Maternal Diabetes: Consequences for the Offspring

An Experimental Model in the Rat

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The physiological changes of pregnancy tend to reset glucose homeostasis in the direction of diabetes. About 2–3% of all pregnant women develop abnormal glucose tolerance in pregnancy. Pregnancy complicated by diabetes leads to increased perinatal mortality and morbidity. Functional and morphological changes are present at cellular and tissue level. Furthermore, there are implications for the long-term effects of maternal diabetes on the offspring.

Progress in understanding the fetal consequences in diabetic pregnancy and its long-term effects has been made possible by the use of rats in experimental models. Hyperglycemia during pregnancy (first generation), induced by streptozotocin (1,2) or during a glucose infusion (3–6), has a profound influence on fetal development and metabolism, and disturbances in glucose handling persist into the second and third generation offspring of these rats.

FETAL AND LONG-TERM RESULTS OF EXPERIMENTAL DIABETES

Granulated β cells can be recognized in the fetal pancreas of the rat from day 17 or 18 of gestation. From day 20 on, the endocrine cells accumulate in clusters; the contribution of β cells to the islet population remains low, but ultrastructurally the β cells appear mature, replete with secretory granules, and comparable to those of adult rats. During the last two days before birth, the islets show a dramatic expansion and the typical organization in mantle islets with a central core of β cells becomes apparent (1).

In fetuses of streptozotocin-diabetic rats, a similar evolution to control fetuses is observed, but the development of the endocrine pancreas is enhanced by the increased blood glucose concentrations, which results in hypertrophy and hyperplasia of the islets from day 20 of gestation until birth. When maternal hyperglycemia is severe, the β cells of these fetuses become degranulated, due to overstimulation by
the excessive glucose concentrations. At day 20 of gestation, decreased pancreatic and plasma insulin concentrations characterize the fetuses of severely streptozotocin-diabetic rats. These data have been confirmed in fetuses of spontaneously diabetic BB rats (7). Similar findings have also been reported in very poorly controlled human diabetes (8). With the appearance of small islets of Langerhans (day 20 of gestation), glucose-stimulated insulin release can be triggered in vivo. The transition from a fetal- to an adult-type of insulin release in response to glucose occurs during the last days of gestation and parallels quantitative rather than qualitative changes within the \( \beta \) cell (9). In contrast, glucose-stimulated insulin release was absent from pancreases of severely hyperglycemic (15.1 mM) fetuses (9). Incubation of fetal islets with other secretagogues also results in the absence of an insulin response in the fetuses of highly hyperglycemic rats. Only arginine induced a sustained monophasic insulin release, suggesting that the defect may be related to stimulus-secretion coupling (3,4).

Diabetes in the maternal rat not only affects pancreatic development and function; it also involves other important aspects of fetal metabolism. Because of accentuated catabolism in the maternal rat, the fuel supply to the fetus is abundant. Fetal glucose concentrations are a reflection of maternal glucose concentrations (1,10). Hepatic glycogen accumulation has been reported to be decreased in hypoinsulinemic fetuses of streptozotocin-diabetic rats (1). The influx of amino acids from the maternal side is significantly reduced in microsomic fetuses of diabetic rats, while amino acid transport to their overweight littermates is greatly increased (11). Amino acid levels are therefore markedly decreased in fetuses of severely diabetic rats (1,10). Plasma triglyceride and non-esterified fatty acid (NEFA) concentrations and liver triglyceride content are highly increased in fetuses of severely diabetic rats (1,10).

Severe diabetes in rats is associated with fetal growth retardation as a result of fetal malnutrition. Fetal hypoinsulinemia and a reduced number of insulin receptors on target cells (12) in fetuses of severely diabetic rats may lead to a reduction in fetal glucose uptake; a reduced fetal glucose uptake has been demonstrated in hypoinsulinemic streptozotocin-injected fetal lambs (13).

After birth, the glucose diet of the fetus changes into the high-fat diet of the suckling rat. The amount of endocrine tissue does not increase further, while the pancreatic insulin content exceeds adult values. Plasma insulin concentrations decrease and remain low till weaning (14). At weaning, the high-fat diet of the suckling rat is changed into a high-carbohydrate diet. The mass of endocrine tissue and plasma insulin concentrations increase, while pancreatic insulin content decreases (14). The suckling-weaning transition in rats is associated with an increase in insulin sensitivity of the peripheral tissues (15), which may be conferred by an enhanced expression of the GLUT4 glucose transporter (16).

Newborns of severely diabetic rats have a decreased body weight. As in the control group, the lactation period represents a steady-state period in the development of the endocrine pancreas. Severely diabetic rats are too ill to feed their offspring properly. The pups, already small at birth, remain smaller than normal, with a lower growth rate and reduced \( \beta \)-cell mass. Malnutrition results in hypoglycemia and subsequent hypo-activity of the \( \beta \) cells (14).
TABLE 1. Body weight, plasma glucose and plasma insulin concentrations of first- and second-generation control and diabetic rats and of their third generation fetuses

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Diabetic</th>
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<tbody>
<tr>
<td></td>
<td>Body weight (g)</td>
<td>Body weight (g)</td>
</tr>
<tr>
<td></td>
<td>Glucose (mmol/liter)</td>
<td>Glucose (mmol/liter)</td>
</tr>
<tr>
<td></td>
<td>Insulin (nmol/liter)</td>
<td>Insulin (nmol/liter)</td>
</tr>
<tr>
<td>First generation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant</td>
<td>290 ± 3</td>
<td>265 ± 4</td>
</tr>
<tr>
<td>(16)</td>
<td>4.1 ± 0.1</td>
<td>22.6 ± 0.5***</td>
</tr>
<tr>
<td></td>
<td>0.38 ± 0.03</td>
<td>0.11 ± 0.01**</td>
</tr>
<tr>
<td>Second generation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonpregnant</td>
<td>213 ± 2</td>
<td>179 ± 2***</td>
</tr>
<tr>
<td>(39)</td>
<td>5.4 ± 0.1</td>
<td>5.3 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>0.17 ± 0.01</td>
<td>0.26 ± 0.01***</td>
</tr>
<tr>
<td>Pregnant</td>
<td>293 ± 3†</td>
<td>270 ± 3***;†</td>
</tr>
<tr>
<td>(35)</td>
<td>4.3 ± 0.1†</td>
<td>4.7 ± 0.1***;†</td>
</tr>
<tr>
<td></td>
<td>0.40 ± 0.02†</td>
<td>0.34 ± 0.01†;†</td>
</tr>
<tr>
<td>Third generation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetuses</td>
<td>2.10 ± 0.03</td>
<td>2.12 ± 0.02</td>
</tr>
<tr>
<td>(65)</td>
<td>2.3 ± 0.1</td>
<td>2.7 ± 0.1**</td>
</tr>
<tr>
<td></td>
<td>0.72 ± 0.05</td>
<td>0.96 ± 0.05**</td>
</tr>
<tr>
<td></td>
<td>(21)</td>
<td>(112)</td>
</tr>
</tbody>
</table>

The measurements were made at 100 days of age in nonpregnant animals, on day 20 of gestation in pregnant animals, and in third generation fetuses. Values are means ± SEM for the number of rats in parentheses.

* p < 0.05, ** p < 0.01, *** p < 0.001, diabetic versus control.
† p < 0.01, ‡ p < 0.001, pregnant versus nonpregnant.

At adult age (3 months), the offspring of diabetic rats appear to have recovered from the influences of a perinatal diabetic environment. They have a morphologically normal endocrine pancreas and normal plasma glucose concentrations (17). Plasma insulin concentrations are normal (18) or increased (19) (Table 1).

Body weight in the offspring of severely diabetic rats remains below normal. Plasma glucagon and triglyceride levels are decreased, but plasma amino acid levels can be regarded as normal (1).

When these offspring, reared by their own diabetic mothers, are submitted to a 3-hour glucose infusion, they manage to maintain glucose levels within the control range, but in the presence of high insulin levels, resulting in an increased insulin-to-glucose ratio (20). In in vivo insulin-captation experiments, an increased renal clearance was found (18). These data suggest that there was insulin resistance in the offspring of diabetic rats.

In order to quantitate and characterize the insulin resistance in the female offspring of streptozotocin-diabetic pregnant rats (SDF rats), we applied the euglycemic hyperinsulinemic clamp at various insulin infusion rates in order to obtain an insulin dose-response curve. The exogenous glucose infusion rate required to maintain euglycemia at steady-state plasma insulin concentrations is generally considered to be a measure of the effect of insulin on total body glucose metabolism. In SDF rats, the dose-response curve was shifted to the right with a decreased maximum effect. This finding indicates that total body glucose metabolism is both less sensitive and less responsive to insulin in SDF rats compared with control rats (21). The use of [3-3H]-glucose allowed us to determine the effect of insulin on hepatic glucose production and peripheral glucose utilization (22). The insulin resistance involves the peripheral tissues as well as the liver (21). The peripheral tissues of SDF rats are less sensitive to insulin.
(half-maximal effect), but they display a normal responsivity to insulin (maximum effect; Fig. 1), confirming previous results of the $^{125}$I-insulin captation experiments (18). In this study, the authors suggested that the increased uptake of radioactive insulin by the kidney might be attributed to a decreased uptake of insulin by the peripheral extrahepatic tissues (18). Since in the clamp studies all rats were in the postabsorptive state, the glucose production rate in these studies equals the actual glucose production rate. The insulin dose-response curve for inhibition of hepatic glucose production (Fig. 2) in SDF rats obviously shows that the liver in these animals is both less sensitive and less responsive to insulin (21).

With the exception of the liver, the hyperinsulinemic clamp does not allow identification of the tissues contributing to the peripheral insulin resistance. To determine which peripheral tissues contribute to the decreased glucose disposal we used the 2-deoxy-[1-$^3$H]-D-glucose technique in basal conditions and during a clamp at physiological hyperinsulinemia. We thus determined the glucose metabolic index, which is a measure for glucose utilization, in five skeletal muscles, the diaphragm muscle, white adipose tissue, and two control tissues (brain and duodenum). As could be
expected, skeletal muscles are primarily responsible for the peripheral insulin resistance that characterizes SDF rats (Fig. 3) (2). Indeed, the glucose metabolic index in the skeletal muscles of SDF rats was 9–29% and 25–70% lower than in control rats under basal conditions and at physiological hyperinsulinemia, respectively. Muscles are the main reservoir of insulin-sensitive tissues within the mammalian body, representing 36–40% of the body weight. Their contribution to the whole glucose turnover is about 36% in postabsorptive control rats and 50% during euglycemic hyperinsulinemia (23).

Offspring of streptozotocin-diabetic rats are resistant to the action of insulin at the hepatic and peripheral level. The tissues contributing to the peripheral insulin resistance are mainly skeletal muscle, as determined with the 2-deoxy-D-glucose technique.

The offspring of diabetic rats develop signs of glucose intolerance when they become pregnant; they have a greater degree of glycemia than do normal pregnant rats, and the number of granulated β cells in the endocrine pancreas does not increase as in normal rat gestation (1). These data would suggest that a defect is present in SDF rats in the pregnancy-induced response of the β cells to glucose. Because normal pregnancy is a state of severe physiological insulin resistance, we wanted to investigate whether the insulin resistance present in SDF rats is further aggravated during
gestation. For this purpose, we again used the euglycemic hyperinsulinemic clamp technique (19). The insulin dose-response curves for the increase of glucose metabolic clearance rate over basal values (Fig. 4) (19) and inhibition of endogenous glucose production (Fig. 5) (19) obviously show that the insulin resistance of pregnancy is not mirrored in SDF rats: there is no further decrease in the peripheral tissue sensitivity to insulin, while there is only a small decrease in the hepatic insulin sensitivity. Overall
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FIG. 4. Insulin dose-response curves for the increase in glucose metabolic clearance rate over basal values in (a) nonpregnant (○—○) and pregnant (●—●) control rats and (b) nonpregnant (○—○) and pregnant (●—●) offspring of streptozotocin-diabetic rats. Data are means, error bars, SEM of 5–8 experiments.

there are no differences in insulin sensitivity between pregnant control rats and pregnant SDF rats (19). This is also apparent from the glucose metabolic indices determined in various peripheral tissues of both pregnant control rats and pregnant SDF rats (Fig. 2) (2). Although the insulin resistance was not markedly aggravated during pregnancy in SDF rats, a syndrome of gestational diabetes ensued in these rats. The increase in circulating insulin concentrations, as seen in normal pregnancy, was blunted; as a result, pregnant SDF rats had lower insulin concentrations than pregnant control rats. In addition, nonfasting glucose levels were increased (Table 1), and NEFA levels were markedly elevated (21).

The exact cause of the hepatic and peripheral insulin resistance in adult offspring of diabetic rats is unknown at present. Insulin action on target tissues might be altered by a decreased receptor number and/or affinity, or by a postreceptor defect (24). Changes in the levels of counterregulatory hormones could also be involved, for example glucagon stimulates insulin-inhibited hepatic glucose production (24). In the basal state and during hyperinsulinemia, glucagon levels are not significantly different in SDF rats and control rats. This suggests that glucagon is probably not involved in the hepatic insulin resistance observed in SDF rats (21). Raised NEFA levels
are known to reduce insulin-stimulated glucose disposal, especially in muscle (25). Although NEFA levels are lower in basal conditions in SDF rats, hyperinsulinemia decreased NEFA to a lesser extent in SDF rats than in control rats. However, plasma NEFA levels do not reach significantly higher levels during extreme hyperinsulinemia in SDF rats. This suggests that NEFA do not inhibit glucose utilization in SDF rats (21).

When the second generation offspring of streptozotocin-diabetic rats become pregnant, they develop gestational diabetes. This means that their fetuses (third generation) also develop in an abnormal intrauterine milieu. Indeed these fetuses display islet hyperplasia, β-cell degranulation (1), hyperinsulinemia, hyperglycemia (Table 1) (19), and they are macrosomic (1).

At adult age, the third generation offspring of streptozotocin-diabetic pregnant rats have impaired glucose tolerance with high glucose levels (20). Similar results were also obtained in the third generation offspring of glucose-infused hyperglycemic pregnant rats (5).

These data clearly show that a diabetogenic tendency is transmitted from the pregnant streptozotocin-diabetic rat to her fetuses, with consequences persisting into adulthood and into the next generation (20). The transmission of diabetes via the
maternal line has been confirmed in the adult offspring of rats made hyperglycemic by a continuous glucose infusion during the last week of pregnancy (5,26). Very recently, Gauguier et al. (27) found, besides a genetic inheritance, a higher maternal than paternal transmission of diabetes in the GK rat, a model of spontaneous non-insulin-dependent diabetes mellitus (NIDDM) without obesity. This finding, however, was not confirmed by Abdel-Halim et al. (28).

The inducing factor of the insulin resistance, which characterizes the adult offspring of severely streptozotocin-diabetic rats, must be the abnormal perinatal milieu of the diabetic maternal rat to which the developing fetus has to adapt. Indeed, normalization of maternal glycemia from day 15 of gestation by islet transplantation prevents the occurrence of a disturbed glucose tolerance in the offspring (29). The studies of Grill et al. (30) and of Ktorza et al. (26) strongly suggest that the diabetic or hyperglycemic intrauterine milieu must be responsible for the metabolic alterations observed in the offspring, since in both studies the offspring were reared by nondiabetic or normoglycemic foster mothers. Ryan et al. (31) also found the existence of an insulin resistance in offspring of streptozotocin-diabetic rats, which appears to be related to the degree of hyperglycemia they were exposed to during fetal life.

**COMPARISON WITH THE HUMAN**

Although hyperglycemia of such severity is rarely encountered in humans, our data suggest that poorly controlled diabetes during pregnancy may affect the glucose-insulin homeostasis in the offspring from diabetic women. It remains difficult, however, to compare the metabolic impact of severe streptozotocin-diabetes in the rat with (treated) insulin-dependent and non-insulin-dependent diabetes in women.

Tight metabolic control before pregnancy and throughout pregnancy has reduced perinatal morbidity and mortality over the last decades. Neonatal problems are predominantly related to overfeeding the fetus, associated with fetal hyperinsulinemia, since the other well-known neonatal complications (hypoglycemia, hypocalcemia, polycythemia, and respiratory distress) can be reduced by intensive management. However, maternal diabetes still compromises fetal development and behavior. An important fetal target organ is the endocrine pancreas.

The human fetal endocrine pancreas comprises about 5% of the total pancreatic volume. The pancreas is derived from two buds of the primitive gut, a dorsal and a ventral primordium; these two buds fuse to form the pancreas. The dorsal primordium develops into the tail and the superior part of the head of the pancreas; the ventral primordium develops into the lower part of the pancreatic head (32). The endocrine pancreatic system is derived from the ductuli. The first stage is the formation of knots, which then become independent from the ductuli to endocrine islets. In these primitive islets the different cell types are intermingled. From about 16 weeks of fetal life typical mantle islets are seen, with a central core of $\beta$ cells (insulin-producing) and a mantle of non-$\beta$ cells. Identification of the different cell types is possible with electron-optical and immunocytochemical methods or by a combination of both (33).
The \( \beta \) cells have large granules, their core can be electron dense (dark granules), sometimes even crystalline, or more electron lucent (light granules). These \( \beta \) granules contain insulin. The \( \alpha \) cells have smaller granules than the \( \beta \) cells, and the core is electron dense with a closely fitting membrane. Some \( \alpha \) cells have larger granules than others. The \( \alpha \) granules contain glucagon. D cells have granules heterogeneous in size and electron density; they contain somatostatin. Pancreatic polypeptide (PP) cells have small and electron-dense granules containing pancreatic polypeptide. The lower part of the pancreatic head, which originates from the ventral primordium, contains a high proportion of PP cells and is called the PP-rich zone. A fifth cell type (D_1 cell) has been described by Van Assche et al. (33), which has very small granules. This cell type occurs in close relationship with nerve fibres. The hormonal content of the granules is still unknown.

The islets of Langerhans in fetuses of diabetic mothers are more numerous and larger than those in normal fetuses. Innumerable small islets composed of only a few cells can be demonstrated. The islet capillaries are congested. The \( \beta \) cells have an enlarged and hyperchromatic nucleus. In about 30% of the cases, an infiltration by eosinophilic polymorphs is present in and around the islets. These immunological changes, as shown by eosinophilic infiltration in the fetal pancreatic islets, are present only in type 1 diabetes and not in infants born to gestational diabetic mothers. It is possible that these immunological changes protect against the development of diabetes in later life (34). Increased volume density of the endocrine tissue and an increased percentage of insulin producing \( \beta \) cells are present in fetuses of insulin-dependent diabetic mothers and of mothers with gestational diabetes. This \( \beta \)-cell hyperplasia is responsible for the fetal hyperinsulinism (34,35). Furthermore, in poorly controlled diabetes, degranulation of the fetal islets can also be observed (8).

It can be concluded that the diabetic intrauterine milieu induces changes in the fetal endocrine pancreas and in fetal metabolism, which can have consequences throughout later adult life. However, there are conflicting data about the incidence of diabetes in the offspring of insulin-dependent diabetic women. Although Farquhar (36) has shown that the incidence of insulin-dependent diabetes is 20 times higher in children of diabetic mothers than in the control population, Warram et al. (37) have shown that children of diabetic fathers have a greater risk of subsequent insulin-dependent diabetes than do children of diabetic mothers. The epidemiological data in gestational diabetes are more consistent. The risk of NIDDM is significantly higher when the mother rather than the father had this disorder (38). Furthermore, 35% of women with gestational diabetes are the daughters of diabetic mothers, compared with only 5% of normoglycemic pregnant women, and gestational diabetes occurs more frequently in the offspring of diabetic mothers (35%) than in the offspring of diabetic fathers (7%) (39). Most convincing are the studies carried out in Pima Indians, in whom there is an extraordinarily high incidence of NIDDM. These studies have clearly shown that, in addition to a genetic transmission of diabetes, diabetes during pregnancy increases the incidence of impaired glucose tolerance in their children. At the age of 15–19 years, the incidence was 33%, versus 1.4% in the offspring of
mothers who developed diabetes after pregnancy (40). An extensive study over several generations showed a significant predominance of NIDDM in great-grandmothers of insulin-dependent diabetics on the maternal side when compared with the paternal side. In addition, a significant predominance of familial diabetes aggregation in first- and second-degree relatives was found on the maternal side when compared with the paternal side. Systematic prevention of hyperglycemia and impaired glucose tolerance in pregnant women has significantly decreased the prevalence of diabetes mellitus in their children (41).

The existence of maternal component in the transmission of NIDDM is widely accepted. Both genetic and environmental factors might contribute to the maternal transmission of diabetes. Besides an intrauterine effect in the transmission of NIDDM, there is transmission of an X-linked susceptibility locus or inheritance of mitochondrial DNA that is transmitted exclusively from mother to offspring (42).

Strict metabolic control is necessary for all pregnant women with diabetes, because the deleterious effects for the offspring, engendered by maternal diabetes, are not confined to the fetal and neonatal period, but extend into adulthood and the next generation.

REFERENCES

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DISCUSSION

**Dr. Schwartz:** I have a question concerning your streptozotocin model where you showed that low-dose streptozotocin results in macrosomia with what you call decreased insulin secretion. I assume what you mean is decreased insulin mass in the β-cell mass. The simplest view that we have had over the years is that hyperglycemia of the mother is transmitted to the fetus who is then stimulated to secrete excess insulin. Your model apparently has macrosomia with decreased insulin.

**Dr. Van Assche:** No, in mild diabetes there is an increased amount of insulin in the fetus and an increase in β-cell function, so the amount of endocrine tissue is increased. Thus in mild diabetes there is hyperinsulinism in the fetus and macrosomia. In severe diabetes, I agree with you, we have hypoinsulinism and we have intrauterine growth retardation. So from that point of view there is a similarity with the human situation.

**Dr. Schwartz:** My other question concerns intrauterine growth retardation (IUGR). My simple mind wonders what is the driving force in that situation. If you look at the infant weight, the controls were, as I recall, around 2000 g and the IUGR infants were 1000 g. If you look at the mass of the β cell or the islets it appears to be about 50% of control in the IUGR offspring, so it seems that the islet mass was proportional to the mass of the infant.

**Dr. Van Assche:** Morphometry means that in a certain area of the pancreas, always in the tail, you measure the proportion of endocrine tissue. This is very difficult to do, and I completely accept your point. To obtain the exact weight of the pancreas is hard because even a tiny bit of fat can change the weight significantly. However, it is a generally accepted morphological principle that "volume density" means the amount of a recognizable part of an organ compared with the total organ mass in a certain area. We have always used an area of 0.5 cm² where we measure morphometrically the amount of endocrine tissue, so in this case the overall weight of the pancreas is not important.

**Dr. Swift:** I would like to emphasize the importance of the length of the baby. I don't know of any data that relate maternal diabetes to the length of the baby at birth. People talk of macrosomia, but what do they mean by macrosomia? In practice they mean obesity, and nobody has ever accurately measured birth length. I would like to hear of any data relating to fetal or infant length.

**Dr. Van Assche:** When we describe macrosomia in the rat this refers not only to increased weight but also to increased length. Our experimental model of intrauterine growth retardation had not only a reduction in weight, but also a reduction in length. Maybe Catalano has more data on the human situation.

**Dr. Catalano:** We have data on maybe 300 babies, about 150 normals and 150 from women with mild gestational diabetes. When the data are corrected for gestational age and sex, we find that despite what we consider adequate control the principal difference between an infant of a diabetic mother and of a control mother is the amount of fat. The distribution of the fat...
is similar to that in a type 2 diabetic, i.e., central rather than peripheral. So in our data at least there was no difference in length or head circumference, etc.

Dr. Dakou: Were the measurements done specifically as part of the study or were they taken from the records? That would introduce a great deal of uncertainty.

Dr. Catalano: They were done prospectively by a specifically trained person.

Dr. Dakou: I was impressed by your data from anencephalic fetuses. It appears that besides nutrient stimulation of the β cell you also need an intact hypothalamic-pituitary axis. Do you need growth hormone related factors to stimulate β-cell growth?

Dr. Van Assche: We developed a model whereby decapitating the fetuses of diabetic mother rats in utero we could confirm what we have shown in the anencephalic human. There is some indication that endocrine stimulation from the hypothalamus and the hypophysis is important. It has also been shown that estrogen in the fetus stimulates endocrine growth.

Dr. Guesry: If I followed what you said correctly, your data would suggest that in countries where the rate of intrauterine growth retardation is very high, as in Bangladesh with a 30% incidence, all those undergrown infant girls are at risk of becoming diabetic themselves.

Dr. Van Assche: It is very difficult to speculate on this. I am not an epidemiologist. I think that intrauterine growth retardation is related to diseases in later life, not only diabetes but also lung disorders and other diseases. From the work of David Barker translated to what is now happening in the underdeveloped countries, this indeed is a problem. We must wait for further epidemiological data.

Dr. Zoupas: From your beautiful studies, can you give us an explanation for sudden intrauterine death in the diabetic mother’s child?

Dr. Van Assche: The only thing we have seen (and this has been supported by the King's College Hospital group) is severe hypoglycemia in the fetus in cases of fetal distress.

Dr. Hoet: You showed that the β cells in the pancreas of a child born to a mother with very severe diabetes were degranulated. Would you like to comment on the vascularity of the islets?

Dr. Van Assche: The vascularity was decreased.

Dr. Bergman: To follow up on this comment, I think there may well be alterations in perfusion patterns, capillary density, endothelial cell transport potential, and so on, and it would be very interesting to look at capillary density morphometrically in these offspring. If vascular abnormalities are present, the insulin resistance might be continued in further generations.

Dr. Van Assche: I completely agree with you; I believe that diabetes in pregnancy and preeclampsia are both endothelial disorders.

Dr. Siadati: What is the cause of transient neonatal diabetes?

Dr. Van Assche: It is suggested that there is an immaturity of the fetal β cell at birth; these infants need insulin and the majority recover. However, as far as I know about 25–30% of them become diabetic in childhood.