

# Diabetes mellitus during pregnancy and increased risk of schizophrenia in offspring: a review of the evidence and putative mechanisms

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**Objective:** To identify converging themes from the neurodevelopmental hypothesis of schizophrenia and the pathophysiology of diabetic pregnancy and to examine mechanisms by which diabetes mellitus in a pregnant mother may increase the risk of schizophrenia in offspring. **Methods:** We reviewed relevant publications on clinical, epidemiologic and animal studies of diabetic pregnancy and the neurodevelopmental aspects of schizophrenia. **Results:** Epidemiologic studies have shown that the offspring of mothers who experienced diabetes mellitus during their pregnancies are 7 times more likely to develop schizophrenia, compared with those who were not exposed to diabetic pregnancy. Maternal hyperglycemia during pregnancy could predispose to schizophrenia in adult life through at least 3 prenatal mechanisms: hypoxia, oxidative stress and increased inflammation. Hyperglycemia increases oxidative stress, alters lipid metabolism, affects mitochondrial structure, causes derangements in neural cell processes and neuronal architecture and results in premature specialization before neural tube closure. The molecular mechanisms underlying these processes include the generation of excess oxyradicals and lipid peroxide intermediates as well as reductions in levels of polyunsaturated fatty acids that are known to cause increased dopaminergic and lowered  $\gamma$ -aminobutyric acid activity. The combination of hyperglycemia and hypoxia in pregnancy also leads to altered immune function including increased tumour necrosis factor- $\alpha$ , C-reactive protein and upregulation of other proinflammatory cytokines. Finally, maternal hyperglycemia could have a lasting impact on fetal cellular physiology, resulting in increased vulnerability to stress and predisposition to schizophrenia via a mechanism known as programming. These prenatal events can also result in obstetric complications such as fetal growth abnormalities and increased susceptibility to prenatal infection, all of which are associated with a spectrum of neurodevelopmental anomalies and an enhanced risk of schizophrenia. **Conclusion:** On the basis of the evidence presented and taking into consideration the projected increases in the rates of diabetes mellitus among younger women of child-bearing potential, it is imperative that the neurodevelopmental sequelae of diabetic pregnancy in general, and the increased risk for schizophrenia in particular, receive further study.

**Objectif :** Dégager des thèmes convergents à partir de l'hypothèse neurodéveloppementale de la schizophrénie, ainsi que de la pathophysiologie de la grossesse diabétique, et étudier le mécanisme par lequel le diabète chez une femme enceinte peut accroître le risque de schizophrénie chez ses descendants. **Méthodes :** Nous avons étudié des publications pertinentes portant sur des études cliniques, épidémiologiques et animales de la grossesse diabétique et des aspects neurodéveloppementaux de la schizophrénie. **Résultats :** Des études épidémiologiques ont montré que les descendants de mères atteintes de diabète de grossesse sont 7 fois plus susceptibles d'être atteints de schizophrénie que ceux qui n'ont pas été exposés au diabète de grossesse. L'hyperglycémie maternelle au cours de la grossesse pourrait prédisposer à la schizophrénie à l'âge adulte à cause d'au moins 3 mécanismes prénataux : l'hypoxie, le stress oxydatif et l'inflammation accrue. L'hyperglycémie accroît le stress oxydatif, altère le métabolisme des lipides, a une incidence sur la structure des mitochondries, perturbe les processus des cellules nerveuses et l'architecture des neurones et entraîne une spécialisation prématurée avant la fermeture du tube neural. Les mécanismes moléculaires qui sous-tendent ces processus comprennent la production de quantités excessives d'oxyradicaux et d'intermédiaires du peroxyde lipidique, ainsi que des réductions des concentrations d'acides gras polyinsaturés reconnus pour causer une élévation de l'activité dopaminergique et une baisse de l'activité acidergique  $\gamma$ -aminobutyrique. La

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combinaison hyperglycémie et hypoxie au cours de la grossesse entraîne aussi une altération de la fonction immunitaire, y compris un accroissement du facteur  $\alpha$  de la nécrose tumorale, des protéines C réactives et une régulation à la hausse d'autres cytokines qui favorisent l'inflammation. Enfin, l'hyperglycémie maternelle pourrait avoir un effet durable sur la physiologie des cellules du fœtus, causant une vulnérabilité accrue au stress et une prédisposition à la schizophrénie via un mécanisme dit de programmation. Ces événements prénataux peuvent aussi causer des complications obstétriques comme des anomalies de la croissance du fœtus et une sensibilité accrue à l'infection prénatale, phénomènes que l'on associe tous à un éventail d'anomalies neurodéveloppementales et à un risque accru de schizophrénie. **Conclusion :** Compte tenu des données présentées et des augmentations projetées des taux de diabète chez les jeunes femmes en âge de procréer, il est impératif d'étudier davantage les séquelles neurodéveloppementales d'une grossesse diabétique en général et le risque accru de schizophrénie en particulier.

## Introduction

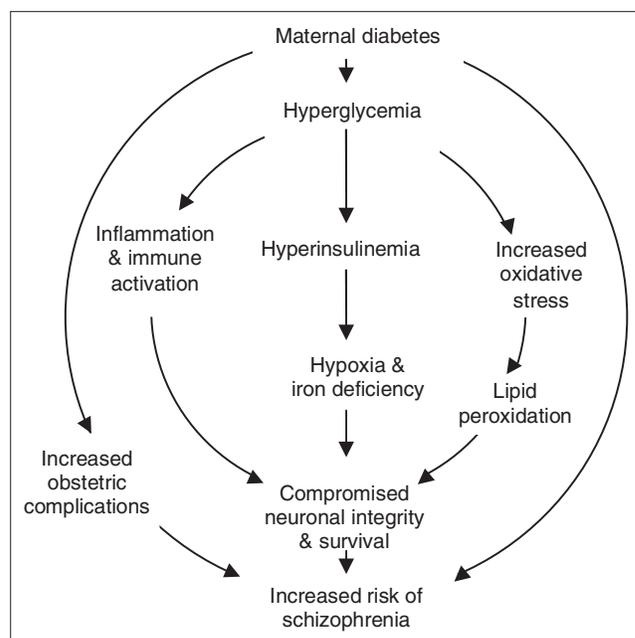
The schizophrenia–diabetes mellitus (DM) comorbidity (SDC) has recently emerged as a significant challenge for clinicians and as a new frontier of the brain–body conundrum for researchers.<sup>1</sup> Although recent research has focused on identifying the mechanisms by which schizophrenia and antipsychotic medications predispose patients to type 2 DM, little attention has been paid to the prospect that maternal DM during pregnancy might increase the risk of schizophrenia in the offspring. Within the framework of the neurodevelopmental hypothesis of schizophrenia, this article examines the role of maternal DM during pregnancy in regard to increased risk for schizophrenia in offspring.

### Neurodevelopmental hypothesis of schizophrenia

The neurodevelopmental hypothesis is widely recognized as the most comprehensive and influential explanation of the etiopathogenesis of schizophrenia to be proposed in recent years.<sup>2</sup> It was originally postulated that a prenatal cytoarchitectural aberration (dubbed a “neuro-dislocation syndrome”) in the developing brain predisposes a person to altered cortical and subcortical dopaminergic transmission and the emergence of psychotic symptoms in adult life.<sup>3</sup> The theory served as a heuristic model and stimulated research in several directions over the past 2 decades, expanding its scope and validity. An updated version of the model has 3 key elements: a set of causative factors, a series of putative mechanisms and an integrative framework capable of generating testable hypotheses. It is now believed that an interaction between multiple susceptibility genes and one or more environmental insults during pre- and perinatal brain development results in impaired neuronal integrity and connectivity, setting off a cascade of events that extend into adult life.<sup>4</sup> The gene complement may include, but is not limited to, the disrupted in schizophrenia 1 (*DISC1*) gene, neuregulin-1, dysbindin, catechol-O-methyl transferase and the G72 protein, which regulate key neurotransmitters such as  $\gamma$ -aminobutyric acid (GABA), glutamate and dopamine (DA) as well as *N*-methyl-D-aspartate receptors.<sup>5,6</sup> The set of acquired or environmental factors (or the “first hit”) that interact with the susceptibility genes to create neuronal dysplasia may include perinatal trauma, hypoxia and infection.<sup>7</sup> Excessive synaptic pruning, substance abuse and hormonal

changes associated with puberty (“second hit”) further enhance the risk, and oxidative stress and excitotoxicity (“third hit”) seem to precipitate the symptoms.<sup>8</sup> In addition to identifying various causative factors and elucidating the interactive mechanisms, the neurodevelopmental hypothesis has also evolved from a static encephalopathy or fixed-lesion model to one that accommodates the role of dynamic and progressive changes in the brain and acknowledges the scope for preventive intervention.

The focus of the present article is to explore how an environmental “first hit” imposed by the intrauterine environment of maternal DM in conjunction with the fetus’ genetic endowment might increase the risk for schizophrenia. A cascade of events initiated by hyperglycemia and mediated by hypoxia, inflammation and oxidative stress may, on their own, increase the risk for schizophrenia, or they may exert their effects via obstetric complications and increased risk of prenatal infection (Fig. 1). We first appraise the evidence supporting the involvement of these factors, after which we present an overview of putative mechanisms that seem to



**Fig. 1:** Pathophysiology of gestational diabetes and schizophrenia in the offspring.

mediate the increased risk. Finally, we consider research strategies aimed at further exploring the link.

#### *Maternal DM in pregnancy and its consequences*

DM complicates up to 7% of pregnancies<sup>9</sup> and is the most common metabolic complication of gestation that increases maternal and neonatal morbidity.<sup>10</sup> DM occurring during the prenatal period is classified into 2 types: gestational DM (GDM) and pregestational DM (PGDM).<sup>11</sup> GDM accounts for 90% of all cases of maternal DM in pregnancy and is diagnosed when impaired glucose tolerance is first detected during pregnancy. Of the remaining cases, 60% have a diagnosis of type 2 DM before pregnancy, while 40% have preexisting type 1 DM.<sup>9</sup> Unlike PGDM, GDM develops less frequently before the third trimester, so the fetus is able to pass through organogenesis free of hyperglycemia,<sup>11</sup> resulting in lower rates of mortality<sup>12</sup> and major birth defects.<sup>13</sup>

The effects of maternal hyperglycemia on fetal development are varied and determined by the severity and the time of onset of DM. Because insulin from the mother does not cross the placenta, the fetus' pancreatic insulin output is solely determined by the glucose levels in the maternal blood.<sup>14</sup> High maternal serum glucose stimulates increases in fetal insulin output resulting in elevated rates of macrosomia,<sup>15</sup> the most common complication of GDM. Macrosomia increases the risk of obstetric complications including trauma, cesarean section<sup>15,16</sup> and perinatal asphyxia.<sup>17</sup> The complications of PGDM, on the other hand, are more common and severe than those of GDM<sup>18</sup> because periconceptional hyperglycemia is teratogenic and can lead to congenital malformations and miscarriage.<sup>19</sup> The risk of congenital malformations in GDM does not differ from that in nondiabetic women (about 2%<sup>17</sup>); however, 5.9% and 4.4% of children born to type 1 and type 2 PGDM mothers, respectively, are adversely affected.<sup>20</sup> The human brain is particularly vulnerable to the effects of hyperglycemia, and the relative risk of central nervous system malformations is 15.5 times higher in diabetic than in normal pregnancies.<sup>21</sup>

### **Maternal DM and schizophrenia in the offspring: a review of the evidence**

A review of the neurodevelopmental hypothesis of schizophrenia on one hand and of the adverse neurodevelopmental consequences of maternal DM on the other provides a compelling argument for considering maternal DM as a risk factor for schizophrenia in the offspring. However, this theoretical plausibility needs to be substantiated by empirical evidence, which is relatively scant at the present time, although there are some significant leads. The epidemiologic, clinical and animal studies are reviewed first to compile data relevant to the current discussion.

#### *Maternal DM and schizophrenia: the epidemiologic link*

An impressive number of studies have accrued on the relation between complications during pregnancy and birth and

the later development of schizophrenia, but few have focused on the contribution of DM in pregnancy. Cannon and colleagues<sup>21</sup> summarized the existing data in their meta-analytic synthesis of the 2 prospective, population-based studies done on this topic. They derived an odds ratio of 7.76 (1.37–43.9;  $p < 0.03$ ) for DM in pregnancy on subsequent risk for schizophrenia in offspring.<sup>22</sup>

A review of the remaining studies on pregnancy and birth complications and their relation to schizophrenia in offspring revealed that none reported data on maternal DM. This puzzling finding is likely to have been attributable to a simple methodological oversight. Studies that examined the link between obstetric complications and schizophrenia often employed either Lewis<sup>23</sup> or Parnas<sup>24</sup> obstetric complications scales, but neither scale contains questions on maternal DM. Moreover, several studies considered obstetric complications as a single variable and failed to report data on specific complications such as maternal DM.

It remains unclear at the present time whether diabetic pregnancy increases the risk for schizophrenia in particular or whether it is a nonspecific risk factor for a neurodevelopmental spectrum of psychiatric disorders. Some evidence suggests that the offspring of children born to mothers with DM have an increased risk for developing attention-deficit hyperactivity disorder,<sup>25–28</sup> although the findings have been inconsistent.<sup>29</sup> In summary, review of the literature suggests that little is known about the relation between diabetic pregnancy and psychiatric illnesses other than schizophrenia.

Epidemiologic studies are instrumental in raising questions, but they are often not equipped to provide conclusive answers. Therefore, we gathered and summarized supporting evidence from clinical populations and animal research studies to examine the plausibility of the association.

#### *Diabetic pregnancy and neurodevelopmental sequelae: human studies*

Studies indicate that brain development is not simply confined to the phase of organogenesis and that the cerebral cortex undergoes changes into the postnatal period<sup>30</sup>; hence, both GDM and PGDM can affect fetal neurodevelopment. Despite the high prevalence of DM, surprisingly little is known about its effects on central nervous system development and the behavioural sequelae of diabetic pregnancy. It has been noted that children born to diabetic mothers exhibit neurodevelopmental abnormalities that include impairments in motor functioning, attention span, activity level and learning ability, some of which are known risk factors in children who later develop schizophrenia.<sup>31–33</sup> Some progeny of PGDM also have impaired intellectual function in childhood.<sup>34</sup> Numerous studies have demonstrated that poor performance or delay in attaining developmental milestones is associated with a higher risk of having schizophrenia later in life, and it is also well known that, on average, patients with schizophrenia have a lower IQ than the general population.<sup>35</sup> Whether the developmental alterations seen in the offspring of diabetic mothers represent risk factors for schizophrenia or are representative of a schizophrenia diathesis is not known.

*Diabetic pregnancy and neurodevelopmental aberrations: animal data*

Observations of the offspring of diabetic animals have also revealed a range of behavioural, neurochemical and cellular/molecular abnormalities that are relevant to the present discussion. Laboratory animals subjected to streptozotocin-induced diabetic pregnancy demonstrated anxiety in challenging situations, including the elevated plus-maze and a social interaction test, and also manifested hyperactivity in the open-field behaviour test.<sup>36</sup> Female, but not male, rats born to diabetic mothers have problems with long-term learning and memory as assessed by the Lashley III maze and an inhibitory avoidance task, and it has been suggested that the hyperactivity noted in such offspring is specific to males. Although there are significant limitations in generalizing these findings to humans, it is well established that a significant proportion of humans who go on to develop schizophreniform spectrum disorders experience clinically significant difficulties with anxiety and hyperactivity as children.<sup>37</sup> Moreover, although cognitively heterogeneous, it is well known that a significant proportion of adults with schizophrenia also have difficulties with learning and memory.<sup>38</sup> Although there are similarities in the behavioural manifestations in the offspring of diabetic animal models and in persons who later develop schizophrenia, the specificity and generalizability of these findings is not known, and the relevance of sex-specific behavioural sequelae to schizophrenia also eludes explanation.

Rats born to mothers who had DM during pregnancy manifest increased levels of DA and norepinephrine (NE) in the hypothalamus,<sup>39</sup> increased DA, NE and serotonin (5-HT) in the midbrain-diencephalon junction and caudate nuclei<sup>40</sup> and decreased brain weight.<sup>41,42</sup> Hyperglycemia has been shown to lead to swelling of the mitochondria of neural tubes in rats.<sup>43</sup> The increase in cell process volume occurs at the expense of angiogenesis and results in premature specialization and formation of neural cell processes before neural tube closure.<sup>44</sup> Alterations in mitochondrial morphology<sup>45</sup> and number<sup>46</sup> have also been reported in the brains of adults with schizophrenia, and cluster analysis of transcriptional alterations in postmortem samples has indicated that genes related to energy metabolism and oxidative stress differentiated almost 90% of schizophrenia patients from control participants, suggesting a high degree of specificity for mitochondrial pathology in schizophrenia.<sup>47</sup> Cytochrome-*c* oxidase, a key enzyme in the mitochondrial electron transport chain, manifests altered activity in the hippocampi of rats that have iron deficiency in their brains, a known consequence of prenatal hyperglycemia.<sup>48</sup> Decreased activity of cytochrome-*c* oxidase has also been found in the frontal cortex and caudate nucleus in persons with schizophrenia.<sup>49</sup>

There is as yet no clear mechanistic explanation of how mitochondrial alterations might lead to schizophrenia; however, it has been hypothesized that dysfunction of brain energy metabolism leading to impairments in fronto-striatal-thalamic circuitry, increases in oxidative stress and/or abnormal intracellular calcium regulation mediate the relation.

**Diabetes in pregnancy and increased risk of schizophrenia: putative mechanisms**

The mechanisms by which DM during pregnancy increases schizophrenia risk are likely to involve an interaction between the diabetic intrauterine environment that is triggered by maternal hyperglycemia and the fetus' prevailing genetic vulnerability.<sup>50,51</sup>

*Pathophysiology of diabetic pregnancy: the environmental hits*

Several biological alterations that are known to occur in maternal DM and to affect fetal neurodevelopment could explain how DM during pregnancy might predispose offspring to schizophrenia. In keeping with a neurodevelopmental diathesis, these alterations result in changes in neurotransmitter systems and membrane and neuronal integrity that have also been implicated in the development of schizophrenia. The most obvious mechanism by which this predisposition might be mediated is hyperglycemia. A defining characteristic of DM, it is known to affect neurodevelopment and to induce immune activation, oxidative stress, hyperinsulinemia, chronic tissue hypoxia and decreased iron levels in the fetus.

**Hyperinsulinemia, hypoxia and iron deficiency**

Fetal hypoxia has often been implicated as a "final common pathway" by which obstetric complications increase future schizophrenia risk.<sup>52</sup> Hyperglycemia present during pregnancy is thought to induce a chronic intrauterine tissue hypoxia in the fetus<sup>53</sup> that is likely triggered by the chronic fetal hyperinsulinemia that develops in response to maternal hyperglycemia.<sup>54</sup> Elevated insulin levels increase oxygen consumption and metabolism in the fetus, and chronic hypoxia results because the placenta is unable to upregulate the delivery of oxygen to meet this demand.<sup>55,56</sup> Hypoxia affects neurodevelopment in several ways ranging from alterations in myelination<sup>57</sup> and cortical connectivity<sup>58</sup> to excitotoxicity and cell death<sup>59</sup> and is relevant to the etiology of schizophrenia.

In the presence of hypoxia, excess erythropoietin and hemoglobin are produced as the fetus attempts to maintain oxygen delivery to tissues.<sup>60</sup> In this state, the fetus' need for iron exceeds its supply, leading to its mobilization from vital tissues such as the brain.<sup>61,62</sup> Human fetuses born to diabetic mothers possess brain iron content that is only 40% of normal.<sup>63</sup> Iron also plays a vital role in neuronal replication,<sup>64</sup> myelin formation<sup>65</sup> and neurotransmitter synthesis, especially DA.<sup>66</sup> In animal models, iron deficiency appears to affect developing brain monoaminergic systems<sup>67</sup> and results in persistent changes in behaviour despite normalization of monoamine and iron parameters postnatally.<sup>68</sup> Moreover, iron deficiency negatively affects cortical development and function, although the regions and extent of changes resulting from this depend on the period in which it is present.<sup>69</sup>

Lozoff<sup>69</sup> has reviewed the effects of altered brain iron on neurodevelopment in humans. Fetal iron deficiency is known to manifest as higher levels of irritability<sup>70</sup> and increased negative emotionality<sup>71</sup> in infants and is predictive of behav-

ioral and developmental problems at age 5.<sup>72</sup> The study also suggests that iron deficiency results in changes in the structure and function of the hippocampus that include alterations in auditory processing and discrimination.<sup>73,74</sup> There are similarities in the auditory processing difficulties seen in infants born to diabetic mothers and those observed in persons with schizophrenia.<sup>75</sup> Changes in myelination and frontotemporal circuitry and lesions in the hippocampi of neonatal rats also result in molecular and behavioural changes similar to those seen in schizophrenia.<sup>76</sup> It is therefore conceivable that brain iron deficiency secondary to DM in pregnancy could alter frontotemporal circuitry, contributing or predisposing offspring to later emergence of schizophrenia.

Elevated insulin levels also reduced amino acid levels in animal fetuses, including concentrations of the nonprotein amino acid taurine, which is known to be involved in fetal brain development.<sup>77</sup> The specificity of this finding and whether this state persists into adult life are not known, although it is interesting to note that taurine levels also appear to be diminished in the cerebrospinal fluid (CSF) of drug-naïve adults with schizophrenia.<sup>78</sup>

#### Diabetes in pregnancy: a proinflammatory milieu

It has been suggested that hyperglycemia is causally related to immune activation in DM<sup>79</sup> and that the chronic fetal hypoxia present in maternal DM may also increase the inflammatory burden incurred by the fetus.<sup>80</sup> Moreover, cytokines, including interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF- $\alpha$ ), are elevated in infants exposed to asphyxia and hypoxic-ischemic encephalopathy<sup>81,82</sup> and have been implicated in neuronal damage after such perinatal insults.<sup>83,84</sup> Proinflammatory cytokines such as TNF- $\alpha$  cross the placenta and are elevated in maternal tissues,<sup>85-87</sup> including the uteri of pregnant diabetic mice.<sup>88</sup> An increase in cytokine release at the fetomaternal interface is vital to tissue remodelling before fetal implantation in mice, and if these signals are excessive or improperly timed, such alterations can result in dysregulation of organogenesis and termination of the pregnancy.

Inflammatory cytokines affect neuronal development as well as the metabolism of neurotransmitters.<sup>89-91</sup> That prenatal infection with various organisms can increase schizophrenia risk has led some to speculate that the effect is mediated by the proinflammatory cytokines accompanying infection.<sup>92,93</sup> Of relevance to schizophrenia, as Gilmore and Murray<sup>94</sup> point out, these mediators of inflammation decrease the survival of hippocampal<sup>95</sup> and cortical neurons<sup>96</sup> in culture and reduce the dendritic complexity of developing cortical neurons.<sup>97</sup> Neuroanatomical alterations associated with prenatal infection with influenza included increased cortical pyramidal cell density<sup>98</sup> and altered cortical generation<sup>99</sup> in mice. Cytokines also reduced the survival of DA and 5-HT neurons<sup>100,101</sup> in animal models. Few human data exist on the neurobehavioural effects of inflammatory prenatal environments, although maternal IL-8 levels in the second trimester were noted to be nearly twice as high in children who later developed schizophrenia, compared with control participants.<sup>102</sup> Levels of TNF- $\alpha$  in the mother during pregnancy have also been found

to correlate with the development of psychotic disorders later in life.<sup>103</sup> Some have even suggested that the dopaminergic abnormalities and the structural<sup>104,105</sup> and functional<sup>106,107</sup> brain changes seen in schizophrenia are due to alterations in cytokine systems.<sup>108,109</sup> Although the precise mechanisms by which these mediators specifically increase the risk of schizophrenia are not known, TNF- $\alpha$  could affect schizophrenia risk via its toxic effects on oligodendrocytes<sup>92</sup> or by stimulating microglia to release IL-2, which is known to affect dopaminergic activity,<sup>93</sup> potentially inducing dysregulation of this system early in life.

Studies in clinical populations suggest that serum or CSF IL-1, IL-6 and TNF- $\alpha$  levels are elevated in those with schizophrenia.<sup>110-115</sup> It has been hypothesized that these alterations are due to pre- or postnatal infectious processes; however, in light of the above evidence, it is possible that these could be secondary to maternal DM exposure. Indeed, some limited data suggest that immune alterations occurring prenatally may persist into postnatal life,<sup>116,117</sup> although these alterations may be state dependent rather than stable and persistent. Given that inflammatory cytokines are increased in diabetic pregnancy and have been implicated in the pathogenesis of schizophrenia, such alterations may be relevant to increased schizophrenia risk seen in infants of diabetic mothers.

#### Diabetes in pregnancy and oxidative stress

Oxidative stress, a state in which oxygen free radicals exceed the body's natural antioxidant defenses, has been implicated in the pathogenesis of GDM, type 2 DM<sup>118</sup> and schizophrenia<sup>119</sup> and may contribute to the increased risk of schizophrenia seen in the offspring of diabetic pregnancies. Hyperglycemia causes the depletion of antioxidants and the generation of reactive oxygen species.<sup>120</sup> Recent studies have demonstrated the presence of increased oxidative stress in women with PGDM and GDM; samples taken from the cord blood of these mothers' infants indicate that this milieu is also shared with the fetus.<sup>121-124</sup>

In animal models, oxyradicals also play a vital role in the timing and progression of neuronal development, differentiation<sup>125</sup> and synaptic plasticity<sup>126</sup>; changes in the balance of these signals can result in alterations in vital neurodevelopmental processes. Moreover, the brain is particularly susceptible to oxidative damage, owing to its high oxygen consumption and poor antioxidant defenses.<sup>127</sup> Free radicals can cause oxidation of lipids,<sup>128</sup> proteins<sup>129</sup> and DNA,<sup>130</sup> inactivating the biological functions of these molecules and potentially leading to cell death.

Oxidative stress experienced early in life might contribute to the pathogenesis of schizophrenia through an attenuation of the brain GABA receptor function<sup>131,132</sup> and reduced synaptic efficiency and action potential generation in hippocampal pyramidal cells,<sup>133</sup> and also via the inhibition of dopamine  $\beta$ -hydroxylase.<sup>134</sup> Given the effects dysmyelination has on neuronal connectivity and its relevance to the pathophysiology of schizophrenia,<sup>135</sup> oxidative stress may specifically increase the risk of schizophrenia via its toxic effects on oligodendrocyte precursors.<sup>136</sup>

Although adults with schizophrenia also manifest alterations in their antioxidant systems, it is not clear whether these are the result of exposure to a state of oxidative stress in utero. According to Yao and colleagues,<sup>119</sup> replicated findings in schizophrenia patients include decreased levels of nonenzymatic antioxidants in peripheral tissues and CSF and increased superoxide dismutase activity. These alterations reflect increased oxidative stress and have been noted in persons ranging from drug-naïve to chronically medicated patients with schizophrenia.

Arachidonic acid (AA) and docosahexaenoic acid (DHA) are fatty acids that are known to play an integral role in the development and maintenance of normal brain and behaviour, and alterations in these and oxyradicals in general may predispose offspring to adverse neurobehavioural outcomes.<sup>137</sup> Arachidonic acid and DHA are essential to the formation of cellular plasma membranes, but when subjected to oxidative stress, they form peroxyradicals and lipid peroxide intermediates, which leads to changes in the fluidity, stability and permeability of these barriers.<sup>131</sup>

Moreover, decreased levels of the polyunsaturated fatty acids AA and DHA are found in peripheral tissues in both mothers with GDM<sup>138,139</sup> and their infants<sup>140,141</sup> and may possibly be due to oxidative damage. Of relevance to the pathophysiology of schizophrenia, lipid peroxidation by free radicals is correlated with altered synaptic transmission, increased DA and decreased GABA uptake by synaptosomes,<sup>126</sup> with decreased prostaglandin synthesis<sup>142</sup> and with changes in the polyunsaturated fatty acids content of cell membranes.<sup>143-146</sup> AA also acts as a second messenger, mediating the effects of neurotransmitters and neurotrophic factors, systems that are integral to neuronal growth, differentiation and survival.<sup>147</sup>

Regardless, it is intriguing that several studies have demonstrated that persons with schizophrenia, like diabetic mothers and their offspring, have decreased levels of AA and DHA in their central and peripheral tissues.<sup>148</sup> Thus it is possible that exposure to DM in prenatal life alters the structure and function of plasma membranes and neurotransmitter systems in such a way that they predispose persons to both DM and schizophrenia. This biochemical alteration may therefore represent an important causative link between the 2 conditions.

#### *Diabetic pregnancy, birth complications and schizophrenia*

The consequences of hyperglycemia are neurodevelopmental as well as somatic. The 3 "groups" of obstetric complications that have been postulated to increase schizophrenia risk include fetal growth retardation, fetal perinatal hypoxia and prenatal complications,<sup>149</sup> and all 3 can be accounted for by maternal DM.

Growth restriction in utero is a risk factor for schizophrenia<sup>150</sup> and is seen in diabetic mothers with vasculopathy.<sup>151</sup> More recent data suggest that both macrosomia and low birth weight are associated with schizophrenia risk.<sup>152</sup> Diabetic mothers deliver more macrosomic offspring and are at higher risk for hypertension and preeclampsia, both of which are associated with fetal hypoxia.<sup>18</sup> The presence of DM in the pre-

natal period also increases the risk of infection.<sup>153</sup> Given that specific prenatal infections are known to increase the risk of schizophrenia in offspring,<sup>154</sup> it is plausible that DM contributes to schizophrenia risk through this mechanism as well.

#### *The final common pathway*

The risk of schizophrenia in the offspring born to diabetic mothers appears to be triggered by hyperglycemia and is mediated by hypoxia, inflammation and oxidative stress (Fig. 1), but it may also contribute to or act in concert with obstetric complications and perinatal infection. These environmental stresses might exert their effects via proinflammatory cytokines, which could initiate various molecular stress cascades and thus serve as a final common pathway to affect fetal brain development and increase risk for schizophrenia. These prenatal environmental conditions could act independently of or in concert with fetal genes to accentuate the schizophrenia diathesis.

#### **Scope and limitations of the hypothesis**

It is important to note that data supporting a relation between DM in pregnancy and schizophrenia risk are rather tenuous and are provided by only 2 epidemiologic studies. As many as 7% of women suffer from DM during pregnancy, and one-third of the general population have obstetric complications,<sup>14</sup> yet relatively few bear children who develop schizophrenia. Neither complications during pregnancy nor complications during delivery are necessary or sufficient causal factors for schizophrenia.<sup>149</sup>

Both schizophrenia and DM are diseases of adulthood with origins possibly outlined at birth. Considering the similarities in their etiopathology and natural history and the increased prevalence of the comorbidity in people with schizophrenia, it is conceivable that the 2 disorders share common genetic elements. In fact, some data suggest that schizophrenia and type 2 DM share common susceptibility genes.<sup>50,51</sup> In particular, 2 genetic loci that have been associated with schizophrenia (2p22.1-p13.2 and 6q21-q24.1) have also been implicated in linkage studies of patients with type 2 DM. Thus the relation observed to exist between DM in pregnancy and schizophrenia in the offspring might also be accounted for, or contributed to, by the fetus' genetic endowment.

The presence of other confounding variables also raises questions about the specificity of this relation. For example, reduced maternal access to food has been identified as a risk factor for schizophrenia<sup>155,156</sup> as well as DM later in life.<sup>157</sup> It may be that schizophrenia and type 2 DM share certain "thrifty" genes or alleles that increase the likelihood of survival in the face of adversity in utero but that put the child at risk for adverse consequences later in life. Further, children of low birth weight, whether or not they were exposed to famine while developing in the womb, appear to be at increased risk for both the conditions.<sup>158,159</sup> Increased body mass index in one's mother, a risk factor for maternal DM, also appears to confer greater subsequent risk of schizophrenia in the offspring.<sup>160,161</sup>

## Future research directions

More direct evidence is needed to substantiate the putative link between gestational DM and schizophrenia and to determine the mechanisms by which maternal DM increases the risk of schizophrenia in offspring. This may include analyses of large population-based birth cohorts and scrutiny of data from high-risk obstetrics clinics. Examining maternal sera for interactions of biological markers of risk, including indices of inflammation and oxidative stress, and the genes that might contribute to this process, could offer further insights into the sequelae of gestational DM. Studies using laboratory animals could strengthen the theory by elucidating the molecular mechanisms, especially the timing of various critical processes.

## Conclusion

Epidemiologic evidence suggests that the offspring of mothers who have DM during pregnancy are at an increased risk for developing schizophrenia in adulthood. The affected children demonstrate behavioural changes, psychomotor impairments, and biochemical and anatomic changes similar to those seen in persons who are at risk for developing schizophrenia, suggesting that the relation is plausible and that it may be specific. A cascade of events triggered by maternal hyperglycemia and mediated by hypoxia, oxidative stress, infection and inflammation leads to various cytoarchitectural and neurochemical aberrations, constituting putative pathophysiological mechanisms underlying the link between diabetic pregnancy and increased risk of schizophrenia.

The current worldwide epidemic of obesity and DM, especially among younger women in their reproductive years, has significant public health implications should the hypothesis that maternal DM in pregnancy is responsible for at least a small proportion of cases of schizophrenia. Exploring this link is critical for understanding the pathophysiology of schizophrenia and may also offer clues toward prevention and effective treatment of both these disorders.

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**Contributors:** Both authors designed this review, acquired and analyzed the data, wrote and reviewed the article and gave final approval for its publication.

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## JPN's top 10 Articles, July 2008 (based on Web views on PubMed Central)

- 1. Long-term lithium treatment and thyroid antibodies: a controlled study**  
Baethge et al.  
*J Psychiatry Neurosci* 2005;30(6):423-27
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