Research Article

Preeclampsia and Consanguinity

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Abstract

Type of the study: case control

Aim: to evaluate the severity of imminent preeclampsia in consanguinity versus non consanguinity groups

Design and patients methods: a highly selective criteria have been chosen for the women to be participated in this study. The study group (N=30) were not only cousins rather their parents were also cousins and most came from the rural area. While the control Group (N=30) were women in whom no consanguinity neither with couple nor their parents were selected. All women were primigravida 20- 30 years in age. They were all taken from labor ward after 37 weeks of gestation, and for each at admission systolic, diastolic blood pressure, serum uric acid, blood urea, blood platelets count and serum fibrinogen and SGPT with SGOT were initially taken at admission. Since all the patients were in severe and imminent preeclampsia they were all pre prepared with $MgSO_4$ as anti convulsant and during preparation serial reading were also taken for all the above parameters at 3 and 6 hours later to measure the area under curve profile AUC. Mean blood pressure was taken instead of systolic and diastolic and calculated by the well documented formula

Results: The ODD ratio for the primary determinant of preeclampsia severity namely blood pressure and proteinurea were higher in the consanguinity group versus control; 6.58 for systolic; 6.73 for diastolic and 4.07 for protein/ creatinine ration in urine, respectively. Serum uric acid and blood urea was also higher for their ODD ratio in the consanguinity group; 5.2 and 5.21 respectively. More importantly the markers of imminent preeclampsia were also significantly higher in the consanguinity group with odd ratio 2.22and 2.61 for SGOT and SGPT respectively. Best subset regression was calculated for the best combination which correlates with mean blood pressure and serum SGPT with Blood urea combinations were having the lowest coefficient of Mallow (Cp); 32.23. From that independent variable a prediction table has been constructed to sort out all the patients with imminent preeclampsia who are most affected and near complications probably and expressed as column of intervals of blood urea with corresponding 1,2.5, 5, 10, 90, 95,97.5 and 99 centile of serum SGPT. The area under 10^{th} centile was shaded with green while above 90^{th} centile with red and in between shaded with yellow color. It is probable that patients who's reading in the red zone or upper yellow zone are at more risk for more serious complications of preeclampsia like adrenal hemorrhage and renal complications and better to expedite their delivery. **Conclusion:** this study has shown that preeclampsia among consanguinity group was much more severe than those in non consanguinity couples. Yet by no mean that respect reflects the true picture in society. A table has been constructed and we over stress here that under no circumstances this table can be used for evaluating, modifying or changing the routine protocol of preeclampsia management.

Key words: preeclampsia severity, consanguinity and pregnancy, consanguinity and pregnancy outcome

INTRODUCTION

As a matter of fact it is well known since the times of Hippocrates that preeclampsia is not more than hypertension, edema and proteinurea which has only one treatment namely termination of pregnancy.[1] Despite the core of idea has remained since 6000 years till now or 400 BC yet 3 major breakthroughs have occurred in understanding the nature of disease.[1] The first was in 1974 when discovered that preeclampsia is associated with failure pseudo vascular development at the level of placenta associated abnormal thromboxane and placental rennin production and both are responsible for hypertension and failure of coagulation system.[2] The second well know and even more famous breakthrough was achieved early in the millennium when preeclampsia was found to be a disease of insulin resistance. However there is a less famous and well known breakthrough which may be summarized as the isolation of at least 100 genes associated with preeclampsia.[3-5] The mechanism in which those genes control preeclampsia is still to be clarified. Some of those genes involved in preeclampsia works through placenta growth factor and endothelia growth factor PIGF and VEF.[6] In women with preeclampsia those factors which are essential to the normal placentation are severely reduced. In other word the genes coding for them are under expressed. Other genes works through soluble endoglbin which is a soluble isoform of co-receptor for transforming growth factor beta (TGF-beta). Endoglin binds to TGF-beta in association with the TGF-beta receptor. Because the soluble isoform contains the TGF-beta binding domain, it can bind to circulating TGF-beta and decrease circulating levels. In addition, TGF-beta is a proangiogenic molecule, so the net effect of high levels of sEng is anti-angiogenic. There is strong evidence that soluble endoglbin increase significantly at least 3 months prior to the onset of preeclampsia.[7] In other word the gene expression for soluble endoglobin is over expressed among women liable for preeclampsia. Up to this point it might be remembered that preeclampsia is a disease of insulin resistance which is well known to be multi factorial inheritance mode.[8] According to the demography of the Iraqi people cousin marriage is widely rife especially in rural areas which may takes ritual style. Since this demographic picture is not seen in the developed countries a study of consanguinity and preeclampsia has been designed to show the effect of consanguinity on preeclampsia severity. So the aim of study is to assess the severity of preeclampsia among consanguinity couples versus non with regard to mean arterial blood pressure versus various independent preeclampsia associated variables.

PATIENTS AND METHODS

Setting: The study was done in Al Yarmook Teaching Hospital between January 2015 and June 201٦. All women enrolled in this study were admitted to labor ward and put into two groups study group and control group according to consanguinity. All the women in the study group N=30 were primigravida and term between 37 and 41 weeks and she is cousin with her husband. In addition the couple's parents were also cousins. All the women in the control group N=30 were primigravida and term between 37 and 41 weeks and she is stranger to her husband and their parents were not related in any form. For both groups the verbal consent to participate in the study was taken as nothing required for the study except the data of their routine investigation. The study protocol was approved by the Arab Board Council as it is authority which responsible for this thesis.

Study design: As it has been mentioned above the study and the control groups contained both normal women (risk free women), meaning they are not hypertensive, diabetic, multiple gestation, Rh negative women, mal position of the fetal head, mal presentation and all other conditions which require modification in their labor, all women in both group were assessed and managed as active management of labor. These include artificial rupture of the membrane at 4 cm cervical dilatation, use of oxytocin to augment labor contractions, implementation of partogram, electronic fetal heart monitoring and analgesia during labor by pethidine. Active management of the second and third stage of labor by putting the patient in lithotomy position and encourage the patient to push with uterine contraction until crowning of the fetal head were episiotomy was done. And Brands Andrew's method of placental delivery after giving oxytocic drug ergometrine immediately after delivery of the fetus was done. That is summary of the management in women with no preeclampsia in both study groups; the consanguinity or study group, or control or non consanguinity group. On the other hand the women with imminent preeclampsia women in both groups underwent totally different course by putting them in the intensive care unit. Women with imminent preeclampsia are those with diastolic blood pressure 110 mmHg or more irrespective of the systolic value. In addition proteinurea assessment is 4 gram or more per 24 hour. Insertion of at least two wide bore cannula and Foleys catheter to monitor the urinary output. Nothing by mouth was also ensured.

Magnesium Sulfate $MgSO_4$ was used as primary anti convulsive drug while hydralazine intravenous infusion was used in our department. In addition at the time of insertion of the cannula 5 cc of blood was sent for biochemistry analysis in ordinary test tube and 2 cc for evaluation of blood platelets in different test tube with anticoagulation material. While from the Foley's catheter tube a sample of 5 cc urine was collected and sent for protein over creatinine ratio as a reflection of the 24 total urinary proteins in urine. The blood biochemistry investigation included serum SGPT, SGOT in iu/L units, Fibrinogen in mg/dl unit to assess the severity of liver and kidney impairment. In addition the platelets count in thousands per ml however we have omitted the three zero digits in the tables for the sake of simplicity for example 150,000 platelets per ml is expressed as 150 /ml. The protein over creatinine ration was measured by Microgram / milligram units so 160 ų/m means 1٦0 microgram protein/milligram creatinine in urine. Both serum uric acid in the blood and urea were measured in mg/dl. In addition to the initial assessment mentioned above meticulous monitoring chart was established with 15- 30 minutes intervals for assessment of the blood pressure and expressed as mmHg and signs of Magnesium sulfate toxicity including respiratory rate, maternal heart rate, reflexes in the knee joint. 10 cc of calcium gluconate was prepared as standby for any possible cardiac arrest from overdose of Magnesium as we don't have in our labs facilities for measuring its serum value. The protocol of giving $MgSO_4$ was initial 4-6 gram loading dose initially followed by 2-3 grams per hour as maintenance dose per hour. While hydralazine 5- 10 mg were put in 200- 300 normal saline and infused slowly until blood pressure drops to 140 over 90 mmHg. In addition to the initial values at admission further assessment of fibrinogen, platelets, SGPT and SGOT and blood urea and serum uric were all assessed after 3 and 6 hours. The purpose of those 2 assessments is to measure the area under curve AUC for every patient with severe or imminent preeclampsia for the sake of statistical comparison at the end of the study. Mean arterial blood pressure was calculated from both systolic and diastolic blood pressure values according to the following formula;

$$MAP \sim DP + \frac{1}{3}(SP - DP)$$

So at end of the study a total of 30 women with consanguinity with her husband and also between their parents were collected as the study group. Further 30 women with no consanguinity neither with her husband and her parents were collected as control Group. Out of 30 patients in the study group 11 women were in imminent or severe preeclampsia that required immediate control of blood pressure and anticonvulsant therapy. Out of 30 patients in the non consanguinity group or control group 3 women were in imminent preeclampsia and managed as exactly as above.

Statistical analysis: The first statistical analysis was done by power analysis to calculate the required sample size for this thesis. Based on the fact that 10% of the overall admissions are hypertensive while according to the criteria we have chosen for the study group the expected incidence is arbitrary evaluated as 50%. With the above incidences and at alpha error 5% and beta error 80% the required minimum sample size was 25 patients for each group study and control with ratio of control over study equal 1. Thanks God that we could collect extra patients further for each group so the sample size was totally 60 patients, 30 women for each group. Unpaired student t test was used to compare continuous data with test for variance set to automatic in the software. Calculation of the value comparable to75 centiles or above were calculated for systolic, diastolic, blood pressure, SGOT, SGPT, serum uric acid and blood urea to evaluate the ODD ratio for each all variables between consanguinity versus control groups. This test was used to evaluate the correlation between consanguinity and every variable by coding the figure 0 for value under or equal 75 centiles and 1 for values above 75 centiles for every variable. The ODD ratio, 95% CI or confidence interval and P value were calculated to evaluate the associated of the main study variables mentioned above with consanguinity. Later we have assessed the area under curve or AUC for every variable mentioned above and their means have been compared by unpaired t student test between the study groups. Area under curve was constructed and measured by taking serial data for each of the above variables at admission and 3 and 6 hours later while she was being prepared by hydralazine amd $MGSO_4$ in intensive care units. In order to evaluate the best predictor of mean arterial blood pressure and other main variables the ***Best Subset Regression*** model has been constructed to evaluate best predictor of mean Blood pressure from SGOT, SGPT for the hepatic function, Platelets counts and serum fibrinogen for the coagulation blood system and uric, blood urea for the urinary system by the calculation of ***Coefficient of Mallow Cp***. The protein/ Creatinine ratio was considered inadequate as predictor in this study due to the large number of varieties of measuring units or the normal range and other issue. At last the best 2 predictor were expressed as table of serum value intervals of one predictor and the 1, 2, 5.5, 10, 90,

95, 97.5 and 99 centiles serum level of the other predictors. Values less than 10 centiles were colored with green or low risk. Values between 10 to 90 centiles were expressed as yellow or moderate risk factor and above 90 centiles serum values were colored with red or high risk factor values which are ominous for preeclampsia complications. The tables can be used for any patient irrespective of consanguinity to sort out high risk patients for preeclampsia complications.

RESULTS

As it has been mentioned in the previous chapter total of 30 consanguinity women versus 30 non consanguinity women were collected all at term with preeclampsia. In table 1 the basic criteria of preeclampsia and age were compared between them and it is noticeable that the primary determinant of preeclampsia severity in the form of systolic, diastolic and mean blood pressure and protein over creatinine ratio were all significantly higher in the consanguinity group. In addition the liver enzymes, coagulation profiles as well as renal marker were also higher in the study group. Yet this finding does not mean it is correlated to consanguinity. In order to verify whether consanguinity is related the ODD ratio for all the above factors mentioned in table 1 have been calculated and unexpectedly all were higher in the consanguinity group as shown by the 95% confidence interval and P value.

The association of all the determinant of preeclampsia severity is genuine finding yet by no mean it can be universal as the collection of patients in both group in this study was not random rather highly selective. This may explain the unusual association between consanguinity and severity of preeclampsia. As a matter of fact the above table is more confusing than explaining as it only tells that consanguinity is correlated to the preeclampsia yet the picture is not only bleak rather vague. In order to expose more about this correlation serial reading after admit ion to the hospital at admission time, 3 and 6 hours of mean blood pressure. Mean arterial blood pressure was calculated by the non linear formula given in the previous section of this study. And here is considered as the dependent variable. On the other hand still serial readings at 0, 3 and 6 hours were done for 6 independent variables through measuring the area under curve of the 3 readings of the followings; Blood urea and serum uric acid for the function of kidneys; Platelets counts and serum fibrinogen for the coagulation status; more importantly serum SGOT and SGPT still at 0, 3 and 6 hours with calculation of the area under curve for each above variable readings. This profile as area under curve is at least 16 times more sensitive than single reading since areas are measured with square units. All the details are given in table figure 1 with the appended table for explanation and table 3 for the rest of the independent variables.

Table 1. The main variables taken at admission for study and control groups with their statistical comparisons

Characteristics	Control Group (N=30)	Study Group (N=30)	P value
Age	24.56±3.62	23.13±3.74	P = 0.1377
Systolic BP	131±28.98	155.86+50.52	P = 0.0228
Diastolic BP	75.30±22.14	94.10±35.53	P = 0.0177
Mean arterial BP	93.95±23.9787	114.68±39.82	P = 0.0176
Mean urine Protein / Creatinine ratio	0.75±1.42	1.91±2.06	P = 0.0138
Women with imminent preeclampsia	3(10%)	11(36.6%)	P = 0.0155
Serum Fibrinogen	250.8±45.8	187.6±16.59	P = 0.0012
Serum platelets(*1000)	252.6±45.6	182.33±91	P = 0.0004
Serum SGOT	26.8±12.37	41.5±21.11	P = 0.0017
Serum SGPT	26.8±14.22	40.53±20.99	P=0.0030
B Urea	22.66±2.77	29.1±10.92	P=0.0028
Serum Uric acid	2.16±2.0	4.40±0.24	P = 0.0002

In figure 1 below which may be unique and unusual the mean blood pressure at 0, 3 and 6 hours was measures as serial data for all women in both study group and compared with unpaired t student test. However un usually here the geometrical mean rather than the arithmetic mean is expressed with median and the 95% confidence interval. The reason behind this is that converting systolic and diastolic blood pressure by the non-linear equation to Mean Blood Pressure has converted the variance from homogenous to none. Since the software used was set to automatic with regard to the variance difference in t student test here it has approximated them by taking the geometrical mean rather than the arithmetic mean.

Table 2. Use ODD ratio and logistic regression to explore correlation between consanguinity and its correlation to various variables among two study groups

Complications	ODD Ratio	95% CI	P value
Systolic > 75 centile	5.2105	1.2784 to 21.2373	*P = 0.0213*
Non-Consanguinity		Reference group	
Diastolic > 76 centile	3.7632	1.037 to 13.64	*P = 0.0308*
Non-Consanguinity		Reference group	
Urinary protein /creatinine >75 centile	3.7632	1.03 to 3.64	*P = 0.04*
None-Consanguinity		Reference group	
SGOT > 75 Centile	2.76	2.01 to 3.64	*P = 0.033*
Non- Consanguinity		Reference group	
SGPT > 75 Centile	4.7	`1.65 to 3.45	*P = 0.01*
Non-Consanguinity		Reference group	
Platelets count < 75 Centile	8.1053	1.6115 to 4.7675	*P = 0.0111*
Non-Consanguinity		Reference group	
Serum Fibrinogen < 75 centile	8.1	1.60 to 4.76	*P = 0.0111*
Non-Consanguinity		Reference group	
blood urea > 75 percentile	5.2105	1.2784 to 21.2373	*P = 0.0213*
Non- Consanguinity		Reference group	
Serum Uric Acid > 75 centile	5.21	1.2784 to 21.2373	*P=0.0003*
Non-Consanguinity		Reference group	

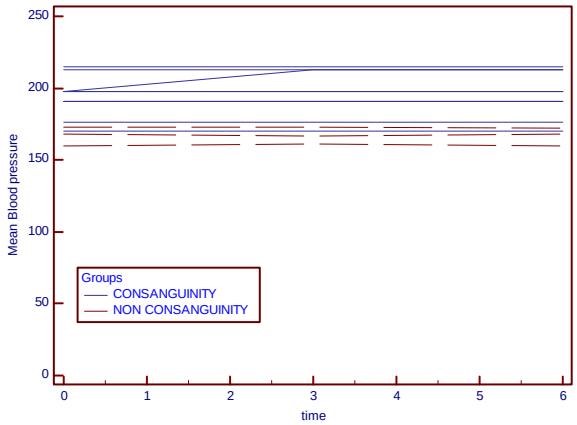

Figure 1. area under curve for mean blood pressure at 0, 3, and 6 hours has been measured for women in both study group and their mean was compared as in the appended table below. *CI; Confidence Interval*

Group	n	Geom. Mean BP	95% CI	Median	Two-tailed pro bability
non consang uinity	3	504.82	465.454 to 547.516	504.0	P<0.0001
consang uinity	11	683.723	662.395 to 705.738	706.5	

Finally compared with t test and as seen in the appended table the difference in the mean blood pressure between the study and control groups for area under curve is highly significant; P<0.0001. Since the profile of blood pressure was taken as serial reading for 0, 3 and 6 hours after admission to the hospital definitely it will be more reliable than single reading as at the admission time only. On the other hand the choice of area under curve is mandatory here as the data are unfit for assessment by linear regression or ANOVA test for serial reading. The above two tests are only applicable when the parameter in study either decrease or increase continuously with time. Here since with 6 hours all the women have not been delivered such data taken serially are unfit to be compared by them rather area under curve has been used as the optimum and only choice.

In the same context 6 independent variables were assessed also in the same manner by area under curve for their serial data taken at 0, 3 and 6 hours and presented in table 3 after the 2 means were compared by t test for serum fibrinogen and platelets count, serum uric acid and blood urea and those are not important as they appear early in every case of preeclampsia. On the other hand serum SGOT and SGPT measured still serially at 0,3 and 6 hours and presented also as area under curve which are raised only in severe preeclampsia are all given as shown with their statistical significance with regard to difference. At what we hope is that the reader does not confuse the readings in the table with the normal range and units of the parameter given in the table. For example blood urea in general is 20- 40 mg/ dl! While the first figure in the table is 230.818 squared units! Meaning this figure is the area

under 3 blood urea estimation at admission or 0 and 3 and 6 hours later and measured here all with unit^2 or squared area and the same for 2 study groups and those areas when compared with t test the P value is 0.0280!

Table 3. mean of area under curve is presented as mean and standard deviation of serum fibrinogen, platelets count, serum uric acid and blood urea, serum SGPT and SGOT with their statistical differences taken Profile of blood urea and AUC in consanguinity versus non women. ***CI; Confidence Interval***

B urea	**n**	**Mean**	**95% CI**	**SD**	**Median**	**Two-tailed probability**
Consanguinity	11	230.818	213.371 to 274.265	45.321	270	P = 0.0280
Non consanguinity	3	176	144.973 to 207.02	12.49	180	
Uric acid	n	Mean	95% CI	SD	Median	Two-tailed probability
Non consanguinity	3	29.6	27.323 to 31.877	0.917	29.4	P = 0.0007
Consanguinity	11	44.727	40.962 to 48.493	5.605	42	
Platelets count	n	Mean	95% CI	SD	Median	Two-tailed probability
Consanguinity	11	400.227	349.327 to 451.128	75.767	396	P < 0.0001
Non consanguinity	3	766.5	667.142 to 865.858	39.997	780	
Serum fibrinogen	n	Mean	95% CI	SD	Median	Two-tailed probability
Non consanguinity	3	730	574.866 to 885.134	62.45	750	P < 0.0001
Consanguinity	11	423.818	389.841 to 457.796	50.576	426	
SGPT	n	Mean	95% CI	SD	Median	Two-tailed probability
Consanguinity	11	403.227	392.329 to 414.126	16.222	403.5	P = 0.0462
Non consanguinity	3	380	342.490 to 417.510	15.1	378	
SGOT	n	Mean	95% CI	SD	Median	Two-tailed probability
Consanguinity	11	408.955	402.176 to 415.734	10.091	408	P = 0.0073
Non consanguinity	3	383	332.961 to 303.039	20.130	391.5	

CI; Confidence Interval

Extraction of the best predictor of mean blood pressure out of the six independent variables by best subset regression-coefficient of Mallow Cp

Table 4. the best arrangement of two combinations with Models with Smallest Cp coefficient

Mean sum of squares	**R^2**	**Adjusted**	**Mallow Coefficient**	**Included pairs of variables**
MSE	R-Squared	R-Squared	Cp	Variables
37.8788	97.2156	97.1179	32.2371	BE
46.0329	96.6162	96.4974	50.8012	DE
51.5325	96.2119	96.079	63.322	CE
54.709	95.9784	95.8373	70.5537	BC
55.8493	95.8946	95.7505	73.1498	AE

Legend

Definition table
Dependent variable: MEAN BP
Independent variables:
A=SGOT serum level
B=SGPT Serum level
C=Platelet as blood counts
D=Fibrinogen serum levels
E=Blood Urea level
F=Uric Acid serum levels

As it has been mentioned before mean blood pressure may be considered as dependent variable while the other 6 variables, renal hematological and renal profiles are independent. Yet having 6 variables is impractical in building a model and for that reason we implemented best subset regression to extract the most 2 independent variables correlated with mean blood pressure via examining the coefficient of Mallow. In this type of formula construction the independent variable which has the lowest Cp or coefficient of Mallow is the factor which has the highest correlation with dependent

variable, mean blood pressure. This should be stressed as the concept of variance is quite different from the concept of distribution and no correlation exist between them and as shown in the table 4 above that the combination of blood urea and serum SGPT has the best correlation with mean blood pressure as they have the lowest coefficient of Mallow.

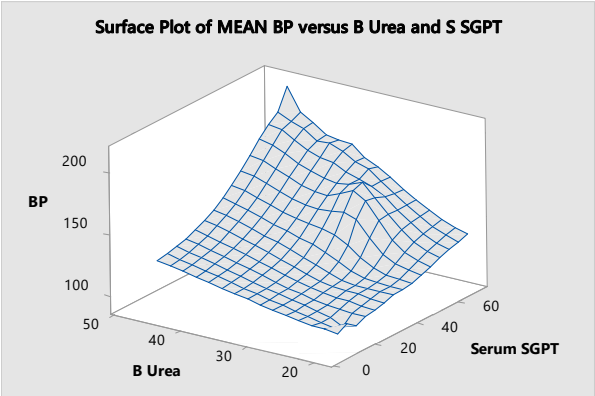

Figure 2. the style of mean blood pressure versus blood urea and serum SPGT levels are presented as mesh plot

In the 3 dimensional surface plots shown in figure shows visually this fact beyond suspicion. It quite obvious that both blood urea and serum SGPT are related strongly in proportional way to mean blood pressure which encouraged as building a screening table which may help the practicing physician in predicting the severity of (severe) preeclampsia or imminent which has no chance of any oral therapy or further prolongation of pregnancy. The details are given bellow.

Table 5. B urea levels column various serum level SGPT centiles in the rows for safe, unsafe and risky situations for women in immanent preeclampsia

Intervals	Serum SGPT levels for corresponding centiles <1, 2.5, 5, 10, 90, 95,97.5,99>							
B Urea mg/ml	**1**	**2.5**	**5**	**10**	**90**	**95**	**97.5**	**99**
20	6.1576	7.9667	9.5227	11.3166	23.9728	25.7667	27.3227	29.1318
25	26.1256	28.0507	29.7063	31.6151	45.0818	46.9907	48.6463	50.5713
30	42.6731	44.5665	46.1949	48.0724	61.3180	63.1955	64.8239	66.7173
35	54.9284	56.6427	58.1171	59.8170	71.8099	73.5098	74.9842	76.6985
40	62.0203	63.4080	64.6016	65.9777	75.6861	77.0622	78.2557	79.6305
45	63.0772	63.9910	64.7769	65.6829	72.0751	72.9812	73.7671	74.6808

In this table the various serum levels intervals of blood urea are given in the left most column while the corresponding rows contains the 1, 2.5, 5, 10, 90, 95, 97.5 and 99 centile of SGPT serum levels. It should be remarked that this table is not for predicting or evaluating mild preeclampsia rather for imminent preeclampsia which has no more treatment apart from termination of pregnancy. Yet termination of pregnancy requires at least 12 hours of highly delicate decline of blood pressure as well as well establishing $MgSO_4$ Therapy in the form of loading and maintenance dose. Serum levels less than 10 centiles are shaded with green. Serum levels with yellow shading are between 10 and 90 centiles. Serum levels above than 90 centiles are shaded with red. It might be preferable that patients with reading in the red zones or high yellow zones to expedite their delivery before developing more serious complications like acute tubular necrosis, pituitary hemorrhage and further details are given in the discussion

DISCUSSION

Well to start with preeclampsia is a disease of abnormal placentation which is accompanied by increased production of placental rennin which causes

hypertension and prostaglandin F2α which causes low grade disseminated intravascular coagulation syndrome or DIC from the early second trimester till delivery even before the onset of preeclampsia occur.[10,11,12] Up to this moment all the finding in this study can be explained namely hypertension, proteinurea, reduced serum platelets and fibrinogen, increased blood urea and serum uric acid and increased serum liver enzymes. However it doesn't explain the differences in consanguinity group and this can be achieved by the second major breakthrough in preeclampsia understanding through the flagged article published in American Journal of Obstetrics and Gynecology in 2011 under the preeclampsia and insulin resistance.[13]

In fact this article represents the second most important major breakthrough in preeclampsia understanding. Since all the insulin resistance diseases are transmitted as multi factorial then according to the strict criteria of patient collection followed in this study multi factorial inheritance should have explained the differences between the study and control group seen in this study. As a matter of fact more 100 genes have been isolated which have been proved to play a key role in preeclampsia genesis. May be the fact that those genes were all evaluated thoroughly represent the third breakthrough in preeclampsia understanding but didn't gain popularity due to the fact that such studies are confined to the advanced western countries only.

As it has been mentioned in the introduction both placental growth factor and endothelial growth factor PIGF and VEGF were both increased in abnormal pregnancy complicated by preeclampsia. It goes without saying that placental growth is simply a complex and intricate new vessel formation in such a way that in almost in 40 weeks in human being the highly complex and intricate architecture of the fetal blood and maternal blood interaction at the level of tertiary villous is so delicate to ensure fetal supply with oxygen and other nutrients while disposing toxic contents like urea and uric acid and CO_2 out of the fetal circulation.

It has been found that both mediators (PIGF, VEGF) were significantly increased among women with preeclampsia since very early in pregnancy. The gene which codes for both factors is over expressed among women with preeclampsia showing intrauterine intra uterine growth restriction and abnormal Doppler velocity in the umbilical artery in the cells of synctiotrophoblast.[14] In addition to this the expression of this gene is related to insulin resistance by unknown mechanism. Insulin resistance is associated with over expression of this poly morph gene.[14] This gene may explain the differences in the severity of preeclampsia among the two study group as its transmission is by multi factorial inheritance and it is very likely that women in the study group has inherited from her both parents.[15]

Though immunological factors are not usually related to genetics rather to the exposure to a certain antigen, it has been found that the secondary wave of trophoblastic invasion mentioned above is somehow related to genetic factors. Practically all women with preeclampsia have failure of secondary wave of trophoblastic invasion of the spiral arterioles to render them responsive to the circulating vasoconstrictors in the maternal blood. This process has been linked to up regulation metalloproteinase 9 and HLA antigen G.[16] Those 2 factors are needed for successful invasion of the trophoblast to be completely normal. It has been found that the gene responsible for production of those2 factors is grossly under expressed with resulting of poor placentation seen among women with preeclampsia at the level of trophoblast invasion. The mechanism is not clear nor is their correlation to insulin resistance understood. Yet it is very likely that it played a role in our study groups as the inheritance of this gene is still multi factorial.

As it has been mentioned above preeclampsia is strongly associated with leakage of protein from the glomeruli and this is the result of gross damage to the endothelial cells. There is strong evidence that endothelial damage and dysfunction is not restricted to the glomeruli rather it is widely generalized especially in the placenta. Since normal pregnancy huge new vessel formation is the rule the place and role of proangiogenic and anti angiogenic factors are of great importance and their balance is very important in the normal pregnancy. Soluble endoglobin which is a form of circulating receptor for transforming growth factor which plays very important role in the new blood vessel formation by binding to a cell surface receptor inducing new vessel formation. Since the last receptor is angiogenic soluble globulin is considered as anti angiogeneic factor.[17]

There is evidence that in preeclamptic women serum levels of soluble globulin precedes the onset of clinical preeclampsia at least 3 months. The reason behind the serum increase of soluble globulin is unknown thought it is associated with insulin resistance. Giving S globulin to rats causes cause hypertension and proteinurea while giving to pregnant rats causes HELLP like syndrome. The increased production of S globulin has correlation with insulin or in other word genetic factors.(14) In Fact

the reasons behind soluble endoglobin gene over expression in preeclampsia are unknown.

The use of area under curve is another topic which deserves some discussion as AUC is very effective as the unit of measurement is expressed as square unit to detect the slightest differences between 2 sets of data. In addition to analysis of all variables in this study by area under curve they were further analyzed by the best subset regression to calculate the best predictor of blood pressure in severe or imminent preeclampsia which was still taken serially at 0, 3, 6 hours after admission. Surprisingly the best predictors were blood urea and serum SGPT. Though it may be strange initially and refused by logics. Yet here we are dealing with imminent preeclampsia in other word those women in which blood changes and liver involvement have already started as they reached the stage of imminent preeclampsia. So the best predictor of mean arterial blood pressure here is not as expected in mild and early onset preeclampsia. The degree of association is measured by Coefficient of Mallow. The 2 best variables chosen were blood urea and SGPT. And from those two variables the correlation with mean arterial blood pressure is evaluated in the form of 3 dimensional mesh surface plot and a table has been predicted from equations which have been skipped from the reader for the sake of avoiding confusion. Yet the table is easy as in the left column the various ranges of blood urea are given while the upper row the serum SGPT for the 1, 2.5, 5, 10, 90, 95, 79.5 and 99 centiles are given. And for further benefit and avoiding any confusion areas less than 10 centiles are shaded with green, areas between 10 and 90 centiles with yellow and areas above 90 centiles with red color. It is expected that women with low blood urea and corresponding serum level of SGPT are still just have entered the stage of imminent preeclampsia and she has somewhat further 110-12 hours before reaching the critical stage.

During this period, it is safe to prepare the patient for induction of labor and control of blood pressure with hydralazine and institution of Magnesium sulfate anticonvulsant therapy which may take in loading and maintenance dose up to 10 hours. Possibly it is safe to wait for this period. While patients in whom readings for blood urea near 90 centile or above with serum SGPT is more than 90 centile with regard to serum value possibly have only few hours before developing more sister complications like intracranial bleeding, adrenal hemorrhage, liver failure and other highly dangerous complications so it is wise to expedite the delivery as soon as possible. That is the rationale behind building this table. Of course the use of this table without prior testing by at least 3 trials is mentioned here only to be condemned. For the time being this table is only for evaluation purposes and should it shows some clinical benefit then further confirmations by trials are encouraged as this area of medical practice remains one of the most challenging fields facing the Obstetrician in charge.

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