally weakened the placental barrier to Cd. This phenomenon may be related to the content of MT in Figure 4. As can be seen from Figure 4, the expression of both MT and Cd-MT complex in placenta is much higher than in maternal and umbilical blood, which indicating the effect of placental barrier. Furthermore, the MT and Cd-MT expression levels in normal group are significantly higher than those in pathological group. Chisolm[17] found that the expression of MT in the placental tissue of HDCP pregnant women was significantly higher than that of normal pregnant women.

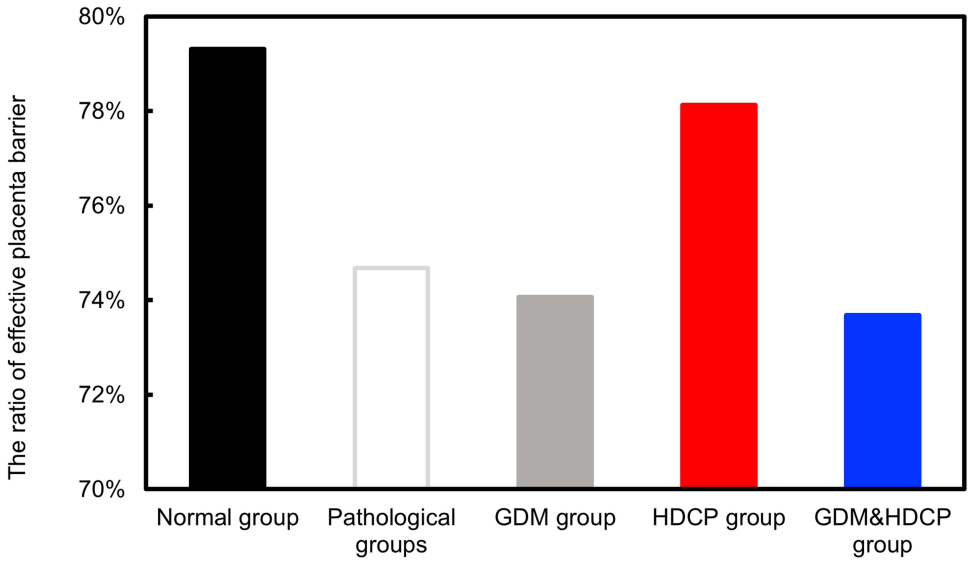

Figure 2 The ratios of effective placental barrier (the percentage of Cd concentrations in maternal blood higher than that in umbilical cord blood).

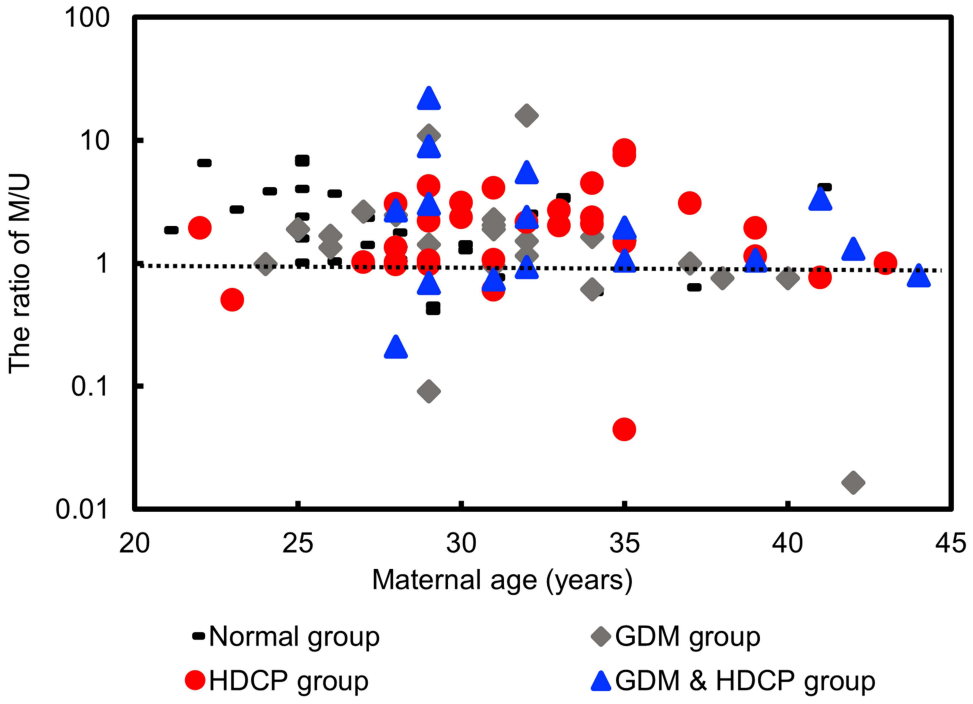

Figure 3 The relationship between the ratio of maternal blood to umbilical cord blood and maternal age.

Discussion

Pregnancy Complications Can Weaken the Placental Barrier

Table 2 shows the distribution of Cd in the maternal fetal system detected in studies around the world. Compared with other studies, the concentrations of Cd in maternal blood, placenta, and umbilical cord blood in Kunming, China were higher than those in Slovenia,[18] Germany (Saudi),[19] Sweden,[20] and Beijing and Zhejiang, China,[21,22] but the concentrations of Cd in maternal blood and umbilical cord blood in Kunming, China were lower than those in Catalonia, Spain[23] and Brazil (Rio de Janeiro).[24] Studies in other regions of the world have reported that the content of Cd in the placenta is higher than that in maternal blood and

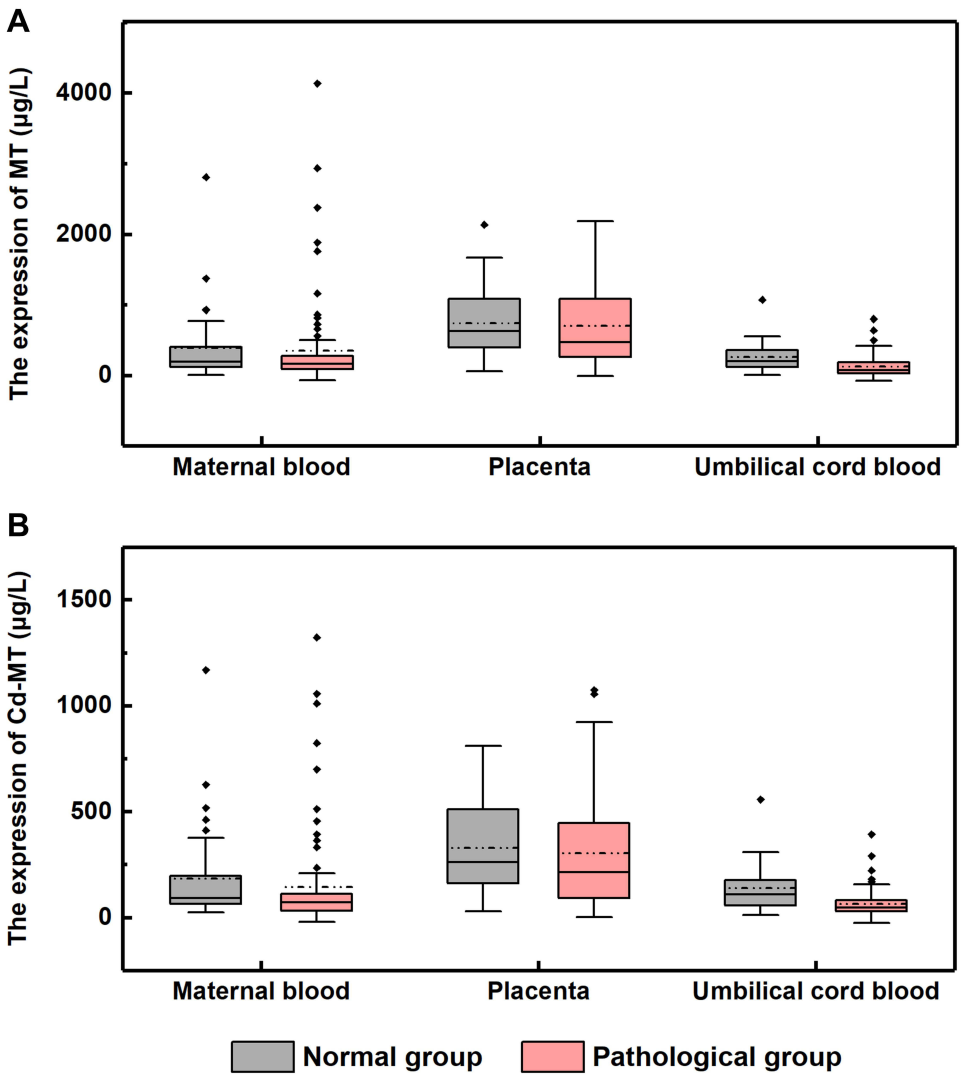

Figure 4 MT and Cd-MT expression levels in placenta, maternal blood and umbilical cord blood between normal group and pathological group. (**A**) Comparison of expression levels of MT; (**B**) Comparison of expression levels of Cd-MT.

umbilical cord blood,[25–27] which is consistent with our results. As a temporary multifunctional organ connecting the mother and fetus,[28] the placenta plays an important role in filtering and blocking harmful substances.[29]

The accumulation of Cd in the placenta is an important process of the placental barrier. The ratio of the effective barrier shows that the placental barrier function of the pathological group is weaker than that of the normal group (Figure 2), which may lead to a higher health risk of prenatal exposure of the fetus in the pathological group to Cd. It is worth noting that our study found that the function of the placental barrier gradually decreased with increasing maternal age, and the increase in maternal pregnancy age may increase the possibility of transferring Cd from the mother to the fetus (Figure 3). There are few relevant reports in other studies. Therefore, the underlying mechanism involved in this finding needs further study. In addition, some studies have shown that the content of Cd in the placenta tends to increase with the age of the mother,[30,31] but this was not found in the results of the present study (Figure 5), which may be due to the limited sample size and requires further examination.

Pregnancy Complications Can Inhibit the Forming of Cd-MT Complex

MT is a highly conserved, cysteine-rich small protein family with multiple key functions such as removing toxic metals and free radicals, maintaining intracellular zinc homeostasis and redox balance, and protecting DNA from damage.[32–34] One hypothesis of

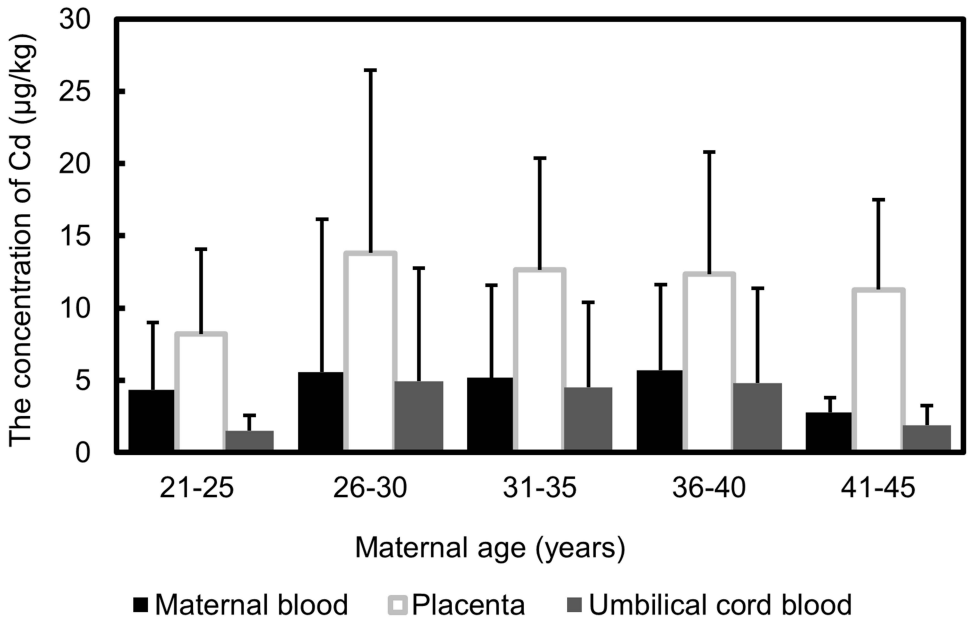

Figure 5 Graphical representation of Cd distribution based on Maternal age statistics.

the placental barrier protection mechanism against Cd is that MT can bind with Cd cations to form a protein complex. Cd is an electrophilic substance, thus inducing the expression of MT.[35,36] Because the thiol (-SH) of MT is nucleophilic, Cd can easily interact with MT, forming a Cd-MT complex in the placenta to reduce the toxicity of Cd. The complex can be retained in placental tissues, thus preventing Cd from transferring into cord blood and the fetus. Therefore, the increased expression of MT seems to be a protective mechanism of the placenta, known as the placental barrier.[37] Mehus's research[38] also showed that MT expression correlated with Cd's contents. However, a certain amount of Cd can still be transported in non-Cd-MT form, as suggested by a study in rats, which cannot be blocked by the placental barrier and accumulates in the liver and kidney of the fetus.[39] Our data presented that pregnancy complications may induce lower expression of MT and Cd-MT, which increasing the toxicity risk of Cd. This would have a long-term impact on the health of newborns and children.[40] Therefore, it is necessary to reduce the exposure of women of childbearing age to the toxic element Cd.

Cd May Induce the Pregnancy Complications, Especially HDCP

Although the etiology of HDCP is not fully understood, much evidence has proven that environmental exposure to Cd is related to the risk of HDCP.[41] Cd plays a role in estrogen-like activity in pregnant women, which can increase the production of autoantibodies, thus inducing HDCP.[42,43] When mice are given Cd, the level of angiotensin II type 1 receptor agonistic antibody (ATI-AA) was significantly increased in the pregnant mouse group, suggesting that the relationship between Cd and ATI-AA was pregnancy dependent.[43] Cd increases the production of immunoglobulin by increasing the expression of AID in B cells, and this immunoglobulin is mainly ATI-AA, which has a strong correlation with preeclampsia, one category of HDCP.[44–46] Therefore, it has been proposed that preeclampsia may be a pregnancy-induced autoimmune disease, and Cd-induced immune abnormalities may be a key pathogenic factor in preeclampsia.[43] Progesterone supplementation may be a possible strategy for the prevention of preeclampsia, because it has the opposite of estrogen, and it can balance the immune abnormalities caused by Cd. Furthermore, Zhang et al's study[47] showed that Cd can affect the level of NO in the body by increasing the production of nitrite (NOx), an indicator of oxidative stress in the placenta. NO damages the vascular endothelium and promotes oxidative stress, thus increasing the risk of HDCP. The occurrence of HDCP is closely related to adverse pregnancy outcomes such as fetal growth restriction (FGR), small gestational age (SGA) newborns, placental abruption and oligohydramnios.[48] Therefore, it is necessary to carefully evaluate the toxic effect of Cd on fetal growth and development in combination with the mother's physical condition.

Strengths and Limitations of the Study

To the best of our knowledge, this is one of the few studies in which collected paired samples of maternal blood, placenta and umbilical cord blood from both normal and pathological group. We clearly observed that the distribution characteristics of toxic metal Cd in the maternal and fetal system and related to pregnancy complications. Our work also has its limitations: Insufficient number of participants was in each group. And the effect of pregnancy complications on the binding ability of MT and Cd remains to be further explored.

Conclusion

This study aimed to investigate the distribution and transfer of Cd in paired samples of placental tissue, maternal blood, and umbilical cord blood in relation to pregnancy complications to provides basic information concerning environmental toxic metal exposure in pregnant women. Both mothers and fetuses are at increased health risk for pregnancy disorders when maternal age, BMI, or body weight increases. The high cesarean rate in the pathological groups indicated that pregnancy complications could induce much higher risks in natural delivery. Increased pregnancy age may increase the possibility of Cd transfer from the mother to the fetus. The results of this study also show that the placental barrier may be weakened because of pregnancy complications, thus increasing the risk of Cd transfer and exposure to the fetus. Fortunately, pregnancy complications may reduce but not completely destroy the functioning of the placental barrier. Moreover, pregnancy complications may induce lower expression of MT, thus forming less complex of Cd-MT in the placenta, which increasing the toxicity risk of Cd. Meanwhile, Cd may induce the pregnancy complications, especially HDCP.

Data Sharing Statement

The data is available upon reasonable request from the corresponding author.

Ethics Approval

This study was approved by the Ethics Review Committee of the First People's Hospital of Yunnan Province (Approval number: KHLL2022-KY085). The data was collected with written permission from the facility director.

Funding

This research was supported by the National Natural Science Foundation of China [grant number: 42167060], Senior Talents Project of Yunnan Health Commission [grant number: L-2018006], Clinical Research Center for Gynecological and Obstetric Disease of Yunnan Province [grant number; 2022YJZX-FC03], and Yunnan Provincial Scientific Innovation Team of Soil Environment and Ecological Safety, Kunming University of Science and Technology [grant number: 2019HC008].

Disclosure

The authors declare that there is no conflict of interest regarding the publication of this article.

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