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Linking EDC-laden food consumption and modern lifestyle habits with preeclampsia: A non-animal approach to identifying early diagnostic biomarkers through biochemical alterations

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ABSTRACT

Preeclampsia (PE), a pregnancy complication characterized by new-onset hypertension with or without proteinuria and/or end-organ damage, and it may be influenced by exposure to endocrine-disrupting chemicals present in processed foods and modern lifestyles. This study explores the potential link using a non-animal approach to identify early diagnostic biomarkers for preeclampsia. Seventy pregnant women aged 21–41 years participated, and completed questionnaires assessing socio-demographic factors, Suboptimal Health Status Questionnaire scores for fatigue, digestive, cardiovascular, immune, and mental health issues, and exposure to endocrine-disrupting chemicals from processed food consumption and daily product use. Peripheral blood samples were analyzed for hormone profiles, complete blood count, and liver function tests (LFT). Statistical analysis revealed that mothers above 27 years old, with a Body Mass Index exceeding 32.59 Kg/m^2, and a Mean Arterial Pressure of 108.5 mmHg exhibited a potential obesogenic effect on preeclampsia development. Socio-demographic factors like, lower economic class, housewife status, primiparous pregnancy, non-graduate education, and rural residence were significantly associated with results. Analysis of biochemical parameters revealed that serum creatinine, blood urea, total protein, platelet count, blood urea nitrogen, bilirubin profile, LFT profile, and thyroid profile showed potential detrimental effects on kidney, liver, muscle, and thyroid function in preeclampsia patients. Notably, PC, serum urea, bilirubin, total protein, serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase (ALP), and thyroid stimulating hormone (TSH) levels were significantly associated with preeclampsia in individuals reporting higher exposure to endocrine disrupting chemicals (EDCs). Minor biochemical alterations were also observed with dairy product consumption. SHS-25 analysis indicated a significant increase in fatigue, and digestive, cardiovascular, immune, and mental health-related issues in patients. Probably, biochemical alterations due to EDC exposure from processed foods and modern lifestyle habits contribute to organ dysfunction in preeclampsia. Identifying these potential biomarkers may pave the way for the development of non-invasive, early diagnostic tools for improved preeclampsia management. This research emphasizes the importance of non-animal testing methods for assessing EDC-related health risks in pregnancy and contributes to the advancement of early PE diagnosis strategies.

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1. Introduction

Preeclampsia (PE) is a multiple-organ dysfunction-specific syndrome that occurs after 20 weeks of pregnancy and is characterized by gestational hypertension, proteinuria, and/or end-organ damage (Burton et al., 2019). Reports from the World Health Organization (WHO) say that the incidence is 2–10% worldwide, while the prevalence of PE is 1.8–16.7% in developed countries and 0.2–6.7% in Asia. In India, the prevalence rate of PE is 28% and the incidence rate is 8–10% of the population (Mou et al., 2021; Sajith et al., 2014). As per the definition of WHO, endocrine-disrupting chemicals (EDCs) mimic hormones or bind to receptors, thus preventing or blocking the binding of specific receptors with their endogenous hormones (Zoeller et al., 2012). EDCs like phthalates, phenols, organochlorine pesticides (OCPs), and perfluoroalkyl substances (PFAS) were reported to be associated with body mass index (BMI) in children and mothers, gestational diabetes, behavioral changes, and PE (Gingrich et al., 2020).

Primary EDC exposure pathways during pregnancy include lifestyle and dietary habits. In addition, occupation might also be one of the most important factors to consider for EDC exposure assessment (Birks et al., 2016). Canned fish, beverages, bottle usage, dairy products, and meat products play a significant role in EDC exposure in Indian diets, especially in urban markets (Hartle et al., 2016). Canned fish is one of the sources of Bisphenol A (BPA), an EDC which shows its presence in pregnant women's urine during the first and third trimesters followed by its presence in 4-year-old children (Casas et al., 2013). EDCs have been found in OCPs, dioxins, polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), and furans, in Indian food baskets along with fruits, vegetables, dairy, and meat products. Dietary EDC exposure has been compared from sources amongst the Indian and European populations (Sharma et al., 2021). Among metropolitan cities like Delhi, diets including meat, seafood, and packaged food products document an increase in the exposure of priority phthalates and BPA levels due to its leaching into the products (Chakraborty et al., 2022). The migration of plasticizers like Di(2-ethylhexyl) phthalate (DEHP) and Di-n-butyl phthalate (DnBP) from Polyethylene Terephthalate (PET) and Low-Density Polyethylene (LDPE) from water bottle casings at different temperatures was found to be in higher than the recommended limits by the Indian Environmental Protection Agency (EPA) (Mukhopadhyay et al., 2022).

Several studies predict that the increased use of EDCs might affect changes in BMI, blood pressure, and biochemical parameters, including Liver Function Test (LFT) markers, creatinine, and platelet levels. Increased serum creatinine levels in PE have been associated with hyperuricemia intravascular volume contraction and renal involvement as a result of endothelial damage and decreased vascular endothelial growth factor (Tesfa et al., 2022). Even low concentrations of phthalates can alter the level of thyroid hormones, such as 3,3′,5-Triiodo-L-thyronine (T3), Thyroxine (T4), and thyroid stimulating hormone (TSH) (Derakhshan et al., 2021; Duan et al., 2018; Sun et al., 2022; Yang et al., 2022). Sex-steroid hormones, including thyroid profiles such as T3, T4, and TSH, were reported to be associated with personal care products (PCPs) (Rivera-Núñez et al., 2022).

Clinical symptoms like acute kidney injury, abnormal liver function, thrombocytopenia, neural complications, and vascular endothelial dysfunction are commonly observed in PE. Elevated serum urea and blood urea nitrogen in PE indicates a decline in glomerular filtration rate and adverse foetal outcomes (Tesfa et al., 2022). Exceptionally increased alkaline phosphatase (ALP) is attributed to placental dysfunction, premature rupture of membrane, and Intrauterine Growth Restriction (IUGR) (Connolly et al., 2022). Abnormal levels of liver enzymes serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) are associated with adverse maternal and neonatal outcomes in PE (Greiner et al., 2023). To identify the physical state of the participants and screening, a standard questionnaire is needed like SHS-25 which might be helpful and determine the risk of PE. This SHSQ was found to be a valuable tool for analyzing hypertensive conditions in PE among the Ghanaian population for early detection (Anto et al., 2019). So, we have used this risk stratification tool to predict PE and various clinical measures with different EDC exposure groups.

Low BPA levels in urine have been associated with cardiovascular disease (CVD), thyroid dysfunction, diabetes, liver abnormalities, and reproductive abnormalities, including PE (Han and Hong, 2016). Epidemiological studies have linked exposure to EDCs, including compounds like pentachlorophenol (PCP) present in modern diets and other EDCs (such as parabens in cosmetics) associating shows lifestyles leading to adverse health outcomes in pregnant women and their fetuses (Engdahl and Rüegg, 2020; Huo et al., 2022; Chan et al., 2021; Salazar et al., 2021). To better understand the relationship between EDC exposure, clinical manifestations, and biochemical alterations in preeclampsia (PE), this study will investigate potential exposure pathways, conduct thorough clinical assessments, and analyze relevant biomarkers.The main aim of this study is to assess the involvement of i) socio-demographic factors with EDC-related commercial product exposure; ii) EDC exposure with changes in biochemical parameters like blood platelets, serum protein, LFT enzymes, and thyroid hormone profiles, including T3, T4, and TSH, among pregnant women; iii) alterations in biochemical parameters among different routes of EDC exposure pathway of pregnant and PE women; and iv) to find out the correlation between SHS and EDCs impact questionnaire assessment among pregnant women.

2. Methodology

2.1. Study design and settings

Participants selected for this study were pregnant women aged 21 to 41, from urban and semi-urban regions of the Chennai metropolitan city. The Institutional Human Ethical Committee (IEC) clearance was obtained from SRM Medical College Hospital and Research Centre (SRM MCHRC), Tamil Nadu (Ethical clearance: 2170/IEC/2020). Inclusion criteria for the control group were pregnant women without hypertension, proteinuria (as per ACOG guidelines), and no significant history of any other obstetric labor complications. Pregnant women with an increase in blood pressure (BP $\geq$ 140/90 mmHg) and protein in the urine (urinary albumin protein $\geq$300mg/24 h) after 20 weeks of pregnancy were chosen. After obtaining written informed consent, pregnant women with preexisting or pregnancy-associated hypertension were examined for testing for PE, as defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP).

2.2. Questionnaire design and collection

About 218 participants were subjected to three questionnaires: demographic profile questionnaire, SHS-25, and EDC impact questionnaires. The questionnaire was prepared in English and Tamil to accommodate the participant's preferred language. Demographic variables include maternal age, weight, height, BMI, pregestational BMI, gestational BMI, BP level, educational background, residential background, occupational background, parity, and socioeconomic status. SHS-25, a standard PE questionnaire, was administered with 25 questions across five domains: fatigue, MH, CVD, digestive, and immune function. Scoring was done based on a 5-point Likert scale. The EDC impact questionnaire aimed to understand the lifestyle of the participants by subjecting them to questions regarding the consumption of coffee, tea, processed foods, canned foods, barbecue chicken, canned water, cosmetics, and cooking utensils, including aluminum, non-stick cookware, and plastic bottles. The EDC exposure groups were categorized based on the responses from the questionnaire. To study the anticipated difference in maternal serum between the two groups (control and PE), an unpaired *t*-test (difference between 2 independent means) was used, and using 95% power, the sample size was calculated

to be 70. The maternal blood samples from 35 participants from each group (Control:35, PE:35) were collected, and serum was separated and frozen at −80 °C until further analysis. To achieve the statistical power (normalization) and based on the inclusion criteria only 70 participants were included in this study.

2.3. Measurement of creatinine, blood urea, blood platelets, total protein, and bilirubin in the serum

Creatinine (Sigma Aldrich; Cat. No.: MAK080), blood urea (Sigma Aldrich; Cat. No.: MAK006), albumin, globulin, and bilirubin total (Sigma Aldrich; Cat. No.: MAK126) from serum samples were measured using kits purchased from Sigma Aldrich. PC was analyzed using automated HD focusing/flow cytometry.

2.4. Measurement of LFT enzymes

Bilirubin direct, indirect, and total (Sigma Aldrich, Cat. No. MAK126) and liver enzymes, including ALP, were measured using the diethanolamine assay (Sigma Aldrich), while AST (Sigma Aldrich, Cat. No. MAK055) and ALT (Sigma Aldrich, Cat. No. MAK052) were measured from serum samples (Vasantharekha et al., 2017).

Table 1
EDC exposures and their pathways during pregnancy- EDCs distributed in the products and the mode of exposure.

Category	Substance	Products	Exposure route		
			Food	Dermal	Occupational
Nonylphenols	4-Nonylphenol, branched and linear	Dish Detergents, Emulsifiers,	Yes		Yes
Tert-Octyl phenols	4-(1,1,3,3-tetramethyl butyl) phenol	Detergents, industrial cleaners, and emulsifiers.		Yes	Yes
Heptyl phenol	4-Heptylphenol	Lubricants	Yes	Yes	Yes
	p-(1,1-dimethylpropyl) phenol	Perfumes, plastic products	Yes	Yes	
Phthalates	Bis(2-ethylhexyl) phthalate; DEHP	Medical devices (IV catheters, dialysis bags, blood bags etc.)	Yes	Yes	Yes
	Di isobutyl phthalate; DIBP	Floorings, adhesives, inks	Yes	Yes	Yes
	Dibutyl phthalate; DBP	Nail products and perfumes		Yes	Yes
	Benzyl butyl phthalate; BBP	Perfumes, hairsprays, glue		Yes	Yes
Benzophenones	Benzophenone-1; 2,4- Dihydroxy benzophenone	Antihistamines, hypnotics and insecticides	Yes	Yes	Yes
	Benzophenone-2; 2,2′,4,4′- tetrahydroxy benzophenone	Sunscreen, Textile, Food packaging	Yes	Yes	Yes
	Benzophenone-3; Oxybenzone	Sunscreen		Yes	Yes
	4,4′-dihydroxy benzophenone	Sunscreen, Printed circuit boards, Adhesives		Yes	Yes
3-BC, MBC, EHMC	3-Benzylidene camphor (3-BC); 1,7,7- trimethyl-3- (phenyl methylene) bicyclo[2.2.1]heptan-2- one	Sunscreen, Perfumes		Yes	Yes
	3-(4-Methylbenzylidene) camphor; 1,7,7- trimethyl-3-[(4-methylphenyl) methylene] bicyclo [2.2.1] heptan-2-one	Sunscreen, Perfumes	Yes	Yes	Yes
	2-ethylhexyl 4-methoxycinnamate	Sunscreen, Perfumes	Yes	Yes	Yes
Bisphenols	Bisphenol F	Coating of drinks and food cans, liners, adhesives	Yes	Yes	Yes
	Bisphenol S	Baby Bottles, Dental implants, water bottles	Yes	Yes	Yes
Per-and poly-fluoroalkyl substances	PFOA, PFOS, PFNA	Non-stick coatings	Yes	Yes	Yes
BHT and BHA	Butylated hydroxytoluene	Food Preservative	Yes		Yes
	Tert.-Butyl hydroxyanisole (BHA); tertbutyl-4-methoxyphenol	Cosmetics, Lubricants		Yes	Yes
Carbon disulphide	Carbon Disulphide	Perfume, Cellophane, Rayon		Yes	Yes
Dithiocarbamates	Metam-sodium	Wood Preservative, Weed control	Yes	Yes	Yes
	Zineb	Fungicide	Yes		Yes
	Ziram	Fungicide	Yes		Yes
	Thiram	Fungicide	Yes	Yes	Yes
Polychlorinated biphenyls (PCBs)	PCB and congeners	Pesticides, fungicides	Yes	Yes	Yes
MTBE	*Tert*-butyl methyl ether; MTBE	Petrol		Yes	Yes
Polybrominated Diphenyl ether	PBDE and different congeners	Cooking utensils, Paints	Yes	Yes	Yes
Parabens	Methylparaben	Food preservative, cosmetics	Yes	Yes	
	Ethyl paraben	Food preservative, Skin creams and lotions	Yes	Yes	
	Propylparaben; propyl 4-hydroxybenzoate	Antiseptic, Preservatives	Yes	Yes	Yes
	Butylparaben; butyl 4-hydroxybenzoate	Cosmetics, Lubricants	Yes	Yes	Yes
Other Phenol Derivatives	4-nitrophenol	Dyes, Leather	Yes	Yes	Yes
	2,4,6-tribromophenol	Wood preservative and Flame retardant	Yes	Yes	Yes
	Resorcinol	Cosmetics and Lotions	Yes	Yes	Yes
PCP, TEBUCONAZOLE, AND TRICLOSAN	Pentachlorophenol (PCP)	Herbicide, Fungicide, Paints	Yes	Yes	Yes
	Tebuconazole	Fungicide	Yes	Yes	Yes
	Triclosan	Anti-bacterial soaps, cosmetics, toothpaste	Yes	Yes	Yes
Phthalates	Diethyl phthalate (DEP)	Plastics, Cosmetics, Medical tubing	Yes	Yes	Yes
	Dihexyl phthalate (DHP)	Plasticizer, Rubbers, Cellulose	Yes	Yes	Yes
	Dicyclohexyl phthalate (DCHP)	Rubbers and resins	Yes	Yes	Yes
	Dioctyl phthalate (DOP)	Wires and cables, medical tubing	Yes	Yes	Yes
	Diisodecyl phthalate (DiDP)	Plasticizers	Yes	Yes	Yes
Quadrosilan	2,6-cis Diphenylhexamethyl-cyclotetrasiloxane	Flame retardant	Yes	Yes	Yes
Triphenyl Phosphate	Triphenyl Phosphate	Electronics, glues and nail polish	Yes	Yes	Yes

2.5. Measurement of the thyroid profile in serum

Thyroid profiles, including T3 (Sigma Aldrich; Cat No. T2877), T4 (Sigma Aldrich; Cat No. T2376), and TSH (Sigma Aldrich; Cat No. 869006-M), from serum samples were measured using Sigma Aldrich kits.

2.6. Statistical analysis

The data were analyzed using Microsoft Excel (version 2205) and GraphPad Prism 8.01 (244). Analyzed data were tabulated in mean ± standard deviation (SD) for continuous parametric variables and demographic categorical variables in percentage. Biochemical parameters were tabulated in mean with SD (M ± SD) for NP and PE. Statistical analysis was done between normotensive pregnant (NP) and PE women by unpaired Student's t-test. $p < 0.05$ was considered statistically significant. EDC exposure pathways and biochemical parameters were analyzed using Tukey's multiple comparison tests in ANOVA. Pearson's correlation coefficient examines the association between EDC total scores and biochemical parameters in pregnant women.

3. Results

3.1. Distribution of EDCs in commercial products used by pregnant women

Since the study participants were from the regions around Chennai metropolitan city, the population was highly susceptible to exposure to many EDC-containing commercial products. During their daily routines, pregnant women commonly utilize a variety of commodities, encompassing toothbrushes, water bottles, utensils, packaged foods, and cosmetics. Table 1 shows the presence of diverse types of EDCs in these products and their route of exposure.

EDCs are almost universal and range from food items, preservatives, food can liners, canned foods, food packages, water bottles, thermal receipts, food colorants, face cream, sunscreen, perfume, eyeliners, lipstick, moisturizers, toothpaste, shampoo, handwash, antibacterial soaps, antiseptics, non-stick coatings, fungicide, insecticide, pesticide, paints, dyes, leathers etc., which are commonly used by the general population. Based on the influence of the EDC exposure pathways with gestational complications like PE, these exposure groups are classified as processed foods, dairy products, cosmetics, and non-stick pans.

Generally, EDCs are classified as persistent (dioxins, PCBs, OCPs, and heavy metals) and non-persistent chemicals (phenols, phthalates, parabens, TCS, PFAS, organophosphates) used by people in day-to-day products. Among these, low molecular weight phthalates such as DEP, DnBP, and DiBP are generally present in non-PVC applications such as cosmetics, paints, medical devices, food packaging containers, etc. Whereas high-molecular-weight phthalates such as DEHP, DiNP, DiDP, DnOP, and BBzP are present in PVC applications like epoxy resins, thermal receipts, medical tubing, PVC plastics, etc., were used by the general population. Parabens are antimicrobial and food preservative agents used in food processing, cosmetics, and pharmaceutical product preparation. BPA is a plasticizer used to produce polycarbonate plastics like water bottles, food can liners, etc., After considering the vast applications of diverse types of EDCs, the exposure assessment needs advanced methods for predicting the exposure pathways. Therefore, the questionnaire-based approach, which is one of the most reliable tools for predicting the route of EDC exposure was used in this study.

3.2. Association of socio-demographic factors with PE

Socio-demographic characteristics were tabulated, including employment status, residency, occupation, education, parity, smoking and drinking habits, socioeconomic status, and secondhand smoking (Table 2). The overall maternal age group of the study participants surveyed ranged with a mean of 28.45 (SD 7.95). Among these, the Mean (M ± G.SD) of NP women's age group was 25.11 ± 1.15 (years), and for the PE group, 27.91 ± 1.2 (years). In this study, the prevalence of PE was high in the above 27 age group. Among the participants surveyed, 100% of women with PE preferred non-vegetarian foods, where 29 % were from urban, 38 % were from rural, and 33 % were from semi-urban regions of Tamil Nadu. In the survey population, 35.48% of PE women were nulliparous, 38.7% were primiparous, and 6.4% were multiparous women. No significant difference was observed in sleeping pattern variation among NP and PE women. The occupational background of study participants indicated that 77.41% were housewives, 9.6% were medical and health service workers, and 12.8% were carrying out other occupations. Since this is a semiurban-based population study, very few participants were farmers. The educational background among the participants indicated that 48.38% were graduates, and 51.61% were non-graduates. The socioeconomic background survey indicates that 77.41% were from the middle class and 22.58% were from the lower class. Among the South Indian population, none of the participants reported smoking and drinking habits, except for a few secondhand smokers.

3.3. Association of anthropometrical variables with PE

The questionnaire used to collect anthropometrical data from the participants included systolic BP and diastolic BP, presented as MAP, and BMI including pregestational and gestational BMI compared

Table 2
Sociodemographic profile of Normotensive pregnant (NP) women and Pre-eclampsia (PE) women.

Demographic variables	NP (GM ± G SD)	PE (GM ± G SD)
Age (years)	25.11 ± 1.15	27.91 ± 1.20
MAP (mmHg)	78.32 ± 1.11	108.11 ± 1.09
Pregestational BMI (Kg/m^2)	23.06 ± 1.19	27.69 ± 1.26
Gestational BMI (Kg/m^2)	25.22 ± 1.18	32.25 ± 1.16
Primiparity	51.61%	38.70%
Nulliparity	41.93%	35.48%
Multiparity	–	6.40%
Non-vegetarian	91.20%	100%
Residential Background		
Urban	28.00%	29.00%
Rural	32.00%	38.00%
Semi-urban	40.00%	33.00%
Occupational background		
Housewife	83.87%	77.41%
Medical & allied	9.60%	9.60%
IT	–	–
Others	6.45%	12.80%
Educational background		
Not graduates	41.93%	51.61%
Graduates	58.06%	48.38%
Socioeconomic status		
Lower class	12.93%	22.58%
Middle class	83.87%	77.41%
Conception		
Spontaneous conception	100%	87.09%
Treatment	–	12.90%
Circadian variables		
Normal sleep	35.48%	48.38%
Sleeping disturbance	48.30%	25.80%
Sleepless	3.22%	25.80%
SHS-25		
Fatigue	14.28 ± 1.41	17.52 ± 1.44 *
CVD	3.63 ± 1.36	4.78 ± 1.69 *
Digestive function	4.51 ± 1.36	5.36 ± 1.56 *
Immune function	3.45 ± 1.26	5.07 ± 1.69 *
Mental Health function	9.14 ± 1.34	14.19 ± 1.58 *
SHS Total	36.45 ± 1.26	49.24 ± 1.35 *

★ represents **p<0.05** compared to Normotensive pregnant women. **GM:** Geometric Mean**, G SD:** Geometric Standard Deviation.

between NP and PE women. Mean arterial pressure (MAP) was calculated from the systolic blood pressure (SBP) and diastolic blood pressure (DBP) of pregnant women (MAP = DBP + 1/3 (SBP-DBP)). Pregestational BMI was calculated based on the pregestational weight and height of the pregnant women. Overall, the PE's mean of MAP, pregestational, and gestational BMI were 108.5 ± 9.84 mmHg, 28.38 ± 6.06 kg/m^2, and 32.59 ± 4.79 kg/m^2. All the values in PE were significantly higher compared to NP (Fig. 1A, B, and 1C). It was observed that there was a two-fold increase in the weight gain from the pregestational to gestational period in PE compared to NP.

3.4. Variations in biochemical parameters between PE and NP

Various biochemical parameters analyzed are listed in Table 3. Serum creatinine, serum urea, BUN, PC, LFT markers (SGOT, SGPT, and ALP), bilirubin, and thyroid profile (TSH) (Figs. 2–5) showed a significant increase in PE compared to NP. Mean levels of the respective parameters were Serum Urea 15.18 ± 2.36 mg/dL (Fig. 2A); Serum creatinine: 0.54 ± 0.07 mg/dL (Fig. 2B); and (BUN) 6 ± 1.25 mg/dL (Fig. 2C), in PE when compared to NP women. A significant decrease in PC, protein markers, bilirubin and thyroid profile (T3, T4) in PE was observed when compared to NP. Overall mean values of PC (201000 ± 38077/Cumm) (Fig. 2D), albumin (3.03 ± 0.23 g/dL), and globulin (2.9 ± 0.12 g/dL), and the total protein (5.9 ± 0.13 mg/dL) was estimated in PE (Fig. 3A). Bilirubin profile such as bilirubin direct (0.06 ± 0.01 mg/dL), bilirubin indirect (0.28 ± 0.03 mg/dL), and bilirubin total (0.38 ± 0.08 mg/dL) was observed to decrease significantly in PE when compared to NP (Fig. 3B). The mean values of LFT markers such as SGOT (Fig. 4A), SGPT (Fig. 4B), and ALP (Fig. 4C) showed a substantial increase in PE (24.78 ± 0.83, 21.67 ± 1.03 and 189.3 ± 27.94 IU/L) when compared to NP. Followed by mean values of T3 (2.51 ± 0.43 mg/dL), T4 (0.76 ± 0.13 mg/dL), and TSH (2.14 ± 0.9 mg/dL) also showed substantial changes in PE compared to NP women (Fig. 5A, B, and 5C).

3.5. Variations in biochemical parameters with different routes of EDC exposure in NP and PE women

EDC impact questionnaire categorized based on the products frequently used by women, such as processed foods, dairy products, cosmetics, and non-stick utensils was used to access different routes of EDC exposure. The questions were related to pregnant women's lifestyle, occupation, and diet. Based on the responses received, the participants were further categorized based on the impact of the exposure route and subjected to biochemical tests. Relevant parameters like PC, serum urea, LFT markers such as bilirubin profile, SGOT, and ALP, TSH, total protein, albumin, and globulin were considered for this analysis. The changes in biochemical parameters based on the different EDC exposure routes were compared between PE and NP (low NP groups) (Table 4). Biochemical parameter changes were analyzed specifically in the group that used processed food, non-stick utensils (Table 4), cosmetics (Table 4), and dairy products (Table 4), and that was compared to the low and high exposed control group. The levels of serum urea (12.67 ± 2.97), SGOT (30.43 ± 9.21), ALP (161.9 ± 45.27 IU/L), and TSH (2.39 ± 1.18 μIU/mL) were significantly increased whereas PC (234800 ± 46247/Cumm), albumin (3.31 ± 0.25), globulin (2.66 ± 0.23), total protein (5.99 ± 0.45), and bilirubin profile (Bilirubin direct: 0.08 ± 0.03, bilirubin indirect: 0.26 ± 0.03 and bilirubin total: 0.33 ± 0.03), significantly decreased in PE group consuming processed food when compared to NP low exposure. The bilirubin and protein profiles were significantly reduced, and SGOT, ALP, and TSH were increased considerably in the PE group using non-stick utensils (Table 4). In the dairy product exposure PE group, only PC, SGOT, and ALP were altered compared to the NP low exposure group (Table 4). In the PE group using cosmetics, the bilirubin profile alone decreased significantly, whereas SGOT, ALP, and TSH increased significantly compared to the low-

Table 3
Biochemical parameters for NP women and PE women.

Biochemical parameters	NP (GM ± G SD)	PE (GM ± G SD)
Platelet count (/Cumm)	351785 ± 1.11	197501 ± 1.21[a]
Serum urea (mg/dL)	8.37 ± 1.15	15.01 ± 1.17[a]
Serum creatinine (mg/dL)	0.39 ± 1.11	0.53 ± 1.15[a]
BUN (mg/dL)	4.54 ± 1.214	5.88 ± 1.22
Total protein (g/dL)	6.63 ± 1.02	5.89 ± 1.02[a]
Albumin (g/dL)	3.49 ± 1.12	3.02 ± 1.08[a]
Globulin (g/dL)	3.13 ± 1.11	2.89 ± 1.04[a]
Bilirubin total (mg/dL)	0.37 ± 1.15	0.51 ± 1.33[a]
Bilirubin Direct (mg/dL)	0.06 ± 1.15	0.15 ± 1.25[a]
Bilirubin Indirect (mg/dL)	0.25 ± 1.18	0.44 ± 1.22[a]
SGOT (AST) (IU/L)	13.75 ± 1.09	24.77 ± 1.03[a]
SGPT (ALT) (IU/L)	7.38 ± 1.15	21.65 ± 1.00
ALP (IU/L)	76.34 ± 1.18	187.41 ± 1.16
T3 (pg/mL)	3.39 ± 1.05	2.47 ± 1.19[a]
T4(ng/mL)	1.27 ± 1.16	0.75 ± 1.21[a]
TSH (μIU/mL)	0.81 ± 1.88	1.96 ± 1.53[a]

[a] Represents **p<0.05** compared to Normotensive pregnant women. **GM:** Geometric Mean, **GSD:** Geometric Standard Deviation. **BUN**: blood urea nitrogen, **SGOT**: serum glutamate-oxaloacetic transaminase, **SGPT**: serum glutamic pyruvic transaminase, **ALP**: alkaline phosphatase, **T3**: triiodothyronine, **T4**: thyroxine, **TSH**: thyroid stimulating hormone.

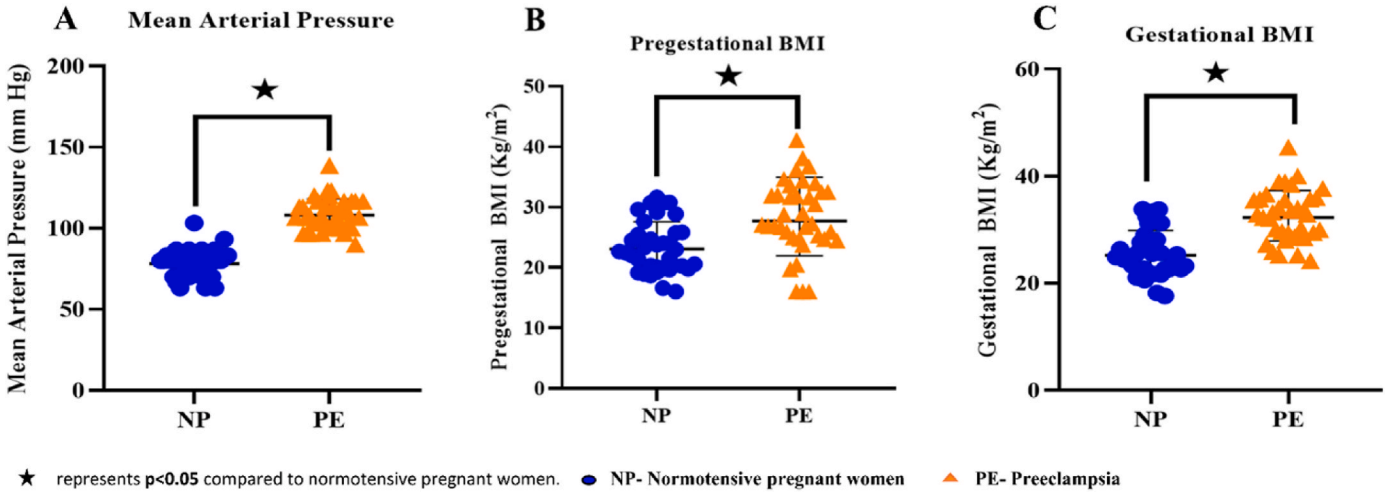

Fig. 1. Anthropometrical data of normotensive pregnant (NP) women and preeclampsia (PE) women. **A)** MAP, **B)** Pregestational BMI, and **C)** Gestational BMI. ★ represents $p < 0.05$ compared to normotensive pregnant women.

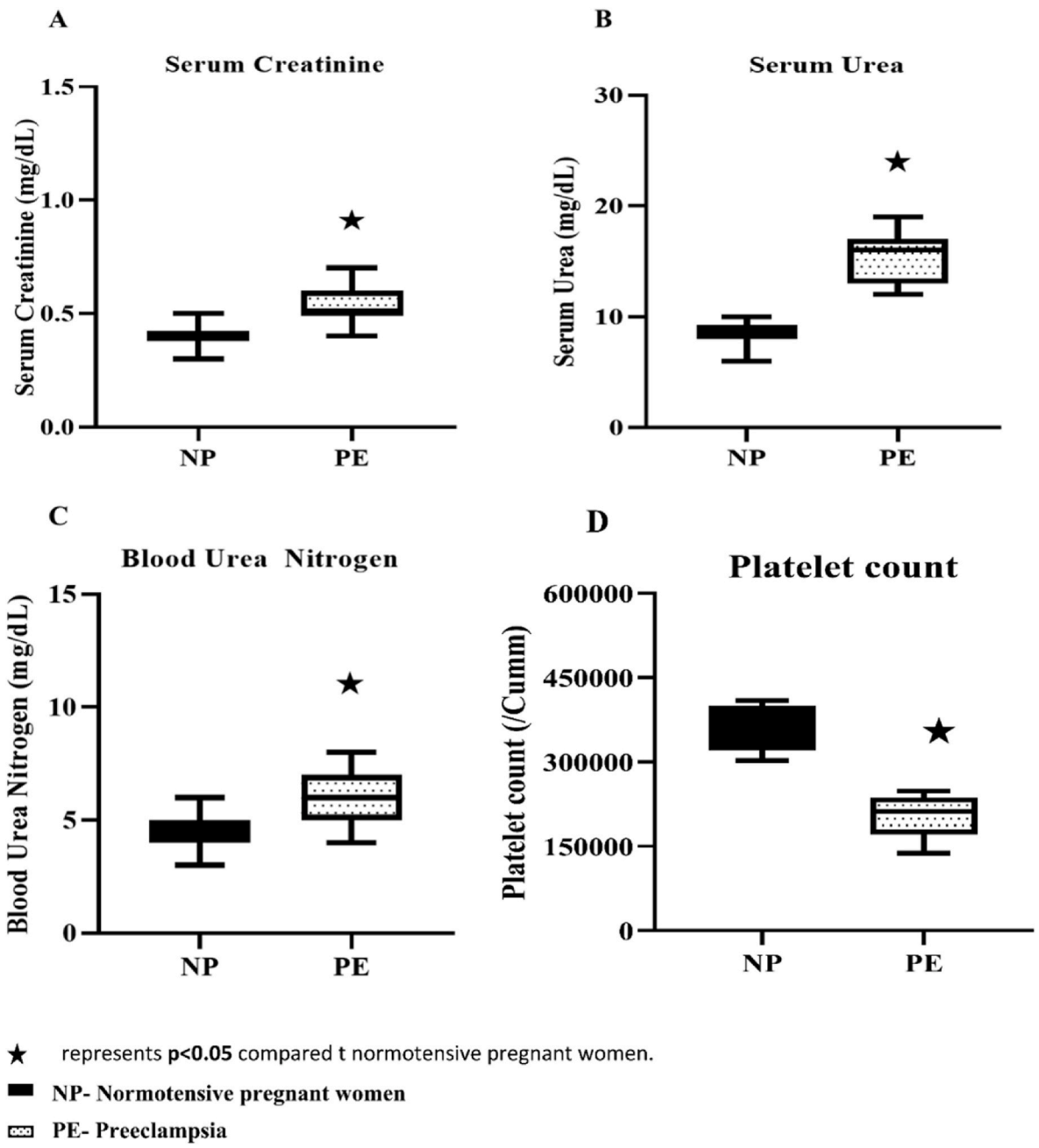

Fig. 2. Comparison of biochemical data for renal dysfunction and platelet count in PE compared to NP women. **A)** Serum creatinine, **B)** Serum Urea, **C)** Blood Urea Nitrogen (BUN), and **D)**. Platelet count.★ represents $p < 0.05$ compared to normotensive pregnant women.

exposure group (Table 4).

3.6. SHS-based score impact among pregnant women

The quality of life among NP and PE women was assessed based on the SHSQ-25 score using five domains in the questionnaire. SHS questionnaire analysis indicated that the fatigue system (Fig. 6A) (18.78 ± 7.78), CVD system (Fig. 6B) (5.51 ± 3.2), digestive system (Fig. 6C) (5.91 ± 5.68), immune system (Fig. 6D) (5.84 ± 3.28) and MH defects (Fig. 6E) (15.76 ± 7.6) in PE women showed significantly higher scores when compared to NP women (fatigue: 15.18 ± 5.63, CVD: 3.82 ± 1.38, digestive 4.73 ± 1.467, immune: 3.56 ± 1.02, MH: 9.56 ± 3.04). The total SHS score (Fig. 6F) was significantly higher in the PE (51.57 ± 16.91) than in NP women (37.41 ± 8.76).

3.7. Correlation of EDC total scores with various biochemical parameters in pregnant women

A positive correlation was observed forserum urea (**R^2=0.5206**), creatinine (**R^2=0.5107**), and BUN (**R^2=0.4121**) (Fig. 7A, B, and 7C), and LFT such as SGOT **(R^2=0.4723)**, SGPT **(R^2=0.6645)**, and ALP **(R^2=0.5745)** with total EDC score (Fig. 8A, B, and 8C) for NP and PE. Similarly, a positive correlation was observed for TSH **(R^2=0.4651)** with EDC total score (Fig. 9A), whereas a negative correlation was observed for T3 **(R^2=0.4236)** and T4 **(R^2=0.5072)** (Fig. 9B and 9C), PC (**R^2=0.4187**), bilirubin total (**R^2=0.5558**) for NP and PE (Fig. 9D and E).

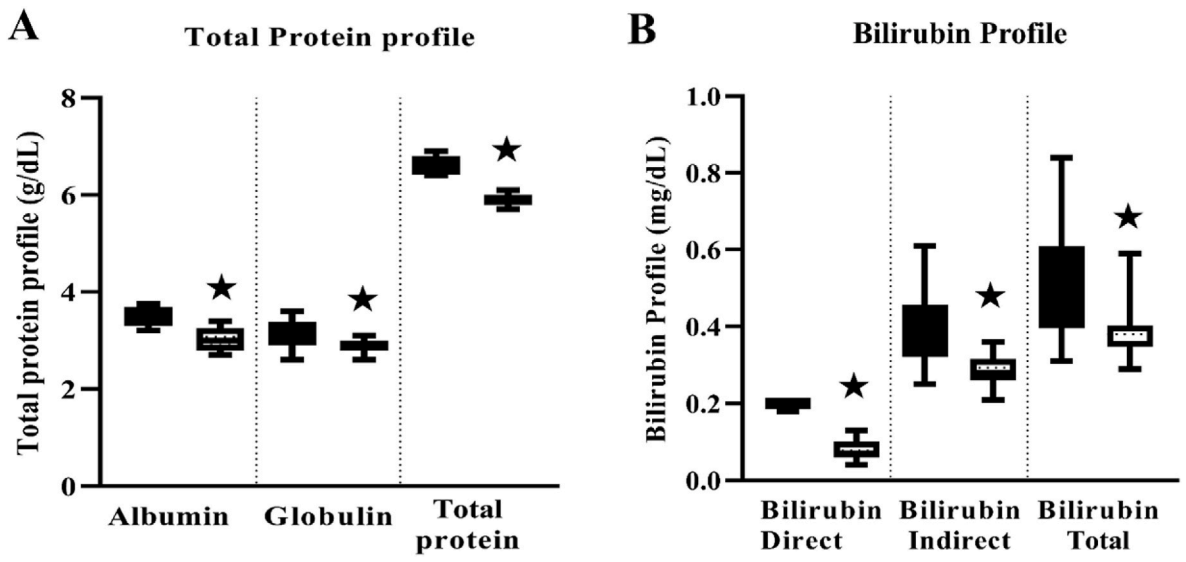

Fig. 3. Comparison of **A)** Total protein profile and **B)** Bilirubin profile (bilirubin direct, bilirubin indirect, and bilirubin total) in PE and NP women.★ represents $p < 0.05$ compared to normotensive pregnant women.

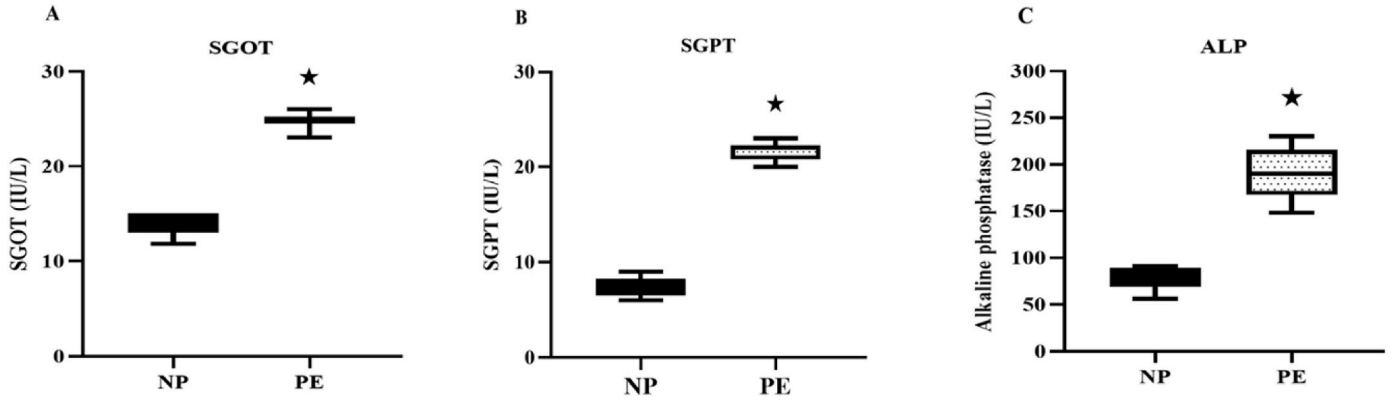

Fig. 4. Comparison of biochemical data for LFT markers in PE compared to NP women. **A)** SGOT, **B)** SGPT, and **C)** ALP.★ represents $p < 0.05$ compared to normotensive pregnant women.

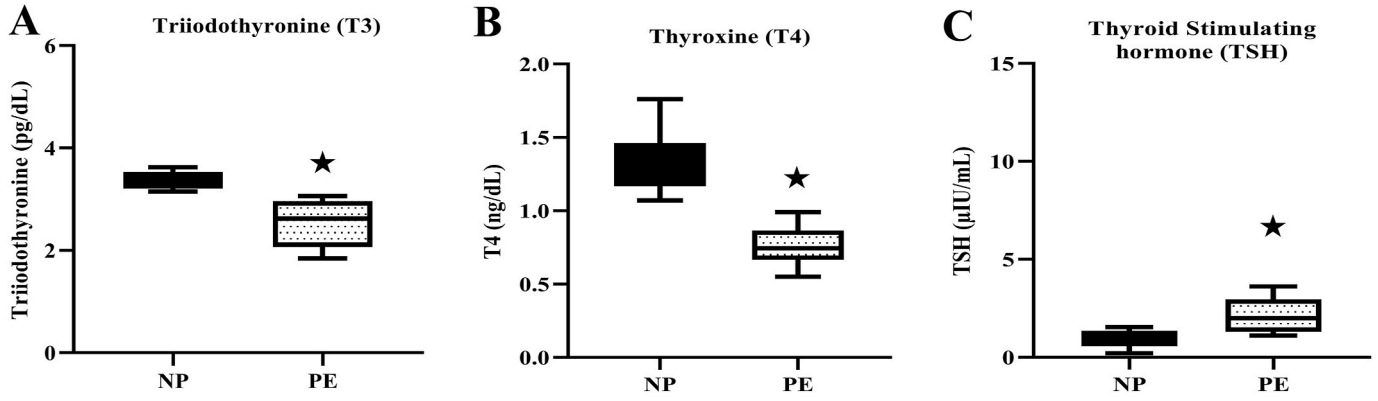

Fig. 5. Comparison of thyroid profile between PE and NP. **A)** Triiodothyronine (T3), **B)** Thyroxine (T4), and **C)** Thyroid stimulating hormone (TSH).★ represents $p < 0.05$ compared to normotensive pregnant women.

3.8. Correlation between SHS and EDC impact among pregnant women

A Pearson correlation was used to understand the relationship between SHS and EDC impact scores in pregnant women. A positive correlation was observed **(R^2=0.5081)**. This indicated an increase in SHS and EDC exposure in PE (Fig. 10).

4. Discussion

Our study identified that EDCs could enter the body of pregnant

Table 4
Comparison of EDC exposure pathway with biochemical parameters for NP and PE.

Pregnant women	Processed foods exposure			Non-stick pan exposure			Dairy products exposure			Cosmetics exposure		
	NP low exposure (GM ± GSD)	NP with exposure (GM ± GSD)	PE with exposure (GM ± GSD)	NP low exposure (GM ± GSD)	NP with exposure (GM ± GSD)	PE with exposure (GM ± GSD)	NP low exposure (GM ± GSD)	NP with exposure (GM ± GSD)	PE with exposure (GM ± GSD)	NP low exposure (GM ± GSD)	NP with exposure (GM ± GSD)	PE with exposure (GM ± GSD)
Platelet count (PC) (/Cumm)	310244 ± 1.20	265408 ± 1.22	229966 ± 1.24[a]	270548 ± 1.23	264496 ± 1.36	259453 ± 1.24	260305 ± 1.39	220471 ± 1.37	257971 ± 1.31	280395 ± 1.26	252251 ± 1.31	236794 ± 1.34
Serum Urea (mg/dL)	10.13 ± 1.16	12.12 ± 1.32	12.4 ± 1.23[a]	12.18 ± 1.32	11.22 ± 1.31	11.13 ± 1.41	12.72 ± 1.31	12.51 ± 1.30	11.97 ± 1.37	12.51 ± 1.28	12.32 ± 1.31	10.26 ± 1.49
Bilirubin Direct (mg/dL)	0.17 ± 1.44	0.133 ± 1.67	0.07 ± 1.39[a]	0.18 ± 1.50	0.12 ± 1.94	0.08 ± 1.59[a]	0.15 ± 1.61	0.08 ± 1.63	0.11 ± 2.78	0.12 ± 1.63	0.13 ± 1.89	0.08 ± 1.25[a]**$**
Bilirubin indirect (mg/dL)	0.41 ± 1.37	0.33 ± 1.13[a]	0.28 ± 1.15[a]	0.36 ± 1.40	0.34 ± 1.30	0.3 ± 1.10[a]	0.41 ± 1.49	0.30 ± 1.51	0.37 ± 1.81	0.35 ± 1.47	0.32 ± 1.40	0.29 ± 1.20[a]
Bilirubin total (g/dL)	0.51 ± 1.48	0.55 ± 1.18	0.33 ± 1.12[a]**$**	0.43 ± 1.46	0.48 ± 1.40	0.45 ± 1.35[a]	0.46 ± 1.44	0.44 ± 1.46	0.54 ± 2.03[a]	0.45 ± 1.43	0.51 ± 1.34	0.37 ± 1.21[a]**$**
Albumin (g/dL)	3.85 ± 1.14	3.58 ± 1.11	3.30 ± 1.08[a]	3.47 ± 1.14	3.37 ± 1.16	3.33 ± 1.11	3.45 ± 1.16	3.3 ± 1.14	3.46 ± 0.08	3.48 ± 1.11	3.54 ± 1.15	3.51 ± 1.07
Globulin (g/dL)	3.16 ± 1.07	2.98 ± 1.03	2.65 ± 1.09[a]**$**	2.8 ± 1.14	3.13 ± 1.21[a]	2.98 ± 1.08	2.94 ± 1.14	2.78 ± 1.19	3.06 ± 1.09	2.76 ± 1.27	2.97 ± 1.35	2.79 ± 1.25
Total protein (g/dL)	7.00 ± 1.08	6.58 ± 1.09	5.97 ± 1.08[a]**$**	6.7 ± 1.10	6.02 ± 1.25[a]	6.33 ± 1.04	6.43 ± 1.08	5.86 ± 1.21[a]	6.33 ± 1.06	6.05 ± 1.19	6.61 ± 1.13[a]	6.43 ± 1.02
SGOT(IU/L)	17.01 ± 1.18	19.21 ± 1.32	29.25 ± 1.35[a]**$**	19.19 ± 1.26	18.39 ± 1.33	23.76 ± 1.37[a]**$**	18.63 ± 1.26	18.73 ± 1.33	22.21 ± 1.34[a]**$**	18.36 ± 1.28	21.19 ± 1.28	23.32 ± 1.53[a]
ALP(IU/L)	73.32 ± 1.37	124.6 ± 1.12[a]	156.6 ± 1.31[a]	101.9 ± 1.58	137.9 ± 1.70	150.8 ± 1.51[a]	87.81 ± 1.42	129.9 ± 1.83[a]	168.7 ± 1.29[a]	87.85 ± 1.67	121.41 ± 1.42	140.7 ± 1.12
TSH (μIU/mL)	1.15 ± 1.78	1.63 ± 1.53	3.01 ± 1.37[a]**$**	0.99 ± 4.11	1.56 ± 2.91	2.68 ± 1.33[a] **$**	1.44 ± 3.49	0.98 ± 3.99	2.34 ± 1.68 **$**	1.15 ± 3.51	1.1 ± 3.91	2.22 ± 1.61[a]**$**

[a] Represents **p<0.05** compared to NP women with low EDC exposure. **$** Represents **p<0.05** compared to NP women with high EDC exposure.

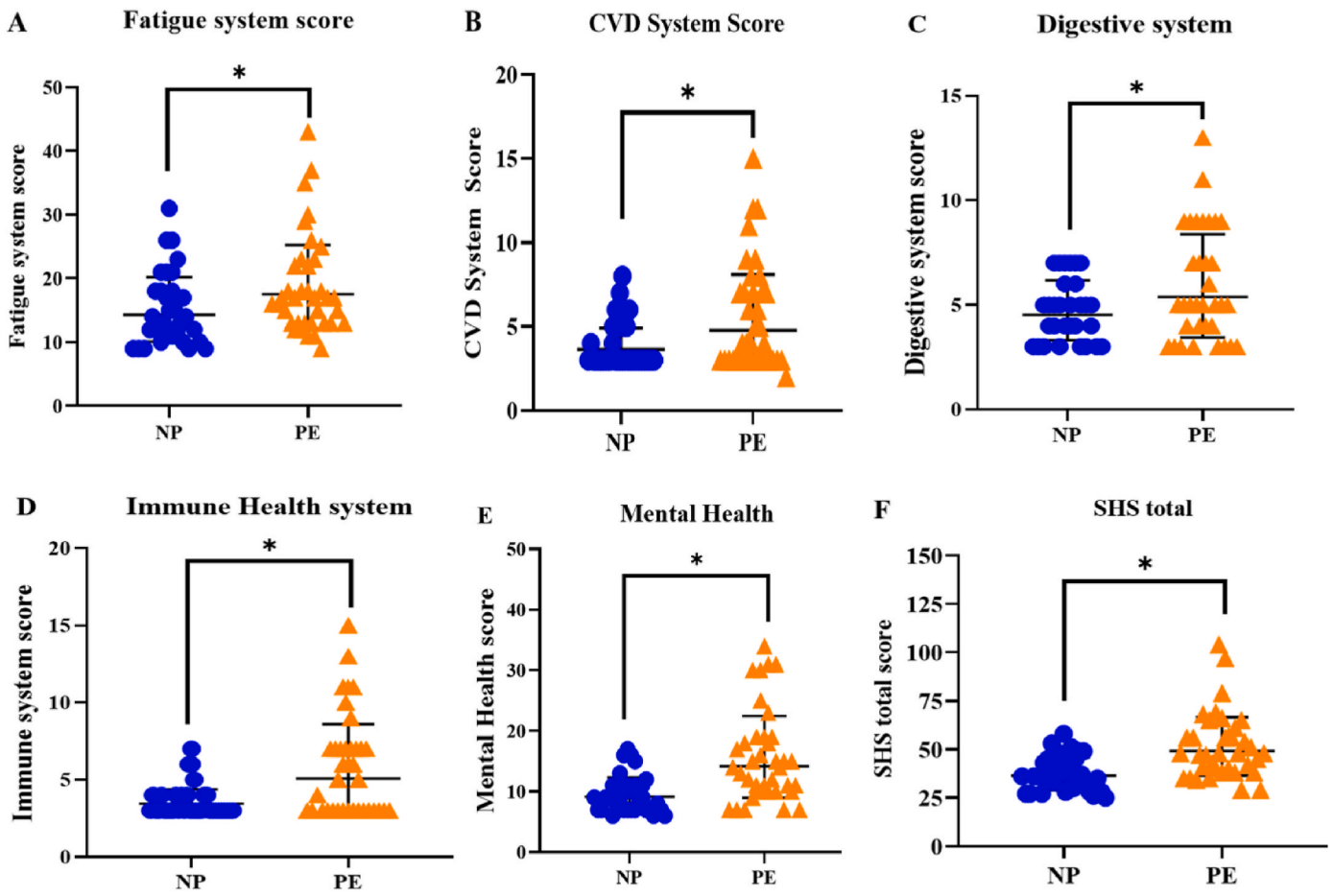

Fig. 6. Suboptimal Health Status questionnaire scores for NP and PE women. **A)** Fatigue system, **B)** CVD, **C)** Digestive system, **D)** Immune health, **E)** Mental Health function, and **F)** SHS score of pregnant women. ✱ represents $p < 0.05$ compared to normotensive pregnant women.

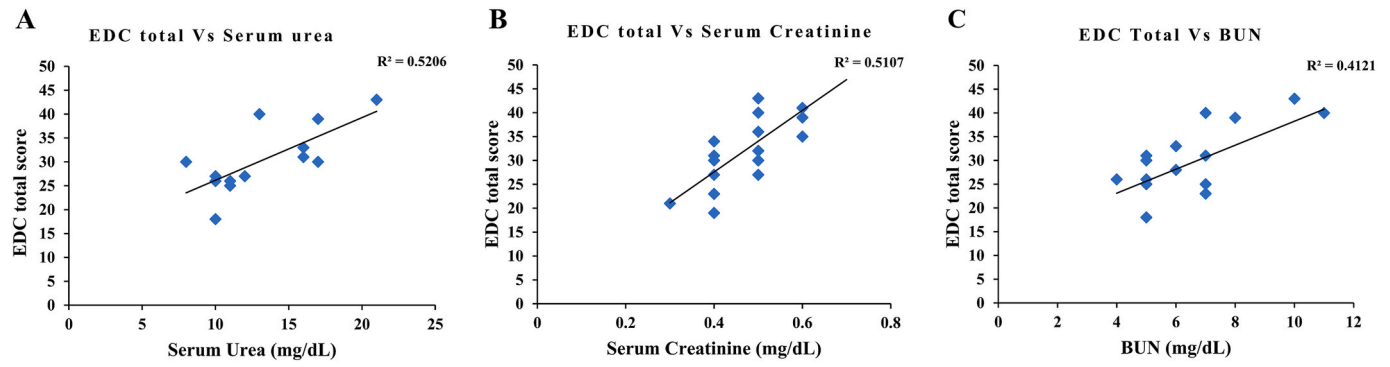

Fig. 7. Pearson positive correlation between EDC total scores and **A)** Serum urea, **B)** **S**erum creatinine, **C)** BUN.

women through different routes of exposure, including ingestion, dermal absorption, and occupational-based pathways. This information was obtained through literature reviews and organized in a table. EDC distribution in commercial products used during the gestational period was identified in the frame questionnaire that might be responsible for pregnancy complications like PE. Study participants in our study are from Chennai metropolitan city and were exposed to diverse types of EDC-containing products in the markets. From which the identified routes were processed foods, dairy products, cosmetics, and non-stick pans. Participants using processed foods were more prone to PE and their biochemical parameters were altered foremost. Followed by non-stick pan, cosmetics, and dairy products usage in PE also showed a higher impact in PE. Phthalates, parabens, and bisphenols are the EDCs present in most processed foods. Perfluorinated compounds and brominated flame retardants were higher in non-stick pans which may harm pregnant women via food ingestion. PCBs are also present in dairy products and many EDCs are exposed via ingestion of animal feeds. Parabens, triclosan, and other phenolic compounds were present highly in cosmetic products exposed via dermal absorption. Further possible exposure routes were identified and tabulated (Table 1). Accumulation of these types of endocrine-disrupting products might be responsible for placental dysfunctions in PE, i.e., due to alteration in biochemical parameters like renal, liver, and thyroid markers when compared to low-exposed NP. Hence, identifying the exposure pathways and

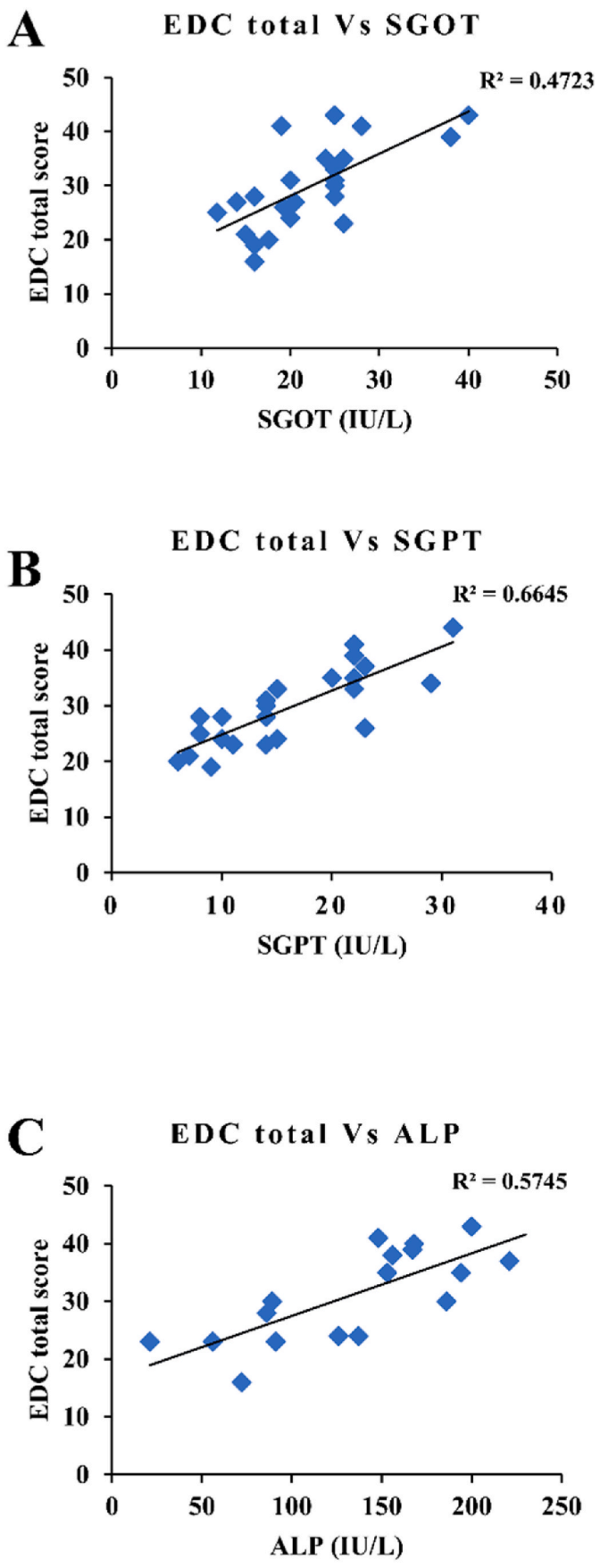

Fig. 8. Pearson positive correlation between EDC total scores and **A)** SGOT, **B)** SGPT, and **C)** ALP.

biochemical markers in PE would be helpful for the early prediction of PE.

Studies say that the globalized changes in food habits and lifestyle have led to adverse effects on pregnant women and the developing fetus (Qian et al., 2020; Tang et al., 2020). Reports from various Environmental Protection Agencies (EPA) worldwide say that more than 50,000 chemicals are listed as endocrine disruptors and are widely distributed in many day-to-day products like plastics, personal care products (PCPs), food can liners, thermal receipts, flame retardants, and non-stick coatings (Demeneix, 2019; Andersen et al., 2012). Risk assessment and analyses of various EDCs from commercial product exposure among pregnant women and children were also reported by the Danish EPA (Pia Brunn Poulsen et al., 2022; DEPA, 2012). Pregnant women are greatly affected since they are highly vulnerable to exposure to these environmental agents, especially EDCs. Several studies reported the presence of these EDCs in the general population, including pregnant women and the developing fetus (Tang et al., 2020). Shekhar et al. reported very high levels of nine phenolic EDCs, including *p*-hydroxybenzoic acid (PHBA), MP, propylparaben (PP), ethylparaben (EP), butyl paraben (BP), bisphenol A (BPA), triclosan (TCS), octyl phenol (OP), and nonyl phenol (NP), in maternal blood and amniotic fluid among pregnant women in the South Indian populations (Shekhar et al., 2017). Six phthalic acid esters including dimethyl phthalate (DMP), diethyl phthalate (DEP), dibutyl phthalate (DBP), benzyl butyl phthalate (BBP), Bis(2-ethylhexyl) phthalate (DEHP), and Di-n-octyl phthalate (DnOP) were reported in the urine samples of people from different age groups including pregnant women residing in the Cauvery delta region of Tamil Nadu, India(Babu-Rajendran et al., 2018). Epidemiological evidence reported the presence of several EDCs, such as BPA, phenols, phthalates, parabens, PFAS, PBDE, etc., in the human saliva, serum, placenta tissue, amniotic fluid, and milk samples and its further transfer to the fetus (Gingrich et al., 2020). Therefore, in our study, the hazardous chemicals were tabulated based on the application and sources of EDCs where a diverse range of EDCs were present in various products (Table 1). This table was used as a basis for identifying the possible routes of EDC exposure in pregnant women using various products.

Pregnant women are generally exposed to these EDCs via ingestion, inhalation, and dermal absorption, through which they enter the bloodstream and cross the placental barrier, leading to various placental abnormalities, including PE (Tang et al., 2020). These EDCs cannot be easily analyzed because of their short half-lives, exposure level variability, and high evaluation expense. Standard guidelines and questionnaires can reduce these significant limitations encountered during exposure assessment. Reports suggest that the questionnaire can be considered a valuable alternative tool for correlating exposure to different sources of EDCs instead of directly analyzing the EDC exposure levels (English et al., 2015; Rivera-Núñez et al., 2022). Some of the primary exposure pathways during pregnancy are lifestyle and dietary habits. Worldwide, several healthcare organizations follow the standard guidelines for a healthy lifestyle. Lifestyle habits such as using PCPs and smoking lead to changes in physical fitness and hormone levels, which further cause several adverse effects in all age groups, including pregnant women and developing fetuses. Hence in our study, the questionnaire-based survey was used to analyze the association of socio-demographic variables with risk factors of PE.

The results of our study showed a strong correlation between maternal age above 27 years, living in rural areas, belonging to a lower economic class, being a housewife, and experiencing a first-time pregnancy with the occurrence of PE. The incidence of PE was higher in non-graduate rural residents, which could be due to the lack of awareness about the presence of EDCs in the products used in their day-to-day lives. Given that the target audience is from South India, it is noteworthy that women refrain from smoking or consuming alcohol due to cultural norms. Consequently, there have been minimal documented instances of women being exposed to secondhand smoke. Sleeping disturbance was also found to be associated with PE in the South Indian semi-urban

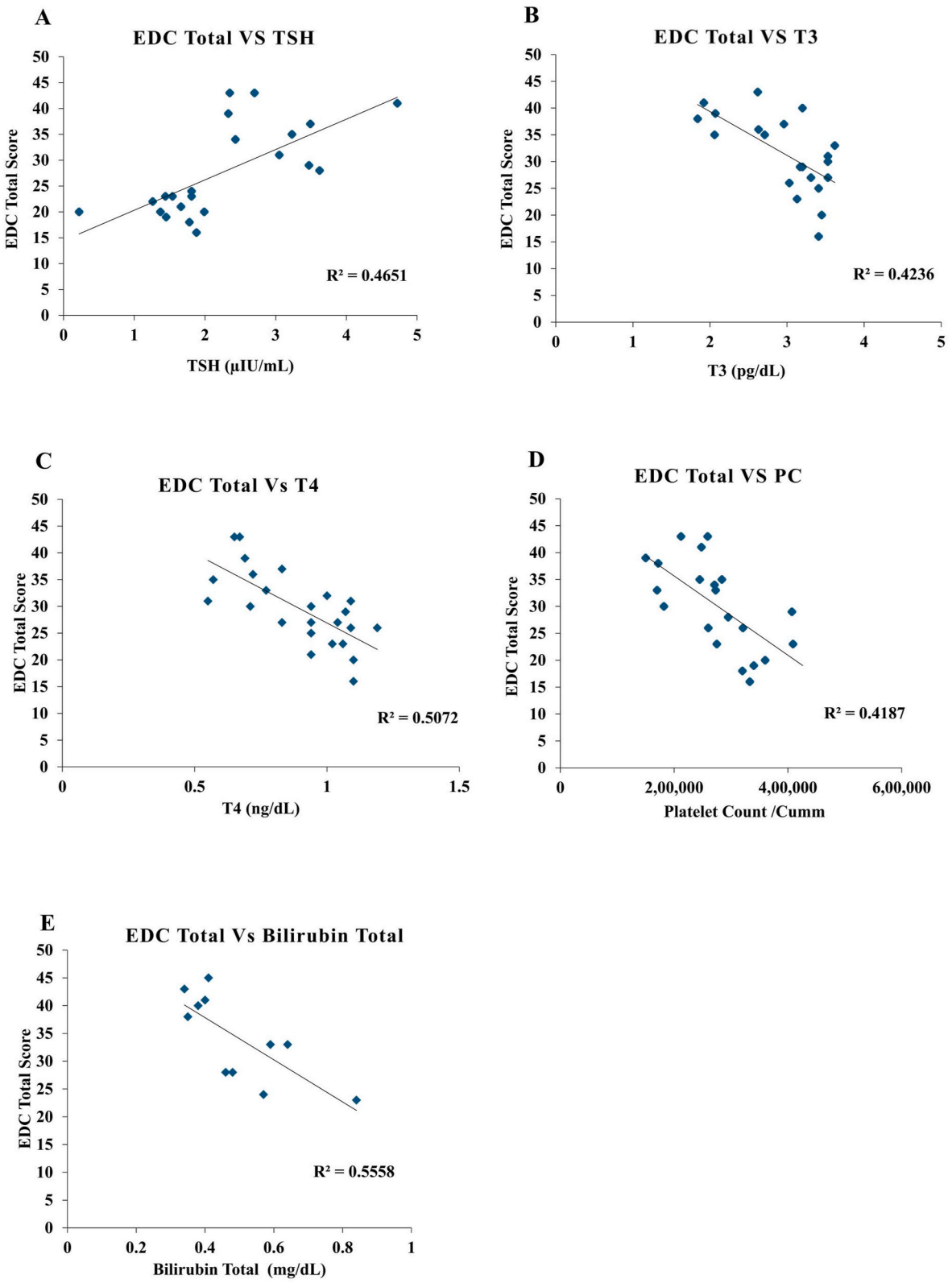

Fig. 9. Pearson positive correlation between EDC total scores and **A)** TSH, negative correlation between EDC total scores and **B)** T3, **C)** T4. Pearson negative correlation between EDC total scores and **D)** platelet count and **E)** Bilirubin total.

women population. A systematic review and meta-analysis conducted using 120 studies revealed that sleeping disturbances were also associated with maternal complications, including PE (Lu et al., 2021). Previous reports also highlight the link between circadian rhythmicity and pregnancy and the relevance of placenta-synthesized melatonin on healthy and complicated pregnancies such as PE (Diallo et al., 2023).

In a case-control study carried out on pregnant women in Ethiopia, the demographic variables such as women aged above 27 years, BMI (>25 kg/m^2), housewives, primiparity, family history of hypertension, and previous history of PE and less antenatal care (ANC) visit showed

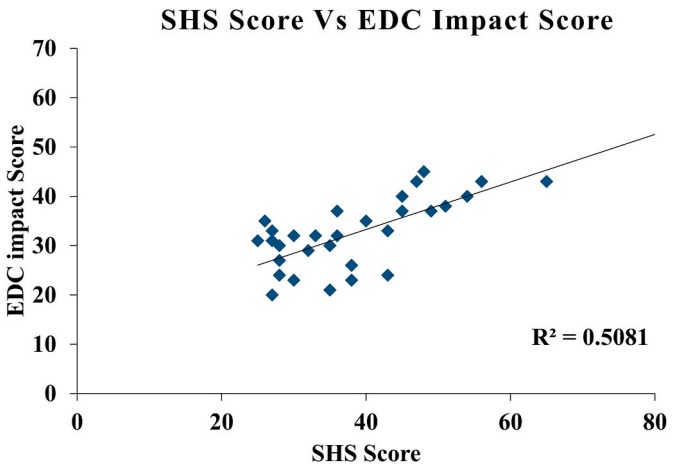

Fig. 10. Pearson positive correlation between EDC impact and SHS score.

association with PE ((Logan et al., 2020). Another study conducted in rural areas of Bangladesh also revealed that PE was common mainly in women with increased BP levels, who require antihypertensive drugs and are irregular for ANC visits (Mou et al., 2021). Pregnant women in Northeast India aged above 25 years, primigravida, lower socioeconomic status, and rural residents showed a higher incidence of PE. The study also revealed other factors, including poverty, illiteracy, shortage of healthcare facilities, and lack of awareness among the general population as features linked with a high incidence of PE among the rural population (Jena and Mohapatra, 2019). While another recent study found that early-onset preeclampsia (EOP) is a more severe condition than late-onset preeclampsia (LOP) in Central India (Singh et al., 2024). Previous history of PE in their earlier pregnancy was indicated as one of the significant risk factors of PE among pregnant women in Karnataka, India based on a case-control study (Ramesh et al., 2014). A Turkish study revealed a low educational background and participants with low income associated with an increased risk of PE (Gülşen and Güner, 2012). Studies from Ethiopia also revealed that low income, and intake of cheap-quality protein in maternal diets as factors associated with PE (Kinshella et al., 2021). The reported studies also supported the evidence from our studies that demographic variables such as maternal age, residential status, occupation, and parity might serve as risk factors in the progression of PE development.

Anthropometrical variables in our study indicated changes in MAP that might be due to blood vessel constrictions in PE, which is one of the crucial events that initiates PE due to insufficient invasion in the cytotrophoblast. A study conducted in Bangladesh revealed that PE was common mainly in women with increased BP levels, who require antihypertensive drugs and are irregular for ANC visits (Mou et al., 2021). Our studies also identified the association of higher BMI (>32.25 g/m2), with dietary habits such as consumption of processed foods with PE. Similarly, in a case-control study performed in South India the maternal age, BMI, gestational age, primiparity, previous history of PE, diet consumption especially non-vegetarian diet, and processed foods were reported to be associated with PE (Jaboi, 2020). A systematic review and meta-analysis study conducted by Iranian scientists revealed that the risk of PE increases with an increase in BMI linked to hypertensive condition (Motedayen et al., 2019). Therefore, anthropometrical variables such as blood pressure and BMI can be considered the most important predictors of PE.

In our investigation, biochemical parameters such as serum creatinine, serum urea, BUN, and total protein were associated with renal dysfunction in PE progression. Serum creatinine, and serum urea, were markedly elevated in PE, whereas total protein, albumin, and globulin were significantly decreased in PE women when compared to NP women. Creatinine is the metabolic product of creatine, which is produced at a constant rate and excreted through the kidneys after filtering. Elevation in the creatinine level is due to the inability of creatinine clearance in the kidney. It can also be used as a diagnostic biomarker in evaluating muscle and kidney dysfunction. Similarly in Ethiopia, a hospital-based case-control study reported a significant increase in the concentration of serum blood urea levels, whereas serum creatinine was also increased without significance in PE as compared with NP women (Tesfa et al., 2022). In Libyan women, the serum urea was significantly increased whereas serum creatinine was not significantly increased in PE compared to NP women (Salma et al., 2022). Hence these studies showed that PE has detrimental effects on kidney function supporting the findings of our study that renal impairment was common among PE.

Albumin was found to be decreased in Japanese women which was correlated with oxidative stress in PE (Kinoshita et al., 2017). PE is linked to an elevation in capillary permeability due to damage in the endothelial cells. This is believed to be the contribution of protein in the urine and lower levels of total protein and albumin in the bloodstream. A similar trend was also observed in our study which indicated a decrease in total protein, albumin, and globulin. Hypoalbuminemia observed in PE may arise due to urinary protein loss and reduced hepatic blood perfusion, both of which can be attributed to hemoconcentration. The underlying mechanism involves elevated filtration pressure within the capillaries (Kinoshita et al., 2017). A study from Ghana also revealed that albumin and total protein were significantly reduced in PE compared to NP women (Anto et al., 2019). A cross-sectional study conducted in Telangana, India revealed that the total protein, and albumin in PE were significantly decreased compared with control women (Khan et al., 2023). There was a statistically significant increase in urea creatinine, serum AST, and ALT levels in PE (Khan et al., 2023). Serum creatinine, total protein, albumin, and globulin, the essential proteins secreted in the kidney are also involved in PE prediction. Therefore, the assessment of these parameters would help monitor the risk of kidney function in PE.

Our study also showed a significant decrease in PC of PE women who are more likely to experience aberrant coagulation and negative maternal outcomes. Alteration in the coagulation and fibrinolysis also play a role in the pathogenesis of PE. Another study conducted in India also showed a significant decrease in PC levels among PE women (Thalor et al., 2019). A systematic review and meta-analysis conducted using 56 reports revealed that PC was significantly lower in PE women irrespective of the severity and onset of PE (Woldeamanuel et al., 2023). Hence PC evaluation can be helpful for the early diagnosis of PE, and it might be considered as an effective marker for PE prediction.

The liver function markers such as SGOT, SGPT, and ALP found to be the most influencing parameters associated with liver dysfunction in PE. Elevation in serum AST levels might be due to arteriolar spasms, which might cause impairments in the brain, heart, liver, and kidney function. ALP, an indicator of liver dysfunction was reported to be significantly higher in hypertensive pregnant women including PE compared to control (Connolly et al., 2022). Similarly, there was a significant increase in LFT enzymes such as AST, ALT, and ALP in PE compared to control women in Riyadh, Saudi Arabia (Al-Jameil N et al., 2015). Miranda et al. also indicated a positive correlation between serum creatinine, and liver markers including AST with PE (Leaños-Miranda et al., 2019). This showed that hepatic dysfunction or abnormal liver function might act as a predictor in the diagnosis of PE even in the early stages of pregnancy.

An imbalance in thyroid hormone profiles, T3, T4, and TSH in PE women was also identified. These hormones are essential for the growth and differentiation of most organ systems, especially in the neurological, reproductive, and endocrinological systems. Reported evidence suggests that minor changes in TSH may adversely affect human health (Vianna et al., 2011). Thyrotropin-releasing hormone (TRH) and TSH regulate the levels of thyroid hormones. Disturbance in factors that influence the balance of the HPT axis may lead to an abnormal thyroid hormone

profile. An Indian study reported an increase in TSH, and a decrease in T3 and T4 levels, indicating a state of hypothyroxinemia in PE (Kharb et al., 2013). Placental dysfunction in PE leads to failure of estrogen production further resulting in the lowering of thyroid hormone. Hence thyroid indicators would help in the diagnosis of PE even in the early trimester.

In pregnant women of Ghana, the SHS questionnaire helped in the assessment of the status of health and disease, as it shared a similar biological or physio pathway with PE which might also be helpful in the early prediction of PE progression. SHSQ-25 can be used as a risk stratification tool for adverse pregnancy outcomes including PE thereby creating an opportunity for predictive, preventive, and personalized medicine (PPPM) (Anto et al., 2019). It is also used for the prediction of CVD and other chronic disease health statuses in Asia, Africa, China, and European countries (Kupaev et al., 2016; Wang et al., 2017).

SHS score in our study using 5 domains (CVD, MH, fatigue, digestive, and immune functions), showed a significant increase in PE. This indicated an increased risk of clinical symptoms such as hyperemesis, nausea, and constipation which are associated with digestive disorders (Anto et al., 2019), increased risk of CVD-related disease in the later life of PE women, and the MH defects score showed that psychosocial stress is common among PE women in South India. The total SHS score was substantially high among the PE group, which indicated that they are likely to develop severe preeclamptic conditions characterized by thrombocytopenia, i.e., platelet deficiency (Sinha, 2020). This condition might be responsible for MH defects in the PE group. The defects in the coagulation system might lead to placental dysfunction. Further injury in the placental endothelial tissue may lead to the consumption of more platelets causing PC deficiency (Thalor et al., 2019). Hence, the SHS-25 questionnaire can be considered an effective prediction tool for the early detection of PE, and it might also be used as a clear indicator of endothelial dysfunction in PE. This questionnaire can also serve as a novel tool for screening the risk of CVD, and a cognitive-related condition. Cognitive deficits were common upon the usage of different EDCs like methylparaben which behaves as an anxiogenic agent even in the developmental stage of zebrafish (Raja et al., 2022). Additionally, reproductive disease outcomes like PCOS were also reported to be associated with exposure to various types of EDCs, and it seems to alter multiple neurological functions, leading to anxiety, depression-like behavior, and mood swings (Ananthasubramanian et al., 2021).

EDC toxicity comprehensively and systematically provides scientific thoughtfulness for the human endocrine system. Due to globalization and modernized lifestyle, many changes have occurred in the lifestyle and dietary habits of the human population. In our study, more than 70% of PE women are housewives and tend to be exposed to more of the EDCs, especially from dietary habits. Based on the EDC impact questionnaire response from the study participants, few alterations in the biochemical parameters were observed among the exposure groups including processed foods, dairy products, cosmetics, and non-stick utensils in PE. One of the major routes of EDC exposure is ingestion, in which the processed food exposure among PE majorly showed significant changes in biochemical parameters such as PC, serum urea, bilirubin profile, total protein, SGOT, ALP, and TSH when compared to high and low NP group. Several studies also reported that EDCs are involved in the alteration of PC, liver function markers, and thyroid markers (Gore et al., 2015; Leaños-Miranda et al., 2019). Given that the participants were from semi-urban and urban areas, the likelihood of exposure to EDCs is elevated in the population of South India due to the adoption of modernized living practices in the metropolitan metropolis. Epidemiological studies have reported the effects of different EDCs on thyroid abnormalities (Tang et al., 2020).

The National Health and Nutrition Examination Survey (NHANES) questionnaire was used in the estimation of urinary BPA in men and women based on the consumption of soda and canned food (LaKind and Naiman, 2011). In this study, after combining the questionnaires, like the food frequency questionnaire (FFQ), 24-h recall questionnaire, and 48-h recall questionnaire into an EDC impact questionnaire it was used to assess the association of dietary habits of pregnant women with EDC exposure. These questionnaires also provided sufficient information about food consumption by considering dietary diaries, recalls, and FFQ. Sharma et al. reported the presence of DEHP and other phthalates in the Indian food baskets. Especially phthalic acid esters, including DEHP, DBP, and BPA, were higher in processed foods, packaged foods, and other non-vegetarian diets in the Indian market (Sharma et al., 2021). The migration of plasticizers DEHP and DnBP from PET and LDPE casing water bottles was higher than the recommended limits by EPA (Chakraborty et al., 2022). The evidence says that even the increased consumption of vegetables, dairy products, poultry, and meat products was reported to have positive associations with BPA and other EDCs (Casas et al., 2013; Hartle et al., 2016). A study conducted among preschool children showed that vegetables and rice consumption are one of the main exposure pathways of BPA analogs (Fan et al., 2022).

Few epidemiological studies reported the influence of lifestyle habits and pesticides on PE and other pregnancy-related complications (Preston et al., 2020; Rolfo et al., 2020). A Persian birth cohort study reported the influence of Teflon containers among pregnant women and secondhand smokers which also showed higher levels of phthalate metabolites like MBP, MBzP, MEOHP, and MEHHP (Golestanzadeh et al., 2022). The PFAS levels in pregnant women were associated with hypertensive disease including PE in the Chinese and US populations (Nielsen et al., 2020; Wikström et al., 2019). The study also reported the association between various phthalate metabolites in the amniotic fluid and maternal characteristics from the self-reported questionnaire. It also noted the frequent use of deodorants by pregnant mothers and their significant association with urinary phthalates like MBzP and MEP.

The identification of exposure pathways was based on the toxicokinetic features of the chemicals, including their absorption, distribution, metabolism, excretion, and toxicity. Evidence from Shekar et al. identified EDC exposure pathways in pregnant women of South India based on the mode of exposure during their gestational period (Shekhar et al., 2017). Sharma et al. explain the challenges faced in the management of EDCs to overcome different exposure pathways like lifestyle and dietary habits and also explain the regulation of laws in the usage of these chemicals in developing countries like India (Sharma et al., 2023). Since most of the participants were from metropolitan cities, they were mainly exposed to EDCs through different routes, such as the use of cosmetics, food preservatives, packaged products, and non-stick coatings. Hence these identified pathways were used in framing the questionnaire in our study which altered the biochemical parameters causing PE.

A systematic review from low-middle-income countries revealed that the consumption of non-vegetarian foods in Zimbabwe, dairy products like coffee consumption in Ethiopia, grains intake in the Iranian diet, and alcohol consumption increased the risk of developing PE (Kinshella et al., 2021). Hence this questionnaire-based study was useful in predicting the association of various socio-demographic factors, anthropometric variables, and biochemical parameters with different routes of EDC exposure involved in the pathogenesis of PE development in the South Indian population.

5. Conclusions

To our knowledge, this study is the first to evaluate the potential role of endocrine-disrupting chemical (EDC) exposure in the pathogenesis of preeclampsia (PE) among women in the South Indian population. Our findings revealed that the use of processed foods, dairy products, and cosmetics containing EDCs worsens preeclamptic conditions, as evidenced by alterations in key biochemical markers. Continuous exposure to EDCs may result in dysfunction of critical organs such as the brain, heart, liver, and kidneys. This research highlights the importance of biochemical markers such as mean arterial pressure (MAP), body mass index (BMI), platelet count, serum creatinine, blood urea nitrogen

(BUN), total protein, thyroid function, and liver function tests (LFTs) as clear indicators of PE. Raising awareness about the risks associated with EDC-containing products during pregnancy may help reduce maternal and fetal abnormalities. Hormonal imbalances due to PE, potentially exacerbated by EDC exposure, can also contribute to psychosocial stress, depression, and anxiety-like behaviors. These findings underscore the urgent need for policies that restrict or limit EDC exposure, especially during the gestational period. Although our questionnaire survey provided valuable insights into EDC exposure and its clinical implications during pregnancy, further studies involving larger populations across different trimesters are necessary to better predict and mitigate PE. Due to the limited sample size, our study could not categorize the severity or onset of PE. Nonetheless, national and international research on EDCs, including their exposure routes, duration, toxic effects, and accumulation in the female reproductive system, is crucial for understanding the full scope of risks. Advances in in silico, in vitro, and in vivo studies, combined with continuous biomonitoring, will enhance the assessment of EDC toxicity. A comprehensive regulatory framework supported by public-private partnerships and community action is essential to raising awareness and mitigating EDC exposure. While there are no standardized clinical tests for diagnosing behavioral or neurological disorders during pregnancy in the context of PE, we acknowledge the neurobehavioral impacts that may arise due to elevated blood pressure and hormonal imbalances. Non-invasive, questionnaire-based screenings for mental health and lifestyle changes could provide valuable insights into the behavioral consequences of PE. Early detection and intervention, particularly in countries like India with stringent safety regulations, may help prevent the escalation of anxiety, depression, and stress during pregnancy. A multidisciplinary approach combining biochemical, behavioral, and neurological assessments could further enhance our understanding of the broader impacts of PE.

CRediT authorship contribution statement

Usha Rani Balu: Writing – original draft, Resources, Formal analysis, Data curation. **Ramasamy Vasantharekha:** Validation, Data curation, Conceptualization. **Chakraborty Paromita:** Writing – review & editing, Validation. **Khalid Ali:** Writing – review & editing, Validation. **Gaurav Mudgal:** Writing – original draft, Supervision, Project administration, Conceptualization. **Kavindra Kumar Kesari:** Visualization, Validation, Supervision, Project administration, Data curation, Conceptualization. **Barathi Seetharaman:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Data curation, Conceptualization.

Data statement

The datasets generated during and/or analyzed during the current study are not publicly available because the participants' consent does not allow for revealing their identities.

Ethical approvals

The study with human subjects was carried out in accordance with the World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. All procedures were performed in compliance with relevant laws and institutional guidelines and as well approved by the Institutional Human Ethical Committee at SRM Medical College Hospital and Research Centre (SRM MCHRC) (Ethical clearance: 2170/IEC/2020). The privacy rights of human subjects have been observed and informed consent was obtained for experimentation with human subjects.

Consent for publication

Individuals are given consent to participate in the study but with the objection to disclosure of their identity to any third party or while publishing the same.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The data that has been used is confidential.

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