



Consequences of gestational diabetes to the brain and behavior of the offspring

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ABSTRACT

Gestational diabetes mellitus (GD) is a form of insulin resistance triggered during the second/third trimesters of pregnancy in previously normoglycemic women. It is currently estimated that 10% of all pregnancies in the United States show this condition. For many years, the transient nature of GD has led researchers and physicians to assume that long-term consequences were absent. However, GD diagnosis leads to a six-fold increase in the risk of developing type 2 diabetes (T2D) in women and incidence of obesity and T2D is also higher among their infants. Recent and concerning evidences point to detrimental effects of GD on the behavior and cognition of the offspring, which often persist until adolescence or adulthood. Considering that the perinatal period is critical for determination of adult behavior, it is expected that the intra-uterine exposure to hyperglycemia, hyperinsulinemia and pro-inflammatory mediators, hallmark features of GD, might affect brain development. Here, we review early clinical and experimental evidence linking GD to consequences on the behavior of the offspring, focusing on memory and mood disorders. We also discuss initial evidence suggesting that downregulation of insulin signaling cascades are seen in the brains of GD offspring and could contribute to the consequences on their behavior.

Key words: insulin resistance, hippocampus, inflammation, depression, learning, memory, programming.

INTRODUCTION

Gestational diabetes (GD) is defined as a form of insulin resistance that initially manifests during the second or third trimesters of pregnancy in previously normoglycemic women. It is expected that GD occurs in up to 10% of all pregnancies, reaching higher incidence in developed countries,

especially in the United States (DeSisto et al. 2014). Epidemiological data also suggest an alarming increase in the number of cases over the last few years (Albrecht et al. 2010). Risk factors for GD include family history of overweight and obesity, nonwhite race and advanced maternal age (Cypriak et al. 2008, Savitz et al. 2008), but independent of risk factor any pregnant woman may manifest this metabolic change.

GD has been associated to macrosomia of the offspring and to sporadic reports of neonatal hypoglycemia, hypocalcemia and respiratory

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distress syndrome (Frías et al. 2007). Despite these observations, until recently GD was considered a transient condition associated with no major consequence to long-term health of the mother or child, since it is expected that only 3-5% of women remain diabetic after labor (Gilmartin et al. 2008) and longitudinal studies following this population are still rare. Therefore, whereas extensive research has focused on unraveling the consequences of obesity and type 2 diabetes (T2D), the long-term effects of GD have been poorly scrutinized and are possibly underestimated (Poston 2011). It is now known that women who developed insulin resistance during pregnancy have a six-fold increase in the risk of developing T2D later in life compared to women who remained euglycemic (Cheung and Byth 2003). However, more recent and concerning evidence point to detrimental effects of GD on the development, metabolism and behavior of the offspring (Daraki et al. 2017, Yessoufou and Moutairou 2011, Garcia-Vargas et al. 2012).

Early studies by Dorner and Mohnike (1976) suggested a higher incidence of diabetes in adults born to mothers with GD, which has been further supported by several other studies (Silverman et al. 1995, Poston and Health 2010). Animal and human studies suggest that the exaggerated glucose transportation across the placenta is the main responsible for fetal hyperglycemia, pancreatic hyperplasia and enhanced insulin secretion, which might generate life-long persistent effects on pancreatic secretory function (Plagemann et al. 1998). Increased hypothalamic inflammation and disrupted insulin signaling in this brain region are classical mechanisms involved in the pathophysiology of T2D, and recent studies using animal models have showed that similar alterations occur in the hypothalamus of GD offspring even before T2D manifests (Melo et al. 2014, Steculorum and Bouret 2011).

Considering that the perinatal period is critical for determination of adult behavior, including levels

of anxiety, impulsivity and stress responses (Bolton and Bilbo 2014), it is expected that the intra-uterine exposure to hyperglycemia, hyperinsulinemia and proinflammatory mediators, hallmark features of GD, might have other consequences to both brain function and behavior. Animal models have been extremely useful in providing insights into this question. However, since GD is a transient and multifactorial condition, animal models that recapitulate all aspects of the disease remain challenging (Pasek and Gannon 2013).

Here, we review emerging clinical and experimental evidence linking GD to late consequences to the behavior of the offspring, especially concerning memory formation and mood disorders. Although preliminary, these early studies point out to GD as an important factor influencing offspring brain health. Moreover, studies from our group and others have recently described how inflammation and disrupted insulin signaling in memory-related brain regions occur in conditions that affect cognition (Bomfim et al. 2012, Lourenço et al. 2013, Neves et al. 2016). Therefore, we also focus on the evidence suggesting that downregulation of insulin receptors and its intracellular cascade are seen in the brains of GD offspring and could contribute to affect their behavior.

ANIMAL MODELS OF GD

Currently available animal models of GD rely on surgical, chemical, nutritional or genetic approaches. For over a century, partial pancreatectomy performed before or during various stages of pregnancy has been described as an efficient method to surgically induce GD in different species, including rodents and dogs (Carlson and Drennan 1911, Markowitz and Soskin 1927, Cuthbert et al. 1936, Jawerbaum et al. 1993). Alternatively, models involving permanent damage to pancreatic β -cells can be induced through the administration of chemicals such as

the nitrosurea derivative streptozotocin (STZ) and alloxan, a pyrimidine derivative (Junod et al. 1969, Lenzen and Panten 1988). Like pancreatectomy, these drugs induce an irreversible state of diabetes in experimental animals due to the drastic reduction of endogenous insulin, giving rise to a condition more closely related to T1D. As a consequence, such models provide limited information on the pathogenesis of GD, although they are useful to characterize the impact of hyperglycemia on the offspring.

As obesity is considered one of the main risk factors for GD, administration of high-fat (HFD), or glucose infusion to pregnant animals have been widely used as experimental models (Bihoreau et al. 1986, Taylor et al. 2005, Srinivasan et al. 2006). Likewise, hyperglycemia and insulin resistance are hallmarks of a number of genetic models used for the study of metabolic diseases. Transgenic mice that do not express leptin or leptin receptors are characterized by an inability to adequately suppress feeding behavior and are classically used to model obesity and T2D. While homozygote knockouts for leptin or its receptor are infertile, heterozygous mice are glucose intolerant and develop GD (Lambin et al. 2007). It is important to mention that, although obese women have an increased risk for developing GD, only about 20% of all GD cases are attributable to obesity (Ferrara 2007, Kim et al. 2012a). Many women develop GD despite being lean, meaning that factors other than increased body mass have an important role in the pathogenesis of the disease, and obesity-related models have limited construct validity. Moreover, HFD alters serum fatty acid profile (Liu et al. 2015), possibly resulting in consequences on the offspring which are not necessarily related to GD.

Pregnancy is associated to a physiological decrease in insulin sensitivity in peripheral

tissues, which are adaptive to allow increased access of the fetus to mother's circulating glucose. Several studies indicate that pancreatic β -cell adaptations to pregnancy are crucial to maintain normoglycemia. Such adaptations include β -cell hypertrophy and proliferation, as well as increased insulin production and secretion (Baeyens et al. 2016). Failure on this physiological pancreatic adaptation or an abnormally increased peripheral insulin resistance may contribute to generate GD. A number of GD mouse models are based on genetic manipulation of factors involved in β -cell adaptation during pregnancy, including prolactin receptor (PrlR) (Lee et al. 2009), c-Met, a tyrosine kinase receptor activated by hepatocyte growth factor (HGF) (Demirci et al. 2012), the serotonin receptor 5Htr2b (Kim et al. 2010), and the nuclear factors menin (Karnik et al. 2007), hepatocyte nuclear factor 4 α (HNF-4 α) (Gupta et al. 2007), Forkhead box D3 (FoxD3) (Plank et al. 2011), and FoxM1 (Zhang et al. 2010). Although these transgenic models may be useful in elucidating how GD impacts the offspring, they target specific signaling pathways, in contrast to the human GD which is polygenic and multifactorial in nature.

The generation of animal models that fully recapitulate GD is challenging, especially as a variety of risk factors, including ethnicity, weight, and family history can contribute to the development of the disease. Also, the severity of hyperglycemia found in some models is not typical of human GD. The main advantages and disadvantages of currently used animal models of GD are summarized in Table I. An ideal animal model would involve normoglycemic females at early pregnancy developing mild hyperglycemia during pregnancy, and returning to normal glucose levels shortly after labor. Another drawback is the fact that, once diagnosed, the condition is treated in humans, suggesting that normalization of glycemia in experimental GD could better reflect the influence of the disease in the offspring.

TABLE I
Advantages and disadvantages of currently available animal models of gestational diabetes.

Strategy	Method	Major Advantages	Major Disadvantages
Surgery	-Pancreateomy	-Affordable	-Not accurate pathogenesis of GD -Irreversible after labor
Chemically Induced	-Streptozotocin -Alloxan	-Affordable -Can be applied to different species	-Not accurate pathogenesis of GD -Potential nonspecific pharmacological consequences -Severe hyperglycemia -Irreversible after labor
Nutritional Manipulation	-High-fat diet -High-sucrose diet -Glucose infusion	-Affordable -Can be applied to larger animals -Reproduces cases of GD associated to obesity	-Ignores genetic contributions of GD -Does not reflect cases of GD not associated to obesity
Genetic Manipulation	-Gene knockouts -Transgenic overexpression	-Spontaneous development of GD -Reproduces genetic contributions of GD - Transient nature	-Not accurate pathogenesis of GD -Not an option for many species

METABOLIC AND BEHAVIORAL CONSEQUENCES OF BRAIN INSULIN SIGNALING DYSFUNCTION

Historically, the skeletal muscle, adipose tissue and liver were considered the main insulin-responsive tissues in control of peripheral metabolism. T2D was classically associated with impaired sensitivity to insulin in these tissues, decreasing glucose uptake and leading to hyperglycemia, even when insulin production and release were normal (Hotamisligil 2008). The brain was considered an insulin-insensitive organ until the late 1970's, when it was demonstrated that i.c.v. infusion of insulin decreased food intake in experimental models (Woods et al. 1979). After this landmark finding, the role of insulin signaling in brain regions that control peripheral metabolism have been extensively scrutinized. The hypothalamus is recognized as a key structure in control of whole body energy homeostasis in response to insulin and other hormones, and it is now known that

hypothalamic insulin resistance plays a central role in obesity and T2D (Arruda et al. 2011, Thaler et al. 2012).

Under physiological conditions, binding of insulin to its receptor triggers its intracellular tyrosine kinase activity. Insulin receptor substrate (IRS) proteins are a family of high molecular weight proteins, of which IRS-1 and IRS-2 are the most extensively studied. IRS-1 is targeted by insulin receptors and undergoes phosphorylation at tyrosine residues, a process recognized as the key initial step of the insulin signaling pathway, which is followed by PI3K activation and Akt phosphorylation. During T2D development, increased levels of pro-inflammatory mediators, especially TNF- α , act on the hypothalamus and peripheral tissues causing activation of intracellular stress kinases which can also target IRS-1, although they phosphorylate serine instead of tyrosine residues (Weissmann et al. 2014, Belgardt et al. 2010). Phosphorylation of IRS-1 at serine residues

inhibits its phosphorylation at tyrosine residues and thus interferes with its ability to engage in insulin signaling even in the presence of insulin (Copp and White 2012).

Insulin and insulin-like growth factor (IGF) receptors in the central nervous system, however, are not restricted to the hypothalamus, being widely distributed throughout the encephalon (Zhao et al. 2004). The hippocampus and cortex have extensive expression of these receptors and are centrally involved in memory formation (Zhao and Alkon 2001). By acting on these brain regions, insulin was shown to be neuroprotective (Plum et al. 2005, Kovacs and Hajnal 2009, Ott et al. 2012, Bomfim et al. 2012) and to affect synapse plasticity (Wan et al. 1997, Biessels et al. 1996) and cognitive function in healthy subjects (Ott et al. 2012, Benedict et al. 2004). Interestingly, growing evidence support that defective hippocampal insulin signaling is related to conditions that affect memory processing, particularly Alzheimer's disease (AD) (Bomfim et al. 2012, Craft and Watson 2004, Ma et al. 2009). TNF- α levels are elevated in the brains of AD patients and transgenic mouse models (Takeda et al. 2010, Salkovic-Petrisic and Hoyer 2007). As in the hypothalamus of T2D patients, hippocampal activation of stress kinases (JNK, IKK and PKR) is also reported in response to increased levels of TNF- α in AD models (Lourenço et al. 2013, Forny-Germano et al. 2014, Ma et al. 2009). As a consequence, IRS-1 serine phosphorylation is increased and insulin signaling is impaired in the hippocampus, contributing to memory impairment in mouse models of sporadic and familial forms of AD (Bomfim et al. 2012). Our group has recently investigated whether similar molecular mechanisms also underlie cognitive impairment seen in sepsis survivors. Sepsis is accompanied by alterations in circulating glucose levels in acute stages and insulin administration was shown to increase survival rates (Gearhart and Parbhoo 2006). These patients often present late cognitive

impairment and some of them never fully recover (Iwashyna et al. 2010, Pandharipande et al. 2013, Semmler et al. 2012). Using an experimental model of sepsis, we were able to mimic the late cognitive impairment seen in patients and found that increased hippocampal expression of TNF- α and impaired insulin signaling in this brain region also accompany sepsis-associated late cognitive decline (Neves et al. 2016). Whether impaired brain insulin signaling is a common denominator of other conditions affecting memory remains to be established.

Even though GD represents a self-limited metabolic condition for the mother, factors such as the high permeability of placental barrier and the maternal pro-inflammatory and hyperglycemic status can be extremely deleterious to the fetus brain. Women with GD have increased plasma levels of inflammation markers, such as C-reactive protein, malondialdehyde (MDA) (Badehnoosh et al. 2017), TNF- α (Friedman et al. 2008) among others (Lowe et al. 2010). Increased expression of the transcription factor peroxisome proliferator-activated receptor γ (PPAR γ) has been described in leukocytes from GD patients compared to healthy pregnant women (Wójcik et al. 2015). Importantly, one study has shown that maternal overweight, but not exposure to intra-uterine hyperglycemia, was associated with increased plasma levels of IL-6 and C-reactive protein in 18-27-year-old offspring from GD mothers (Kelstrup et al. 2012). Animal studies have shown that both placenta and brains of GD fetuses have increased levels of pro-inflammatory markers (Tang et al. 2015, Melo et al. 2014). In the hypothalamus, the pro-inflammatory profile appears to be long-lasting, since high expression of IL1- β mRNA and increased protein levels of NF κ B/p-JNK were described in the hypothalamus of adult mice born from high-fat diet-fed mothers (Melo et al. 2014). Levels of endoplasmic reticulum stress markers were also higher in the brains of these adolescent animals delivered by GD females,

suggesting that obesity-induced insulin resistance during pregnancy is associated to persistent changes in physiological protein synthesis (Melo et al. 2014). In addition, leptin resistance and reduced neural projections within hypothalamic nuclei of adult mice born from hyperglycemic dams were also reported (Steculorum and Bouret 2011). These findings suggest that hypothalamic effects of GD in the offspring might be a consequence of inflammation or disrupted central insulin response. In this scenario, it seems plausible that the insulin signaling pathway in brain regions involved in learning and memory might also be affected, and this hypothesis has never been directly addressed.

EMERGING EVIDENCE OF LONG- LASTING INFLUENCE OF GD TO BRAIN AND BEHAVIOR OF THE OFFSPRING

MEMORY AND BRAIN INSULIN SIGNALING

Epidemiological, clinical and experimental studies support that GD can interfere with intra-uterine brain development and influence behavior later in life. Impaired performance in explicit memory tasks have been reported in 1-year-old babies (Deboer et al. 2005, Riggins et al. 2010), whereas a slower development of cognition and language was found in 18-month-old babies from obese and diabetic mothers compared to the offspring of healthy subjects (Torres-Espinola et al. 2015). These cognitive deficits appear to be reversible, as older children from diabetic mothers have normal performance in different memory tasks (Riggins et al. 2010). These findings are suggestive of delayed neurocognitive development in the offspring of GD mothers.

Incipient studies have suggested that brain insulin signaling is involved in neurological deficits of offspring from diabetic mothers. One interesting study recorded fetal brain activity triggered by glucose ingestion in healthy or GD pregnant subjects, and associated diabetes to a slower brain

response of the offspring (Linder et al. 2015). Using a STZ rat model, Jing et al. (2014) found a decreased expression of IGF-1 and increased expression of insulin receptors in brains of E14, E16 and E18 fetuses from diabetic mothers, effects that were accompanied by reduced number of dendritic spines and smaller levels of the pre-synaptic protein synaptophysin. Authors found that these alterations were absent in fetuses from rats treated with insulin throughout pregnancy, suggesting that they are directly linked to hyperglycemia. Another study evaluated the expression of IGF-1 and insulin receptors specifically in the hippocampus of pups from STZ-treated pregnant rats. Authors found that IGF-1 receptor expression was decreased in the hippocampi of P7 and P14 male rats born from STZ-treated dams, whereas hippocampal insulin receptor expression was slightly increased at P0, but significantly reduced in P14 rats born from diabetic dams compared to control groups (Hami et al. 2013). Structural and electrophysiological alterations have also been described in the hippocampus of rodents born from GD mothers. A decreased number of neurons was found in the pyramidal layers of CA1 and CA3 hippocampal regions at postnatal days 7 and 21, in the offspring of STZ-treated rats (Golalipour et al. 2012). Chandna et al. (2015) reported that hippocampal neurons in newborn pups from STZ-treated females showed altered action potential kinetics along with a more hyperpolarized resting membrane potential. Despite these changes in neonatal hippocampal excitability, animals in this study showed normal memory acquisition as adults.

MOOD DISORDERS

Classical studies in developmental psychobiology and physiology have shown how variations in perinatal environment are associated with changes in behavior that persist throughout life. Increased impulsivity, anxiety levels and depressive-like

behavior, among other emotional behaviors, have been described as a consequence of the exposure to different stressful environments during development (Zhang and Meaney 2010). Studies which directly investigated whether intra-uterine exposure to hyperglycemia and hyperinsulinemia were associated to altered anxiety levels showed confounding results. While some of them report no differences in anxiety levels among rats born from GD dams when diabetes was induced before pregnancy (Kinney et al. 2003, Ramanathan et al. 2000), one study reported decreased anxiety levels in the offspring when STZ was administered during mid pregnancy (Chandna et al. 2015), a condition which more closely resembles the time course of GD development in humans.

Mood-relevant neurotransmitter systems in the fetus brain may also be affected by GD, since changes in catecholamine system were observed in several hypothalamic nuclei of newborn and adolescent offspring from GD rats (Plagemann et al. 1998). Until now, there are no studies directly evaluating whether animals or patients born from diabetic mothers show increased depressive-like behavior or whether they are more susceptible to becoming depressive following a second hit later in life, as previously described for other conditions.

NEUROPSYCHIATRIC DISORDERS

Early-life exposure to several common viruses and bacteria has been linked to the development of neuropsychiatric disorders. Manipulation of maternal immune system appears to be a common denominator important for determination of later outcomes (Estes and MacAllister 2016). In fact, a broader range of environmental distresses during the prenatal period have been associated to the development of schizophrenia and autism later in life (Reisinger et al. 2015). Clinical evidence suggest that the offspring of GD mothers have increased risk of developing schizophrenia (Van

Lieshout and Voruganti 2008, Boksa 2004) and autism (Gardener et al. 2009, Xiang et al. 2015) during adolescence and adulthood. Interestingly, a schizophrenic-like phenotype was successfully reproduced in male rats born from STZ-treated dams, as these animals showed disruption of pre-pulse inhibition response in their young adulthood (Chandna et al. 2015). This behavior persisted even when euglycemia was ensured by insulin treatment during pregnancy, but authors did not further evaluate the mechanisms underlying this interesting behavioral finding.

NEURODEGENERATIVE DISEASES

Alzheimer's disease (AD) is the most common form of dementia in the elderly. Increasing evidence suggests that AD development is influenced by events that take place throughout life, manifesting itself as a consequence of cumulative factors (De Felice, 2013). It has been hypothesized that adverse environments early in life may influence how neurons interact with microglia and astrocytes, making cells over reactive when exposed to the amyloid- β peptide, which is generated in the brain under physiological conditions and form large extracellular deposits during disease development (Ferreira and Klein 2011). Epidemiological data on how gestational diabetes and maternal obesity influence the development of AD and other neurodegenerative disease are still lacking. In an interesting study using a classical AD transgenic model (3xTg), female mice were treated with a high-fat diet during pregnancy and lactation. Maternal obesity did not increase A β load in the brains of adult offspring, but higher levels of phosphorylated Tau protein were found in the hippocampus of these animals, which was associated to a worsened performance in several memory tasks (Martin et al. 2014). Similar experiments were performed in Tg2576 AD transgenic mice, and an increased amyloid- β burden was found in the brains of the

offspring as a result of maternal obesity (Nizari et al. 2016). Interestingly, Hawkes et al. (2015) showed that exposure of pregnant mice to high-fat diet leads to changes in multiple components of the neurovascular unit of the offspring, which impairs perivascular clearance of A β from their brains, favoring amyloid deposition. Although these studies clearly support a possible role of gestational health on the development of neurodegenerative diseases in adult life, more studies should be performed in order to directly investigate the consequences of intra-uterine exposure to hyperglycemia, hyperinsulinemia and inflammatory markers in the development of neurodegenerative disorders later in life as well as scrutinize the possible underlying mechanisms.

CONCLUSIONS

The developing brain is extremely sensitive to endogenous and exogenous signals. GD is a condition where fetuses are exposed to high circulating levels of glucose and increased pro-

inflammatory mediators during a critical period of brain development (Melo et al. 2014, Tang et al. 2015). Although gross malformations are reported in 3-5% of children delivered by GD mothers (Wren et al. 2003, Gharehbaghi and Ghaemi 2010), hypothalamic dysfunction and obesity are expected to affect 30-40% of the offspring (Kim et al. 2012b). Therefore, other changes to brain function, behavior and development of brain diseases could be expected in the offspring of GD (Figure 1). Defects in brain insulin signaling might explain at least in part this delayed cognitive development of GD offspring, and this hypothesis has never been directly addressed. However, downregulation of insulin signaling mediators has already been reported in experimental models of GD. GD is a transient and multifactorial condition which makes it challenging to experimentally recapitulate. We believe that further studies should be performed in order to enable the development of new animal models for GD, so that long-term consequences to both mothers and offspring can be assessed in light of the disease's complexity.

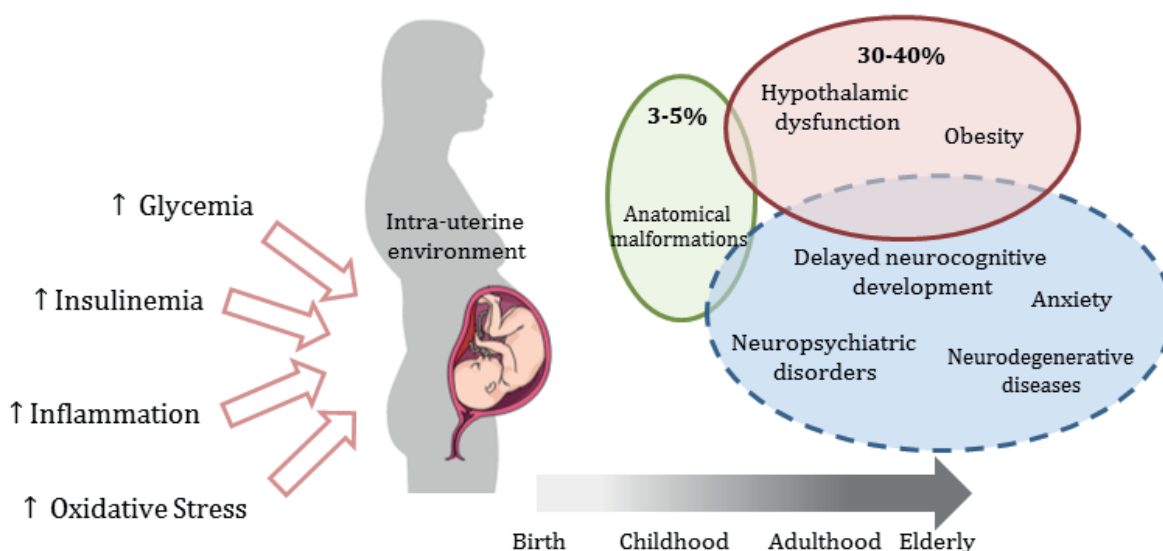


Figure 1 - Consequences of gestational diabetes (GD) to the offspring. Intra-uterine exposure to hyperglycemia, hyperinsulinemia, inflammation and oxidative stress, hallmarks of GD, is associated to anatomical malformations (green circle) and hypothalamic dysfunction/obesity (red circle) in the offspring. Emerging evidence suggest that GD might be associated to behavioral and neurophysiological defects in the offspring (dashed blue circle), which may only manifest at childhood, adulthood or old age.

In developed countries, screening for GD is mandatory and treatment of this condition reaches a high percentage of these patients, suggesting that glycemia is kept within normal levels during the rest of gestation. In animal models, maintenance of euglycemia by insulin treatment has been associated to reversion of several effects in the central nervous system of the offspring (Jing et al. 2014, Hami et al. 2013). However, standard treatment regimens are not always effective in prevention of other classical complications of GD in patients (Crowther et al. 2005, Landon et al. 2009), and there remains a need to improve treatment of diabetic pregnant women. Moreover, considering that increased levels of pro-inflammatory markers may have a key role in brain development and central insulin resistance, normalization of these markers to physiological levels in response to the classical treatment used for GD should be addressed.

Lifestyle intervention in pregnant obese women was also shown to reduce circulating levels of inflammation markers (Renault et al. 2015) and it is expected that nearly 50% of GD cases could potentially be prevented if we reduced the risk of overweight and obesity to that of normal-weight women (Kim et al. 2012a). Therefore, changes in lifestyle habits, such as frequent exercise and healthy diet, remain the best known ways of preventing GD and its undesired long-term effects.

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