**Diplomarbeit**

# Disturbed maternal metabolism in early pregnancy and neonatal outcome


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Graz, 27.09.2019

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*Graz, am 27.09.2019* *Janine Christin Brück eh*

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## Abstract

**Background:** Early pregnancy is a critical period as it plays an important role in determining early developmental processes and ensuring successful pregnancy outcome. The development is influenced by genetics and the maternal situation, which creates the fetal environment. Therefore and in times of diabetes and obesity it is important to understand the effects of a disturbed maternal metabolism on the neonatal outcome.

**Methods:** Procedure of this work consists in a literature review, which was mainly done by using PubMed. The examined period of early pregnancy was determined as the period up to 15 weeks of pregnancy, including the first trimester. Adverse neonatal outcome was defined as large for gestational age (LGA), macrosomia and body composition, i.e. higher percentage of fat mass. Main search keywords were “early pregnancy” “adverse neonatal outcome” “LGA”, “macrosomia”, “body composition”, “diabetes”, obesity” and “metabolic inflammation”. Relevant studies were analysed. Furthermore references cited in relevant studies were reviewed. Results were subsequently summarized. In total 150 references were used.

**Results:** This review demonstrates that in recent years, more and more studies have been conducted on the period of early pregnancy. Various parameters associated with a disturbed maternal metabolism affect the phenotype of the newborn during the first trimester. Not only higher fasting plasma glucose, but dyslipidemia consisting of increased triglyceride and decreased HDL levels, lower adiponectin values, higher PAPP-A concentrations and placental growth in early pregnancy are associated with an increased risk for LGA, macrosomia and adverse body composition.

**Discussion:** The described results show the particular relevance of early pregnancy for adverse neonatal outcome. Further research needs to be done and might improve the treatment of pregnancies at risk. As a desirable goal there might be a detection of women at higher risk for adverse pregnancy outcomes early in pregnancy. Furthermore interventions such as diet, exercise and/or medication may be applied earlier and have

beneficial effects on neonates such as reduced birth weight and altered body composition, i.e. less body fat.

## Zusammenfassung

**Hintergrund:** Die Frühschwangerschaft ist eine kritische Phase, da sie eine wichtige Rolle bei der Gestaltung von Entwicklungsprozessen und der Gewährleistung eines regelrechten Schwangerschaftsablaufs spielt. Die Entwicklung wird durch genetische und maternale Faktoren beeinflusst, die zusammen die intrauterine fetale Umgebung prägen. In Zeiten von Diabetes und Adipositas ist es daher von zunehmender Relevanz, die Auswirkungen eines gestörten mütterlichen Stoffwechsels auf den Phänotyp des Neugeborenens zu verstehen.

**Methoden:** Die Methodik dieser Arbeit besteht in einer systematischen Literaturrecherche, die vorwiegend mittels Pubmed durchgeführt wurde. Der untersuchte Zeitraum der Frühschwangerschaft wurde als Zeitraum des ersten Trimenons bis hin zur 15ten Schwangerschaftswoche definiert. Das Ergebnis wurde als LGA, Makrosomie und höherer Prozentsatz an Körperfett am Neugeborenen gemessen. Die wichtigsten Suchbegriffe lauteten "Frühschwangerschaft", "Neugeborenenschädigung", "LGA", "Makrosomie", "Körperzusammensetzung", "Diabetes", "Fettleibigkeit" und "metabolische Entzündung". Relevante Studien wurden analysiert. Darüber hinaus wurden die in relevanten Studien zitierten Referenzen überprüft. Die Ergebnisse wurden anschließend zusammengefasst. Insgesamt wurden 150 Referenzen verwendet.

**Ergebnisse:** Diese Literaturrecherche zeigt, dass in den letzten Jahren zunehmend Studien erschienen sind, die sich mit der Phase der Frühschwangerschaft beschäftigen. Verschiedene Parameter die mit einem gestörten maternalen Metabolismus einhergehen, beeinflussen den Phänotyp des Neugeborenen schon während des ersten Trimenons. Nicht nur eine höhere Nüchternplasmaglukose, sondern auch Dyslipidämie bestehend aus erhöhten Triglycerid- und ernidriegten HDL-Spiegeln, niedrigere Adiponektinwerte, höhere PAPP-A-Konzentrationen und ein höheres Plazentawachstum in dieser frühen Phase, sind mit einem erhöhten Risiko für LGA, Makrosomie und einer ungünstigen Körperzusammensetzung des Neugeborenen mit erhöhtem Fettanteil verbunden.

**Diskussion:** Die aufgeführten Resultate zeigen die besondere Relevanz der Frühschwangerschaftsphase für die Entwicklung und Prägung des Phänotyp des Neugeborenen. Weitere Forschung ist erforderlich, um die Behandlung von Risikoschwangerschaften zu optimieren. Ziel wäre dabei die Früherkennung von Frauen mit einem erhöhten Risiko für ein unerwünschtes Outcome. Darüber hinaus können Interventionen wie Diäten, Bewegung und/oder eine medikamentöse Therapie früher erfolgen und sich günstig auf das Neugeborene auswirken, z.B. durch ein verringertes Geburtsgewicht und/oder reduzierten Körperfettanteil.

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## List of Abbrevations

| | |
|---|---|
| ADA | American Diabetes Association |
| ADP | Air displacement plethysmography |
| AFI | Amniotic fluid insulin |
| AGA | Appropriate for gestational age |
| BMI | Body mass index |
| ß-HCG | ß human chorionic gonadotropin |
| CRP | C-reactive protein |
| FFA | Free fatty acids |
| FPG | Fasting plasma glucose |
| GDM | Gestational diabetes mellitus |
| GLUT | Glucose transporter |
| GWAS | Genome wide association studies |
| GWG | Gestational weight gain |
| HAPO | Hyperglycemia and adverse pregnancy outcome |
| HbA1c | Hemoglobin A1c |
| hCG | Human chorionic gonadotropin |
| HDL | High density lipoprotein |
| HPL | Human placental lactogen |
| IADPSG | The International Association of the Diabetes and Pregnancy Study Groups |
| IDDM | Insulin dependent diabetes mellitus |
| IGF | Insulin-like growth factor |
| IGF-1 | Insulin-like growth factor 1 |
| IOM | Institute of Medicine |
| LDL | Low density lipoprotein |
| LGA | Large for gestational age |
| LH | Luteinizing hormone |
| LCPUFA | Long chain polyunsaturated fatty acids |

| | |
|---|---|
| NEFA | Non-esterified fatty acids |
| NGT | Normal glucose tolerance |
| OGTT | Oral glucose tolerance test |
| PAPP-A | Pregnancy associated plasma protein |
| P-CS | Primary caesarean section |
| PGH | Placental growth hormone |
| PIH | Pregnancy induced hypertension |
| RGWG | Rate of gestational weight gain |
| TC | Total cholesterol |
| TG | Triglycerides |
| TNF-α | Tumor necrosis factor α |
| VLDL | Very-low density lipoprotein |
| WHO | World Health Organisation |

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# 1 Introduction

## 1.1 Physiological changes during early pregnancy

### 1.1.1 Hormones in early pregnancy

The embryo increasingly produces human chorionic gonadotropin (hCG) after implantation in the endometrium. HCG has functional and structural similarities with luteinizing hormone (LH). Thus, in the first trimester the progesterone formation in the corpus luteum graviditas can be maintained. The hCG reaches its maximum concentration in 8 to 10 weeks of pregnancy and then falls off again (Werny and Schlatt, 2019).

The placenta will take over progesterone and estrogen production during this period. Both increase continuously with their concentrations during the course of pregnancy. Progesterone prevents rejection of the endometrium and is therefore considered the most important factor in maintaining pregnancy. Among other functions, estrogen promotes the release of pituitary prolactin and stimulates gland proliferation of the female breast (Werny and Schlatt, 2019). *In vitro* Prolactin is able to enhance ß-cell proliferation and insulin secretion (Huang, Snider and Cross, 2009). Prolactin first starts to rise during week 4 and 5 of pregnancy (Barberia *et al.*, 1975). It then increases throughout gestation in a linear pattern (Rigg, Lein and Yen, 1977).

In addition, the placenta secretes the human placental lactogen (HPL), whose concentration increases continuously from the 10th week of pregnancy. This hormone causes various changes in the maternal metabolism, such as an increase in blood glucose levels, an increase in lipolysis and differentiation of the mammary gland. In the fetus it promotes erythropoiesis. HPL is antagonistic to insulin. It may thus be involved in the development of gestational diabetes (Werny and Schlatt, 2019).

Another important hormone during pregnancy is human placental growth hormone (PGH), as it plays an important role in regulation of placental growth and development (Velegrakis, Sfakiotaki and Sifakis, 2017). PGH is expressed by the

placenta and serum levels increase from the 5th week of pregnancy throughout gestation (Chellakooty *et al.*, 2004). PGH is essential for the physiological adaptation of maternal metabolism to pregnancy. PGH also regulates Insulin-like growth factor-1 (IGF-1) and therefore directly and indirectly affects various processes (Caufriez *et al.*, 1990), as it stimulates gluconeogenesis, lipolysis and anabolism. Moreover, it influences fetal growth and placental development. Therefore PGH might be a predictor for adverse pregnancy outcomes (Velegrakis, Sfakiotaki and Sifakis, 2017).

### 1.1.2 Normal maternal metabolism during early pregnancy

Metabolic changes in early pregnancy are a necessary adaptation to meet the demands of both the fetus and the mother. It lays the foundation of regular growth and development of the fetus and prepares the mother for the physiological demands of pregnancy and later on for labour and lactation. Not only carbohydrate metabolism, but also protein and fat metabolism are essential parameters for the internal environment (Hadden and McLaughlin, 2009). This adaptation includes impaired insulin sensitivity, increased ß-cell response, increased blood glucose levels as well as changes in the levels of circulating free fatty acids, triglycerides, cholesterol and phospholipids (Di Cianni *et al.*, 2003).

#### 1.1.2.1 Carbohydrate metabolism

In early pregnancy the responsiveness to insulin is increased as well as the production of insulin. This enhanced responsiveness is a consequence of the hormonal change, leading to an anabolic condition and setting the stage for neoplasm of fat tissue as well as the growth in maternal organs. At the same time fasting glucose values decrease (Breckwoldt, Kaufmann and Pfleiderer, 2007). The main reason for this might be the total increase in plasma volume (Hadden and McLaughlin, 2009). As a result there is a higher risk for hypoglycemia along pregnant diabetics (Breckwoldt, Kaufmann and Pfleiderer, 2007).

Glucose is the main nutrition source for the fetus (Hadden and McLaughlin, 2009). Besides, it is the main stimulator of insulin secretion (Desoye and Van Poppel, 2015). Compared to the third trimester basal endogenous glucose production is 30 % lower during week 12 and 14 of normal gestation (Catalano *et al.*, 1992).

#### 1.1.2.2 Lipid metabolism

There is an enhancement of all circulating lipids, especially triglycerides, which makes pregnancy a hyperlipidemic state. Change of morphology and function in adipocytes allows this modification of lipid metabolism. They become hypertrophic and can therefore store more fat. In addition fat storage is facilitated by the increased number of receptors on adipocytes, coupled with increased insulin sensitivity (Baird, 1986).

Due to these mechanisms and hyperphagia there is an enhanced body fat accumulation in the period of early pregnancy (Herrera, 2002b), which serves the mother as energy source while glucose is conserved for the fetus. During the first 15 weeks of pregnancy the woman gains 3.3 kg fat within physiological adaptation (Clapp *et al.*, 1988). This is regulated by the placenta producing leptin and the initial increased responsiveness to insulin, leading to an increased lipogenesis with a high release of free fatty acids and glycerol from the adipose tissue as well as a reduced activity from the lipoproteinlipase (Herrera, 2002a). The maternal liver is the main recipient for free fatty acids and glycerol, which are metabolized into ketone bodies and glucose and therefore able to overcome the placental barrier sustaining fetal metabolism (Herrera, 2002a).

In addition, maternal liver uses lipolytic products to synthesize triglycerides, which then enter maternal circulation. An increased triglyceride transfer between the lipoprotein fractions, as well as the decrease in extrahepatic lipoprotein lipase (LPL) activity, result in increased triglyceride levels in lipoprotein fractions. Triglycerides cannot be transferred directly through the placenta. An interplay of lipoprotein receptors, LPL and intracellular lipase activities in the placenta enable the supply of the fetus with fatty acids (Herrera, 2002a).

#### 1.1.2.3 Amino acid and protein metabolism

The changes in protein metabolism are evident early in pregnancy. On the one hand, there is a decrease in urea production as well as plasma amino nitrogen. The rate of branched-chain amino acid transamination decreases, whereas the rate of weight-specific protein turnover per kilogram of body weight remains unchanged (Kalhan, 2000).

Amino acids are an essential source for fetal growth (Kalhan, 2000). Most essential and non-essential amino acids are decreased during the first trimester compared to non-pregnant women. Glucogenic amino acids and amino acids of the urea cycle reduce the most. The significantly lower concentrations remain throughout pregnancy (Di Giulio *et al.*, 2004). The transport of the amino acids from the mother via the placenta to the fetus takes place actively via a concentration gradient. These special transport mechanisms could play a role in the development of macrosomic children in a diabetic environment (Hadden and McLaughlin, 2009).

## 1.2 The Fetus in early pregnancy

### 1.2.1 Fetal development and growth

There are critical stages in fetal development where nutrient imbalance can have negative consequences for fetal growth and body composition (Symonds *et al.*, 2009). These critical phases are characterized by a high rate of cell division of the fetus, which makes it susceptible to environmental influences (McCance and Widdowson, 1974). Early pregnancy is the period during which the fetus forms and a pronounced increase in length occurs (Symonds *et al.*, 2009). Therefore disruption of nutrient metabolism at this early stage of pregnancy primarily affects placental and fetal hyperplasia (Villar and Belizan, 1982). Furthermore during this critical period, when the fetus is particular vulnerable to external influences, maternal imbalances in hormone levels cause hormonal response mechanisms to be programmed to interact

with the environment, as well as the tissue's sensitivity to certain hormones (Csaba, 1980; Symonds *et al.*, 2009).

### 1.2.2 Embryogenesis

A few days after implantation, gastrulation forms the various cell populations of the three cotyledons. The cells of the endoderm form the digestive tract and its internal organs, and the cells of the mesoderm differentiate into the musculoskeletal system, including all the muscles and cells of the blood and the immune system. Ectoderm cells develop into the nervous system and the skin. The embryonic axes and thus a basic body shape are formed (Werny and Schlatt, 2019).

Embryogenesis progresses continuously in the process of organogenesis. This takes place from the 3rd to the 8th week of pregnancy. During this time, the various organs develop from the three cotyledons. Brain, eyes and heart arise very early. The heart begins to beat in the fifth week of pregnancy. After completion of the organogenesis, fetogenesis begins at the 9th week, in which the development of the organs takes place (Werny and Schlatt, 2019)

### 1.2.3 Fetal metabolites

The first trimester is an anabolic state. Maternal metabolism and nutrient intake determine the amount of nutrients reaching the placenta (Cetin, Alvino and Cardellicchio, 2009). Availability of maternal nutrients (Figure 1) and transportability through the placenta to the fetus thus determine fetal growth (Zeng, Liu and Li, 2017).

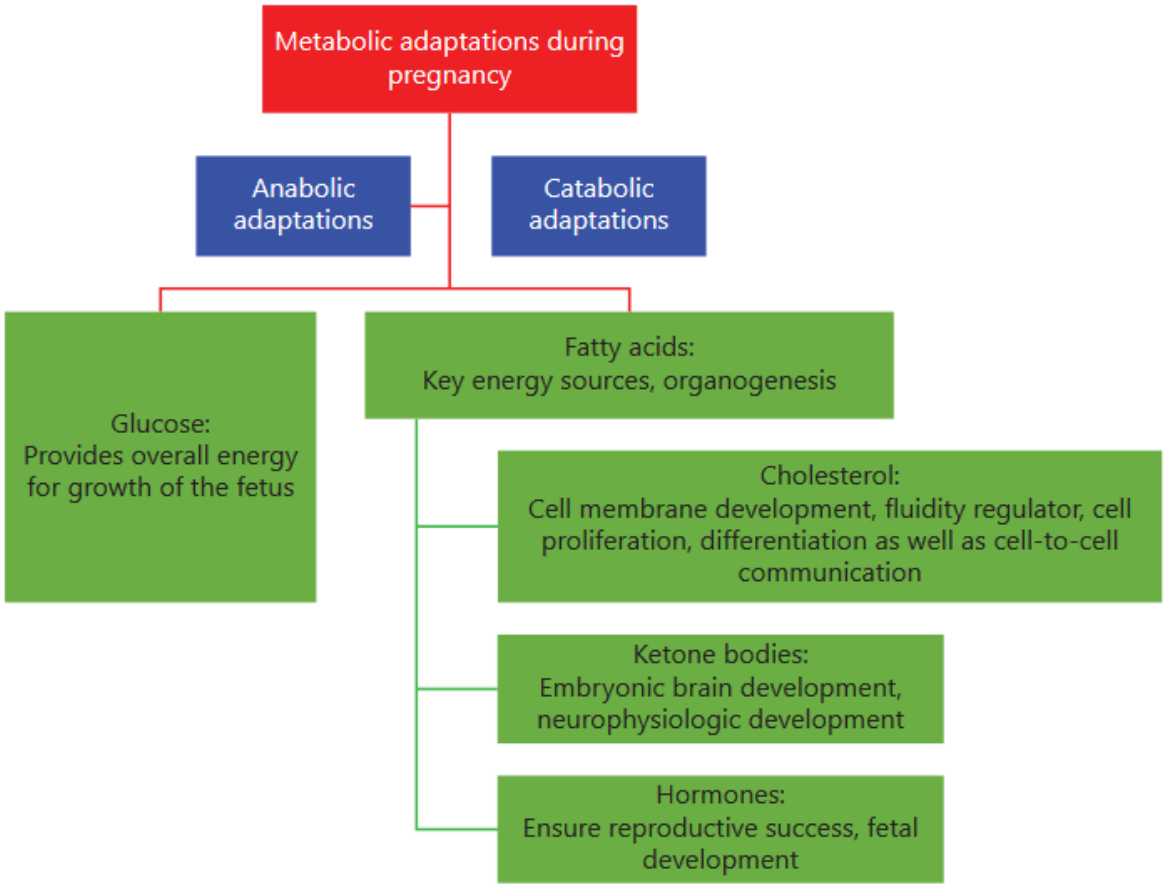


**Figure 1: Fetal metabolites** (Zeng, Liu and Li, 2017)

The main energy source for the fetus is glucose. Contribution of fetal gluconeogenesis is low. Due to the high demand a fast transfer of maternal glucose is necessary. Therefore glucose transporter proteins (GLUT) transfer maternal glucose via concentration gradient (Zeng, Liu and Li, 2017). Early fasting plasma glucose in the 9$^{th}$ week of pregnancy is already associated with an risk for LGA (Riskin-Mashiah *et al.*, 2009). Also first trimester HbA1c correlates with the incidence of LGA and macrosomic infants (Mane *et al.*, 2017; Bashir *et al.*, 2019).

The fetus also uses lipids including fatty acids (FA) and cholesterol as source of energy. These can be obtained by an endogenous metabolic supply via fetal lipids or exogenous by the maternal placental circulation. Triglycerides cannot directly cross the placenta, it is only permeable to fatty acids (Bhattacharya and Stubblefield, 2016). Fatty acids are essential for the development of white adipose tissue and organogenesis (Mennitti *et al.*, 2015). Higher triglyceride levels measured between 6

and 8 weeks of pregnancy are already associated with an increased risk for LGA (Liang *et al.*, 2018). However, a recently published study using mendelian randomization could not find a causal relationship between maternal triglyceride levels and neonatal birth weight (Warrington *et al.*, 2019).

Cholesterol is an important component for fetal development because of its function as key element of cell membranes. In addition, the steroid hormones are derived from cholesterol. During the first trimester, the fetus takes 20 % of the sterols for cholesterol synthesis from the mother. In early pregnancy there is a large requirement for cholesterol as the fetus growth rapidly between 10 to 14 weeks of gestation (Woollett, 2005). Compared to non-pregnant women cholesterol concentration is already higher in the first trimester and increases sharply throughout pregnancy (Martin *et al.*, 1999). Obesity and diabetes are associated with hypercholesterolemia. Fetuses with hypercholesterolemic mothers showed a higher prevalence of fatty streaks in the aorta (Napoli *et al.*, 1997).

### 1.2.4 Hormones

Fetal growth and the development of individual fetal tissues are regulated by hormones. They are of great relevance to intrauterine programming. Decisive hormones include insulin, insulin-like-growth-factor (IGF), adiponectin, and glucocorticoids with regard to adapting fetal development to prevailing intrauterine environment and nutrient availability. On the one hand, the hormones have direct effects on fetal growth via genes and on the other hand, indirectly through their influence on placental growth, fetal metabolism and production of growth hormones and other hormones by the feto-placental tissue. Therefore it can be deduced that endocrine changes are not only the cause, but also the result of intrauterine programming (Fowden and Forhead, 2004). A variety of hormone receptors is expressed by the placenta enabling her to respond to endocrine changes by the fetus or the mother. Glucocorticoids and insulin-like-growth factor cause a change in the morphological and functional characteristics of the placenta. As an interaction the placenta in turn affects the nutrient supply of the fetus (Vaughan *et al.*, 2014).

In the first trimester of pregnancy compared to non-pregnant women IGF-1 decreases (Persechini *et al.*, 2015). IGF-1 then slightly rises during second trimester and strongly increases in the third trimester. An above-average increase from the first to second trimester is associated with higher birth weight (Åsvold *et al.*, 2011).

### 1.2.5 Fetal pancreas

Fetal insulin secretion begins with 11 weeks of pregnancy (Adam *et al.*, 1969). At week 14 of gestation amniotic fluid insulin (AFI) can already be measured. Increased AFI levels at early second trimester are associated with a glucose tolerance at some point of pregnancy. Whereas among women with glucose levels above 7.1 mmol/L, AFI concentrations correlate with an increased risk for macrosomia (Carpenter *et al.*, 2001). *In vitro*, the fetal pancreas of diabetic mothers compared to non-diabetic mothers, responded with an increased insulin secretion to glucose incubation in week 11 to 15 of gestation. Also ß-cell mass and insulin content of the diabetic fetuses were increased (Reiher *et al.*, 1983). Diabetic environment thus seems to influence respond mechanisms at this early stage of pregnancy. Maternal glucose passes the placenta and produces a hyperglycaemic environment, which then induces ß-cell hyperplasia in the fetal pancreas. Insulin is considered a fetal growth factor and hyperinsulinism especially accelerates the growth of connective tissue, fat and muscle (Hübler, 2018).

## 1.3 Dysregulation of metabolism

The conditions that mainly lead to an impaired metabolism during early pregnancy and thus to an adverse neonatal outcome are diabetes, overweight, obesity and excessive gestational weight gain. Thus they are related to each other, each one affects intrauterine environment (Figure 2) (Lawlor, 2013).

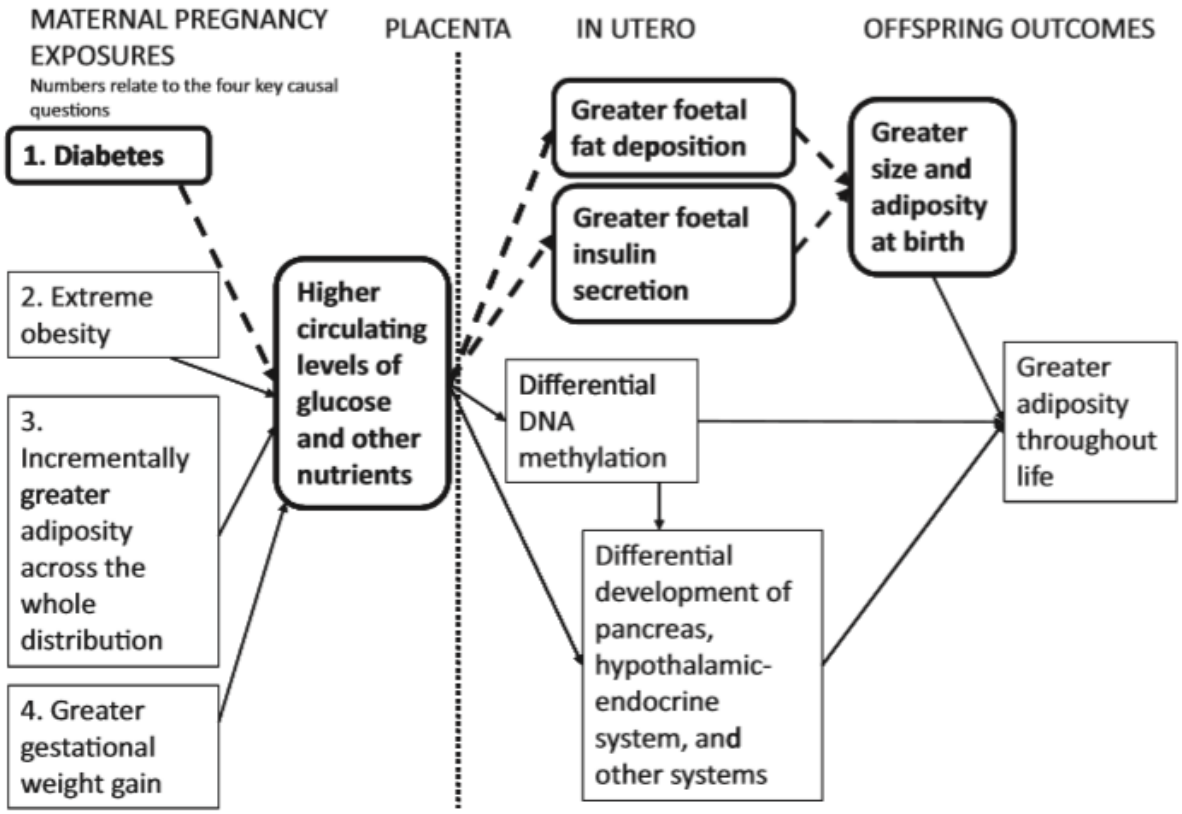


**Figure 2: Potential mechanisms resulting in greater neonatal size and adiposity at birth** (Lawlor, 2013 - page 8)

### 1.3.1 Diabetes in pregnancy

A pregnant woman with diabetes can either be a previously diagnosed type-1 or type-2 diabetic or may have an in pregnancy newly discovered gestational diabetes mellitus (GDM) (Lawlor, 2013). Every sixth child is born to a mother with diabetes mellitus. About 88% of these are attributable to gestational diabetes (Lefkovits, Stewart and Murphy, 2019).

#### 1.3.1.1 Type-1 diabetes

Type-1 diabetes is an immune-mediated or idiopathic disease, characterized by the destruction of pancreatic ß-cells, which results in an absolute insulin deficiency. The proportion of type-1 diabetics is only 5 to 10 percent. Not only a genetic predisposition, but also environmental influences contribute to the destruction of ß-cells. Since the type-1 autoimmune derailment disposition is not tissue specific, these patients also have an increased incidence of other immune disorders such as Hashimoto thyroiditis or myasthenia gravis (American Diabetes Association, 2006). Pregnant women with type-1 diabetes will be treated with insulin throughout pregnancy (Lawlor, 2013). In early pregnancy, the incidence of hypoglycaemia is 5-fold higher in type-1 diabetics than before gestation (Ringholm *et al.*, 2012).

#### 1.3.1.2 Type-2 diabetes

90 to 95% of diabetics are suffering from type-2 diabetes, which is characterized by insulin resistance, due to a progressive loss of ß-cell function. These patients often do not require insulin therapy. Most type-2 diabetics are obese or have an increased percentage of body fat, which in turn has a negative impact on insulin resistance. Genetic factors also contribute to the development of insulin resistance. But most of all, a bad lifestyle shaped by overeating, lack of exercise and stress contributes to the onset of disease. These factors are also the main courses of obesity (American Diabetes Association, 2006).

If a woman with type-2 diabetes gets pregnant, who has pre-conceptually not been in need of medical therapy, metformin or insulin therapy might become necessary during pregnancy (National Institute for Health and Care Excellence, 2015).

#### 1.3.1.3 Gestational diabetes mellitus

Due to the World Health Organisation (WHO) GDM has been defined as any degree of hyperglycemia if this occurs for the first time during pregnancy. GDM is usually not diagnosed during the first trimester (Lawlor, 2013).

Risk factors for the development of GDM (Lefkovits, Stewart and Murphy, 2019):

- glucose intolerance or GDM in the past history
- maternal body mass index >30kg/m²
- family history of diabetes
- previous LGA infant
- ethnic origin associated with a high prevalence of type-2 diabetes

#### 1.3.1.4 Diagnosis in early pregnancy

As there are many pregnant women unaware of their pre-existing diabetes mellitus, the American Diabetes Association recommends screening for women with risk factors at first antenatal visit (American Diabetes Association, 2018). A diagnose in the first trimester by standard diagnostic criteria should therefore be treated as pre-existing diabetes, because GDM diagnosis in early pregnancy by FPG levels or OGTT is not yet evidence based (McIntyre *et al.*, 2016).

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study clearly showed an association between fasting plasma glucose levels within ranges considered as non-diabetic and adverse neonatal outcome (Metzger *et al.*, 2009). These results required a rethinking of the diagnostic criteria. Hence The International Association of Diabetes and Pregnancy Group (IADPSG) published new recommendations (Figure 3) (Lapolla, Chilelli and Dalfrà, 2011).

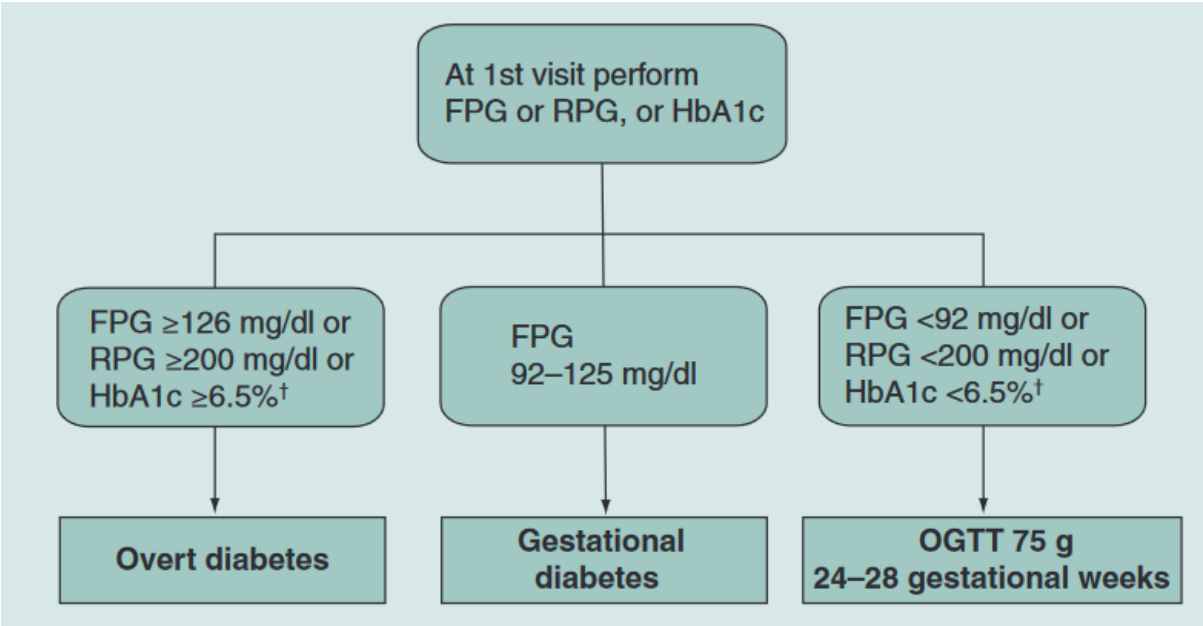


**Figure 3: IADPSG recommendations** (Lapolla, Chilelli and Dalfrà, 2011)

Based on these recommendations, the WHO published new guidelines for diagnosis and classification of hyperglycaemia in pregnancy in 2013:

1) Hyperglycaemia first detected at any time during pregnancy should be classified as either pre-existing diabetes in pregnancy or GDM.
2) If one or more of the following criteria are met, diabetes should be diagnosed:

- fasting plasma glucose ≥ 7.0 mmol/l (126 mg/ dl)
- 2-hourplasma glucose ≥ 11.1 mmol/l (200 mg/dl) following a 75g oral glucose load
- random plasma glucose ≥ 11.1 mmol/l (200 mg/ dl) in the presence of diabetes symptoms

3) If one or more of the following criteria are met, Gestational diabetes mellitus should be diagnosed

- fasting plasma glucose 5.1-6.9 mmol/l(92 -125 mg/dl)
- 1-hourplasma glucose ≥ 10.0 mmol/l (180 mg/dl) following a 75g oral glucose load
- 2-hourplasma glucose 8.5-11.0 mmol/l (153 -199 mg/dl) following a 75g oral glucose load

('Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline.', 2014)

### 1.3.2 Maternal obesity

The rate of maternal obesity is increasing (Leddy, 2008). Due to a nationally representative study in the UK the incidence of maternal obesity in first trimester was doubled between 1989 and 2007 (Heslehurst *et al.*, 2007). While in UK prevalence of maternal obesity is highest among European countries, other countries also show alarming statistics (Figure 4) (Devlieger *et al.*, 2016).

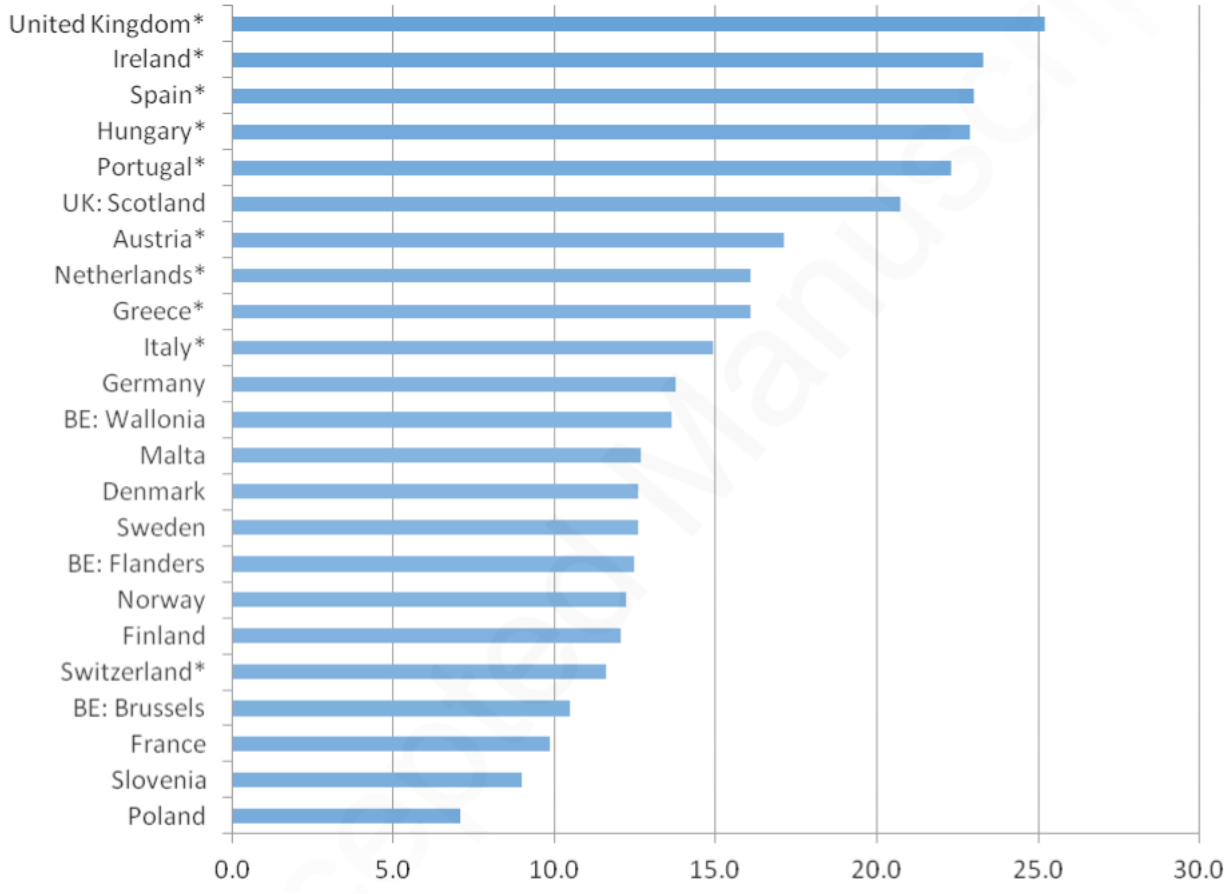


**Figure 4: Distribution of maternal obesity in Europe** (Devlieger *et al.*, 2016)

The definition of obesity in pregnancy is met at a BMI of 30kg/m² or more, measured at the first antenatal visit. Obesity is divided into three classes: BMI 30 – 34.9 is defined as class one, BMI 35 – 39.9 as class two and BMI 40 and more is defined as class three or morbid obesity. A BMI between 25 and 29.9 is referred to as overweight (Chodankar *et al.*, 2018). There are many complications associated with maternal obesity. Obese pregnant women have an increased risk for multiple complications in pregnancy, especially GDM, pre-eclampsia, gestational hypertension, miscarriage and obstetric problems (Chodankar *et al.*, 2018). In case of additional excessive weight gain during pregnancy, the complication rate is even higher (Devlieger *et al.*, 2016).

During the first trimester maternal obesity correlates with high triglyceride levels and very low-density lipoproteins (VLDL), as well as increased insulin levels (Catalano and Demouzon, 2015; Mouzon and Lassance, 2015).

### 1.3.3 Gestational weight gain

The institute of medicine revised the guidelines for gestational weight gain in 2009 as the numbers of overweight and obese women at childbearing age increased rapidly (Catalano and Demouzon, 2015). Excessive gestational weight gain is a relevant issue. 38% of normal, 64% of overweight and 46% of obese women, based on general population on the United States, gained too much weight during pregnancy (Rasmussen and Yaktine, 2009).

Recommendations were based on existing literature on maternal and offspring outcome (Viswanathan *et al.*, 2008). Cesarean delivery and post-partum retention as maternal risks as well as preterm birth, extremes of birth weight and childhood obesity as offspring risks were associated with gestational weight gain (Rasmussen *et al.*, 2010). Basis for the recommendations (Table 1) is pre-pregnancy BMI.

| Prepregnancy BMI (kg/m²) | Total Weight Gain | | Rates of Weight Gain* Second and Third Trimesters | |
|---|---|---|---|---|
| | Range (kg) | Range (lb) | Mean (Range) (kg/wk) | Mean (Range) (lb/wk) |
| Underweight (less than 18.5) | 12.5–18.0 | 28.0–40.0 | 0.51 (0.44–0.58) | 1.0 (1.0–1.3) |
| Normal weight (18.5–24.9) | 11.5–16.0 | 25.0–35.0 | 0.42 (0.35–0.50) | 1.0 (0.8–1.0) |
| Overweight (25.0–29.9) | 7.0–11.5 | 15.0–25.0 | 0.28 (0.23–0.33) | 0.6 (0.5–0.7) |
| Obese (30.0 or higher) | 5.0–9.0 | 11.0–20.0 | 0.22 (0.17–0.27) | 0.5 (0.4–0.6) |

**Table 1: GWG recommendations by the IOM** (Rasmussen *et al.*, 2010)

For the first trimester, calculations assume a total weight gain of 1.5kg for obese and total weight gain of 2kg for the remaining pregnant women (Rasmussen and Yaktine, 2009).

Due to side effects, no medical intervention is recommended for gestational weight loss. Therefore in order to avoid excessive gestational weight gain physical activity, dietary control and behavior modification are the methods of choice (Catalano and Demouzon, 2015). Ideally, weight loss should be sought before pregnancy (Rasmussen, Catalano and Yaktine, 2009).

## 1.4 Impact of disturbed maternal metabolism

### 1.4.1 Impact on fetal growth and development

#### 1.4.1.1 Child complications of pre-existing diabetes in early pregnancy

During the first trimester, the prevalence of congenital malformations in diabetic patients is three to five times higher. The exact pathomechanism responsible for diabetic embryopathy has not yet been fully elucidated. Various mechanisms for the teratogenic effects of hyperglycemia are discussed. A specific diabetic embryopathy however, does not exist. First, the caudal regression syndrome is associated with diabetic embryopathy. The caudal regression syndrome is a disorder of the lower spinal segments with aplasia or hypoplasia of the coccyx and lumbar spine (Schaefer-Graf and Kautzky-Willer, 2016).

Malformations of the heart occur 4 times more frequently in embryos of diabetic mothers (Martínez-Frías *et al.*, 1998). In second place are neural tube defects, which occur 3 times more often. The third most common malformations affect the kidneys. Poor metabolism in the first trimester is associated not only with malformations but also with increased prevalence of abortion and early symmetric growth restriction (Schaefer-Graf and Kautzky-Willer, 2016).

#### 1.4.1.2 Metabolic effects on the neonate

Due to the hyperinsulinism there is an increased oxygen demand, which manifests itself in an increased erythropoiesis and polycythemia with high neonatal hematocrit. In fetuses of diabetic women increased erythropoietin levels and an increased number of erythrocytes were detected in the plasma, which correlate with the glucose and insulin concentrations in the amniotic fluid and fetal blood. The combination of polycythemia and liver immaturity leads to an increased prevalence of hyperbilirubinemia in the newborn (Schaefer-Graf and Kautzky-Willer, 2016).

Newborns of diabetic women have five times more frequently a respiratory distress syndrome, since hyperinsulinism has an influence on the formation of surfactant in the fetal pneumocytes by influencing enzymatic processes. Chronic stimulation of the fetal pancreas and resulting ß-cell hypertrophy leading to increased insulin secretion can cause neonatal hypoglycaemia if substrate intake fails. In addition, malfunctioning maternal metabolism is more likely to cause neonatal hypocalcaemia and hypomagnesaemia (Schaefer-Graf and Kautzky-Willer, 2016).

### 1.4.2 Placental changes

In early pregnancy insulin response to glucose is positively correlated with placental weight at term, suggesting that maternal insulin is an important growth factor for placenta at this early stage of gestation (O'Tierney-Ginn *et al.*, 2015). Placentas of pregnant women with a disturbed metabolism are usually heavier and larger. There is an overall increase in the villus surface as well as the vascular surface inside the villi

(Mayhew *et al.*, 1994). In early pregnancy, there is also a higher density of insulin receptors on syncytiotrophoblasts (O'Tierney-Ginn *et al.*, 2015).

Placental development and growth is thus significantly influenced by disturbed maternal metabolism during early pregnancy and the glucose-insulin-axis. Changes in maternal glucose or insulin levels might affect transplacental glucose transfer. An increased maternal glucose concentration causes an increased glucose flux across the placenta, triggering ß-cell hyperplasia and increased insulin secretion among the fetus (Figure 5) (Desoye and Van Poppel, 2015).

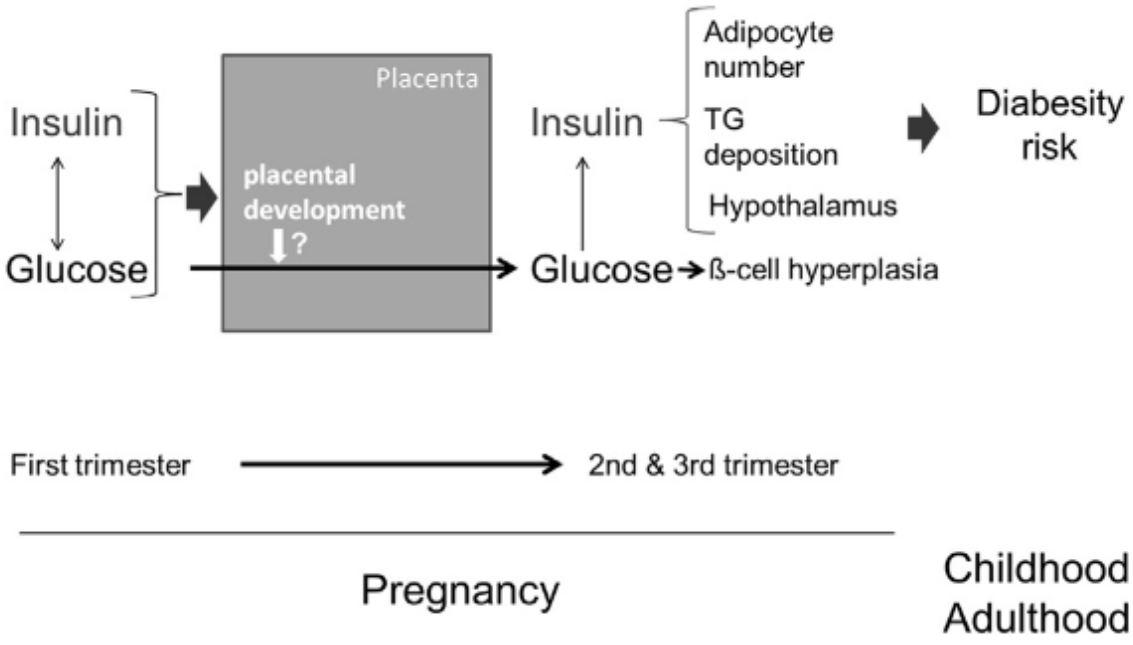


**Figure 5: Early maternal metabolism leading to neonatal adiposity** (Desoye and Van Poppel, 2015)

Insulin, in turn, affects the fetal fat tissue by causing an increase in adipocytes as well as triglyceride deposition. Thus the concept in Figure 5 shows how disturbed maternal metabolism in early pregnancy may lead to adverse neonatal outcomes (Desoye and Van Poppel, 2015).

### 1.4.3 Metabolic inflammation

Obesity is a state of chronic low-grade inflammation, which leads to a systemic metabolic dysfunction (Ouchi *et al.*, 2011). This “metainflammation” is primarily caused by metabolites and excess consumption of nutrients and therefore different from a normal acute proinflammatory reaction. It is the metabolic cells that even start the inflammatory process and thus destroy metabolic homeostasis. In addition, in the context of metainflammation, an increased infiltration of immune cells into the fatty tissue occurs. Another important difference to the acute proinflammatory response is the chronicity of metabolic inflammation. There is a gradual cytokine expression and infiltration of immune cells that persists (Gregor and Hotamisligil, 2011). A major part of inflammatory cytokines, including adiponectin, TNFa, IL-6, leptin and resistin is secreted by adipose tissue (Volpe *et al.*, 2007). However, the placenta and skeletal muscle also produce cytokines (Lappas *et al.*, 2005).

Adiponectin is a plasma protein, which also influences insulin resistance and glucose hemostasis (Mazaki-Tovi, Kanety and Sivan, 2005). Adiponectin is exclusively produced by adipose tissue (Mazaki-Tovi, Kanety and Sivan, 2005). Proinflammatory factors such as TNF-α and IL-6 inhibit the secretion of adiponectin (Ouchi *et al.*, 2011). Serum adiponectin starts to reduce during the first trimester of pregnancy in case of obesity, type-2 diabetes and GDM (Williams *et al.*, 2004; Thagaard *et al.*, 2017). The adiponectin concentrations increase throughout pregnancy (Worda *et al.*, 2004). During normal early pregnancy, adiponectin levels seem to be equal to those in non-pregnant women (Naruse *et al.*, 2005).

In adiposse tissue leptin acts as proinflammatory factor (Tessier, Ferraro and Gruslin, 2013). Furthermore, leptin acts via central hypothalamic pathways, inhibiting insulin secretion, stimulating glucose transport and influencing tissue metabolism. Leptin levels increase during the first trimester and throughout pregnancy, positively correlated with GWG and BMI and fat mass (Hardie *et al.*, 1997; Wauters, Considine and Van Gaal, 2000). GDM adipose tissue produces higher amounts of Leptin than non-diabetic women (Lappas *et al.*, 2005). Leptin plays a role in maternal-fetal exchange processes and thus effects growth and development of the fetus (Tessier, Ferraro and Gruslin, 2013).

## 1.5 Influence of genetics on early pregnancy

### 1.5.1 Maternal genotype

The mother's genotype influences the pattern of weight gain during pregnancy. The mother's total weight gain is predicted by genetic variants associated with obesity and diabetes. The pregravid BMI is also associated with gestational weight gain, which means that both BMI and maternal genotype influence gestational weight gain (Stuebe *et al.*, 2010).

Due to Warrington *et al.* common maternal genetic variants cause 20% of the variability in GWG (Warrington *et al.*, 2018). The GWG is composed as follows: 55% increased maternal tissue, 15-20% placenta and amniotic fluid and 20-25% fetal tissue (Pitkin, 1976). The maternal genome is involved in tissue expansion, placental size, amniotic fluid and fetal growth. The fetal genome in contrast is not involved in tissue expansion (Warrington *et al.*, 2018).

Another recently published genome wide association study (GWAS) estimated that in total even 40% of the birth weight variation can be explained by genetics. This 40% is composed of 28.5% fetal genetic variation, 7.6% maternal genetic variation and covariance (Warrington *et al.*, 2019).

### 1.5.2 Fetal programming

Various epidemiological and clinical findings indicate that not only the genetic disposition, but also influences in the pre- and perinatal phase have a lasting influence on the health of the newborn. The epigenetic illustration of phenotypic development describes the ability of organisms to adapt to different environmental conditions through different individual developmental pathways, especially in the early stages of life (Bateson *et al.*, 2004).

Programmed consequences for the fetus can be caused by insults including maternal obesity and diabetes, as they influence the fetal intrauterine environment

(Lock *et al.*, 2017). The environmental factors are able to modify epigenetic states and result into the development of abnormal phenotypes. Therefore mitotically heritable changes in gene expression but not in the DNA sequence can impact the fetal development and programming (Jaenisch and Bird, 2003). Other mechanisms of perinatal programming include changes in mitochondrial function, as well as receptor and synaptic formation, thereby affecting the cells. Changes in organ function occur through variation in organ structure, vascularization and innervation. In addition, by a misadjustment of control systems of homoestoasis and endocrine function circuits, the regulation axis permanently adjusted (Schleußner, 2016).

There is a strict regulation of epigenetic processes that accompany embryonic development. Between these epigenetic processes there are interactions that influence the unique gene expression program that organizes the development of each cell. Most of these processes affect metabolism, whereas embryogenesis and development are the most vulnerable periods (Skinner, 2011).

## 1.6 Adverse neonatal outcome

Disturbed maternal metabolism in early pregnancy affects the neonatal phenotype. For this literature review outcome measures were LGA, fetal macrosomia and neonatal body composition.

### 1.6.1 LGA and fetal macrosomia

Large for gestational age refers to newborns that are too large for their gestational age, defined by birth weights above the 90th percentile. Fundamental to this are weight curves, based on a normal distribution of birth weights at different gestational ages (Schneider, Schneider and Lobmaier, 2016).

Fetal macrosomia is defined as birth weight higher than 4500g. Nearly 10% of pregnancies are complicated by macrosomia (Turkmen, Johansson and Dahmoun, 2018). Birth weight is an indirect measure of growth. It is composed of various

amounts such as fatty tissue, muscle mass, skeleton and water content (Bhattacharya and Stubblefield, 2016).

#### 1.6.1.1 Maternal complications due to LGA and macrosomia (Jolly *et al.*, 2003)

- Prolonged labour
- Instrumental vaginal delivery
- Perineal trauma
- Emergency caesarean section
- Postpartum haemorrhage
- Greater uterine distension
- Extended hospital stay related to increased maternal morbidity

#### 1.6.1.2 Fetal risks due to LGA and macrosomia (Nesbitt, Gilbert and Herrchen, 1998)

- Fetal asphyxia
- Shoulder dystocia
- Birth trauma
- Neonatal hypoglycemia
- Increased susceptibility to obesity and diabetes in later life

### 1.6.2 Body composition and measurement

The common indicators for body composition consist of fat-free mass, fat mass and total body water (Sanin Aguirre, Reza-López and Levario-Carrillo, 2004). There are different possibilities to measure neonate body composition. The methods used in the following results were either air displacement plethysmography (ADP) or sum of four skinfolds.

For measurement of skinfold thickness a skinfold caliper is used. It is therefore non-invasive and fast. Biceps, triceps, subscapular and suprailiac skinfold are measured (Rodríguez *et al.*, 2005).

Air displacement plethysmography is an indirect method of measurement in which the volume of the newborn is measured by the displaced volume of air within a closed chamber. Body weight and volume are used to calculate the density and determine the absolute and relative mass of body fat and fat-free mass, using special formulas and fixed density values for fat and fat-free mass (Fields, Goran and McCrory, 2002).

### 1.6.3 Potential biomarkers for early detection of adverse neonatal outcome

Biomarkers are measurable parameters. They may be useful to predict accelerated fetal growth leading to LGA or macrosomia. As GDM, obesity and excessive GWG are the main contributors to a disturbed intrauterine environment in early pregnancy associated predictors might as well correlate with adverse neonatal outcome and therefore be a predictive value.

One important component is fetal nutrient supply. Especially glucose as main energy source of the fetus might be a relevant predictor (Zeng, Liu and Li, 2017). Blood glucose levels and HbA1c as biomarkers of glycaemic control may indicate fetal growth. Due to the connection with dyslipidemia it might also be of predictive value to measure lipid levels, including triglycerides, cholesterol, VLDL, LDL and HDL (Nahavandi *et al.*, 2018). Particularly hypertriglyceridemia and low HDL-concentrations are correlated with metabolic abnormalities (Wang *et al.*, 2015).

But also endocrine and metabolic hormones play an important role. Adiponectin is a potential biomarker for adverse neonatal outcomes, as adiponectin levels in diabetic or obese women are significantly lower (Georgiou *et al.*, 2008). Also Leptin should be considered as a predictor, but has less evidence strength than adiponectin (Powe, 2017). AFI might also be a meaningful biomarker, but as it is not reliable measureable until 14 weeks of gestation, it does not meet our defined period of early pregnancy (Carpenter *et al.*, 2001).

Placental changes are related to diabetic and obese environment (Nahavandi *et al.*, 2018). Higher early PGH levels are associated with the incidence of GDM (Eleftheriades *et al.*, 2014)

Biomarkers of inflammation, including TNF-α and C-reactive protein (CRP) should be examined (Powe, 2017). TNF-α is an independent predictor of insulin resistance (Kirwan *et al.*, 2002). Higher first trimester CRP levels however have shown to be associated with the later development of GDM, but are associated with BMI and might therefore not provide additional information about increased risk for fetal growth (Powe, 2017).

The first trimester markers used for aneuploidy screening PAPP-A and ß-HCG are pregnancy associated. Their role in screening for aneuploidies and preeclampsia is well established and they might as well provide information on other adverse neonatal outcomes (Poon *et al.*, 2011).

## 2 Methods and Material

This literature review is a summary from existing literature found on the period of early pregnancy associated with adverse neonatal outcome. Adverse neonatal outcome was defined as large for gestational age (LGA), macrosomia and body composition, i.e. higher percentage of fat mass. Early pregnancy was determined as the period up to 15 weeks of pregnancy. Research was mainly conducted via the online database Pubmed, furthermore sources available at the library of the Medical University of Graz were used.

The following search words were mainly used at the beginning of research: “early pregnancy”, “first trimester”, “adverse neonatal outcome”, “LGA”, “macrosomia”, “body composition”, “diabetes”, “obesity” and “metabolic inflammation”. Relevant studies were analyzed. Furthermore references cited in relevant studies were reviewed.

After familiarization with the subject, a more targeted search was started for possible predictors for the desired adverse neonatal outcome: “fasting plasma glucose”, “HbA1c”, “Adiponectin”, “Gestational weight gain”, “Leptin”, “Lipids”, “Triglycerides”, “HDL”, “LDL”, “Cholesterol”, “ß-HCG”, “PAPP-A”, “PGH” and “placental development”. These terms were always related to the period of early pregnancy, ideally for the first trimester, but at most up to 15 weeks of pregnancy. Many studies found had to be excluded, as they referred to early pregnancy as first half of pregnancy or even until 24 weeks. The remaining results were subsequently summarized.

The literature management program “Mendeley” helped to collect and sort researched sources. It also offered the opportunity to quote collected sources directly. In addition, the program is able to create a bibliography. Books and sources published between 1969 and 2019 were utilized. In total 150 references were used.

# 3 Results

A considerably amount of studies that examine the contribution of a disturbed early period to shaping the neonatal phenotype, define adverse neonatal outcome by LGA, macrosomia or higher percentage of fat mass. Other studies measured adverse outcomes as obstetric complications, including shoulder dystocia, cesarean delivery, birth injuries or preterm birth (Alunni *et al.*, 2015; Boriboonhirunsarn and Kasempipatchai, 2016; Hong *et al.*, 2016). Further studies used neonatal hypoglycemia, hyperbilirubinemia or asphyxia as parameters to measure neonatal outcome (Hawkins *et al.*, 2008; Easmin *et al.*, 2015). For this review only studies elucidating a correlation with LGA, macrosomia or newborn body composition were used.

## 3.1 Fasting plasma glucose level

Following the HAPO study, which established associations between elevated maternal glucose levels and adverse pregnancy outcomes, but included only the period between the 24 and 32 weeks of pregnancy, a study by Riskin-Mashiah *et al.* was published in 2009. The aim of the study was to establish a link between adverse pregnancy outcomes and early pregnancy. Therefore 6129 women were included and a fasting glucose test was carried out during the first trimester at median of 9.5 weeks. Women with pre-gestational diabetes or fasting glucose level >105 mg/dl were excluded, taking only a non-diabetic range into consideration. Seven fasting glucose categories were defined as follows: category 1 below 75 mg/dl, category 2 between 75 to 79 mg/dl, category 3 between 80 to 84 mg/dl, category 4 between 85–89 mg/dl, category 5 between 90 to 94mg/dl, category 6 between 95 to 99 mg/dl and category 7 between 100 to 105 mg/dl. An increase in frequency of LGA neonates from 7.9% in the lowest glucose category to 19.4% in the highest could be shown, indicating a

strong association between fasting first trimester maternal plasma glucose level and adverse neonatal outcome (Figure 6) (Riskin-Mashiah *et al.*, 2009).

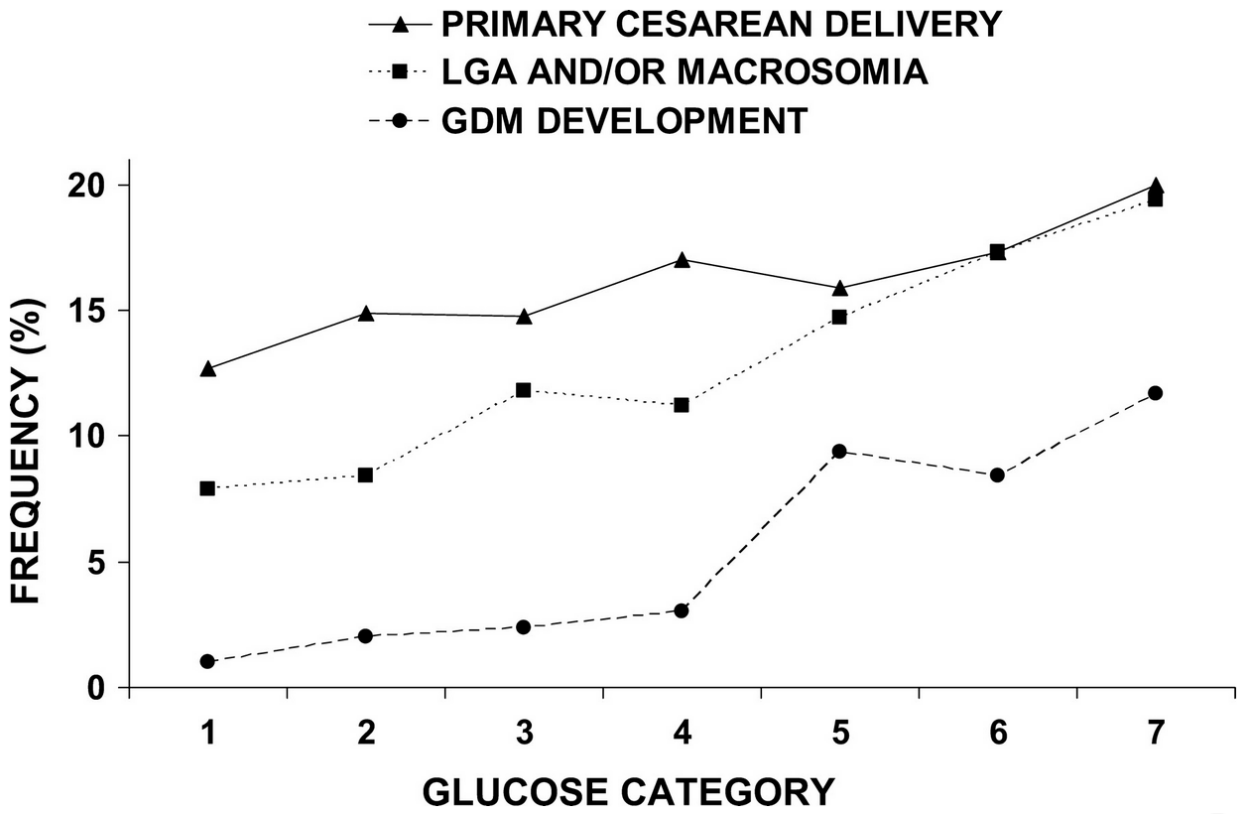


**Figure 6: Correlation of fasting plasma glucose levels and frequency of neonatal outcome** (Riskin-Mashiah *et al.*, 2009)

Another retrospective study concerning maternal fasting plasma glucose was conducted by Liu *et al.* and published in 2014. FPG was measured at the first prenatal visit with the aim to determine, whether it is correlated to neonatal birth weight. Of the 2284 pregnant women included in the study, 462 had GDM and 1822 were of normal glucose tolerance (NGT). There was no significant difference in the FPG level between the GDM and NGT mothers until the 12th week of pregnancy. From the $12^{th}$ to the $16^{th}$ week the FPG level of GDM mothers was significantly higher. In addition, the FPG level correlated with neonatal birth weight (Liu *et al.*, 2014).

Liu *et al.* published another retrospective study in 2016. Again they tested the fasting plasma glucose level at the first prenatal visit (First Visit FPG), but also

examined lipid profiles at time of mid-gestation. The aim of the study was to investigate an association between these parameters and neonatal birth weight. Due to the results of the study First Visit FPG was associated with neonatal birth weight, although no correlation with lipid parameters in mid-pregnancy could be found (Liu *et al.*, 2016). However, the HbA1c was also measured between the 24th and 28th week of pregnancy, which allows a conclusion on the glucose level 2 - 3 months before measurement, thus allowing the connection to an early glucose metabolism (Bennett, Guo and Dharmage, 2007). This value was associated with triglyceride and apolipoprotein B levels in mid-gestation. The triglyceride levels were again associated with neonatal birth weight (Liu *et al.*, 2016).

## 3.2 HbA1c

A study conducted in Qatar examined neonatal outcomes of early glycaemic controlled pregnancies. The pregnant women were screened during the first trimester using a fasting blood glucose test and measuring HbA1c. After 24 weeks of pregnancy they were screened again, using a 75g oral glucose tolerance test (OGTT). 419 women with type-2 diabetes were compared to normoglycaemic women. First trimester HbA1c was associated with an increased risk for LGA (Bashir *et al.*, 2019).

Mane *et al.* also examined the role of first trimester HbA1c as a predictor of adverse neonatal outcome. As primary outcome they chose macrosomia. Within their Multiethnic Cohort study they screened 1228 pregnant women. Women who met the American Diabetes Association (ADA) diagnostic criteria for diabetes mellitus in the first trimester were excluded, as well as those with preexisting diabetes. The included women did not receive any intervention. As a result the rate of macrosomia in women with an HbA1c measurement between 5.9% and 6.4% during early pregnancy was three-fold higher than in pregnant women without preexisting diabetes. Independently from women who might develop GDM later in pregnancy, HbA1c helps to identify women at higher risk for adverse neonatal outcome (Mane *et al.*, 2017).

Hughes *et al.* measured HbA1c at a median of 47 days gestation, trying to find the optimal threshold for detection of diabetes in early pregnancy and examine associated adverse neonatal outcomes. 74% of women with an HbA1c greater than or equal to 5.9% had an abnormal OGTT at some point of gestation. Women with HbA1c between 5.9% and 6.4% had an increased risk for LGA, compared to women with an HbA1c value below 5.9% (Hughes *et al.*, 2014).

Already in 1999 Rey *et al.* published a study measuring glycosylated hemoglobin during the first trimester and throughout pregnancy among pregnant type-1 or type-2 diabetics (Rey, Attié and Bonin, 1999). Aim of the study was to determine a threshold of HbA1c associated with adverse neonatal outcome and thus identify glycosylated hemoglobin as predictor for macrosomia. Maternal HbA1c levels were higher in mothers giving birth to LGA infants than in those delivering AGA neonates throughout all stages of pregnancy. However compared to third trimester levels, the study found glycosylated hemoglobin concentration higher or equal to 5.5% during the first trimester best predictor for macrosomia (Rey, Attié and Bonin, 1999).

Another study that appeared during this period also dealt with the concentration of HbA1c in pregnant women with insulin-dependent diabetes mellitus (IDDM) meanwhile known as type-1 diabetes (Gold *et al.*, 1998). HbA1c was measured every 2 to 4 weeks and the mean HbA1c was calculated for every trimester. HbA1c during the first 12 weeks of pregnancy was strongly associated with birth weight. The authors emphasize that HbA1c measurement really indicates a 6 to 8 weeks previous glycemic status and therefore reflects preconception period and early first trimester. Thus this study also comes to the conclusion that the predictive value of first trimester HbA1c concerning birth weight is greater than in later trimesters (Gold *et al.*, 1998).

## 3.3 Early diagnosed Gestational diabetes mellitus

Another approach was taken by Bartha *et al.* who made a comparison between the neonatal outcome of pregnant women with early-onset and late-onset GDM. 3986 women were screened at their first prenatal visit, using a 50g OGTT. About 6 percent

were diagnosed with GDM. 27.7 percent developed GDM in early pregnancy and 72.3 percent had a later development. Most of the women with early-onset GDM were diagnosed during the first trimester. Although the pregnant women with early onset GDM had an increased risk of hypertension and neonatal hypoglycemia, neonatal weight and the occurrence of macrosomia were not significantly higher. However it is possible that the early intervention to improve glucose homeostasis prevented complications normally associated with early disturbed glucose metabolism (Bartha, Martinez-Del-Fresno and Comino-Delgado, 2000).

Seshiah *et al.* also conducted a retrospective cohort study on the detection of diabetes in early pregnancy and the impact on neonatal outcome. The screening of the pregnant women was done by means of a 75g OGTT, irrespective of trimester. The women diagnosed with diabetes were then divided into different groups according to the gestational week of their diagnosis. About 41.4 percent were diagnosed during the first trimester. Neonates of these women were appropriate for gestational age like those of women with normal glucose tolerance. Neonates born to women with diabetes diagnosed beyond 30 weeks of pregnancy had a significantly higher birth weight compared to those born to GDM women diagnosed during the first 12 weeks (Seshiah *et al.*, 2008).

Another retrospective case control study from Sweeting *et al.* published 2015, compared the pregnancy outcome among high-risk women with an early diagnose of GDM and women with pre-existing type-2 diabetes and those in whom GDM was diagnosed after 24 weeks of pregnancy. The study came to the conclusion that pregnancy outcome of women diagnosed with GDM during the first trimester were similar to those of women with preexisting diabetes. Even though the screening and intensive intervention took place early, the high risk GDM women who were diagnosed during the first trimester still had a correlation with LGA and macrosomia (Sweeting, Park and Hyett, 2015).

## 3.4 Maternal lipid levels

A Chinese study conducted by Liang *et al.* as well examined the correlation between triglyceride levels in early pregnancy and LGA neonates. Triglyceride levels, serum total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) were measured at different stages of pregnancy during 6 to 8 weeks, at 16, 24 and 36 weeks. The incidence of LGA correlated with triglyceride levels at early trimester (Figure 7). The confounding factors GDM, GWG, pre-gravid BMI and parity also had an association. With a triglyceride level higher than or equal to 1.7mmol/L in early trimester, the risk of giving birth to a child with LGA was 1.538 times higher. After stratifying the factor pre-BMI in two groups, only non-overweight/obese women had a higher risk for an adverse neonate outcome (Liang *et al.*, 2018).

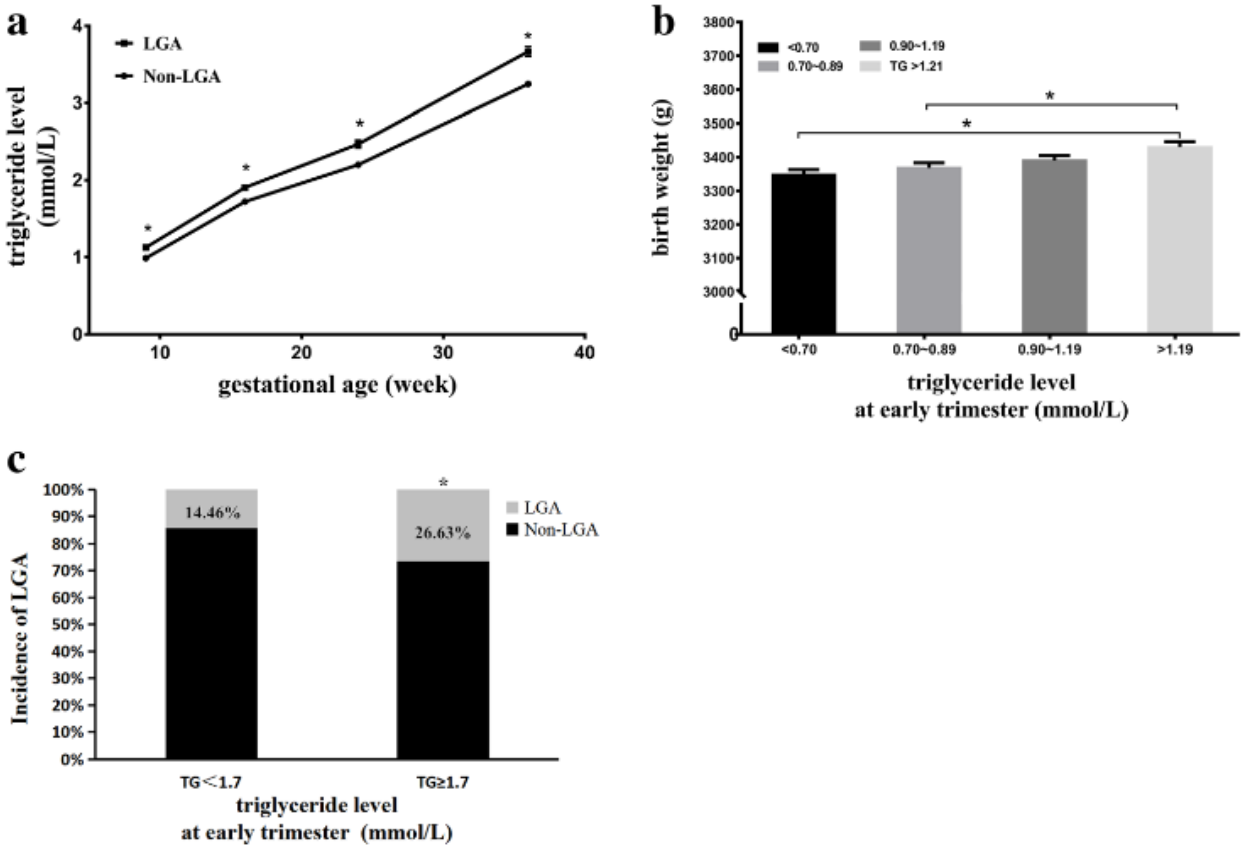


**Figure 7: a) Triglyceride levels LGA and Non-LGA, b) Different triglyceride level ranges and birth weight, c) Incidence of LGA of different triglyceride levels at first trimester** (Liang *et al.*, 2018)

Another prospective study from Iran published in 2017 chose a similar approach. Their aim was to elucidate the correlation between FPG, plasma lipid profiles and TG in first trimester with an increased risk of delivering LGA infants and the development of GDM. Maternal glucose concentration and fasting lipid levels among 954 pregnant women without pre-existing diabetes were measured at average week 9 of pregnancy. To calculate a triglyceride index (TG index), the formula natural log (fasting TG (mg/dl) x FPG (mg/dl)/2) was used. FPG levels, triglycerides and TG index were strongly associated with the risk of being diagnosed with GDM and giving birth to LGA infants. TG index was determined to be strongest predictor for neonatal outcome. Interestingly, 18.4% of included healthy women were diagnosed with GDM using the IADPSG criteria (Pazhohan, Rezaee-Moradali and Pazhohan, 2019).This value is well above the known incidence in Iran, which is 4% in the capital and varies between 1.3 and 8.9% in the rest of the country (Khoshnniat-Nikoo, Abbaszadeh-Ahranjani and Larijani, 2009).

A Dutch study conducted by Vrijkotte *et al.* also evaluated the correlation of triglyceride levels in early pregnancy and birth weight. Non-fasting serum triglycerides and total cholesterol levels were measured at median gestational age of 13 weeks. 2505 pregnant women were included, those with a higher pre-pregnancy BMI and those with more gestational weight gain during early pregnancy had significantly higher triglyceride levels. Moreover women with the highest triglyceride levels had a significantly higher risk of delivering LGA newborns. Cholesterol levels on the other hand were not associated with weight for gestational age (Vrijkotte *et al.*, 2011).

A prospective study from Poland looked at pregnant women with type 1 diabetes and their lipid levels during early pregnancy, mid pregnancy and near delivery. 30 women of the included 114 pregnant diabetics gave birth to LGA infants. Women who delivered LGA neonates, had higher triglycerides, lower HDL and similar HbA1c during the first trimester compared to those delivering AGA newborns. Lower HDL and higher triglycerides during early pregnancy were significantly associated. They hypothesized that high HDL levels might protect the fetus from an overload of non-esterified fatty acids (NEFA). Total cholesterol and LDL were not associated with

LGA at any stage of gestation. In this study HbA1c during first trimester was not associated with LGA newborns (Gutaj, Wender-Ozegowska and Brązert, 2017).

Wang *et al.* also examined the association between early lipid profiles and adverse pregnancy outcomes in a retrospective study with 5218 participants. TC, TG, HDL and LDL levels were measured and divided into quartiles. First trimester lipid profiles correlated with adverse pregnancy outcomes (Wang *et al.*, 2017).

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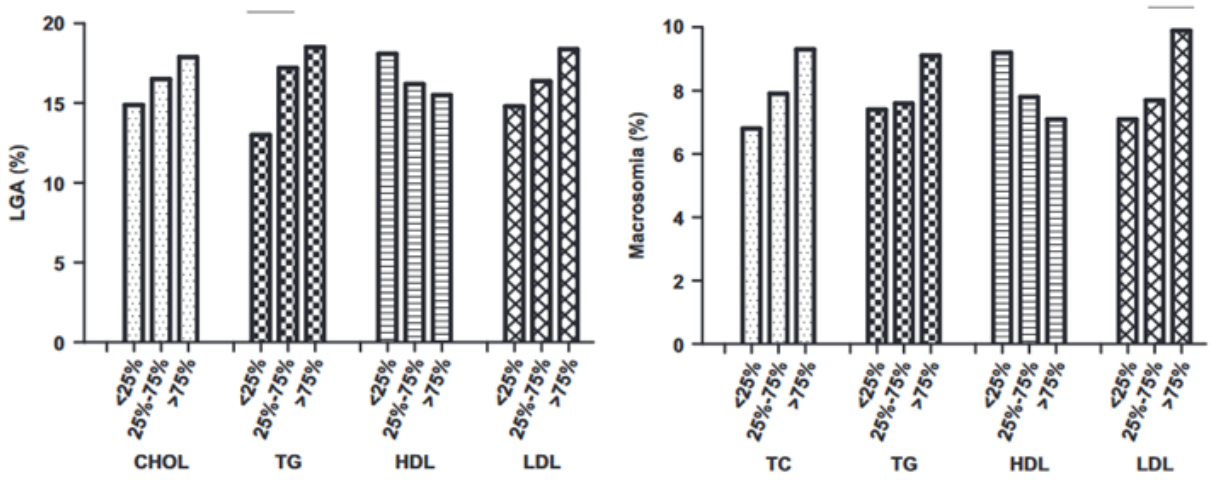


**Figure 8: Early pregnancy lipid levels and adverse neonatal outcome** (Wang *et al.*, 2017)

Figure 9 shows that with the increase of TG, TC and LDL levels also the incidence of LGA and macorosmia increases. Women with concentrations above 75$^{th}$ percentile and an additional HDL value below 25$^{th}$ percentile showed the highest risk for adverse neonatal outcome (Wang *et al.*, 2017).

Another cross-sectional study from the Baskent University Adana Research Center not only took fasting glucose levels into consideration, but also maternal lipid levels. Fasting glucose levels, serum triglycerides, cholesterol, very low-density lipoprotein (VLDL), LDL, HDL and PAPP-A were measured in blood samples within the first trimester and related to birth weight. Even though not statistically significant, the pre-pregnancy weight was greater in mothers delivering LGA neonates. An association between any first trimester lipids including triglycerides and birth weight could not be established. The only significant correlation could be found between

lower PAPP-A concentrations during first trimester and small-for-gestational age (SGA) newborns (Parlakgumus *et al.*, 2014).

## 3.5 Adiponectin

Serum adiponectin starts to reduce during the first trimester of pregnancy in case of obesity, type-2 diabetes and GDM (Williams *et al.*, 2004). Therefore maternal serum adiponectin might be an early marker for adverse neonatal outcome due to metabolic disturbances caused by obesity and diabetes in early pregnancy.

A case-control-study conducted by Nanda *et al.* and published in 2011, tried to elucidate the association between maternal serum adiponectin during early pregnancy and macrosomia (Nanda *et al.*, 2011). Therefore serum adiponectin levels were measured at 11 to 13 weeks of gestation, including 50 women who gave birth to macrosomic infants and 300 women who delivered phenotypically normal neonates. Macrosomia was defined as birth weight above the $95^{th}$ percentile. As result serum adiponectin concentrations in women giving birth to newborns with macrosomia were significantly lower. However, the adiponectin concentration also decreases with weight in a normal pregnancy and is lower in women who smoke, as well as in women of African or South Asian origin. On the other hand, with the age of the mother, the adiponectin concentration also increases (Table 2) (Nanda *et al.*, 2011).

| Maternal characteristics | Control ($n = 300$) | Macrosomia ($n = 50$) |
|---|---|---|
| Maternal age in years, median (IQR) | 32.2 (26.9–35.6) | 34.8 (31.3–37.9)* |
| Maternal weight in kg, median (IQR) | 63.3 (57.0–70.0) | 76.5 (66.5–89.3)* |
| Maternal height in cm, median (IQR) | 162 (160–168) | 166 (162–169) |
| Crown-rump length in mm, median (IQR) | 64.0 (58.7–69.6) | 67.2 (60.0–73.0) |
| Racial origin | | |
| Caucasian, *n* (%) | 189 (63.0) | 28 (56.0) |
| African, *n* (%) | 86 (28.7) | 14 (28.0) |
| South Asian, *n* (%) | 10 (3.3) | 6 (12.0)* |
| East Asian, *n* (%) | 6 (2.0) | 0 |
| Mixed, *n* (%) | 9 (3.0) | 2 (4.0) |
| Parity | | |
| Nulliparous, *n* (%) | 148 (49.3) | 10 (20.0) |
| Parous, no previous macrosmia, *n* (%) | 140 (46.7) | 29 (58.0) |
| Parous, previous macrosomia, *n* (%) | 12 (4.0) | 11 (22.0)* |
| Cigarette smoker, *n* (%) | 28 (9.3) | 3 (6.0) |
| Conception | | |
| Spontaneous, *n* (%) | 296 (98.7) | 48 (96.0) |
| Assisted, *n* (%) | 4 (1.3) | 2 (4.0) |
| Birth weight in kg, median (IQR) | 3.4 (3.2–3.7) | 4.7 (4.5–4.9)* |
| Birth weight percentile, median (IQR) | 50.5 (32.6–68.7) | 99.1 (98.7–99.7)* |
| Maternal serum adiponectin | | |
| ng/mL, median (IQR) | 12 035 (8 595–17 085) | 8 257 (5 258–13 171) |
| Multiple of the median, median (IQR) | 1.02 (0.70–1.29) | 0.82 (0.56–1.02)* |

**Table 2: Comparison between macrosomia and control group** (Nanda *et al.*, 2011)

According to the study 40% of pregnant women at risk of giving birth to macrosomic infants could already be detected during early pregnancy by combination of maternal characteristics and serum adiponectin concentrations (Nanda *et al.*, 2011).

Another study, conducted by Migda *et al.* also examined the serum adiponectin concentration during the first trimester and its association with macrosomia. They compared neonatal outcomes of 124 pregnant women with metabolic syndrome criteria to 30 healthy controls. Measurement took place during the 11 and 13 + 6 weeks of gestation. This study also found that maternal adiponectin levels during first trimester were significantly lower in women who delivered macrosomic neonates. In addition they also identified fasting glucose, higher E-selectin and BMI levels as significant predictors of an increased risk of macrosomia, whereas a BMI higher than 24.5 kg/m² was considered the best predictive value (Migda *et al.*, 2016).

## 3.6 ß-HCG and PAPP-A

Looking for an early pregnancy predictor for adverse neonatal outcome, Canini *et al.* examined the association of free ß-HCG and PAPP-A and birth weight. 1630 women were included and measured between 10 to 14 weeks of pregnancy. PAPP-A concentrations during late first trimester were significantly higher in women giving birth to LGA infants (Figure 8) (Canini *et al.*, 2008).

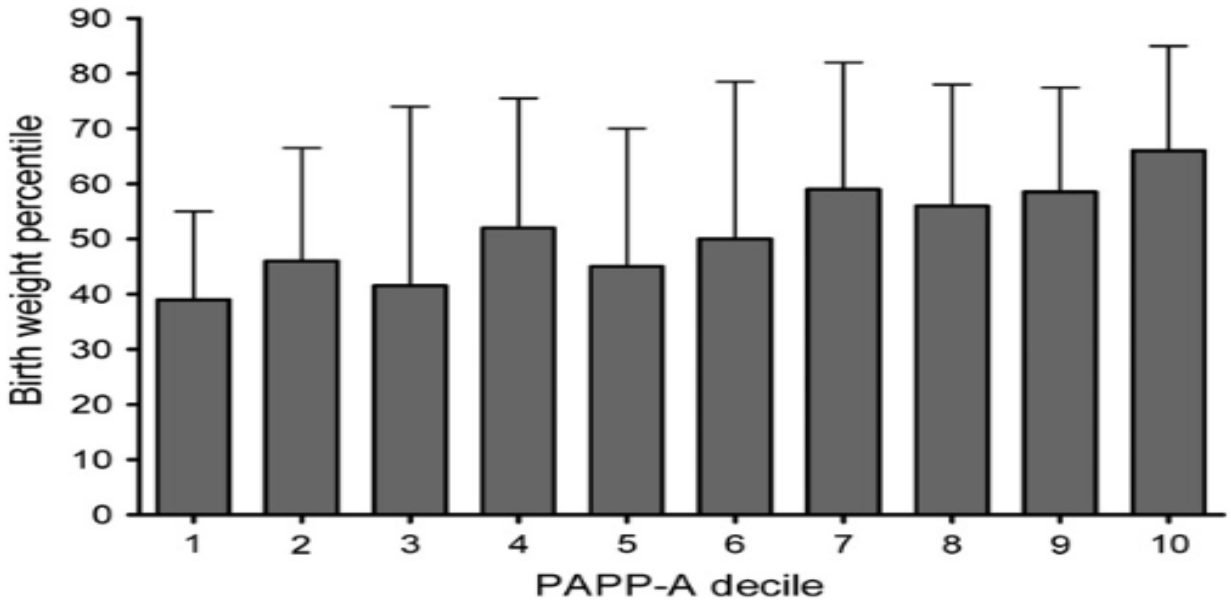


**Figure 9: First trimester Maternal serum PAPP-A deciles correlated to birth weight precentiles** (Canini *et al.*, 2008)

Multivariate analysis even found PAPP-A to be an independent predictor for LGA. ß-HCG was not associated with birth weight (Canini *et al.*, 2008).

One year later another study by Goetzinger et al. was published, examining the same values. 3035 pregnant women, seen for first trimester aneuploidy screening, were included. Low PAPP-A levels seemed to reduce risk of LGA. But neither PAPP-A nor free ß-HCG levels significantly correlated with higher occurrence of LGA (Goetzinger *et al.*, 2009).

Compared to that, the results published by Peterson *et al.* in 2008 differ. Like Goetzinger *et al.* they included pregnant women seen for the first aneuploidy screening, in total 1371. PAPP-A concentrations correlated with birth weight. In

addition, a significant association with macrosomia could be demonstrated. The authors thus identified PAPP-A as a potential marker of placental function (Peterson and Simhan, 2008).

Also Poon *et al.* included women seen between 11 and 13 weeks of pregnancy for aneuploidy screening. Maternal characteristics, fetal nuchal translucency, PAPP-A and ß-HCG were measured in 36743 pregnant women and examined for an association with macrosomia. Aim of the study was in particular to find an association with the combination of these components. Macrosomia was defined as birth weight above the 90$^{th}$ percentile. The combination of maternal characteristics and first trimester markers identified 34 % of women who gave birth to a macrosomic infant. Maternal characteristics that correlated with an increased incidence of macrosomia were maternal weight, height, a history of diabetes mellitus and previous delivery of a macrosomic child (Poon *et al.*, 2011).

## 3.7 Gestational weight gain

GWG is a topic that is mentioned by many studies, but only a few focus on weight gain in early pregnancy. An American prospective cohort study examined the effects of excessive weight gain during first trimester on the newborn (Josefson *et al.*, 2016). Only women with normal glucose tolerance were included, based on the guidelines of IADPSG. Maternal weight was measured at the first antenatal visit, early second trimester, at the time of OGTT at 24 to 28 weeks gestation and at the last prenatal visit. Neonatal outcome was set as birth weight and body composition, measured by air displacement plethysmography. The increase in weight was compared with the guidelines for gestational weight gain of IOM. From the IOM recommendations, a total weight gain of 1.5 kg for obese and 2 kg for normal weight women can be derived for the first trimester (Rasmussen and Yaktine, 2009). Newborns body composition of mothers with excessive weight gain and guideline met weight gain did not differ. Using an exploratory group-based trajectory model three weight gain trajectories were determined: steady minimal, steady moderate and early and overall excessive weight gain (Figure 9) (Josefson *et al.*, 2016).

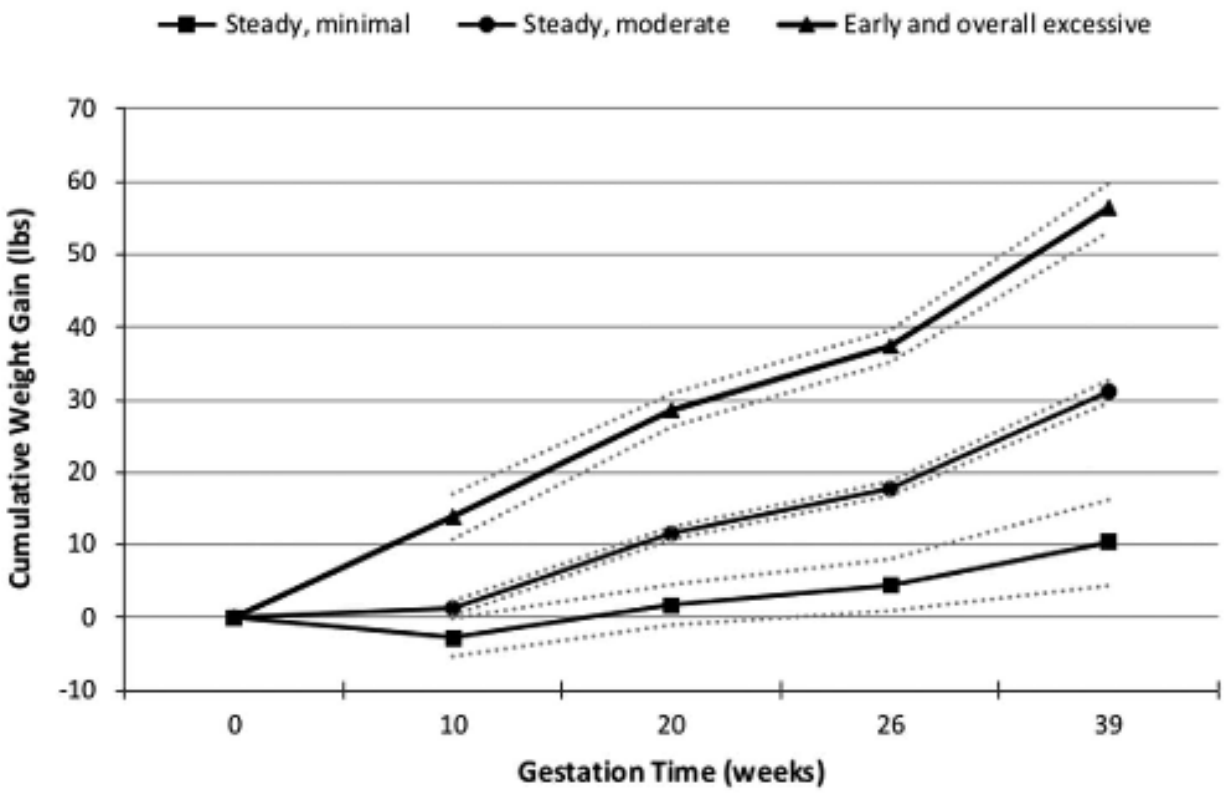


**Figure 10: Gestational weight gain trajectories among women with normal glucose tolerance** (Josefson *et al.*, 2016)

79% of pregnant women included in this study showed a steady, moderate weight gain. 9% had an early and overall excessive weight gain. The subgroup with excessive weight gain during first trimester correlated with adverse neonatal outcome. Neonates born to mothers with excessive gestational weight gain during early pregnancy showed a significantly higher birth weight and a significantly higher amount of fat mass than those born to mothers with moderate weight gain (Josefson *et al.*, 2016).

Another study published in 2016 likewise compared different timing of excessive gestational weight gain during pregnancy trying to find a correlation with neonate body composition. 607 glucose tolerant women were included. Newborn anthropometry was estimated by sum of four skinfolds. Women were divided in four groups: overall non-excessive, early excessive, mid/late excessive and overall excessive. Limit for normal weight gain in the first trimester met the recommendations

of 2 kg total weight gain in the first 12 weeks, which corresponds to 0.17 kg per week. 32 % of included women showed an early excessive GWG. Women with excessive weight gain in mid/late pregnancy but not in early gestation gave birth to the heaviest newborns. However, in this group maternal pre-pregnancy BMI was higher compared to the other groups. A difference in body composition could not be established. Even though the weight difference was statistically significant, it was still relatively small (Ruchat *et al.*, 2016).

A Korean large cohort study published in 2015 also examined the association of rates of gestational weight gain (RGWG) at different stages of pregnancy and adverse neonatal outcome defined as macrosomia and LGA. 2789 pregnant women were included and weight was measured multiple times during gestation (Figure 9) (Cho, Hur and Lee, 2015).

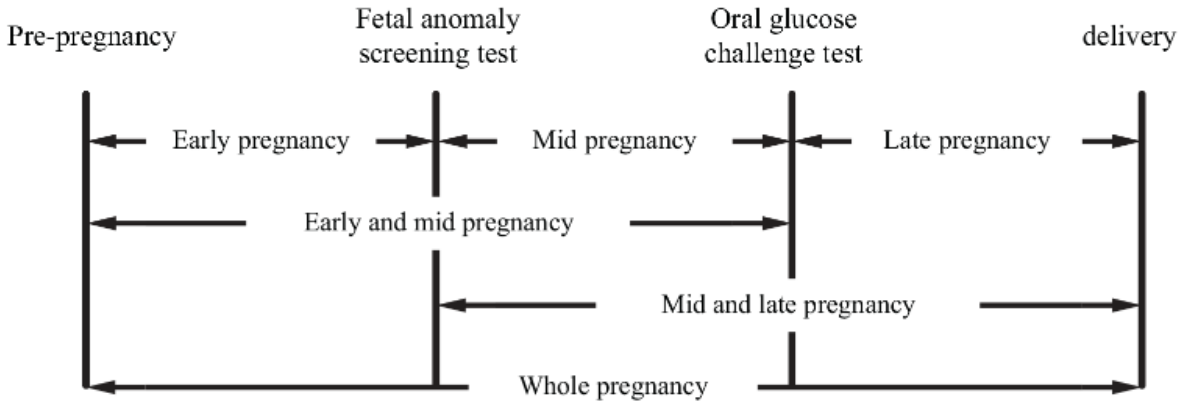


**Figure 11: Timetable of weight measurement and term definition** (Cho, Hur and Lee, 2015)

RGWG at early pregnancy was not only significantly associated with macrosomia and LGA, but also with primary caesarean section (P-CS), GDM and pregnancy-induced hypertension (PIH). RGWG of mid-pregnancy did not correlate with adverse neonatal outcome. Based on pre-pregnancy BMI three groups were formed, dividing the women into an underweight, normal and obese group. The correlation of early RGWG and adverse neonatal outcome differed significantly between those groups. In the underweight group there was no significant association. In the normal weight group however early RGWG significantly correlated with LGA

and macrosomia, as well as GDM, PIH and P-CS. Interestingly, there was only an increased risk for PIH in the obese group. The rate of gestational weight gain therefor is a predictor for adverse neonatal outcome but depends on pre-pregnancy BMI (Cho, Hur and Lee, 2015).

## 3.8 Obesity

Another study that needs to be mentioned as it examines the association between maternal obesity and birth weight as well as neonatal fat mass was conducted by Mitanchez *et al.* (Mitanchez *et al.*, 2017). 226 obese pregnant women with pre-pregnancy BMI higher than 30 and 222 normal weight women with pre-pregnancy BMI between 18.5 and 24.9 were included in this prospective cohort study. Women with pre-existing diabetes were excluded. Neonatal fat mass was measured by means of skinfold thickness. All included women were screened for GDM via 75g OGTT during 24 and 28 weeks of pregnancy, obese women were additionally screened in the first trimester via fasting blood glucose. 45.2 % of obese women were diagnosed with GDM, half of them in the first trimester. Between the two groups birth weight did not differ significantly. The sum of skinfolds however was significantly higher in newborns of obese mothers. Though after sex-specific analysis only the sum of skinfolds in girls, but not in boys, was significantly higher in neonates born to obese women (Mitanchez *et al.*, 2017).

## 3.9 Sex-specific effects of first trimester

Not only Mitanchez *et al.* elucidated sex-specific differences in birth weight and neonatal body composition. In a prospective cohort study conducted in Berlin, Hartwig *et al.* examined the sex-specific effect of maternal progesterone in early pregnancy on neonatal birth weight. Progesterone and estradiol levels were measured at the recruitment visit between 4 and 12 weeks of gestation. 623 pregnant women were included. Progesterone did not significantly correlate with neonatal birth weight, but

an increase in maternal progesterone by 1 ng/ml was associated with an increase in birth weight by 10.17 g in girls only. A significant association of estradiol with birth weight could not be established in either sex. Since there was no sex-specific difference in progesterone levels, the authors concluded that this positive effect on girls birth weight might indicate sex-specific placental function (Hartwig *et al.*, 2013).

## 3.10 Placental volume and PGH

Another study focusing on disturbances in early pregnancy leading to adverse neonatal outcome, dealt with placental influences on forming the neonate phenotype. In an observational study, Ringholm *et al.* examined the correlation between placental growth hormone (PGH) as well as Insulin-Like Growth factor-1 (IGF-1) and the risk of pregnant women with type-1-diabetes of giving birth to LGA infants. In addition, they measured weight at 14 weeks and before delivery, to calculate an early compared to a total gestational weight gain. PGH levels during first trimester were significantly lower in women delivering LGA neonates (Figure 10). Furthermore, PGH levels correlated negatively with GWG during early pregnancy. IGF-1 levels were not associated with an increased risk for LGA. The authors speculated that the lower PGH levels during the first trimester might be followed by catch-up growth leading to LGA newborns (Ringholm *et al.*, 2015).

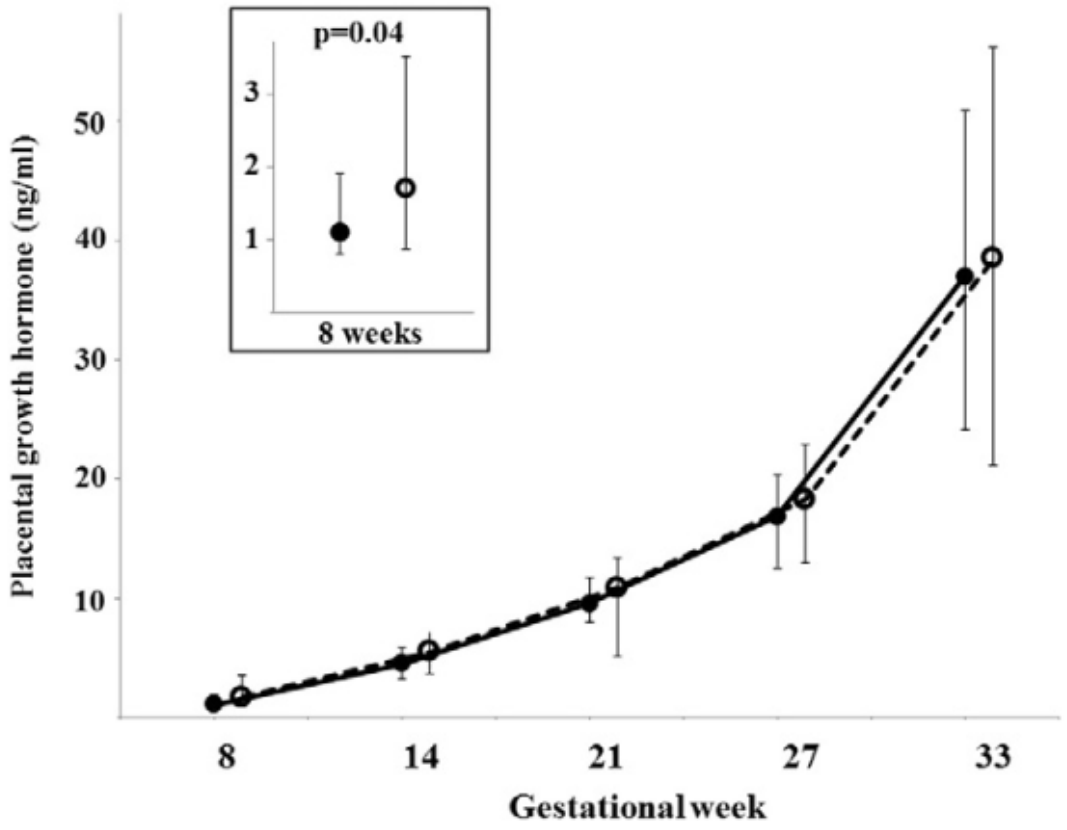


**Figure 12: PGH levels during gestation; Inserted box: dot = LGA, circle = non LGA** (Ringholm *et al.*, 2015)

Schwartz *et al.* also investigated the influence of early placental development on the newborn in a study published in 2014. Different to Ringholm *et al.* they chose placental size as possible predictor for LGA and macrosomia. Placental volume was measured via 3-dimensional ultrasound during 11 to 14 weeks and 18 to 24 weeks of gestation. Besides placental volume they examined the correlation of mean placental and chorionic diameters. A higher placental volume during first trimester was significantly associated with both macrosomia and LGA. Mean placental and chorionic diameters were not correlated with adverse outcome at this early stage of pregnancy. Consequently early placental growth seems to already determine part of macrosomia and LGA and can therefore be seen as a significant predictor of adverse neonatal outcome (Schwartz *et al.*, 2014).

## 3.11 Accelerated fetal growth

Another recently published Swedish study attempted to directly measure fetal growth in early pregnancy using ultrasound and relate it to the prevalence of LGA and macrosomia (Simic, Wikström and Stephansson, 2017). 68771 women were included in this large population-based cohort study. LGA was defined as birth weight greater than the 97$^{th}$ percentile. Fetal growth was measured in the first trimester and in early second trimester. Based on the measurements, the discrepancy between the estimated and the expected gestational age was presented by days. About 20% of fetuses had a positive discrepancy more than 2 days between the two biometric measurements. These fetuses did not have an increased risk for LGA. Fetuses with a discrepancy of 7 days or even more at early second-trimester ultrasound had an 80% increased risk of LGA. Accelerated fetal growth thus starts during early pregnancy and contributes to LGA and macrosomia (Simic, Wikström and Stephansson, 2017).

## 3.12 Early lifestyle intervention

Only few studies on the association of early lifestyle interventions and neonatal outcome have yet been conducted.

The Healthy heart study examined an association between physical activity in different periods of pregnancy and its effect on the newborn. Outcome measures were birth weight, neonatal fat mass and fat-free mass. 826 women were included and their total energy expenditure was determined via The Pregnancy Physical Activity Questionnaire meeting the guidelines of the American College of Obstetricians and Gynecologists for physical activity during the different trimesters. The questionnaire was completed at three different times during pregnancy: at median 17 weeks, 27 weeks and after delivery. Nearly half of the included pregnant women were obese and only 17.4 % met the guidelines. Guideline recommended physical activity in the early, mid and late pregnancy was not associated with neonatal outcome. Only increasing levels of total energy expenditure in late

pregnancy were associated with reduced neonatal adiposity. A significant linear trend could not be found (Harrod *et al.*, 2014).

Badon *et al.* also examined a correlation between physical activity in different periods of pregnancy and birth weight. Among the 3310 included women leisure-time physical activity was evaluated via questionnaire. Based on activity descriptions total energy expenditure was calculated. The pre-pregnancy activity of one year before pregnancy was assessed as well as the physical activity of the first 15 weeks of gestation, referred to as early pregnancy. Women were categorized as either active in pre-pregnancy or early pregnancy. In women with normal preconceptional weight, pre-pregnancy and early pregnancy activity was inversely associated with birth weight and in addition, early pregnancy activity was associated with an increased risk for LGA. Both categories did not interact, suggesting that both periods affect neonatal outcome independently. In conclusion the authors determined pre-pregnancy activity to be an indicator for maternal fitness, whilst activity in early pregnancy affects fetal growth and neonatal birth size (Badon *et al.*, 2016).

# 4 Discussion

Purpose of this thesis was to review how disturbances in the critical period of early pregnancy contribute to shaping the neonatal phenotype. The first part of this thesis deals with the basics of impaired maternal metabolism compared to normal pregnancy and the development of the fetus during the first trimester. Diabetes, obesity and excessive gestational weight gain are identified as main contributors and their impact on intrauterine environment is clarified, including metabolic inflammation. In addition, the influence of genetic components on neonatal birth weight is elucidated.

Core of the work consists in the presentation of current state of literature examining an association between possible predictors in early pregnancy and adverse neonatal outcome. As disturbed maternal environment alters the physiological interplay of many factors, the summary of findings includes a wide range of influential factors.

However, there are only few studies dealing with the period of early pregnancy that meet the criteria of only examining the first 15 weeks of gestation. The remaining studies mainly chose birth weight and thus LGA and macrosomia as adverse outcome. Only few measured outcome as body composition.

Overall, the results indicate that there are some potential predictors of early pregnancy for adverse neonatal outcome, proving that disturbed fetal growth begins in the first trimester. Not only gestational diabetes triggers this condition, but pre-existing diabetes, obesity and excessive weight gain. Pre-pregnancy BMI is one of major factors associated with increased birth weight and higher percentage of fat mass in the newborn.

It is therefore not surprising, that besides plasma glucose, other metabolic factors correlate with the incidence of macrosomia, LGA and adverse body composition.

For the lipids, only higher triglyceride and lower HDL levels in first trimester showed a correlation with increased birth weight in most studies. Triglycerides thus appear to be of greater relevance in the context of a disturbed intrauterine environment than other lipid subtypes. It therefore raises the question if a fasting lipid screening in early pregnancy should be included in care of pregnant women.

Sweeting *et al.* suggest that an early screening could be arranged at the time of first trimester aneuploidy screening (Sweeting, Park and Hyett, 2015). It would thus be quite useful to use components of the combined test as predictive values. Canini, Peterson and Poon demonstrated a correlation of increased PAPP-A levels with higher risk for macrosomia and LGA. Only Poon detected an independent association with ß-HCG (Poon *et al.*, 2011). Furthermore, Poon *et al.* tried to establish a combined screening system, using not only PAPP-A and ß-HCG but as well maternal characteristics and nuchal translucency. A study published 5 years later following the same approach added uterine artery pulsatility index as component, predicting 39.8 % of LGA and 47.4 % of macrosomic infants respectively at a false-positive rate of 10 % (Frick *et al.*, 2016). Further research needs to be done to what extend the components, whose significance for the detection of aneuploidies and preeclampsia is clarified, can identify an increased risk for LGA or macrosomia.

Of course plasma glucose also plays an essential role in early pregnancy in determining the offspring phenotype. Bashir, Mane, Hughes, Rey and Gold identified HbA1c as predictor for adverse neonatal outcome (Gold *et al.*, 1998; Rey, Attié and Bonin, 1999; Hughes *et al.*, 2014; Mane *et al.*, 2017; Bashir *et al.*, 2019). Liu *et al.* emphasize the importance of FPG screening not only to indicate GDM but also to predict fetal growth, as the influence of hyperglycemia on the fetus begins earlier than diagnosis of GDM (Liu *et al.*, 2014). Risk of macrosomia persists as glycemia increases. Due to Seshiah *et al.* women with normal glucose tolerance at first antenatal visit should therefore be screened again at subsequent visits (Seshiah *et al.*, 2007).

One of the major issues is if an early treatment of hyperglycemia in pregnancy really improves prognosis. Seshiah *et al.* demonstrated that infants born to GDM mothers

diagnosed during the first trimester of pregnancy had a lower risk of adverse neonatal outcome, than those born to mothers diagnosed after 30 weeks. Good glycemic control in later weeks of pregnancy does not seem to avert fetal risk for increased birth weight. The authors recommend that women with high-risk for GDM should be screened as soon as possible to enable early intervention (Seshiah *et al.*, 2008). In contrast Sweeting *et al.* found poorer neonatal outcome of newborns delivered by mothers with diagnosis of GDM during the first trimester than diagnosed with late GDM. Even though they were screened early and received earlier insulin initiation with a higher maximum daily dose (Sweeting *et al.*, 2016).

Adverse neonatal outcome occurs even in women with good glycaemic control. Murphy *et al.* showed that glycaemic controlled pregnant women with type-1 diabetes still spend more than 9 hours per day hyperglycaemic and even 3 hours per day extremely hyperglycaemic (Murphy *et al.*, 2007). Temple *et al.* concluded that pre-pregnancy care improved glycaemic control in early pregnancy, but did not reduce the risk of macrosomia (Temple, Aldridge and Murphy, 2006).

Further research needs to be done examining the benefits of an early intervention. How can fetal changes in a disturbed maternal environment be prevented?

Management of pre-pregnancy BMI and excessive gestational weight gain in early pregnancy is an important approach in the prevention of adverse neonatal outcome. Villamor *et al.* recommend overweight and obese women to lose weight before pregnancy and even appeal to normal weight women to prevent preconceptional weight gain (Villamor and Cnattingius, 2006). This might sound like the simplest solution, but is relatively challenging in implementation. In most cases, this requires a complete change of lifestyle, including physical activity and dietary change. However, the complexity of lifestyle factors and the burden of obesity on the woman and her family complicate finding a suitable intervention (Bick, 2015). Unfortunately only few studies on the consequences of early lifestyle intervention for the offspring have been conducted so far.

An important part of weight reduction is exercise. Physical activity during pregnancy might increase the blood flow and oxygenation of the fetus (Hopkins and Cutfield, 2011). It might as well reduce the availability and delivery of glucose and FFA in obese women (Harrod *et al.*, 2014). Interestingly, a high frequency of physical activity during the first trimester reduces PGH concentration and sets a trend towards lower placenta volume and lower PAPP-A levels (Ferland *et al.*, 2013). However, in the study conducted by Harrod *et al.* only 17 % of the participants managed to implement the guideline recommended physical activity, proving the difficulty to fulfill potential interventions (Harrod *et al.*, 2014).

In addition, excessice GWG even in women with normal pre-pregnancy BMI is not only associated with adverse neonatal outcome, but also with the predisposition to retain or gain weight after pregnancy (Bick, 2015). Future health implications are therefore a relevant topic. In summary it turns out, that intervening effectively remains a challenge.

Another challenging problem occurs in the fact that disturbed early maternal metabolism is not only associated with adverse neonatal outcome, but also has long-term implications on the offspring health.

For example pre-pregnancy BMI is not only associated with increased birth weight and higher fat mass in newborns, but also with obesity in young adulthood (Stettler *et al.*, 2000). Adolescent obesity again is associated with adult obesity (Must *et al.*, 1992). Maternal obesity is associated with the prevalence of GDM and both are associated with birth weight. Birth weight is directly associated with later BMI. In addition mother and her offspring share genes that cause obesity (Gillman *et al.*, 2003).

Also mean birth weight and proportion of macrosomic neonates have increased (Ørskou *et al.*, 2001). Birth weight is key indicator of pregnancy outcomes. LGA and macorsomia are major causes of obstetric and perinatal morbidity and additionally are directly associated with increased risk of cardio-metabolic diseases in offspring (Warrington *et al.*, 2019).

It is therefore obvious that also the prevalence of obesity in childhood has risen over the past three decades (Ng *et al.*, 2014). Childhood obesity is also positively correlated with the emergence of type-2 diabetes among children and adolescents (Boney *et al.*, 2005). A vicious circle is created, which needs to be interrupted.

Must *et al.* already conducted in 1992 that BMI appears to be programmed early in life and that prevention of obesity in childhood and adolescence may be the best approach to reduce the risk of associated morbidity and mortality in adults (Must *et al.*, 1992). As an adverse intrauterine environment already shapes the neonatal phenotype in the period of early pregnancy, prevention might have to start in this period. A better understanding of associated mechanisms might help to manage early pregnancy to achieve a better outcome.

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