Diploma thesis

Gestational diabetes mellitus and its long-term consequences for the mother and her offspring

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Kurzfassung

Die vorliegende Arbeit beschäftigt sich mit dem Schwangerschaftsdiabetes und die sich daraus ergebenden Langzeitfolgen für Mutter und Kind. Es wird vermutet, dass die am häufigsten auftretenden Auswirkungen, erhöhtes Risiko für die Entwicklung eines Diabetes mellitus Typ 2 und die Entwicklung des Metabolischen Syndroms mit all ihren Krankheitsbildern, sind für beide, Mutter und Kind.
Bei den untersuchten Studien in Bezug auf die Mutter wurden vor allem Glucosetoleranztests während und nach der Schwangerschaft durchgeführt um das erhöhte Auftreten des Diabetes mellitus Typ 2 nach einer pathologischen Schwangerschaft zu beweisen. Auch wurden die Kriterien des Metabolischen Syndroms untersucht. Generell kommen viele Evidenz basierte Studien zu dem Schluss, dass obwohl zum Teil unterschiedliche Populationsgrößen unterschiedlich lange nachfolgend untersucht wurden, das mütterliche Risiko der Entwicklung eines Diabetes mellitus Typ 2 und des Metabolischen Syndroms nach einem Schwangerschaftsdiabetes signifikant erhöht sind.
Studien, die das erhöhte Risiko für die Entwicklung des Diabetes Mellitus Typ 2 und des Metabolischen Syndroms des Kindes untersucht haben, beschäftigten sich vor allem mit dem Geburtsgewicht und der späteren Entwicklung der Adipositas und den Kriterien des Metabolischen Syndroms. Da die Autoren die Nachkommen von Müttern mit Schwangerschaftsdiabetes längere Zeit studierten, zeigt sich ein signifikanter Zusammenhang zwischen dem Gestationsdiabetes und der späteren Entwicklung des Metabolischen Syndroms auch für das Kind.
Bei dieser Arbeit handelt es sich um eine reine Literaturrecherche, wobei ausgewählte Studien diverser Autoren miteinander in Vergleich gebracht wurden. Obwohl zum Teil unterschiedliche Untersuchungsmethoden angewandt wurden, wie etwa der Glucosetoleranztest, der entweder mit 75 g oder mit 100 g Glucose durchgeführt wurde, stimmen die grundlegenden Aussagen bzw. Erkenntnisse überein. Dies gilt für die Studien der Mutter als auch für die der Nachkommen. Die untersuchten Studien besagen, dass das Risiko für die Entwicklung eines Diabetes mellitus Typ 2 und des Metabolischen Syndroms signifikant er-

höht ist, für beide, Mutter und Kind und dies in Zusammenhang mit der Entwicklung eines Schwangerschaftsdiabetes.

Abstract

The following thesis is dealing with gestational diabetes mellitus and the long-term consequences for the mother and her offspring. Evidence based studies suggest that the risk for developing type 2 diabetes mellitus and metabolic syndrome later in life is more pronounced by mothers who suffered from GDM during pregnancy.

In order to analyze which long-term consequences for mother and child are reliable, selective studies were compared. The overall questions are:

1. Which diagnostic criteria are determined for long-term consequences within the different studies?
2. Are any screening similarities between the selected studies observable?

The analyzed and compared studies related to the mother observed primarily glucose tolerance tests during and after pregnancy for demonstrating the increased incidence of Type 2 diabetes mellitus after gestational diabetes mellitus. In addition diverse criteria for the metabolic syndrome were also measured. Although different sizes of study groups were studied for a different long time, the maternal risk of developing Type 2 diabetes mellitus or metabolic syndrome after gestational diabetes mellitus is conformable significantly increased.

Studies which investigated the increased risk for developing Type 2 diabetes mellitus or metabolic syndrome later in life for the offspring, the birth weight was mainly investigated and the development of obesity as well as the metabolic syndrome. Because the authors studied the offspring of mothers with previous gestational diabetes mellitus for a longer time period, because of these longer study time period a significant correlation between gestational diabetes mellitus and the later development of the metabolic syndrome for the child was observed.

Although different analytical methods were used, the elementary findings are the same. This is valid for the studies about the mother just as well for the off-spring.

The researched studies indicate that the risk for developing type 2 diabetes mellitus and metabolic syndrome are significantly elevated for mother and child.

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1 Introduction

This thesis is dealing with gestational diabetes mellitus (GDM) and the long-term consequences for the mother and their offspring.

Many studies claimed that the risk for developing Type 2 diabetes mellitus and metabolic syndrome (MS) after GDM is significantly increased for the mother and the offspring. This thesis is engaged to show a significant correlation between GDM and the development of Type 2 diabetes mellitus or MS for both, mother and child.

Because GDM is an increasingly problem, there are a great number of studies dealing with this topic. The diagnosis of GDM influences significantly the health for the mother and her child in the future. Some authors declare that women with previous diagnosed GDM have an 18 – 50 % risk for developing type 2 diabetes mellitus 5 years after pregnancy (1), others stated that the prevalence goes up to 70 %. Some authors investigated the risk for developing type 2 diabetes mellitus in the offspring of GDM mothers. They found out that they have even an 8-fold risk for developing type 2 diabetes mellitus at age 19 – 27 years (2).

MS could be one of the consequences of maternal GDM for both, mother and child. For this reason it is very important to recognize maternal GDM in time in order to manage this disease accurately. Therefore physicians should pay attention to this type of population. The knowledge and an appropriate therapy are requirements for an effective and continuous improvement.

In the following thesis these two disease patterns will be defined accurately. In the subsequent chapters the specifics of the methods which were used are demonstrated. After this, diverse studies from different authors who investigated the long-term consequences after GDM were summerized and analyzed for both, the mother and their offspring. Also the influences for the placenta will be shown. Finally, a discussion about the analyzed studies will be found.

1.1 Gestational Diabetes Mellitus

1.1.1 Definition

„Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy" (3). This diagnosis is independent whether insulin or only diet is used for therapy and excludes women with previous diabetes mellitus (3, 4).

GDM develops in approximately 4 % of all pregnancies in Caucasian women, although pregnancy is a carbohydrate-intolerant state (3, 5). The insulin resistance seen in normal pregnancies begins near the midpregnancy and progresses through the third trimester to levels of insulin resistance which are seen in patients with Type 2 diabetes (5).
It is hypothesized that an inadequate insulin secretion in combination with an insulin resistance are responsible for the development of GDM. The cellular mechanisms for this insulin resistance are still unknown but it appears that it is a result of increased adipose tissue from the mother in combination with the insulin-desensitizing effects of hormonal products of the placenta. Progesteron, for example, causes insulin resistance and estrogen is protective. Both hormone levels are increased in early pregnancy. Also cortisol rises during pregnancy until its concentration is threefold higher at the end of pregnancy. It has been shown that under infusion of high amounts of cortisol, the hepatic glucose production climb and insulin sensitivity is decreased. Another important hormone, the human placental lactogen, whose level rises at the beginning of the second trimester leads to a decrease of phosphorylation of insulin receptor substrate and effect insulin resistance (5).

1.1.2 Diagnostic strategies

For an adequate glucose management for GDM it is very important performing a risk assessment at the first prenatal visit. So, women with a high risk for de-

veloping GDM can be recognized and they should have a glucose testing as soon as possible. High-risk women are defined as they suffer from obesity, glycosuria, or have a personal history of GDM as well as a strong family history of diabetes mellitus type 2. If the first glucose test point out to be negative, women should undergo a further test between 24th and 28th weeks of gestation.

Women with an average risk (not classified as low risk or high risk, initially designated high risk but did not have GDM at early testing (5) for developing GDM should be tested between 24th and 28th weeks of gestation.
Women who have a low risk do not necessitate a glucose test but they have to fulfil some criteria like age < 25, normal weight before pregnancy, no diabetes in first-degree relatives, no history of poor obstetric outcomes, no history of abnormal glucose tolerance and they have to be members of an ethnic group with a low prevalence of GDM (3). In the low-risk group the risk for developing GDM represents less than 2 % (4).

There are two approaches for the diagnosis of GDM in women with a high or an average risk:
Firstly, the One-Step approach is a diagnostic oral glucose tolerance test (OGTT) which is done without prior plasma or serum glucose screening.
Secondly, the Two-Step approach precedes an initial screening. The women undergo a 50 g glucose challenge test (GCT) and after 1 h the plasma or serum glucose concentration will be measured. The women who exceed the glucose threshold value on the GCT have to perform an OGTT.
Both approaches are conducted with an OGTT (3) and the criteria of the World Health Organization (WHO) who recommens a glucose load of 75 g (4) but it exists a diagnostic criteria for a 100 g OGTT, too. The guidelines are from the original work of O`Sullivan and Mahan (3) however some authors showed that the 75 g OGTT is not as well validated as the 100 g OGTT and that more women meet the diagnostic criteria for GDM when tested with the 100 g OGTT then when they accomplish the 75 g OGTT (3, 5).

	mg/dl
Fasting	95
1-h	180
2-h	155
3-h	140

Table 1: The cut off glucose levels of GDM with a 100 g oral glucose load

	mg/dl
Fasting	95
1-h	180
2-h	155

Table 2: The cut off glucose levels of GDM with a 75 g oral glucose load

For both tables there is validity for:
"Two or more of the venous plasma concentrations must be met or exceeded for a positive diagnosis. The test should be done in the morning after an overnight fast of between 8 and 14 h and after at least 3 days of unrestricted diet (≥ 150 g carbohydrate per day) and unlimited physical activity. The subject should remain seated and should not smoke throughout the test." (3).

Diabetes is diagnosed if the fasting plasma glucose level exceeds 126 mg/dl or a casual plasma glucose is far beyond 200 mg/dl is measured and endorsed on a following day and excludes the need for any glucose challenge.

1.1.3 Therapeutic strategies

It is very important to observe the maternal glucose metabolism and so it is recommended to do a daily self-monitoring of blood glucose. If women are treated with insulin it has been shown that postprandial glucose measurement is more significant than the preprandial blood glucose measurement. Furthermore the blood pressure and the urine protein monitoring should be watched, whether a hypertensive disorder can be detected. When fasting plasma glucose is > 105

mg/dl or pregnancy progresses past term the surveillance should be increased because of a higher risk for fetal demise.
All women with GDM should receive a nutritional counselling which is consistent with the recommendations of the American Diabetes Association. Furthermore a medical nutrition therapy (MNT) depending on individual maternal weight and height is recommended (3). The MNT should meet the needs for perpetuation of the pregnancy without results of a postprandial hyperglycemia by providing the optimal dietary prescription (4). The therapy also should go hand in hand with the maternal blood glucose goals that are approved (3).
For obese women (body mass index (BMI) > 30) the daily calorie intake should be restricted to about 30 to 33 % from their usually calorie intake. It has been demonstrated that this method decreases the hyperglycemia and plasma TG. If MNT fails to maintain fasting whole blood glucose levels ≤ 95 mg/dl or 2 h post-prandial levels ≤ 120 mg/dl, insulin therapy is recommended. Fetuses which can benefit from maternal insulin therapy (fetuses with an asymmetric growth) can be detected by an ultrasonography in the early third trimester.

Women should be motivated to live an active lifestyle because moderate exercise can reduce maternal glucose concentrations.
It is recommended to have the delivery during the 38th week because elongation of the pregnancy leads to a higher risk for a macrosomic baby with accompanied risks (3).

1.1.4 Metabolism

Changes in metabolism during normal pregnancy

The changes in the metabolism during pregnancy are needed to ensure the supply of nutrients and energy for the fetus and also the supply of precursors for fetal and placental growth and the synthesis for placental hormones.
In the first half of pregnancy nutrients and energy will be stored by the maternal metabolism. This storage is needed in the second half of pregnancy when the fetus and the placenta are rapidly growing. During the first half of pregnancy the

mother eats more and the insulin sensitivity is increased. With this changes the glucose and lipid uptake by the adipose tissue is easier and so the adipose tissue mass is growing during this time.

But later, during the second half of pregnancy the metabolism changes. Now, a state of increased insulin resistance is shown which leads to a decrease in glucose uptake by maternal tissues. Consequently, the demand of glucose by the fetus which is very high (30 – 50 g of glucose/day) is met. The glucose supply to the fetus is via passive glucose diffusion and is triggered from the glucose concentration of the mother (5). The higher glucose concentration in the mother the higher glucose uptake by the fetus is shown. In this way the increased incidence of macrosomic babies in pregnancies complicated by GDM could be explained. This issue will be described later on. The reason why pregnancy induces insulin resistance is not fully understood. One reason may be the increased decomposition of insulin by the placenta, so insulin removal is accelerated and plasma glucose levels are elongated in the fetus. The most important fact is that a high level of TG and non-esterified fatty acids in combination with increased plasma levels of placental lactogen and increased lipolysis leads to an increased cell metabolism of fatty acids which leads in series to a decreased cell uptake of glucose. Maybe also higher levels of TNF-alpha in maternal plasma can lead to the insulin resistance because of a decreased expression of insulin receptors (5).

Also the lipid profile is changing during normal gestation mainly during the second half where plasma TG and cholesterol levels are elevated. The increased levels of the TG are a result of an increased hepatic synthesis of VLDL-TG and a decreased lipoprotein lipase (LPL) activity in the adipose tissue while late gestation. Also some hormonal changes have been investigated. During late gestation when the estradiol level is highest the hepatic synthesis of TG is stimulated and in consequence the VLDL-TG level rises. The placental lactogen is another factor which is involved in combination with the insulin resistance which increases adipose tissue lipolysis at the end of pregnancy; by this way a lot of fatty acids are offered to the liver. The lower levels of adiponectin also contributes to the higher triglyceride synthesis of the liver because there is an decline of beta-oxidation and so the fatty acids became re-esteriefied and are used for the synthesis of TG. These TG are used from the placenta where lipoprotein

lipase is present. The VLDL-TG became hydrolized and fatty acids are released which are taken up by placental cells. Therefore some studies show a positive relationship between maternal TG and birthweight (5).
Higher levels of cholesterol in the fetus, mainly as low density lipoprotein (LDL), are important for the synthesis of steroid hormones and it is needed as a precursor for the synthesis of cell membranes which is very high during the second half of pregnancy.
Also the protein metabolism changes during pregnancy. At the end of pregnancy it is shown that amino acids are stored for tissue synthesis. Therefore, the nitrogen retention is four times higher than in early pregnancy. Generally, the level of amino acids declines to 15 – 20 % in late gestation and they are energy dependent uptake transported through the placenta. So, the fetal plasma levels of amino acids are very high because of the rapid protein accretion that is seen in the fetus during the late pregnancy (5).

Changes in metabolism during pregnancy complicated by gestational diabetes mellitus

GDM develops because of beta-cell dysfunction, decreased insulin sensitivity, increased insulin resistance and other factors, described elsewhere in this article.
Glucose uptake in maternal tissues is insulin-dependent and in GDM when the insulin level decreased and the insulin resistance should be compensated than hyperglycemia develops. Because of the maternal hyperglycemia and a normal function of the placenta a hyperglycemia develops also in the fetus because of the materno-placenta-fetal transfer of glucose which is concentration-dependent. As a consequence for the fetal hyperglycemia a fetal hyperinsulinism develops. Insulin is a growth factor for the fetus and so this leads to fetal macrosomia with all the consequences and complications for the delivery which are described elsewhere in this article.
The fetal hyperinsulinism remains after delivery and the risk of hypoglycemia for the baby increases because the glucose supply from the mother is suddenly stopped after delivery. The hypoglycemia must be corrected because this could

lead to a brain damage for the newborn (5). This and other risks for the newborn are discussed elsewhere in this article.

Beside glucose alterations during GDM also the lipid profile changes. Women with GDM have higher plasma levels of TG and cholesterol as women with normal pregnancy. Increased levels of both TG and cholesterol lead to structural changes in LDL. Higher TG levels cause small and more dense LDL particles so they are more prone to oxidation. During normal pregnancy this effect may be blunted because of higher levels of estradiol and vitamin E which are very effective anti-oxidants. But GDM leads to an exacerbated dyslipidemia and the anti-oxidant defense will be given no more. The increased LDL oxidation is celltoxic and can damage the placenta which has consequences for the fetus. The transfer of nutrients and oxygen can be affected and so it leads to a compromise in fetal growth. Finally, because of high levels of TG and cholesterol during GDM increased fatty streaks in fetal arteries can be seen (5).

In summery macrosomic newborns due to higher levels of TG and newborns with growth retardation because of increased LDL oxidation which leads to placenta insufficiency, can be seen during pregnancy complicated by GDM (5).

During GDM higher levels of essential and nonessential amino acids are found in umbilical venous and arterial blood compared to normal pregnancies. But this increase of the fetal amino acids is not related to maternal concentrations, only ornithin is higher in the plasma of women with GDM. The elevated plasma amino acid concentration in umbilical, but not in maternal circulation, suggests that placental amino acid exchange and/or feto/placental metabolism changes in GDM. *In vitro* studies demonstrate that the expression of System A, which mediates the transfer of neutral amino acids like alanine, serine and glutamine, is elevated during pregnancies complicated by gestational diabetes mellitus. However it does not seem that this could be the reason for the accelerated fetal growth. The specific transporter for leucine, system L, also shows an increase in microvillous plasma membranes isolated from GDM pregnancies with large babies for their gestational age. But other authors did not find an elevated activity of these transporters (5).

1.2 Metabolic Syndrome

Metabolic disturbances now known as the MS was first described by Kylin in the 1920s as a cluster of hypertension, hyperglycaemia and gout. Two decades later it was noticed by Vague that upper body adiposity was most often associated with metabolic disorders seen in diabetic and cardiovascular diseases. In 1989, Kaplan called it “The Deadly Quartet” and others named it “The Insulin Resistance Syndrome” (5). But today the most used term for this metabolic disturbance is “metabolic syndrome”.
In the literature a number of current definitions for this disease is described. The most accepted of these definitions have been produced by the World Health Organization (WHO), The European Group for the Study of Insulin Resistance (EGIR) and the National Cholesterol Education Program – Third Adult Treatment Panel (NCEP ATP III). All groups agree on the main components of the MS: obesity, insulin resistance, dyslipidaemia and hypertension but they differ in some clinical criteria to identify such a cluster.

WHO definition (1999)

The WHO definition is based on the assumption that insulin resistance is one of the major determining factors for developing the MS. Insulin resistance or impaired glucose tolerance or diabetes must be identified to make the diagnosis. Additionally to insulin resistance two other conditions must also be identified for the diagnosis of the MS. The WHO definition includes also the presence of microalbuminuria as a further criteria and as a result of hypertension.

EGIR Definition (1999)

The EGIR definition is a modified version of the WHO definition and is used only in non-diabetic subjects, because it is simpler to use in epidemiological studies. EGIR uses the fasting insulin levels to estimate insulin resistance and impaired

fasting glucose levels. The definition alters also in hypertension, lipid status and the cut-points for central obesity.

NCEP ATP III Definition (2001)

This definition was made to facilitate diagnosis in clinical practice and differs from other definitions in two aspects. It does not include the measurement of insulin resistance as a component and therefore not “glucose-centric”. The ATP guidelines declare that three or more of five conditions have to apply for diagnosing the MS. These terms are: central obesity, elevated blood pressure, elevated triglyceride level, reduced high density lipoprotein (HDL)-cholesterol and elevated fasting glucose concentrations. In terms of obesity the waist circumference is used as the measuring method.

	WHO (1999)	EGIR (1999)	NCEP ATP III (2001)
	Glucose intolerance, IGT or diabetes and/or insulin resistance together with two or more of the following:	**Insulin resistance (defined as hyperinsulinaemia – top 25% of fasting insulin values among the non-diabetic population). Plus two of the following:**	**Three or more of the following five risk factors:**
Fasting plasma glucose		≥ 6.1 mmol/l (110 mg/dl) but non-diabetic	≥ 5.6 mmol/l (100 mg/dl)
Blood pressure	≥ 140/90 mmHg	≥ 140/90 mmHg or treatment	≥ 130/85 mmHg
Triglycerides	Raised plasma triglycerides: ≥ 1.7 mmol/l (150 mg/dl) and/or	> 2.0 mmol/l (178 mg/dl) or treatment and/or	≥ 1.7 mmol/l (150 mg/dl)
HDL-cholesterol	Women: < 1.0 mmol/l (39 mg/dl)	< 1.0 mmol/l (39 mg/dl) or treatment	Women: < 1.29 mmol/l (50 mg/dl)
Obesity	Women: waist-hip ratio > 0.85 and/or BMI > 30 kg/m2	Women: waist circumference ≥80 cm	Women: waist circumference > 88 cm
Microalbuminuria	Urinary albumin excretion rate ≥ 20 µg/min or albumin:creatinine ratio ≥ 30 mg/g		

Table 3: Summary of the metabolic syndrome definitions

Due to the fact that different MS definitions exist a comparison of data of these studies it is not possible. For general use there is a strong need for one simple

definition or diagnostic tool for clinical practise identifing patients with increased risk of developing diabetes mellitus type 2. A further advantage would be an easier comparison of different studies regarding to the prevalence of the syndrome in different populations.
For this reason, The International Diabetes Federation (IDF) held an expert workshop in May 2004 to discuss this problem. The new definition should be easier to use in clinical practice and should better predict cardiovascular disease.
All participants at the workshop agree that following general features, including diagnosis of MS:

- Abnormal body fat distribution (increased abdominal fat, assessed by waist circumference)
- Insulin resistance (correlates with the risk of Type 2 diabetes)
- Atherogenic dyslipidaemia (elevated TGs and decreased HDL-cholesterol concentrations)
- Elevated blood pressure (is associated with obesity and glucose intolerance and varies from one population to another)
- Proinflammatory state (elevated C-reactive protein (CRP) level is found in people with the MS. There is a significantly relationship between CRP levels and adiposity as well as insulin resistance)
- Prothrombotic state (associated with an increase of the plasminogen activator inhibitor-1 (PAI-1)

New IDF metabolic syndrome world-wide definition

To describe a new definition, the ATP III definition was used as a starting point to modify and to update the current objectives. The insulin resistance, as recognized, is an important component for the diagnosis of MS but its measurement is not essential to the new definition. For the definition to suffer from MS, a person must have central obesity plus any two of four additional factors, according to the new definition which is summarized in Table 4. These factors are:

- Elevated TG level: ≥ 1.7 mmol/l (150 mg/dl)
- Reduced HDL-cholesterol: < 1.03 mmol/l (40 mg/dl) for men and < 1.29 mmol/l (50 mg/dl) in women (or treatment)
- Raised blood pressure (sBP ≥ 130 or dBP ≥ 85 mmHg) (or treatment)
- Raised fasting plasma glucose (FPG ≥ 5.6 mmol/l (100 mg/dl) (or diagnosed type 2 diabetes).

Central obesity	Waist circumference in Europids ≥ 94 cm for males and ≥80 cm for women plus any two of the following:
Raised triglycerides	≥ 1.7 mmol/l (150 mg/dl) or treatment
Reduced HDL-cholesterol	< 1.03 mmol/l (40 mg/dl) in men and < 1.29 mmol/l (50 mg/dl) in women or treatment
Raised blood pressure	sBP: ≥ 130 mmHg or dBP: ≥ 85 mmHg or treatment
Raised fasting plasma glucose	Or previously diagnosed type 2 diabetes If > 5.6 mmol/l or 100 mg/dl, oral glucose tolerance test is strongly recommended but is not necessary to define presence of the syndrome

Table 4: The new IDG metabolic syndrome definition

Once the diagnosis of the MS occurs, the patients should be more watched and monitored than healthy women. The patients should change their lifestyle which includes:

- Moderate calorie restriction
- Moderate increase in physical activity
- Change dietary composition

If possible, a normal BMI and/or normal waist circumference should be a long-term target of lifestyle intervention. There is also the possibility for drug therapy, but it only should be given if patients are at high risk for cardiovascular disease (6).

2 Methods

The data for this thesis were obtained from a systematic literature search. Therefore, the database “PubMed” was used and several articles were searched for different keywords in the time from 1965 until 2009.
The keywords which were used are:
Child,
Children,
Gestational diabetes mellitus,
Malformation,
Metabolic syndrome,
Offspring,
Placenta.
These keywords were also used in combination with each other. Additionally, some references taken out from selected articles were used for my thesis. Furthermore chapters out of the “Textbook of Diabetes and Pregnancy” (5) were included mainly for the introduction part. The papers which were chosen helped to verify the hypothesis and aims of this thesis.
The criteria were the investigation of the glucose values of the mother and the child for examine the risk for developing type 2 diabetes mellitus after GDM. Also the birth weight was an important criteria for verifying the statement that offspring of GDM mothers were macrosomic at birth. Some authors investigated the blood pressure and lipid profile from mother and child, to make a conclusion about the development of the MS after GDM.

3 Complications for the mother related to gestational diabetes mellitus

The diagnosis of GDM has implications for the pregnancy and also for the future health of the mother and automatically initiates intervention (7).
Women with prior GDM are exposed to a higher risk for developing diabetes mellitus type 2 after pregnancy. They also have a higher BMI, an altered lipid profile with increased LDL cholesterol- and TG levels in combination with decreased HDL cholesterol levels and higher blood pressure as compared with women with a history of a normal pregnancy (8). These changes can be sum up to the term of MS, syndrome X or insulin resistance syndrome.

In the following studies are described and interpreted. Either the consensus or non-consensus of these clinical trials is also part of this chapter.

Pallardo et al. (8) investigated the association between impaired glucose metabolism and cardiovascular risk profile. He studied 838 Caucasian women between 1992 and 2000 with a history of GDM, 3 – 6 months after delivery. The authors made the diagnosis of GDM with a 3 h, 100 g OGTT in all pregnant women with a screening test (50 g OGCT) showing a 1 h value ≥ 140 mg/dl. The screening test took place at the first prenatal visit if clinical characteristics with a high risk of GDM (obesity, family history of diabetes, personal history of GDM) appeared or between 24^{th} – 28^{th} weeks of gestation. For the postnatal assessment, a 75 g OGTT was made. Pallardo et al. classified the outcome as normal (fasting glucose < 110 mg/dl and 2 h glucose < 140 mg/dl), impaired fasting glucose (IFG) (fasting glucose ≥ 110 mg/dl and < 126 mg/dl and 2 h glucose < 140 mg/dl), impaired glucose tolerance (IGT) (fasting glucose < 110 mg/dl and 2 h glucose ≥ 140 mg/dl and < 200 mg/dl), IFG plus IGT (fasting glucose ≥ 110 mg/dl and < 126 mg/dl and 2 h glucose ≥ 140 mg/dl and < 200 mg/dl) and diabetes (fasting glucose ≥ 126 mg/dl or 2 h glucose ≥ 200 mg/dl) according to the World Health Organization (WHO) criteria. The results are shown in Table 5. The study revealed a significantly increased prevalence for

cardiovascular risk factors only in the IFG and diabetes group. The prevalence for hypertension and obesity was significantly increased in IFG compared with normal glucose status. The IFT plus IGT group showed a significantly increase for abnormal lipids and obesity compared with normal glucose status. Also in the diabetes group these two characteristics were significantly increased. On the other side, IGT showed no significantly increase for cardiovascular risk factors (8).

Postpartum	Prior GDM, n=838	%
Normal glycemic status	681	81.3
DM	30	3.5
IFG	40	4.8
IGT	62	7.4
IFG + IGT	25	3

Table 5: The prevalence of impaired glucose metabolism in women with prior GDM, by Pallardo et al.

DM: Diabetes Mellitus, IFG: impaired fasting glucose, IGT: impaired glucose tolerance

The results of Pallardo et al. demonstrate the incidence of abnormal glucose metabolism after a pregnancy complicated by GDM and so the cardiovascular risk profile as a long-term consequence.

Lin et al. (9) studied also the postpartum metabolic outcome in women with previous GDM. From 2001 – 2003 235 women were diagnosed with gestational diabetes mellitus. They were exposured to a 50 g GCT of 1 h plasma glucose level ≥ 140 mg/dl at 24 – 28 weeks of gestation, followed by two abnormal values in a 100 g OGTT. The women were determined as having GDM if they fulfilled the Carpenter and Coustan modification of the National Diabetes Data Group criteria (requiring two of the following: fasting glucose ≥ 95, 1 h ≥ 180, 2 h ≥ 155, 3 h ≥ 140 mg/dl). From the 235 women 127 prior-GDM women returned at follow-up between 6 weeks to 2 years postpartum. The 127 women underwent a 75 g OGTT and they were divided into three groups: normal glucose tolerance (NGT), abnormal glucose tolerance (AGT) like impaired fasting

glucose or impaired glucose tolerance, and diabetes mellitus (DM) based on the criteria from the American Diabetes Association. The results are shown in Table 6. The authors described a significant difference between the three groups due to the MS and HbA1c levels. The MS was defined in 2001 in the Adult Treatment Panel (ATP) III guidelines. There are also significantly higher prepregnancy BMI, a greater number of abnormal glucose values in 100 g OGTT and higher 100 g OGTT glucose values on fasting between women with postpartum DM or AGT and NGT women. P-value of 0.05 or less was considered statistically significant (9).

	DM	**AGT (IGT or IFG)**	**NGT**	**p-value**
n (%)	17 (13.4 %)	37 (29.1 %)	73 (57.5 %)	
Prepregnancy BMI (kg/m2)	23.7	23.5	21.6	0.011
100 g OGTT				
Fasting plasma glucose (mg/dl)	125.3	100.2	91.8	< 0.001
1-hour	229.6	209.3	200.9	0.001
2-hour	244.9	190.3	180.9	< 0.001
3-hour	199.6	151.7	142.4	< 0.001
Numbers of abnormal values in 100 g OGTT ≥ 3	86.7 %	85.7 %	57.5 %	0.004
Metabolic syndrome	23.5 %	8.1 %	2.7 %	0.010
HbA1c (%)	6.6	5.3	5.2	< 0.001

Table 6: Comparison of postpartum clinical variables among the 270 prior-GDM women, by Lin et al.

Nearly the same diagnostic criteria were used by Eroglu et al. (10). This study investigated the metabolic disorders in patients with prior GDM between 2001

and 2005; results were recorded 10 – 15 months after delivery. The results demonstrated a significant relation between fasting glucose levels and glucose levels after an OGTT between 36 patients with recent GDM compared to 33 controls with normal pregnancies. GDM was diagnosed with a 3 h 100 g OGTT at 24^{th} – 28^{th} weeks of gestation and was considered to be positive if two or more elevated values occurred. Women were referred for the OGTT if their plasma glucose levels were ≥ 135 mg/dl in a 50 g GCT. Eroglu et al. described also that women with prior GDM had significantly higher waist to hip ratios than women in the control group. The lipid profile was altered also in the GDM group in comparison with the control group, in particular for TG, whereas HDL cholesterol levels did not differ between the two groups (10). The exact details are shown in Table 7. P-value less than 0.05 were considered statistically significant.

	Prior GDM group n = 36	**Control group n = 33**	**p-value**
BMI (kg/m2)	25.7	24.5	NS
Waist:hip ratio	0.80	0.75	< 0.05
Fasting plasma glucose (mg/dl)	93.4	83.5	< 0.05
1 h plasma glucose (mg/dl)	149.1	101.8	< 0.05
2 h plasma glucose (mg/dl)	100.2	84.9	< 0.05
HDL cholesterol (mg/dl)	53.7	51.5	NS
Triglycerides (mg/dl)	89.8	61.3	< 0.05

Table 7: Post-partum data in women with prior GDM and control women, by Eroglu et al.

Further results in this research field were described by Catalano et al. (11) who studied 103 patients with recent GDM from 1987 through 1989. The authors investigated the incidence and risk factors of abnormal postpartum glucose tol-

erance in women with GDM. The patients were screened for GDM using a 50 g 1 h oral glucose load between the 24th – 28th weeks of gestation. Women with risk factors for GDM (previous GDM, history of fetal macrosomia, maternal obesity, prior stillbirth, persistent glucosuria and family history of DM Type 2) were screened at their first visit and again between 24th – 28th weeks of gestation. Patients with a venous plasma glucose value > 135 mg/dl had to do a 100 g 3 h OGTT. The diagnosis of GDM was made with the criteria of Carpenter and Coustan, if two or more of these plasma glucose concentrations were met or exceeded: fasting: 95 mg/dl, 1 hour: 180 mg/dl, 2 hours: 155 mg/dl and 3 hours: 140 mg/dl. The GDM patients had a 75 g 2 h OGTT 6 weeks after delivery. Twenty-three out of the 103 patients revealed abnormal diagnosis: 3 manifest diabetes, 4 impaired glucose tolerance and 16 unremarkable (11). Catalano et al. confirmed significant differences due to the glucose metabolism after a pregnancy complicated with gestational diabetes, too. More detailed information is shown in Table 8. Probability levels of ≤ 0.05 were considered significant.

Diagnosis	**Normal** **n = 80**	**Abnormal** **n = 23**	**p-value**
Pregravid BMI (kg/m2)	27.2	32.5	0.003
Gestational age at diagnosis (weeks)	27.7	22.4	0.0009
3 h, 100 g OGTT (mg/dl)			
Fasting	96.5	117.2	0.0001
1 hour	206.5	216.6	0.23
2 hours	185.0	206.2	0.015
3 hours	128.2	154.7	0.007
Insulin therapy during gestation	32 (40 %)	18 (78 %)	0.003

Table 8: Summery of clinical OGTT data and significant differences compared to control, by Catalano et al.

A long-term study regarding of glucose tolerance after a pathologic pregnancy was made by Metzger et al. (12). The authors investigated the glucose tolerance five years after gestational diabetes mellitus. 274 women with GDM participated at this study and the screening and diagnostic criteria from the National Diabetes Data Group (NDDG) and the three International Workshop Conferences on GDM sponsored by American Diabetes Association (ADA) were used. Metzger et al. also classified GDM according to the level of fasting glucose. The postpartum OGTTs were done with 100 g of glucose. Diabetes was diagnosed when fasting plasma glucose (FPG) was ≥ 140 mg/dl or when FPG was < 140 mg/dl but plasma glucose concentrations at 2 h and at least one other intervening sample during the OGTT were ≥ 200 mg/dl. Impaired glucose tolerance (IGT) was defined when FPG was < 140 mg/dl and when the plasma glucose value at 2 h was < 200 mg/dl, whereas an intervening plasma glucose value was ≥ 200 mg/dl. Subjects with values below IGT were defined as normal. Generally, Metzger et al. found that about 25 % of women with previous GDM are developing diabetes within 1 year and 5 – 6 % per year thereafter. Thus, after 5 years, approximately 50 % of these subjects with GDM had developed diabetes (12). Exact numbers are shown in Table 9.

	normal	**IGT**	**diabetes**
Early postpartum (n)	108	32	37
After 5 yr follow-up	91	33	48

Table 9: The short- and long-term development of glucose alterations after GDM. Early postpartum period: ≤ 6 months after delivery, by Metzger et al.

Farrell et al. (13) investigated the subsequent maternal glucose tolerance 12 months after delivery and the prevalence of infant malformations. The infant malformations are discussed elsewhere in this article. 86 women were diagnosed as having GDM by a 3 hour 100 g OGTT, using the criteria of O´Sullivan as recommended by the First International Workshop-Conference on Gestational Diabetes. Thus 12 months after delivery the cumulative prevalence of abnormal glucose tolerance was 14/42 (33.3 %), 10/42 being manifest diabetic (26 %). Of the 14 patients 9 required insulin during pregnancy.

Like Metzger et al. (12) also Löbner et al. (14) studied the long-term effects of previous gestational diabetes mellitus. The authors investigated the predictors of postpartum diabetes in women with GDM between 1989 and 1999. In a number of women (n=302) GDM was diagnosed with a 75 g OGTT following the criteria of the German Diabetes Association if two of three capillary blood glucose values exceeded the following limits: > 5 mmol/l (fasting) before OGTT, > 10.6 mmol/l after 60 min, and > 8.9 mmol/l after 120 min, respectively. The patients were retested at 9 months and 2, 5, 8 and 11 years postpartum. Löbner et al. found that the postpartum progression to diabetes in autoantibody-negative women was significantly influenced by whether insulin treatment was required during pregnancy, by BMI, and by the number of previous pregnancies (14). More details are shown in Table 10. However, age at delivery, weeks of gestation and the birth weight of the child were identified as no significant risk factors. The family history to DM was considered not to be statistically significant. The postpartum diabetes risk was incremental with increasing CRP concentrations, furthermore CRP concentrations correlated significantly with BMI.

	n = 270	**8-year diabetes risk in %**	**p-value**
Insulin			
Yes	92	84.5	< 0.0001
No	178	23.2	
BMI			
< 30 kg/m2	187	34.6	0.003
> 30 kg/m2	80	50.1	
Previous pregnancies			
None	125	33.0	
1	88	53.9	0.34
2	36	64.8	0.54

> 2	21	75.0	0.0001
First-degree relatives with DM 1/2			
No	155	38.1	0.10
Yes	98	57.3	
Serum CRP at 9 month			
1st quartile	36	32.9	0.04
2nd – 4th quartile	111	55.8	

Table 10: CRP concentrations, categorized as quartiles, by Löbner et al.

< 0.8, 0.8 – 2.5, > 2.5 – 6.5, > 6.5 mg/l.

A p-value < 0.05 was considered significant.

Unlike as the previous authors Lauenborg et al. (15) investigated the prevalence of the MS in women with previous gestational diabetes mellitus. For the GDM group, in the years 2000 -2002, they included 481 women with prior GDM diagnosed during the periods 1978 – 1985 and 1987 – 1996. The control group has consisted of 1000 age-matched women. The pregnant women were screened for GDM by a risk factor-based method, and the diagnosis GDM was based on Danish criteria. All women with prior GDM were treated with diet only. The definition for the MS was made with the criteria of the WHO 1999, ATP III 2000 and EGIT 2002 (15). The various definitions are listened in the chapter “Metabolic Syndrome”. Lauenborg et al. demonstrated that the prevalence for the development of diabetes mellitus after a pregnancy complicated by GDM was ten times higher than in the control group. As other studies have shown the lipid profile is also altered for the prior GDM group with higher levels of TG and lower levels of HDL cholesterol. The MS was three times higher in the prior GDM group than in the control group (15). Some phenotypic characteristics of the prior GDM group in comparison with the control group are shown in Table 11 and the prevalence of the MS and some other categories are shown in Table 12. P-value < 0.05 was considered significant.

	Prior GDM group (n = 481)	Control group (n = 1000)	p-value
BMI (kg/m2)	27.9	24.6	< 0.0005
Waist circumference (cm)	91	78	< 0.0005
Glucose intolerance	67.6 %	19.2 %	< 0.0005
Therefrom diabetes	39.9 %	3.3 %	< 0.0005

Table 11: Phenotypic characteristics of the prior GDM group compared with the control group, by Lauenborg et al.

BMI	< 25 kg/m2	≥ 30 kg/m2	p-value
Prior GDM group			
Glucose intolerance	50.3 %	79.1 %	< 0.0005
Insulin resistance	25.7 %	86.9 %	< 0.0005
Hypertension	13.9 %	40.7 %	< 0.0005
Dyslipidemia	17.6 %	49.7 %	< 0.0005
Central obesity	14.9 %	100.0 %	< 0.0005
Metabolic syndrome	11.4 %	70.6 %	< 0.0005
Total number	149	180	
Control group			
Glucose intolerance	10.8 %	37.6 %	< 0.0005
Insulin resistance	11.7 %	60.8 %	< 0.0005
Hypertension	19.8 %	53.2 %	< 0.0005
Dyslipidemia	9.7 %	35.7 %	< 0.0005
Central obesity	7.5 %	100.0 %	< 0.0005
Metabolic syndrome	2.6 %	50.0 %	< 0.0005
Total number	531	172	

Table 12: The prevalence of the individual components and the metabolic syndrome stratified by BMI in the prior GDM group and control group, by Lauenborg et al.

The follow-up consequences after suffering from GDM are of general clinical interest therefore Heitritter et al. (1) investigated the subclinical inflammation and vascular dysfunction in women with prior gestational diabetes mellitus. This study investigated 25 women with a history of GDM and 23 women with a history of normal pregnancy at least 1 year post delivery. Women were defined as having a history of GDM using the 1979 National Diabetes Data Group criteria. The criteria applied to the diagnosis of GDM if the patients had a 100 g glucose load and had at least two values equalling or exceeding the following: fasting glucose 100 mg/dl, 1 h glucose 190 mg/dl, 2 h glucose 165 mg/dl and 3 h glucose 145 mg/dl. Women were defined with a normal pregnancy if they underwent a 50 g glucose load test with a 1 h value less than 140 mg/dl. Heitritter et al. revealed that women with previous GDM had a higher blood pressure and a mean arterial pressure (MAP). The prepregnancy BMI and the current BMI were higher in the group with a history of GDM. Eleven (48 %) women with prior GDM had a positive family history of DM2 and seven (30 %) normal controls had a positive history of DM2, so this difference was considered to be not statistically significant. Women with prior GDM had also increased levels of fasting glucose and TG compared to women in the control group. The inflammatory markers, CRP, IL-6, PAI-1 and adiponectin, were also measured. The results revealed that the CRP, IL-6 and PAI-1 levels were higher whereas the adiponectin level was lower in the GDM group compared with the control group. However, IL-6 and PAI-1 levels were considered to be not statistically significant. More information demonstrates following Table 13 and Table 14 below. Statistical significance was defined as a p value < 0.05.

Parameter	Normal (n = 23)	GDM (n = 23)	p-value
Prepregnancy BMI (kg/m2)	21.4	25.8	0.002
Current BMI (kg/m2)	23.2	27.8	0.002
Waist circumference (cm)	75	88	0.001
Systolic BP (mm Hg)	107	111	
Diastolic BP (mm Hg)	59	65	0.002

MAP (mm Hg)	78	85	0.004

Table 13: Baseline characteristics, by Heitritter et al.

Parameter	Normal (n = 19)	GDM (n = 18)	p-value (adjusted for BMI)
Central systolic (mm Hg)	102	110	0.075
Cardiac output (ml/sec)	74	70	0.040
Stroke volume (ml/beat)	75	65	0.011

Table 14: Hemodynamic data, by Heitritter et al.

Also Toescu et al. (16) wanted to know more about the risks of the development of atherosclerosis and the long-term cardiovascular health of women with diabetes and so he investigated the changes in lipid profile and markers of oxidative stress in normal pregnancy in comparison with pregnancy complicated by diabetes. 2 hours post-prandial venous blood samples from 17 normal pregnant women and 12 GDM women were collected at the end of each trimester (T1, T2, T3). Toescu et al. measured cholesterol and TG, which were significantly higher throughout pregnancy in all groups but without significant differences between normal and GDM´s. LDL cholesterol was also measured which revealed significantly higher levels in the diabetic group, however, specific discussion about the lipidmetabolism was not noted in this article. Total antioxidant capacity (TAC) was significantly lower in all diabetic groups compared with the control group, which can be interpreted with a greater oxidative stress in diabetic patients. The precise data are shown in Table 15.

TAC during each trimester	Normal pregnancy (n = 17)	Gestational diabetes mellitus (n = 12)
T1	265.5	Not applicable
T2	285.3	275.8
T3	319.9	294.2

Table 15: TAC during each trimester in normal and diabetic pregnancy. Normal range for healthy adults for TAC: 300 – 460 µmol/l, by Toescu et al.

In summery the data of the analyzed studies can be summerized in a common conclusion, although some authors had chosen different methods and types of analysis:

Pallardo et al. (8) studied the cardiovascular risk profile and considered that all clinical parameters were significantly increased in women with abnormal glucose metabolism. The incidence of impaired glucose metabolism was also investigated. But the numbers of patients which were investigated by Pallardo et al. were too small and therefore results are not so significant because the postdelivery period with 3 to 6 months, was too short. It can be speculated that maybe some of the diabetic patients returned back into a normal glucose metabolism after this time.

Lin et al. (9) investigated the metabolic outcome after a pathological pregnancy. The investigated groups until 2 years postpartum in this study used the same diagnostic criteria as Pallardo et al. Lin et al. classified within the criteria a higher number of diabetes or impaired glucose tolerance postpartum than Pallardo et al. had shown, although Lin et al. analyzed a less number of patients.

Farrell et al. (13) described also a large number of impaired glucose metabolism after GDM. In comparison to the others he used only a 100 g 3 h OGTT for the diagnosis of gestational diabetes mellitus. Although this study observed the group for 12 months postdelivery (for a longer period!) Farrell et al. used a smaller number of subjects.

Catalano et al. (11) achieved nearly the same results although the authors followed the group only 6 weeks post partum. Catalano et al. studied also the risk factors of abnormal glucose intolerance and their results regarding the prepreg-

nancy BMI are in good agreement with Lin et al. and Löbner et al. The numbers of patients with abnormal values in a 100 g 3 h OGTT were important risk factors for Lin et al., Eroglu et al. and Catalano et al., respectively. Löbner et al. revealed the relevance of previous pregnancies. The different studies are also in agreement because they used the same diagnostic criteria. Maybe the results of Catalano et al. are demonstrated an adverse comparison because of the short period the study took place.

Lauenborg et al. (15) studied the long-term effects of previous GDM and the study is in agreement with the results of Löbner et al. regarding prepregnancy BMI. Both considered that this parameter is an important risk factor for development of diabetes mellitus type 2 later in life. Lauenborg et al and Löbner et al. received the same results because both studied the long-term effects of GDM also the number of participants are similar although they used different criteria for diagnosing GDM.

Lauenborg et al. investigated also the prevalence of the MS after a pathologic pregnancy and so the study is in concordance with the results of Lin et al. who studied this topic, too.

Heitritter et al. (1) and Toescu et al. (16) studied the effects on vascular function after GDM in the mother. Heitritter et al. revealed a statistical correlation between BMI (both prepregnancy and current BMI) and the prevalence of abnormal glucose metabolism or rather the prevalence of the MS. Heitritter et al. figured out that in women with GDM the vascular system is seriously affected regarding to blood pressure, cardiac output and stroke volume, respectively. Toescu et al. (16) studied the incidence of total antioxidant capacity (TAC) in maternal blood, where TAC is significantly decreased in diabetic women compared with the control group. TAC correlates with the antioxidant protection status and if it is too less than the imbalance between free radical damage (e. g. the oxidation of lipids) and antioxidant protection is impaired (16).

In summary, the above mentioned studies demonstrate the high risk of developing diabetes mellitus type 2 after a pregnancy complicated by gestational diabetes mellitus. The risk factors which predict this process are all parameters for the definition of the MS and so the development of this disease is also higher. Consequently, the cardiovascular risk factors are very important for this high-risk group which was shown by some authors.

4 Complications for children of mothers who developed gestational diabetes mellitus

GDM has not only implications for the mother, furthermore impaired glucose metabolism has consequently implications also for the child.

The most frequent consequence is the macrosomia of the child. This phenomenon results from the higher glucose supply which is offered from women with GDM and their hyperglycaemia. Glucose, which is the main growth substance and cannot be synthesized by the fetus, arrives the fetus via facilitated diffusion through the placenta. This results in fetal hyperglycaemia and hypertrophy of the islet tissue with insulin hypersecretion. At term when the glucose supply from the mother is abruptly interrupted the fetal insulin hypersecretion leads to a fetal hypoglycaemia, which is another complication for children born to a GDM mother (5). This thesis is well described by Jørgen Pedersen in 1952 and is called the Pedersen theory.

Macrosomia is defined as a birth weight > 4000 g (> 4500 g) or ≥ 90th percentile for gestational age. A birth weight over 4000 g is found in 5.5 – 10 % of all infants, but the incidence is 10 – 33 % in newborns from diabetic mothers. There are two types of macrosomia: the first type is the symmetric macrosomia and is a result of genetic factors, not a result of an abnormal supply of nutrients in utero. This problem accounts for 70 % of cases. The second type of macrosomia is asymmetric and is typical for maternal diabetes. This type is characterized by organomegaly and an abnormal thoracic and abdominal circumference, which are relatively larger than the head circumference. Another difference between macrosomic infants from healthy mothers and macrosomic infants from mothers with GDM is the body composition of the fetuses. Different studies compared the body composition analysis of infants of women with normal glucose tolerance and GDM. There was no significant difference found in birth weight or fat-free mass between the groups but there was a significant increase in fat mass and percent body fat in the infants of the GDM mothers. For this reason other possible complications or long-term consequences should be con-

sidered, like the development of MS, obesity, coronary heart disease, hypertension and type 2 diabetes later in life (5).

In this chapter some studies will be evaluated especially that with topics of macrosomia:

Gillman et al. (17) studied correlation of maternal GDM, birth weight and adolescent obesity. He compared data from 7981 girls and 6900 boys at an age of 9 to 14 years in 1996. The achieved parameters were overweight, defined as BMI greater than 95th percentile, and a risk for overweight, defined as BMI between the 85th and 95th percentiles. The diabetes history of the mother was obtained by a questionnaire, including whether she had GDM during index pregnancy. Gillman et al. found a significant relationship between maternal BMI, and as a consequence, maternal GDM status and birth weight with a significantly increase of later obesity which is shown in Table 16. In Table 17 it is shown an association between each 1-kg increment of birth weight and the prevalence of overweight which is approximately 30 % (17).

	n	Mean maternal BMI (kg/m2)	Mean birth weight (kg)	No. (%) at risk for overweight	No. (%) overweight
Girls					
Maternal GDM	246	27.2	3.55	35 (15.2)	16 (6.5)
No maternal GDM	7735	25.0	3.44	966 (13.1)	377 (4.9)
Boys					
Maternal GDM	219	26.8	3.68	37 (19.5)	29 (13.2)
No maternal GDM	6681	24.9	3.58	951 (15.6)	581 (8.7)

Table 16: Association between maternal BMI and GDM status and birth weight and number of participants who were overweight and at risk for overweight (defined above), by Gillman et al.

Birth weight category (kg)	n	Mean BMI (kg/m2)	No. (%) at risk of over-weight	No. (%) overweight
Girls				
0.5-<2.5	255	18.6	28 (11.3)	8 (3.1)
2.5-<3.0	1006	18.6	116 (12.0)	43 (4.3)
3.0-<3.5	3146	18.8	370 (12.3)	128 (4.1)
3.5-<4.0	2638	19.2	340 (13.7)	148 (5.6)
4.0-<4.5	806	19.4	125 (16.7)	56 (6.9)
4.5-<6	130	19.9	22 (18.3)	10 (7.7)
Boys				
0.5-<2.5	178	18.7	20 (12.3)	15 (8.4)
2.5-<3.0	626	19.0	78 (13.6)	53 (8.5)
3.0-<3.5	2182	18.9	290 (14.4)	170 (7.8)
3.5-<4.0	2598	19.1	388 (16.3)	224 (8.6)
4.0-<4.5	1062	19.6	168 (17.6)	109 (10.3)
4.5-<6	254	20.0	44 (20.5)	39 (15.4)

Table 17: Mean BMI and number of participants who were overweight and at risk for overweight by gender and birth weight category, by Gillman et al.

Hillier et al. (18) investigated also the relationship between fetal macrosomia risk and maternal glucose status and their weight gain during pregnancy. From the years 1995 to 2003, 41,540 women had a 50 g GCT for GDM screening; 6,397 had a 3 hour, 100 g OGTT. Both the National Diabetes Data Group and Carpenter Coustan criteria for GDM diagnosis were used. Maternal weight gain was stratified in two groups: 40 lb or fewer compared with more than 40 lb. Table 18 shows that excessive weight gain during pregnancy had nearly double the risk of fetal macrosomia independently of maternal glucose status compared with those who gained 40 lb or fewer. Macrosomia was defined as birth weight of 4,000 g or more (18).

	Weight gain less than 40 lb		Weight gain more than 40 lb	
GCT/OGTT Screen Results	**n**	**Macrosomia (%)**	**n**	**Macrosomia (%)**
Normal GCT	21,396	11.3	6,188	18.4
+ GCT, normal OGTT	1,892	11.0	428	19.9
+ GCT, 1 abnormal C&C or NDDG value	814	16.0	176	27.3

Table 18: Fetal macrosomia risk in association with maternal glucose status and weight gain during pregnancy, by Hillier et al.

+ GCT = 1 hour, 50 g GCT more than 140 mg/dl; OGTT = 100 g glucose tolerance test; GDM = two or more values exceed the threshold by C&C or NDDG criteria.

Vohr et al. (19) explored the development of adiposity in macrosomic and normosomic infants of mothers with GDM and control subjects between birth and age 1 year. 192 infants were studied between 1991 and 1993 and they were classified in four groups: 47 large for gestational age (LGA) infants of GDM mothers, 47 appropriate for gestational age (AGA) infants of GDM mothers, 55 LGA control infants and 44 AGA control infants who were evaluated at birth and age 1 year. All mothers were screened for GDM between 24th and 28th weeks of gestation with a 1 h 50 g GCT. If the mothers had values greater than 130 mg/dl they underwent a 100 g OGTT. The O´Sullivan criteria modified by Carpenter and Coustan were used. LGA was defined as birth weight > 90th percentile and AGA was defined as birth weight > 10th and < 90th percentile. Control mothers had a GDM screening with values < 130mg/dl. Data from the newborn and from the children at age 1 year were collected, including birth weight, birth length and multiple anthropometric measurements, including weight, length, head circumference, subcutaneous skinfold measurements and circumferences, for using the results as a primary indicator of childhood adiposity. Table 19 shows that mothers with GDM who delivered LGA or AGA and control mothers who delivered LGA infants had a higher prepregnancy weight than control mothers who delivered AGA infants. Table 20 shows the newborn characteristics and the

child anthropometric measurements at age 1 year. This study shows a relationship between prepregnancy weight, weight gain and mean glucose values during the second and third trimester in GDM mothers and the newborn BMI. It is also shown that LGA newborn from GDM mothers have increased central adiposity with increased abdominal skinfold thickness and waist circumference at age 1 year, compared with all the other three study groups (19).

	GDM mothers of:		**Control mothers of:**		
	LGA infants	**AGA infants**	**LGA infants**	**AGA infants**	**p**
n	47	47	55	44	
Prepregnancy weight (kg)	70.7	70.0	66.4	61.1	0.008
Prepregnancy BMIkg	26.6	27.3	24.2	23.5	0.001
Weight gain (kg)	14.1	10.6	17.4	15.7	0.0001
BMI >27 kg/m2	19/47	22/47	9/55	9/44	0.002
Fasting glucose (mg/dl)	92	88			NS
2-h postprandial glucose (mg/dl)	124	101			0.0005

Table 19: Maternal pregnancy anthropometric measurements, by Vohr et al.

	Infants of GDM mothers		**Infants of control mothers**		**p**
	LGA	**AGA**	**LGA**	**AGA**	
n	47	47	55	44	
Newborn:					
Birth weight	4,039	3,268	4,110	3,292	0.0001

(kg)					
BMI (kg/m2)	14.2	12.4	14.1	12.5	0.0001
Study weight (kg) (age 2 days)	3,874	3,126	3,941	3,169	0.0001
Arm circum-ference (cm)	12.8	11.5	13.0	11.6	0.0001
Chest cir-cumference (cm)	35.7	32.9	35.9	33.4	0.0001
Calf circum-ference (cm)	13.4	11.8	13.4	12.0	0.0001
Tricep skin-fold (mm)	4.7	3.4	4.5	3.6	0.0001
Subscapular skinfold (mm)	5.6	3.8	5.2	4.0	0.0001
Abdominal skinfold (mm)	5.4	3.4	4.8	3.8	0.0001
Suprailiac skinfold (mm)	5.0	3.4	4.5	3.7	0.0001
Medial calf skinfold (mm)	6.6	4.8	6.1	5.3	0.0001
Children at 1 year					
Weight (kg)	11.1	9.6	10.7	9.8	0.0001
BMI (kg/m2)	18.4	17.1	17.5	17.2	0.006
Arm circum-ference (cm)	16.9	16.6	16.9	16.2	0.45
Chest cir-cumference	49.0	47.2	48.6	47.7	0.003

(cm)					
Calf circumference (cm)	21.2	20.0	21.0	20.1	0.0004
Waist circumference (cm)	47.4	44.4	45.9	45.4	0.0001
Hip circumference (cm)	48.5	45.7	47.6	46.3	0.0001
Triceps skinfold (mm)	9.5	7.3	8.9	8.9	0.01
Subscapular skinfold (mm)	7.5	5.4	6.5	6.1	0.002
Abdominal skinfold (mm)	8.1	5.8	6.8	6.4	0.002
Suprailiac skinfold (mm)	7.2	4.6	6.1	5.9	0.003
Medial calf skinfold (mm)	14.9	13.0	14.7	13.3	0.03

Table 20: Anthropometric measurements at birth and at age 1 year, by Vohr et al.

Vääräsmäki et al. (20) studied the association between maternal GDM and the manifestations of MS among adolescents. Women were screened for GDM between 26th and 28th weeks of gestation. The indications for screening were glucosuria, prior GDM, suspected fetal macrosomia, previous macrosomic infant (birth weight > 4,500 g), maternal prepregnancy BMI greater than 25 kg/m2, and age greater than 40 years. A 75 g OGTT was performed with following values: 5.5 mmol/l fasting glucose, 11.0 mmol/l 1 hour and 8.0 mmol/l 2 hours after initial load. The diagnosis of GDM was made if 1 or more values were abnormal. The reference mothers had no indications for the OGTT. Measurements regarding to MS were done in the offspring at age 16 years, this is BMI, waist

circumference, blood pressure, glucose and lipid profile. Table 21 shows significantly increases in several points for offspring of GDM mothers compared to controls. Table 22 shows the prevalence and risk of MS in adolescents of GDM mothers. The most striking differences are seen in central obesity whereas lipid profile and blood pressure does not demonstrate significant differences between the groups (20).

	OGDM group	Reference group
n	87-96	3,525-3,709
Systolic blood pressure (mmHg)	117	115
Diastolic blood pressure (mmHg)	68	67
BMI (kg/m2)	20.8	20.2
Waist (cm)	73.3	71.5
LDL cholesterol (mmol/l)	2.20	2.20
HDL cholesterol (mmol/l)	1.33	1.39
Cholesterol (mmol/l)	4.20	4.20
Triglycerides (mmol/l)	0.79	0.72
Glucose (mmol/l)	5.30	5.10

Table 21: Outcome measures in the offspring of GDM mothers and reference group at age 16 years, by Vääräsmäki et al.

Diagnosis	Prevalence in OGDM group		Prevalence in reference group	
	No.	%	No.	%
Metabolic syndrome	5	5.9	54	1.6
Central obesity (waist)	16	17.0	261	7.1
Central obesity (BMI)	6	6.4	70	1.9
Raised triglycerides	2	2.2	119	3.4
Reduced HDL cholesterol	13	14.4	627	17.9

Raised blood pressure	11	11.8	490	13.3
Raised fasting blood glucose	21	23.6	520	15.3

Table 22: Prevalence and risk of metabolic syndrome in offspring of GDM mothers and reference group at age 16 years, by Vääräsmäki et al.

The long-term consequences were also studied by Hillier et al. (21). He studied the relationship between maternal glycaemia in pregnancy and the development of childhood obesity. During 1995 and 2000 a GDM screening with a 1 hour 50 g GCT was performed and GDM was diagnosed with a 3 hour 100 g OGTT according to National Diabetes Data Group (NDDG) criteria. 5 to 7 years after delivery the weight of the offspring was measured and then classified by maternal positive GCT (1 h ≥ 7.8 mmol/l) and OGTT results (1 or ≥ 2 of the 4 time points abnormal: fasting, 1 h, 2 h, or 3 h by Carpenter and Coustan and NDDG criteria).Table 23 shows that there is a positive relationship between childhood obesity and increasing maternal glucose screen values. It is also demonstrated that the risk of childhood obesity of mothers with GDM by NDDG criteria, which is a treated GDM, was less compared with the risks for the groups with lower degrees of hyperglycaemia, which were untreated (21).

Maternal glucose scale		**Child´s weight >85th percentile**	**Childs´s weight >95th percentile**
	n	**Prevalence**	
Women with normal GCT	7,609		
43-94 mg/dl	1,987	21.6	10.3
95-108 mg/dl	1,953	23.6	12.0
109-121 mg/dl	1,801	23.3	13.4
122-140 mg/dl	1,868	25.5	13.2
Women with GCT/OGTT	9,439		
Normal GCT	7,609	23.5	12.2
+GCT, normal OGTT	999	23.3	12.8

+GCT, 1 abnormal C&C or NDDG	288	26.7	15.3
+GCT, GDM-C&C	173	34.7	20.2
+GCT, GDM-NDDG, treated	370	27.8	17.3

Table 23: Prevalence and risk of childhood obesity at age 5-7 years, stratified by the glycaemia of the mother during pregnancy, by Hillier et al.

Like other authors also Lee et al. (22) investigated the relationship between the maternal glucose metabolism and the long-term adverse effects on the glucose metabolism and cardiovascular disease (CVD) risk factors in their offspring. From 1995 to 1997 a 1 hour 50 g GCT was performed during 24^{th} - 28^{th} weeks of gestation. If the plasma glucose value exceeded 130 mg/dl, a 3 h 100 g OGTT was done during 28^{th} – 32^{nd} weeks of gestation. GDM diagnosis criteria of the National Diabetes Data Group were used. Several anthropometric and laboratory measurements were done in 298 offspring (202 were the offspring of GDM mothers and 96 were the offspring of mothers with impaired glucose tolerance, which was defined as one abnormal value on the 3 h OGTT) between age 3 - 5 years. They received also an OGTT by loading the offspring with 1.75 g of glucose per kg of bodyweight. Table 24 shows the different anthropometric and laboratory measurements of offspring of IGT and GDM mothers which were done at the first visit. No statistical significance was found between the groups. In contrast, Table 25 shows that the mean BMI of the offspring of GDM mothers who were 5 years old or more were significantly higher than that of the offspring of IGT mothers. This development is not seen between the groups if they were at age 3 years. Statistical significance was defined as $p < 0.05$ (22).

	IGT	**GDM**
Age (years)	4.0	4.2
Systolic blood pressure (mmHg)	92.3	93.3
Diastolic blood pressure (mmHg)	59.0	59.6

Skinfold thickness (mm)	9.3	8.5
Body fat (%)	20.2	18.9
Total cholesterol (mmol/l)	4.2	4.4
Triglyceride (mmol/l)	0.8	0.9
HDL-cholesterol (mmol/l)	1.4	1.4
Fasting plasma glucose (mmol/l)	4.7	4.8
2-h plasma glucose (mmol/l)	5.3	5.3
BMI (kg/m2)	16.1	16.1

Table 24: CVD risk factors of offspring of IGT and GDM mothers at the first visit. All results are not statistical significant, by Lee et al.

	OGDM (n)	**OIGT (n)**	**p**
3 years			
BMI	15.9 (100)	16.5 (53)	NS
≥5 years			
BMI	16.9 (35)	15.7 (19)	<0.05

Table 25: A comparison of BMI of the offspring of IGT and GDM mothers according to age, by Lee et al.

Boney et al. (23) investigated the prevalence of MS in childhood in association with birth weight, maternal obesity and GDM. He subclassified four groups: large-for-gestational-age (LGA) offspring of mothers with GDM (LGA/GDM), appropriate-for-gestational-age (AGA) offspring of mothers with GDM (AGA/GDM), LGA/control and AGA/control. The diagnosis of GDM fulfilled the modification of the National Diabetes Data Group criteria described by Carpenter and Coustan, control mothers passed the 1 h 5 g GCT. The definition of MS, based on the adult criteria defined by NCEP were modified for children: obesity was defined as BMI > 85th percentile for age, elevated blood pressure (BP) as systolic or diastolic BP > 95th percentile for age, HDL concentration < 5th percentile for age, and triglyceride concentration > 95th percentile for age. Glucose intolerance was defined according to definition of the adults: > 110 mg/dl fasting plasma glucose or a 2 hour postprandial glucose level of > 140 mg/dl. So, the

MS was defined as ≥ 2 criteria of the following 4 criteria: obesity, hypertension, evidence of dyslipidemia (low HDL levels or elevated triglyceride levels), and glucose intolerance. The children were evaluated at age 6, 7, 9 and 11 years. Results are shown in Table 26. There is a statistical significant higher prevalence of childhood obesity in the LGA/GDM group compared with the other groups, but there is no significant difference among the groups with respect to BP, lipid profile and glucose levels. Here, it is only the group of 11 years old children listed (23).

	No./Total (%)			
	LGA/GDM	**AGA/GDM**	**LGA/Control**	**AGA/Control**
Obesity (BMI >85th percentile)	7/20 (35)	9/38 (24)	8/26 (31)	6/25 (24)
BP >90th percentile	4/19 (21)	5/38 (24)	3/26 (12)	2/24 (8)
HDL level <5th percentile	4/10 (40)	4/21 (19)	4/18 (22)	3/11 (27)
Triglyceride level >95th percentile	3/14 (21)	2/30 (7)	1/24 (5)	2/19 (11)
Abnormal glucose level	0/15 (0)	2/31 (6)	4/24 (17)	1/21 (5)

Table 26: The incidence of components of metabolic syndrome, only the measurements of the 11 years old children are shown, by Boney et al.

The results from the different authors are nearly identical. Although they all used different definitions, the essence was analogue. It is shown that the prevalence of macrosomia and childhood obesity is significantly increased in offspring from GDM mothers, also the risk for the development of MS is higher.

Gillman et al. (17) used a great number of individuals for the investigation of adolescent obesity in association with maternal gestational diabetes and birth weight. He studied the groups at age 9-14 years to show the long-term effects. Also Vääräsmäki et al. (20) studied the offspring of GDM mothers to demonstrate an association between glucose metabolism of the mother and the manifestation of MS in offspring with age 16 years. But his study group was composed of 95 individuals which he compared with 3,500 control subjects. The

study group was too small or the control group too big so, the significance is not so significant. Although Boney et al. (23) also studied the prevalence of MS 6 - 11 years later he used another definition for obesity in childhood. Boney et al. defined obesity as BMI greater than 85th percentile and Gillman et al. defined obesity as BMI greater than 95th percentile. For this reason the results cannot be compared one-to-one, but the tendency is the same.

Lee et al. (22) investigated the prevalence of cardiovascular risk factors in children from GDM mothers. These measurements are in agreement with the measurements for the MS risk. His conclusion is the same like the conclusion from Boney et al. and Vohr et al. (19) who investigated the incidence of adiposity in macrosomic and normosomic infants of GDM and control mothers at age 1 year. The comparison between Lee et al. and Boney et al. are better because both studied their groups between ages 5-11 years. But the results of Vohr et al. show a tendency in the same way although he studied his subjects only at age 1 year.

5 Placenta

5.1 Composition and function

The placenta is a new endocrine gland which develops during gestation (24). It is disc-like with a diameter at about 15 - 20 cm and the thickness is usually between 1.5 and 3 cm. After removing membranes, maternal blood clots and the cord the weight of the placenta is about 450 - 550 g (5).
The placenta consists of the fetal trophoblast and the decidua which is maternal tissue, between these cell layers there is the so-called intervillous space. In this space maternal blood circulates, however the blood from the mother is never in contact with the fetal blood (25). The placenta transfers almost all nutrients and gases to the fetus and on the other side it also transports all waste products from the fetus back to the mother´s circulation (5). Therefore, the placental transfer of maternal fuels and nutrients to the fetus takes place by facilitated diffusion, like glucose, or by actively transport, like amino acids. The free fatty acids, for example, cross the placenta by gradient-dependent diffusion in small particles (24).

5.2 Pathology

Some different kinds of pathologies appear in the placenta in pregnancies complicated by GDM.
The size of the placenta is associated with infant birth weight, so macrosomic babies, who are seen in diabetic pregnancies, are associated with a large and thicker placenta (26). This membrane thickening leads to a fetal hypoxia because of the greater distance between the maternal and the fetal circulations. The consequence is a stimulation of placental synthesis of angiogenetic factors such as fetal growth factor (FGF), vascular endothelial growth factor (VEGF) and placental growth factor (PGF)-1 (5). Responsible for this could be the development of chorangiotic placentas (5) and the resultant higher blood flow with

an increased maternal substrate flux to the placenta (26). The chorangiosis is defined as a vascular hyperplasia of the chorionic villi (27).The chorangiosis and the placental villous immaturity are the two most documented pathologies of the placenta in diabetic pregnancies.

On the other side diabetic pregnancies often are associated with hypertension which can cause vascular damage of the uterus. In this case the placenta is often reduced in size and weight because of a decreased blood flow (5).

Daskalakis et al. (27) investigated pathologic differences of the placenta in pregnancies complicated by GDM compared to non-diabetic controls. Forty pregnancies complicated by GDM were compared with forty non-diabetic pregnancies. The GDM was diagnosed between the 28^{th} - 35^{th} weeks of gestation. GDM was diagnosed with a 100 g OGTT at 24^{th} – 32^{nd} weeks. The patients were treated with diet or, if necessary, with insulin. The inclusion criteria was a good glucose control with HbA1c levels < 7 %.

The control group with normal pregnancy was included with a negative 50 g oral GCT (OGCT) and no obstetrical complications. The OGCT was done between 24^{th} - 28^{th} weeks and was considered negative with plasma glucose after 1 h < 140 g/dl.

Some histological pathology was carried out:

1. Lymphohistiocytic villitis (it was diagnosed by the presence of numerous lymphocytes and macrophages in the villous stroma)
2. Presence of NFRBC (nucleated fetal red blood cells; as a mark of fetal hypoxia when present in the umbilical cord or the villi)
3. Ischemia (was defined when increased maturation and branching of villi were present)
4. Infarction (assessed at gross examination, was present when at least 10 % of the placental volume was infracted)
5. Villous fibrinoid necrosis (a condition where villous stroma is replaced by fibrinoid)
6. Villous immaturity (it was defined when there was decreased formation of terminal villi and increased presence of immature intermediate villi in relation to gestational age)

7. Chorangiosis (i.e. vascular hyperplasia of the chorionic villi, was defined as the occurrence of 10 or more villi with 10 or more capillaries in 10 or lower power microscopic fields)
8. Hydropic villi (were diagnosed when large terminal villi were present with edematous fluid, with an increase of villous macrophages, and with an artifactual separation of the trophoblast lining from the underlying stroma)
9. Fetal vessel thrombosis (was diagnosed when a large fetal stem villous vessel was partially or completely occluded by a thrombus)
10. Avascular villi (were diagnosed when a group of at least 5 fibrotic avascular villi without inflammation or mineralisation was observed)

The fetal birth weights and the weights of the placentas were significantly higher in the diabetic group than in the control group.
Degenerative lesions such as fibrinoid necrosis and vascular lesions like chorangiosis were mainly seen in the diabetic group. Villous immaturity and the presence of NFRBC were significantly higher in the diabetic group than in the control group.
On the other side, there was no significant difference between the two groups in regard of the vessel infarction and ischemia (27).

Saldeen et al. (28) reviewed that in placentas from diabetic pregnancies occur more frequently incidence of vascular pathologies like obliterative endarteritis, fibromuscular sclerosis and mural thrombosis. These changes affect the feto-placental circulation in a negative way.
Saldeen (28) also reported that some lesions like relative immaturity, endarteritis, venous congestion are more frequently in GDM and he reported that mural thrombosis, ischemia, infarction and chorangiosis were found only in the GDM group (28).

6 Discussion

The results of the analyzed studies from diverse authors are in good agreement, although different examination methods and definitions were used. The risk for development of type 2 diabetes mellitus and the MS later in life are significantly increased for both, the mother and her offspring.

Glucose values of the mother during and after GDM pregnancy were measured and the risk for impared glucose tolerance is very high. Some authors correlate these conclusions with the prepregnancy and postdelivery BMI and they argue that because of these further information the risk/prediction for developing MS after a GDM pregnancy is higher than after normal pregnancy. The cardiovascular risk factors were also investigated where significant alterations for the GDM mother were diagnosed. These changes were not seen in young children, so it would be of general interest to follow the offspring of GDM mothers for a longer time period.

Very interesting is the fact that one author investigated the birth weight and the BMI from newborns and additionally the fat mass, respectively. The results indicate that there was no difference regarding the birth weight and BMI. However the newborn from GDM mothers had a higher fat mass than the newborn from control mothers. For this reason it can be assumed that GDM children are exposed to significant higher risk developing type 2 diabetes mellitus or MS with all associated diseases like obesity, higher blood pressure or altered lipid profile.

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