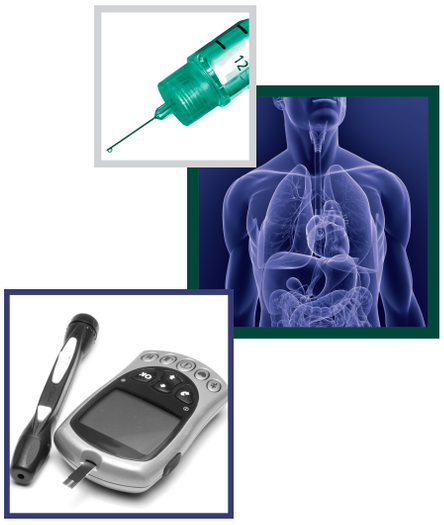
REVIEW



Neurocognitive outcome of children exposed to severe hypoglycemia *in utero*

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Practice Points

- While optimizing blood glucose control during pregnancy, management strategies should also aim to avoid severe hypoglycemia.
- Children born to mothers with Type 1 diabetes, who were exposed to severe hypoglycemia *in utero*, may need to be monitored for neurocognitive deficits and provided with early intervention when appropriate.
- Expecting mothers with Type 1 diabetes should be screened early, ideally in preconception, for risk factors for severe hypoglycemia as these mothers may benefit from closer monitoring to help prevent severe hypoglycemia during pregnancy.

SUMMARY Severe hypoglycemia (lost of consciousness or convulsion) has been reported in up to 40% of pregnancies complicated by Type 1 diabetes and in up to 22% of cases there is more than one episode reported during pregnancy. This article reviews relevant literature and explores the potential impact of severe hypoglycemia during pregnancy on the neurocognitive development of children. As no human research has specifically examined this issue, we will first review research that has used animal models followed by a review of studies that have investigated the impact of maternal diabetes on the neurocognitive outcome of the offspring. Research on the impact of severe hypoglycemia on young children's neurocognitive outcomes will also be examined. Finally, the direction and need for further research in this field will be discussed.

Type 1 diabetes complicates five out of 1000 pregnancies [1]. In the last few decades, advances have been made in the understanding of the pathophysiologic changes that take place during pregnancies complicated by diabetes. Better glucose control in preconception and during pregnancy has improved the outcome for mothers and their offspring. However, these pregnancies are still at higher risk than routine pregnancies and the complex metabolic changes that take place in the mother pose potential long-term risks to her offspring.

It has long been recognized that maternal diabetes can affect the development of the fetal nervous system, with the result being poorer neurocognitive outcomes in the offspring relative to children of nondiabetic mothers [2–7]. Chronic fetal hypoxia, fetal iron deficiencies and hyper- and hypo-glycemia are all a function of the lack of adequate maternal glycemic control during pregnancy and pose potential risks to the developing brain [8]. Therefore, maintaining tight metabolic control is recommended to decrease maternal and fetal complications and mortality [9].

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Severe hypoglycemia (inability to self-treat with or without loss of consciousness or seizures) is one of the most frequent side effects of intensified diabetes management [10]. It has been reported in up to 45% of pregnancies complicated by Type 1 diabetes [11–16] and in up to 31% of cases, more than one episode has been reported during pregnancy. These rates have been remarkably stable over the last 30 years despite changes in management approaches, including improved education of patients, new insulin analogs and new technologies. This may be partly due to the tighter metabolic targets aimed at during pregnancy. The Diabetes Control and Complication Trial (DCCT) [10] defines hypoglycemia as 'an episode, in which the patient requires the assistance of another person and which is associated either with a blood glucose level less than 2.8 mmol/l, or prompt recovery after oral carbohydrate or glucagon or intravenous glucose'. Using this definition, Rosenn *et al.* found that 67% of pregnant women with Type 1 diabetes had such an episode [11]. They also noted that 79% of women had at least one blood glucose monitoring value of less than 1.9 mmol/l. Studies have also shown that most episodes of severe hypoglycemia occur in the first half of the pregnancy [11,13–16], the most critical time for organogenesis.

Evidence suggests that acute and chronic hypoglycemia leads to neurological dysfunction [17] and that children exposed to hypoglycemia can develop impairments in cognitive function [18–22] and are at increased risk for epilepsy [23]. Although it has been suggested that the developing brain is less vulnerable to hypoglycemic injury than the mature brain, evidence from animal studies and clinical evidence suggests that the developing nervous system is sensitive to the adverse effects of hypoglycemia [17]. The primary goal of this article is to review the animal and human literature on the adverse effects of severe hypoglycemia in mothers on outcomes of offspring, in particular neurocognitive outcomes. In addition, as the focus of this article is on the effects of severe hypoglycemia on the developing brain, relevant research on the impact of severe hypoglycemia on children's neurocognitive outcomes will also be discussed.

Birth defects

Animal studies

In rodents, the negative impact of maternal hypoglycemia on fetal development is convincing [24–28]. It has been associated with growth retardation [25,26], skeletal [27], and cardiac malformations, and altered function [28] depending upon the timing of the hypoglycemic episode during gestation. *In vitro* experiments in mouse embryos have found that younger embryos (gastrulation vs neurulation phase) were more sensitive to short-term hypoglycemic exposure [25]. These experiments also found that short-term hypoglycemic exposure led to dysmorphogenesis, while longer and more severe exposure was required to also induce growth retardation. Hypoglycemia has also been shown to affect brain development, in particular the hippocampus, a structure that plays a significant role in recognition memory, in the perinatal rat pup [29]. A study of 7-day-old postnatal rat pups subjected to hypoglycemia, either induced by insulin or by 12 h of fasting, found that the acute onset of insulin-induced hypoglycemia did not allow for protective adaptive processes, such as use of ketone bodies as a source of alternative fuel, and as a result did not provide the protective effect for perinatal hypoxic-ischemic brain damage that is observed in adults [30].

Human studies

In humans, the link between hypoglycemia and birth defects was initially suggested by studies of women affected by psychiatric disorders treated with repeated insulin shock therapy in the first trimester of pregnancy. The report by Impastato *et al.* found that six out of 19 infants born to mothers who received this therapy early during pregnancy had congenital anomalies [31]. Of the mothers of these six babies, five had received 5 h of therapy before week 10 of gestation. Studies in women with diabetes have shown a significant decrease in rates of congenital abnormalities with improved metabolic control in the preconception and pregnancy period [32–35]. Despite this improvement, the most recent large-scale study using the National Birth Defect Prevention Study cohort (birth registered between 1997 and 2003: 4895 control subjects and 13,030 infants born to mother with diabetes) still identified an overall odds ratio of 3.17 for a single defect and 8.6 for multiple defects in infants born to mothers with diabetes compared with infants of nondiabetic mothers [36]. These findings suggest there may be an increased risk of congenital abnormality induced by severe hypoglycemia that has not been recognized. The lack of any definitive evidence regarding this association may be because: first, the impact of severe hypoglycemia has not

been specifically investigated and; second, the size of the samples in previous studies were not large enough to pick up the small increase in congenital anomalies in infants born to mothers with hypoglycemia compared with infants born to nondiabetic mothers.

Neurocognitive outcome

■ Animal studies

Although animal models could be used to examine the impact of intrauterine exposure to hypoglycemia on the cognitive function of animal offspring, no such studies were identified through a PubMed search or review of the research literature.

■ Human studies

In utero exposure to severe hypoglycemia

For obvious ethical reasons, research that directly examines the effect of severe maternal hypoglycemia on the human fetus is not feasible. However, a few small studies have observed the fetuses of mothers with Type 1 diabetes during induced mild maternal hypoglycemia in the third trimester of pregnancy [37–39]. They reported an increase in fetal limb and body movement and fetal heart rate accelerations that did not reach statistical significance, and stable fetal heart rate and breathing movements during mild maternal hypoglycemia.

In humans, the specific impact of severe hypoglycemia during pregnancy on the cognitive development of the offspring has not been examined. A number of studies have investigated the neurocognitive development of children of pregnancies complicated by diabetes (Table 1); however, none has specifically examined the effect of severe hypoglycemia on neurocognitive outcome. For example, Sells *et al.* investigated the neurodevelopmental consequences of maternal Type 1 diabetes in 109 infants and found that if the diabetes was well controlled, beginning in the first trimester, the intellectual and language functioning of the offspring through to 3 years of age was normal [4]. However, when diabetes was less well controlled, language development of children at 3 years of age was depressed relative to the offspring of well-controlled mothers and mothers without diabetes. The Rizzo *et al.* study is the only one that reported on the effect of hypoglycemia during pregnancy on cognitive functioning of the offspring [3]. They used a hypoglycemic index that was composed of the weekly frequency of symptomatic hypoglycemia and blood glucose readings less than 2.8 mmol/l in the second and third trimester. This index was correlated with the children's scores on assessments of mental development at 2 years of age, and assessments of intelligence at 3–5 years of age. Their sample included 89 children of women with pregestational diabetes, 99 children of women with gestational diabetes and 35 children of women without diabetes. No relationship was found between hypoglycemia and cognitive function. However, they did not differentiate between women with Type 1 diabetes and Type 2 diabetes, nor did they specifically examine the impact of severe hypoglycemia.

Preliminary results of our ongoing longitudinal study (follow-up to 7 years of age), which is investigating the long-term impact of severe hypoglycemia during pregnancy on the offspring, were presented at the Canadian Diabetes Association Annual Meeting in 2008 [40]. At 18 months of age, children were assessed on the Bayley Scales of Infant Development – Second Edition. This test consists of three scales, the Mental Scale, the Motor Scale and the Behavior Rating Scale. Of the 79 children assessed, 11 were born to mothers with Type 1 diabetes who experienced at least one episode of hypoglycemia during pregnancy, 16 were born to mothers with Type 1 diabetes without severe hypoglycemia during pregnancy and 52 to healthy mothers without diabetes. Results indicated that children born to mothers with Type 1 diabetes who experienced at least one episode of severe hypoglycemia during pregnancy had significantly lower scores on the Mental Development Index and the Behavior Rating Scales of the Bayley Scales compared with children of healthy mothers without diabetes.

■ Postnatal exposure to severe hypoglycemia

The impact of hypoglycemia on developing brain structures and functions during the fetal and neonatal periods, and early childhood is of increasing interest and there continues to be debate about the long-term neurocognitive consequences. Since no published studies have specifically examined the impact of severe maternal hypoglycemia on the neurocognitive outcomes of offspring, it is pertinent to review two other situations involving hypoglycemia that could have significant effects on the developing brain: neonatal hypoglycemia and severe hypoglycemia in children with diabetes.

Table 1. Effect of *in utero* exposure to diabetes on neurocognitive outcome of children.

Study (year)	Number of subjects	Type of diabetes	Mentions SH?	Tools	Results	Ref.
DeBoer *et al.* (2005)	13 CMD; 16 controls	Gestational or pregestational diabetes	No	Elicited/deferred imitation paradigm at 1 year of age; Bayley Scales of Infant Development	Deferred imitation performance significantly poorer in CMD compared with controls; CMD had slightly lower MDI scores on the Bayley than controls	[78]
de Regnier *et al.* (2007)	45 CMD: 14 high risk (birthweights >2SD above the mean or with ferritin level less than 35 ng/dl, 31 low risk; 70 controls	Gestational or pregestational diabetes	No	Auditory, visual and crossmodal recognition memory assessed using ERP recordings in the newborn period, at 6 and 8 months, respectively	High-risk CMD showed differences in the development of the temporal slow wave, which is associated with memory, compared with low-risk CMD and controls	[79]
Hod *et al.* (1999)	31 CMD; 41 controls	21 with Type 1 diabetes, 10 with Type 2 diabetes	No	MDI, PDI and orientation/ engagement on the Bayley Scales of Infant Development-II at 1 year	CMD obtained significantly lower scores on all aspects of development – mental, psychomotor and orientation/engagement – compared with controls	[2]
Nelson *et al.* (2000)	26 CMD; 34 controls	26 with diabetes mellitus	No	Visual recognition memory assessed using ERP recordings and behavioral (looking time) measures at 6 months; the Bayley Scales of Infant Development-II were administered at 12 months	ERP measures showed evidence consistent with memory deficits in the CMD; looking time measures and the Bayley MDIs failed to distinguish between the groups	[80]
Nelson *et al.* (2003)	11 CMD; 16 controls	7 gestational diabetes, 4 pregestational diabetes	No	Crossmodal (tactile to vision) recognition memory was evaluated using ERPs at 8 months of age; tested behaviorally on ability to recognize and discriminate faces at 8 months; The Bayley Scales of Infant Development were administered at 12 months of age	ERPs indicated that CMDs did not show any evidence of recognition of the palpated object on crossmodal tasks, whereas controls showed evidence of crossmodal recognition; neither CMD nor controls showed behavioral evidence of visual recognition memory; controls had slightly higher MDI scores than CMDs	[81]
Ornoy *et al.* (1998)	57 CMD; 57 controls	48 with Type 1 or Type 2 diabetes (Note: the 57 CMD children were born to these mothers)	No	Touwen-Prechtl neurological examination; Pollack tapper test, Wechsler Intelligence Scale for Children – Revised; Bruininks-Oseretsky Motor Development Test; Southern California Integration Test; The Connors Abbreviated Parent Teacher Questionnaire	No group difference between the CMD group and controls on measures of intelligence and sensory motor functions; the CMD group performed less well than controls on measures of neurological function and hyperactivity and inattention	[6]

BOTMP:SF: Bruininks-Oseretsky Test of Motor Proficiency: Short Form; CMD: Children born to mothers with diabetes; ERP: Event-related potential; KTEA: Kaufman Test of Educational Achievement: Short Form; MDI: Mental Development Index; PDI: Psychomotor Development Index; SD: Standard deviation; SH: Severe hypoglycemia.

Table 1. Effect of *in utero* exposure to diabetes on neurocognitive outcome of children (cont.).

Study (year)	Number of subjects	Type of diabetes	Mentions SH?	Tools	Results	Ref.
Persson *et al.* (1984)	73 CMD; no controls	53 with Type 1 diabetes, 20 with gestational diabetes	No	IQ (Terman-Merril method) at 5 years of age	No relationship between maternal acetonuria and IQ	[73]
Ratzon *et al.* (2000)	57 CMD (note: the 57 CDM were born to these mothers); 57 controls	48 with Type 1 or Type 2 diabetes	No	Bruininks-Oseretsky Test of Motor Proficiency	CMD performed less well than controls on tests of fine and gross motor skills; significant negative correlation between motor performance and severity of hyperglycemia in CMD	[82]
Riggins *et al.* (2009)	20 CMD; 20 controls	15 with gestational diabetes, 3 with Type 1 diabetes 2 with Type 2 diabetes	No	Behavioral measures of memory; visual recognition memory assessed using ERPs	When memory demands were high, recall was significantly impaired in the CMD compared with controls; ERP results suggested that both encoding and retrieval processes were compromised	[7]
Rizzo *et al.* (1991)	188 CMD; 35 controls	89 with pregestational diabetes, 99 with gestational diabetes	Yes: hypoglycemia index derived from number of weekly symptomatic hypoglycemia and number of readings less than 2.8 mmol/l	MDI of the Bayley Scales of Infant Development at 2 years, average IQ score from the Stanford-Binet Intelligence Scale at 3, 4 and/or 5 years	Lower MDI and IQ correlated with higher levels of β-hydroxybutyrate in the third trimester; no association with A1C or hypoglycemia	[3]
Rizzo *et al.* (1995)	196 CMD; no controls	95 with pregestational diabetes, 101 with gestational diabetes	No	PDI of the Bayley Scales of Infant Development at 2 years, average standard score on the BOTMP:SF given at 6, 8 and/or 9 years	Increased A1C and β-hydroxybutyrate significantly associated with lower scores on 6–9 years assessments of motor functioning; weak correlation with 2-year assessment	[83]

BOTMP:SF: Bruininks-Oseretsky Test of Motor Proficiency: Short Form; CMD: Children born to mothers with diabetes; ERP: Event-related potential; KTEA: Kaufman Test of Educational Achievement: Short Form; MDI: Mental Development Index; PDI: Psychomotor Development Index; SD: Standard deviation; SH: Severe hypoglycemia.

Table 1. Effect of *in utero* exposure to diabetes on neurocognitive outcome of children (cont.).

Study (year)	Number of subjects	Type of diabetes	Mentions SH?	Tools	Results	Ref.
Rizzo *et al.* (1997)	139 CMD; no controls	75 with pregestational diabetes, 64 with gestational diabetes	No	Wechsler Intelligence Scale for Children – Revised, KTEA	Verbal, performance and full-scale IQ scores, and Bannatyne's indices of verbal conceptualization ability, acquired knowledge, spatial ability and sequencing ability, which were inversely correlated with measures of maternal lipid and glucose metabolism in the second and third trimesters; KTEA arithmetic scores were similarly correlated with measures of maternal lipids in the third trimester, all correlations indicate that poorer maternal metabolic regulation was associated with poorer child performance	[5]
Sells *et al.* (1994)	109 CMD (70 early entry, 21 days postconception; 39 late entry, after 21 days postconception); 90 controls	Insulin-dependent mothers	No	Stanford-Binet Intelligence Scale, Language measures (i.e., Peabody Picture Vocabulary Test, Vinelnad Communication subscale) and head circumference at 3 year	No differences in the Stanford Binet scales for the three groups; late entry CMD had poorer scores on language measures and smaller head circumference	[4]
Silverman *et al.* (1998)	139 CMD; number of controls unknown	Both Type 1 and 2, actual proportion not given	No	MDI and PDI of the Bayley Scales of Infant Development at 2 years, average score on the Stanford-Binet Intelligence scale at 3, 4 and/or 5 years, and average score on the Wechsler Intelligence Scale for Children – Revised administered between 7 and 11 years; average score on the BOTMP:SF at 6,8 and/or 9 years	Aberrant maternal metabolic control (A1C and β-hydroxybutyrate) was associated with poorer intellectual and psychomotor development at each age	[70]
Yamashita *et al.* (1996)	33 CMD; 34 controls	24 noninsulin-dependent, 6 insulin-dependent, 3 gestational diabetes	No	Tanaka-Binet intelligence scores at 3 years	Lower scores in CMD	[72]

BOTMP:SF: Bruininks-Oseretsky Test of Motor Proficiency: Short Form; CMD: Children born to mothers with diabetes; ERP: Event-related potential; KTEA: Kaufman Test of Educational Achievement: Short Form; MDI: Mental Development Index; PDI: Psychomotor Development Index; SD: Standard deviation; SH: Severe hypoglycemia.

Hypoglycemia is a common finding in newborns [101] and the risk is increased in premature and small-for-gestational-age infants, infants of mothers with insulin-dependent and gestational diabetes, and infants with hyperinsulinema [41–43]. Follow-up studies of hypoglycemic infants from these risk groups have shown that these infants are at risk for neurodevelopmental deficits. Two of the largest of these studies have found that moderate hypoglycemia was strongly associated with reduced neurodevelopmental scores at 1.5, 3.5 and 5 years of age [44,45]. Stenninger *et al.* reported that neonatal hypoglycemia was associated with brain dysfunction in attention, motor control and perception [46]. A recent study that investigated the effects of neonatal hypoglycemia on developmental outcomes in children with hyperinsulinism reported that one third of this group had some degree of developmental delay and that children presenting in the first week of life and those with medically unresponsive hyperinsulinism were more likely to demonstrate developmental delays [47].

Hypoglycemia also occurs in up to 14% of healthy-term newborns [48,49] and in 16% of large-for-gestational-age term newborns born to nondiabetic mothers [50]. It has been assumed that hypoglycemia in healthy-term infants is harmless and is not associated with impaired neurodevelopmental outcomes. This contention was supported by Brand and colleagues who found that transient hypoglycemia in healthy-term large-for-gestational-age newborns during the first day of life was not associated with poorer neurodevelopmental or behavioral outcomes at 4 years of age when compared with large for gestational age newborns without hypoglycemia [51]. By contrast, Burns *et al.* reported mild-to-severe neurologic impairment in 75% of infants who experienced at least one episode of neonatal hypoglycemia (i.e., blood or plasma glucose concentration of ≤2.6 mmol/l) [52]. These impairments included neurodevelopmental delays (26 out of 34), cognitive functioning below reference ranges (i.e., developmental quotient less than 85 [13 out of 34], motor impairments [9 out of 34] and white matter abnormalities on MRI at postnatal age of less than 6 weeks). However, no relationship was found between severity and duration of hypoglycemia and neurodevelopmental outcomes. In summary, the above research suggests that neonatal hypoglycemia is a risk factor for neuropsychological impairment, and that premature and term-born infants with transient symptomatic hypoglycemia are at greater risk of cognitive and motor impairment compared with infants without hypoglycemia.

In recent years, a number of studies have examined the specific role of severe hypoglycemia on neuropsychological functioning of children with Type 1 diabetes. Results have not always been consistent and the wide variation in neurocognitive skills addressed by the different studies makes it difficult to draw any conclusions regarding the pattern of existing cognitive deficits. Furthermore, it is hard to isolate the effects of hypoglycemia from the impact of duration of the disease or the role of hyperglycemia. The results of these studies suggest, however, that severe hypoglycemia has a negative impact on specific neuropsychological functions (i.e., spatial intelligence, verbal and spatial memory, verbal fluency, visuomotor and visuospatial skills and response speed). These abnormal findings have been linked with age at diagnosis, duration of diabetes, frequency of severe hypoglycemia and intensive therapy [18,20,53–57]. Researchers have found a link between hypoglycemia and lower verbal IQ, poorer performance on the select, focus and inhibition components of attention [18,58] and poorer results on delayed recall of verbal information [20,57,59] and spatial information [57]. Northam *et al.* [56] and Hershey *et al.* [20] have also reported a decrease in speed of processing. Ryan *et al.* noted that in adolescents in whom diabetes developed before 5 years of age, impairments were evident on a broad range of neuropsychological measures, including attention, memory, visuospatial abilities, eye–hand coordination, and mental and motor speed [22]. Furthermore, as a group, these adolescents achieved significantly lower scores on measures of intelligence. They suggested that these deficits could be due to mild brain damage that develops as a consequence of multiple episodes of serious hypoglycemia early in life. A recent study by Rankins *et al.* that examined neuropsychological functioning and neurometabolite profiles in three children with Type 1 diabetes after their first episode of severe hypoglycemia with seizures, found that acute hypoglycemia had transient effects of neuropsychological functioning [60]. In all cases, these children showed below-expected performance following the severe hypoglycemic event and significant improvement at follow-up 6 months later. Similarly, hypoglycemic seizures were also found to have transient effects on neurometabolite profiles. In the frontal lobe, *N*-acetyl

aspartate levels were reduced following the hypoglycemic seizure but returned to more normal levels 6 months later, whereas in the temporal lobe, trimethylamine levels were somewhat elevated after the seizure but returned to more normal levels by 6 months. It is important to note, however, that some studies have not found an association between severe hypoglycemia and poorer performance on neuropsychological measures [61,62]. Thus, although not completely conclusive, the literature suggests that severe hypoglycemia has a negative impact on brain development and neurocognitive functioning (specifically on memory, attention and speed of processing) in children with early onset of diabetes, and that deficits in neurocognitive abilities may become more evident as these children mature.

Possible mechanisms

During gestation and through a complex interplay of hormonal adaptations, maternal glucose metabolism changes to meet both maternal and fetal demands. On the maternal side, during the first trimester, insulin sensitivity is normal if not even higher than prior to pregnancy [63]. The maternal insulin resistance of the second and third trimester is probably a means to ensure increased availability of glucose to the fetus [64]. Glucose crosses the placenta through facilitated diffusion, (i.e., a combination of direct diffusion and active transport through glucose transporters). Fetal glucose concentrations are maintained at levels lower than maternal levels, creating a glucose gradient across the maternal–fetal barrier. Early in pregnancy, the transplacental glucose transport is mainly by direct diffusion, resulting from the glucose concentration gradient. As gestation progresses, the transplacental glucose transport capacity is increased by the presence of greater numbers of glucose transporters [65]. During maternal hypoglycemia, the glucose concentration gradient across the placenta is decreased, leading to decreased availability of glucose to the fetus. In late gestation, the fetus can more easily compensate for maternal glucose variation by modulating the activity of the glucose transporters. Therefore, in theory, the period when the fetus is more dependent on maternal glucose levels to maintain euglycemia is also the period when severe hypoglycemia occurs more often during pregnancy.

Possible mechanisms by which hypoglycemia could cause brain dysfunction in fetuses and children are altered cell growth and function. Insulin and insulin receptors have been found in the brain [66]. It is thought that insulin is a growth-promoting factor important in brain development [66]. This is also implicated in the synthesis and reuptake of neurotransmitters, such as norepinephrine, dopamine and serotonin [67]. Glucose plays an important role by providing the substrate to produce the energy required in the synaptic transport of neurotransmitters [67]. Since glucose is not stored in the brain, any interruption in supply would interfere with the normal chemical signaling by neurotransmitters between the brain cells. In a developing brain, glucose may not only be used for energy but also for synthesis of structural compounds. Support for the role of glucose in the development of brain structures has been found in research with preterm infants in whom hippocampal abnormalities have been linked to hypoglycemia [68,69]. Although the developing brain of a fetus or a child may be more flexible in use of nonglucose fuels (lactate or ketones bodies) for energy, it could also be more prone to permanent alteration of processes in neurosignaling. These changes would explain altered neuropsychological functioning in the offspring of mothers with Type 1 diabetes who experienced severe hypoglycemia during their pregnancy. Furthermore, depending on the timing of the event(s) during brain development, the affected function(s) may differ.

Discussion

The research reviewed has not addressed what the effect of exposure to maternal severe hypoglycemia during pregnancy on the long-term neurocognitive outcome of the offspring is. The animal studies performed on embryos did not follow the embryos to term and, therefore, have not investigated the impact of hypoglycemia on the survival and neurodevelopment of the offspring. Although rodent models could be used to assess the consequences of maternal hypoglycemia during pregnancy on the pups, they cannot be used to assess the consequences of maternal hypoglycemia during pregnancy on the more complex neurocognitive functioning of children.

Human studies have found no or mild neuropsychological deficits in children born to mothers with diabetes [2–4,70–73]; however, none of these studies was specifically designed to investigate the impact of severe hypoglycemia. Furthermore, most of these studies included participants with gestational, Type 1 and Type 2 diabetes in their diabetic group. No attempt was made to

differentiate between women with these different types of diabetes. This has resulted in a bias since woman with gestational diabetes and Type 2 diabetes are at a lower risk of severe hypoglycemia during pregnancy [12,14,74] than women with Type 1 diabetes. The few studies that have specifically examined Type 1 diabetic mothers have concentrated on investigating the effects of the presence of ketonuria or ketonemia and metabolic control (A1C) on the neurocognitive outcome of the offspring [4,71,73].

Studies that have examined the effects of *in utero* exposure to diabetes on offspring have focused mainly on general developmental or intellectual outcomes [2,3,70,72,73]. Few have examined the impact of maternal Type 1 diabetes, and more specifically severe hypoglycemia, on children's attention, memory, language, visuomotor, academic and higher order planning, and organizational abilities. Yet these are the functions most affected by postnatal exposure to severe hypoglycemia. Furthermore, with the exception of two studies that followed children up to 9 and 11 years of age, respectively [70,71], the long-term neurocognitive outcomes of the offspring have only been studied in children up to 5 years of age. However, in children, the neuropsychological consequences of Type 1 diabetes of onset before the age of 5 are sometimes not seen until school age (6 years and above). Therefore, long-term follow-up of children of mothers with severe hypoglycemia during pregnancy is warranted. Ideally, the mothers need to be followed prospectively from conception to the end of pregnancy to assess metabolic control and incidence of severe hypoglycemia. The offspring need to be followed from birth (for the presence of neonatal factors influencing outcome) until at least 7, if not 10, years of age as some neurocognitive deficits may emerge only as the child matures. Neurocognitive assessment should include measures that assess both global neurocognitive outcome and specific functions, such as attention, memory and speed of processing.

Based on present research findings, both the Canadian and American Diabetes Associations have recommended extreme caution to avoid severe hypoglycemia in young children with diabetes [75,76]. In the past, the Canadian Diabetes Association had also recommended avoidance of severe hypoglycemia during pregnancy [77]. However, despite the absence of new evidence on the long-term effect of severe hypoglycemia on the offspring of mothers with diabetes, the most recent version of clinical practice guidelines does not include a warning about the potential risk to the fetus of severe hypoglycemia in pregnancy. Rather, it states that 'there do not appear to be significant adverse effects on the neonate from maternal hypoglycemia' [9]. This statement is based on a single study by Reece *et al.* [37]. However, this study should not be used to conclude that maternal severe hypoglycemia has no, or minimal, effect on the fetus or neonate for many reasons, the main ones being its timing during pregnancy (third trimester), the absence of severe hypoglycemia symptoms in the mothers, the small number of participants and the lack of long-term follow-up. The recent International Diabetes Federation recommendations also fail to mention possible risks to the fetus associated with severe hypoglycemia. Although the importance of near normal glycemia to reduce maternal and fetal complications associated with Type 1 diabetes in pregnancy is undeniable, the effect of severe hypoglycemia on both the mothers and the offspring should not be overlooked. Absence of data does not mean absence of effect. The medical community should continue to work at using emerging tools, such as educational programs, new insulin analogs, insulin pumps and continuous blood glucose monitoring, to strive for near-normal glycemia while avoiding severe hypoglycemia throughout pregnancy.

Future perspective

This article identified the need for further studies of children born to mothers with Type 1 diabetes affected by severe hypoglycemia during pregnancy. If the concerns raised here are proven, then ongoing development of new treatment strategies using education and new technologies, such as insulin analogs, continuous insulin infusion pumps and continuous glucose monitoring, to achieve near normal glycemia without significant hypoglycemia during pregnancy will need to be pursued.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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