REVIEW OF LITERATURE

Preeclampsia is a major cause of preterm birth and an early marker for future cardiovascular and metabolic diseases, whereas preterm delivery is associated with immediate neonatal morbidity and has been linked to remote cardiovascular and metabolic disease in the newborns [8-12].

In a series of Caucasian women with pregnancy-induced hypertension, Ward K et al in 1993 observed a significant association of preeclampsia with a molecular variant of angiotensinogen, T235, found previously to be associated with essential hypertension [15].

Brien et al in 2003 identified thirteen cohort studies, comprising nearly 1.4 million women. The risk of preeclampsia typically doubled with each 5–7 kg/m$^2$ increase in prepregnancy body mass index. This relation persisted in studies that excluded women with chronic hypertension, diabetes mellitus or multiple gestations, or after adjustment for other confounders [16].

Fisher Susan J in 2004 said the pregnancy complication preeclampsia, which is characterised by the sudden onset of maternal hypertension, proteinuria and edema. Cytotrophoblast invasion is shallow and vascular transformation incomplete. These findings, together with very recent evidence from animal models, suggest that preeclampsia is associated with abnormal placental production of vasculogenic/angiogenic substances that reach the maternal circulation with the potential to produce at least a subset of the clinical signs of this syndrome [17].

Funai et al in 2005 said findings, together with other recent cohort studies, define preeclampsia as a risk marker for mortality from cardiovascular disease. They suggest that the observation of a normal blood pressure after
preeclampsia should not discourage the search for other cardiovascular risk factors or abrogate the need for other preventive measures [18].

**Maly Alexander et al** in **2005** found quantitative changes in the villous vascular tree in PGDM that are not detectable by conventional light microscopy and suggest that morphometric analysis of the capillary tree may have diagnostic importance in this entity. The findings differ significantly from those previously reported in pregestational diabetes and do not differ significantly from those reported in PE without intrauterine growth restriction that is limited Pathological changes [19].

**Barak Shlomi et al** in **2007** said, eight of the 16 (50%) placenta specimens were positive for one or more periopathogenic bacteria in the preeclampsia group, compared to only two of the 14 samples (14.3%) from controls. Bacterial counts were statistically significantly higher in the preeclampsia group for all of the periopathogenic bacteria examined (*P* ≤0.0055). Although all of the target periopathogenic bacteria were found in the preeclampsia group, only three (*P. gingivalis*, *T. forsythensis*, and *T. denticola*) were found in the control group [20].

**Melchiorre K. et al** in **2008** said the first-trimester uterine artery resistance index (RI) was significantly higher in women who subsequently developed preterm pre-eclampsia (mean RI, 0.79) than in those with a normal outcome (mean RI, 0.70; *P* = 0.0001) or those who developed pre-eclampsia at term (mean RI, 0.72; *P* = 0.002). The uterine artery Doppler data in this study suggest that preterm pre-eclampsia is strongly associated with defective invasion of the spiral arteries, in contrast to the findings in term pre-eclampsia which may be a consequence of placental deterioration at term [21].
Zafarmand M.H et al in 2008 said the findings of this study among Caucasian Dutch women, aged 49 to 70 years, demonstrated that the presence of the T allele of the M235T polymorphism in the Angiotensinogen is associated with self-reported hypertensive disorders in pregnancy [22].

Georgiou H.M et al in 2008 said compared to controls, women with gestational diabetes exhibited elevated plasma insulin and reduced plasma adiponectin concentrations at 28 weeks gestation. Significant differences in insulin and adiponectin concentrations were also observed in plasma at 11 weeks gestation. Bivariate logistic regression analysis showed that both insulin and adiponectin are associated with subsequent development of gestational diabetes [23].

Zook K.J et al in 2009 in a study sample included 203 infants with estimated gestational age of 28±3 weeks; 45% had placental infarctions and 26% placental vasculopathy. Infants with neutropenia and thrombocytopenia did not have an increased occurrence of placental infarction or maternal vasculopathy but were more likely to be of small gestational age (SGA) and of lower gestational age compared with infants without neutropenia or thrombocytopenia [24].

Colomiere Michelle in 2009 said the post receptor defects are present in the insulin signaling pathway in placenta of women with pregnancies complicated by diabetes and obesity. In addition, expression studies demonstrate post receptor alterations in insulin signaling possibly under selective maternal regulation and not foetal regulation [25].

Merwe J. L. van der et al in 2010 said compared to late preeclampsia, placentas in the early preeclampsia group were smaller, had more infarction
and inappropriate maturation. Placentas from the late-onset preeclampsia group showed increased decidual arteriopathy and abruptio placentae compared to controls. So the early- and late-onset preeclampsia placentas showed clear histopathological differences, whereas late-onset preeclampsia and normal term placentas differed less. These findings support the contention that early- and late-onset preeclampsia are different subclasses of disease [26].

Hiden U and Desoye G. in 2010 said Diabetes, in pregnancy is associated with a derangement of hormones, cytokines, metabolites and growth factors in the maternal and foetal compartment. These may influence placental growth and development that are tightly regulated in time and space. The distinct effects of the diabetic environment depend on the time in gestation when diabetic insult occurs. Because of its establishment in the second half of gestation, gestational diabetes mellitus will influence placental processes in late gestation, whereas pre-gestational diabetes such as Type-I and Type-II diabetes may also affect processes in the first trimester. Altered placental function in pre-gestational diabetes may include changes in invasion ultimately leading to an enhanced risk of early pregnancy loss, growth restriction and pre-eclampsia, as well as a long-term stimulatory effect on placental growth leading to placentomegaly, which is frequently associated with diabetic pregnancies.

Diabetes later in gestation affects vascularisation, storage of maternal nutrients in particular glycogen and lipids and may also enhance oxygen transfer. It is still unresolved if the placental alterations in diabetes ultimately contribute to or prevent the foetal phenotype often seen in diabetes i.e., excessive foetal fat accretion [27].

Verma Ranjana, Mishra Sabita & Kaul Jagat Mohini in 2010 found in the placenta of diabetic pregnant, gross abnormalities were uncommon but
microscopic examination exhibited, to a varying degree, lesions like syncytial knots, fibrinoid necrosis, villous edema, villous fibrosis and capillary proliferation.

These findings indicate that control of hyperglycemia only partially prevents the development of placental abnormalities which must be due to some other constituent factor of diabetic state [28].

Salbaum J. Michael & Kappen Claudia in 2010 said, maternal diabetes during pregnancy is a well-known teratogen that increases the risk for birth defects, such as neural tube defects (NTDs). Salbaum J. Michael & Kappen Claudia shown that maternal diabetes profoundly affects gene expression in the developing embryo, in particular a suite of known NTD genes [29].

Ahmed Khairy Makled et al 2011 in a study over Morphometric placental studies in normal pregnancy and pregnancy complicated by pre-eclampsia with or without intrauterine growth retardation found The villous diameter and the capillary surface area were significantly reduced in pregnancy complicated by pre-eclampsia with IUGR and the villous surface area was significantly reduced and capillary diameter more in pregnancy complicated by pre-eclampsia without IUGR [30].

Pasricha Navbir in 2012 in a study over Pregnancy induced hypertension (PIH) found mean placental weight and volume was found to be much lower in the study group. Macroscopic features like retroplacental haematoma, grossly discernable infarcts and calcification was found to be more in the placentae of mothers suffering from PIH. The mean birth weight of babies in PIH was less as compared to the control group; also the incidence of still births was more [31].
Baloch Abdul Hafeez, Memon Salma Farrukh and Ansari Asmat Kamal in 2012 found the weight and surface areas of placentae were significantly low in the hypertensive group whereas thickness of placenta and number of cotyledons were almost same in hypertensive and control groups.

Microscopically increased number of syncytial knots, chorionic villi with excessive collagen was observed in placentae of hypertensive women. In hypertensive group birth weight of neonates was significantly low than control group [32].

Mamun A.A et al 2012 found in a study suggest that maternal hypertensive disorder in pregnancy predicts adult offspring BP [33].

Nag U, Chakravarthy VK and Rao DR in 2013 said macroscopic study revealed that, compared to the controls there was trend of less placental diameter in eclamptic group (p=0.0001). Cotyledon number was found to be significantly less in eclampsia (p=0.0001). Cytotrophoblast invasion are limited to the superficial decidua, and few arterioles are breached due to abnormalities in adhesion molecule switching by invasive cytotrophoblasts, suggesting that this subpopulation of trophoblast cells fails to differentiate properly in hypertensive placenta. Patients with pregnancy induced hypertension are found to have increased risk of low birth weight babies, which may be the result of smaller placental weight and area [34].

Barker D et al 2013 said, a greater number of maternal cotyledons were associated with higher blood pressure. Among boys, a greater number of cotyledons was associated with higher systolic and diastolic pressure but not with higher pulse pressure. Diastolic pressure rose by 2.2 mmHg (95% CI 0.6 to 3.7, p = 0.007) for every 10 additional cotyledons. Among girls, a greater
number of cotyledons was associated with higher systolic pressure and pulse pressure but not with higher diastolic pressure. Pulse pressure rose by 2.7 mmHg (1.1–4.3, \( p < 0.001 \)) for every 10 additional cotyledons [35].

Khaskhelli Lal Baksh in 2013 observed in morphological examination of placentae showed larger, heavier and more cotyledenous placentae group as compared to controls. Similarly microscopic examination revealed dilated blood vessels, necrotic and degenerative foci in placentae of diabetics as compared to controls [36].

Kate Bramham in 2014 found the incidences of adverse outcomes in women with chronic hypertension were compared with women from the US national population dataset and showed higher risks in those with chronic hypertension: relative risks were 7.7 for superimposed pre-eclampsia compared with pre-eclampsia, 1.3 for caesarean section, 2.7 for preterm delivery <37 weeks’ gestation, 2.7 for birth weight <2500 g, 3.2 for neonatal unit admission, and 4.2 for perinatal death [37].

**Following Facts Established by Review of Literature:-**

- Risk of Preeclampsia typically double with each rise of 5-7 Kg/m\(^2\) increase in pregnancy body mass index.
- Preeclampsia associated with defective invasion of uterine spiral artery, causing poor placental development.
- Gestational Diabetes Mellitus increases the risk of birth defect as Neural tube defect.
- Cotyledon number reduced significantly in eclampsia.
- Size and weight of placenta increases in women with Gestational Diabetes Mellitus.
• Angiotensinogen polymorphism increases the risk of hypertension.
• Adiponectin precipitate the Gestational Diabetes Mellitus (GDM).

**What is lacking in Review of Literature**

• Can risk of Preeclampsia also be double with increase pregnancy body mass index with history of chronic HTN, GDM or multiple gestations?
• Can Angiotensinogen polymorphism affect Gestational Diabetes Mellitus?
• Can Adiponect affect Preeclampsia?