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REVIEW

Some of the experimental and clinical aspects of the effects of the maternal diabetes on developing hippocampus

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Abstract

Diabetes mellitus during pregnancy is associated with an increased risk of multiple congenital anomalies in progeny. There are sufficient evidence suggesting that the children of diabetic women exhibit intellectual and behavioral abnormalities accompanied by modification of hippocampus structure and function. Although, the exact mechanism by which maternal diabetes affects the developing hippocampus remains to be defined. Multiple biological alterations, including hyperglycemia, hyperinsulinemia, oxidative stress, hypoxia, and iron deficiency occur in pregnancies with diabetes and affect the development of central nervous system (CNS) of the fetus. The conclusion from several studies is that disturbance in glucose and insulin homeostasis in mothers and infants are major teratogenic factor in the development of CNS. Insulin and Insulin-like growth factor-1 (IGF-1) are two key regulators of CNS function and development. Insulin and IGF-1 receptors (IR and IGF1R, respectively) are distributed in a highly specific pattern with the high density in some brain regions such as hippocampus. Recent researches have clearly established that maternal diabetes disrupts the regulation of both IR and IGF1R in the hippocampus of rat newborn. Dissecting out the mechanisms responsible for maternal diabetes-related changes in the development of hippocampus is helping to prevent from impaired cognitive and memory functions in offspring.

Key words: Maternal diabetes; Cognition complications; Teratogenic factor; Hippocampus

Core tip: Diabetes mellitus is the most seriously metabolic condition in pregnancy that affects the hippocampal development and function of the offspring. Multiple biological alterations, including hyperglycemia and hyperinsulinemia are occurring in maternal diabetes and impair the neurodevelopment of the fetus. Insulin-like growth factor-1 (IGF-1) and insulin are important regulators of development of central nervous system. It has clearly showed that maternal diabetes disturb the regulation of both insulin receptors and IGF-1 receptors in the hippocampus of rat newborn. This article is a brief review of the literatures that suggests a probable

mechanism of how diabetes during pregnancy affects the hippocampus development in the offspring.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic common metabolic illness characterized by hyperglycaemia associated with insulin deficiency or insulin resistance. There are two major types of DM: type 1 DM (T1DM) results from chronic and progressive destruction of the beta-cells of the islets of Langerhans in the pancreas. T2DM is primarily characterized by both insulin resistance and relative insulin deficiency[1,2].

DM is one of the most common and most important metabolic condition affecting up to 7% of pregnancies. Several population studies show that the diabetes during pregnancy affects the health of both mothers and their infants[3-6].

There are two main types of DM occurs in pregnancy period: pregestational DM (PGDM) and gestational DM (GDM)[7]. GDM accounts for approximately 90% of all cases of diabetes in pregnancy. Of the remaining cases, 60% have preexisting T2DM before pregnancy, while 40% have a diagnosis of pre-conceptual T1DM[8].

In a study in the United Kingdom, it was found that PGDM occurs in approximately 1 out of 250 pregnancies, with two-thirds of them having T1DM and the remaining one-third having T2DM[9]. At present, type 2 diabetes is the most prevalent form of diabetes affecting women of reproductive age in the developed countries, with a mean prevalence of 27.6% in United Kingdom[10]. Last data from Australia also showed that T2DM affected about 55% of pregnancies[11]. Overall, GDM complicated from 2% to 12% of all pregnancies. So, however, the incidence of T1DM appears to be relatively constant and similar to the rate in young adults throughout the world; the incidence of T2DM is specially rising in developed world[9,12]. Furthermore, the overall numbers of children born to mothers with diabetes will significantly rise in the next decades.

COMMON CONGENITAL MALFORMATIONS IN DIABETIC MOTHER INFANTS

An increasing number of evidence clearly showed that infants born to diabetic mothers are in increased risk of fetal and neonatal anomalies which results in increased infant mortality and morbidity rates. Although, the wide spectrum of the effects of diabetes in pregnancy on the fetus development are determined by the time of onset and the severity of DM[6,13,14].

Despite considerable progress in the clinical management of pregnant women who have diabetes, the prevalence of major congenital anomalies is approximately 3 times more in infants of diabetic women in comparison to the offspring of normal mothers[12,15,16].

According to previous works, diabetes in pregnancy has been accompanied by increased risk of a wide range of fetal complications and malformations, including respiratory distress syndrome, macrosomia, organomegaly, obstetric, metabolic and hematological complications[13,14,16,17].

The overall rate of major congenital anomalies in infants born to diabetic mothers is about 6% to 13%, which is approximately 2-3 times higher than that of the normal condition. However, the prevalence of major structural malformations in the children born to mothers with diabetes are to 10 times greater in comparison to the general population. The frequencies of perinatal mortality are also five-fold higher in women with diabetes compared with normal women[12,14,16,18].

The prevalence of Minor congenital anomalies in infants born to 802 mothers with GDM, 117 mothers with PGDM, and 380 normal mothers were assessed by Hod *et al*[19] (1992). They found a range between 19.4% and 20.5% in prevalence of minor congenital anomalies in their infant in all groups studied without any marked difference between groups. In their study, there was no correlation between the type and prevalence of minor congenital anomalies with the severity and the time of onset of the diabetes in mothers. Neither there was any relationship between the type or prevalence of minor congenital anomalies with the type or appearance of major congenital anomalies[19].

Overall, the defects in central nervous system, heart, kidney, and skeletal system are among the commonest congenital malformations in the offspring of diabetic pregnancies[3,14,16,18].

PATHOGENESIS OF COMMON COMPLICATIONS IN DIABETIC INFANTS

As yet, the exact mechanisms by which maternal diabetes alters the development of growing fetuses are not completely understood, and no distinct teratogenic mechanism has been identified to clearly explain a reason for this range of congenital anomalies observed in the infants born to diabetic mothers[20,21].

Many of the developmental effects of diabetic pregnancies on the fetus can be attributed to maternal glucose (metabolic) control. In normal pregnancies, the blood glucose level in women remains within a tight range. Consequently, the blood glucose concentration in the fetus is fairly constant as the glucose in the mother's blood crosses the placenta freely. Nevertheless, in pregnancies complicated by DM, there are great

variations in the maternal blood glucose level[12,14,22]. Pedersen *et al*[23] (1954) emphasized the correlation between high blood glucose concentration in pregnant women with hyperglycemia during fetal period[23], which stimulated the pancreas of the fetuses, leads to beta-cell hyperplasia and hypertrophy with increased insulin secretion and content[23,24].

Several lines of studies also emphasized the direct correlation between high blood glucose concentration in mothers as revealed by increased level of glycosylated hemoglobin (HbA1c) with increased frequency of congenital malformations in offspring[22,25]. Towner *et al*[26] (1995) found a striking correlation between pregestational elevated HbA1c in early pregnancy with the increased risk of fetal congenital malformations[26]. There is enough evidence accumulates to support this hypothesis that the tight glycaemic control in early and before pregnancy may reduce the frequency of anomalies in the infants born to diabetic mothers[22]. Therefore, the prevalence of congenital abnormalities in children born to mothers with diabetes has decreased in the last three decades probably as a result of the overall progress in monitoring of blood glucose concentrations in diabetic pregnant women[27-29].

In addition, fetal hyperinsulinemia also has been shown in the offspring of diabetic mothers. On separation of the newborn from the mother, the glucose former no longer is supported by placental glucose transfer, may develop neonatal hypoglycemia[30,31].

In earlier works, chronic fetal hyperinsulinemia in the third trimester of pregnancy has been produced in monkeys. The researchers showed that *in utero* hyperinsulinemia results in an organomegaly and fetal macrosomia, except for kidney and brain[32,33]. Increased plasma erythropoietin levels and body fat content was also evident in infants of diabetic mothers[34].

Insulin is a hormone that primarily functions as an anabolic hormone of fetal development and growth resulting in macrosomia and visceromegaly[14]. On the basis of *in vitro* and animal studies on the pancreas, the simplified hyperinsulinemia - hyperglycemia hypothesis has been expanded in earlier studies[35,36].

Ketones in the mother's blood readily cross the placenta, but they cannot be cause fetal hyperinsulinemia; so, they might not influence fetal growth and development[14].

In experimental diabetic rodents, fetal hyperglycemia, neonatal hypoglycemia, and disturbances in prostaglandin and arachidonic acid metabolism have been reported to result in congenital anomalies in their offspring[14,37]. In diabetic pregnancies in rats, it is clearly established that the elevated intracellular free oxygen radicals concentrations have been accompanied by the increased risk of embryopathies[38]. Nevertheless, hyperglycemia-induced fetal malformations in rodents have been demonstrated to associate with the number of genomic DNA mutations[39]. Therefore, there are animal studies showing that the free radical scavengers and antioxidants may decrease the risk of teratogenicity of maternal diabetes[40,41].

DIABETIC PREGNANCY AND NEURODEVELOPMENTAL SEQUELAE IN HUMAN

Both PGDM and GDM can affect fetal neurodevelopment[42-45]. Although the untoward effects of maternal diabetes on pregnancy outcomes with respect to congenital malformations have generally been appreciated, the effect of maternal diabetes on the development of central nervous system (CNS) in the fetuses and its behavioral sequelae remains to be completely defined. A limited number of long-term follow-up studies of neurodevelopmental outcomes in diabetic pregnancies have been reported[46-50]. Nevertheless, it is demonstrated that children born to diabetic mothers are more likely to have neurodevelopmental abnormalities including impairments in learning ability, activity level, attention span, and motor functioning. Interestingly, some of these deficiencies are well-known as risk factors in children who develop schizophrenia later, but the degree of risk is variable and may be related to the severity of metabolic derangement in the mothers with diabetes[42,46,50,51].

Examination of cognitive functioning and the behavior of the children born to diabetic mothers offers the opportunity to functionally assess the CNS development[52]. Hence the assessment of the behavior and cognition in the offspring of diabetic mothers may clarify the maternal diabetes effects on the development of CNS.

The results of earlier studies clearly demonstrated that the diabetes during pregnancies may results in intellectual and behavioral functioning disturbances in the infants[45,46,49,53]. These data suggest a teratogenic effect of diabetes in pregnancy on the function of CNS in fetuses and provides the earliest indicator of postnatal CNS deficiencies reflected in intellectual and behavioral problems observed in the children of mothers with diabetes[54].

Earlier reports on the neurologic development in infants of diabetic mothers revealed serious CNS deficits, even in the absence of structural malformations. These alterations were significantly less severe when maternal diabetes was medically controlled and treated, but some alterations in cognitive function may persist throughout childhood[6,42,45,48,51].

To elucidate the effects of diabetes during pregnancy period on cognitive functioning in the children, Yamashita *et al*[45] (1996) studied 33 pregnant women (24 with T2DM, 6 with T1DM, and 3 with GDM). Their long term follow-up research showed that maternal diabetes significantly affects the development of intellectual functioning in infants. Although, they report no differences in IQ score among offspring of three groups[45]. In another

study, Churchill *et al*[55] (1969), found that diabetic mothers had offspring with significantly lower mean IQs than control infants. In a cohort study of fifty infants at 1, 3, and 5 years of age born to diabetic mothers, Stehbens *et al*[56] (1977) reported an adverse effect of diabetes in pregnancy on CNS structure and function in their children. They also found that three infants born to diabetic mothers had major neurologic anomalies and six of them had IQs less than 80.

Rizzo *et al*[57] (1991) reported a strikingly correlation between diabetes in mothers during pregnancy and lower IQ in their children. In another study, the same researcher found significant correlations between second- and third-trimester regulation of glycemia and results on the Brazelton Neonatal Behavioral Assessment Scale; they reported an association between increases in maternal glucose levels with poorer infant responses[58].

Other investigators have not found any differences in cognitive scores[59-61]. Children born to diabetic mothers may sustain minor neurological damage which does not necessarily affect their scores in IQ tests[49]. For example, Persson *et al*[60] reported more encouraging results in 73 infants born either to mothers with T1DM or to mothers with GDM; all subjects available for follow-up at 5 years of age had normal results on neurologic examinations, as well as normal IQs, and there was no relation between maternal diabetes and IQ[60].

In a retrospective study at considerable variance with most other reported studies, Yssing *et al*[62] (1975) reported a 36% incidence of cerebral dysfunction or related conditions in 740 infants of diabetic pregnancies; 18% had a major cerebral disability. In a study by Haworth *et al*[63] (1976) on infants of diabetic pregnancies, noted an about 30% increase in the incidence of neurological and intellectual development impairments[63]. No differences in behavioral adjustment and academic achievement between children born to T1DM mothers and children of normal mothers were reported in Hadden *et al*[64] study.

In addition, poorer habituation performance were also found in fetuses of diabetic pregnancies when compared to fetuses born to normal mothers[65]. Since habituation reflects the fetal CNS performance, the observed habituation abilities differences between the diabetic and normal groups suggests differences in their CNS function or maturation[65,66]. Recent investigations also have been demonstrated that there is a significant correlation between diabetes during pregnancy and increased risk of some psychologic disturbances including schizophrenia in their children[67,68].

Together, these studies suggest a wide-range of teratogenic effects of maternal diabetes on the development and function of fetal CNS[67]. However, no single molecular mechanism can fully explain the effects of maternal diabetes on fetal neurodevelopment because the CNS development is complex and regulated by a number of signaling molecules and transcription factors.

DIABETES IN PREGNANCY AND NEURODEVELOPMENTAL ABERRATION IN ANIMALS

Neurodevelopmental assessment of the offspring born to diabetic dams have been revealed a wide spectrum of behavioral, neurochemical, cellular, and molecular impairments[69-72]. Experimental models subjected to streptozotocin - induced type 1 diabetic pregnancies developed significant deficits in cognitive behaviors[68]. Kinney *et al*[73] (2003) found that the only female offspring born to diabetic dams showed deficits in long-term memory and learning. These results have suggested that the *in utero* diabetic condition has gender-specific effects on CNS development[73].

In a study by Plagemann *et al*[74] (1998), alterations in catecholamines levels in the hypothalamic nuclei of newborns born to diabetic animals were evaluated. They reported an increased hypothalamic dopamine (DA) and norepinephrine (NE) concentrations in the offspring born to diabetic rats at birth. Twenty one-day-old pups born to diabetic mothers, NE levels were strikingly increased in the ventromedial hypothalamic nucleus and the lateral hypothalamic area (LHA), while DA levels were significantly elevated in the paraventricular hypothalamic nucleus and the LHA. The authors concluded that there are strikingly differences in hypothalamic catecholaminergic systems during early development in the rat newborns born to diabetic animals[74].

It has been shown that PGDM is associated with an increases risk of neural tube defects (NTDs), also known as diabetic embryopathy. The prevalence of NTDs in the offspring of diabetic mothers is 3 to 10-fold higher than that of in general population[75-77]. In earlier studies, the mitochondrial morphological changes has been shown in developing neural tubes subjected to a diabetic environment during the same time period when the NTDs are induced in diabetic pregnancies[72,78]. Altered activity of cytochrome-c oxidase also has been manifested in the rat hippocampus that have iron deficiency in their brains due to fetal hyperglycemia[79]. It has also been hypothesized that dysfunction in energy metabolism of developing brain leads to oxidative stress elevation and abnormal regulation of intracellular calcium[80-82].

NEUROPATHOPHYSIOLOGY OF DIABETIC PREGNANCY

Several well-known biological alterations occur in mothers with diabetes that affect fetal neurodevelopment. These biological changes lead to alterations in neurotransmitter systems, synaptic membranes, neuronal integrity, and growth factors expression that have also been implicated in the development of neurodevelopmental and neurocognitive sequelae in offspring born to diabetic mothers[14,42,69,72,74].

The hyperglycemia is the most distinct mechanism by which these predispositions might be mediated. The defining characteristics of diabetes during pregnancy, these are clearly showed to have effects on developing CNS and to induce fetal hyperinsulinemia, chronic tissue hypoxia, decreased in fetal iron levels and increased oxidative stress[20,83-85].

Hyperinsulinemia, hypoxia, polycythemia and iron deficiency

It is revealed that fetal polycythemia induced by DM in pregnancy is likely triggered by the chronic *in utero* hyperglycemia and hyperinsulinemia and develops in response to higher concentration of blood glucose in mothers[20,42]. A study by Mimouni *et al*[86] (1986) showed an incidence of 29.4% fetal polycythemia in infants born to diabetic mothers in comparison to 5.9% in normal conditions. One of the reasonable explanations is that *in utero* hyperglycemia and hyperinsulinemia produces a hypermetabolic state in the developing fetuses, which results in relative tissue hypoxia, leading to polycythemia *via* excess production of erythropoietin. Elevated fetal plasma erythropoietin concentrations in diabetic pregnancies suggests an increased prevalence of chronic fetal hypoxia during development. Although there are no distinct mechanisms for fetal hypoxia in diabetic pregnancies[34].

Hypoxia affects the fetal CNS development including alterations in myelination, changes in cortical connectivity, excitotoxicity, and neuronal or glial cell death[87-89].

In the hypoxia state, excess erythropoietin and hemoglobin are produced[90]. So, the developing fetuses need for iron exceeds its supply that leads to Iron mobilization from vital tissues including the fetal brain[91,92]. It is showed that human infants born to diabetic women possess brain iron content 40% less than that in normal pregnancies[93].

Several authors have reviewed the role of iron on CNS development and function[94-96]. Iron is one of the key component of the many enzymes involve in essential reduction or oxidation reactions, neuronal replication, synthesis and catabolism of neurotransmitters and myelin production[97-101]. The uptake of Iron into the brain is maximal during the rapid brain development and growth, which coincides with the peak of myelinogenesis[99-101]. In experimental animals, iron deficiency demonstrated to affect the development of neurotransmitter systems in the brain results in behavioral alteration[98,102]. Moreover, iron deficiency in fetuses is also known to manifest as increased negative emotionality and higher levels of irritability in infants and is a predictive factor in the behavioral and developmental problems at 5 age old children[103]. There are studies suggesting that iron deficiency during brain development leads to alterations in the hippocampal structure and function[104].

Moreover, in animal models, hyperinsulinemia during *in utero* period reduced the fetal amino acid concentrations, including levels of the nonprotein amino acid taurine, which is showed to be involved in the development of the brain[105].

Diabetes during pregnancy as a proinflammatory milieu

Diabetes during pregnancy is associated with the disbalance of pro-inflammatory pathways supported by increased circulating concentrations of inflammatory molecules[106,107]. It is demonstrated that inflammatory cytokines affect the neuronal development and metabolism of neurotransmitters[108]. In experimental models, cytokines reduced the survival of dopaminergic and serotonergic cells[109]. Earlier investigations demonstrated that cytokines, including tumor necrosis factor alpha and interleukin-6, are increased in infants exposed to diabetes *in utero* and have been implicated in neuronal damage[110,111]. It is also clearly showed that imbalances in the regulation of cytokines have been increasingly associated by a number of prevalent and severe neurodevelopmental disorders[112,113].

Currently, a limited number of human studies demonstrating the effects of inflammatory prenatal environment on neurobehavioural development in children[114]. Evidence from a few studies suggests that immune alterations that occur in prenatal period may persist into postnatal life[115,116]. Therefore, increased inflammatory cytokines in diabetic pregnancies may be relevant to neurodevelopment alterations exhibited by the infants born to diabetic women.

Diabetes in pregnancy and oxidative stress

Enhanced oxidative stress plays important roles in embryo development and implicated in the pathogenesis of some neurodevelopmental disorders observed in infants of diabetic mothers[83-85]. Free radicals can inactivate the biological functions of proteins and lipids and potentially leading to cell death[117,118]. It is showed that GDM is associated with an increased concentration of oxidative stress, due to both defect in the antioxidant defenses and/or overproduction of free radicals[83-85]. Although, there are several studies demonstrating the presence of elevated oxidative stress in PGDM and GDM states. Some works also suggested that this milieu can be shared with the developing fetus[83-85,119].

In experimental animals, it is emphasized that oxygen radicals play crucial roles in the progression and timing of the development and differentiation of neurons, and synaptic plasticity; so, imbalance in these signals can lead to changes in development of CNS[120,121]. On the other hands, the developing CNS is particularly susceptible to increase in oxidative stress, owing to its poor antioxidant defenses and/or high oxygen consumption[122].

Oxidative stress might contribute to the pathogenesis of some of neurodevelopmental disorders *via* an attenuation with gamma-aminobutyric acid receptor function in the brain, decreased synaptic efficiency in hippocampal cells, and inhibition of dopamine β-hydroxylase[123-125]. On the other hand, there are evidence

indicating that maternal diabetes-induced NTDs are associated with some metabolic difficulties such as increase in superoxide dismutase activity and decreased in arachidonic acid level[126]. There are evidence from human models indicating a potential role of elevated oxidative stress in neurodevelopmental diseases[127-131]. Moreover, the incidence of congenital anomalies in infants of diabetic mothers has been reported to be significantly reduced by antioxidants supplements therapy including Ascorbic Acid and vitamin E. These data suggest that elevated oxidative stress is associated with the pathophysiology of fetal dysmorphogenesis[132,133].

Role of insulin-like growth factor-1 and insulin in maternal diabetes - induced neuropathies

Insulin- like growth factor-1 (IGF-1) and insulin belong to the insulin superfamily and exert profound effects in the CNS development and function. Evidence of these peptides actions on CNS comes from a wide variety of *in vitro* and *in vivo* experimental data, the latter predominantly derived from rodent studies. In several studies, the authors demonstrated that the insulin and IGF-1 have a wide spectrum of biological actions in the developing CNS including neuronal/glial cell proliferation, differentiation, survival, synaptogenesis, longevity, and neuroregeneration. Most of these biological functions are mediated *via* two transmembrane receptors: the insulin receptor (IR) and the IGF-1 receptor (IGF1R)[69,70,134-142].

The IR and IGF1R, which are homologus in structure, are composed of two α-subunits and two β-subunits linked by disulphide bonds. The extracellular α- subunit binds to their cognate ligand. The β-subunit comprises an extracellular domain and a cytoplasmic domain that contains intrinsic protein tyrosine kinase activity. The binding of either IGF-1 or insulin to α-subunit of their cognate receptors stimulates phosphorylation of the β subunit on serine and tyrosine residues. The autophosphorylation of the β subunit then results in the phosphorylation of cellular substrates and signal transfer cascade for IGF-1 and insulin[141,143,144].

Using ligand binding autoradiography and *in situ* hybridization, several line of human and animal investigations have found that IR and IGF1R are irregularly distributed in developing and mature brain with the highest densities in the hippocampus, cerebral cortex, olfactory bulb, cerebellum, and hypothalamus. Interestingly, some of brain regions show a marked difference in the density of InsR and IGF1R between embryonic *vs* mature brain, implying a key role for these ligands in brain development[145-147].

There are evidence from several researches implicating defects in IR and IGF1R signaling result in congenital developmental defects seen in offspring of diabetic mothers[145,148-150]. Ramsay *et al*[151] (1994) in their study was found that expression of IGF-1 in the brain were declined in swine newborns born to diabetic dams when compared to that of control animals.

The hippocampal formation subserves important physiological and behavioral functions including spatial learning and memory and is a part of brain that particularly vulnerable to changes in blood glucose level[152-154]. In an investigation by Tehranipour *et al*[155] (2008) the effects of maternal T1DM on density of hippocampal pyramidal cells immediately after birth were examined. Those study results were clearly indicated that maternal diabetes can decreased the numerical density of pyramidal cells in the hippocampus of rat newborns, especially in CA3[155].

Interestingly, the studies By Hami *et al*[156] (2012) showed that there are prominent gender-and laterality-differences in expression and distribution pattern of InsR and IGF1R in the developing rat hippocampus. The authors concluded that these differences may be a probable mechanism for the control of sex and laterality differences in development and function of the rat hippocampus[156].

In another study by Hami *et al*[69] (2013), the effects of diabetes in pregnancy on gene expression and protein concentration of IGF1R and IR in the developing rat hippocampus at postnatal days 0, 7, and 14 were evaluated. In that study, the authors found a markedly upregulation of both IR and IGF1R expression in the hippocampus of diabetic group newborns at first postnatal day. At the same time point, they showed only slight changes in their hippocampal protein transcripts. In 7-d old rats, there was a significant decreased in IGF-1R gene expression and protein levels in the newborns born to diabetic dams. Moreover, they found a down regulation in hippocampal IGF1R transcripts in 14-d old diabetic group offspring. Two weeks after birth, the IR gene expression was significantly declined in the hippocampus of diabetic newborns. The authors claimed that maternal diabetes strongly altered the regulation of both IR and IGF1R during development of rat hippocampus[67].

CONCLUSION

The Incidence of congenital anomalies in infants born to diabetic women is more common in comparison to children of normal population. There are multiple lines of evidence that suggest the disturbances in intellectual and behavioral functioning observed in the children of diabetic women are accompanied by modification of hippocampus structure and function. The etiology and pathogenesis of these impairments induced by diabetes during pregnancy have spurred considerable efforts for clinically and basically researches. The final goal at these investigations was to find the teratogenic factors, which may enable preventive or protective measures to be taken in pregnancies with diabetes. Nevertheless, the exact mechanism by which diabetes during pregnancy affects the CNS development remains to be defined. Until now, several biological changes are defined to occur in diabetic mothers and to affect development of CNS (*i.e.*, disturbance in glucose and insulin homeostasis, oxidative stress, hypoxia, and iron deficiency). Moreover, the new researches on genetic

predisposition involves in teratogenicity of diabetes in pregnancy starts to define new genes and their products involved in the etiology of CNS malfunctions and malformations observed in offspring born to diabetic mothers. Hyperglycaemia and hyperinsulinemia in the mothers and their fetuses are thought to be major factors in teratogenicity of maternal diabetes on the CNS development. There are sufficient evidences for this hypothesis as concise control of glycemia in mothers reduces the incidence of anomalies exhibited with the offspring born to diabetic mothers. Recent evidence clearly indicated that maternal diabetes markedly influences the regulation of both IR and IGF1R - as two important regulators of development and function of CNS - in the developing rat hippocampus. Dissecting out the mechanisms responsible for maternal diabetes-related changes in the development of hippocampus is helping to prevent from impaired cognitive and memory functions in offspring.

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