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A Study of Stress Induced Biochemical Changes In Pregnancy

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Abstract:-
Aim*:- To assess the risk of stress induced biochemical changes in pregnancy in view of their significant impact in developing diabetes and coronary heart disease through metabolic syndrome.*
Materials and Methods*:- 15 cases of Primis in first trimester.*
15 cases of Primis in third trimester with normal blood pressure.
15 cases of Primis in third trimester with PIH.
Fasting blood glucose,Serum total proteins, Serum total triglycerides,Serum total cholesterol, Serum HDL-Cholesterol and Serum Ceruloplasmin were estimated.
Results*:- There was increase in levels of fasting glucose, total triglycerides, total cholesterol and ceruloplasmin and decrease in levels of HDL and total proteins as the pregnancy is progressing with further exaggeration in PIH.The change in normal pregnancy is serum hypertriglyceridaemia which may be as high as two to three folds in third trimester over the levels in non pregnant women.A significant decrease in HDL levels were observed in pre-eclamptic pregnant women.Plasma ceruloplasmin (CP) activity increased significantly ($p<0.05$) as pregnancy progressed.There was 3.60 fold increase in risk of pre-eclampsia among women with total cholesterol > 205mg / dl and 4.15 fold increase in risk of pre-eclampsia among women with triglycerides > 133mg /dl.*
Conclusion*:- The present study concludes that pregnancy is a stressful condition resulting in varied biochemical changes. These changes are exaggerated when pregnant women have associated hypertension which is a risk factor of metabolic syndrome and they are possibly prone to diseases like diabetes mellitus, coronary artery diseases and stroke.*
Keywords:- *Metabolic syndrome, PIH, Preeclampsia, coronary artery diseases, stroke, Hypertriglyceridaemia, Ceruloplasmin.*

I . Introduction

Stress is inevitable in everyday life and it affects mental and physical well-being both beneficially and detrimentally. 'Stress' was defined by Hans Selye, a physician who investigated stress as "the non-specific response of the body to any demand"[1] and the cause of stress as "stressor". These stressors may be physiological or psychological. Physiological stressors like trauma, infection affect human organ systems directly through catabolic changes. Psychological stressors affect human organ systems directly via the psycho-neuro-endocrino-immune network[2] and also by modulation of human behavior. One individual's perception of a particular stressor will differ from another's. Factors affecting stress perception may be related to environment and related to physical interaction of environment with the individual (objective) or related to individual feelings (subjective). Among these three factors, the individual related psychological factors (subjective) are those most directly affect the individual health.

Brain-to-immune pathway -Two major axes have been proposed in the stress response: The Sympathetic Adreno-Medulla pathway (SAM) and The Hypothalamus-Pituitary-Adrenal(HPA) axis.The fight or flight response and emotions are associated with increased activity in sympathetic nervous system. There are two pathways by which these sympathetic signals are conveyed to target organs. One through direct neural connections where norepinephrine acts as a neurotransmitter and the other through SAM pathway where epinephrine is released from adrenal glands and travel through blood stream. The sympathetic neural fibers descend from brain into a neural terminal both in primary and secondary lymphoid tissues. Immune cells also express catecholamine receptors. So catecholamines,norepinephrine and epinephrine activate immune response including an increase of NK cells and cytotoxic T-cells[3].Cortisol the main secreted hormone in HPA axis is the major stress related hormone[4]. Major immune organs like spleen and thymus are rich in cortisol receptors.There is consistent order of response in change levels of mediators between SAM and HPA axes, i.e. an increase of cortisol levels was observed after an increase of catecholamine levels. This suggests that catecholamines may promote cortisol secretion so that the two main axes of brain-to-immune pathway communicate with each other. Pro-inflammatory cytokines like IL-1, IL-6 and TNF-α can activate SAM and HPA axes[5]. IL-1 particularly was shown to be capable of increasing permeability of blood brain barrier. Cytokines released are affecting peripheral nerves and brain as well as peripheral immune cells. These pro-inflammatory cytokines are also

demonstrated to initiate sickness behavior like fatigue, sleepiness and anorexia. This suggests that there is direct interaction between immune cells and brain.So it is proposed that intercellular interactions and intracellular mechanisms in each level of psycho-neuro-endocrino-immune network enable the immune system to maintain homeostasis in health.

Acute stress is defined as stress that has its effects within one day.In the nervous system, acute stress activates the secretary neurons through aminergic and GABA-ergic innervations in the autonomic nervous system[6]. In the immune system acute stress increases the number of NK-cells in the blood stream and NK cytotoxic activity. Acute stress acting through the SAM and HPA axes 1) Promotes inflammation as an alarm response which in turn stimulates SAM axis to produce catecholamines which in turn promotes the secretion of pro-inflammatory cytokines.

2) Increases the levels of cortisol which can counteract the alarm signal and suppress activation of the immune system. Cortisol has been considered as main stress hormone which can suppress the immune response by affecting targets mainly through its glucocorticoid receptors.

Sustained stress is defined as stress that has its effects for more than one day, i.e. over more than one circadian rhythm. Sustained stress induces various changes in psycho-neuro-endocrino immune network. It increases blood brain barrier permeability and inhibitory GABA-ergic nervous activity was attenuated under sustained stress[7.] Sustained stress has been demonstrated to alter tissue specific distribution of lymphocyte sub-population and specifically peripheral NK-cell levels are decreased[8]. Mechanisms which contribute to suppress cellular immune responses are 1) Due to sustained exposure to high levels of cortisol is associated with multiple positive feedback loops in HPA axes and it exacerbate the imbalance of interactions within psycho-neuro-endocrino immune network. 2) Accumulated negative feedbacks from repetitive responses in both SAM and HPA axes result in impaired reactions in their hormone secretions. Any type of stress either physiological or psychological triggers a characteristic hypermetabolic state in which resting energy expenditure is increased along with body temperature. The extent and pattern of metabolic changes vary with the type as well as severity of stress experienced. The stress syndrome shows certain common features like 1) Marked increase in release of amino acids from tissue proteins particularly from skeletal muscle.2) Increase in hepatic gluconeogenesis resulting in hyperglycemia. 3) Increase in synthesis of specific proteins for example those proteins involved in acute phase of inflammatory response and those concerned with repair of injured tissue.

Carbohydrate Metabolism:-Tissue injury prompts increased levels of cytokines, glucagon, cortisol, catecholamines and insulin. In presence of stress insulin does not display its usual spectrum of actions. Insulin resistance in stress is promoted by high concentrations of counter regulatory hormones. They minimize glucose utilization by tissues resulting in hyperglycemia.

Hyperglycemia ↑ATP, ↑NADH→↓Glucose utilisation → ↓Glycolysis

The other effects of stress on carbohydrate metabolism are Gluconeogenesis and increased Glycogenolysis.

Lipid Metabolism:-Increase in oxaloaceticacid and acetyl CoA → ↑Cholesterol synthesis

Protein Metabolism:- Cortisol, Catecholamines → ↑ protein degradation→ ↑Proteolysis→ ↑↑ amino acids. Amino acids released enter the liver and these are responsible for increased Apo-protein synthesis, increased triglyceride synthesis and increase in cholesterol esterification.↑ Apo-protein synthesis→ ↑↑ Lipoprotein synthesis. This increased lipoprotein synthesis in stress is responsible for hyper lipoproteinemia. Stress when managed properly provides us the drive to meet new challenges. However when physical or emotional stress builds up to uncomfortable levels it can be harmful for pregnant woman. In short, a high level of stress can cause fatigue, sleeplessness, anxiety, poor appetite or overeating, headaches and backaches. When a high level of stress continues for a long period it may contribute to potentially serious health problems such as lowered resistance to infectious diseases, high blood pressure and heart diseases. Studies also suggest that high levels of stress may pose special risks during pregnancy. Pregnancy related discomforts such as nausea, fatigue, frequent urination,backache can be stressful in pregnant women. Hormonal changes are also responsible for mood swings experienced during pregnancy.

Effects of stress on pregnancy:--1) Preterm labour:- Corticotrophin Releasing Hormone (CRH) is the first hormone our brain secretes when we are under stress. Pregnant women who experience high levels of stress have high levels of CRH in their blood[9]. CRH released prompts the body to release chemicals called prostaglandins which trigger uterine contractions. This is the reason for preterm labour.2) Low birth weight**:-** Stress related hormones such as norepinephrine constrict blood flow to placenta[10]. So the baby may not receive the nutrients and oxygen it needs for optimal growth. This results in low birth weight.3) Alterations in brain development**:-** Exposure to uncontrollable stress during pregnancy results in a heightened elevation of plasma corticosterone[11]. This was accompanied by a significant decrease in maternal levels of corticosteroid binding globulin which suggest increase circulating levels of free corticosterone .In unbound state corticosterone may be highly effective in producing alterations in brain development of offspring. Chronic stress causes decreased weight gain, higher blood pressure, lower endothelial-derived relaxing factor and lower fetal weight.

Another important stress induced effect in pregnancy is PIH (pregnancy induced hypertension). Preeclampsia is a more serious form of PIH. It is diagnosed when a mother's blood pressure is higher than 140/90 in the last 20wks of pregnancy. An abnormal lipid profile is known to be strongly associated with atherosclerotic cardiovascular disease and has a direct effect on endothelial dysfunction. Most important feature in toxemia of pregnancy is hypertension which is supposed to be due to vasospastic phenomenon in kidney, uterus, placenta and brain. Altered lipid synthesis leading to decrease in PGI_2 / TxA_2 ratio is also supposed to be an important way of pathogenesis in PIH[12]. Thus abnormal lipid metabolism seems important in pathogenesis of PIH. The hormonal imbalance is a prime factor for etiopathogenesis of PIH and this endocrinal imbalance is well reflected in alteration of serum lipid profile. Women who develop hypertension during pregnancy face a higher risk for stroke, coronary heart disease, hypertension and microalbuminuria later in life[13]. Women in whom PIH eventually develops are more likely to enter pregnancy overweight and some of the risk factors characterizing atherosclerosis such as dyslipidaemia (hypertriglyceridemia, low levels of HDL, and raised small LDL cholesterol)[14], insulin resistance[15] and endothelial dysfunction[16] are demonstrated. These metabolic aberrations like increased adiposity, dyslipidaemia, hyperglycemia and elevated blood pressure are reminiscent of metabolic syndrome. This syndrome is considered as an independent risk factor for cardiovascular disease.[17] Based on documented evidence the women who suffer from PIH present a syndrome similar to metabolic syndrome and these women seem at increased risk of developing cardiovascular disease later in life.

II. Materials and methods

Controls- For the present study women who were selected were primis of first trimester without hypertension, proteinuria and edema who were taken as Group A(15 cases).

Cases- In this study women who were primis in third trimester were divided into two groups (B & C). In Group B (15 cases) women selected were with gestational age between 28 weeks and 39 weeks without hypertension, proteinuria and edema. In Group C (15 cases) women selected were with gestational age between 28weeks and 39weeks with hypertension, proteinuria and with or without edema. All cases and controls that were pregnant were asked to come to biochemistry laboratory on overnight fasting at 9 A.M. After brief clinical examination i.e. taking relevant history, recording blood pressure, measuring weight; blood sample was taken for the measurements of following parameters-- Estimation of glucose, Serum total proteins, Lipid profile(Total triglycerides,Total cholesterol,HDL), Ceruloplasmin levels.

III. RESULTS

Table 1: GROUP A: Primis in first trimester

S.No	Age	G age in wks	Total Protein (gm/dl)	FG mg/dl	TCH mg/dl	HDL mg/dl	TTG mg/dl	Cerulo Plasmin (Ravin Units)	Systolic (mmHg)	Diastolic (mm Hg)	Wt Kgs
1	21	12	7.3	60	126	50	88	190	110	80	41
2	17	12	7.6	72	152	62	104	150	116	70	41
3	21	10	7.1	67	131	60	103	370	100	80	42
4	23	11	7.6	64	127	51	119	290	110	70	40
5	24	10	7.0	71	202	58	152	300	110	80	76
6	18	11	7.0	60	178	58	163	230	120	70	45
7	19	12	6.5	68	159	58	112	170	110	70	45
8	17	10	6.7	60	158	52	91	140	110	80	47
9	24	10	7.0	64	184	55	114	210	110	80	70
10	20	11	7.7	70	208	51	162	240	110	80	55
11	19	10	7.6	67	144	50	108	120	118	80	50
12	19	10	8.4	69	148	58	102	140	110	80	36
13	31	10	7.7	86	166	55	172	190	110	70	70
14	21	11	7.3	64	210	56	189	380	120	70	68
15	18	11	7.1	65	137	52	108	120	110	80	35
Mean	20.8	10.79	7.306	67.133	162	55.06	125.8	216	111.6	76	50.73
S.D.±		0.798	0.474	6.5122	28.695	3.881	32.426	85.255	5.0709	5.07	13.687

Table 2: GROUP B: Primis in third trimester with normal blood pressure

S.No	Age	G age in wks	Total Protein (gm/dl)	FG mg/dl	TCH mg/dl	HDL mg/dl	TTG mg/dl	Cerulo Plasmin (Ravin Units)	Systolic (mmHg)	Diastolic (mm Hg)	Wt Kgs
1	20	38	6.5	64	242	56	204	390	110	70	57
2	22	36	5.2	71	214	50	168	480	110	70	70
3	28	36	7.3	77	250	48	134	400	110	70	65
4	20	36	5.0	72	180	48	175	420	100	70	50
5	25	34	7.0	68	184	45	162	360	110	80	55
6	20	39	6.4	80	192	50	220	400	120	80	56
7	18	39	6.2	78	130	47	218	470	120	80	45
8	20	38	6.3	82	177	50	123	540	120	70	39
9	20	39	6.0	81	183	46	140	380	120	80	50
10	19	39	6.5	75	185	45	150	230	120	70	51
11	18	37	7.0	76	193	55	216	500	120	70	54
12	20	37	6.2	82	176	50	182	250	100	60	55
13	20	38	6.6	71	198	57	219	410	110	80	56
14	19	33	5.8	74	150	48	212	420	110	80	50
15	17	36	5.6	73	209	45	217	330	120	80	65
Mean	20.4	37	6.24	74.93	190.86	49.33	182.66	406	113.33	74	54.5
S.D.±		1.85	0.6467	5.2707	30.568	3.921	34.933	84.588	7.2374	6.3245	7.909

S.No	**Age**	**G age in wks**	**Total Protein (gm/dl)**	**FG mg/dl**	**TCH mg/dl**	**HDL mg/dl**	**TTG mg/dl**	**Cerulo Plasmin (Ravin Units)**	**Systolic (mmHg)**	**Diastolic (mm Hg)**	**Wt Kgs**
1	**21**	**38**	**4.2**	**90**	**210**	**45**	**216**	**550**	**140**	**90**	**50**
2	**19**	**39**	**5.7**	**85**	**158**	**42**	**194**	**640**	**130**	**90**	**56**
3	**22**	**34**	**6.8**	**70**	**228**	**42**	**171**	**480**	**140**	**90**	**50**
4	**20**	**36**	**4.5**	**88**	**205**	**45**	**174**	**600**	**130**	**100**	**66**
5	**19**	**37**	**4.2**	**98**	**255**	**46**	**189**	**490**	**140**	**100**	**70**
6	**22**	**32**	**3.5**	**80**	**225**	**45**	**234**	**550**	**150**	**100**	**54**
7	**19**	**36**	**6.5**	**78**	**161**	**42**	**209**	**390**	**140**	**100**	**57**
8	**22**	**37**	**6.0**	**100**	**248**	**45**	**220**	**390**	**150**	**110**	**52**
9	**19**	**37**	**6.8**	**74**	**243**	**44**	**202**	**460**	**130**	**100**	**50**
10	**21**	**36**	**5.6**	**84**	**233**	**42**	**248**	**360**	**150**	**110**	**50**
11	**20**	**38**	**6.0**	**76**	**241**	**46**	**217**	**500**	**170**	**100**	**65**
12	**22**	**36**	**4.6**	**102**	**210**	**43**	**214**	**620**	**130**	**110**	**55**
13	**21**	**37**	**5.2**	**82**	**215**	**46**	**190**	**540**	**140**	**100**	**48**
14	**20**	**36**	**3.8**	**68**	**240**	**45**	**236**	**580**	**150**	**100**	**60**
15	**20**	**38**	**4.6**	**106**	**190**	**43**	**210**	**620**	**130**	**90**	**52**
Mean	**20.4**	**36.46**	**5.2**	**85.4**	**217.46**	**44.06**	**208.26**	**518**	**141.33**	**99.33**	**55.6**
S.D.±		**1.725**	**1.0875**	**11.81**	**29.539**	**1.579**	**22.089**	**89.567**	**11.254**	**7.0373**	**6.74**

Table 3: GROUP C: Primis in third trimester with PIH

Table: 4

GROUP A : Primis in first trimester
GROUP B : Primis in third trimester with normal blood pressure

	GROUP A		GROUP B		P value	Significance
	Average	S.D.±	Average	S.D.±		
FG	67.133	6.5122	74.93	5.2707	<0.01	Significant
Total Cholesterol	162	28.695	190.86	30.568	<0.05	Significant
Total Triglycerides	125.8	32.426	182.66	34.933	<0.001	Highly Significant
HDL	55.06	3.881	49.33	3.921	<0.01	Significant
Total proteins	7.3	0.474	6.24	0.6467	<0.001	Highly Significant
Ceruloplasmin	216	85.255	406	84.588	<0.001	Highly Significant

Table:5

GROUP B : Primis in third trimester with normal blood pressure
GROUP C: Primis in third trimester with PIH

	GROUP B		GROUP C		P value	Significance
	Average	S.D.±	Average	S.D.±		
FG	74.93	5.2707	85.4	11.818	<0.01	Significant
Total Cholesterol	190.86	30.568	217.46	29.539	<0.05	Significant
Total Triglycerides	182.66	34.933	208.26	22.089	<0.05	Significant
HDL	49.33	3.921	44.06	1.579	<0.001	Highly Significant
Total proteins	6.24	0.6467	5.2	1.0875	<0.01	Significant
Systolic BP	113.33	7.2374	141.33	11.254	<0.001	Highly Significant
Diastolic BP	74	6.3245	99.33	7.0373	<0.001	Highly Significant
Ceruloplasmin	406	84.588	518	89.567	<0.01	Significant

Table:6

GROUP A : Primis in first trimester
GROUP C: Primis in third trimester with PIH

	GROUP A		GROUP C		P value	Significance
	Average	S.D.±	Average	S.D.±		
FG	67.133	6.5122	85.4	11.818	<0.001	Highly Significant
Total Cholesterol	162	28.695	217.46	29.539	<0.001	Highly Significant
Total Triglycerides	125.8	32.426	208.26	22.089	<0.001	Highly Significant
HDL	55.06	3.881	44.06	1.579	<0.001	Highly Significant
Total proteins	7.3	0.474	5.2	1.0875	<0.001	Highly Significant
Systolic BP	111.6	5.0821	141.33	11.254	<0.001	Highly Significant
Diastolic BP	76	5.07	99.33	7.0373	<0.001	Highly Significant
Ceruloplasmin	216	85.255	518	89.567	<0.001	Highly Significant

IV. Discussion

In the current study it is seen that there was increase in levels of fasting glucose, total triglycerides, total cholesterol and ceruloplasmin and decrease in levels of HDL and total proteins as the pregnancy is progressing with further exaggeration in PIH. Catalano et al[18] in their studies stated that there was a significant increase in fasting hepatic glucose production in late gestation when compared to early gestation. The increase in fasting hepatic glucose production is evidence for decreased hepatic insulin sensitivity in late gestation. The increase in fasting hepatic glucose production is believed to be necessary to provide for the increase in fasting fetal and placental glucose requirements in late gestation. Jayanta De et al in their studies showed that there is serum hypertriglyceridaemia which may be as high as two to three folds in third trimester over the levels in non pregnant women. The principle modulator of this hypertriglyceridaemia is estrogen as pregnancy is associated with hyperestrogenaemia. Estrogen induces hepatic biosynthesis of endogenous triglycerides which is carried by VLDL. Serum triglycerides concentrations also rose in PIH pregnant women [19]. In their studies a significant decrease in HDL levels were observed in pre-eclamptic pregnant women.

Daniel et al studied the relationship between early pregnancy plasma lipid concentrations and pre-eclampsia. Women who subsequently developed pre-eclampsia had 13.6% and 15.5% higher concentrations of triglycerides and LDL/HDL ratios than did control subjects with $p<0.05$. The HDL cholesterol concentrations were 7.0% lower in women with pre-eclampsia than did controls. There was 3.60 fold increase in risk of pre-eclampsia among women with total cholesterol > 205mg / dl and 4.15 fold increase in risk of pre-eclampsia among women with triglycerides > 133mg /dl. In his studies he concluded that early pregnancy dyslipidemia is associated with increased risk of pre-eclampsia. Smith et al studied that plasma Cu and plasma ceruloplasmin (CP) activity increased significantly ($p<0.05$) as pregnancy progressed. Plasma ceruloplasmin concentration increases about 10 fold during development and further rises up to threefold during pregnancy . Elevated serum

ceruloplasmin has been found to be a risk factor for coronary heart disease[20] and a strong correlation exists between serum ceruloplasmin and serum lipid oxidation. Isomaa et al[21] established the link between the metabolic syndrome and cardiovascular disease in their studies. It has been shown that clustering of the risk factors associated with this syndrome acts synergistically resulting in a higher risk of cardiovascular disease. Prevalence of the metabolic syndrome was 3.4- fold and 4.9- fold higher in women who had PIH in their first pregnancy compared with those with normotensive pregnancy. zetabolic syndrome may play a role in the pathophysiology linking PIH to long-term cardiovascular disease[22]. From these studies it is suggested that the metabolic syndrome could represent the biologic link explaining the increased morbidity and mortality from later cardiovascular disease observed among women who have had PIH. These findings emphasize the importance of introducing measures to prevent, screen for, and treat the metabolic syndrome shortly after the index pregnancy among women who have had PIH.

V. Conclusion

From the present study it is concluded that pregnancy is a stressful condition as evidenced by changes in biochemical parameters like increase in fasting glucose, abnormal lipid profile and decrease in total protein levels as the pregnancy is progressing. These changes are exaggerated when these pregnant women have associated hypertension which is one of the risk factors of metabolic syndrome. Thus these pregnant women are possibly prone to diseases like diabetes mellitus, coronary artery diseases and stroke.

So in this study it is seen that pregnancy with hypertension is possibly associated with metabolic syndrome. By properly managing the stress in pregnancy, complications like PIH due to stress can be avoided and by properly managing the hypertension the risk of CAD and stroke in future can be reduced. So, every one especially pregnant women needs to identify subjectively the personal and work related sources of stress in their life and know effective ways to deal to minimize them thus one can lead a healthy life.

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