REVIEW ARTICLE

Cognitive Functions in Pregnant Women

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Abstract

Aim: This review aims to analyze current evidence about how pregnancy and pathologies which occur during pregnancy may affect the function of a woman's brain, and how those changes may influence cognitive functioning.

Background: During pregnancy occur adaptive changes in a woman's body which are necessary for proper fetal development. Pregnancy also induces structural and functional alterations within the brain. Cognitive functions are the group of mental processes responsible for learning or information processing; hence, their proper function is essential in daily living and achieving set goals. Literature shows evidence of deleterious effects on cognitive functions caused by conditions such as diabetes mellitus, hypertension, obesity, or depression within the group on nonpregnant individuals. There are also studies evaluating cognitive functions in pregnancy complicated with various diseases (including pregnancy-related ones).

Review results: Gathered publications show mixed results regarding cognitive functions in pregnancy and diseases associated with pregnancy. Results indicate a poorer function of cognitive domains in pregnant women, in contrast to nonpregnant ones, which may correlate with hormone levels. Regarding hypertensive disorders, data provide evidence of worse cognitive processing and greater risk of dementia in women with preeclampsia. The literature lacks evidence about the influence on cognition in women with gestational diabetes; however, diabetes mellitus show strong correlations with cognitive deterioration putatively associated with glucose metabolism dysfunction. Obese individuals show a decline in many cognitive domains, which may predispose them to further weight gain. Depression is associated with poorer cognitive performance; however, anxiety and depressive states may be responsible for subjective cognitive dysfunction during pregnancy.

Conclusion: Research shows mixed results regarding the connection between cognition and both pregnancy-related diseases, which may stem from a lack of properly designed studies.

Clinical significance: More research about cognitive functions and pregnancy is needed due to the growing prevalence of the abovementioned diseases and their harmful effect on brain function even long after delivery.

Keywords: Brain function, Cognitive functions, Depression, Gestational diabetes, Obesity, Preeclampsia, Pregnancy.

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Brain Changes in Pregnant Woman

Pregnancy and postpartum is a very specific period in women's life, which is characterized by many physiological changes of an adaptive nature. These changes in women's bodies are designed to the demands of fetal growth and development, but also they enable pregnant women proper care of the baby after birth. These changes especially affect the reproductive organs and the circulatory system. Nonetheless, functional changes in the brain, mainly understood as neural plasticity, are also very interesting. Data describing the brain's changes that occur dynamically during pregnancy come mainly from animal studies. Numerous changes in the structure of the central nervous system (CNS) associated with the activity of female sex hormones were observed for the first time in animal models. The changes found at the cellular level were neurogenesis, synaptic remodeling, and changes (increase and, or decrease) in dendritic morphometry, spine density, and astrocyte density.[1]

Human studies are based primarily on the assessment of brain structure and function before and after pregnancy. Studies comparing women who have given birth with nulliparous ones are also carried out. An interesting neuroimaging study by Hoekzema et al. has shown that pregnancy is associated with the reduction of the gray matter volume in regions that support social cognition. These changes were very specific to a group of mothers. Moreover, changes in gray matter volume were also associated with postpartum maternal affection. Based on the observations described, it was concluded that this is an expression of the process of adaptation to motherhood. It is also evidenced that the brain changes induced by pregnancy persist after pregnancy.[2]

Similar observations were made in the study of Chinese researchers who performed the magnetic resonance imaging (MRI) among eight nonpregnant female volunteers and nine women who had vaginal delivery in the first 24 hours after birth. It was found that pregnant women were characterized by cerebral cortex atrophy.

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Atrophy was ranging from 6 to 13%.[3] The same publication also describes the differences in electroencephalography (EEG) and transcranial Doppler ultrasonography (TCD). Pregnant women showed increased electrical activity of the brain in the middle parietal part and a decrease in the temporoparietal junction. Also, the bilateral pulsation index parameter in the flow through the internal carotid arteries and externally tested with TCD was lower in the pregnant population.[3] The above publications prove the significant influence of pregnancy and motherhood on the structure and functioning of a woman's brain.

Cognitive Functioning in Pregnant Women during Physiological Pregnancy

Physiological changes in a woman's body related to pregnancy result mainly from fluctuations in the level of endogenous hormones and their effects on target cells. These activities are necessary for the maintenance of pregnancy, delivery, and lactation. Careful observations provided information on the functions of individual female hormones during the development of pregnancy and after delivery. Whereas the influence of hormones on the cognitive functioning of the brain is not clear. However, in scientific publications, the colloquial term "pregnancy brain" is utilized.[4]

Several reports indicate changes in the neural structure of the brain regions which are responsible for information storage or processing, and for modulating the emotional response.[5] In contrast, experimental studies do not allow recognizing a global decline in cognitive functions in the pregnant population. Studies by Farrar et al. and Christensen et al. show a decrease in cognitive functioning in individual domains while maintaining the level of functioning of others.[5,6]

The first study indicated a reduction in spatial recognition memory as a component of executive functions (EFs) in the pregnant group, while no significant correlation of cognitive results with the level of hormones was found.[5] In the second one (cohort prospective study of nearly 200 pregnant women or mothers) in relation to a large control group, the researchers examined the correlation of pregnancy and motherhood with worse cognitive functioning over many years. The neuropsychological assessment which included the domains of cognitive speed, working memory, immediate and delayed recall, revealed no significant associations between pregnancy and maternity with poorer cognitive outcomes, apart from a worse Digits Backwards score as an element of working memory.[6] It is worth noting that both of these findings concern functions dependent on the activity of the prefrontal cortex of the brain.

An interesting issue is the attempt to determine the relationships between the levels of individual hormones involved in the course of pregnancy. The study on 55 pregnant women analyzed the correlations of the levels of estradiol, progesterone, testosterone, cortisol, and prolactin with the results of a battery of neuropsychological tests. Already in the initial analysis, it was shown that pregnant women in both antenatal and postpartum examinations obtained worse results compared to the control group in the field of verbal recall and processing speed. This study described significant associations of cortisol, prolactin, and estradiol levels, while the nature of the relationship was either linear or inverted-U function (prolactin).[7] The differences in the reports regarding the significance of the influence of pregnancy on the cognitive functioning of pregnant women indicate the validity of further observations, while the reported correlations of hormones with the results of cognitive tests suggest the direction of future research.

Cognitive Functions in Hypertensive Diseases of Pregnancy

Nowadays, the prevalence of hypertensive diseases of pregnancy (HDP) is growing. Hypertensive diseases of pregnancy are responsible for approximately 5–10% of complications during pregnancies throughout the world.[8] With growing gestation, the mother's cardiovascular system activates alterations necessary to adapt to changing blood pressure (BP) levels. However, due to many factors (environmental, medical ones), those regulating mechanisms may get depleted and cause a greater risk of BP leading to pathology.[9]

Definition and Classification of Hypertensive Diseases of Pregnancy

Diagnosis of hypertension in pregnancy is made if the value of taken BP exceeds 140 mm Hg systolic or 90 mm Hg diastolic in two measurements separated in time. European guidelines describe the following classification of HDP:

- Preexisting (chronic) hypertension—which appears before pregnancy, during early pregnancy, i.e., before 20 weeks of gestation, or sustains after 6 weeks postpartum.
- Gestational hypertension—which is first diagnosed after 20 weeks of pregnancy and subsides during 6 weeks postpartum.
- Preeclampsia (PE) and eclampsia syndrome—Preeclampsia is defined as hypertension that develops after 20 weeks of gestation and coexists with at least one of subsequent disorders: proteinuria, thrombocytopenia, renal insufficiency, liver dysfunction, neurological disorders, hemolysis, or fetal growth restriction. Eclampsia is a severe form of PE characterized as the new onset of tonic–clonic seizures.
- Preeclampsia superimposed of chronic hypertension—defined as development of PE in women with chronic hypertension.[8,10]

Consequences of Hypertensive Diseases of Pregnancy

Hypertensive disorders in pregnancy may cause a wide spectrum of complications in many organ systems to both mother and her child; hence, they contribute to greater rates of perinatal morbidity and mortality.

Chronic hypertension may predispose to complications such as renal failure, stroke, or respiratory failure; however, the greatest consequence associated with this disorder is superimposed PE.[11] Superimposed PE may develop even in 20–40% of obstetricians with chronic hypertension.[12] Even higher maternal morbidity and mortality may ensue from superimposed PE in comparison to PE which develops in a woman without the chronic hypertension.[13]

In gestational hypertension, the risk of PE estimates around 50% which is linked to many adverse outcomes.[14] Both gestational and chronic hypertension may lead to dangerous perinatal complications like fetal growth restriction, abruption of the placenta, which contribute to significantly increased risk of miscarriage, premature birth, or even intrauterine fetal death.[11] Gestational hypertension is the risk factor for the development of chronic hypertension, risk of cardiovascular diseases, including myocardial infarction.[15]

Preeclampsia affects organs due to endothelial dysfunction leading to microangiopathy, damaged perfusion, vasoconstriction,

and maladaptive response to greater BP in vessels. Therefore, PE may lead to disorders like a hepatic failure, acute kidney injury, electrolyte abnormalities, thrombocytopenia, or neurological complications. Eclampsia is the most dangerous complication of PE resulting from encephalopathy owing to hypoperfusion. Apart from seizures, cortical blindness, hemorrhagic stroke (due to coagulopathy), or posterior reversible encephalopathy syndrome (PRES) also pertain to neurological complications.[11]

Similar complications may ensue from superimposed PE; however, as we have mentioned, the perinatal risk is greater.

Hypertensive Diseases of Pregnancy and Brain Function

Literature shows that HDP affect many organs in a woman's body, including the brain, which leads to serious complications. In many guidelines, the best medication for gestational hypertension or PE and eclampsia is a cessation of the pregnancy—delivery.[16,17]

But let us concentrate a little bit more on the brain. Hypertensive diseases of pregnancy, especially PE and eclampsia, inflict great damage to the brain, which may lead to stroke, seizures, or temporary blindness. The question is, whether HDP can prompt other symptoms which occur even after the postpartum period? Those particular symptoms include problems with memory, concentration or attention, problems with processing information and hinder daily functioning—namely cognitive functions.

Literature shows evidence that many researchers have tackled the problem of cognitive performance in women whose pregnancies were complicated with HDP.

The study of Postma et al. performed the long-term follow-up study scrutinizing the connection between the history of PE or eclampsia and cognitive functioning in women.[18] They also analyzed the quality of life within their study group. The results indicate that women with a history of PE, perceived cognitive deterioration, worse quality of life, and showed psychological problems in comparison to women with normotensive pregnancies. The study also showed that women who had eclampsia reported even more issues with cognitive functioning. Authors suggest that the possible explanation for these results may stem from trauma experienced due to pregnancy burdened with PE or eclampsia which manifests in significant worrying and feeling acute stress. Such symptoms may contribute to the development of psychiatric pathologies in the postpartum period or even in later life, i.e., post-traumatic stress disorder (PTSD) or depression, which are associated with cognitive deterioration.[19–22]

The results of research conducted by Mielke et al. showed that women with a history of HDP gained worse scores in tests assessing processing speed in comparison to subjects with normotensive pregnancy. However, both groups did not differ regarding EFs, language, or memory. Researchers also evaluated MRI results to search for brain changes. They found that women with a history of HDP had both greater brain atrophy and white matter lesions (WMLs).[23]

In the field of cognition, researches show mixed results. In a study by Dayan et al. (who also scrutinized the relation between the history of PE and cognitive deterioration in the long-term follow-up), women with a history of PE showed lower scores of cognitive domains such as executive functioning or psychomotor speed; however, those results were statistically insignificant.[24] Another data did not show any differences regarding EFs, working memory, or attention between the study group and controls.[25] On the contrary, another study found that the history of PE was related to cognitive decline in EFs, as well as in verbal learning and attention.[26]

The association between the history of PE and the increased risk of dementia has been proved. The strongest connection was with vascular dementia; however, authors found associations with the heightened risk of Alzheimer's diseases (AD) as with other subtypes of dementia (although weaker in statistical analysis).[27,28]

How does HDP Affect Brain?—Putative Mechanisms

Common Risk Factors

Pregnancy itself may be a particular test of women's susceptibility to cardiovascular diseases (CVD) development in later life. Hypertensive diseases of pregnancy are risk factors for CVD and also share similar risk factors as CVD.[29,30] The nature of PE is involved with impairment of vessels and in this manner may be connected with greater dementia development in the future. The pathogenesis of PE is associated with endothelial dysfunction and greater inflammatory response.[28] Both factors contribute to the occurrence of plaques in the vessels, leading to atherosclerosis, blockage of small vessels with further angiopathies. In the brain, those mechanisms may lead to cerebral lesions and infarctions and hence may explain cognitive declines reported by patients.[31]

White Matter Lesions

The cerebral cortex is perceived as the center of cognitive functions, but another structure with a major contribution is white matter. White matter forms neural tracts which are spread throughout the brain. Those tracts form connections between gray matter regions in cortical and subcortical areas, therefore enable conveying information regarding emotion and cognition.[32,33]

Injuries of white matter are associated with cognitive decline and the development of dementia.[33] For better classification of white matter involvement in cognitive deterioration, the term "white matter dementia" was created.[34] Brain injury resulting in demyelination of axons may be responsible for postponed impulse transmission in the brain and hence, contribute to cognitive dysfunction in domains such as EFs, memory, attention, or language processing.[32]

Research showed that WMLs were found more frequently in women with PE and eclampsia than women with a normotensive pregnancy.[35,36] Even though WMLs are involved in dementia in the elderly, yet no evidence shows the clinical consequences of WML in cognitive dysfunction in young women with HDP. Such results may eventuate from neuroplasticity and cognitive reorganization or be the result of the inadequate methodology utilized in various studies.

Subjective Cognition

Researches utilizing a battery of objective cognitive tests still show mixed results regarding the connection between cognition and PE. Some authors allude to the term "subjective cognition" to explain the lack of evidence measured in objective tests performed in women who presented worse cognitive functioning in autoquestionnaires.[25] Self-reported cognitive decline may stem from few aspects. Women who were enrolled in studies were too young during the cognitive evaluation. Therefore, lack of evidence regarding cognitive deterioration might be a result of compensatory brain capacity due to young age. A similar explanation might be responsible for the inconsistent results of neuroimaging studies about the connection between WML and

cognitive functions after PE.[23,36] However, it is speculated, whether WMLs could be a radiological sign indicating the susceptibility of hypertensive disorder in later life.[37] After reaching an elderly stage of life, compensatory brain capacity might get depleted and then manifest in cognitive decline.

Cerebral Blood Flow

Pregnancy is challenging for the cardiovascular system and requires adaptions like reconfiguration or reconstructions of blood vessels. Hypertensive diseases of pregnancy exert great influence on cerebral blood flow (CBF) even in the postpartum period.[38] Women with chronic hypertension and superimposed PE show greater cerebral perfusion pressure and increased resistance of cerebral vessels.[39] Patients with PE have impaired autoregulation mechanisms leading to increased CBF velocity.[40,41] Lack of proper adaptations may result in greater blood–brain barrier (BBB) permeability, heightened hydrostatic pressure, or damage of microvessels. This in turn may lead to microbleeding, cerebral edema, neuroinflammation, and neuronal damage.[42–44] The theory explaining neurological symptoms in eclampsia involves insufficient autoregulation of CBF which predisposes to vasogenic edema and hence to PRES.[45,46] Therefore, impaired autoregulation is linked to poorer cognitive functions and enhanced risk of vascular dementia in the future.[47] It is worth noting that HDP do not cease with delivery, but may exert detrimental consequences in later life.[48]

Blood-brain Barrier Impairment

Blood–brain barrier (BBB) is a specialized barrier that maintains brain homeostasis by regulating the exchange between blood and the cerebral microenvironment. Studies show the connection between increased CBF and greater BBB permeability which may cause damage to the brain.[49,50] Neuroimaging studies proved the association between PE/eclampsia and BBB impairment.[51] Preeclampsia is associated with an increased inflammatory response with elevated levels of proinflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and microglia activation.[52] Neuroinflammation may be responsible for deteriorated neurological injury, greater vulnerability to eclampsia-like seizures, and contribute to the development of eclampsia.[53,54] Literature shows evidence that neuroinflammation during conditions with raised inflammatory levels influences brain function in domains of learning or memory.[55,56] Moreover, BBB disruption in conjunction with inflammatory mechanisms contribute to cognitive decline.[57] To our knowledge, the literature does not provide evidence of the association between neuroinflammation and cognitive decline in women with PE/eclampsia. However, this mechanism may be responsible for symptoms reported by women with a history of HDP and for a greater risk of dementia in later life.

Gestational Diabetes Mellitus and Brain Function

Gestational diabetes mellitus (GDM) is a frequent complication during pregnancy. According to International Diabetes Federation (IDF) in 2019 approximately 20 million, or 16% of pregnancies worldwide were complicated with hyperglycemia. One in six births was associated with GDM.[58] Those numbers will be growing, and due to serious consequences associated with GDM, it is crucial to put more effort to prevent and support pregnant women suffering from this disease.

On a molecular basis, GDM develops due to the impairment of β-cells in the pancreas as a result of excessive insulin production. The dysfunction is caused by hyperglycemia and augmented insulin resistance.[59,60]

The state of hyperglycemia may inflict grievous consequences both to the mother and her child, for instance, preterm birth, PE, fetal overgrowth resulting in macrosomia, or fetal hyperglycemia which may even lead to stillbirth.[61–65] It is well known that GDM predisposes to the development of type 2 diabetes mellitus (T2DM) or CVD, but also GDM has been linked to a greater risk of affective disorders, such as depression.[66]

It has been shown that the relationship between T2DM and depression is bidirectional. Type 2 diabetes mellitus facilitates the pathogenesis of depression, and depression is a risk factor for T2DM. Studies show a similar connection between GDM and depression.[67] Gestational diabetes mellitus may lead to mood disorders *via* disturbances in the hypothalamic-pituitary-adrenal axis (HPA), hyperinflammation, or hyperinsulinemia.[68] On the contrary, depression may contribute to further exacerbation of hyperglycemia and glycemic control.[69]

To date, many studies show the influence of T2DM on brain function. However, none are presenting how GDM leads to cognitive impairment. Gestational diabetes mellitus exerts adverse effects on the brain in a shorter period—during pregnancy—in contrast to T2DM. Nonetheless, both diseases show similar consequences, like a greater risk of CVD, mood disorders, and obesity. Therefore, GDM and T2DM may similarly affect the brain. Moreover, it has been shown that GDM shares similar gene polymorphism as AD. Building on the model of T2DM, I will shortly discuss mechanisms that lead to cognitive deterioration.[70]

Cognitive Dysfunction in Type 2 Diabetes Mellitus

The issue of the development of cognitive deterioration in patients with T2DM has been well studied. Diabetes can lead to functional and structural changes in the brain, and thus incur impaired cognitive processing in many domains. Published data show worse performance in speed of information processing, EFs, poorer verbal learning, attention, and psychomotor efficiency.[71,72] Evidence of the Maastricht Aging Study showed that diabetic patients had greater cognitive decrements in major domains like information processing and word recalling, in comparison to nondiabetic controls in a long-term evaluation.[73]

Along with cognitive decline, it was hypothesized that T2DM might be associated with the pathophysiology of dementia. Especially, that factors related to diabetes, i.e., hyperinsulinemia, hyperglycemia, and greater insulin resistance are considered as AD risk factors.[74] It has been shown that patients with T2DM have a higher risk of AD development.[75–77] Moreover, T2DM seems to be associated with around 50% greater susceptibility to dementia.[78] Another significant argument pointing to the relationship between T2DM and dementia is that AD has been defined as "type 3 diabetes". Some researchers utilize this term because insulin and insulin-like growth factor 1 (IGF-1) take part in neuronal homeostasis and signaling processes within the brain. Those processes enable learning and making memories, but in case they are disturbed, they seem to contribute to AD pathogenesis and neurodegeneration.[77]

Data present associations between cognitive dysfunction and inadequate glycemic control. Type 2 diabetes mellitus patients showed augmented dysfunction in domains such as memory,

attention, and psychomotor speed in comparison to subjects with impaired fasting glycemia or normal glucose levels.[79]

Higher levels of glycosylated hemoglobin (HbA1c) are associated with greater cognitive decline. Yaffe et al. showed results indicating that HbA1c correlated with worse scores of the Wisconsin card sorting test (WCST) which measures EFs.[80,81] Authors even suggest that HbA1c might be a parameter utilized to predict a greater risk of dementia development in the future.

Literature also shows mixed results regarding this topic. Some studies present that dementia develops owing to vascular changes during diabetes, rather than AD-like alterations within the brain.[82–84] Also, methodologies of some studies might be responsible for inconsistent results. Complications associated with T2DM and concomitant diseases may affect the brain as well and contribute to poorer cognitive functioning, for instance, hypertension, visual impairment, stroke, or depression.[85–88] In this manner, different mechanisms (not necessarily associated with T2DM) could influence brain function.

Another issue worth commenting on is how soon T2DM exerts adverse alterations in the brain and how aging may contribute to cognitive deterioration. van den Berg et al. performed a study that assessed two groups of patients two times: at the baseline measurements and after 4-year follow-up. Results demonstrated that, in comparison to healthy controls, patients with T2DM had worse outcomes in the processing of information, EFs, and attention. However, over a 4-year evaluation, changes in poorer cognitive outcomes were rather the results of aging than the detrimental influence of diabetes itself.[89] Literature also presents reports indicating rapid cognitive deterioration in T2DM patients within a relatively short time of 3–6 years.[90,91] Also in a group of elders T2DM accelerated cognitive dysfunction for 9 years.[92]

Hyperglycemia and Insulin Resistance

Studies suggest that insulin is responsible for adverse brain changes linked to poorer cognitive outcomes. Insulin resistance shows a negative correlation with cognitive performance even in individuals without diabetes.[93,94] Another study suggests that insulin resistance may impact brain glycose metabolism and be associated with changes similar to alterations observed in AD.[95]

Insulin resistance is related to hyperinsulinemia and hyperglycemia.[96] Hyperinsulinemia and hyperglycemia are associated with an excessive amount of advanced glycation end products (AGEs). Those compounds are associated with reduced elasticity of blood vessels and in this mechanism create greater blood flow restriction.[97] Higher glucose levels also contribute to adverse effects within microvascular systems. Within the brain, they may lead to small infarcts in various brain areas, thus may aggravate cognitive processing.[96,98]

Studies present findings between AGEs and the pathogenesis of AD. Advanced glycation end products play role in the formation of fibrillary tangles and amyloid plaques which are responsible for neuronal death and further neurodegeneration processes associated with AD development.[99]

Studies show that reduced neurogenesis, owing to AGEs abundance, complicate forming episodic memory, including verbal and spatial memory.[97] Individuals with prediabetes showed neuropathological changes in comparison to controls with normoglycemia. Increased glucose levels positively correlate with cognitive decline, which may later accelerate age-related cognitive deterioration processes.[100] Study performed by Munshi et al. observed a negative correlation with poorer results of tests assessing EFs.[101]

Presented evidence sheds light on causes of cognitive deterioration during diabetes. Some factors influence the degree to which T2DM affects the brain. Among them are the duration of the disease, the level of hyperglycemia and glycemic control, and also the presence of concomitant diseases.

Neuroimaging

Many papers present evidence of cognitive impairments in T2DM patients, which are expressed in neuropsychological tests and questionnaires. Literature comprises neuroimaging studies that scrutinized the relationship between diabetes and structural and functional changes within the brain.

Inappropriate levels of glucose levels in diabetes were associated with diminished cortical thickness. Studies noted a significant reduction of the volumetric brain in the area of the hippocampus, which is responsible for processes related to memories.[98,102] Similar alterations were observed in frontal lobes which are essential for EFs. Moreover, hyperglycemia may impair cortical and subcortical neuronal pathways. In MRI scans, these lesions are presented as white matter hyperintensities. Insulin resistance, HbA1c, and high glucose variability are associated with greater WMLs, which contribute to worse performance in attention, memory, and EFs.[103]

Effects of insulin resistance were evaluated in positron emission tomography (PET) studies. In contrast to healthy controls, individuals with prediabetes showed lower activation in prefrontal regions of the cerebral cortex while subjects were performing cognitive tasks. Authors suggest that insulin resistance might be a marker of AD-like cognitive deterioration even before the full onset of mild cognitive impairment (MCI).[95]

To conclude, brain imaging studies show evidence linking T2DM to cortical and subcortical brain shrinkage.[104] Those structural alterations may contribute to cognitive deterioration in diabetic patients.

Importance of Cognitive Functions

Executive functions are responsible for the regulation of human actions to achieve a particular goal.[105] Therefore, it is necessary for this cognitive domain to work properly to manage chronic diseases, like T2DM. Regarding EF, patients use them to control glycemia levels throughout the day. To do that patients have to control themselves and apply proper diet (calculate nutritious values of food), monitor glucose levels, and exercise. During the day, many factors may have an impact on proper glucose levels, e.g., stressful situations. When the daily routine is disturbed, EFs are utilized to take proper actions necessary in maintaining an intended level of glucose.

In case when EFs are deteriorated, T2DM patients may get easily distracted by cues from the environment which can hinder achieving the goal of euglycemia. Such cues can be high-caloric food. When self-control is weakened, there is a high chance that patient will stop their diet routine and yield to the temptation of eating unhealthy food.

It has been shown that diabetes may also affect work productivity in conjunction with worsened EF (due to hyperglycemia).[106] Also impaired EF may contribute to difficulties with managing emotions. Executive functions may also influence the greater risk of depression development in T2DM.

Similar adjustments in daily routine are required of women with GDM. If insulin resistance or hyperglycemia affects their brain function in similar ways to T2DM, those patients may also struggle in obtaining euglycemia owing to cognitive deterioration. This is particularly important because complications of GDM are grievous to both mother and her child.

Future Directions

As I have mentioned, glycemic control may affect cognitive performance. Increased glycemia might exert adverse outcomes in brain functioning and result in having difficulties during daily duties or worse quality of life. Pregnancy is a state of greater insulin resistance and higher levels of glucose in the blood which are necessary for proper fetal development. During the complication such as GDM, it is essential to commence proper management, not only to prevent consequences related to GDM but also to keep appropriate brain function of the mother.

Unfortunately, the medical database lacks evidence about how GDM affects cognitive functioning. Gestational diabetes mellitus significantly differs from T2DM and most of all lasts in a shorter period. However, GDM is a risk factor for diabetes development and affects many systems of women's bodies. Therefore, it may influence brain function as well, as contribute to cognitive impairments in later life—for instance, those associated with aging. Hence, definitely more, properly planned studies are needed. Those researchers should evaluate cognitive factions with follow-up after a short and long time. Then, obtained results would explain to what degree GDM is linked (or not) to cognitive deterioration.

Cognitive Functions and Obesity

As health professionals, currently, we are struggling with the obesity pandemic. According to WHO, over 1.9 billion adults were overweight and 650 million of them were obese (2016).[107] Even among children and adolescents overweight is increasing with every year. Around 340 million of them were overweight or obese.

Obesity is considered a chronic disease with multifactorial pathophysiology. In pregnancy, obesity is very challenging due to adverse outcomes to both mother and fetus. Obesity predisposes to complications related to pregnancy like GDM, hypertensive disorders in pregnancy, prolonged labor, and a greater chance of delivery via cesarean section.[108,109] Moreover, obesity is associated with a greater risk of wound infections or postpartum depression.[110]

Concerning fetus, evidence indicates the association between obesity and miscarriage, fetal growth abnormalities (fetal growth restriction and fetal macrosomia), greater risk of preterm birth, still birth, or neonatal death after delivery.[109,111–114] Children born from pregnancies complicated with GDM show an increased risk of developing obesity, insulin resistance, or diabetes mellitus.[115,116]

Obesity is defined based on body mass index (BMI). In pregnant women, the diagnosis of obesity is made if BMI value equals 30 kg/m^2 or more from the calculations using height and weight before pregnancy or from the first trimester of pregnancy (during the first visit).[117]

Cognitive Functions in Obesity

Obesity affects almost every system of the human body and also contributes to worse cognitive processing. Studies showed that patients with excessive BMI had worse results in neuropsychological tests assessing memory, attention, and visuospatial domains.[118–120] In comparison to healthy subjects, overweight individuals demonstrated abnormalities of working memory.[121] Several studies also demonstrated that obesity is a risk factor for developing dementia, even in the independent manner of T2DM.[122–124] Even research of children and adolescents indicates significant differences in cognitive performance between the group of obese and normal-weight participants. Obese children showed deficits in short-term memory and verbal abilities. Furthermore, even neuroimaging studies of obese children show essential abnormalities in brain structure, like WMLs or lower cerebral volume which suggest that excess of adipose tissue may inflict damage to the developing brain.[125,126]

Data show evidence of putative bidirectional mechanisms between obesity and cognition. Impairments of EFs may contribute to further weight gain. As has been mentioned before, EF enable control of human behavior to goals. However, disorders of processes that manage self-control may facilitate overconsumption and eating high-caloric food, leading to further weight gain.[127]

Dopaminergic Signaling as a Link between Obesity and Cognitive Factors

Institute of Medicine established gestational weight gain (GWG) guidelines, which are based on the BMI.[128] Gestational weight gain has been linked to several perinatal and intrapartum complications.[129–131] Therefore, the prevention of GWG is an essential issue that needs more investigation leading to novel prophylactic and therapeutic programs to support women suffering from obesity.

Eating healthy food abundant in vegetables, fruits, and proteins is recommended. However, women report troubles with implementing a proper diet, due to food cravings, easier access to fast foods, or the presence of unhealthy food within their environment (i.e., household members have a high-caloric diet).[132]

Dopamine (DA) is a key neurotransmitter involved in food intake control. Disturbances in DA signaling within the brain may result in reward-seeking behaviors, have looking for natural rewards as high-caloric food.[133] Several theories which involve dopaminergic signaling were conceived to explain the pathophysiology of obesity.

- Reward surfeit theory suggests that food consumption commences greater reward responsiveness within brain circuits of the brain. This mechanism stimulates further overconsumption.[134]
- The incentive sensitization model postulates that repeated intake of highly palatable food containing great amounts of sugar or fat may increase response within reward regions to cues associated with these types of foods. In this manner, it may explain difficulties with adjusting proper eating habits in overweight women.[135]
- Reward deficit theory indicates that changes within the reward circuit in obese persons are associated with lower response to food in comparison with healthy ones. Therefore, obese people consume greater amounts of palatable foods to compromise the deficit.[136]
- Inhibitory control deficit theory demonstrates that individuals with EF dysfunction of inhibitory control are more prone to food cues in the environment and eat more.[137] (This theory explains the bidirectional role of cognitive functions of weight gain in obese people.)

The work of Stice and Yokum showed that gene polymorphisms that modulate neurotransmitter signaling within the brain are associated with obesity development.[138,139]

Mechanisms explaining poorer cognitive functioning in obese individuals show mixed results. Among presumed mechanisms, researchers mention obesity-induced low inflammation or microbiota.[140,141] The role of DA transmission is also suggested, because DA plays an essential role in conveying information within cognitive pathways, especially in the prefrontal cortex—which is the principal bran area of executive functioning.[142] We performed a study scrutinizing the role of DA gene polymorphisms, associated with obesity, in cognitive functioning in obese subjects. The results indicated that DA gene polymorphisms linked to obesity, contribute to the performance of EFs in this group.[143]

Multidimensional Approach of Prevention

Obesity develops due to several mechanisms and is associated with complications affecting the brain. Evidence presents that behavioral therapy and psychological interventions may diminish the negative role of cognitive factors or mood disturbances supporting further GWG and development of obesity-related complications. Novel preventive programs are needed, especially those tackling aspects associated with cognitive dysfunction. Hence, pregnant women will learn new skills enhancing the chance of appropriate weight gain during pregnancy, as well, as the possibility of weight loss in her later life.[144,145] Such action could prevent serious complications associated with obesity.

Depressive Disorders and Cognitive Functions

Mood disorders are also frequent during pregnancy as during other times of women's life. The definition of perinatal depression points to the occurrence of major or minor depressive episodes during pregnancy or within the first 12 months after the delivery.[146] Symptoms associated with this disease include depressed mood, anhedonia, disruption of sleep or appetite, having low self-esteem.[147]

Maternal depression is associated with several complications concerning the mother and developing fetus.[148,149] Perinatal depression has been associated with a greater risk of PE or preterm birth.[150] Moreover, women experiencing depression during pregnancy tend to care less about themselves and in some cases, may even show risk-taking behaviors.[151,152] To date, many studies show deleterious correlations with fetal brain development and perinatal depression. Children show social and cognitive deficits as well as greater predisposition to neuropsychiatric disorders.[153,154]

Unfortunately, the evidence of depression is growing and often perinatal depression remains missed by healthcare professionals and then, untreated. Therefore, more effort should be put into the management and screening of mood disorders in pregnancy.

Cognitive Aspects of Depression

Devastating consequences of maternal depression also include the mother's brain function during the antenatal and postpartum periods. However, literature shows scarce evidence regarding this topic. Research is mostly focused on the function of memory in pregnancy, while one research is related to rodents.[155,156] Some papers do not prove any connections between worse cognitive outcomes and maternal depression.[157–159] Evidence suggests that women report subjective cognitive deterioration due to felt stress and anxiety related to a depressive state. Therefore, authors suggest that problems with memory or concentration may arise from symptoms of depression.[158] Maternal depression may exert a negative influence on a woman's self-assessment rather than inflict cognitive deterioration.[157,159]

Pregnancy is a unique time in a woman's life. Along with pregnancy, new challenges occur like different lifestyles or worries about the newborn. This challenge contributes to greater levels of anxiety and stress and contributes to the development of mood disorders associated with pregnancy. Similarly, enduring stress may predispose to the occurrence of subjective symptoms of cognitive decline.[160]

Studies on nonpregnant individuals show evidence that depressive disorders have a negative impact on EFs, namely inhibition control.[161] Neuroimaging studies presented a greater amount of WMLs in depressive individuals which may explain cognitive deterioration.[162] Worse processing in inhibition control and working memory (which are the components of EF) may result in difficulties with changing focus from negative stimuli to new information.[163] As a model, imagine the medical consultation between a mother with maternal depression and a perinatologist about abnormalities found in ultrasound during prenatal diagnosis. During the conversation, a mother with depression will mostly focus on a potential threat to her unborn child. She will have trouble in changing her attention to proposed methods of treatment after the delivery. Of course, getting to know that something wrong is with a child is grievous for every expecting mother. Nonetheless, women with mood disorders might be more demanding and during making the conversation it is worth knowing, that they might require more time to process received information.

Worse EF performance may result in neglect of self-care and management during pathologies of pregnancies, like taking anti-hypertensive drugs or monitoring glucose levels.[98,105] Hence, obese patients with GDM and depression may have great problems with compliance.

Obesity, Depression, and Diabetes

Due to the greater prevalence of obesity, mood disorders, and diabetes, we can describe a standard model of the high-risk pregnant patient: the one who is obese received inadequate results of oral glucose tolerance test (suggesting gestational diabetes). As I have mentioned earlier, both obesity and diabetes are risk factors for mood disorders. One theory suggests that obesity and depression have the same pathophysiology.[164] Results of our study showed the connection between particular dopaminergic genes polymorphisms and greater intensity of depressive symptoms and BMI values, which suggest that one way of common pathogenesis may derive from alternations within dopaminergic signaling.[165]

The term "metabolic mood disorders" emphasized the interdependence between depression, obesity, and hyperglycemia.[166] Apart from alterations in dopaminergic signaling described above, both diseases are associated with dysregulation of the immune system causing inflammation or hormonal dysregulation in the HPA. Even neuroimaging studies show similar findings like WMLs, brain shrinkage, or abnormal activity of the prefrontal cortex (a key element in cognitive processes).[167]

Both depression and metabolic syndrome may have a synergistic effect on worse cognitive functions. A study by Sullivan et al. showed that cognitive decline progressed faster in patients

with diabetes and depression within 3 years, regardless of glycemic control.[168] Another study showed similar findings–patients with T2DM and depression obtained worse results in memory and EF in comparison to healthy controls and subjects with T2DM.[169]

To conclude, mood disorders may affect cognitive functioning and impair daily living. Growing evidence points to the association with metabolic disorders, i.e., obesity and T2DM, making such patients in need of more health control. Unfortunately, little is known about a similar connection in pregnant women due to the lack of performed studies. Owing to the growing prevalence of metabolic and mood disorders and their deleterious complications, more evidence in this field might significantly improve treatment outcomes and preventing programs in the group of pregnant women.

Summary

Literature shows mixed results regarding the influence of pathology of pregnancy on cognitive functions in pregnant women. Such results may ensue from a lack of properly performed studies in this group of patients. More research is definitely needed, due to the growing prevalence of diseases associated with pregnancy, which could potentially affect brain functions during pregnancy, postpartum, or exert deleterious effects on cognitive functions in later life.

Studies performed in this field may give interesting results, especially those women (during the antenatal or postpartum period) report difficulties associated with domains of cognitive functions, like memory. So far, a scarce amount of evidence showed by objective neuropsychological tests may result from cognitive brain capacity in young women, or be associated with mood disorders like depression.

Nonetheless, the assessment of cognitive functions in pregnant women, or the evaluation of how the pathology of pregnancy affects cognition will bring essential data, which can be later utilized in creating novel prevention and therapeutic programs. Such programs could contribute to a better quality of women's life and facilitate complying with recommendations made by a healthcare professional.

Cognitive deterioration in pathologies such as diabetes mellitus, obesity, or hypertensive disorders shows how the whole body is connected. Even though there are pathologies related to different organs, they still affect brain function and in this manner may impair processes such as memory, attention, or information processing, which we use every day to fulfill daily tasks and accomplish future goals.

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