

Research Article

A Case Control Study of Gene Environment Interaction in Pre-Eclampsia with Special Reference to Organochlorine Pesticides

Saloni Kamboj^{1*}, Kiran Guleria², Tusha Sharma³, Richa Sharma⁴, Bannerjee BD⁵

¹Senior Resident, Department of Obstetrics & Gynecology, UCMS >BH, Delhi, India

²Director Professor, Department of Obstetrics & Gynecology, UCMS >BH, Delhi, India

³Research Associate, Department of Biochemistry, UCMS >BH, Delhi, India

⁴Associate Professor, Department of Obstetrics & Gynecology, UCMS >BH, Delhi, India

⁵Director Professor, Department of Biochemistry, UCMS >BH, Delhi, India

***Corresponding Author:** Saloni Kamboj, Senior Resident, Department of Obstetrics & Gynecology, UCMS >BH, Dilshad Garden, Delhi - 110095, India, E-mail: salonikamboj17@gmail.com

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Abstract

Objectives: To study and compare the frequency of GSTM1 & T1 gene polymorphism in cases (Pre-eclampsia) and controls (normal pregnancy), to estimate and compare serum levels of Glutathione-S-Transferase enzyme in cases and controls, to quantify and compare Organochlorine pesticides levels in maternal blood of cases and controls and to evaluate the correlation; if any; amongst GSTM1 & T1 gene polymorphism, GST activity and Organochlorine pesticides levels in cases.

Methodology: Maternal blood samples of 66 Pre-eclampsia cases and equal number of matched control

were collected. Samples were analyzed for OCPs levels, GST activity and GST M1 and T1 gene polymorphism.

Results: β -HCH, Heptachlor, Dieldrin, Endosulphan-I levels were found in higher amounts in cases as compared to controls. GSTT1-/GSTM1- (double null polymorphism) was significantly high in cases as compared to controls. GSTT1-(null) genotype was exclusively associated with severe pre-eclampsia. When GST activity was correlated with genotypic variation of GSTT1/M1 gene, null genotypes significantly downregulated GST activity, lowest being with double null genotype.

Conclusions: There is a possible role of gene-environment interaction in the pathogenesis of pre-eclampsia. An interaction of increased levels of pesticides with GST polymorphisms (null type) causes low levels of GST enzyme levels (an anti-oxidant) resulting in increased oxidative stress causing pre-eclampsia.

Keywords: Pre-eclampsia; Organochlorine; Pesticides; Hypertension; Polymorphism; Glutathione-S-Transferases; Oxidative Stress

1. Introduction

Pre-eclampsia is a multi-system disorder characterized by hypertension (blood pressure of $\geq 140/90$ mm Hg) and proteinuria (≥ 300 mg/day) [1, 2]. Hypertensive disorders complicate 5-10% of pregnancies [3]. Recent studies have investigated the role of genetic susceptibility and gene-environment interactions in pre-eclampsia [4]. However, despite the strong correlation between oxidative stress and pre-eclampsia, only a handful of genes have been investigated. A family of enzymes, Glutathione-S-Transferases, play a critical role in providing protection against electrophiles and products of oxidative stress [5]. Genetic polymorphisms in genes encoding GST have been defined [6, 7]. Association of hypertension in general with pesticides has been studied a lot but association with pre-eclampsia has recently received some attention.

However, despite being universal exposure of antenatal population to organochlorine pesticides, only some women are susceptible to adverse effects of pesticides as a result of certain gene polymorphisms (GSTM1 & T1) which lead to decreased excretion and thus accumulation of greater amounts of pesticides in their systems; thus manifesting adverse effects. This is how

the gene environment interaction comes into play in pathogenesis of pre-eclampsia. The present study aimed at estimating and comparing the frequency of GSTM1 & T1 gene polymorphism, serum levels of Glutathione-S-Transferase enzyme and organochlorine pesticides levels in cases (pre-eclampsia) and controls (normal pregnancy), and to evaluate the correlation; if any.

2. Materials and Methods

This was a hospital based case control study in which 66 pre-eclampsia cases (according to ACOG Criteria [8] Blood pressure of 140 mmHg systolic or higher or 90 mmHg diastolic or higher that occurs after 20 weeks of gestation on two occasions 6 hours apart in a woman with previously normal blood pressure & Proteinuria, defined as urinary excretion of 0.3 g protein or higher in 24 hour urinary specimen or $\geq 1+$ dipstick) were recruited. For each case, a gestational age, parity and BMI matched control was recruited. Females with Age <18 years or >35 year, women with occupational exposure to pesticides, Chronic hypertension, thyroid disorders, chronic liver disease, heart disease, Pre-existing or gestational diabetes mellitus, Chronic renal disease, Thrombophilias –familial or acquired, Systemic lupus erythematosus, Hydramnios, pregnancies complicated by foetal abnormalities and women in active labor were excluded.

A questionnaire survey of the women was done to collect general demographical information in order to define the inclusion/exclusion criteria. Women confirmed their participation by signing a consent form and this study was approved by the Institutional Ethical Committee for Human Research. Five ml of maternal blood was drawn from each recruited subject. Out of 5 ml, 3 ml of blood was collected in an EDTA vial & 2 ml was collected in plain vial. Two ml blood in EDTA vial

was used for DNA extraction for polymorphism study. Two ml of blood in plain vial was used to study the GST activity in serum and one ml of blood in EDTA vial was used for organochlorine pesticides residues analysis.

2.1 Estimation of genetic polymorphism

DNA extraction was done using blood sample, deionized water, centrifugation & extracted DNA was used for PCR analysis. A single assay using a multiplex PCR was performed for simultaneous gene amplification. 50 ng of DNA was amplified in a 50- μ l multiplex reaction mixture containing 30pmol of each of the following GSTM1 primers in a medium consisting of 1.5 mM MgCl₂, 200 μ mol dNTPs, 5 μ l 10X PCR buffer (10X 500 mM KCl), 100 mM Tris-HCl, (pH 9.0) and 2 U TaqDNA polymerase. The PCR protocol included an initial melting temperature of 94°C for 5 minutes followed by 35 cycles of amplification (2 min at 94°C, 1 min at 59°C, and extension for 1 min at 72°C). A final 10 min extension step at 72°C terminated the process. The final PCR products from the co-amplification of GSTM1(215 bp) and GSTT1(480 bp) were visualized on an Etidium Bromide- stained 2.0% agarose gel to look for gene polymorphism present / absent.

2.2 Gst activity levels

The estimation of GST activity is based on principle that GST catalyzes the conjugation of L-glutathione to CDNB through the thiol group of the glutathione. The reaction product, GS-DNB Conjugate, absorbs at 340 nm. The rate of increase in the absorption is directly proportional to the GST activity in the sample. The linearity of the reaction was determined by plotting the absorbance values against time. The change in absorbance (DA₃₄₀)/minute, in the linear range of the

plot, for the sample and for the blank was calculated by subtracting A₃₄₀ (initial reading) from A₃₄₀ (final reading) and dividing the result by reaction time (min.).

Equation used:

$$\frac{(\Delta A_{340})/min \times V(ml) \times dil}{\epsilon_{mM} \times V_{enz}(ml)} = \mu mol/ml/min$$

Where

V = the reaction volume (for test in 96-well plate = 0.2 ml)

dil = the dilution factor of the original sample

V_{enz} = volume of the enzyme sample tested

ϵ_{mM} = extinction coefficient for CDNB

Conjugate at 340 nm = 5.3 mM⁻¹ (path length - 0.552 cm)

2.3 Organochlorine pesticide levels

OCP residue extraction was done using hexane and acetone (2:1) according to the method of Bush et al. Clean-up was done by the USEPA method using Florisil (Sigma) by column chromatography. Quantification of organochlorine residue levels was done by a Perkin Elmer Gas chromatography system equipped with 63Ni selective electron capture detector. Limits of detection were <0.05 pg perchloroethylene with nitrogen. Quantitative analysis of OCP residues in each sample was done by comparing the peak heights with those obtained from a chromatogram of a mixed organochlorines standard of known concentration. Ten samples of each maternal and cord blood in triplicate were spiked with a mixed standard of organochlorine pesticides. Furthermore, a quality check sample was always run with each set of samples for pesticides analysis.

2.4 Statistical analysis

Data was analyzed by SPSS Software (version 20.0), binary logistic regression was performed to compare

genotypic variation. Pearson’s coefficient of correlation was used to test correlation between levels of GST and pesticides. To correlate if high levels of organochlorine pesticides are associated with gene polymorphism and rise in blood pressure (SBP/DBP) in pre-eclampsia, multiple linear regression analysis was employed. P-value of <0.05 was considered significant.

3. Results

Six thousand three hundred women were screened during the study period from labor wards of GTB hospital. Out of these, 550 pregnancies were complicated with pre-eclampsia. The incidence of pre-eclampsia in the present study was 8.73%. Out of recruited cases, 21% were severe pre-eclampsia and 78% were pre-eclampsia without severe features. While estimating genetic polymorphism, women with double null genotype of GSTT1 & M1 were found to be at six times greater risk of development of pre-eclampsia (Table 1). While comparing the distribution of genetic polymorphism between non-severe & severe pre-eclampsia groups, GSTT1 null type was significantly associated with severe pre-eclampsia inferring thereby that GSTT1 null genotype may indicate the severity of disease in an individual. In other words, women with single null genotype of GSTT1 have eighteen times greater risk of development of pre-eclampsia (Table 2). GST acts as an antioxidant in body quenching all ROS

produced in the body. There was no significant difference in GST values between cases and controls & between two subgroups of pre-eclampsia.

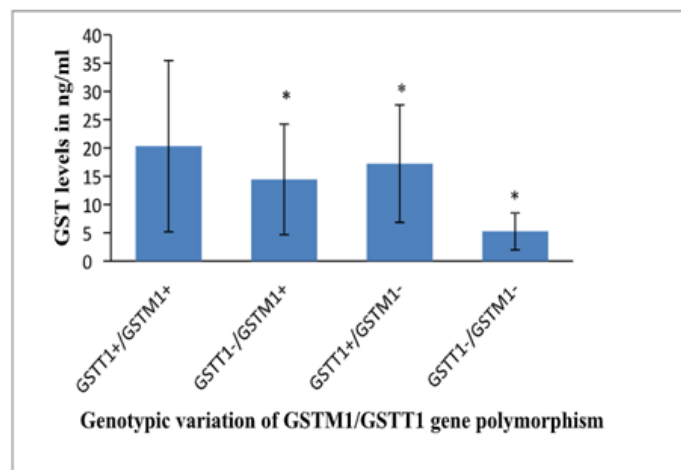
However when GST activity was correlated with genotypic variation of GSTT1/M1 gene, null genotypes down-regulated GST activity significantly, lowest activity observed with double null genotype (Figure 1) Significantly higher levels of β-HCH, Heptachlor, Dieldrin and Endosulphan were found in maternal blood of pre-eclampsia cases as compared to controls (Table 3). Significantly low levels of GST activity were associated with four pesticides (β- HCH, Endosulphan-I & II and Heptachlor); so pesticides were found to have an association with decreased antioxidant levels, hence increased oxidative stress. The interaction of GSTM1 genotype (null) and increased levels of DDT in blood resulted in significant increase in DBP levels (Table 4). The interaction of GSTT1 genotype (null) and high levels of β-HCH and heptachlor in blood also resulted in significant increase in DBP level (Table 4). The interaction of GSTM1 genotype (null) and increased levels of β-HCH in blood resulted in significant increase of in SBP levels (Table 5). Similarly the interaction of GSTT1 (null) genotype and increased levels of β-HCH in blood resulted in significant increase in SBP level (Table 5).

| Genotypes | Cases (n=66) | Controls (n=66) | OR | 95% CI | p-value |
|-----------------|--------------|-----------------|------|--------------|---------|
| GSTT1+ / GSTM1+ | 14 | 29 | | | |
| GSTT1+ / GSTM1- | 11 | 14 | 1.62 | 0.590-4.492 | 0.347 |
| GSTT1- / GSTM1+ | 12 | 13 | 1.91 | 0.696-5.256 | 0.209 |
| GSTT1- / GSTM1- | 29 | 10 | 6.00 | 2.298-15.704 | 0.000 |

Table 1: Genotypic distribution of Glutathione-S-Transferase (GSTT1/GSTM1) genotypes in study groups.

| Genotypes | Pre-eclampsia without severe features (n=52) | Severe pre-eclampsia (n=14) | OR | 95% CI | p-value |
|-----------------|--|-----------------------------|-------|---------------|---------|
| GSTT1+ / GSTM1+ | 13 | 1 | | | |
| GSTT1+ / GSTM1- | 11 | 0 | 0.00 | 0.00- not det | 0.99 |
| GSTT1- / GSTM1+ | 5 | 7 | 18.20 | 1.76-188.06 | 0.015 |
| GSTT1- / GSTM1- | 23 | 6 | 3.39 | 0.36-31.36 | 0.282 |

Table 2: Correlation of genotypic distribution of GST with severity of pre-eclampsia.



*p-value < 0.05; GST levels were significantly downregulated between group 1 & 2; 1 & 3; 1 & 4; 2 & 4 and 3 & 4

Figure 1: GST activity and correlation with GST gene polymorphism.

| Organochlorine pesticides (ppb) | Cases n=66 (mean ± SD) | Controls n=66 (mean ± SD) | p-value |
|---------------------------------|------------------------|---------------------------|---------|
| α HCH | 2.02 ± 2.02 | 1.63 ± 1.81 | 0.251 |
| β HCH | 6.32 ± 2.23 | 4.79 ± 2.41 | 0.000 |
| γ HCH | 1.98 ± 1.66 | 1.84 ± 1.46 | 0.612 |
| Heptachlor | 3.93 ± 2.36 | 2.61 ± 1.54 | 0.000 |
| Aldrin | 1.60 ± 1.57 | 1.58 ± 1.43 | 0.956 |
| Endo-I | 3.08 ± 2.82 | 1.27 ± 1.87 | 0.000 |
| Dieldrin | 3.07 ± 2.18 | 1.49 ± 1.64 | 0.000 |
| DDE | 3.13 ± 2.19 | 3.65 ± 3.35 | 0.294 |
| Endo-II | 1.21 ± 1.38 | 1.46 ± 3.01 | 0.533 |

| | | | |
|------------|-------------|-------------|-------|
| DDT | 0.64 ± 0.99 | 0.41 ± 0.81 | 0.146 |
|------------|-------------|-------------|-------|

*p value ≤ 0.05 has been considered as significant.

Table 3: Estimation & comparison of maternal blood organochlorine pesticide levels in study groups.

Significantly higher levels of β-HCH (6.32 ± 2.23 ppb, p=0.00), Heptachlor (3.93 ± 2.36 ppb, p=0.000), Dieldrin (3.07 ± 2.18 ppb, p=0.000), Endosulphan I (3.08 ± 2.82 ppb, p=0.000) were found in maternal blood of pregnancies with pre-eclampsia as compared to controls.

| GSTM1/GSTT1 interaction | Blood sample of study subjects (GSTM1) | | Blood sample of study subjects (GSTT1) | |
|--|--|---------|--|---------|
| | B-value | p-value | B-value | p-value |
| GSTM1/GSTT1 (null vs present type) | -3.692 | 0.432 | -4.257 | 0.373 |
| α-HCH | 0.419 | 0.329 | 0.391 | 0.359 |
| Interaction term of GSTM1/GSTT1-α-HCH levels | -0.737 | 0.248 | -0.599 | 0.354 |
| GSTM1/GSTT1 (null vs present type) | 0.044 | 0.983 | 24.871 | 0.001 |
| β-HCH | 2.343 | 0.062 | 3.127 | 0.001 |
| Interaction term of GSTM1/GSTT1-β-HCH levels | -4.339 | 0.025 | -5.875 | 0.001 |
| GSTM1/GSTT1 (null vs present type) | 1.159 | 0.784 | 1.889 | 0.661 |
| γ-HCH | 1.035 | 0.101 | 0.753 | 0.214 |
| Interaction term of GSTM1/GSTT1-γ-HCH levels | -2.172 | 0.011 | -2.331 | 0.008 |
| GSTM1/GSTT1 (null vs present type) | 0.197 | 0.963 | -1.644 | 0.697 |
| Aldrin | 1.497 | 0.052 | 1.627 | 0.040 |
| Interaction term of GSTT1/GSTM1-Aldrin levels | -2.978 | 0.046 | -2.276 | 0.101 |
| GSTM1/GSTT1 (null vs present type) | 2.451 | 0.575 | 3.173 | 0.468 |
| Dieldrin | 1.794 | 0.221 | 1.644 | 0.258 |
| Interaction term of GSTM1/GSTT1-dieldrin levels | -5.648 | 0.006 | -5.868 | 0.005 |
| GSTM1/GSTT1 (null vs present type) | 0.034 | 0.993 | 0.877 | 0.822 |
| Endosulfan-I | 2.333 | 0.060 | 2.527 | 0.040 |
| Interaction term of GSTM1/GSTT1-Endosulphan-I levels | -4.039 | 0.015 | -4.311 | 0.010 |

| | | | | |
|---|---------|-------|---------|-------|
| GSTM1/GSTT1 (null vs present type) | -1.644 | 0.697 | 0.197 | 0.963 |
| Endosulfan-II | 1.627 | 0.040 | 1.497 | 0.052 |
| Interaction term of GSTM1/GSTT1-Endosulphan-II levels | -2.276 | 0.101 | -2.978 | 0.046 |
| GSTM1/GSTT1 (null vs present type) | 12.398 | 0.001 | 1.107 | 0.810 |
| pp-DDT | 8.833 | 0.001 | 0.711 | 0.131 |
| Interaction term of GSTM1/GSTT1-ppDDT levels | -10.187 | 0.001 | -1.581 | 0.025 |
| GSTM1/GSTT1 (null vs present type) | 4.623 | 0.418 | 5.376 | 0.321 |
| PpDDE | 5.991 | 0.005 | 6.256 | 0.002 |
| Interaction term of GSTM1/GSTT1-ppDDE levels | -5.367 | 0.033 | -5.677 | 0.020 |
| GSTM1/GSTT1 (null vs present type) | 0.735 | 0.871 | 12.433 | 0.001 |
| Heptachlor | 0.822 | 0.085 | 8.869 | 0.001 |
| Interaction term of GSTM1/GSTT1-Heptachlor levels | -1.516 | 0.026 | -10.248 | 0.001 |

*p value <0.005 is significant; B=regression coefficient

Table 4: Regression model testing an interactive effect of OCPs (ppb) and GSTM1/GSTT1 genotype on diastolic BP (mmHg) in study subjects.

| GSTM1/GSTT1 interaction | Blood sample of study subjects (GSTM1) | | Blood sample of study subjects (GSTT1) | |
|---|--|---------|--|---------|
| | B-value | p-value | B-value | p-value |
| GSTM1/GSTT1 (null vs present type) | -4.383 | 0.427 | 2.306 | 0.349 |
| α -HCH | -0.388 | 0.516 | 2.421 | 0.537 |
| Interaction term of GSTM1/GSTT1- α -HCH levels | 0.772 | 0.304 | -0.456 | 0.364 |
| GSTM1/GSTT1 (null vs present type) | 11.398 | 0.001 | 15.536 | 0.001 |
| β -HCH | 8.833 | 0.001 | 5.334 | 0.007 |
| Interaction term of GSTM1/GSTT1- β -HCH levels | -10.286 | 0.001 | -9.769 | 0.001 |
| GSTM1/GSTT1 (null vs present type) | -5.253 | 0.274 | 1.371 | 0.654 |
| γ -HCH | -0.744 | 0.343 | 0.325 | 0.919 |
| Interaction term of GSTM/GSTT1- γ -HCH levels | 1.391 | 0.158 | -0.271 | 0.665 |

| | | | | |
|---|--------|-------|--------|-------|
| GSTM1/GSTT1 (null vs present type) | -6.532 | 0.250 | 19.501 | 0.008 |
| Aldrin | -3.580 | 0.110 | 8.046 | 0.018 |
| Interaction term of GSTT1/GSTT1-Aldrin levels | 3.748 | 0.164 | -4.187 | 0.005 |
| GSTM1/GSTT1 (null vs present type) | -1.221 | 0.767 | 2.349 | 0.685 |
| Dieldrin | 0.861 | 0.555 | -0.756 | 0.774 |
| Interaction term of GSTM1/GSTT1-dieldrin levels | 0.984 | 0.587 | -0.163 | 0.890 |
| GSTM1/GSTT1 (null vs present type) | -6.367 | 0.132 | 4.980 | 0.309 |
| Endosulfan-I | 0.131 | 0.902 | 1.012 | 0.738 |
| Interaction term of GSTM1/GSTT1-Endosulphan-I levels | 2.679 | 0.047 | -0.640 | 0.509 |
| GSTM1/GSTT1 (null vs present type) | 6.402 | 0.133 | 3.799 | 0.198 |
| Endosulfan-II | 5.107 | 0.023 | 1.556 | 0.663 |
| Interaction term of GSTM1/GSTT1-Endosulphan-II levels | -3.616 | 0.126 | -0.384 | 0.522 |
| GSTM1/GSTT1 (null vs present type) | -3.719 | 0.456 | -4.017 | 0.571 |
| pp-DDT | 2.814 | 0.155 | -4.715 | 0.116 |
| Interaction term of GSTM1/GSTT1-ppDDT levels | 2.455 | 0.303 | 1.823 | 0.221 |
| GSTM1/GSTT1 (null vs present type) | 0.961 | 0.654 | 4.054 | 0.099 |
| PpDDE | 0.986 | 0.591 | 3.169 | 0.321 |
| Interaction term of GSTM1/GSTT1-ppDDE levels | -6.467 | 0.189 | -0.700 | 0.166 |
| GSTM1/GSTT1 (null vs present type) | -9.974 | 0.110 | 3.044 | 0.099 |
| Heptachlor | 0.431 | 0.654 | 3.176 | 0.344 |
| Interaction term of GSTM1/GSTT1-Heptachlor levels | 1.992 | 0.069 | -0.699 | 0.167 |

*p value <0.005 is significant; B=regression coefficient

Table 5: Regression model testing an interactive effect of OCPs (ppb) and GSTM1/GSTT1 genotype on systolic BP (mmHg) in study subjects.

4. Discussion

Pre-eclampsia is a pregnancy related disease with an unpredictable course that can have serious consequences for the mother and the fetus. It is very essential to

analyze the etiological factors and carry out further research in targeted interventions to prevent pre-eclampsia. In this prospective case-control study we made an effort to find an association among genetic

polymorphism in GST gene (genetic factors), GST enzyme activity and organochlorine pesticides (environmental insult) in pre-eclampsia and the possible mechanisms underlying this association. The incidence of pre-eclampsia in the present study was 8.73%, which is consistent with those reported from most of the studies in developing countries. One of the most important systems involved in metabolism and detoxification of ROS, xenobiotics and carcinogens is that of Glutathione-S-Transferase (GST) [5]. Null genotypes of GSTT1 and GSTM1 have been linked with an increased risk of several multifactorial traits including cancers and cardiovascular diseases [9]. In present study, the frequency of GSTM1/GSTT1 genotypic variation was studied and it was found that GSTM1-/T1- (both null deletion) genotype was significantly higher in subjects with pre-eclampsia as compared to controls. This is in concordance with a previous study by Sahar S et al. [10] where GSTM1- / GSTT1- (both null type) genotype was a potential genetic factor to predict development of essential hypertension and permit early therapeutic interventions. Human beings are constantly being exposed to variety of environmental contaminants like organochlorine pesticides. The problem of pesticide residue is very high in India due to poor safety measures during use and implementation despite low average consumption of pesticide than many other developed countries. The result in our study has also shown higher levels of various pesticides residues in blood samples of women with pre-eclampsia. The findings of the present study are in agreement with previous studies, where higher levels of OCPs in pregnant women may cause adverse reproductive outcomes as these pesticides can act as xenoestrogens as well as create oxidative stress [11-13]. Women are exposed to a variety of reproductive toxins, but not all who are exposed have adverse reproductive

outcomes. It is speculated that an individual's reproductive risk associated with these toxins may be modified by genetic variation in metabolic detoxification activity. Mustafa et al. [14] in 2013 reported that when GSTM1 genotype was absent (null), increasing levels of β -HCH increased the risk of preterm delivery significantly. Ours study is probably the first human study where attempts have been made to show that increase in pesticide levels in body result in pre-eclampsia in the presence of double null GST genotype due to decrease in antioxidant levels. Pre-eclampsia is a significant health problem both in developed and in developing world despite enhanced standard of antenatal care. Newer etiologies like environmental factors (pesticides) and specially gene-environment interactions need to be established to set appropriate preventive strategies in order to bring incidence and mortality under control. The results of our study reconfirmed that there is a possible role of gene-environment interaction in the pathogenesis of pre-eclampsia. An interaction of increased levels of pesticides with GST polymorphisms (null type) caused low levels of GST enzyme levels (an anti-oxidant) resulting in increased oxidative stress, thus causing pre-eclampsia. Thus we can conclude from the present study that continuous indirect exposure of pesticides in general population are detrimental to health and may result in adverse reproductive outcome like pre-eclampsia. Our study has proven the hypothesis that environmental factors (pesticides) interact at genetic level (gene polymorphism) to ultimately cause pre-eclampsia by altering the oxidative stress pathway. We recommend further such studies on a larger population to prove gene environment interactions causing pre-eclampsia. We notice that even after being banned by various organizations, use of these pesticides is still prevalent as shown by increased blood levels.

Therefore, use of such harmful chemicals should be banned with immediate effect. Food safety and standards authority of India should implement stringent regulations to keep a check on the levels of pesticides found in food samples. Pregnant population in India should be encouraged to consume more antioxidants (natural & vitamins) to combat the oxidative damage caused by environmental exposure.

Author Contributions

S.K. – Patient recruitment and did the study

K.G. - Conceptualised the study and data analysis

T.S. – Biochemical Analysis

R.S. – Helped in literature search

B.B. – Provided inputs in methodology

Declaration of Interests

None

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