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HABILITATIONSSCHRIFT

Management of pregnancies with gestational diabetes based solely on maternal glycemia versus glycemia plus fetal growth

Zur Erlangung der venia legendi
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Content

1. Introduction

1.1 Intention of the presented work

Gestational diabetes mellitus (GDM) is one of the most common complications in pregnancies. Presently, 3-5% up to 14% of the pregnant women are affected, dependent on the ethnical group investigated. Actual estimations suggest that the prevalence of GDM will significantly increase in the near future due to the rising rate of obesity and glucose intolerance in young women in industrialized countries. Optimal medical care has to be provided to avoid short and long term sequelae for the fetus and the mother. On the other side there is clearly a need for a concept of management of GDM which guarantees a reasonable balance of efficacy and costs. For more than two decades there is an ongoing discussion about the optimal management strategy in pregnancies with GDM.

In 2001 the guidelines for diagnosis and therapy of GDM in Germany had been modified based on the suggestions of an expert panel of the German Society of Obstetrics and Gynecology (DGGG) and the German Diabetes Association (DDG). The major goal of this attempt was an adaptation of the German guidelines to the international standard. Although a concept was developed that considers all available data well as clinical experience and best practicability, several questions remain. There is controversy about the best glycemic thresholds for the diagnosis of GDM as well as the optimal glucose targets during pregnancy. While intensive glucose control in women with GDM has been proven to reduce neonatal morbidity, the rates of accelerated growth (macrosomia) and it's associated complications are still elevated, as compared to the normal obstetrical population. Thus, do we have to modify our criteria for insulin therapy to reduce morbidity? In studies that target to reduce macrosomia, intensive insulin therapy was required in the majority of the women. This does not seem reasonable. How can we identify pregnancies with a high risk for neonatal morbidity? Are the maternal glucose values reliable predictors for morbidity or do we have to include other parameters to improve the outcome? Do we really have to monitor intensively the glucose metabolism in all woman with GDM?

This manuscript constitutes a part of the ongoing attempt to find for answers to these questions. It summarizes the quintessence of almost 10 years of clinical research in the field of gestational diabetes. Our research covers various aspects of pregnancies complicated by diabetes including congenital anomalies, maternal and fetal predictors for neonatal morbidity, predictors for postpartum diabetes after GDM and the influence of contraception on the

development of diabetes after pregnancies with GDM and. Based on the clinical experience in our Diabetic Prenatal Care Clinic we became more and more aware of an urgent need to modify the principles of the management of GDM. When looking at the outcome parameters it seemed that several of the women were under-treated, while others were over-treated when therapy was based solely on strict glycemic control.

In the first part, based on own data and several studies by others this thesis assesses the importance of maternal glucose values to predict adverse neonatal outcome. In the second part, the results of intervention trials done by our group will be presented that investigated a modified management combining maternal and fetal criteria to guide therapy. The advantage of this approach will be demonstrated that provides the opportunity to adjust the intensity of surveillance and therapy based on antenatal risk assessment.

1.2.   Gestational diabetes

1.2.1. Epidemiology and pathophysiology

GDM is defined as glucose intolerance of varying degrees of severity with onset or first recognition during pregnancy [1]. The prevalence of GDM is dependent on the prevalence of type 2 diabetes in the given population and varies from 1-14% with 2-5% being the most common figure [2-4]. Risk factors for GDM are increasing age, positive family history of diabetes, increasing obesity and descent from selected ethnic groups with high prevalence of diabetes.

Pregnancy is associated with profound hormonal changes that have a direct effect on the carbohydrate tolerance. In the 1st trimester, progesterone and estrogen rise but counterbalance regarding their insulin action. Once the 2nd trimester is entered, human placental lactogen (HPL) , cortisol and prolactin increases, causing decreased phosphorylation of the insulin receptor substrate-1 [5] and profound insulin resistance [6, 7]. In most women, pancreatic insulin secretion adapts to this need, but in those with underlying beta-cell defects, hyperglycemia ensues. Women typically return to euglycemia postpartum but defects in insulin secretion and action are still evident. [8]

1.2.2   Morbidity

Maternal morbidity

Maternal hyperglycemia in GDM is rarely severe enough to cause concern for the mother. Women with GDM are more likely to develop hypertensive disorders than women without GDM which might be partly related to the underlying risk factors for GDM (obesity, increasing age). There is a higher risk of vaginal and urinary infections causing preterm labor. At delivery, neonatal macrosomia results in a higher risk of C-section and birth traumata for mother and child. A pregnancy with GDM indicates a maternal long-term risk of diabetes in later life. Approximately 10-15% of the women remain diabetic postpartum [9, 10], the cumulative risk is approximately 50% for diabetes and 75 % for any other impairment of glucose intolerance within 10 years after the index pregnancy. [10-13]

Fetal and neonatal morbidity

Fetal hyperinsulinism secondary to an excessive supply of substrate due to maternal hyperglycemia (Pederson hypothesis) [14] is the underlying cause for all short-and long term complications of GDM. The primary perinatal concern in GDM remains the excessive fetal

growth (fig 1). Macrosomia is significantly more common in pregnancies with GDM even when GDM is treated according to standard recommendations. Fat accumulation tends to be truncal with a larger shoulder circumference which leads to an increased risk for cephalopelvic disproportion and shoulder dystocia. [15] Other significant acute neonatal morbidities include hypoglycemia, hyperbilirubinemia, hypocalcemia and polycthemia.

Figure 1: Macrosomic newborn with diabetic fetopathy

The infant of women with GDM inherits an increased susceptibility for glucose intolerance not only due to genetic disposition but due to the exposure to hyperglycemia in utero. Studies in Pima Indians demonstrated that children from the same mother who were born after the mother developed diabetes were more obese and more likely to have insulin resistance [16]. Numerous studies support an increased risk for obesity in the offspring. [17, 18]

1.2.3   Diagnostic management

There is a lively ongoing discussion about the diagnostic procedure for detection of GDM. The major controversies exist regarding universal screening versus diagnostic limited to women with risk factors and the diagnostic criteria for GDM. It would exceed the capacity of this text to go into the details of this discussion. The following presentation will be limited to the major issues of the current recommendations valid for Germany [19] which represent a modified version of the Recommendations of the Fourth International Workshop Conference on GDM. [1]

Screening for GDM should be performed in every woman with 24-28 weeks of gestation. The diagnosis of GDM is based on the results of an oral glucose tolerance test (oGTT). The evaluation for GDM may be done in one or two steps. The one - step procedure requires a complete 75 g oGTT in all women. When two or more glucose values exceed the glycemic thresholds of fasting 90mg/dl, 180 mg/dl after 1 hour and 155 mg/dl after two hours, the criteria for GDM are met.[20] The two-step procedure uses a 50 g glucose load (glucose challenge test) as selection criteria for the oGTT; it may be applied without regard to the time of day or last meal. The diagnostic oGTT is reserved for women with glucose values above 140 mg/dl in the screening test. When performed between 24-28 weeks of gestation, the screening test has a sensitivity of 80% at a 140 mg/dl cut point [1]. Women with high-risk for GDM should be tested as soon as feasible and testing should be repeated at 24-28 weeks if GDM is not diagnosed. The cutoff values for the oGTT are derived from the original data from O'Sullivan from 1964 evaluating an increased risk for development of type 2 diabetes of the mother in later life. [21]
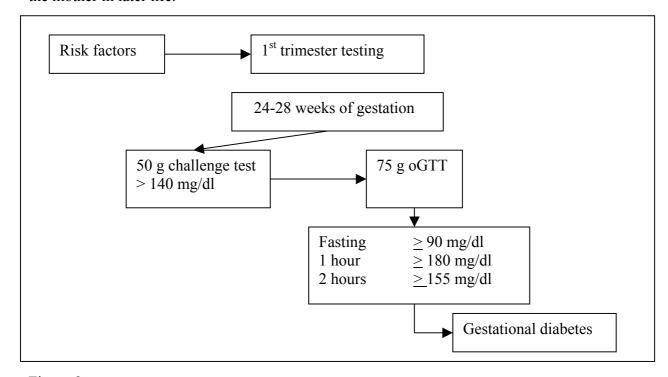
Figure 2:

Diagnostic procedure for GDM

In contrast to the recommendations of the German Diabetes Association, currently (up to spring 2003) the German health system covers only a diagnostic for GDM in women with risk factors for GDM following the one-step procedure. About 50% of the women with GDM are missed by this selective testing. [2] Thus in this text, all presented studies which had been

performed in Germany, are based on a population of women with GDM who were identified by selective testing. Additionally in the time period of the studies, the diagnosis of GDM was based on the O'Sullivan criteria (90/165/145 mg/dl) in most institutions in Germany.

1.2.4   Therapy

Antepartum treatment of women with GDM should be focused on the prevention of fetal complications. Dietary education is the first step in the treatment for GDM. The nutritional prescription should provide the caloric needs for pregnant women of 30 kcal per kilogram of actual body weight. The total intake should be reduced to 25 kcal for overweight women. Self monitoring of blood glucose is superior to less frequent measurements in the clinic. The recommended frequency of the glucose profiles consisting of 3 pre-and 3 postprandial measurements varies between twice per week or daily. Glycemic goals during pregnancy are fasting values < 90 mg/dl, 1 hour postprandial < 140 mg/dl and 2 hour values < 120 mg/dl. [19] In women who fail to achieve or maintain normoglycemia additional insulin therapy is recommended. Physical activity after meals increases glucose consumption and insulin sensitivity and it had been shown that in women with GDM insulin therapy could be avoided by a strict exercise protocol. [22]

2.   Own contributions

2.1.   The influence of maternal glycemia on embryogenesis

2.1.1   Introduction and summary

Preexisting diabetes is a well known risk factor for congenital anomalies since maternal hyperglycemia during time of embryogenesis has a teratogenic effect of the development of the embryo. [23-28] Data from animal and clinical studies have demonstrated a correlation of the degree of maternal hyperglycemia during early pregnancy and the occurrence of malformations in the embryo. [29-31] Preconceptional care and optimizing of maternal glucose control can reduce the rate of anomalies to the level of the normal population. [27, 32, 33] In women with preexisting diabetes, a great body of data is available to assess the risk for diabetes based on the level of maternal glucose values. Congenital anomalies typical for diabetes affect primarily the heart, central nervous system, kidneys and the axial skeleton.

Figure 3: Newborn with caudal regression syndrome - the most specific but rare congenital anomaly in pregnancies complicated by diabetes (from Smith's Recognizable Patterns of Human Malformation)

Disturbance of fetal development causing these disorders must occur during the first 8 weeks of pregnancy. Thus, GDM is not considered as risk factor for congenital malformations because it typically develops not before the late second trimester coincident with the decreasing insulin sensitivity at this time. But the definition of GDM as any glucose intolerance diagnosed first in pregnancy, comprises a wide range of metabolic

decompensation - from mild intolerance to overt hyperglycemia. It can be speculated that women with severe hyperglycemia at time of diagnosis of GDM might have had hyperglycemia in early pregnancy high enough to impart a risk for malformation to their children. So far, there had been very few data to quantify the risk of malformations in these heterogeneous population of women with GDM.

- Congenital malformations in offspring of women with GDM

Our study aimed to determine the incidence of congenital anomalies in women with hyperglycemia diagnosed first in pregnancy and to identify clinical predictors for an increased risk for anomalies. A total of 3743 infants of mothers with GDM who attended the Diabetic Clinic of the Los Angeles County-University of Southern California Women's and Children's Hospital between 1987 and 1995 could be analyzed. Infants with genetic syndromes and aneuploidy were excluded. The incidence of was 2.9% for major congenital and 2.4% for minor anomalies. There was no difference in maternal historical or glycemic parameters between mothers of pregnancies with normal infants and infants with minor anomalies thus we combined them for the further analysis. The multivariate analysis revealed that the fasting glucose concentration at time of diagnosis was the only independent predictor (Odds ratio 1.13 for each 10 mg/dl increase, 95% CI 1.08-1.16) for major malformations. The fasting glucose is an easy accessible clinical parameter since it is part of the diagnostic procedure. Thus we examined if there is a threshold glucose value for an increased risk. The population was divided into subgroups according their fasting glucose values using strata of 20 or 40 mg/dl respectively. There was an abrupt increase in the risk for major congenital anomalies at a serum glucose concentration > 120 mg/dl and again at >260 mg/dl (table 1).

Table 1: Rate of and odds ratio for the risk of major congenital malformations in a population of women with hyperglycemia diagnosed first in pregnancy

Fasting glucose (mg/dl)	Total population		Subgroup with normal oGTT 1- 4 month postpartum	
	Rate	OR (95%CI)	Rate	OR (95%CI)
≤ 120	62 (2%)	1.0	22 (1.7%)	1.0
121-260	39 (5%)	2.6* (1.7 - 3.8)	8 (3.7%)	2.1* (1.1-4.82)
> 260	7 (30%)	20.5* (8.5-50.7)	0	

* p< 0.05

The majority of our study population belonged to the ethnic group of Mexican-American who are characterized by a high degree of glucose intolerance due to insulin resistance. To exclude that our results were valid only for women with presumably undiagnosed preexisting type 2 diabetes, we repeat the analysis in a subgroup of women with normal oGTT (n= 1600) 1- 4 month postpartum. We identified the same cut-off at 120 mg/dl but there was no case of fasting glucose > 260 mg/dl in this subgroup.

• Patterns of congenital anomalies and their relationship to initial maternal hyperglycemia

In pregnancies with type 1 diabetes there is a predominance of organ systems which are frequently affected by congenital anomalies. In this second study we aimed to investigate 1.) the types of malformations in infants of mothers with GDM or type 2 diabetes and 2.) whether the types of anomalies occurring are related to the level of maternal hyperglycemia at entry to care. We hypothesize that some organ systems are more susceptible to hyperglycemia than others . Study subjects were again retrieved from our database of diabetic women attending the Diabetes Clinic of the Los Angeles County women's hospital. Diagnosed major congenital malformations were categorized by the number and type of affected organ systems.

In a total of 3764 women with GDM and 416 women with known type 2 diabetes mellitus. Maternal historical (age, prepregnancy BMI, prior pregnancy with macrosomia, stillbirth or anomalies) and clinical parameter (gestational age at first prenatal visit, first trimester exposure to sulfonylurea agents) and value of the initial fasting glucose and HbA1c were investigated regarding their relation to anomalies. 143 infants (3.4%) with major anomalies were identified, with a prevalence of 2.9% in GDM and 8.9% in type 2 diabetes. The most frequently affected organ systems were cardiac (37.6%), musculo-skeletal (16%) and central nervous system (9.8%).

In 16% of the infants multiple organ systems were affected. There was no predominance seen of any organ system affected with increasing fasting glucose values (figure 4). But major anomalies involving multiple organ systems were associated with significantly higher glucose levels (166 ± 64 mg/dl) than malformations which were limited to one affected organ system (141 ± 55 mg/dl, p=0.006.)

2.1.2   Discussion

In this first large-scale study in women with GDM, we could confirm the tight relationship between maternal glycemia and the rate of congenital anomalies that had been

% of major anomalies
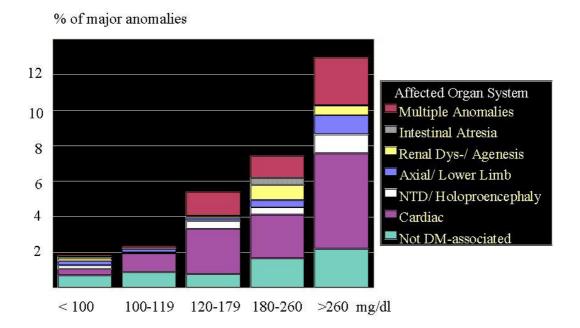
Figure 4:

Distribution of affected organ systems in infants with major anomalies according to the
fasting glucose value at entry to care

demonstrated in women with preexisting type 1 diabetes. Additionally, we saw the same
predominance of anomalies affecting the heart, skeleton and central nervous system in a
mixed population of women with GDM and known type 2 diabetes as reported from
pregnancies with type 1 diabetes.

The overall rate of major anomalies was slightly higher than in non-diabetic women of
our population. Our women with GDM had an unusual wide range of the degree of glucose
intolerance partly due to the high level of insulin resistance in the Mexican-American
population in Los Angeles. [34] There is a great chance that women with fasting glucose values
above our second identified threshold for an increased risk for anomalies (260 mg/dl) had
undiagnosed type 2 diabetes before pregnancy. But already glucose levels below the level
required for the diagnosis of diabetes outside pregnancy at the time of study (fasting glucose
140 mg/dl) were related with in increased rate for anomalies. [35] A second analysis in a
subgroup of women with normal postpartum oGTT and therefor little chance of having
preexisting diabetes confirmed that women who develop severe glucose intolerance first in
pregnancy are also at risk for an infant with congenital anomalies. We have no information
about the glucose values in early pregnancy since in general screening for GDM is

recommended not before 24-28 weeks of gestation. Thus, we could only speculated about the degree of hyperglycemia during embryogenesis which is required to cause anomalies. Interestingly our identified threshold of a fasting glucose value >120 mg/dl was identical with the threshold which was reported for 1st trimester glucose measurement in women with type 1 diabetes. [31] Regardless the final classification of diabetes after pregnancy, our data provide a useful tool to counsel women with hyperglycemia diagnosed first in pregnancy about their risk for major anomalies based on their fasting glucose levels at time of diagnosis. Ultrasound examination on a high level of expertise should de offered to women with fasting glucose > 120 mg/dl with special attention to the most frequently affected organ systems. Additionally, the high chance for anomalies involving multiple organ systems have to be considered since increasing glucose levels had been associated with a higher number of affected organ systems in the infants of our population. Further prospective studies are needed to develop strategies to identify preconceptionally women without overt diabetes but glucose intolerance sufficient to cause congenital anomalies. A minority of the women would have qualified for routine diabetes testing which is limited to women with age > 45 or other risk factors like prior GDM. [36] But even with routine testing the women who appeared to be at risk would not have been detected considering the existing diagnostic criteria for diabetes outside pregnancy at the time of the study. The rate of major anomalies was more than double in women with fasting glucose > 120 mg/dl, a level which was classified as normal by the recommendations of the American Diabetes Association from 1996. [36] Meanwhile the diagnostic criteria for diabetes outside pregnancy had been modified and a repeat fasting glucose measurement of 125 mg/dl in venous plasma and 110 mg/dl in capillary blood qualifies for the diagnosis of diabetes. [37]

2.2 The influence of maternal glycemic values on fetal growth and neonatal morbidity

2.2.1 Studies in pregnancies with borderline glucose intolerance

2.2.1.1 Introduction and summary

The diagnosis of GDM is based on the glucose values obtained by an oral glucose tolerance test. There is an ungoing discussion for three decade about the thresholds for defining maternal glucose intolerance in pregnancy which resulted in a great variation of glucose values used for the definition of GDM (table 2).

Table 2: Different diagnostic criteria used for diagnosis of GDM

	1964 O'Sullivan & Mahan	1979 NDDG[a]	1982 Carpenter & Coustan	WHO	1998 ADA[b]	Germany Until 2001	2001 DDG[c]	
Load (g)	100	100	100	75	100	75	75	
Method	SM-N[d]	GO/HK[e]	GO/HK	GO/HK	GO/HK	GO/HK	GO/HK	
Medium	VB[f]	VP[g]	VP	VP	VP	CB[h]	CB	VP
Fasting (mg/dl)	90	105	95	126	95	90	90	95
1H	165	190	180		180	165	180	180
2H	145	165	155	140	155	145	155	155

[a]National Diabetes Data Group
[b]American Diabetes Association
[c]German Diabetes Association
[d]Somogy-Nelson
[e]Hexokinase/Glukoseoxigenase,
[f]Whole venous blood
[g]Venous plasma
[h]Capillary blood

All used definitions were derived from the original criteria from O' Sullivan and Mahan from 1964. [21] But these were based on the subsequent maternal risk for diabetes and did not investigate the risk for fetal or neonatal morbidity. Furthermore there is more and more evidence that the relationship between maternal glycemia during pregnancy and neonatal morbidity behaves more like a continuum, with no precise threshold to discriminate between high and low risk fetus. [38] [39] For termination of thresholds for increased morbidity an untreated population of women with glucose intolerance in pregnancy would be needed. Since it is unethical to withhold a therapy that had been shown to reduce morbidity, the studies addressing this issue were limited to women with glucose intolerance below the existing

thresholds for gestational diabetes. They investigated the outcome either in women with positive glucose challange test but negative oGTT or in women with only one pathologic value in the oGTT.

- Fetal hyperinsulinism, neonatal obesity and placenta immaturity

The aim of the present study was to determine the impact of borderline glucose intolerance on diabetic fetopathy indicated by neonatal obesity, fetal hyperinsulinism and placenta immaturity. Our study was performed between 1992 and 1993 at the Department for Obstetrics at the Vivantes Medical Center Neukoelln in Berlin. We involved 325 women with risk factors for GDM who were tested for glucose intolerance by a 75 g oGTT. The O'Sullivan criteria were applied for diagnosis of GDM. Diabetes care consisting of diet education and frequent glucose profiles was limited to women with GDM, defined as usual by two pathologic values in the oGTT. The study population was divided into women with normal oGTT, women with one abnormal value (IGT= impaired glucose tolerance) and women with GDM and neonatal outcome was compared between the groups. Neonatal parameters tested were as followed: birth weight, large-for.gestational-age birth weight (LGA), skinfolds at three sites of the newborn (figure 5), amniotic fluid insulin at time of delivery, cord blood glucose and insulin, neonatal glucose and villous maturation of the placenta. Neonatal obesity was defined according percentile rankings obtained by skinfold measurements that had been previously performed in 250 consecutively born infants.

Figure 5:

Skinfold measurement at the triceps in a newborn

Women with one abnormal value had significantly higher rates of LGA infants and infants with central obesity, of hyperinsulinism and neonatal hyperglycemia compared to women with normal oGTT with a rate similar to women with GDM. Central obesity and hyperinsulinism with consecutive neonatal hypoglycemia was even more frequent than in pregnancies with GDM. Severe placental immaturity was seen most frequently in GDM pregnancies but again the rate in IGT was significantly higher compared to normal pregnancies.

- Neonatal Hypoglycemia in LGA newborns

Neonatal glucose testing is routine part of neonatal care in infants of mothers with known diabetes. Additionally, neonatal glucose testing is recommended in all LGA infants (birth weight> 90th percentile) independently of the diabetic status of the mother. Excessive growth is the major clinical sign of fetal hyperinsulinism due to maternal hyperglycemia in pregnancy. Macrosomic newborns are at increased risk for neonatal hypoglycemia when after delivery the insulin secretion has to be adapted to the sudden drop in glucose supply. Universal testing in all LGA newborns implicates unnecessary diagnostic in infants at low or no risk for hypoglycemia since only a minority of macrosomia is caused by diabetes. Therefor we investigated the rate of hypoglycemia in LGA newborns of non-diabetic mothers and whether maternal or neonatal risk factors for hypoglycemia could be identified. In 887 LGA infants, we observed hypoglycemia within the first day of life in 16% of the infants with a steep decrease of the incidence after the first two hours.

There was no clinical useful predictor for hypoglycemia unless glucose values of an oGTT in pregnancy were available. In the subgroup of infants of mothers with oGTT the 1 hour-glucose value was an excellent discriminator between infants at low, intermediate or high risk for hypoglycemia. Three cutoff points with stepwise increase in the rate of hypoglycemia were identified. The rate of hypoglycemia was 2.5% for glucose values $\leq$ 120 mg/dl, increased to 9.3% for values of $\geq$ 120 and $\leq$ 179 mg/dl and further to 22% for $\geq$ 180 and $\geq$ 239 mg/dl.

2.2.1.2. Discussion

Several groups have been shown that women with glucose intolerance below the existing thresholds for gestational diabetes have a higher rate of macrosomia, cesarean delivery and preeclampsia. [38-42] The best evidence comes from the Toronto Tri Hospital study, a prospective study that involved 3600 women with normal oGTT, patients and care

givers were blinded to the glucose values. They could demonstrate a graded increase in adverse maternal-fetal outcome with increasing maternal carbohydrate intolerance. [38] In addition to other studies which were limited to clinical complications known to be increased in diabetes, we could confirmed the influence of borderline glucose intolerance on very specific parameters for diabetic fetopathy. Beside macrosomia and hypoglycemia also hyperinsulinism, trunk obesity and placenta immaturity were significantly more frequent in untreated women with IGT than in normal women. Our second work related to this topic concentrated on macrosomic infants of non-diabetic mothers. We could show that the risk of neonatal hypoglycemia in these infants is tightly related to the 1-hour oGTT value of the mother. Interestingly, the identified threshold corresponds to the threshold for an abnormal 1-hour value according to the Carpenter and Coustan criteria for GDM. [20] Thus, all mothers of the infants at greatest risk for hypoglycemia had IGT that was not treated because the oGTT did not fulfill the criteria for GDM. Secondly, our data support the clinical importance of a general screening for GDM since without available oGTT values a risk assessment for hypoglycemia in LGA newborns seems not be possible.

2.2.2   The impact of maternal obesity

2.2.2.1 Introduction and summary

The hypothesis of Pedersen proposed that glucose from the maternal circulation is a major regulator for fetal growth. [14] A large body of clinical and experimental studies supported that maternal hyperglycemia enhances fetal growth by an excessive glucose supply to the fetus at a time when the fetal pancreas is able to respond by increasing its production of insulin. [43-45] Although the stimulation of insulin secretion starts with 11-15 weeks of gestation [46], accelerated growth due to maternal diabetes occurs at around 28 weeks, presumable because of the fetal capacity to store triglycerides at that time. [47] Thus, it is obvious that maternal hypergylcemia is a risk factor for macrosomia, however the regulation of fetal growth is far more complex and is influenced by many factors. The clinical experience indicates that despite of tight glucose control neonatal macrosomia occurs. On the other side, normosomic infants are born to mothers with hyperglycemia.

• The correlation of maternal obesity and high rates of fetal macrosomia

Existing studies are limited to the investigation of the influence of maternal glycemia and LGA at time of birth. Our study aimed to examine the correlation of maternal glucose values and fetal growth at different gestational weeks of pregnancies in normal and overweight women with GDM. In 406 women with GDM or IGT a total of 919 serial ultrasound examinations was performed. A fetal abdominal circumference > 90th percentile according to gestational age [48] was defined as fetal macrosomia. Glucose values at diagnosis - oGTT , entry glucose profile and HbA1c – and the glucose values of the profiles performed at 5 different categories of gestational weeks were compared between pregnancies with and without fetal macrosomia diagnosed at correspondent gestational ages. Each analysis was adjusted for maternal obesity, defined as body mass index (BMI) ≥ 30 kg/m^2. [49] There was no difference in glucose values either at entry or during pregnancy between pregnancies with or without fetal macrosomia either in lean nor in obese women. In contrast, the fetal macrosomia rate was significantly higher in obese compared to lean women at each category of gestational age and at birth.

• Determinants for *in utero* macrosomia at different gestational ages

Our first work revealed the strong influence of maternal obesity on fetal growth. In a second step, we investigated the influence of other maternal parameters. We use the above described population to determine independent predictors for fetal macrosomia at different periods of pregnancies and at birth. We included maternal historical (prior pregnancy with LGA or GDM, prepregnancy BMI and parity) and glycemic parameters at entry (oGTT, HbA1c and mean fasting and postprandial glucose values of the daily profile) and the glucose values of the profiles at the different periods of pregnancy. We found different parameters univariately associated with accelerated growth at different times of pregnancy: LGA in a previous pregnancy, parity, prepregnancy obesity, fasting of the oGTT or fasting glucose at 32GA. The independent predictors are displayed in figure 6.
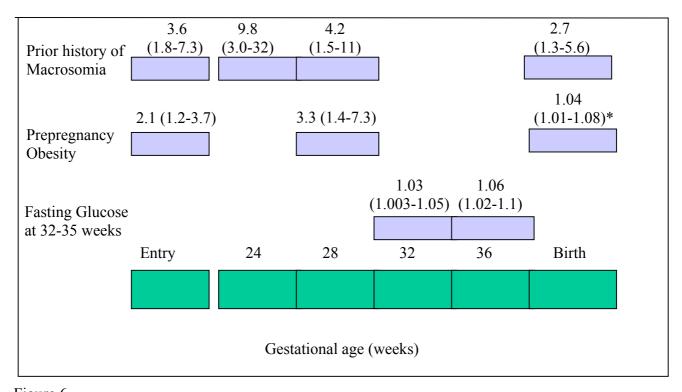

Figure 6

Timeline of independent predictors for an AC≥90th percentile at entry, in different gestational age categories and for large-for-gestational age birth weight in pregnancies with GDM and IGT. (Odds Ratio and 95%CI given). Obesity was defined as BMI ≥ 30 kg/m2. OR per 5 mg/dl increase of fasting glucose

2.2.2.2. Discussion

The complexity of fetal growth occurs at several levels determined by the mother, the placenta and the fetus. Both of our presented studies revealed the strong influence of maternal obesity on the risk for accelerated growth. At no time in pregnancy, a higher rate of fetal macrosomia was associated with higher maternal glucose values but with obesity. Obesity is often associated with elevated lipids and proteins and peripheral hyperinsulinism which had been shown to be related to the risk for macrosomia. [50-52] Lipids and amino acid levels are influenced by the carbohydrate metabolism but there is no linear correlation between the elevation of glucose and non-glucose nutrients. Thus, the effect of hyperlipidemia and hyperacidemia on fetal growth cannot be eliminated solely by glucose control. When we looked for other maternal predictors in the second analysis, we found independent predictors that represent the three major determinants of fetal growth. A history of a prior LGA infant representing the genetic influence, maternal obesity reflecting genetic and non-glucose fuels and the fasting hyperglycemia indicating an increased glucose supply to the fetus. In the early pregnancy the influence of genetic factors predominates; about 15% of the variation in birth weight is due to genetic predisposition. [53] It could be shown that an early symmetric accelerated growth is not associated with fetal hyperinsulinism. [54] In the early third trimester maternal obesity became a strong predictor coincident with the time of fetal adipocyte proliferation and lipid storage. Maternal glycemia appears to have the strongest influence in the late trimester, the time when accelerated growth in diabetic pregnancies was described [55, 56]. Maternal hyperglycemia leads via fetal hyperinsulinism to an increase of the insulin sensitive tissue, like the adipose tissue.

In summary, our GDM management that was focused on tight glucose control could not lower the macrosomia rate in obese women. Considering the strong influence of non-glucose related parameters, a modified approach in obese women might be more effective to lower the high rate of LGA infants in these women.

2.3. The importance of the fetal abdominal circumference in pregnancies with diabetes

2.3.1. Introduction and summary

As demonstrated above, the reliability of maternal glycemic values to predict diabetic morbidity in the newborn is limited. Normalization of maternal hyperglycemia could lower the rate of adverse outcome in pregnancies with GDM but the rate of macrosomia and neonatal morbidity is still elevated compared to the normal obstetrical population. [1] In studies with very strict control the macrosomia rate had been lowered to 10% but this management required intensive insulin therapy in 66-100% of the women. [57-59] Furthermore, in gestational diabetes aggressive lowering of the maternal glucose levels may lead to an increased rate of intrauterine growth retardation and an adverse perinatal outcome for small-for-gestational-age newborns. Attainment of strict control in all women with GDM might result in unnecessary treatment in low-risk pregnancies and absorption of limited resources needed for intensive therapy in high-risk pregnancies. Therefor some researchers were looking for other predictors besides maternal glycemia to identify pregnancies at high risk for morbidity. One approach is based on fetal growth [60-62] and limits intensive insulin therapy to pregnancies with accelerated growth of the fetal abdominal circumference (AC). Diabetes associated macrosomia is characterized by an asymmetric growth of the fetal abdomen versus head and long bones due to the stimulation of the insulin sensitive fat tissue by fetal hyperinsulinism (fig.1). [63, 64] In diabetic pregnancies, the fetal AC (fig. 7) measured in the early third trimester revealed to be a good predictor for a LGA newborn. [47, 55, 56]

Figure 7

Measurement of the fetal abdominal circumference

The second approach uses amniotic fluid insulin to diagnose fetal hyperinsulinism. [65-68] The level of fetal insulin is supposed to correspond to the level of insulin in the amniotic fluid secondary to the urinary excretion. When insulin levels are elevated, insulin therapy is either initiated or intensified. Although this approach offers a direct estimation of the fetal reaction on maternal glycemia, it is not widely accepted because it requires an amniocentesis as an invasive procedure to obtain amniotic fluid.

• Fetal abdominal circumference as predictor for neonatal macrosomia

Existing data demonstrate the tight relation of the fetal AC in the third trimester with the LGA status at birth but there is a paucity of data investigating the predictive power of the fetal AC compared to maternal parameters known to influence fetal growth. Therefor we determined independent predictors for LGA and their predictive power. Secondly, we aimed to create a score of the discriminatory parameters and quantitated the predictive power by receiver operator characteristics (ROC) curves analysis. In 728 women treated for GDM four independent predictors could be identified: a history of GDM, prior delivery of an infant > 4000 g birth weight, prepregnancy BMI $\geq$ 30 kg/m^2 and fetal AC $\geq$ 90th percentile at entry with the fetal AC being the strongest predictor (OR 3.9) (unpublished data 5.3). None of the glycemic parameters revealed to be predictive. The area under ROC curve of a score based on the three historical risk factors was 0.66, which could be increased to 0.71 by inclusion of fetal AC at entry to diabetes therapy (p>0.05). The negative predictive value (NPV) for women with no risk factor was 0.90 and improved to 0.93 when the fetal AC was considered as well. Subsequent ultrasound examinations did not improve predictive power of the score.

• Correlation of amniotic fluid insulin levels and fetal abdominal circumference at time of amniocentesis

The fetal AC measurement is an indirect approach to assess fetal morbidity in pregnancies with diabetes based on a clinical manifestation of fetal hyperinsulinism. But since fetal growth is influenced by many other factors beside the fetal insulin levels there is still a concern of over- or under-treatment when insulin therapy is administered solely depending on the fetal AC. Thus, we investigated the correlation between amniotic fluid insulin (AF insulin) and fetal AC percentiles at time of amniocentesis performed in the third trimester in 121 diabetic women. In a second step, we aimed to find a threshold for fetal AC measurements that identifies low vs high risk levels of AF insulin without performing an amniocentesis. We could show that AF insulin levels were significantly correlated with the

AC percentiles (r=0.3, p=0.0005) by linear regression. Division of the cohort according to AC percentiles revealed a significant stepwise increase in AF insulin ≥ 7 µU/ml at the 80th percentile of the AC. An amniotic fluid insulin ≥7 µU/ml was previously defined as 90th percentile of a normal obstetrical population by our group. [69] But the negative predictive value (NPV) was low (77.6 %) and the ROC curve confirmed that there was no good threshold of the fetal AC to identify an AF insulin ≥7 µU/ml (fig 8). In contrast an AC threshold ≥ 75th percentile could reliably identify fetal hyperinsulinism with an AF insulin ≥16 µU/ml. All 10 cases of AF insulin ≥16 µU/ml were identified with a NPV of 100% (74/74).
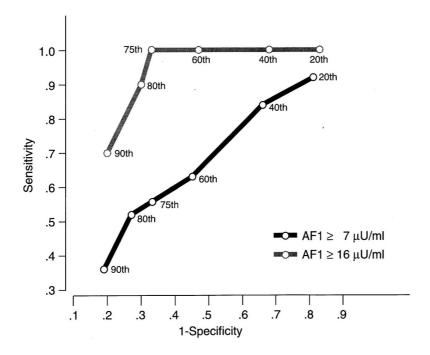
Figure 8: ROC curves for the fetal abdominal circumference to identify amniotic fluid insulin ≥ 7 µU/ml and ≥ 16 ≥ 7 µU/ml

2.3.2. Discussion

Both our studies support the importance of the fetal AC in the management of pregnancies with diabetes. The percentiles of the fetal AC corresponded to the level of the fetal insulin indirectely determined by the AF insulin. The fetal AC ≥ 90th percentile was the strongest predictor for an LGA infant within a wide selection of tested parameters. In contrast, as we expected from our previous studies, the maternal glycemic values in this treated population were not predictive. We can only speculate if maternal glycemia would be more discriminative in an untreated population with a wider range of glycemic values.

Surprisingly, the predictive power of a score created from historical data was only slightly improved by inclusion of the fetal AC. Easy obtainable historical data by itself seem to provide enough information for clinicians to antenatally estimate the risk for an LGA newborn. All predictors in a single or combined fashion are superior in identifying an infant at low risk for excessive growth (NPV) while the sensitivity and specificity did not exceed 77% or 53%, respectively. Similar, the identified threshold fetal AC for an increased risk for severe fetal hyperinsulinism was highly reliable in excluding hyperinsulinism but weak in predicting elevated insulin levels > 16 µU/ml. For moderately elevated insulin levels the fetal AC offers no reliable tool for risk assessment. Almost 50% of the cases would have been missed by the identified AC threshold for AF insulin > 7 µU/ml. Kainer et al, the only group so far that investigated the relation of amniotic fluid insulin and the fetal AC also found the AC measurement to be useful only in identifying high levels of insulin. [70] Our finding corresponds to the data of Weiss et al who had demonstrated that neonatal morbidity was mostly limited to AF insulin levels which were increased 2 - 3 fold above normal. [66] There is evidence that excessive birth weight is limited to markedly AF insulin levels about ≥ 20 µU/ml [66, 71]. Similarly, long term effects of fetal hyperinsulinism like an increased rate of childhood obesity also appear to be restricted to the levels of AF insulin ≥ 20 µU/m. [72] These insulin levels correspond closely to the insulin level of ≥ 16 µU/ml that according to our data can be identified by an AC ≥ 75th percentile. Interestingly, the AC threshold of the 75th percentile found by our study to identify severe hyperinsulinism was identical to the AC threshold which has been recommended for initiating insulin therapy in GDM. [60-62]

2.4.   Intervention studies – management of GDM based on fetal growth

2.4.1   Introduction and summary

Fetal growth in pregnancies complicated by diabetes is related to maternal glycemia but it is controversial to what extend hyperglycemia determines morbidity. [1] In agreement with other groups, we could show that the relation of neonatal morbidity and maternal glucose values seems to behave in a continuous fashion. [38, 42, 73-76]   Thus, the glucose targets that we aim to achieve during pregnancies are arbitrary and consensus based. Recently it had been shown that the 97th percentile of the 1-hour postprandial glucose value of women with normal glucose tolerance is far below the recommended cutoff for insulin therapy of 140 mg/dl. [77] The best evidence that the same maternal glucose values may result in different outcome comes from observations in twins. [78] Applying the strategy of tight glucose control on all women misses the change to target intervention on pregnancies with high risk for morbidity. In a pilot study limited to women with normoglycemia it was demonstrated that a single measurement at entry to therapy could identify a fetus at risk for macrosomia. Intensive insulin therapy could lower the macrosomia rate by 3 fold in this high risk population compared to those who were treated with diet only. The overall macrosomia rate of the study population was reduced without applying insulin to the majority of the women. Our subsequent studies which will be presented in the following aimed (1) to extend this approach to women with hyperglycemia and (2) to proof the applicability of this strategy in a population with a different ethnic background and without prior stratification according to the maternal glycemia status.

• Fetal growth based approach applied in Latino women limited to women with maternal hyperglycemia

Eighty-nine women with GDM and venous fasting glucose levels $\geq$ 105 < 200 mg/dl after a 1 week trial of diet were randomized to a standard and an experimental group. The standard group was treated with insulin due to maternal hyperglycemia. In the experimental group insulin therapy was limited to pregnancies with a fetal AC > 70th percentile at entry or in one of the subsequent monthly ultrasound examinations. Additionally, insulin was applied when maternal glucose exceeded fasting > 120 mg or postprandial 200 mg/dl. There was no difference in maternal characteristics at entry between the two study groups. According to the protocol, the glucose values during pregnancy were lower in the standard group compared to the experimental group. In the experimental group (n=48), insulin therapy was applied in 27

(56%) women because of fetal AC > 70th percentile, in 3 women because of fasting glucose > 120 mg/dl or non-compliance and in 18 (=38%) insulin could be withhold. The neonatal outcome did not differ between the groups with overall low rates of LGA newborns (6.3 vs 8.3 % for standard versus experimental group). Delivery by Cesarean section was performed more frequently in the experimental group but this could not be explained by complications related to diabetes. Despite intensive insulin therapy the LGA rate in women with fetal AC > 70th percentile at entry was higher than in women with normal fetal growth.

• Evaluation of the fetal growth based approach in a Caucasian population without respect to maternal glycemia status

In this study women with diagnosis of GDM according O'Sullivan criteria were enrolled who attended the Diabetic Prenatal Care Clinic either of the Charité or of the Vivantes Medical Center in Berlin. Both institutions take care of a multiethnic population with a rate of approximately 40% women from Turkey, Arabian countries or East Europe. Women from Latin-America are rare. The women were randomized to a standard (n=100) and an ultrasound group (US-group, n=99) when fasting glucose < 120 mg/dl and postprandial values < 200 mg/dl in the glycemic profiles after one week of diet. In the standard group, women stayed on diet unless fasting glucose > 90 mg/dl and/or postprandial glucose >120 mg/dl. The US-group was started on insulin if fetal AC exceeded the 75th percentile at entry or at any examination thereafter corresponding to a 4 week examination schedule at 20, 24, 28, 32 weeks of gestation. Additional, insulin was recommended in case of severe maternal hyperglycemia defined as fasting glucose ≥ 120 mg/dl or postprandial ≥ 200 mg/dl. The two groups were similar regarding historical data, glycemic data and the rate of fetal AC at entry. In the US-group insulin was given exclusively based on AC > 75th percentile. Neonatal outcome was not significantly different in both groups. When we analyzed a subgroup of women with GDM according to Carpenter and Coustan criteria (n=161) the results were identical with the exception of a higher rate of insulin use in the standard group. In a secondary analysis in women with euglycemia and AC >75th percentile (n=34) the rate of LGA, C-section and neonatal hypoglycemia was lower in the insulin treated US-group compared to corresponding women in the standard-group. In those pregnancies with maternal hyperglycemia but AC< 75th percentile (n=35) there was no adverse outcome in the US-group although insulin was withheld.

2.4.2   Discussion

Both our studies demonstrated that a management based on relaxed glycemic criteria combined with fetal AC measurements is a safe approach for mother and child independent on the ethnic background of the study population. The measurement of the fetal AC with ultrasound reliably identified fetuses at low risk for accelerated growth. This supports the prior work of Bochner, Landon and Ogata. [47, 55, 56] In GDM managed by a fetal-growth based approach the neonatal outcome was similar to pregnancies guided solely by maternal glycemia even in selected women with hyperglycemia from a population of Mexican-Americans that is known to have a high rate of severe glucose intolerance. [34] Insulin therapy could be avoided in 38 % of these women and in 43% of Caucasian women with hyperglycemia investigated in Berlin. The "Berlin study" combined the two pilot studies from Los Angeles and included both women with normoglycemia and hyperglycemia. The overall rate of insulin use was slightly higher in the US-group compared to the standard approach. This reflects the mild degree of glucose intolerance when diagnosis of GDM is based on the low diagnostic criteria for GDM of O'Sullivan. [21] When we excluded women who did not fulfill the Carpenter and Coustan criteria that require higher post challenge glucose values, the insulin use in both study arms was similar. When we looked at the women who were treated differently in the US-group compared to the standard group we realized a better outcome in the US-group: a tendency toward a lower SGA rate in women with hyperglycemia but normal fetal growth and a lower LGA rate in women with euglycemia but accelerated growth. The last finding confirmed the study of Buchanan. [60] Interestingly, in both studies the LGA rate was unexpectedly low in the standard group. It can be only speculated about the influence of increased attention and motivation under the conditions of a clinical trial and the frequent demonstration of fetal growth by serial ultrasound examinations.

3.   Relevant original publications

3.1   The influence of glycemia on the embryogenesis

(1)   **Schaefer**, UM, Songster, G., Xiang, A, Berkowitz, K, Buchanan, TA, Kjos, SL. Congenital Malformations in Offspring of Women with Hyperglycemia First Detected During Pregnancy. Am J Obstet Gynecol. 177 (1997) 1165-71

(2)   **Schaefer - Graf,** UM, Buchanan, TA, Xiang, A, Songster, G, Montoro M, Kjos, SL. Patterns of Congenital Anomalies and Relationship to Initial Maternal Fasting Glucose Levels in Pregnancies Complicated by Type 2 and Gestational Diabetes. Am J Obstet Gynecol. 182 (2000) 313-20

3.2   The influence of maternal glycemia and maternal obesity on fetal morbidity

3.2.1. The impact of borderline glucose intolerance

(1)   **Schäfer-Graf,** UM**,** Dupak, J, Vogel, M, Dudenhausen, JW, Kjos, SL, Buchanan, TA, Vetter, K. Hyperinsulinism, Neonatal Adiposity and Placental Immaturity in Infants born to Women with One Abnormal Glucose Tolerance Test Value. J Perinatal Med. 26 (1998) 27-36

(2)   **Schaefer-Graf,** UM, Rossi, R, Bührer, C, Siebert, G, Kjos, SL, Dudenhausen, JW , Vetter, K.   Rate and risk factors of hypoglycemia in large-for-gestational-age newborns of non-diabetic mothers. Am J Obstet Gynecol (2002), 187, 913-7

3.2.2. The impact of maternal obesity

(1)   **Schaefer-Graf**, **UM,** Heuer, R , Kilavuz , Ö, Pandura, A, Henrich, W, Vetter, K. Maternal Obesity not Maternal Glucose Values Correlates Best with High Rates of Fetal Macrosomia in Pregnancies Complicated by Gestational Diabetes.

J Perinatal Med (2002), 30, 313-321

(2)   **Schaefer-Graf, UM**, Kjos, SL, Heuer, R, Brauer, M, Vetter, K, Dudenhausen, JW. Determinants for *in Utero* Macrosomia at Different Gestational Ages in Pregnancies Complicated by Gestational Diabetes and Impaired Glucose tolerance
Diabetes Care (2003), 26,193-198

3.3.   The fetal abdominal circumference as predictor for fetal hyperinsulinism and macrosomia at birth

(1)   **Schaefer-Graf**, UM, Henrich, W, Bühling, KJ, Kjos, SL, Heinze, T, Engel, A, Buchanan, TA, Vetter, K, Dudenhausen, JW. Amniotic Fluid Insulin levels and Fetal Abdominal circumference at time of Amniocentesis in Pregnancies with Diabetes. Diabetic Medicine 20 (2003) , 349-35

(2)   Ute M. **Schaefer-Graf**, Christoph Bührer, David A Sacks, Gerda Siebert, Ömer Kilavuz, Siri L. Kjos, Joachim W. Dudenhausen, Klaus Vetter. Does the addition of sonographic measurements of fetal abdominal circumference enhance the prediction of large-for-gestational-age newborns in pregnancies treated for gestational diabetes? Diabetes Care (2003) submitted

Predicting neonatal macrosomia in women treated for gestational diabetes: Evaluation of a score based on maternal history and fetal ultrasound

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Key words: ultrasound, diabetes, pregnancy, predictors, large-for-gestational age newborns

Condension

Maternal historical parameters and the fetal abdominal circumference predict an LGA infant but the predictive value is limited and is only slightly improved by the inclusion of ultrasound.

Abstract

Objective: The aim of treatment of women with gestational diabetes (GDM) includes prevention of the development of a large-for-gestational-age infant (LGA). To reserve intensified interventions for women at increased risk, we investigated potential LGA predictors and asked if inclusion of fetal ultrasound could enhance predictive power.

Research Design: In 728 women treated for GDM, maternal history variables, maternal glycemic values, and fetal abdominal circumference (AC) at entry and thereafter were compared between LGA and non-LGA infant women. Parameters identified by univariate analysis were investigated for their ability to predict LGA individually or collectively.

Results: A history of GDM (OR 1.9), prior delivery of an infant >4000 g birth weight (OR 2.2), prepregnancy BMI $\geq$30 kg/m^2 (OR 2.4), and fetal AC $\geq$90th percentile at entry (OR 3.9) but not glycemic values were independent predictors of LGA. The area under a receiver operator characteristics curve of a score based on historical risk factors was 0.66. The area increased to 0.71 or 0.72 after inclusion of one or two fetal AC measurements, respectively. The negative predictive value for women with no risk factor excluding or including ultrasound at entry (n=437 and 356) was 0.90 and 0.93, respectively (p > 0.05). Subsequent ultrasound examinations did not improve predictive power.

Conclusions: In women treated for GDM, maternal history and sonographically-determined measures of fetal AC independently predict delivery of an LGA infant while glycemic values do not. However, the predictive value of these parameters is limited and is only slightly improved by the inclusion of ultrasound.

Introduction

Excessive growth due to fetal hyperinsulinism is a major clinical problem in pregnancies complicated by gestational diabetes (GDM). Presumably, infants born large-for-gestational-age (LGA) to mothers with GDM have been exposed to hyperglycemia in utero for prolonged periods of time and therefore are more prone to its long-term metabolic sequelae. In addition, LGA infants are at increased risk for obstetrical complications, and the rate of birth injuries of LGA infants born to GDM mothers even exceeds that of LGA infants born to non-GDM mothers. [1]

To prevent the development of a LGA infant, interventions during pregnancy are focussed on the maintenance of maternal glucose values within a strict range supposed to reduce the risk for neonatal macrosomia and other morbidities. Despite apparently successful efforts toward maternal glycemic control the macrosomia rate in pregnancies complicated by gestational diabetes (GDM) is often reported to be higher than in a normal obstetrical population. [2-4] Antenatal risk assessment for LGA might improve the management of women who have GDM. In the present study, we evaluated the predictive ability of antenatal risk factors for the development of a large-for-gestational-age (LGA) infant and specifically assessed the contribution of individual or serial measurements of the fetal abdominal circumference (AC) by ultrasound. A score was created of the discriminatory variables, and its predictive power quantitated by receiver operator characteristics (ROC) curve analysis.

Research Design and Methods

Study population

Subjects were retrospectively selected from the population of women with glucose intolerance who attended the Diabetes Clinic of the Department of Obstetrics of an urban community hospital between 1994 and 2000 and had been entered into an ongoing database. Study inclusion criteria were: 1.) documented glucose intolerance first diagnosed in pregnancy ; 2.) accurate gestational age, confirmed by an ultrasound examination before 20 weeks of gestation; 3.) singleton pregnancy; 4.) at least one complete fetal biometry determined by ultrasound at entry to diabetic therapy; 5.) absence of identified fetal anomalies; 6.) documented data regarding maternal obstetrical history and anthropometry and 7.) documented delivery data.

Reflecting obstetrical standards in Germany, testing for GDM in our study subjects was performed selectively in women with risk factors. In women with historical risk factors testing was preformed in the first trimester otherwise whenever risk factors first occurred (e.g.

glucosuria) or were diagnosed (e.g. fetal macrosomia). The diagnosis of GDM was established by a 75g oral glucose tolerance test (oGTT) with determination of capillary blood glucose levels by glucose oxidase (Beckman Glucose Analyzer, Brea, CA). Diagnostic criteria for GDM valid in Germany at the time of study were: fasting $\geq$90 mg/dL (5.0 mmol/l); 1 hour $\geq$165 mg/dL (9.1 mmol/l), 2 hour $\geq$145 mg/dL (8.0 mmol/l) (adopted from O'Sullivan [5]). Diagnosis of GDM required at least two abnormal values, and of impaired glucose tolerance (IGT) one abnormal value.

Women with GDM and IGT were educated regarding an individualized diabetic diet based on prepregnancy weight (30 kcal/kg/d) with caloric restriction for obese women (25 kcal/kg/d). All women were instructed to self-monitor blood glucose (SMBG) by performing a daily glucose profile (3 preprandial and 3 1-h-postprandial measurements) twice a week using a reflectance meter with electronic memory (Advantage Glucose meter, Roche Diagnostics, Germany). Accuracy of the glucose meters was tested biweekly by comparison with a laboratory glucose measurement (glucose oxidase). Insulin therapy was recommended when the mean of all glucose values of a profile exceeded 100 mg/dL (5.5 mmol/l) after a two-week trial of diet. Insulin dose was adjusted to achieve fasting glucose values $\leq$90 mg/dL (5.0 mmol/l) and 2 hour postprandial values $\leq$120 mg/dL (6.6 mmol/l). Women treated with insulin therapy were asked to perform glucose profiles every day.

An initial ultrasound examination with complete fetal biometry was scheduled at the entry visit and monthly in conjunction with Diabetes Clinic visits. The fetal abdominal circumference (AC) was measured in the standard cross-section view of the abdomen. [6]

Potential risk factors and outcome data

Maternal parameters assessed included age, parity, history of prior macrosomia (birth weight $\geq$90th percentile for gestational age in at least one previous pregnancy [7]) or GDM, prepregnancy body mass index (BMI) and weight gain during current pregnancy. Glycemic parameters included gestational age (GA) at time of diagnosis, glycosylated hemoglobin levels (HbA$_{1c}$) at diagnosis, glucose levels of the diagnostic oGTT and from of the daily glucose profiles during pregnancy and insulin use.

The only fetal measurement utilized was the AC percentile for gestational age. All ultrasound measurements performed during the study were divided into 5 categories according to gestational age at time of examination, i.e. < 24, 24/0 –27/6, 28/0-31/6, 32/0-35/6, and 36/0 to 40/0 weeks/days. For purposes of data analysis AC measurements were

classified as either $\geq$ or $< 90^{th}$ percentile for gestational age according to standards published by Hadlock, et al. [6]

Newborn parameters included birth weight and length and classification of the infants as large-for-gestational-age (LGA) or non-LGA. LGA was defined according the 90th percentile for gestational age using current German growth curves. [7]

Statistical analysis

Differences between pregnancies resulting in LGA and non-LGA neonates at birth were tested for statistical significance by the Mann Whitney U test (continuous variables) or by $\chi 2$ analysis (categorical variables). Data are presented as mean $\pm$ SD.

A multivariate logistic regression analysis was performed to determine independent predictors of LGA neonates with their associated odds ratios. The sensitivity, specificity, positive and negative predictive value (PPV/NPV) to predict LGA were calculated for each predictor and for scores which combined all identified predictors. The scores were created based on the number of absent or present of identified risk factors, either with or without inclusion of a fetal AC $\geq 90^{th}$ percentile as additional risk factor diagnosed exclusively at the first or at the first or second ultrasound. The predictive values were calculated for different cutoff points; absence of any versus presence of at least 1 risk factor, presence of 0-1 versus at least 2 risk factors and 0-2 versus at least 3 risk factors. The predictive power of each score was described by the area under a ROC curve.

All statistical analyses were performed with the statistical program SPSS 10.0 (SPSS, Chicago).

Results

A total of 1058 women had been entered in the database until December 2000. Of these, 54 women were excluded because of preexisting diabetes, and 276 women because of missing data, thus leaving 728 women for the final analysis. 552 (75.8 %) of the women were diagnosed with GDM, and 176 (24.2%) with IGT. While GDM women had significantly higher oGTT values, as compared to IGT women (fasting: 96.7 $\pm$ 22.0 vs 81.5 $\pm$ 23.9 mg/dL; 1 hour 204.1 $\pm$ 31.1 vs 179.9 $\pm$ 35.6 mg/dL; 2 hours 158.8 $\pm$ 37.1 vs 120.3 $\pm$ 25.3 mg/dL; p< 0.0001 for all comparisons), higher entry HbA$_{1c}$ levels (6.1 vs 5.4 %, p=0.05), and required insulin therapy more often (16.7.2% vs 6.3 %, p = 0.001), 3rd trimester glycemic control after initiation of therapy was not different between GDM and IGT women, as measured by fasting

and postprandial glucose values. Historical parameters did not differ significantly between the two groups, as did AC measurements at entry (AC $\geq$ 90th percentile, 21.7 % vs 24.7%) or LGA at birth (16.3 vs 13.6 %). Therefore, women with GDM and IGT were analyzed together.

A total of 1712 ultrasound examinations were available for analysis. Out of 728 subjects, in 35.1 % one ultrasound examination, in 23.7% two and in 41.2 % three to five examinations were performed. The entry ultrasound examinations were distributed almost equally between those performed prior to 28 weeks (38.1%), between 28 to 31/6 (29.0%) and 32/0 to 36/0 weeks /days (34.9). (Only 8 scans at entry were performed beyond 36 weeks of gestation) At entry, an AC $\geq$ 90th percentile was found in 22.4 % (177) of the pregnancies and there was at least one event of an AC $\geq$ 90th percentile throughout pregnancy in 26.5% (193) of the infants.

A total of 114 (of 728, 15.7%) women delivered an LGA infant. Table 1 displays maternal characteristics of mothers of LGA compared to those of non-LGA infants. (table). There was no difference in gestational age at diagnosis between pregnancies resulting in a LGA infant compared to AGA newborns. The LGA rate was 16.4% when GDM was diagnosed < 28 weeks of gestation and 14.9% for $\geq$ 28 weeks (p= 0.3). A fetal AC $\geq$ 90th percentile at entry or thereafter was found more frequently among babies destined to be LGA (p<0.0001, table 1). LGA infants were delivered significantly earlier than non-LGA newborns thus the maternal parameter weight gain was examined for difference between the two groups after adjusting for gestational age at delivery.

The multivariate regression analysis revealed four independent predictors for a LGA newborn (table 2). Calculations of the predictive power of the identified predictors are displayed in table 2. The NPV value of the fetal AC was slightly improved by a second ultrasound while a third measurement did not further increase the predictive power. Ultrasound examinations performed at different gestational ages (20/0-23/6, 24/0 –27/6, 28/0-31/6, 32/0-35/6, or > 36/0 weeks/days) had virtually identical NPV values (88.1% - 91.0%).

Scores were created combining the three identified historical risk factors, either with or without inclusion of one or two fetal AC measurements. For primiparae only the maternal BMI and the fetal AC was used as risk factors for the score. The predictive power is displayed in table 3. The area under the ROC curve was 0.61 for historical risk factors alone, 0.71 with inclusion of one and 0.72 of two ultrasound examinations. The area under the ROC curves of the two scores including ultrasound did not differ significantly compared to the score based only on historical factors (p = 0.12 and 0.14, respectively).

Comment

In this large-scale retrospective study of pregnant women treated for glucose intolerance, we identified and evaluated antenatal risk factors for delivery of an LGA infant and specifically assessed the value of repeat fetal AC ultrasound measurements. There are three major findings: First, a history of a prior baby weighing $\geq$ 4000 g, a prior maternal history of GDM, a maternal BMI $\geq$ 30 kg/m^2 were predictors of LGA babies. Second, fetal AC at entry was the strongest predictor of LGA neonates. However, the addition of the first fetal AC measurement to the maternal historical predictors improved the predictive power only slightly, and additional ultrasound examinations were of no further value. Third, all predictors, individually or collectively, had a limited ability to predict a LGA infant in this cohort of women.

In contrast to others' works, this study included detailed data documenting maternal glycemic values at entry and thereafter, and numerous consecutive ultrasound measurements of fetal growth. None of the glycemic parameters either at entry or thereafter was associated with LGA at birth. In untreated pregnant women with impaired glucose tolerance glucose values have, however, been found to be related to macrosomia. [8] The more stringent criteria defining need for treatment in our study and subsequent good glycemic control might explain the complete loss of the discriminative power of the glycemic parameters. In addition, factors besides maternal concentrations of glucose have been reported to be associated with birth weight. [9, 10,11]

The strongest predictor of an LGA neonate was a fetal AC $\geq$ 90th percentile at entry with a 4-fold increase of the risk for LGA. A large amount of data investigated the predictive power of ultrasound measurements for macrosomia at birth. [12-18] There is an agreement about the unsatisfied accuracy of the estimation of fetal weight obtained by ultrasound at term to predict an LGA newborn, especially in diabetic pregnancies or in extremely overweight infants. [17] Sonographic weight estimates are derived from cross-sectional data. Fetuses with accelerated growth due to maternal diabetes have been shown to have an increase in adipose tissue, which is less dense than fat-free tissue (e.g. muscle and bone). Thus the application of tables derived from an unselected patient population may lead to sonographic overestimation of fetal weight [19, 20]. This might explain our finding of a high false positive rate of the AC in predicting LGA babies which is consistent with the reports of others [13, 15]. However, there is evidence that the fetal AC is the best of all fetal measurements to identify macrosomic

growth. [12, 13, 15, 18] Recently, our group demonstrated that a fetal AC < 75th percentile reliably excluded fetal hyperinsulinism at a level which is known to be associated with morbidity. [21]

Few studies have assessed the utility of serial measurements in predicting birth weight, [15] but failed to provide information on how much incremental improvement in prediction is accrued with each additional examination. According to our data, the predictive power of repeat ultrasound examinations does not differ considerably from those of a single examination at entry. Surprisingly, the gestational age when the AC was obtained seemed to have a limited influence on the NPV. Most of the existing studies performed the AC measurement during a defined tight period (30-36 weeks) [14, 15] and did not determine the predictive power at different times of pregnancy.

In summary, there are antenatal maternal and fetal factors in GDM pregnancies which are significantly associated with an increased risk for accelerated growth but the delivery of an LGA infant in pregnancies complicated by GDM seems not to be predictable. Neither a single parameter, nor the combination of multiple maternal risk factors nor the inclusion of measurements of the fetal AC showed a satisfying predictive power. Likely due to the low incidence of LGA in our cohort, identification of those with a low LGA infant risk was possible with reasonable accuracy. The establishment of more specific, and easily reproducible sonographic measures of evolving diabetic fetopathy in utero as part of the routine ultrasound examination could further enhance the clinical value of involving fetal ultrasound.

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Table 1

Maternal characteristics and glycemic values in GDM pregnancies with and without LGA newborns(continuous variables expressed as mean ± SD)

	Non LGA (n= 115)	LGA (n=617)	p-value
Maternal history			
Age (years)	30.5 ± 5.4	31.1 ± 5.2	0.2
Multiparae (%)	54.9	67.0	0.01
Prepregnancy BMI (kg/m^2)	26.9 ± 6.0	29.9 ± 5.9	0.000
Prepregnancy BMI >30 kg/m^2 (%)	24.8	42.1	0.000
Prior GDM (% of multiparas)	19.2	37.7	0.001
Prior Macrosomia (> 4000 g) (% of multiparas)	14.2	41.8	0.000
Maternal glycemic values			
Gestational age at diagnosis	26.5 ± 5.6	26.0 ± 5.9	0.4
Oral glucose tolerance test			
- fasting (mg/dl)	92.7 ± 24.3	93.9 ± 18.5	0.6
- 1-h mg/dl)	198.2 ± 34.3	196.9 ± 43.2	0.7
- 2-h (mg/dl)	148.8 ± 38.6	151.5 ± 38.2	0.5
IGT (%)	24.6	20.9	0.6
Glycemic values at study entry			
Fasting of the profile	80.6 ± 14.1	83.4 ± 14.1	0.064
Postprandials of the profile	112.7 ± 15.3	116.5 ± 14.5	0.3
HbA1c (%)	5.7 ± 1.3	5.9 ± 1.2	0.09
Mean of fasting glucose during pregnancy			
28-31/6 weeks	81.5 ± 14.7	83.4 ± 15.3	0.4
32-35/6 weeks	79.3 ± 12.1	82.4 ± 12.2	0.58

Mean of postprandial glucose during pregnancy

28-31/6 weeks	106.3 ± 18.5	107.5 ± 18.6	0.7
32-35/6 weeks	105.5 ± 17.3	104.9 ± 17.5	0.8
Weight gain (kg)	11.8 ± 7.7	12.7 ± 5.9	0.3
Insulin use (%)	13.3	11.8.	0.2
Fetal and neonatal parameter			
AC ≥ 90th percentile at entry (%)	17.7	47.8	< 0.0001
At least 1 AC ≥ 90th percentile (%)	21.4	53.9	0.0000
GA at delivery (weeks)	39.0 ± 1.7	38.6 ± 1.9	0.04
Delivery by Cesarean Section (%)	17.9	24.3	0.07

Table 2

Sensitivity , specificity , positive and negative predictive value (PPV, NPV) of the identified independent predictors for LGA in pregnancies with GDM

	OR (95% CI)	Sensitivity	Specificity	PPV	NPV
Prior pregnancy with macrosomia	1.9 (1.07-3.5)	39.5	92.0	28.1	87.3
Prior pregnancy with GDM	1.9 (1.2-4.2)	31.6	89.4	26.3	86.7
Maternal BMI ≥ 30 kg/m^2	1.9 (1.2-3.)	42.5	75.5	24.2	87.6
AC ≥ 90th percentile at entry	3.9 (2.4-6.2)	48.7	82.4	33.7	89.6
At least 1 event of AC ≥ 90th in 1st or 2nd US	3.8 (2.4-6.1)	59.4	78.9	33.5	91.5
At least 1 event of AC ≥ 90th in 1st, 2nd or 3rd US	3.7 (2.3-6.3)	57.4	79.1	33.8	90.5

Table 3

Predictive values of a score based on the presence or absence of the identified risk factors (prior pregnancy with macrosomia or GDM, maternal BMI $\geq$ 30 kg/m^2) without or with inclusion of the fetal abdominal circumference $\geq$ 90th percentile as risk factor obtained by 1 or 2 ultrasound examinations. In primiparae only maternal BMI and fetal AC were considered

Cohort dived according to No. of risk factors	0 vs At least 1 RF Primiparae	Multiparae	0-1 vs At least 2 RF Primiparae	Multiparae	0-2 vs at least 3 RF
Score without US					
Spec	75.5	64.4		92.6	99.8
Sens	39.5	64.0		23.6	8.7
NPV	90.9	90.4		86.4	85.5
PPV	23.8	25.1		37.5	90.0
Score with 1st US					
Spec	62.7	53.7	93.9	87.8	97.8
Sens	61.7	77.2	23.5	44.7	15.8
NPV	85.6	92.6	81.8	89.5	86.2
PPV	30.8	23.6	51.6	40.5	58.1
Score with 1st and 2nd US					
Spec	61.6	52.9	91.3	79.3	94.3
Sens	63.7	78.0	36.2	59.6	28.1
NPV	86.2	92.9	92.2	91.0	87.6
PPV	30.8	23.6	55.8	34.1	47.8

3. 4   Intervention studies evaluating a fetal-growth-based management of GDM

(1)   Buchanan, TA, Kjos, SL, **Schaefer,** U, Peters, RK, Xiang, A, Byrne, J, Berkowitz, K. Utility of Fetal Measurements in the Management of Gestational Diabetes. Diabetes Care 21 (1998) 99-106

 (2)   Kjos, SL., **Schaefer - Graf**, UM., Byrne, JD., Berkowitz, K., Sutherland, C., Montoro, M., Buchanan, TA. A Randomized Trial Utilizing Glycemic plus Fetal Ultrasound Parameters vs. Glycemic Parameters to Determine Insulin Therapy in Gestational Diabetes with Fasting Hyperglycemia, Diabetes Care 24 (2001) 1904-1910

(3)   **Schaefer-Graf** UM, Kjos SL, Ostary Fauzan, Buehling KJ , Siebert G Barbara Ladendorf B, Bührer C, Dudenhausen JW, Vetter K. A randomized trial evaluating a predominately fetal-growth-based strategy to guide management of gestational diabetes in Caucasian women. Diabetes Care 27 (2004) 297-302

4.   Summary , discussion and perspectives

The standard management of pregnancies complicated by GDM is focused on the avoidance of maternal hyperglycemia. [1, 19, 79] Diet education and self-glucose-monitoring is recommended in all women. Insulin therapy is added if the glucose values of the daily profiles exceed a certain threshold. [19] There is strong evidence that in GDM pregnancies maternal, fetal and neonatal morbidity increases with increasing maternal hyperglycemia. [43, 80-83] However, the relationship seems to behave in a continuous fashion [40, 41, 73, 74, 84], and diagnostic criteria for GDM as well as glycemic targets during pregnancy are rather based on expert opinion or consensus than on evidence. A great diversity exists regarding the criteria for the diagnosis of GDM. All threshold glucose values for the oral glucose tolerance test (oGTT) that had been used to define glucose intolerance are modifications of the original O'Sullivan criteria established in the early Sixties [21], and show a variation of up to 25 mg/dl for the post challenge glucose levels. [1, 19, 20, 85-87] Regarding glycemic control during pregnancy there is controversy if measurements at one hour postprandial are superior to the determination of two hour postprandial glucose values. [43, 88-90] The glucose targets show the same wide variation as the diagnostic criteria. Overall, over the years the rate of adverse outcome in pregnancies with GDM had been reduced, and stillbirth is now rare in treated women with GDM. However, despite good glucose control the rate of neonatal morbidity is still elevated compared to pregnancies of women with normal glucose tolerance. [1, 73, 91-93] The same phenomenon is seen in pregnancies of women with preexisting type 1 diabetes. [45, 94] Some groups aimed to solve the dilemma by applying very tight glucose control to all women with GDM. This approach could reduce the rate of accelerated growth but resulted in insulin therapy and the demand of a high frequency of glucose monitoring in the majority of the women. [57-59] This strategy appears to be cost intensive and questionable with respect to the occurrence of morbidity only in a minority of cases and lacks evidence based data indicating the necessity of intensive treatment in all women.

The primary goal of the present work was to determine to what extent maternal glycemia in GDM pregnancies treated according to the standard management predicts neonatal morbidity. In a second step, we investigated whether inclusion of fetal growth patterns improves the neonatal outcome and provides an additional clinical tool for antenatal risk assessment. Our studies covered four major questions. Are maternal glucose values helpful to assess the risk for morbidity in early pregnancy of women with GDM? Are the

existing glucose criteria for diagnosis and treatment of GDM reliable to identify pregnancies at increased risk for diabetic morbidity? What are the major determinants of accelerated growth in treated GDM pregnancies? Are concepts of management based on fetal growth criteria save and what are the advantages compared to the standard approach?

It is well known since the early Sixties that preexisting type 1 diabetes is associated with an increased risk for congenital anomalies in the offspring and that the rate of malformations is positively correlated with the degree of maternal hyperglycemia at time of embryogenesis. [23, 24, 26, 27, 29, 33, 95, 96] Up to 1995, there was a paucity of data investigating the occurrence of congenital anomalies in GDM. Malformations had not been considered as a problem in GDM pregnancies since pregnancy induced glucose intolerance is supposed not to occur before the second trimester. Thus, we retrospectively investigated the rate and risk factors of congenital anomalies in a large cohort of 3700 women with hyperglycemia first detected in pregnancy (i.e. GDM) who attended the Diabetic Prenatal Care Clinic of the Women's Hospital of the University of Southern California in Los Angeles. The fasting glucose value at time of diagnosis was the strongest predictor for major malformations and we identified a glucose level of 120 mg/dl as threshold of an increased risk for anomalies. [97] The rate of major anomalies increased from 2.1% to 5.2 % for fasting glucose levels between 120-260 mg/dl. Interestingly, our identified threshold of 120 mg/dl corresponds to the glucose level in the first trimester previously identified for an increased risk for malformations in pregnancies with preexisting type 1 diabetes. [31] Furthermore, we investigated the pattern of congenital anomalies and their relationship to maternal fasting levels at diagnosis. We saw the same predominance of organ systems affected as in type 1 diabetes and a tight relation of the severity, i.e. the number of affected organ systems, and the level of fasting hyperglycemia. [98]

Our findings were opposing the hypothesis that the physiologic decrease of glucose tolerance in pregnancy does reach a significant level far beyond embryogenesis. We were faced to the argument that a fair amount of the women in our population presumably had undiagnosed type 2 diabetes before pregnancy. The ethnic background of our predominantly Mexican-American women allows speculations about a high rate of undiagnosed type 2 diabetes although a fasting of 120 mg/dl does not even fulfill the recently lowered criteria for diabetes outside pregnancy. [37] However, when we excluded women with persisting diabetes postpartum diagnosed by an oGTT 4-16 weeks postpartum, we still confirmed our results. Considering the course of the development of pregnancy induced glucose intolerance, the women presumably have had even lower glucose values in the first trimester. Another aspect

was the high rate of obesity in the study population that is common in women with GDM. Obesity and the associated hyperinsulinemia by itself is a risk factor for malformations. [99, 100] Experimental studies demonstrated that diabetic embryopathy is associated with an excess of radical oxygen species. It had been shown that hyperglycemia leads to increased embryonic levels of the products of lipid peroxidation. [101] The physiologic increase of lipoxygenase activity is normally counterbalanced by an increase in the antioxidant system activity. [101, 102] It might be that in obese women with increased number of adipocytes a lower degree of hyperglycemia is sufficient to disturb this counterbalance. For obstetrical clinical care during pregnancy, the speculation of an underlying undiagnosed type 2 diabetes is of minor relevance and per definition the diagnosis of GDM comprises a wide range of severity of glucose intolerance. [1] In conclusion, we could positively answer our question that maternal glucose values are helpful to assess the risk for morbidity in early pregnancy of women with GDM. High fasting glucose levels at diagnosis clearly indicate a risk for congenital malformations and should prompt an intensive specified fetal ultrasound examination. Our findings had been confirmed by recent studies. [103-106]

In contrast to the obvious tight relation between maternal glucose values and embryonic morbidity in early pregnancy, we are faced with a different situation in the later course of pregnancy. The data of our studies indicate that neither the current diagnostic criteria nor the glucose values during therapy reliably predict neonatal morbidity. The diagnosis of GDM requires at least two pathologic glucose values independently of the applied criteria - either O'Sullivan, Carpenter and Coustan, ADA or WHO. We investigated specific parameters of diabetic morbidity in pregnancies of women with only one elevated glucose value in the oGTT according to O'Sullivan criteria, defined as impaired glucose tolerance (IGT). The rate of elevated amniotic fluid insulin (> 7 µU/ml), hypoglycemia (< 30 mg/dL), neonatal obesity, LGA and severe immaturity of the placenta was significantly higher in newborns of women with IGT compared to those from women with a normal oGTT. [73, 107] Neonatal obesity was defined as the sum of skinfold thickness measurements obtained at three sites of the body above the 90th percentile of gender-specific percentile rankings which were previously determined by measurements of skinfolds in 250 consecutive newborns with gestational age > 37 weeks. Hyperinsulinism, hypoglycemia and neonatal obesity were virtually even more frequent in IGT than in treated GDM pregnancies.

We also confirmed the impact of borderline glucose intolerance in a study that was primarily designed to determine the incidence and timing of and risk factors for hypoglycemia

in large-for-gestational-age (LGA) newborns of non-diabetic mothers. Excessive fetal growth may indicate fetal hyperinsulinism that exposes the newborn at high risk of hypoglycemia when the glucose supply suddenly drops after delivery. Therefore, frequent glucose testing is recommended in LGA newborns. [108, 109] Hypoglycemia occurred in 16% of the infants and the only predictor for hypoglycemia was the 1-hour glucose value of the maternal antenatal oGTT. [110] A threshold glucose level of 180 mg/dl revealed to be a good discriminator for an increased risk of hypoglycemia. The incidence sharply rises to 25% compared to 2.5% for 1-hour glucose value < 120 mg/dl and 9.3 % for 120-179 mg/dl. Interestingly, the glucose level of 180 mg/dL corresponds to the 1-hour glucose threshold of the Carpenter and Coustan criteria for the oGTT. [20] Thus, a majority of the mothers of newborns with high risk for hypoglycemia had untreated IGT.

Our observations of the impact of IGT on the neonatal outcome are in agreement with other studies using either one abnormal oGTT glucose value or increasing glucose values below the diagnostic criteria for GDM to define borderline glucose intolerance. [38-42, 92, 111] In contrast to these studies, we included highly specific parameters like amniotic fluid insulin that had not been investigated in IGT before. The data of others and our group reflect the major deficit of all currently applied criteria. They are all derived from the original O'Sullivan criteria that had been design to investigate the relation of antenatal oGTT values and the risk for maternal diabetes in later life. They did not consider the risk for neonatal morbidity. The multicenter HAPO-study involving 25000 pregnancies has been started in the year 2000 (HAPO= hyperglycemia adverse pregnancy outcome) to finally determine oGTT thresholds for short and long term morbidity of the offspring. [112] The results will not be available before 2004/5. When currently available criteria were applied, based on our data the requirement of at least two pathologic values in the oGTT to initiate therapeutic intervention does not appear to be justified and should be reconsidered. The actual German guidelines for diagnosis and therapy of GDM reflect the impact of IGT and recommend diet education and glucose control similar to GDM pregnancies. [87]

As mentioned before, good glycemic control during pregnancy according to the recommended glycemic goals is not able to normalize the morbidity rate in GDM pregnancies. In our own population, we could lower the macrosomia rate of 24% in the early Nineties [73] by the implementation of self-glucose monitoring in all women. However, the current rate is still about 18%. [89, 113] Thus, we retrospectively investigated the relation of maternal glucose values during the course of pregnancy and fetal growth pattern in a

population of 400 women with IGT or GDM. Since the fetal abdominal circumference (AC) is known to be a good predictor for LGA at birth [47, 55, 56] (own unpublished data 5.1), we have chosen a fetal AC < and $\geq$ 90th percentile to discriminate between pregnancies with normal and accelerated growth. [48] We compared pre-and postprandial glucose values of the daily profiles at 5 different periods of pregnancy with the AC measurements at corresponding gestational ages. There was no difference in glucose values between pregnancies with AC < and $\geq$ 90th percentile either at diagnosis or later in pregnancies, with the exception of the fasting glucose values between 32-35 weeks of gestation. In contrast, there was a tight relation to the maternal BMI. The rate of fetal AC $\geq$ 90th percentile and LGA at birth was significantly higher in women with BMI $\geq$ 30 kg/m^2 compared to lean women (28% vs 14% at entry). [113]

In a second step, we evaluated various parameters influencing fetal growth and determined independent predictors for an AC $\geq$ 90th percentile at diagnosis, during pregnancy and for LGA at birth. A history of LGA and obesity with BMI $\geq$ 30 kg/m^2, either alone or combined, were independent predictors for an AC $\geq$ 90th percentile at entry, at 24-27 (history of LGA) and 28-31(both) weeks of gestation and for LGA at birth. In contrast, the fasting glucose at 32-35 weeks proved to be the only predictors at 32-35 and 36-40 weeks. [89] The identified predictors and the periods of their major influence on fetal growth reflect the primary impact of genetic and epigenetic factors in previous pregnancies (history of LGA) in the early third trimester (obesity), of recent maternal parameters in the mid third trimester and the influence of the stimulation of growth by elevated maternal glucose in the late third trimester. The majority of the women (> 90%) had good glucose control which might explain the limited influence of maternal glucose values. But this also implicates that tighter glucose control might not be efficient because of the strong contribution of other factors. e.g. maternal obesity. Maternal obesity is known to be an independent risk factor for macrosomia in pregnancies with impaired [114] as well as normal glucose tolerance [115-117] due to peripheral hyperinsulinism [118] and increased levels of serum lipids and amino acids in face of normal maternal glucose values. [50, 51] Macrosomic infants of obese mothers show the same disturbances in lipids profiles as their mothers [119] and the neonatal fat mass determines 43% of the variance in birth weight although it accounts only for 14% of the total body weight. [120, 121]

In conclusion, the existing glucose criteria for diagnosis and treatment of GDM do not appear to be reliable to identify pregnancies at increased risk for neonatal morbidity. Thus, a tailored management concept which considers the individual maternal conditions, might

improve the efficacy and outcome of care in GDM. In obese women, prepregnancy counseling about the adverse effects of obesity on pregnancy outcome and a moderate caloric restriction might reduce additional obesity associated morbidity. It was shown that a 33% caloric restriction lowers triglycerides without marked ketonuria. [122] However, the effect of interventions during pregnancy seems less promising than prepregnancy counseling since the majority of obese women demonstrate low weight gain in pregnancy.

The limited predictive ability of maternal glycemia for neonatal outcome is not only caused by the impact of maternal fuels besides glucose but also by the alterations in placental transport and consumption of fuels associated with diabetes, [123-125] and the individual susceptibility of the fetus to oversupply. [78, 126] Fetal-based management strategies aimed to avoid these uncertainties by concentrating directly on the target, the fetus. The measurement of fetal insulin was one approach established by Weiss. [65] The level of fetal insulin can be determined by amniotic fluid insulin (AF insulin) secondary to the urinary excretion of insulin. [68, 127] Diabetic fetopathy is causally related to fetal hyperinsulinism. [14, 44, 128] The Weiss approach directed intensive insulin therapy to women with elevated AF insulin levels without respect to maternal glycemia. The disadvantage of his strategy was that amniotic fluid is accessible only by an invasive amniocentesis. Another approach used fetal overgrowth identified by ultrasound as a clinical marker for presumed fetal hyperinsulinism [60-62], and directed insulin therapy to pregnancies with an accelerated growth of the fetal AC. Determination of fetal growth is an indirect approach to assess hyperinsulinism and there was concern about over- or under-treatment when therapy is predominately based on fetal growth. Thus, we evaluated our data from amniocenteses in women with diabetes derived from times when determination of AF insulin was part of our routine management. We could demonstrate a weak but significant correlation between the fetal AC at time of amniocentesis and the level of AF insulin. Moderately elevated levels (90th percentile = 7 µU/ml) were poorly identified but a level of 16 µU/ml was excluded by an AC < 75th percentile with a negative predictive value of 100%. [129] Kainer et al [70], demonstrated similar results in a population consisting exclusively of women with type I diabetes. Interestingly, the identified AC threshold corresponds to the AC percentile that is used in the fetal-growth-based approach to initiate insulin therapy. The level of 16 µU/ml is still below the levels reported by other researchers to be associated with short [66, 71] and long term morbidity. [72] After establishing a correlation between the fetal AC and AF insulin we were additionally interested to determine the power of the AC to predict LGA at birth. Although an AC > 90th percentile at entry was the strongest

independent predictor, the predictive power of the ultrasound was only slightly higher than that of maternal history predictors like BMI, history of GDM or LGA. A second ultrasound slightly added to the predictive power (own unpublished data in 2.3.1) when evaluated in a single fashion. But when all predictors were combined for a score, the second ultrasound did not improve the predictive power. Similar to the predictive power for AF insulin, ultrasound seemed to be more helpful to exclude than to predict LGA at birth.

The utility of the fetal AC to guide metabolic therapy in women with GDM was first investigated in a pilot study by the group of Buchanan and Kjos from Los Angeles. Their study population was limited to women with glucose values that would not have prompted insulin therapy based on a standard guidelines. Insulin was given in pregnancies with a fetal AC $\geq 75^{th}$ percentile diagnosed by a single ultrasound at entry to care. [60, 61] The macrosomia rate could be reduced by 3 fold compared to pregnancies with AC $\geq 75^{th}$ percentile but no insulin therapy (13 vs 45%) and reached the level of pregnancies with AC $< 75^{th}$ percentile at entry. This first study addressed the question whether morbidity could be lowered by targeted intervention in pregnancies identified as high risk based on fetal growth. A second study was designed to investigate whether the ultrasound-based approach also allows to avoid intensive intervention, i.e. insulin therapy and intensive glucose monitoring, in pregnancies at low-risk despite maternal hyperglycemia that would have required insulin therapy. [62] Insulin was not given when the fetus did not demonstrate accelerated growth in serial ultrasound examinations during pregnancy. Women with severe hyperglycemia had been excluded. Indeed, insulin therapy could be avoided in 38% of the women in the ultrasound-guided group without adverse neonatal or maternal outcome. Both studies were performed in predominantly Mexican-American women who are genetically determined to have a high rate of insulin resistance and obesity that might have had an important impact on the results. Therefore the wide applicability of the therapy concept was questioned. However, we could confirm the benefit and safety of the fetal-growth-based approach in a Caucasian population of 200 women included in a study in Berlin [135] .We combined the approaches of both pilot studies and included both women who presented euglycemia under diet therapy and those with hyperglycemia. We did not find any adverse outcome either in the mother or in the offspring in pregnancies guided predominately by fetal growth compared to those guided solely by maternal glycemia. When we divided the population according to the selection that was done in the two previous pilot studies, we found the same reduction of LGA rate in women with euglycemia but accelerated fetal growth and save of insulin therapy in women with hyperglycemia but normal fetal growth. In the ultrasound-guided group, maternal

hypoglycemia prompting clinical intervention occurred in no case when insulin therapy was applied based on accelerated growth despite maternal glucose levels below the standard thresholds for the initiation of insulin therapy. Maternal jeopardy by hypoglycemia had been a serious concern when we transferred the fetal-growth-based approach to a population with milder glucose intolerance than normally seen in Mexican-Americans. Insulin therapy was given exclusively based on a fetal AC $\geq 75^{th}$ percentile. No women developed a level of severe hyperglycemia which was included as additional criteria for insulin therapy in the protocol.

Our studies in pregnancies complicated by GDM demonstrated that in women presenting high fasting glucose values at diagnosis the maternal glucose values are extremely reliable to assess the risk for disorders in embryogenesis resulting in congenital anomalies. In the majority of the women with GDM congenital malformation are not a concern. In the later course of pregnancy, maternal glucose values are of limited use to predict neonatal morbidity and a new management approach that is predominantly based on fetal growth instead of maternal glycemia showed promising results. Considering the knowledge about glucose metabolism in pregnancy and the numerous factors influencing the fetal development, we were not surprised about the low predictive power of maternal glucose values in treated GDM pregnancies. The normalization of maternal glucose values is indisputably beneficial for mother and offspring in pregnancies with a high level of hyperglycemia like in preexisting type 1 and 2 diabetes. However, the majority of women with GDM demonstrate only moderately elevated values. In these women, insulin therapy often results only in a reduction of fasting glucose values by 10 mg/dl or postprandial glucose by 20-30 mg/dl. There is evidence that the thresholds for the initiation of insulin therapy are still higher than the glucose values of the normal obstetrical population. Parretti et al[77] reported a 1-hour postprandial glucose value of 114 mg/dl as 97th percentile even at 38 weeks of gestation. If we attempt to reach this level, we will end up with an unacceptable high rate of insulin use. No doubt that maternal glucose supply is an important factor but it is only one parameter in the whole cascade that determines the outcome. A management solely based on maternal glycemia does not consider other maternal fuels or characteristics, placental function and the individual susceptibility of the fetus for disturbances. Twin studies demonstrated impressively the occurrence of fetal hyperinsulinism in one and normal insulin values in the other fetus.[78] These data support our clinical experience. We saw fetuses obviously presenting disproportional growth with an AC $> 90^{th}$ percentile and the mother had glucose values far

below the thresholds for insulin therapy [135]. On the other side, we had normally grown fetuses with maternal glycemia that would require insulin therapy when we followed the recommendations. In extreme cases, we caused growth restriction. We had 6 small-for-gestational-age (SGA) newborns in the standard group of the Berlin study when we had to give insulin in fetuses with normal AC (table 3, Box B, 6.1). Additionally we should keep in mind that we based our decision for insulin therapy on self-glucose-monitoring. This implicated considerable problems like the accuracy of reflectance meters, the individual technique of the women and an improved compliance in diet at days selected for glucose profiles.

Following critical data analysis and present knowledge it is obvious that an additional tool beside maternal glucose is needed to identify GDM pregnancies at risk for neonatal morbidity. Why do we not include the target - the fetus himself ? The approach based on the identification of fetal hyperinsulinism via measurement of amniotic fluid insulin presents the most reliable method but can not be widely recommended because of the requirement of an amniocentesis. However, the fetal-growth-based management uses a method to target GDM pregnancies with need for intensive intervention which is part of the routine in prenatal care. However, there are two concerns that should be addressed when we discuss the utility of this approach. First, the unsatisfying accuracy of ultrasound to predict birth weight or the development of LGA, especially in diabetic pregnancies [130] or extremely overweight fetuses. [131] This is caused by the limitation of the technique itself combined with the individual capacities of the ultrasonographers and the high rate of obesity in GDM women. In fetuses with accelerated growth due to maternal diabetes, we are additionally faced with an increase in adipose tissue that is less dense than fat-free tissue, e.g. muscle and bone. Thus the use of growth percentiles derived from an unselected patient population may lead to sonographic overestimation of fetal weight. [121, 132] This might explain our finding of a high false positive rate of the AC in predicting LGA babies which is consistent with the reports of others. [55, 56] The specificity of the fetal AC to predict an LGA newborn was about 80% thus 20 of 100 women would have been treated with insulin without having a fetus at risk. On the other side, data from Weiss showed that only 50% of the fetuses presented elevated insulin levels with a maternal mean blood glucose level of 100 mg/dl. [66] This mean glucose level corresponds to the recommended fasting and postprandial glucose levels for initiation of insulin therapy. [19] Thus, using the standard glycemia-based approach 50 of 100 women are treated with insulin without having a fetus at risk.

What are the perspectives in the care of women with GDM? The increase of obesity in young women accompanied with a high risk for GDM will face us with rising numbers of women with GDM seeking care. Official surveys in Germany estimate a rate of 19% obese teenagers for 1995 which increased up to 32 % for the year 2000. [133, 134] Thus, we have to optimize the allocation of resources for treatment by targeting high-risk pregnancies for intensive intervention. Strict glucose control in all women without additional risk assessment might cause avoidable financial and emotional costs and will eventually consume valuable resources. The fetal-growth-based concept of care includes antenatal risk assessment and therefore might not only improve the efficacy of care but also help to improve cost-efficient treatment. In our study, almost 60% of the women in the ultrasound group identified to be at low-risk performed glucose profiles without clinical consequences. We neither discussed the values, nor were the women encouraged to observe their diet. They were not aware of the thresholds for insulin therapy. We can only speculate about the effect of self-glucose-monitoring in these women since they could not be blinded to the numbers showing up on the reflectance meters. In future, we might be able to adjust the frequency and intensity of glucose control based on the risk assessment by fetal growth, resulting in a considerable reduction of monitoring in low-risk women. Intensive glucose monitoring is the most cost intensive parameter in the diabetic management of GDM pregnancies and adds an unpleasant diagnostic technique for the mothers. In contrast, ultrasound is well accepted by the women and part of the routine prenatal care. Based on recent costs and diagnosis of GDM estimated at 28 weeks of gestation, the calculated expenses were 160 Euro for glucose monitoring consisting of 2 profiles per week and 220 Euro if 3 profiles would be performed. Our data indicate that 90% of the cases with AC > 75th percentile are diagnosed by a 1st or a 2nd ultrasound examination (unpublished data 6.1) and that a 3rd examination will add only little predictive power (unpublished data 5.1). When we assume 2 ultrasound examinations and e.g. 2 profiles per month, we will end up with a total amount of 37 Euro. The first ultrasound does not add additional cost since one exam of fetal growth is part of the German prenatal care protocol. Thus, we estimate that our approach will cut down the costs for diabetic care in GDM by 4 or 6 fold, respectively.

Our studies indicate that GDM therapy assignment based on fetal ultrasound assessment in addition to limited baseline maternal glycemic values is a safe, more pleasant and likely less cost intensive approach. Still, several topics need further investigations. We will have to determine to what extend glucose monitoring could be reduced in low-risk

pregnancies with moderately GDM without increasing risk of adverse neonatal and maternal outcome. Second, whether this strategy is not only safe but also represents a significant improvement of the outcome remains to be proven in larger cohorts. Last, the establishment of more specific, and easily reproducible sonographic measures of evolving diabetic fetopathy in utero as part of the routine ultrasound examination would further enhance the clinical value of involving fetal ultrasound.

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Abbreviations

AC	Fetal abdominal circumference
ADA	American Diabetes Association
AF insulin	Amniotic fluid insulin
AGA	Appropriate-for gestational-age newborn
FCG	Fasting capillary glucose
GCT	Glucose Challenge test
GDM	Gestational diabetes mellitus
IGT	Impaired glucose tolerance
OGTT	Oral glucose tolerance test
LGA	Large-for-gestational newborn
NDDG	National diabetes data group
NPV	Negative predictive value
NICU	Neonatal intensive care unit
SGA	Small-for-gestational-age newborn
Standard-group	Study group management by maternal glycemia
US-group	Study group managed by criteria of fetal growth
ROC curves	Receiver operator characteristics curves
WHO	World Health Organization

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