Gestational Diabetes and Its Effects on the Fetus

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ABSTRACT

Although the common effects of gestational diabetes on the fetus are known, the outcome of a diabetic gestation is ambiguous. There is concern for complications in the fetus at delivery due to enlarged size of the fetus, as well as concerns for birth defects, fetal distress, diabetes and obesity. Yet, although there is a correlation in the previous disorders and gestational diabetes, many of the mechanisms that cause these complications are unknown. By studying the pathology of gestational diabetes, researchers have learnt that the placenta controls fetal growth and provides a great deal of protection for the fetus. Therefore, many of the effects of diabetes are masked by the placenta. The problems that arise from gestational diabetes are often the result of a subtle disturbance of the fetuses' metabolism or from some obstruction of the placenta's ability to protect the fetus. Therefore, to properly understand the effects of gestational diabetes, it is necessary to know not only the effects of diabetes but also the mechanics of the placenta, the changes it undergoes during gestational diabetes and the effects of these changes on the fetus.

INTRODUCTION

Gestational diabetes is a complex disorder arising from glucose intolerance during pregnancy. It affects two to three percent of pregnancies in developed countries. Although gestational diabetes is rarely dangerous for the mother, the fetus can develop many problems that make detection and treatment of this disorder very important. The risks to the fetus include stillbirth, macrosomia, hypoglycemia, jaundice, respiratory distress syndrome, polycythemia, hypocalcemia, congenital abnormalities, obesity and diabetes (Kjos and Buchanan, 1999).

Although in a diabetic patient the effects of diabetes are easily predicted and understood, for the fetus of a diabetic gestation, the mechanisms of disease are poorly understood and rarely predictable. The reason for this is that the placenta has an amazing ability to protect the infant from the diabetic effects of the mother.

GENERAL EFFECTS OF INSULIN

To properly understand the effects of diabetes, it is necessary to understand one of the most important hormones that regulate glucose metabolism. Insulin is secreted by beta cells located in the islet of Langerhans in the pancreas. Insulin is a synthesized in the beta cells in three stages: firstly a large molecule, pre- proinsulin, with a molecular weight of 11,500, secondly as proinsulin with a weight of 9,000, and finally insulin with a weight of 5,808. Insulin has a very short half-life of six minutes in the blood. Therefore, since the half-life is so short, insulin's important effects are short lived (Guyton & Hall, 2005).

Insulin enhances glucose utilization and storage. It is required to store glucose for later use, while limiting high glucose levels in the blood. The body, specifically the brain, requires glucose as a primary source of energy. Without glucose the central nervous system becomes depressed; when glucose levels drop below 70 mg/dl, the patient will become extremely nervous, tremble,

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often break out in a cold sweat, and may hallucinate; when blood glucose levels drop below 50 mg/dl, the patient will lose consciousness and, as the blood glucose drop further, the patient will enter a coma which could cause permanent damage to the central nervous system. However, exceedingly high levels of blood glucose result in hyperglycemia, which results in cellular dehydration- because glucose causes a large amount of osmotic pressure in the extracellular fluid. Exceedingly high levels of glucose in the blood cause the kidneys to release glucose in the urine, which can further deplete the body of it fluids and electrolytes because a large amount of water will be released in the urine with the glucose (Guyton & Hall, 2005).

One of the primary stimulators of insulin is glucose. This directs high levels of glucose in the blood into cells throughout the body for use, lowering blood glucose levels. Additionally, gastrointestinal hormones also stimulate insulin production and secretion at the time of consumption before glucose even reaches the blood. These hormones are released through signals to the pancreas as the stomach is stretched when food enters the stomach. This is important so that a bolus of insulin is available immediately once glucose enters the blood to be stored in the liver as glycogen. Without insulin, glucose in the blood does not enter the cells. Insulin causes eighty percent systematic cells to be permeable to glucose within seconds of its release. This is the primary mechanism that causes the blood glucose level to drop to normal levels. Once insulin binds with the alpha subunit of insulin receptors, the beta subunit of insulin receptors, the beta subunit of the receptor undergoes tyrosine phosphorylation. This then causes a signal transduction cascade which activates glucose transport vesicles allowing glucose to enter the cell. Sixty percent of the glucose from a meal is immediately stored in the live as glycogen. Insulin has a direct effect on many important enzymes in the liver. Insulin inhibits liver

phosphorylates, which breaks glycogen into glucose. Insulin enhances activity of glucokinase, which phosphorylates glucose so that once the glucose enters the cell it gains a negative charge preventing it from diffusing out of the cell. Insulin also activates glycogen synthase which is active in the polymerization of glucose to glycogen (Guyton & Hall, 2005).

When insulin is absent from the blood, the reverse effects occur. Finally, glycogen is broken down by the enzyme phosphorylase, and then the glucose phosphate molecule is separated from the phosphate by the enzyme glucose phosphate which allows glucose to diffuse into the blood. Also lack of insulin causes the body to transport less glucose into the cell and inhibit use of glucose for metabolism. These mechanisms elevate the blood glucose levels to within a normal range for use by the central nervous system (Guyton & Hall, 2005).

In line with insulin's role in reducing excess glucose from the blood, insulin also inhibits metabolism of lipids. Additionally, when the liver has absorbed the maximum amount of glucose that it can convert into glycogen, insulin activates the glycolytic pathway and splits the glucose into pyruvate which is then converted into acetyl coenzyme A (AcCoA) and then further synthesized into fatty acids. This process is further enhanced by excess amount of citrate and isocitrate formed during glucose utilization (which is heightened when insulin is present) which activates acetyl-CoA carboxylase, a necessary step in lipid synthesis (Guyton & Hall, 2005).

Conversely, when there is a lack of insulin, the primary source of energy in the body is from fats. When insulin is not present in the blood, hormone-sensitive lipase is activated in adipose tissues which cause large amounts of triglycerides and fatty acids to be released into the blood. One effect of these excess fatty acids is that the liver will convert these free fatty acids into phospholipids and cholesterol. Lack of insulin can raise the percentage of cholesterol and lipids in the blood from .6% to above 3.5%, which is implicated in the clogging of the arteries. Additionally, increase use of fatty acids for energy causes a rise on acetoacetic acid acetone and Beta-hydroxybutyric acid, collectively called ketone bodies, which in large quantities cannot be metabolized by the body and is a condition known as ketosis, its effects will be discussed in connection to the pathology of diabetes (Guyton & Hall, 2005).

PHYSIOLOGY OF DIABETES MELLITUS

As discussed above, when insulin is not available or not effective, there is a decrease in the amount of glucose used by the body, and, therefore, an increase in the amount of glucose in the blood, which causes dehydration of cell tissue. This is primarily because glucose is not readily diffused through the cell membrane, causing an increase in the osmotic pressure in extracellular fluid; therefore, the extracellular fluid retains water and retracts water from the cells. The excess glucose in the circulation is excreted by the kidneys in the urine, which enhances dehydration because heightened osmotic pressure in the renal tubules prevents reabsorption of water from the urine (Guyton & Hall, 2005).

The absence of insulin increases the use of fatty acids for metabolism. This causes an extreme amount of ketone bodies to be formed. The amount of keto acids can rise tenfold when the body is not deriving energy from glucose. These acids will destroy the bicarbonate component of the body which is necessary to serve as a buffer. This will lead to acidosis which will lead to coma and death if the blood pH falls below 7.0. The acidosis is increased because the excess of keto acids are excreted by the kidneys only in the non-acidic form, commonly when the acids are combined with sodium. The depletion of sodium from the blood leads to larger

amounts of hydrogen ions in the blood, thereby increasing the effects of acidosis. An additional concern because of increased fatty acid metabolism is arteriosclerosis. Since there is an excess amount of fatty acids and cholesterol present in the blood, arteries can become clogged (Guyton & Hall, 2005).

PATHOLOGY OF GESTATIONAL DIABETES

Perkins, Dunn and Jagasia (2007) explain that even normal pregnancies portray an increasing resistance to insulin throughout the pregnancy. The placenta's production of human chorionic somatomammotropin (HCS) inhibits insulin's effect on the mother's peripheral tissues to uptake glucose, providing an abundance on nutrients for the fetus. Furthermore, HCS stimulates insulin production in the fetus causing an increased uptake of nutrients. As the fetus and placenta grow, more HCS is produced until a normal pregnancy the mother's insulin sensitivity decreases by fifty percent by the third trimester. Additionally, Catalnao et al. (2006) show the effct of insulin desensitization on lipid metabolism. Normally, insulin causes adipogenesis- an increase in lipid storage- however, placenta hormones cause the adipocytes to lyse, contributing to the available nutrients for the fetus.

Pregnant women with gestational diabetes have an additional forty percent decrease in insulin control from non-diabetic pregnant women, according to Catalano et al. (2003). They note defects in both the response of beta cells in the pancreas and in the signal transduction pathways of the insulin receptors as the cause of the glucose intolerance associated with gestational diabetes. There may be several different causes for the decreased response preventing beta cells from producing sufficient insulin: the additional stress on the body to pregnancy may "unmask" a predisposed genetic propensity to Type 2 diabetes. Alternatively, studies have shown the presence of antibodies obstructing beta cell function suggesting a possible link to Type 1 diabetes. Studies have shown that the increased desensitization of insulin on peripheral tissues in gestational diabetes is caused by a marked decreased ability of the beta subunit of the insulin receptor to undergo tyrosine phosphorylation. Additionally, there is a marked decrease in up-regulation of insulin receptors, decreasing the effect of insulin. These defects contribute a large amount of nutrients to the mother's blood, which produces a hyperglycemic environment, as well as the additional effects of insulin resistance, a primary use of fats for metabolism, which can clog arteries and lead to acidosis.

CONCERNS OF GESTATIONAL DIABETES FOR THE MOTHER

Interestingly, the major concerns associated with diabetes are not a strong concern for the mother in a case of gestational diabetes. Whereas a long-term diabetic patient may have clogged arteries and signs of acidosis, the mother does not normally develop such grave complications, probably because of the relatively short duration of gestational diabetes. However, the effects of hyperglycemia, dehydration and release of glucose from the urine- decreasing dehydration, are a concern.

The most serious complication associated with gestational diabetes is hypertension, according to Kjos and Buchanan (1999). There is a positive correlation to the mother's glucose levels and blood pressure. Therefore, careful monitoring and control of the mother's blood glucose levels and blood pressure is important to avoid complications associated with preeclampsia.

The most serious postpartum complication for mothers who develop gestational diabetes is an increased chance of developing diabetes unrelated to pregnancy. There is a significantly high chance of developing diabetes if the gestational diabetes developed in the first trimester or if the mother is obese (Kjos and Buchanan, 1999).

DETECTION AND CONTROL OF GESTATIONAL DIABETES

Kjos and Buchanan (199) suggest that an initial screening for signs of gestational diabetes be administered at the time of the first visit. Only women who are at risk to gestational diabetes need to be administered a glucose intolerance test. Again, at the end of twenty-four weeks, women should be reassessed for indications of gestational diabetes.

Gestational diabetes is usually treated through the mothers' diet (Kjos and Buchanan, 1999). Monitoring of blood levels is important to ensure that the blood glucose levels do not rise to levels that may harm the fetus. If the blood glucose levels are not controlled with diet or if there are indications of fetal complications to diabetes, it may be necessary to treat the mothers with insulin.

MACROSOMIA

Macrosomia is the most common problem associated with gestational diabetes. Because of the fetus' large size, there are complications during labor and delivery, which can lead to death. The simple cause of excess fetal growth is due to excess amount of nutrients available from the mother's hyperglycemia. This view is, indeed, substantiated through studies which show a correlation between the degree of fetal size and the degree of maternal blood sugar levels. However, fetal response to gestational diabetes varies tremendously among different racial and ethnic groups. In fact, only twenty to thirty percent of infants born to mothers affected by maternal diabetes are affected with macrosomia. This suggests that gestational diabetes causes a complex metabolic disturbance which can have many effects on the fetus (Kjos & Buchanan, 1999).

Alonso et al. (2006) explain that the placenta undergoes many changes due to a diabetic gestation. Since the placenta is the primary means of providing nutrients to the fetus, these changes are thought to protect the fetus. Osmond et al. (2000) show that transport of glucose across the placenta, uptake of nutrients from the mother, and utilization of glucose by the placenta is reduced as a result of gestational diabetes. This would explain the poor correlation between gestational diabetes and macrosomia. Therefore, he suggests that the fetus is affected with macrosomia and other conditions when this protection is not working properly. Growth of the fetus and placental must be regulated by some endocrine control. Insulin is the probable hormone to regulate pathways in the placenta, since it has already been determined that insulin receptors are located on the placenta, even though insulin is not necessary for glucose to pass through the placenta. Furthermore, the locations of these receptors change from the maternal side of the placenta during the first trimester to the fetal side of the placenta, suggesting that both the mother and the fetus control functions of the placenta.

Interestingly, Alonso et al. (2006) report that the average weight of fetuses from a diabetic environment had a smaller mass than the control group while the weight of the placentas from the diabetic group was much larger. His theory is that insulin activates the "diabetic placenta" by first increasing its weight and then to start a signal pathway to protect the placenta

and fetus from the diabetic environment. He further supports his theory by showing that there are additional insulin receptors on the placenta, showing that insulin plays a primary role in the protection of the placenta. However, he does not explain what function enlargement of the placenta has or how the placenta protects the fetus.

GREATER OCCURRENCE OF DIABETES AND OBSESITY AS ADULTS IN CHILDREN

The focus of many studies is what the effect of early life in the uterus has on a person's entire life. Perhaps, conditions such as obesity, hypertension and diabetes arise from the conditions in utero. Holness et al. (2000) suggest that a number of important metabolic and biochemical functions that are important for regular control of glucose later in life begin as a fetus, and therefore, the conditioning of how to properly maintain these system work is learned first in the uterus as well. Any disruption in the life of the fetus can cause a predisposition to later metabolic conditions. Holness et al. (2000) assumes that a child born with a low birth weight will have developed to compensate for the lack of nutrients available. The consequence of this is periods of impaired growth in tissues necessary to properly function later. Bo et al. (2003) also believe that a decreased growth rate of a fetus will lead to metabolic abnormalities later in life that may cause an increased risk of diabetes and obesity. Their study confirmed that fetal growth is correlated to risk of diabetes later in life. The understanding is that a fetus' metabolism is conditioned to the environment and this has an effect for the fetus' entire life.

Malee and Wu (1999) conducted a study of the changes in level of adrenocortical steroids as a result of gestational diabetes. Since maternal diabetes often increases a fetus' hormone levels, they hypothesized that the increased incidence of diabetes later in life of children born from a mother who was affected with diabetes could be a result of increased glucocoritisol which inhibits insulin efficacy. They assert that any function altered in the uterus can be "imprinted" in the fetus and have an effect throughout the life of the fetus, similar to the theory of Bo et al. (2003).

Although they did not find higher levels of corticosteroids in fetuses from diabetic gestations or normal gestations, there was an observed increase in adrenal activity. They found elevated levels of aldosterone, which is also produced in the adrenal cortex, and may indicate that diabetes has an effect later in the fetus' life on corticosteroids as well. Furthermore, even though the level of corticosteroids did not rise, some of the mRNA was found in abundance. Although increased levels of mRNA do not always cause increased hormone levels, it could indicate an "imprint" on the fetus' adrenal cortex activity due to gestational diabetes. Therefore, there is reason to believe that children born from a diabetic gestation may be affected with diabetes later in life due to a malfunction of the fetus' corticosteroid control of insulin.

Schroeder et al. (1997) conducted a study on a rat skeletal and myocardial tissue to determine the effects of gestational diabetes. They learned that while the hyperglycemic environment of the fetus did not produce more insulin, the glucose transporters in the muscle tissue decreased by sixty-five percent. They assume this process is a defense to limit the amount of glucose entering the cells. Schroeder et al. (1997) further predict that perhaps this may cause a predisposition for the gestational diabetic fetuses to develop diabetes later in life, since the low levels of glucose transporters develops insulin resistance in the skeletal muscle tissue. This may

be another mechanism in human fetuses that cause metabolic change in utero that affects the adult life of the fetus.

HYPOXIA AND HYPOXIA-RELATED CONDITIONS

Hypoxia, a decreased percentage of oxygen in the blood of the fetus, has been noted as a concern during a diabetic pregnancy in the third trimester. While no studies have been done to address the specific cause of hypoxia in gestational diabetes, Lassus et al. (2003) note that vascular endothelial growth factor is significantly lower in the cord blood of fetuses' from diabetic pregnancies. Vascular endothelial growth factor is important to vascular development. In the absence of this growth factor, mice die. In acute hypoxia expression of vascular endothelial growth factor occurs rapidly within a few hours. It seems that hypoxia occurs to the fetus because it is unable to regulate proper vascular maintenance and growth due to some inhibition of vascular endothelial growth factor.

Loukovaara et al. (2004) preformed an experiment to determine the cause of hypoxia related conditions, such as periventricular leukomalacia and cerebral palsy. It is known that inflammation is correlated to these two conditions and the study's aim is to determine if hypoxia causes the inflammation. They measured C-reactive protein (CRP) which rises in response to inflammation or stress. They found that CRP is positively correlated to hypoxia, and therefore that hypoxia is a likely cause of inflammation. Therefore, not only is hypoxia a danger to the fetus of a diabetic gestation but also periventricular leukomalacia and cerebral palsy.

Loukovaara et al. (2004) further wanted to ascertain whether the diabetic pregnancy will cause inflammation in the fetus. Furthermore, since inflammation is a risk factor for diabetes, perhaps this is the reason that children from diabetic pregnancies are at greater risk to diabetes later in life. They concluded that the cord serum CRP was no different in gestational diabetic pregnancies than normal pregnancies, and therefore, there is no evidence that increased risk to diabetes later in life is due to chronic inflammation. However, their study does not exclude the possibility of chronic inflammation in cases where the gestational diabetes was not controlled. Therefore, they conclude that more research on the relationship between chronic inflammation and diabetes is justified.

CONGENITAL ABNORMALITIES

Congenital abnormalities occur in six to ten percent of infants of diabetic gestations (Menegola et al. 1999). These deformities include "(in order of risk ratio): caudal regression syndrome, situs inversus, double uteter, renal agenesis, cardiac anomalies, and anencephaly" (Menegola et al., 1999, p.65). Menegola et al.'s study found that the earlier the embryo was exposed to a diabetic environment, the greater chances were of malformation. He even hypothesizes that after a certain period of development the effects of diabetes will not cause malformation.

Menegola et al. (1999) explain that embryos placed in a diabetic environment have a high level of free oxygen radicals and a low level of scavenging enzymes. Studies have shown that correcting the levels of free radicals also corrects the rate of mutations in the embryos. Rat embryos taken from a diabetic mother contained a significantly lower amount of glutathione is not produced by the embryo until a later stage than when mutations are likely to occur.

Therefore, Menegola et al. (1999) hypothesize that the effects of diabetes on the fetus may cause mutations are linked to low levels of glutathione. However, since whole rat embryos had to be implanted in a diabetic environment only after the chance of mutation had already passed (otherwise the control embryos would also have a high rate of mutation), Menegola et al. (1999) were unable to prove their theory in their experiment with rat embryos.

RESPIRATORY DISTRESS SYNDROME

One congenital abnormality that is a result of maternal diabetes is, as Malee and Wu (1999) note, delayed expression of surfactant proteins. Surfactants are produced by the septal cells in the alveoli and are important for proper function of the lung. The surfactants lower the surface tension of alveolar fluid so that the water molecules are not as strongly attracted by hydrogen bonding. If the surfactant was not present, the alveoli would collapse. This malformation is implicated in the greater incidence of respiratory distress syndrome in infants born from a mother gestational diabetes.

CONCLUSION

While the effects of diabetes have been known for quite some time, the effects that a diabetic environment has on a fetus are still unknown. It appears that complications due to diabetes are protected because of the protective role of the fetus, as Alonso et al. (2006) reported. However, although Alonso et al. (2006) do explain the activation of the protective role of the placenta, they do not explain how the placenta protects the fetus, what mechanism causes the rate of glucose transport across the placenta to decrease and what the role the enlarging of the placenta is. Clearly, much more research must be done to answer these important questions.

Another important question is whether the placenta plays a role in masking the effects of other complications due to gestational diabetes, for instance hypoxia and congenital malformations. Many studies of complications from gestational diabetes, such as Loukovaara et al. (2004) and Menegola et al. (1999) have difficulties studying the effects of gestational diabetes in the fetus, because the effects are so unpredictable; it seems that this would be due to the protection of the placenta. Perhaps a better understanding of the changes that the placenta undergoes during gestational diabetes will lead to better studies of the effects of gestational diabetes, and an understanding of the factors that predispose human infants to complications due to gestational diabetes. One approach would be to examine the placentas of fetuses which are affected with complications from gestational diabetes and compare them to the placentas from a diabetic environment that did not produce those same complications.

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