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Editorial

Retrograde Inflammation Contributes to Psychological Stress and Depression in Gestational Diabetes Mellitus

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Gestational Diabetes Mellitus (GDM) is defined as any degree of glucose intolerance with the onset or first recognition during the present pregnancy at 24-28 weeks of gestation.[1] In the recent past, there is an increased incidence of diabetes during pregnancy with almost 21 million births (16.2%) affected due to hyperglycemia. Prevalence of GDM in India is 18.9%, ranging between 3.8% to 41% in various parts of the country.[2] The major maternal and neonatal adverse effects of GDM include increased risk of preterm delivery, pre-eclampsia, caesarean section delivery, development of Type 2 Diabetes Mellitus (T2DM) post-delivery, fetal macrosomia, neonatal hypoglycemia, neonatal respiratory distress, and childhood obesity and insulin resistance, followed by impaired glucose tolerance and T2DM later in life. Women with history of GDM have a sevenfold increased risk of developing T2DM, with 20-70% risk in the first decade after delivery and GDM increases the future Cardiovascular Disease (CVD) risk by twofold. It is important to note that studies have consistently shown that women with a history of GDM have a higher prevalence of cardiometabolic risk factors, such as dyslipidemia, hypertension, obesity, and metabolic syndrome, compared to their peers. Additionally, by three months postpartum, this adverse cardiovascular risk factor profile is evident.

Depression during pregnancy has been reported to adversely affect women and their children.[3] Anxiety, psychological stress and depression are associated with GDM.[4] Psychological stress and depression in GDM severely affect the maternal and fetal outcomes. Also, it has been reported that the prenatal depression in GDM is linked to post-partum depression for a longer duration and adverse Cardiovascular (CV) consequences. Recently we have reported the decreased heart rate variability (HRV) and cardiovagal modulation associated with depression in women during antenatal period, which exposes them to CV risks. However, till date the mechanism that causes CV risks in GDM have not been well studied and the association of CV risks to mental illness in GDM has not been reported. It is important for healthcare workers to know the relationship between stress and depression with fetomaternal outcomes, and if the depression-associated problems can be prevented in the perinatal period. In a recently conducted pilot study at 36th week of gestation in 15 women having GDM, we observed that cardiometabolic risks, adverse fetomaternal outcomes and poor psychophysical health were improved by practice of short course of yoga.[5] But, in this study due to less sample size, we could not assess the enormity of cardiometabolic risks, the mechanisms that could lead to development of these risks and the link of depression to the risks and the maternal-fetal outcomes.

Inflammation has long been proposed as a pathophysiologic mechanism of depression.[6] There is accumulating evidence that anti-inflammatory interventions could be promising antidepressants, particularly in patients with increased peripheral inflammatory biomarkers. Elevated C-Reactive Protein (CRP), Tumor Necrosis Factor alpha (TNF-α), and Interleukin-6 (IL-6) are the major molecular inflammatory signature associated with depression in general population. Among the chemical mediators, high-sensitive C-Reactive Protein (hsCRP) and IL-6 are mainly reported to be associated with GDM. However, till date the association of CRP and IL-6 with depression and cardiometabolic risks in GDM has not been studied. Oxidative stress and endothelial dysfunction have also been implicated in the pathophysiology of GDM. But the association of oxidative stress and endothelial dysfunction with stress and depression-mediated increased cardiometabolic risks in GDM has not been reported yet. In GDM, a cardiometabolic risk intensifies in later part of pregnancy. We have already investigated and observed the link of retrograde inflammation, oxidative stress, endothelial dysfunction and decreased cardiovagal modulation to stress and depression at 36th week of pregnancy in gestational diabetes mellitus.[7]

It has been stated earlier that elevated IL-6 activity may lead to depression through stimulation of hypothalamic-pituitary-adrenal axis or by influencing the metabolism of neurotransmitters.[8] Other suggested mechanisms are that IL-6 may increase the activity of Indoleamine-2,3-Dioxygenase (IDO), which catalyses tryptophan that in turn activate kynurenine pathway and reduce availability of serotonin in the brain.[9] As a result, quinolinic acid, 3-hydroxy kynurenine, and the neurotoxic N-methyl-d-aspartate

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glutamate agonist are produced, which causes oxidative stress and contributes to the neurodegeneration and depression. IL-6 is also reported to be involved of in neuro-inflammation and Brain-Derived Neurotropic Factor (BDNF)-mediated depression in various mental disorders.[10] Therefore, future studies should focus on the association of IL-6 with BDNF and brain activity of serotonin and IDO to understand the role of neuro-inflammation in the causation of depression in GDM.

Persistent increase in IL-6 has been reported in stress reactions and in patients with depression. In recently concluded study, the increased IL-6 were found to be strongly associated with stress and depression in GDM women receiving antidiabetic treatment.[10] All these evidences suggest for future studies to address if restoration of IL-6 level could be the key to treatment of depression associated with inflammation in GDM. In developing countries like India, the glycemic control and fetomaternal outcomes are poor in GDM due to various socio-economic factors that include poor compliance to treatment.[11] Therefore, studies should be designed to assess if non-pharmacological interventions like yoga instituted early in the pregnancy can improve cardiovagal modulation and prevent the development of stress and depression in GDM.

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