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Research Article

Preeclampsia Predictability Tools using Trace Metal Screening and Angiogenic Markers is Clinically Valuable

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Abstract

Background: Preeclampsia at molecular and cellular levels was observed as a disease of placentation that is affected by interaction of various factors that could trigger the disease pathological course and behavior. Prenatal environmental metals exposure is considered a cornerstone factor that could trigger the clinical presentation of preeclampsia due to toxic effects of some trace metals, besides the deficiency of some trace elements is considered a crucial issue in cell apoptosis and remodeling is one of the characteristic features of trophoblastic invasion.

Aim: To investigate the predictability value of trace metal screening in predictability of preeclampsia clinical development.

Methodology: The current research clinical trial is prospective in manner that recruited 420 research study subjects from January 2017 till April 2019 ,inclusive research criteria were singleton gestations with no congenital fetal anomalies all recruited research study subjects had full clinical history taking and examination during antenatal visits urinary samples obtained during 10th till 15th gestational weeks were assessed for the trace metal profile investigated and angiogenic markers. Urine samples were collected at 10th till 15th gestational weeks and stored at − 80 °C until analysis after delivery, preeclampsia diagnosis and diagnosis date were abstracted from medical records. Preeclampsia was clinically defined as elevated maternal blood pressure (>140mmHg systolic and/or >90mmHg diastolic) and proteinuria (>300 mg/24 h or a protein/creatinine ratio >0.20) after 20 gestational weeks.

Results: Cr chromium at Cut off point >0.92 have AUC= 0.747, statistical Sensitivity= 80.0, statistical Specificity=60.8, PPV=13.6, NPV =97.5, Se selenium at cutoff point ≤ 35.4 have AUC= 0.759, statistical Sensitivity=83.3, statistical Specificity=62.6, PPV=14.6, NPV =98.

Conclusion: The current study provokes the clinical value for trace metal screening in detectability of preeclamptic risk of development, however future research efforts are requiring correlating the clinical risk of disease development according to the environmental trace metal levels.

Introduction

Preeclampsia is a global reproductive disease that is characterized by elevated blood pressure levels and proteinuria after 20 gestational weeks, various theories were proposed by researchers that leaves preeclampsia pathophysiology a complex disease as regard the pathophysiological basis [1-3]. Preeclampsia at molecular and cellular levels was observed as a disease of placentation that is affected by interaction of various factors that could trigger the disease pathological course and behavior. A growing interest all over the world is to reveal any biomarkers that could early detect the disease development in a manner that could improve the clinical management of the disease reducing the morbidity and mortality issues [4-6].

Disordered physiological process of spiral artery remodeling, have raised the interest of using angiogenic biomarkers for predictability of preeclampsia risk, soluble fms-like tyrosine kinase-1 and placental growth factor are prominent angiogenic biomarkers that could reflect the effectiveness and adequacy of placental angiogenesis process and are considered family members of vascular endothelial growth factors .integration of both biomarkers particularly when used in the form of ratio was observed by prior research groups to be highly effective in detectability of pre-eclamptic issues arousal [7-9]. Prenatal environmental metals exposure is considered a cornerstone factor that could trigger the clinical presentation of preeclampsia due to toxic effects of some

trace metals, besides the deficiency of some trace elements is considered a crucial issue in cell apoptosis and remodeling is one of the characteristic features of trophoblastic invasion. cadmium (Cd) and lead (Pb), have been observed by various researchers could cause teratogenic impacts on the fetal developmental process particularly within the first gestational trimester besides their well demonstrated raised risk of preeclampsia development [10-12].

On the other hand, it was demonstrated in an interesting manner that the elevated, exposure to essential metals, e.g. selenium (Se) and zinc (Zn), within the safe recommended range values is correlated to higher fertility potential and reduced preeclampsia clinical risk. Those research findings could be justified by the fact that toxic metals could trigger oxidative stress within the placental environment besides causing impaired trophoblastic invasion .another issue of concern that have been displayed from prior research groups is that the toxic metals could provoke immunological abnormalities that would consequently affect the trophoblastic invasion process that relies on complex immunological interactions that safe guard the fetus from allograft process of rejection and it is well known that the affection of immunological adaptive process integrity is a pathophysiological triggering issue for preeclampsia development [13-15]. Essential metals are considered the molecular factors that reduce the oxidative stress that would cause cellular damage therefore their existence in adequate physiological levels would prevent oxidative stress pathological sequale that is well observed in preeclampsia and infertility cases in numerous research efforts [16-18].

Methodology

The current research clinical trial is prospective in manner that recruited 420 research study subjects from January 2017 till April 2019 ,inclusive research criteria were singleton gestations with no congenital fetal anomalies had full clinical history taking and examination during antenatal visits. urinary samples and venous blood samples obtained during 10th till 15th gestational weeks. urinary samples were assessed for the trace metal profile investigated and venous blood samples were assessed for angiogenic markers, exclusive research criteria were cases with multiple pregnancies and fetal anomalies observed during sonographic scanning during last first trimetric scanning, or the mid trimetric full anomaly scanning during antenatal visits all cases were followed up for medical disease development such as DM and preeclampsia development according to preeclampsia development the cases were categorized into two research groups preeclampsia and non-preeclampsia research groups the research data of both groups were statically analyzed in a comparative a manner in correlations to the levels of trace metals investigated and angiogenic markers. Urine samples were collected at 10th till 15th gestational weeks and stored at – 80 °C until analysis after delivery, preeclampsia diagnosis and diagnosis date were abstracted from medical records. Preeclampsia was clinically defined as elevated maternal blood pressure (> 140mmHg systolic and/or > 90mmHg diastolic) and proteinuria (> 300 mg/24 h or a protein/creatinine ratio > 0.20) after 20 gestational weeks.

Urinary Trace Metals Analysis

Twenty four hour urine samples were collected at 10th till 15th gestational weeks and stored at – 80 °C in airtight polypropylene containers until analysis after delivery. Trace metals were analyzed using inductively coupled plasma mass spectrometry (ICP-MS), The metals analyzed included arsenic (As), barium (Ba), beryllium (Be), Cd, copper (Cu), chromium (Cr), mercury (Hg), manganese (Mn), molybdenum (Mo), nickel (Ni), Pb, Se, tin (Sn), thallium (Tl), uranium (U), tungsten (W), and Zn.

Plasma Biomarkers of Angiogenesis

Venous blood samples(5 ml) obtained during 10th till 15th gestational weeks under complete aseptic conditions, allowed to clot and then centrifuged at 3000 rpm for 10 minutes to separate serum that was collected in sterile Eppindorff tube and stored at -10°C till be assayed for circulating maternal sFlt-1 and PlGF Assay of circulating maternal sFlt-1 and PlGF During 10th till 15th gestational trimester using ARCHITECT immunoassays (Abbot Laboratory, Abbott Park, IL, USA). Specifically, unbound PlGF concentrations from 1 to 1500 pg/mL have been assayed and total (unbound and bound) sFlt-1 concentrations from 0.10–150 ng/mL were measured. The ratio of sFlt-1 to PlGF was also calculated for analysis the combined intra- and intraassay coefficients of variation were < 7% for both PlGF and sFlt-1.

Statistical Analysis

Data were collected, revised and performed using SPSS version 23. The data were presented as numbers, percentages, mean, standard deviations and median with inter-quartile range (IQR) and the differences between the two groups were assessed using T-tests, Mann-Whitney test, Chi-square tests, or Fisher's exact tests, when appropriate. Logistic regression analysis for urinary metals as predictors of preeclampsia adjusted for specific gravity, smoking during pregnancy, educational attainment, infant sex, ART, calcium supplementation, pre-pregnancy BMI, and gestational age at study visit to assess. Also, Receiver operating characteristic curve was used to assess the best cut off point with its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under curve (AUC) of the significant urinary metals associated to preeclampsia. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant at the level of < 0.05.

Results

Table 1 reveals and displays the Demographic characteristics of the investigated research groups in which there was no statistical significant difference as regards maternal age, education, smoking and alcohol consumption during pregnancy, parity, gestational DM, Usage of Multivitamins, Calcium Supplements, Iron Supplement During Pregnancy, Maternal sFlt-1Expression (p values=0.453, 0.295 ,0.407, 0.703, 0.869, 0.407, 0.809,0.063, 0.681, 0.410 consecutively)whereas there is statically significant difference

between both research groups as regards Pre-pregnancy BMI (kg/m2), Previous Preeclampsia Diagnosis, Use of ART, Chronic Hypertension, Infant Sex (males), Maternal PLGF Expression ,Maternal sFlt-1/PLGF Ratio (p values <0.001, <0.001, <0.001, <0.001, 0.004, <0.001, 0.004 consecutively).

Table 2 reveals and displays the comparative analysis between preeclamptic and non -preeclamptic research groups as regards trace metals from urine samples (µg/L) Showing no statistical significant difference concerning As arsenic, Ba barium, Cd cadmium, Cu copper, Hg mercury, Mn manganese, Mo molybdenum, Ni nickel, Sn tin, Tl thallium, Zn zinc, Be beryllium, U uranium, W tungsten(p values=0.205, 0.269, 0.307, 0.137, 0.604, 0.731, 0.073, 0.299, 0.227, 0.399, 0.066, 0.185, 0.105, 0.538 consecutively) whereas the levels of Pb lead, Se selenium , Cr chromium whereas statistically significantly different between both research groups (p values =0.020, <0.001, <0.001 consecutively). Table 3 reveals and displays the Adjusted logistic regression analysis for urinary metals as predictors of preeclampsia revealing that there was no statistical significance as regards As arsenic, Ba barium, Cd cadmium, Cu copper, Hg mercury, Mn manganese, Mo molybdenum, Ni nickel, Pb lead, Sn tin, Tl thallium, Zn zinc, Be beryllium, U uranium, W tungsten (p values= 0.125, 0.673, 0.713, 0.512, 0.670, 0.295, 0.091, 0.733, 0.356, 0.654,0.654, 0.513, 0.812, 0.903, 0.511 consecutively) whereas there was stoical significance concerning, Se selenium, Cr chromium (p values=0.032, 0.002 consecutively).

Table 1: Demographic characteristics of the Studied Groups.

	Preeclamptic	Non-Preeclamptic	Test value	P-value	Sig.
	No. = 30	No. = 390			
Maternal Age (years), mean±SD	31.25 ± 5.37	32.13 ± 6.24	0.751•	0.453	NS
Pre-pregnancy BMI (kg/m2), mean±SD	27.35 ± 3.67	24.32 ± 4.32	**3.738•**	**<0.001**	**HS**
Maternal Education, no. (%)			3.702*	0.295	NS
< High School	6 (20.0%)	49 (12.6%)			
Technical College	3 (10.0%)	61 (15.6%)			
Junior College or Some College	12 (40.0%)	116 (29.7%)			
> College	9 (30.0%)	164 (42.1%)			
Maternal Smoking During Pregnancy, no. (%)	3 (10.0%)	24 (6.2%)	0.685*	0.407	NS
Maternal Alcohol Use During Pregnancy, no. (%)	1 (3.3%)	19 (4.9%)	0.145*	0.703	NS
Parity, no. (%)			0.027*	0.869	NS
Nulliparous	14 (46.7%)	176 (45.1%)			
Parous	16 (53.3%)	214 (54.9%)			
Previous Preeclampsia Diagnosis, no. (%)	4 (13.3%)	6 (1.5%)	**16.674***	**<0.001**	**HS**
Gestational Diabetes, no. (%)	3 (10.0%)	24 (6.2%)	0.685*	0.407	NS
Use of ART, no. (%)	8 (26.7%)	20 (5.1%)	**20.769***	**<0.001**	**HS**
Chronic Hypertension, no. (%)	4 (13.3%)	7 (1.8%)	**14.542***	**<0.001**	**HS**
Use of Multivitamins During Pregnancy, no. (%)	21 (70.0%)	281 (72.1%)	0.058*	0.809	NS
Use of Calcium Supplements During Pregnancy, no. (%)	8 (26.7%)	55 (14.1%)	3.449*	0.063	NS
Use of Iron Supplement During Pregnancy, no. (%)	3 (10.0%)	49 (12.6%)	0.169*	0.681	NS
Infant Sex (males), no. (%)	10 (33.3%)	234 (60.0%)	**8.137***	**0.004**	**HS**
Maternal sFlt-1Expression (ng/mL), mean±SD	6.13 ± 1.63	5.93 ± 1.25	0.825•	0.410	NS
Maternal PLGF Expression (pg/mL), mean±SD	267.2 ± 36.14	431.8 ± 45.32	**19.416•**	**<0.001**	**HS**
Maternal sFlt-1/PLGF Ratio, median (IQR)	25.3 (14.2 – 36.5)	12.5 (9.3 – 21.4)	**4.325≠**	**0.004**	**HS**

Bold indicates significant

Data were presented as mean±SD, number and percentages and median with inter-quartile range (IQR)

•: Independent t-test; *: Chi-square test; ≠: Mann-Whitney test

Table 2: Comparison between pre-eclamptic and non-pre-eclamptic patients regarding trace metals from urine samples (µg/L).

	Preeclamptic	Non-Preeclamptic	Test value≠	P-value	Sig.
	No. = 30	No. = 390			
As	16.29 ± 3.52	17.33 ± 4.38	1.269	0.205	NS
Ba	2.37 ± 1.1	2.1 ± 1.3	1.107	0.269	NS
Cd	0.14 ± 0.07	0.15 ± 0.05	1.022	0.307	NS

Cu	9.43 ± 1.8	8.79 ± 2.3	1.489	0.137	NS
Hg	0.61 ± 0.23	0.58 ± 0.31	0.519	0.604	NS
Mn	0.88 ± 0.26	0.86 ± 0.31	0.344	0.731	NS
Mo	44.3 ± 12.33	47.8 ± 10.27	1.757	0.079	NS
Ni	3.67 ± 1.09	3.45 ± 1.12	1.039	0.299	NS
Pb	0.35 ± 0.10	0.39 ± 0.09	**2.327**	**0.020**	**S**
Se	29.8 ± 6.73	36.1 ± 7.25	**4.609**	**<0.001**	**HS**
Sn	0.55 ± 0.23	0.62 ± 0.31	1.211	0.227	NS
Tl	0.12 ± 0.09	0.13 ± 0.06	0.844	0.399	NS
Zn	286 ± 73.5	263 ± 65.3	1.842	0.066	NS
Be*	1.15 ± 0.31	1.18 ± 0.09	1.329	0.185	NS
Cr*	1.14 ± 0.32	0.81 ± 0.32	**5.443**	**<0.001**	**HS**
U*	1.01 ± 0.31	1.08 ± 0.22	1.625	0.105	NS
W*	0.89 ± 0.21	0.93 ± 0.35	0.617	0.538	NS

Bold indicates significant. As arsenic, Ba barium, Cd cadmium, Cu copper, Hg mercury, Mn manganese, Mo molybdenum, Ni nickel, Pb lead, Se selenium, Sn tin, Tl thallium, Zn zinc, Be beryllium, Cr chromium, U uranium, W tungsten. ≠: Independent t-test

Table 3: Adjusteda logistic regression analysis for urinary metals as predictors of preeclampsia

	Adjusted OR (95% CI)	p-value
Single contaminant models		
As	0.68 (0.53 – 1.22)	0.125
Ba	1.11 (0.58 – 1.62)	0.673
Cd	0.87 (0.62 – 1.75)	0.713
Cu	0.78 (0.35 – 1.89)	0.512
Hg	0.87 (0.70 – 1.33)	0.670
Mn	1.32 (0.65 – 3.17)	0.295
Mo	0.55 (0.32 – 1.32)	0.091
Ni	0.92 (0.67 – 1.45)	0.733
Pb	1.12 (0.76 – 1.85)	0.356
Se	**0.33 (0.12 – 0.89)**	**0.032**
Sn	0.91 (0.53 – 1.65)	0.654
Tl	0.77 (0.53 – 1.73)	0.654
Zn	0.92 (0.47 – 2.31)	0.513
Be	1.16 (0.34 – 4.04)	0.812
Cr	**3.45 (1.56 – 7.64)**	**0.002**
U	1.07 (0.36 – 3.20)	0.903
W	0.72 (0.27 – 1.93)	0.511

Bold indicates significant. OR: Odds ratio, CI confidence interval, As arsenic, Ba barium, Cd cadmium, Cu copper, Hg mercury, Mn manganese, Mo molybdenum, Ni nickel, Pb lead, Se selenium, Sn tin, Tl thallium, Zn zinc, Be beryllium, Cr chromium, U uranium, W tungsten.

aAdjusted for specific gravity, smoking during pregnancy, educational attainment, infant sex, ART, calcium supplementation, pre-pregnancy BMI, and gestational age at study visit

Table 4 and Figure 1 reveal and display that, Cr chromium at Cut off point >0.92 have AUC=0.747, statistical Sensitivity=80.0, statistical Specificity=60.8, PPV=13.6, NPV =97.5, Se selenium at cutoff point ≤35.4 have AUC=0.759, statistical Sensitivity=83.3, statistical Specificity=62.6, PPV=14.6, NPV =98.

Table 4: Receiver operating characteristic curve for Cr and Se as a predictor for patients with preeclampsia.

	Cut off point	AUC	Sensitivity	Specificity	PPV	NPV
Cr	>0.92	0.747	80.0	60.8	13.6	97.5
Se	≤35.4	0.759	83.3	62.6	14.6	98

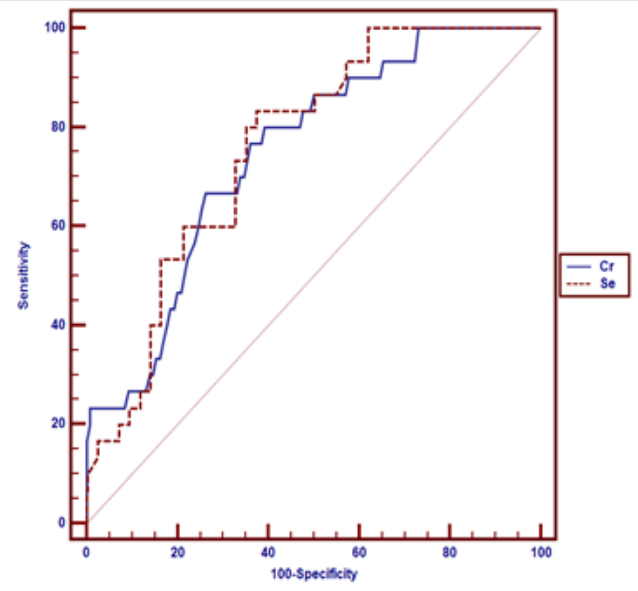

Figure 1: Receiver operating characteristic curve for Cr and Se as a predictor for patients with preeclampsia.

Discussion

Trace metals and angiogenic biomarkers are of increasing research interest since investigative approaches in prior research efforts have revealed that angiogenic markers are reflecting the trophoblastic invasiveness process that is markedly impaired in preeclampsia pathological developmental course [19-21]. Furthermore it was observed that trace metals were observed to be of cornerstone importance to be maintained within normal safe acceptable physiological levels that would maintain the cellular metabolic and division activities that are well observed in the process of placentation and spiral artery remodeling ,on the other hand it was observed that the toxic impact of lead could impair the cellular apoptotic processes that are required for spiral artery remodeling besides it teratogenic impact. Preeclampsia although it is the disease of theories it is considered triggered by environmental exposure levels to various issues such as trace metals that interact in a manner that affect the oxidative stress process and early physiological development of the placenta [22,23].

An increased requirement for early screening and diagnosis of preeclampsia is crucial to upgrade the management protocols of this challenging obstetric clinical scenario [24,25]. A prior research group of investigators performed a research effort similar to the current study as regards the approach and methodology have revealed and displayed among their research results that there is raised risk for preeclampsia pathological development correlated to the detectability of chromium in the investigated urine early in gestation and a decreased clinical risk of preeclampsia development correlated to raised urinary Selenium denoting that selenium regarding its antioxidant properties is a safe guard against preeclampsia pathological development ,interestingly those research results show great harmony and similarity to the current study results denoting the clinical value of examining trace metals in gestation to predict clinical risk of preeclampsia [26,27]. Furthermore another research team of investigators gave observed that urinary cadmium, besides other toxic and essential trace metals, is correlated in a statically significant manner to reduced circulating PlGF levels and urinary copper is correlated to elevated sFlt-1 serum levels and an elevated sFlt-1/PlGF ratio, suggesting a linkage and correlation between physiologically impaired placentation process and clinical risk of preeclampsia those research observations have shown great harmony with the current study findings and could be justified by the fact that the placentation process is highly sensitive at cellular and molecular levels atha could be affected by any alterations in the environmental zone of placental development such as exposure to toxic metals [28,29]. Recent research efforts have displayed that chromium exposure causes raised expression of oxidative stress bio markers and apoptotic signaling within developing trophoblast tissues in experimental animals justifying the current study findings based on molecular-level research evidence the linkage between preeclampsia development and chromium toxic exposure levels [1,3,5,9].

Interestingly previous research efforts have observed that there is correlation between urinary cadmium and lead lower PlGF serum levels. Both Cd and Pb are trace metals found in contaminated air, soil, or water. Cd levels tend to be higher foods, e.g. rice and grains, and some drinking water systems denoting that the environmental pollution exposure is a cornerstone issue for preeclampsia clinical risk being raised within the affected population that relies on the geographical zone affected by the pollutant [2,10,13]. Another research meta-analyses have revealed that higher plasma or serum copper is correlated in a statically significant fashion to raise with preeclampsia risk ,those research findings could be justified by the fact that modest rise in copper levels could trigger the of reactive oxygen species raised productivity and oxidative stress, that are well demonstrated to be correlated to raised risk for preeclampsia development [15,19,26]. The current research study findings are well supported by prior molecular level observations that, toxic and essential metals have complex interactions within the placental tissue particularly in early phases of development. e.g. antagonistic molecular interactions between cadmium and selenium maternal serum levels affecting placental apoptotic gene expressive patterns [20,23,28].

Conclusion and Recommendations for Future Research

The current study provokes the clinical value for trace metal screening in detectability of preeclamptic risk of development ,however future research efforts are require to correlate the clinical risk of disease development according to the environmental trace metal levels ,besides future research efforts should be multicentric in fashion with larger sample sizes that could elucidate the best trace metals that could be implemented in screening to reveal the risk of developing preeclampsia.

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