Dietary intake in pregnant women with pre-gestational diabetes mellitus and effects on pregnancy outcome

A prospective longitudinal observational study

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Master thesis in Human Nutrition

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Abbreviations

BMI	*Body Mass Index*
BIA	*Bioelectrical impedance analysis*
E%	*Percentage of energy*
DM	*Diabetes mellitus*
GDM	*Gestational diabetes mellitus*
HbA1c	*Glycated hemoglobulin concentrations*
IOM	*Institute of medicine*
LADA	*Latent Autoimmune Disease in Adults*
MUAC	*Mid upper arm circumference*
MODY	*Maturity-onset diabetes of the young*
MUFA	*Monounsaturated fatty acids*
NNR	*Nordic Nutrition Recommendations*
PGDM	*Pre-gestational diabetes mellitus*
PUFA	*Polyunsaturated fatty acids*
SFA	*Saturated fatty acids*
Type 1 DM	*Type 1 diabetes mellitus*
Type 2 DM	*Type 2 diabetes mellitus*

Abstract

Background: Pregnancies complicated with pre-gestational diabetes mellitus are associated with an increased rate of adverse effects for both mother and fetus. Even though strict metabolic control of glucose & close monitoring and follow up by the tertiary unit reduces the risk of complications, pregnancy outcome is not as good as in healthy pregnancies. There are very few studies that have investigated the association of diet, metabolic control, and pregnancy outcome of pre-gestational diabetes mellitus pregnancies.

Objectives**:** The study aims to determine the effects of diet during pregnancy in women with pre-gestational diabetes on pregnancy outcomes macrosomia and prematurity.

Methods: A prospective longitudinal study of women with pre-gestational diabetes mellitus. This study is a part of a larger project (the DiaDoppler study) which was carried out by "the research group for pregnancy, fetal development, and birth" at Obstetrics and Gynecological Department of Haukeland University Hospital during the period 2013 – 2016. Women with pre-gestational diabetes in Hordaland county were referred to Haukeland University Hospital as soon as pregnancy was diagnosed. Finally, 49 women were included & followed longitudinally in the study. At the first prenatal visit, basic and health information was collected. Anthropometric measurements, blood samples & dietary data were collected three times during pregnancy such as around gestational weeks 9,24, and 36. Dietary intake was measured by 3-day dietary records in 26, 24, and 19 women, respectively.

Results: Out of 49 deliveries 19 were macrosomia babies (39%). Gestational weight gain & Hb1Ac in 1st trimester were higher in women who had a macrosomia baby. No dietary factors were significantly different between women with macrosomia babies throughout pregnancy. Out of 49 deliveries, 15 babies (31%) were delivered preterm. Hb1Ac was higher in the 1st & 2nd trimester of women with preterm delivery. Dietary factors associated with prematurity were dietary intake of fiber in 1st and 2nd trimester and lower intake of energy, fat, and protein in 2nd trimester.

Conclusions: In this study, there are significant associations of metabolic control with birth outcomes, and low intake of energy, fat, protein in 2nd trimester in those women with preterm delivery. Higher Intake of dietary fiber particularly in 1st trimester was associated with increases in gestational age at birth. Macrosomia is associated with gestational weight gain & metabolic control, but not with dietary intake. More studies are needed to study the effect of diet on pregnancy outcome in women with pre-gestational diabetes mellitus.

1. Background

1.1 Introduction

Diabetes mellitus is an endocrine disorder of long-standing high blood glucose (hyperglycemia) due to relative or absolute insulin deficiency, insulin resistance, or both. Etiological risk factors are age, family history, physical activity, obesity, and dietary patterns. Diabetes mellitus in pregnancy is a major challenge for pregnancy outcomes and associated with increased risk of abortion, stillbirth, and malformation. Mothers with pre-gestational diabetes mellitus (PGDM) had a 2.6 % rate of stillbirth while this rate was 0.8 % in non-diabetic mothers in 1998 in Norway (1). Appropriate nutrient intake plays a major role in the treatment of pregnant women with pre-gestational diabetes mellitus but has been surprisingly rarely investigated.

1.2 Epidemiological perspective of Diabetes Mellitus

The International Diabetes Federation (IDF) indicated that in 2013, 382 million people (8.3 % of the global population with equal rates in both women and men) had Diabetes mellitus (DM). 1.6 million people died due to DM worldwide in 2016, thus, it was the 7th leading cause of death globally. Global figures have risen until 2019 to approximately 482 million adults (20-79 years) who were living with DM while an increase to 700 million in 2045 is estimated. It is estimated that 10% of global health expenditure is spent on diabetes mellitus (2, 3.5).

According to the Medical Birth Registry of Norway, 58 in 1000 pregnant woman had a diagnosis of diabetes mellitus in 2018, of these, the rates were as follows for the different types of DM 4.1/1000 type 1 DM, 1.9/1000 type 2 DM and 50/1000 Gestational Diabetes Mellitus (GDM) in Norway. In the county Hordaland figures were as follows 86.6/1000 women had a diagnosis of DM in pregnancy in 2018: 5.5/1000 type 1 DM, 1.1/1000 type 2 DM, and 75/1000 GDM (6).

1.3 Types of Diabetes mellitus

Diabetes mellitus can be classified into 1) Type1 Diabetes mellitus which has immune pathogenesis (mostly) and is characterized by severe insulin deficiency. 2) Type2 Diabetes mellitus, results from a combination of insulin resistance and less severe insulin deficiency. 3) Gestational diabetes mellitus, diabetes mellitus diagnosed during the period of pregnancy,

particularly in the 2nd or 3rd trimester of pregnancy, and 4) and other specific types of diabetes mellitus such as genetic defects of beta-cell function (MODY), diseases of the exocrine pancreas (cystic fibrosis, hemochromatosis), drug or chemical induced diabetes mellitus, infections (congenital rubella), etc. (7).

Pre-gestational diabetes is defined as any type of diabetes diagnosed before pregnancy. Common heath consequences of Diabetes mellitus are risk of cardiovascular diseases, stroke, diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy. Diabetic retinopathy is one of the important causes of blindness and diabetic neuropathy of foot ulcers (8). Pre-gestational diabetes mellitus is associated with worst pregnancy outcomes: increased rate of still birth, malformations, prematurity, and macrosomia. Since type 2 DM is usually occurring at later life stages, type 1 DM is most common in PGDM.

1.3.1 Type1 Diabetes Mellitus (Type1DM)

Type 1 Diabetes Mellitus, also called juvenile diabetes or insulin-dependent diabetes, appears during childhood or adolescence, but it can also develop in young adults. It is a chronic disease in which the pancreas (beta cells of islets of Langerhans) produces little or no insulin. Therefore, type 1 diabetes mellitus patients need replacement of the functions of β cells to achieve blood levels of glucose as close to the normal range as possible and to avoid complications from hyperglycemia. Insulin and Insulin analogues are used to solve the problem of patients with diabetes type1(9).

Type1 Diabetic mellitus belongs to a family of human leucocyte antigen (HLA) associated immune-mediated organ-specific diseases. Genetic susceptibility is polygenic, with a contribution from the HLA region. Increased susceptibility to Type1 Diabetic Mellitus is inherited but the disease is not genetically predetermined (2). Type 1 Diabetic Mellitus is an autoimmune disorder; therefore, it can be associated with other specific autoimmune diseases such as autoimmune thyroid diseases, celiac diseases, Addison's disease, and pernicious anemia (2). Type 1 diabetes has no cure and needs lifelong treatment. Treatment focuses on managing blood sugar levels with insulin, diet, physical activity, and lifestyle to prevent complications.

More than 1.1 million children and adolescents below 20 years are living with Type 1 DM around the globe. Every year around 300 children get type1 diabetes mellitus in Norway (11). Approximately 28,000 type1 diabetic patients live in Norway in 2013 (0.6 percent of

population) (11,12). The number of pregnancies in women with pre-gestational diabetes in Norway is estimated to be 228 in 2018 according to the medical birth register. There are ethnic and racial disparities in women with pre-gestational diabetes (14).

1.3.2 Type 2 Diabetes Mellitus (Type2DM)

Type 2 Diabetes mellites is the most common type of Diabetes. Type2 DM is generally characterized by insulin resistance where insulin does not work properly. Type2 DM is common in older age, but its prevalence is increasing in younger ages due to a rising level of obesity, an unbalanced diet, and inadequate physical activity. There are several risk factors for Type2 DM such as a family history of Type2 DM, overweight or obesity, inadequate physical activity, ethnicity, history of gestational diabetes, increasing age, stress, and unhealthy diet. Physical activity, a healthy diet, avoid smoking, excessive intake of alcohol and added sugar, and maintain normal body weight are the key factors to prevent Type2 DM (15). In particularly the incidence of type 2 DM risk can be reduced by 20 - 30% when consuming high fiber in the diet (16).

1.3.3 Maturity-onset Diabetes of the young (MODY)

Maturity-onset diabetes of the young (MODY) is a genetically and clinically heterogeneous subtype of type 2 diabetes, comprises a heterogeneous group of monogenic disorders characterized by a primary defect in pancreatic β-cell function, early-onset, and autosomal dominant inheritance, expecting for about 1-5% of all diabetes diagnoses. Mutations in 14 genes are responsible for most MODY cases described so far (17,18).

1.3.4 Latent Autoimmune Disease in Adults (LADA)

LADA is an autoimmune diabetes that is characterized by considerable degree of heterogeneity, it appears at any age. LADA is distinct from Type 1 DM due to its adult age of onset and slower progression towards insulin requirement. LADA may be a mix of type 1 and type 2 DM, anyway, patients with LADA present with clinical and biochemical features closer to Type 1 DM than Type 2 DM (19).

1.3.5 Gestational Diabetes Mellitus (GDM)

“Gestational diabetes mellitus (GDM) defined as any degree of glucose intolerance with an onset, or first recognition during pregnancy” (20). The Norwegian guidelines define

gestational diabetes as a fasting blood glucose level between 5.3 to 6.9 mmol/l and/or a two-hour level of blood glucose between 9.0 and 11.0 mmol/l after oral glucose tolerance test (21).

Gestational diabetes is the most common medical complication of pregnancy and associated with maternal and neonatal adverse outcomes. Pregnancy is associated with insulin resistance (IR) and hyperinsulinemia that may further develop into Gestational diabetes mellitus. During pregnancy, progressive insulin resistance starts around mid-pregnancy and progresses during the third trimester. While in early pregnancy, insulin secretion is not much changed. Insulin sensitivity starts to decline progressively, during the 2^{nd} trimester of pregnancy and is further reduced during the rest of the pregnancy, being worst in the late third trimester. Insulin secretion increases gradually from 2^{nd} trimester and peak in 3^{rd} trimester. Insulin resistance usually disappears with the delivery and the disappearance of the placenta. Therefore, GDM usually develops in the late second trimester and disappears after delivery.

GDM develops when a woman's pancreas does not secrete enough insulin to keep up with the metabolic stress of insulin resistance (22). Also, increased maternal fat deposition, inadequate exercise, and increased calorie intake lead to this state of relative glucose intolerance. The decline of insulin sensitivity is mediated by increase level estrogen, human placental lactogen, progesterone and some other factors (22).

The common risk factors for GDM are obesity, higher age, history of Gestational diabetes, family history of diabetes, and an ethnic group with high prevalence type2 diabetes (23). Women with GDM are at risk of developing type 2 diabetes in the future, Therefore, it is very important to follow up the women after delivery (20).

1.4 Insulin

1.4.1 Physiological Function of Insulin

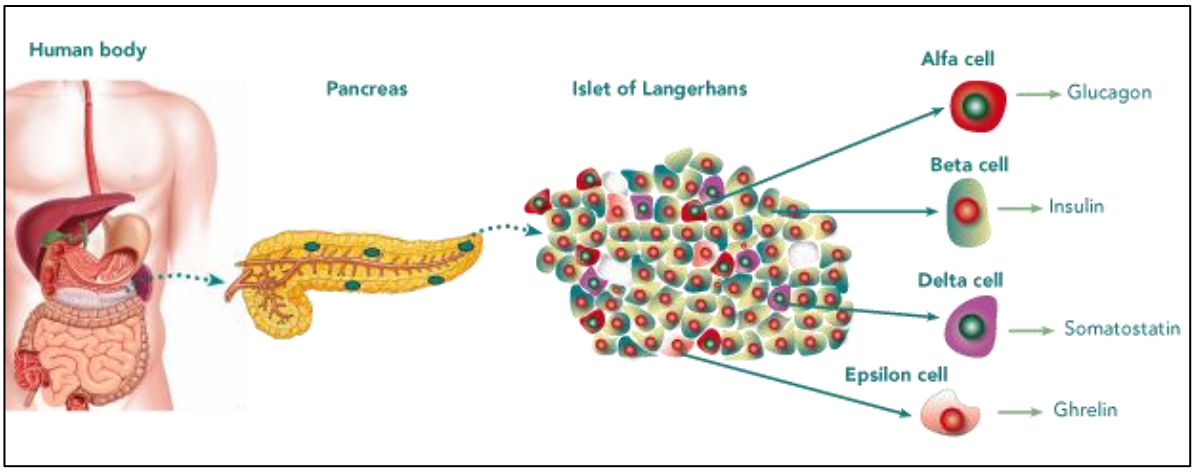

Figure 1. The production of insulin in the pancreas (24)

As illustrated in figure 1, Pancreas contains exocrine ducts and endocrine islets of Langerhans. Islets of Langerhans are built up by 70-80% of beta cells, alfa, delta, and epsilon cells (24).

Endocrine pancreas controls blood glucose in the human body by producing and releasing both insulin and glucagon to the blood. Insulin is coded for on chromosome 11 and synthesized in the beta cells of the pancreatic islets. Insulin is a peptide hormone and, consists of 51 amino acids. it is important for metabolism and utilization of energy from the ingested nutrients - especially glucose (25). Insulin is released upon when high glucose levels reach in blood. Insulin facilitates glucose entry into the muscle (glucose uptake) and other tissues via the GLU4 transporter, stimulates glucose into glycogen (storage) conversion in the liver (glycogenesis) and stimulate glycolysis (oxidation of glucose to pyruvate) in liver and muscles, promotes the synthesis of fatty acids in the liver (lipogenesis) and inhibits the breakdown of fat in adipose tissue, increases the uptake of amino acids in muscles and contributes in protein synthesis (26). After secretion, insulin enters the portal circulation and is carried to the liver. Around 50% of secreted insulin is extracted and degraded in the liver. The residue is broken down by the kidneys. The liver is the principal organ of glucose homeostasis (2).

The brain is the major consumer of glucose and brain function depends on the continuous supply of glucose. Even though brain glucose uptake is obligatory, it is not dependent on

insulin. Insulin action in the fasting and postprandial states are different. In the fasting stage, its main action is to regulate glucose release by the liver but in the postprandial stage, it additionally promotes glucose uptake by fat and muscle (2).

Cell membranes are not inherently permeable to glucose. So, glucose transport (GLUT) proteins carry glucose through the cell membranes. GLUT1, allow basal non-insulin stimulated glucose uptake into many cells. GLUT2 transports glucose into beta cells a prerequisite for glucose sensing. It is also present in the renal tubules and hepatocytes. GLUT3 enables noninsulin mediated glucose uptake into the brain neurons and placenta. GLUT4 facilitates much of the peripheral action of insulin. It is the channel for glucose uptake into muscle and adipose tissue following the stimulation of the insulin receptor. The insulin receptor is a glycoprotein, coded for on the short arm of chromosome 19, attached the membrane of many cells (2).

1.4.2 Insulin therapy

In the case of insulin-dependent diabetes, there are a variety of different insulin types being used to treat DM patients. Insulin types are classified according to their speed of onset, peak and duration of action into rapid-acting insulin, short-acting insulin, intermediate-acting insulin, and long-acting insulin.

Rapid-acting insulin reaches a peak in action at approximately one hour but will last 2 to 4 hours, while long-acting insulin releases slowly to reach the bloodstream and stabilizes a stable effect on blood glucose, and that remains constant for 24 hours. Long-acting insulin can be used in combination with rapid- or short-acting insulin.

Insulin can be administered by a syringe, injection pen, or an insulin pump that delivers a continuous flow. It is administered through the subcutaneous, intramuscular, or intravenous route, or taken into the lungs by inhalation. Insulin dose can be adjusted for food intake, physical activity, and health-related problems (ex- vomiting). Self-monitoring of blood glucose will give guidance for insulin dosage adjustments.

Insulin dose prior to diabetic pregnancy is determined by pre-pregnancy BMI, physical activity, and HbA1c levels. Mean weakly requirement of insulin dosage increase in 3 to 7 weeks of diabetic pregnancy followed by a decline from week 7 to 15 weeks of pregnancy.

The weakly insulin dose gradually increases and reaches the maximum at 35 weeks of gestation and declined thereafter (27,28).

Traditionally, patients with type1 DM have been thought to have lower BMI, however current trend indicates that the prevalence of overweight and obesity increases in type1 DM patients compared to the general population. Weight gain in type1 DM patients is related to clinical factors such as insulin therapy. Insulin is an anabolic hormone that inhibits protein catabolism and increases lipogenesis, resulting in fat accumulation. So, the intensity of insulin therapy influences weight gain. Despite the weight gain, insulin treatment reduces Hb1Ac and long-term reduction of microvascular & macrovascular complications (29). Nowadays insulin therapies more closely mimic physiologic insulin secretion and do better glycemic control in diabetic patients (30).

1.5 Diabetes and pregnancy

1.5.1 Introduction in diabetic pregnancy

Pre-existing diabetes in pregnancy is closely associated with increased risks both for the woman and the developing fetus. Miscarriage, pre-eclampsia, and preterm delivery are more common in women with pre-gestational diabetes (31). In addition, stillbirth, congenital malformations, macrosomia, birth injury, perinatal mortality, and postnatal hypoglycemia are common in babies born to women with diabetes (31). High blood glucose levels can harm the fetus, especially in the first 8 weeks of pregnancy (32). The risks of adverse outcomes are much lower with gestational diabetes than with pre-gestational diabetes (33). Recurrent hypoglycemia is more common in type 1 DM than type 2 DM (34). Adequate pre-conceptional care, especially the level of glycemic control reduces the frequency of congenital malformations and improves the outcome of pregnancy (35).

There are several challenges for maintaining normoglycemia in women with DM who become pregnant, including morning sickness, hormonal changes during pregnancy, and increasing adipose tissue deposits in pregnant women (32,36).

Every pregnant woman is advised to follow some regulations to have a healthy baby, for example, weight and fat control, avoid overdoses of vitamin A, optimizing folate and iodine, abstinence from alcohol and other drugs. In addition to this, women with pre-gestational diabetes should plan their pregnancy carefully, in order to be able to adjust the diet to maintain optimal blood glycemic level, to achieve appropriate maternal weight gain, maintain

nutritional health status and to support a healthy pregnancy and optimal growth and development for the baby (37). Proper surveillance, metabolic control, and good obstetric care can reduce the adverse effects of diabetes on pregnancy outcome in diabetic patients (38).

1.5.2 Diabetic pregnancy & Diet

The Norwegian Directorate **of** Health recommends pregnant women with DM to have a diet with a low glycemic index, consuming multiple and regular meals, distributing carbohydrate intake evenly between meals, and limiting the intake of sweet foods and beverages. The glucose increase after a meal primarily depends on the amount and quality of the carbohydrates in the meal. Pregnant women with DM are recommended to take at least 175 grams of carbohydrate per day (IOM 2007). The dietary tips are adapted to the woman's BMI and recommended weight gain (39).

The diabetic mother can eat healthy food without sugar. Daily food intake will be divided at least 4 - 5 meals per day. Mother can take brown bread, drink milk daily, and spread over 3 meals. High intake of vegetarian foods such as whole grain, legumes, corn, peas, lentils, carrots, broccoli, cauliflower, paprika, lettuce, cucumber, and fresh fruits. DM mothers can eat up to 3 fruits per day at 1 fruit at a time. Low glycemic fruits are a better choice such as blueberries, strawberries. Fish, trimmed meat, chicken, and low intake of processed animal, fatty foods and limit the use of salt in food preparation are fine. It is advisable to substitute vegetables or brown bread instead of large amounts of rice, potatoes, spaghetti, and pasta. It is better to restrict artificial sweeteners in food (40,41). Fish contain rich omega 3 fatty acids, vitamin D, iodine & selenium, these are essential for fetal brain development. Eating fish at least 2 to 3 times a week is advisable (42). The increased intake of dietary fiber during pregnancy has many benefits to the pregnant woman including lowering the risks of diabetes & association with lower daily insulin requirements, reducing risks of preeclampsia, and preventing constipation (43). If diabetic women are overweight or obese, they should restrict high saturated fatty acid-containing foods like butter, cheese, ghee, meat fat of pork, lamb, processed meats like salami, sausages, and hard margarine (40,41).

In recent years, there was a lot of focus on the importance of the pre-conceptional period, and it is now clear that nutrition before pregnancy is associated with maternal, neonatal, and long-term child health (4). This is especially important to women with diabetes. Nutritional status of women is a deciding factor of embryonic and fetal growth at conception. In diabetic

women nutritional status and metabolic control are important during this period. Most of the fetal organs form between 3 to 7 weeks of pregnancy (10).

Diet should play a central role in the treatment of pregnant women with pre-gestational diabetes however, there are only a few studies that investigated dietary intake during pregnancy in women with pre-gestational diabetes, and most recommendations are so far not specific for women with diabetes, but are similar to the recommendations given to all pregnant women.

1.6 Measuring dietary intake:

Measuring dietary intake is not an easy task, and different methods are available, which have their disadvantages and advantages. Information on dietary intake can either be prospective (e.g. by food diaries or records) or retrospective (e.g. food frequency questionnaires 24 h recalls). Especially the retrospective methods rely on memory and the compliance of the participant (45).

1.6.1 24-hour dietary recall

This is a dietary assessment tool that contains a structured interview in which participants are asked to recall all food and drink they have consumed in the previous 24 hours.
An advantage of this method is that dietary information can be easily obtained. A single 24-hour recall is not enough to express an individual's usual intake of food and nutrients. Multiple single days recalls on different individuals can show a valid measure of the intake of a group or population. The success of the 24 hours recall depends on the subject's memory, cooperation, and communication ability, the ability of the subject estimates of portion size consumed, the degree of motivation of the participant, and the persistence of the interviewer. Repeated 24 hours recall should reflect different seasons of the year to estimate the average food intake of individuals a longer period. The repeated 24-hour dietary recall is useful for assessing the average usual intake of a large population. It is used international comparisons of the relationship of nutrient intakes to health & susceptibility to chronic diseases. (45)

1.6.2 Dietary records or food diaries

This is typically obtained for 3 or 4 days. It is a prospective, open survey method gathering data about the foods consumed over a previously specified time (46). For the estimated food record, the respondent is asked to record, at the time of consumption, all foods and beverages eaten, either as weight or measured in household measures. Method of preparation and

cooking is usually also recorded. Disadvantages include that the quality of the record can be declined with increased recorded days. and that the process of recording food intake can lead to a change in food intake. The registration of the foods consumed will minimize the problem of food omissions due to memory failure. Dietary records are usually considered as a reference method in validation studies. (45)

1.6.3 Food frequency questionnaire (FFQ)

FFQ consists of a list of foods and drinks with response categories to indicate the usual frequency of consumption over the period queried. The FFQ aims to assess the frequency with which food items are consumed during a specified period. It is originally designed to provide descriptive qualitative information about the usual food consumption patterns. FFQ is designed to obtain qualitative, descriptive data on the usual intakes of foods over a long period. FFQ must be culture specific. It is less suitable for pregnant women as pregnancy may lead to dietary changes, although it has been used in large cohort studies of pregnant women, e.g. the Norwegian Mother and Child Cohort Study (MoBa) (45,105).

1.7 Assessment during pregnancy

Nutritional status is defined as an individual's health status as it is influenced by the uptake and usage of nutrients. Optimal nutritional status is described as consuming enough, but not excessive, sources of energy, essential nutrients, and other dietary components such as fiber, not containing toxins or contaminants (47).

Different methods are available for measurement of nutritional status. Measurement of dietary intake is one option to assess nutritional status. Other assessment methods include anthropometry, biochemical measurements, and clinical assessment.

In Pregnancy, it is important to monitor nutritional status as this has implications for both mother and fetus. Pregnancy is a demanding situation to maintain nutritional status. In most cases, normal ranges or reference ranges will be changed due to the metabolic changes in pregnancy. There are norms for adequate gestational weight gain, depending on maternal pre-pregnancy BMI and changes in biochemical measurements due to pregnancy (e.g. the physiological anemia of pregnancy)

1.7.1 Anthropometrics methods

These are a series of quantitative measurements and useful to assess the size, proportions, and compositions of the human body. The core elements of anthropometry are height or

recumbent length, weight, body mass index (BMI), circumferences (waist, hip, head, and mid-upper arm), and skinfold thickness. It is safe, non-invasive, easy to obtain, relatively low cost and the calculation is simple. Disadvantages include its low sensitivity and dependency on scoring. (48)

BMI is a commonly used index of nutritional status and a gauge of malnutrition in children and adults. Body mass index (BMI) is a simple index of weight(kg) for height (m), it is commonly used to classify underweight, normal weight, overweight, and obesity. BMI is defined as the weight in kilograms divided by square of the height in meters.

Underweight:<18.5 kg/m^2, Normal weight :18.5-24.9 kg/m^2, Overweight: 25-29.9 kg/m^2, Obesity (grade 1): 30- 34.9 kg/m^2, Obesity (grade 2): 35- 39.9 kg/m^2 , Obesity (grade 3): ≥ 40 kg/m^2 (Nordic Nutrition Recommendations – 2012 ,(78)).

BMI values in adults are age independent & the same for both sexes. In pregnancy, the pre-pregnancy BMI is important for the recommendations for weight gain. The pre-pregnancy BMI distribution in Norway in 2018 was underweight 3.8%, Normal weight 60.8%, Overweight 22.7%, Obese 12.7% according to the Norwegian Institute of Public Health (49). More than one in three women had overweight or obesity at the beginning of the pregnancy, every seventh had obesity (49).

MUAC is a viable measurement in children or pregnant women as a marker of nutritional status. MUAC is the circumference of the left upper arm, measured at the mid-point between the tip of the shoulder (acromion process) and the tip of the elbow (olecranon process). The use of MUAC as a predictor of nutritional & health-related outcomes. Even though there are significant associations between low MUAC and adverse health outcomes, particularly among pregnant women, there was not enough evidence to conclude (50). However, MUAC is closely correlated with BMI, and can be used as a surrogate for BMI in patients were BMI measurement is not possible. MUAC is an alternative marker to assess women at risk of adverse pregnancy outcome in places where weighing is not possible for pregnant women (12).

Skinfolds have been used for body composition calculation before Bioelectrical impedance analysis became available. Triceps skinfold is still used, together with MUAC, to calculate the mid-upper arm muscle circumference.

Skinfold thickness measurements are easy, simple, and quick to obtain, however in obese children accuracy and precision are not reliable. Skinfold equations are population-specific but poor accuracy in individuals and groups (51). In pregnancy, skinfold thickness measurements can be attained from overweight and obese pregnant women to determine Body Fat % and can be utilized in a research site (15).

Measurement of waist circumference is used to assess the waist and central fat, and these measurements are a convenient, quick, and robust measure of abdominal fat and not so accurate as a measure of internal visceral fat. Waist circumference is a better indicator than BMI and waist-to-hip ratio to detect central obesity, and waist circumference is strongly correlated with intraabdominal fat content and cardiovascular risk factors. (51,52). Women with small abdominal circumference in third trimester of pregnancy is associated with an increased risk of provider preterm delivery (96).

Bioelectrical impedance analysis (BIA**)** is a simple, noninvasive, relatively cost-effective, easy doing, a painless, quick and commonly used method to estimate body composition (quantity of fat mass, fat-free mass), and particularly useful in large epidemiologic studies. The method is based on the differences in conductivity of fat mass and fat-free mass of the body. A low electrical current is being sent through the body. The method uses the placement of dual electrodes (voltage electrodes-black, current electrodes-red) on the person's non-dominant side of the hand and foot. The device measures how this signal is obstructed through different types of tissue. While tissues which contain more fluid and electrolytes have high conductivity, fatty tissues are nonconductor of electrical charge. As BIA determines the flow resistance when passing current through the body. it provides body water estimation and from this, body fat mass can be calculated. Body fat mass is calculated by reducing free fatty mass from body weight. Pacemaker users, platinum containing's object users are not advisable to do BIA. It is debated whether BIA can be used in pregnancy. BIA during the 2nd trimester of pregnancy are independently associated to the birth weight (79,80).

1.7.2 Laboratory measurements

Biochemical tests are used to determine nutrient levels in blood and urine. Serum proteins such as albumin and prealbumin are being widely used by clinicians to determine patients' nutritional status. Other serum markers such as retinol-binding protein (RBP), transferrin, total cholesterol, and C-reactive protein (CRP) and total lymphocyte count (TLC), 24-hour urine creatinine are to be used for estimation of fat-free mass and muscle mass (53).

There are many physiological changes occur during pregnancy. These physiological alterations in pregnancy result in many significant changes in laboratory test values. Some of these changes are, such as the reduction in hemoglobin levels, which is the physiological anemia of pregnancy. Similarly, the renal alterations leading to lower creatinine values in pregnancy.

1.7.3 Clinical evaluation

There is a limited number of tools used for the assessment of nutritional status. The most-used tool is the Subjective global assessment (SGA), which is a clinical technique that assesses nutritional status based on features of the history and physical examination and scores patients on a scale ranging from well-nourished to severely undernourished. SGA is being well-validated in a variety of patient populations. SGA can easily be trained to a variety of clinicians and this technique is reproducible. clinical examinations are used to detect signs of nutritional problems. (54)

1.8 Pre-gestational diabetes and glycemic control during pregnancy

The goal of medical management of pre-gestational diabetes is to maintain maternal blood glucose levels within normal limits throughout pregnancy. It is the aim to achieve good glycemic control before conception and maintain through pregnancy and postpartum.

Glycemic control during pregnancy is assessed by frequent daily self-monitoring of blood glucose and periodic measurement of HbA1c. Blood glucose level is maintained through adjustments of diet and insulin therapy. Insulin requirements during the first trimester of pregnancy are like those prior to pregnancy in women with type 1 diabetes. Dosing is continually adjusted based on self-monitoring of blood glucose and HbA1c results (55).

HbA1c is the result of an irreversible non-enzymatic binding of glucose to plasma proteins, specifically hemoglobin (Hb). HbA1c test reflects the average level of blood sugar over the past 8 to 12 weeks. It is also called glycated hemoglobin test. Glucose in the blood binds with hemoglobin in red blood cells. So, the HbA1c test measures how much glucose is bound. Since red blood cells live for about 12 weeks, the test shows the average level of glucose in the blood for the past 12 weeks. (56). A major advantage is that this test can be done at any time of the day and does not need any special preparation such as fasting or dietary preparation. HbA1c level can be affected by a variety of genetic, hematologic illnesses. The most common factors affecting HbA1c levels are hemoglobinopathies, chronic anemia (iron deficiency, B12

deficiency), chronic kidney disease (uremia), hemolysis, and accelerated red blood cell turnover (erythropoiesis), for example malaria (57). The HbA1c range is usually lower in pregnancy because of the physiologic expansion of the red blood cell mass, iron deficiency and decreased erythrocyte life span in pregnancy. Therefore, pregnancy itself reduces HbA1c levels, HbA1c targets are lower in pregnant women with diabetes compared with nonpregnant women with diabetes (55). The normal range of HbA1c is 4.7–6.3% in nonpregnant women, 4.5– 5.7% in early pregnancy, and 4.4–5.6% in late pregnancy (58).

1.9 Pregnancy complications

Pregnancy complications are health-related problems that occur during pregnancy. Common maternal complications in diabetic pregnancy are miscarriages, abnormal gestational weight gain, preeclampsia, polyhydramnios, preterm delivery, stillbirth, hypoglycemia, hypertension, deterioration of retinopathy, nephropathy, neuropathy & increased risk for caesarian section delivery. Common fetal complications in diabetic pregnancy are excessive fetal growth (macrosomia), premature birth, neonatal hypoglycemia, congenital abnormalities, and intrauterine growth retardation.

Regular monitoring during pregnancy allows early detection of health-related problems that could arise in pregnancy and their treatment. It will give increase the chance to have a normal pregnancy and the birth of a healthy baby.

(a) Gestational weight gain can be described as weight gained between conception and just before the birth of the infant. Weight gain during pregnancy is not only important for this pregnancy but also important for the long-term health of mother and baby.

Energy intake requirements in pregnancy are used for resting metabolism, diet-induced thermogenesis, and physical activity, maternal and fetal growth in pregnancy and thus equals to energy expenditure plus energy storage. Resting metabolic rate increases during pregnancy due to pregnancy-related physiological demands. The change depends on changes in body weight and composition, heart rate, stroke volume, cardiac output, thyroid hormone, insulin-like growth factor1, and is related to fetal growth & development. The requirement of energy storage depends on pre-pregnancy BMI. This difference decides the energy intake requirements of pregnant women (59,60).

The weight gain recommendations are inversely proportional to pre-pregnancy BMI, therefore, allow for more weight gain for women who were underweight before pregnancy.

The recommended weight of these women is 12.5–18 kg. For women of normal weight, the recommended amount of weight gain during pregnancy is 11.5 to 16 kg, and weight gain for women who are classified as overweight is 7–11.5 kg and for 5-9 kg to obese, according to the 2009 Institute of Medicine guidelines (59,61,78). Average gestational weight gain in Nordic countries is between 14 -16.5 kg (78). Gestational weight gain depends on pre-pregnant body mass index, hereditary factors, diet pattern, socio-economic status, smoking, and physical activity (62).

Gestational weight gain above or below the recommended range is a serious obstetric problem. The prevalence of inadequate gestational weight gain varies among races and populations. Health risks related to inadequate weight gain during pregnancy involve a greater risk of premature birth and a low birth weight baby and an increased risk of mortality and morbidity (64). Excess weight gain is indicated as a risk factor for giving birth to a high birth weight baby compared with its gestational age, giving birth to a baby with macrosomia, gestational diabetes, pregnancy-induced hypertension (preeclampsia), cesarean section, mother's obesity later in life (62). Early pregnancy weight gain is associated with an increased risk of GDM (41).

(b) Pre-eclampsia is a serious condition that may threaten the life of both mother and child. The cause of pre-eclampsia is unknown; however, the cure occurs after delivering the placenta. Preeclampsia is characterized by high blood pressure and albuminuria. It is defined as systolic blood pressure is equal or more than 140 mm Hg or diastolic blood pressure is equal or more than 90 mm Hg on two occasions at least four hours apart in the second half of pregnancy in a previously normotensive woman and proteinuria (equal or more than 300 mg/24 hours). The probability of having pre-eclampsia is increased to the women who have a previous history of pre-eclampsia, diabetes mellitus, hypertension, obesity, multiple pregnancies, and women who are more than 40 years old. Pre-eclampsia is occurring in 3-5 % of normal pregnancies, and diabetic women have a higher risk of pre-eclampsia (65). Preeclampsia risk is 2 to 4-fold higher in type 1 or type 2 diabetes mellitus. Women with type 1 DM complicated with preeclampsia have an increased risk of retinopathy and nephropathy (66).

(c) Birthweight is another outcome of interest. In Norway, the average birth weight between 2003 and 2006 was 3710 g in boys and 3580 g in girls according to Bergen's growth study

(67). When comparing birth weights, it is important to adjust the birth weight according to gestational age, as the weight of the fetus is increasing during the last weeks of pregnancy.

Macrosomia is defined as birth weight is more than 4,000 g irrespective of gestational age or above the 90th percentile which is corrected for gestational age, sex, and parity. It affects 3-15% of all pregnancies in the population (68). Macrosomia causes some delivery complications for both mothers and babies. There are some factors associated with fetal macrosomia such as genetics, duration of gestation, diabetes mellitus, obesity, multiparity, and ethnic factors (69). Macrosomia is associated with increased risk for being overweight or obese in later life (108). Women with DM have high blood glucose, the baby gets too much glucose through the placenta, baby's pancreas senses it, and resulting hyperinsulinemia. Hyperinsulinemia stimulates the storage of glycogen in the liver and increased the production of adipose tissue. Insulin is a growth factor and leads to accelerated fetal growth.

Instead of absolute values of birth weight, often z scores are used

The z score is a very useful statistic that helps us to find the probability of a score occurring within normal distribution and make it possible to compare two scores which are from different normal distributions.

The Z-score system shows the anthropometric value as several standard deviations or Z-scores below or above the reference mean or median value (70). For z scores for birth weight, data as gestational age, and sex of child are considered.

(d) Neonatal hypoglycemia is defined as blood glucose is equal or less than 2.6 mmol/l or 47 mg/dl and severe neonatal hypoglycemia as blood glucose are equal or less than 2.0 mmol/l in a neonatal baby. Neonatal hypoglycemia is the most common metabolic problem in neonates. The incidence of neonatal hypoglycemia is 25% of all deliveries in the first 48 hours of life in neonates above 35 weeks gestation. After clamping of the umbilical cord, neonates blood glucose declines in the first hours of life. For healthy neonates, hypoglycemia is brief and transient. Prolonged hypoglycemia may occur due to insufficient glucose supply, inadequate glycogen storage, or increased glucose usage due to excessive insulin production or increased metabolic demand (71). Glucose is a vital source of energy required continuously by the infant. Neonatal hypoglycemia can cause long term neurological and developmental consequences. Low birth weight babies, large for gestational age babies, infant of diabetic mothers are prone to get neonatal hypoglycemia (71,72).

(e) A preterm/premature baby is defined as a baby born alive before 37 weeks of gestation (74). Approximately 15 million babies are born as premature and preterm complications are leading cause of death among under 5 years of children. Preterm birth can be subcategorized based on gestational age as, extreme preterm (less than 28 weeks of gestation), very preterm (28-32 weeks), moderate to late preterm (32-37 weeks). Approximately 1in 10 babies are born as preterm, and many survivors are living with a disability, learning difficulties, and visual & hearing problems (75,76). Common causes of preterm are multiple pregnancies, diabetes, high blood pressure, infections, and unknown reasons (75). A study which took place in Israel indicates that the prevalence of spontaneous preterm delivery was 7.1% in non-diabetics, 10.0% in with gestational DM, and 25.5% in those with pre-gestational DM (77).

1.10 Study aims and hypothesis

This thesis is part of a larger study that had the aim to investigate the effect of metabolic control in women with pre-gestational diabetes on the development of the fetus and the birth outcomes. This thesis will focus on diet in women with pre-gestational diabetes and on associations with metabolic control in the women and birth outcomes such as macrosomia, and prematurity. In addition to these dichotomous outcomes, the continuous outcome variables z score of birth weight and gestational age at birth are used.

1.11 Objectives

The goal of the study is to determine the association of diet during pregnancy in women with pre-gestational diabetes with pregnancy outcomes.

- To investigate the association of diet, metabolic control, and pregnancy outcomes z score of birth weight and macrosomia.
- To investigate the association of diet, metabolic control, and pregnancy outcomes gestational birth weight and prematurity.

2. Patients and Methods

2.1 Study design

This study is part of a larger project (the DiaDoppler study). the DiaDoppler study is a prospective longitudinal observational study (follows the same subjects repeatedly over a period) of women with pre-gestational diabetes. The study is conducted in collaboration with "the research group for pregnancy, fetal development, and birth" at Obstetrics and Gynecological Department of Haukeland University Hospital (A.Lund MD PhD).

The study protocol was approved by the regional committee for Medical Research Ethics (REK vest 2011/2030). The participants were provided with oral and written information in detail about the study and 52 women gave written consent. Three participants withdrew after 1st prenatal visit. Participation was voluntary and the women could withdraw from the study at any time. Participants could send feedback by email if they want, anytime during the study period.

This study was carried out at the Department of Obstetrics and Gynecology, Haukeland University Hospital. DiaDoppler monitor maternal health status, fetal development, and fetal circulation in diabetic pregnancies. This study includes ultrasound scanning every fourth week of pregnancy and takes several fetal measurements such as fetal heart rate (CTG-cardiotocography), fetal circulation, biometrics, etc. Anthropometric measurements, blood samples, and body composition of the diabetic pregnant women were done, and measurements during and after birth.

2.2 Study Population

The study population consists of pregnant women with pre-gestational diabetes who received prenatal health care at Haukeland University Hospital, Bergen. The study period was between August 2013 and May 2016.

2.2.1 Recruitment

Women with pre-gestational diabetes in Hordaland county were referred to Haukeland University Hospital as soon as pregnancy was diagnosed. All women with PGDM at the hospital received study information by mail and based on the inclusion and exclusion criteria were asked to participate during their first prenatal visit at Obstetrics and Gynecological Department of Haukeland University Hospital (n=82). They were informed thoroughly about

the study and consequences by A.Lund MD PhD. In addition to this, there was information about the study on the internet home page of Haukeland University Hospital.

Inclusion criteria were pre-gestational diabetes and singleton pregnancies. The exclusion criteria were multiple pregnancies, diabetes due to other than type1or type2 and inability to understand the English or Norwegian language. If abortion occurred, they would have been excluded automatically.

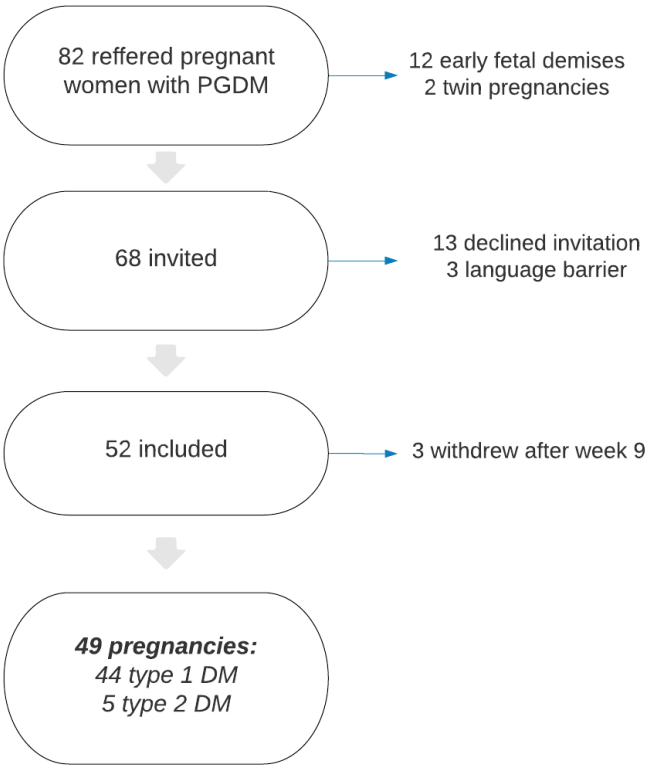

Figure 2 Inclusion of participants in the study (Flow chart) (110)

Finally, 49 women were included in the study. Out of these 49 participants, 44 women had type 1 DM, and 5 had type 2 DM. Three women with Type I DM participated in two consecutive pregnancies. All participants used insulin treatment during pregnancy. Participants self-declared their ethnic identity, in the Type1 DM 39 were Norwegian, 4 from other European countries and one Norwegian with parents from Chile. In the Type2 DM, one was Japanese American, one Chilean Norwegian, one from the Philippines, and two Norwegian.

2.2.2 Measurements

At the first visit, basic and health information was collected such as age, parity, ethnicity, blood group, education, occupation, duration of diabetes, diabetic complication, medication, alcohol

Consumption, smoking habits, other diseases, past and present obstetric history, and family history of diabetes.

The following measurements were made at baseline and throughout the pregnancy and were used to describe the study population:

Mother

- weight, height, BMI, waist, and mid-arm circumference
- Bioelectrical impedance analysis (by Tanita) (weight, fat mass, muscle mass)
- HbA1c: - Mean HbA1c of each trimester was calculated from all available measurements (which were individual for each women). The frequency of attendance of the women was different, and therefore a mean HbA1c was calculated from all visits in a respective trimester of pregnancy.
- Dietary intake of energy, macronutrients added sugar and fiber as measured by 3day dietary records.

2.3 Pregnancy outcome

In the current analysis, the following outcomes of interest were analyzed.

Infant birth weight: Health personnel measured neonatal birth weight by standard methods at the maternity ward. Macrosomia was defined as birth weight by gestational age $\geq 97.5^{th}$ percentile for a Norwegian population (73) A z-score using birth weight, gestational age, and sex, were calculated, where macrosomia corresponds to Z score > 1.96.

Gestational age at birth was calculated either based on early ultrasound (Crown Rump Length) or the date of the 1^{st} day of last menstrual period.

Preterm delivery is defined as a baby born alive before 37 weeks of gestation.

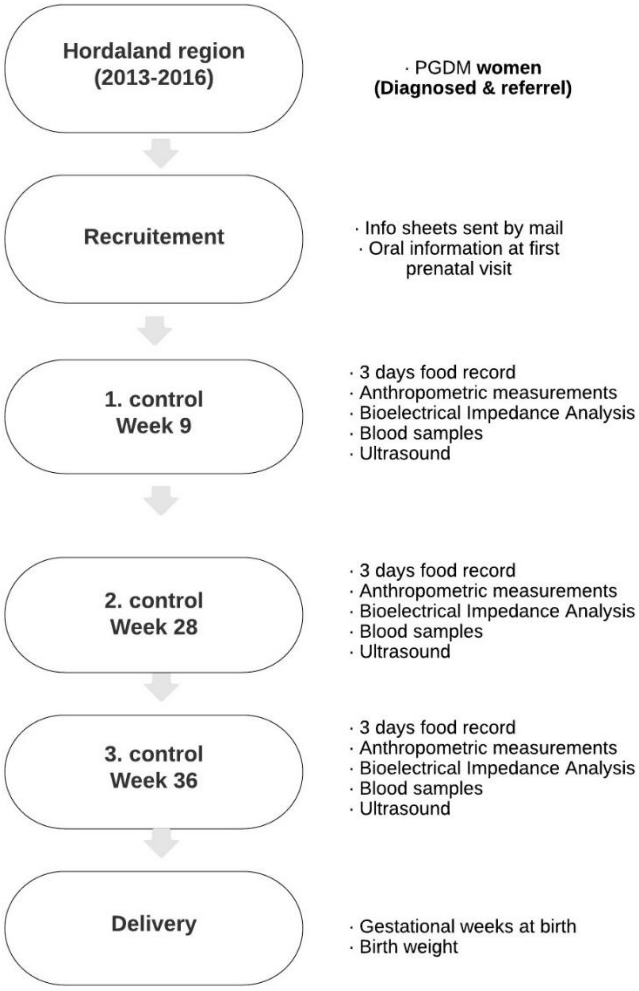

Figure 3 Flow chart of data collections at different stages (13)

Dietary data were collected three times during pregnancy such as around gestational weeks 9,28, and 36. Patients had ultrasound scanning at gestational week 9,20,24,28,32, and 36. Anthropometrical measures, biological impedance analysis, and blood samples, 3 days food record were done at gestational weeks 9,24and 36.

The dietary assessment method used in this study was three days of food records. Food records were taken for 3 consecutive days, including two weekdays and one weekend day. Participants got instructions on how to do 3 days of food recording.

The Participants were instructed to record intake of all food and beverages, and were asked to preferably weigh the food, otherwise, use household weights and measures. Participants were asked to register the label of groceries and the recipes of homemade cooking, together with the amount eaten of every meal.

They were specifically asked to record food ingested to monitor blood glucose, use of vitamin and mineral supplementation should also be recorded. Completed dietary registrations were put in prepaid envelops and returned to the study center or brought back to the next study visit.

Each study visit, blood sample was taken for the HbA1c test. Results were obtained from the Clinical Biochemistry Laboratory at Haukeland University Hospital.

Pregnancy outcome was recorded at each control and information of neonate sex, mode of delivery, birth weight, length, head circumference, waist & arm circumferences, Apgar score, and other maternal and neonatal complications were collected from clinical records at Obstetrics and Gynecological Department of Haukeland University Hospital.

2.4 Data analysis

Dietary intake analysis

The food records of participants were "3 days" food intake records of each participant of each trimester were analyzed by using "kostholdplanleggeren" (kostholdsplanleggeren.no) (63), a tool made for the calculation of nutritional contents of foods from the Norwegian Directorate of Health. The dietary intake of macronutrients of each participant was calculated manually both in grams and as a percentage of total energy intake.

2.5 Statistical analysis

Collected data were analyzed with statistical package for the social sciences software (SPSS version 24). The results were expressed as mean, standard deviation, median and interquartile range, or as number, percentage, and frequency. As only a subgroup of women submitted dietary information, these were first compared to the entire study group. Within the women who submitted dietary data, the outcomes "macrosomia" and "prematurity" were analyzed. Dietary data from each trimester and dietary changes from 1^{st} to 2^{nd} to 3^{rd} trimester were compared by non-parametric tests for independent variables.

Further, correlation analysis using spearman rank correlation of dietary data of each trimester and the continuous variables "z score of birth weight" and "gestational age at birth" was made.

P-values of less than 0.05 was regarded as significant.

3. Results

Data from 49 women were available throughout pregnancy, and of these, 26 submitted dietary data during 1st trimester (Table-1). Out of 49 women, 44 (90%) women suffered from Type 1DM, and 5 (10%) women suffered from Type 2DM. The median duration of diabetes was 17 years. Of these 49 PGDM women, 20 were nulliparous and 29 were parous 1+. The average maternal age was 30±4 years which was comparable with the average age of women giving first birth in Norway in 2018 (29.5 years). The median admission time to the study was at 9.4 weeks gestational age. The median Pre-pregnancy weight was 70 kg. The mean pre-pregnancy BMI was 26.8 ± 5.4 kg/m^2 in this study.

3.1 Table 1: Maternal & neonatal characteristics of the final study population

	All women (n=49)		Women with dietary data in 1st trimester (n=26)	
	Mean ± SD or N (%)	Median (25th to 75th percentile)	Mean ± SD or N (%)	Median (25th to 75th percentile)
Diabetes mellitus type1	44 (90%)		24 (92%)	
Diabetes mellitus type2	5 (10%)		2 (8%)	
Age (years)	30 ± 4	31 (27,33)	29.4 ± 4.5	28.5 (26,33)
Education n=45 ≤12y 13-16Y ≥17	3 22 20		Not available	
Parity 0 1+	20 (40.8%) 29 (59.2%)		12 (46%) 14 (54%)	
Gestational age at inclusion, week	10.2 ± 2.6	9.4 (8.5,11.1)	10.2 ± 2.5	9.7 (8.8, 11.1)
Weight (pre-pregnancy), kg n=44	73 ± 14	70 (63,82)	70.4 ± 5.6 (N=22)	67.5 (63.8,76.3) (N=22)
Height, cm	167 ± 6	168 (162, 171)	166.6 ± 5.6	167 (162,171)
BMI (pre-pregnancy)	26.8 ± 5.4	25.4 (22.8,29.2)	26.0 ± 4.2	25.1(23,28.9)
Duration of DM		17 years	Not available	
Maternal diabetic complications				
- Hypothyroidism	9 (18%)		5 (19%)	
- Hypertension	7 (14%)		3 (11.5%)	
- Retinopathy	9 (18%)		4 (15.4%)	
- Nephropathy	1 (2%)		0	

Table 1: Maternal & neonatal characteristics of the final study population.

Results for those women who provided dietary data at 1st trimester: - 26 of 49 returned “3 days” food record from 1st trimester (53%), 24 during 2nd trimester,19 during 3rd trimester. Out of 26 women who provided dietary data at 1st trimester, 24 (92%) women suffered from type 1DM, and 2 (8%) women suffered from Type 2DM. The average maternal age was 29.4 ± 4.5 years. The median Pre-pregnancy weight was 67.5 kg, the mean pre-pregnancy BMI was 26 ± 4.2kg/m^2.

3.2 Table 2: Characteristics of pregnancy and birth

	All women		Women with dietary data in 1st trimester.	
	Mean ± SD or N (%)	Median (25th to 75th percentile	Mean ± SD or N (%)	Median (25th to 75th percentile
Gestational age (birth)	37.8 ± 2.6	38.6 (36.7,39.6)	38.1 ± 2.1	38.8 (36.7, 39.6)
Preeclampsia	3 (6%)		Not available	
Preterm birth	15 (31%)		7 (28%)	
Induction of labor	30 (60%)		14 (56%)	
Normal vaginal delivery	20 (40%)		4 (16%)	
Operative vaginal delivery	7 (14%)		7 (28%)	
Cesarean section	22 (45%)		14 (56%)	
- elective	9 (41%)		Not available	
- acute	13 (59%)			
Infants' characteristics (n=49)				
Sex (male/ female)	25/24		10/16	
Birthweight (g)	3591± 892	3695 (3150,4150)	3626 ± 697	3690 (3228,4138)
Birthweight Z score	1.05 ± 1.70	0.9 (0.1,2.0)	1.04 ± 1.43	0.97 (0.2, 2.0)
Transfer to an intensive neonatal unit	20 (40%)		Not available	
Perinatal death	1(2%)			
Malformation	2 (4%)			

Table 2: Characteristics of pregnancy and birth.

In all women, mean gestational age at birth was 37.8 ± 2.6 weeks, and the boys to girl's birth ratio was 1.04 /1, which almost resembles the Norwegian population birth ratio (1.07/1). Mean birth weight was 3591± 892 g, Cesarean birth was 45 % of all births. Premature birth was 31 % in this study group, Perinatal death occurred in one pregnancy, 4 % (n=2) of babies were born with a congenital malformation. 40% of babies were transferred to the intensive neonatal unit after birth.

Results from women who provided dietary data in 1st trimester were very similar to the entire cohort.

3.3 Table 3: Anthropometric measurements and HbA1c of the women during pregnancy

		All women		Women with dietary data in 1st trimester	
		Mean ± SD	Median (25th ,75th percentiles)	Mean ± SD	Median (25th ,75th percentiles)
Weight pre-pregnancy (n=44)	kg	74 ± 14	70 (63 ,82)	70 ± 10 (n=22)	68 (64,76)
Weight 1st trimester (n=47)	kg	77 ± 15	71 (67, 81)	74 ± 14 (n=25)	71 (66,78)
Weight 2nd trimester(n=42)	kg	85 ± 14	82 (76,91)	83 ± 15 (n=23)	80 (75, 85)
Weight 3rd trimester(n=40)	kg	90 ± 15	87 (81,100)	89 ± 15 (n=22)	84 (79,94)
MUAC 1st trimester (n=47)	cm	32 ± 5	31 (29,36)	31 ± 4 (n= 25)	30 (29, 33)
MUAC 2nd trimester(n=42)	cm	33 ± 4	32 (30,36)	32 ± 3 (n = 23)	32 (30, 33)
MUAC 3rd trimester (n=39)	cm	33 ± 4	32 (30,35)	32 ± 4 (n= 22)	32 (30, 34)
Waist 1st trimester (n=47)	cm	93 ± 15	91 (82,99)	91 ± 12 (n= 25)	91 (82, 97)
Waist 2nd trimester (n=42)	cm	106 ± 12	104 (98,112)	104 ± 11 (n = 23)	103 (98, 107)
Waist 3rd trimester (n=39)	cm	113 ± 12	111(105,120)	112 ± 12 (n= 22)	112 (104, 118)
HbA1c 1st trimester	%	6.7 ± 0.7	6.5 (6.0, 7.0)	6.5 ± 0.6	6.5 (6.0,6.9)
HbA1c 2nd trimester	%	5.9 ± 0.6	5.9 (5.5,6.3)	5.8 ± 0.6	5.9 (5.3,6.3)
HbA1c 3rd trimester	%	6.0 ± 0.6	6.0 (5.6,6.5)	6.0 ± 0.6	6.1 (5.3,6.5)

Table 3: Anthropometric measurements and HbA1c of the women during pregnancy.

MUAC- Mid upper arm circumference, Waist C-Waist circumference, HbA1c - Glycated hemoglobulin concentrations

Pre- gestational BMI (n=49) revealed that 49% of them were normal weight (n=24), 28% were overweight (n=14), and 22% were obese (n=11), and these figures were similar in women who provided dietary data at 1st trimester (13 women normal weight (50%), 8 women (30%) overweight, and 5 women (20%) were obese).

The mean glycated hemoglobin test (HbA1c) among those with dietary data at 1st trimester showed that 12 women (50%) had less than 6.5% and 12 women (50%) had more than 6.5 %. 2 values were missing.

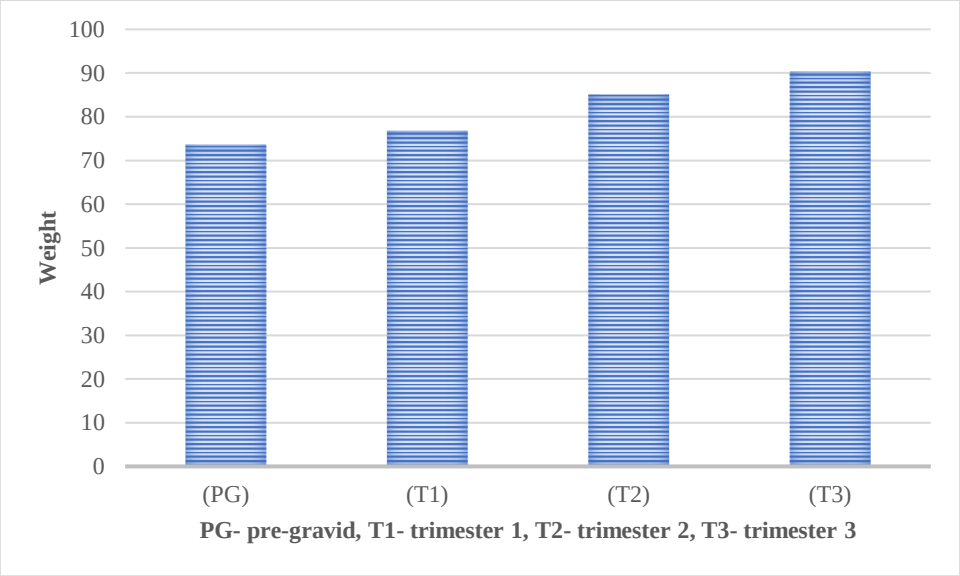

Figure 4. Mean weight changes during pregnancy (n=49).

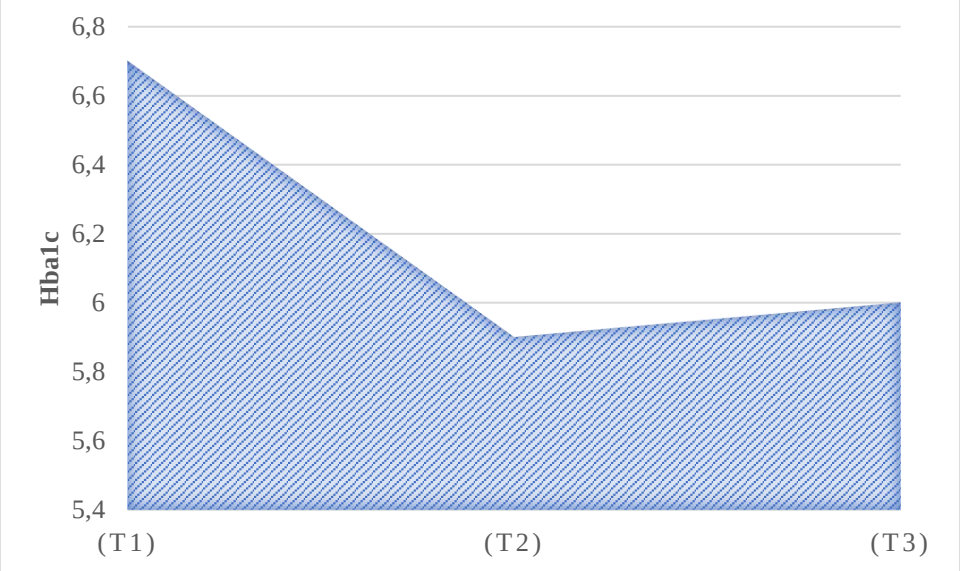

Figure 5. Mean Hb1Ac% in 1st 2nd 3rd trimester (n=49).

3.4 Table 4: Dietary data of the women with PGDM

	Trimester 1 (n=26)		Trimester 2 (n=24)		Trimester 3 (n=19)	
	Mean (SD) or N (%)	**Median (25th to 75th percentile)**	**Mean (SD) or N (%)**	**Median (25th to 75th percentile**	**Mean (SD) or N (%)**	**Median (25th to 75th percentile**
Energy (kcal/d)	2102 ± 410	2129 (1773, 2378)	2174 ± 447	2125 (1821, 2458)	2300 ± 662	2352 (1734, 2766)
Protein (g/d) energy %	90 ± 20 17.0 ± 3.7	91 (72, 106) 16.4 (14.7, 19.8)	95.8 ± 20.5 17.8 ± 2.9	94 (77, 111) 17.8 (16.6, 20.1)	101 ± 33 17.0 ± 2.6	100 (78, 122) 17.7 (15.0, 18.8)
Fat (g/d) energy %	81 ± 21 34.5 ± 6.6	84 (65, 102) 34.5 (29.5, 37.8)	89 ± 23 36.7 ± 5.0	86 (76, 95) 37.0 (33.0, 41.0)	89 ± 32 35.0 ± 6.0	87 (70, 107) 35.0 (31.0, 40.0)
Carbohydrate (g/d) energy %	242 ± 67 45.8 ± 8.6	257 (200, 279) 46.0 (40.9, 51.6)	236 ± 65 43.0 ± 6.7	225 (186, 276) 43.0 (38.0, 47.0)	259 ± 85 45.0 ± 6.9	230 (187, 338) 45.6 (39.0, 49.0)
Added sugar (g/d) energy %	38 ± 23 7 ± 4.3	39 (18, 54) 8 (3.5, 9.6)	37 ± 22 6.6 ± 3.4	37 (16, 51) 6.5 (3, 8.7)	38 ± 29 6.6 ± 4.7	33 (11, 68) 5 (2,11)
Dietary fiber (g/d)	25.6 ± 9.0	26.0 (17.5, 31.5)	24.6 ± 8.0	22.0 (17.0, 31.0)	29.0 ± 11.0	26.0 (20.0, 33.0)
SFA (g/d)	31.0 ± 8.7	31.5 (23.5, 37.3)	34.8 ±9.9	34.0 (31.0, 39.0)	32.6 ± 11.0	31.0 (26.0, 41.0)
tFA (g/d)	0.7 ± 0.5	1.0 (0, 1.0)	0.9 ± 0.5	1.0 (1.0,1.0)	0.8 ± 0.5	1.0 (1.0, 1.0)
MUFA (g/d)	28.7 ± 8.9	29.5 (21.0, 35.0)	30.0 ± 9.0	29.0 (25.0, 34.0)	33.0 ± 14.0	32.0 (24.0, 39.0)
PUFA (g/d)	12.0 ± 4.0	12.0 (9.0, 15.0)	14.9 ± 7.5	13.5 (10.0, 15.0)	14.6 ± 8.0	13.0 (10.0, 18.0)
Omega 3 fatty acids (g/d)	3.0 ± 1.3	3.0 (2.0, 4.0)	3.3 ± 2.0	2.5 (2.0, 4.8)	3.0 ± 1.8	3.0 (2.0, 5.0)
Omega 6 fatty acids (g/d)	9.3 ± 3.7	10.0 (6.0, 11.0)	11.5 ± 5.8	10.0 (8.3, 12.0)	11.0 ± 6.4	10.0 (7.0, 14.0)
Cholesterol (mg/d)	286 ± 134	284 (174, 367)	309 ± 184	247 (205, 367)	303 ± 136	277 (195, 405)

Table 4: Dietary data of the women with PGDM.

SFA- saturated fatty acids, MUFA - monounsaturated fatty acids, PUFA - polyunsaturated fatty acids, E%- energy percentage, Omega 3 FA - Omega 3 fatty acids, Omega 6 FA Omega 6 fatty acids

Participants handed over a “3 days” food record from the first trimester (53%), from the second trimester (49%), from third trimester (39%).

Total mean energy intakes in the 1st, 2nd, and 3rd trimester were 2102, 2174, and 2300 kcal, respectively. Total carbohydrate intake was 45 E% in the 1st and 3rd trimester, and 43 E% in 2nd trimester. Total protein intake was 17 E% throughout the pregnancy. Total fat intake was 35 E% in the 1st and 3rd trimester, and 37 E% in 2nd trimester.

Total added sugar intake was 6-7 E% throughout the pregnancy.

Total intake saturated fatty acids (SFA) were 13.3 E% in 1st trimester, 14.4 E% in 2nd trimester, and 12.8 E% in 3rd trimester. Total intake of monounsaturated fatty acids (MUFA) was 12.3 E% in 1st trimester, 12.4 E% in 2nd trimester, 12.9 E% in 3rd trimester. Total intake of polyunsaturated fatty acids (PUFA) was 5.1 E% in 1st trimester, 6.2 E% in 2nd trimester, and 5.7 E% in 3rd trimester.

The average intake of dietary fiber was 25-26 g /day in 1st trimester, less than 26 g/day in 2nd trimester, and 29 g /day (median 26 g /day) in 3rd trimester.

The average intake of Omega 3 FA was 3 g daily, and the average intake of Omega 6 FA was 10 g daily throughout the pregnancy.

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3.4.1 Table 4.1: Dietary changes during pregnancy

	Change from 1st to 2nd trimester (n=19) (Mean ± SD)	Change from 1st to 3rd trimester (n=15) (Mean ± SD)
Energy (kcal)	23 ± 370	184 ± 510
Protein (g/d)	2.5 ± 25.0	12.4 ± 26.9
Fat (g/d)	4 ± 23	11 ± 25
Carbohydrate (g/d)	-6 ± 72	9 ± 79
Dietary fiber (g/d)	-2 ± 7	0 ± 9

Table 5.1: Dietary changes during pregnancy.

Among the women who submitted dietary data, 19 submitted data from both the 1st and the 2nd trimester, and 15 provided data from the 1st and 3rd trimester (Table 4,2). From 1st to 2nd trimester, there was only a marginal increase in energy intake, while the increase was 184 kcal per day in the 3rd trimester. For comparison, the Nordic Nutrition recommendation recommends an increase of 329 kcal per day in the 2nd trimester an increase of 537 kcal per day in the 3rd trimester (78)

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3.5 Table 5: correlations of dietary intake during pregnancy with pregnancy outcomes (z-score of birth weight & gestational age at birth)

		Z- Score birth Weight	Gestational age Weeks
1st trimester (n=26)	Energy Kcal/d	- 0.122	0.14
	Protein g/d	- 0.199	0.025
	Fat g/d	- 0.055	- 0.168
	Carbohydrates g/d	- 0.099	0.082
	Added sugar g/d	0.062	0.064
	Dietary fiber g/d	- 0.267	**0.419**
	Protein E%	- 0.037	0.045
	Fat E%	- 0.020	- 0.050
	Carbohydrates E%	0.141	0.024
	Added sugar E%	0.167	0.004
2nd trimester (n=24)	Energy Kcal/d	- 0.174	**0.503**
	Protein g/d	- 0.167	**0.451**
	Fat g/d	- 0.275	**0.582**
	Carbohydrates g/d	- 0.128	0.272
	Added sugar g/d	**- 0.394**	0.196
	Dietary fiber g/d	**- 0.348**	**0.512**
	Protein E%	0.051	- 0.025
	Fat E%	0.058	0.196
	Carbohydrates E%	- 0.054	- 0.175
	Added sugar E%	**- 0.422**	0.096
3rd trimester (n=19)	Energy Kcal/d	0.239	- 0.052
	Protein g/d	0.123	- 0.103
	Fat g/d	0.185	- 0.059
	Carbohydrates g/d	0.266	- 0.095
	Added sugar g/d	0.155	- 0.179
	Dietary fiber g/d	**0.308**	- 0.059
	Protein E%	- 0.132	- 0.044
	Fat E%	- 0.116	0.134
	Carbohydrates E%	0.244	- 0.145
	Added sugar E%	0.118	- 0.184

Table 6: correlations of dietary intake during pregnancy with pregnancy outcomes (z-score of birth weight & gestational age at birth).

Very few significant correlations of dietary intake in 1st trimester with birth outcomes of birthweight and gestational age at birth. Of note, dietary fiber was associated inversely with birthweight and positively with gestational age at birth.

In the 2nd trimester, intake of fat, fiber, added sugar was inversely correlated with birthweight and energy, fat, protein, and carbohydrates intake were positively correlated with gestational age at birth.

In the 3rd trimester, intake of energy, carbohydrates, and fiber was positively correlated with birth weight and while no correlation was seen with gestational age at birth.

3.6 Table 6: correlations of maternal factors with pregnancy outcomes

		Z- Score birth Weight	**Gestational age at birth**
Pre-pregnancy	Weight (kg)	0.007	- 0.048
	Height (m)	**- 0.302**	- 0.059
	Maternal age	0.146	- 0.007
	Weight gain (kg)	**0.382**	- 0.024
	Weight gain /week	**0.401**	- 0.052
1st trimester (n=26)	HbA1c (%)	**0.429**	**- 0.427**
	Maternal body weight (kg)	0.165	- 0.181
2nd trimester (n=24)	HbA1c (%)	**0.457**	- 0.128
	Maternal body weight (kg)	0.249	**-0.311**
3rd trimester (n=18)	HbA1c (%)	**0.471**	- 0.228
	Maternal body weight (kg)	**0.325**	- 0.274

Table 7: correlations of maternal factors with pregnancy outcomes.

Maternal age and mothers' pre-gravid weight was positively correlated with birth weight.

In the 3rd trimester, maternal weight and HbA1c were positively correlated with birth weight.

Generally, mothers' weight, Hb1Ac was positively correlated with Z-score birth weight & negatively correlated with gestational age at birth.

3.7 Table 7: factors related to preterm delivery

	Term delivery Mean (SD)	**Preterm delivery Mean (SD)**	**p-value Wilcoxon test**
Numbers	34	15	
Maternal age	30 ± 4	29 ± 3	0.437
Z score birth weight	1.0 ± 1.5	1.2 ± 2.2	0.740
Gestational age at birth	39 ± 1	34.7 ± 2.8	0.000
Height (cm)	166.6 ± 5	166.7 ± 8	0.912
Pre-gravid weight (kg)	75 ± 16	70 ± 9	0.603
HbA1c % 1st trimester	6.6 ± 0.8	7.0 ± 0.6	**0.036**
HbA1c %2nd trimester	5.8 ± 0.6	6.0 ±0.7	0.190
HbA1c % 3rd trimester	6 ± 0.5	6.3 ± 0.9	0.184
	n=19	n=7	
Carbohydrate (g/d) 1st trimester	243 ± 69	239 ± 67	1.000
Carbohydrate (g/d) 2nd trimester	248 ± 67	202 ± 50	0.177
Added Sugar (g/d) 1st trimester	40 ± 24	33 ± 20	0.497
Added Sugar (g/d) 2nd trimester	40 ± 23	27 ± 17	0.199
Dietary fiber (g/d) 1st trimester	28 ± 9	20 ± 6	**0.041**
Dietary fiber (g/d) 2nd trimester	26 ± 8	19 ± 7	0.056
Fat intake 1st trimester (g/d)	81 ± 21	80 ± 24	0.910
Fat intake 2nd trimester(g/d)	95 ± 22	68 ± 12	**0.002**
Protein intake 1st trimester (g/d)	92 ± 19	85 ± 24	0.461
Protein intake 2nd trimester (g/d)	101 ± 20	81 ± 14	**0.027**
Energy intake 1st trimester (kcal)	2122 ± 467	2051 ± 200	0.692
Energy intake 2nd trimester (kcal)	2306 ± 416	1779 ± 282	**0.003**
	n=15	n=4	
Change in energy (kcal) intake 1st to 2nd trimester	86 ± 387	-214 ± 173	0.124
Change in protein (g/d) intake 1st to 2nd trimester	8 ± 23	-17 ± 26	0.124
Change in fat intake (g/d) 1st to 2nd trimester	9 ± 22	-14 ± 21	0.080

Change in carbohydrate (g/d) intake 1st to 2nd trimester	-7 ± 75	-4 ± 67	0.736
Change in fiber intake (g/d) 1st to 2nd trimester	-3 ± 8	0 ± 4	0.530

Table 8: factors related to preterm delivery.

Out of 49 deliveries 15 babies were delivered as preterm, and 34 babies were born at term. The average gestational age for preterm delivery was 34.7 ± 2.8 weeks. Significant difference observed for Hb1Ac in 1st trimester (p-value: 0.036), and non-significantly in the 2nd & 3rd trimester also.

26 mothers submitted diet records in 1st trimester, out of these 19 delivered term babies and 7 mothers delivered preterm baby. In 1st trimester, the only observed difference was the fiber intake. In the 2nd trimester energy, fat, protein intake was significantly lower in preterm delivery mothers.

Only 19 mothers submitted diet records in 2nd trimester, out of these 15 delivered term babies and 4 mothers delivered preterm baby. There were no significant changes in energy, protein, and fat intake from 1st to 2nd trimester in mothers who delivered preterm and those who delivered at term.

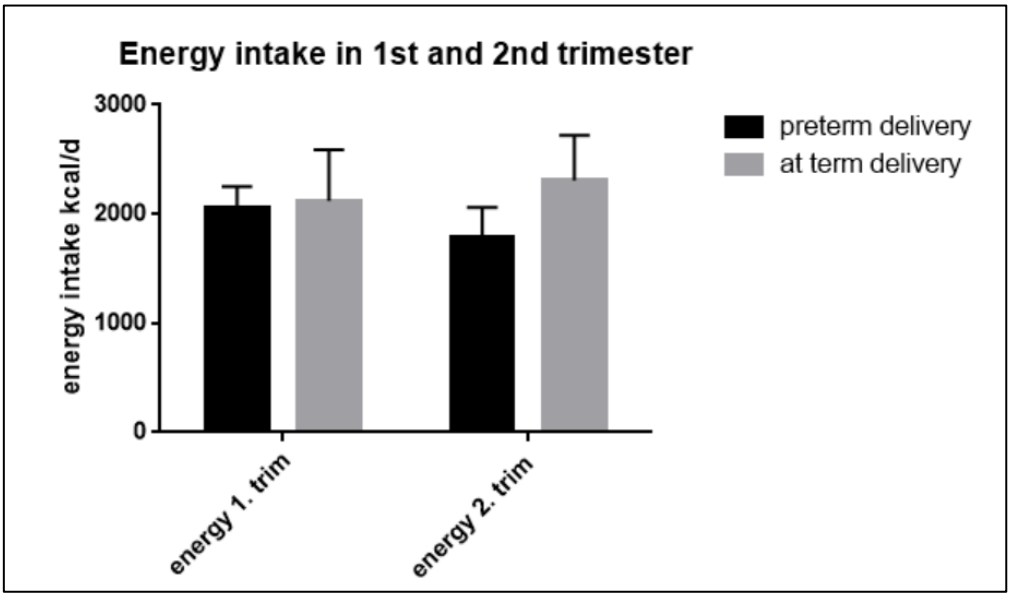

Figure 6. Energy intake in women accounting to prematurity.

Energy intake was significantly different in 2nd trimester

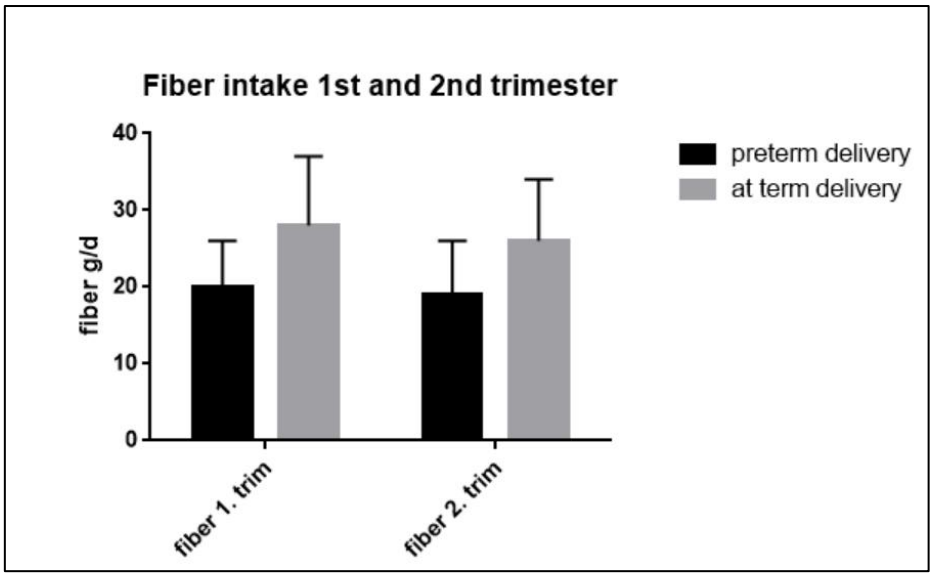

Figure 7. Fiber intake in 1st & 2nd trimester according to prematurity.

Fiber intake was significantly different in 1st trimester and p=0.06 in 2nd trimester

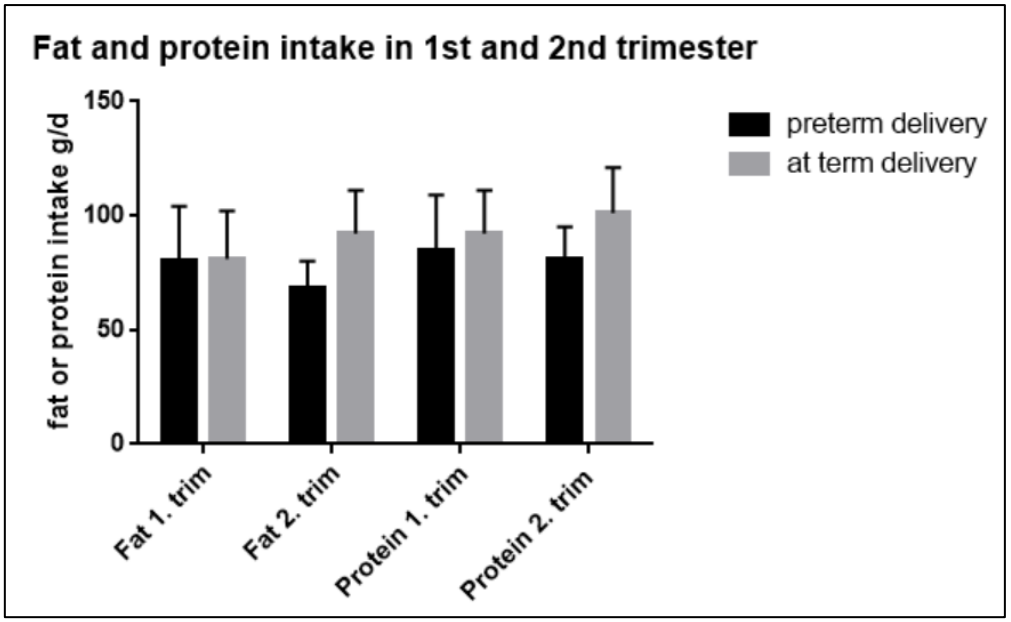

Figure 8. Fat and protein intake in in the 1st & 2nd trimester according to prematurity.

Fat and protein intake were significantly different in 2nd trimester

3.8 Table 8: Macrosomia (women with dietary data: 15 infants without macrosomia, 11 infants with macrosomia)

	No macrosomia (n=30)	Macrosomia (n=19)	P value Wilcoxon test
Maternal age (years)	30.2 ± 4.3	29.8 ± 3.8	0.696
Weight gain (kg)	12.2 ± 5.8 (n = 27)	17.1 ± 6.2 (n = 18)	**0.012**
Z score birth weight	0.019 ± 1.0	2.679 ± 1.2	0.000
Gestational age at birth (weeks)	37.6 ± 3.1	38.1 ± 1.4	0.813
Height (cm)	166.2 ± 5.5	167.6 ± 6.6	0.530
Pre-gravid BMI (kg/m^2)	26.7 ± 5.9	27.1 ± 4.5	0.320
HbA1c % 1^{st} trimester	6.5 ± 0.8	6.9 ± 0.6	**0.045**
HbA1c % 2^{nd} trimester	5.7 ± 0.7	6.1 ± 0.5	0.061
HbA1c % 3^{rd} trimester	5.9 ± 0.6	6.3 ± 0.6	**0.014**
Women with dietary data			
Carbohydrate (g/d) 1^{st} trimester	250 ± 67 (n = 15)	231 ± 69 (n=11)	0.610
Carbohydrate (g/d) 2^{nd} trimester	249 ± 70 (n=10)	229 ± 57 (n=9)	0.720
Carbohydrate (g/d) 3^{rd} trimester	241 ± 83 (n=8)	279 ± 88 (n=7)	0.357
Added Sugar (g/d) 1^{st} trimester	36 ± 22 (n = 15)	41 ± 24 (n=11)	0.574
Added Sugar (g/d) 2^{nd} trimester	42 ± 24 (n=10)	34 ± 17 (n=9)	0.447
Added Sugar (g/d) 3^{rd} trimester	35 ± 31 (n=8)	41 ± 28 (n=7)	0.669
Dietary fiber (g/d) 1^{st} trimester	28 ± 10 (n = 15)	22 ± 8 (n=11)	0.134

Dietary fiber (g/d) 2nd trimester	27 ± 10 (n=10)	22 ± 6 (n=9)	0.243
Dietary fiber (g/d) 3rd trimester	28.8 ± 14.1 (n=8)	29.0 ± 6.6 (n=7)	0.970
Fat intake (g/d) 1st trimester	86 ± 16 (n = 15)	73 ± 25 (n=11)	0.148
Fat intake (g/d) 2nd trimester	91 ± 14 (n=10)	83 ± 21 (n=9)	0.356
Fat intake (g/d) 3rd trimester	91 ± 35 (n=8)	87 ± 30 (n=7)	0.812
Protein intake (g/d) 1st trimester	95 ± 20 (n = 15)	84 ± 19 (n=11)	0.134
Protein intake (g/d) 2nd trimester	98 ± 20 (n=10)	92 ± 18 (n=9)	0.549
Protein intake (g/d) 3rd trimester	100 ± 39 (n=8)	102 ± 27 (n=7)	0.911
Energy intake (kcal)1st trimester	2207 ± 364 (n = 15)	1960 ± 441(n=11)	0.164
Energy intake (kcal)2nd trimester	2257 ± 336 (n=10)	2078 ± 369 (n=9)	0.356
Energy intake (kcal)3rd trimester	2241 ± 677 (n=8)	2364 ± 678 (n=7)	0.698
	n = 10	n = 9	
Change in energy intake (kcal)1st to 2nd trimester	-31 ± 365	83 ± 388	0.437
Change in protein intake (g/d)1st to 2nd trimester	-4 ± 21	10 ± 29	0.447
Change in fat intake (g/d)1st to 2nd trimester	2 ± 15	7 ± 31	0.447

Change in carbohydrate intake (g/d)1st to 2nd trimester	-7 ± 89	-6 ± 52	0.604
Change in fiber intake (g/d)1st to 2nd trimester	-3.5 ± 7.5	-0.7 ± 6.3	0.400

Table 9: Macrosomia (women with dietary data: 15 infants without macrosomia, 11 infants with macrosomia).

Out of 49 deliveries, 19 were macrosomia babies (39%). Gestational weight gain is higher in mothers who gave birth to a macrosomia baby (p- value: 0.012).

Hb1Ac was higher throughout pregnancy in mothers who gave birth to a macrosomia child. 1st trimester (p- value: 0.045), 2nd (p- value: 0.061) and 3rd trimester (p- value: 0.014).

Among the women who submitted diet records in 1st trimester, 15 delivered non-macrosomia babies and 11 mothers delivered macrosomia babies. There was no significant difference in the intake of energy, carbohydrate, fat, protein, or fiber between the groups throughout pregnancy.

Among the women who submitted diet records in 2nd trimester, 9 delivered macrosomia babies, and 10 mothers delivered non-macrosomia babies. No differences in dietary intake between the groups were observed.

Fiber intake in 1st and 2nd trimester was lower in mothers who delivered macrosomia babies. Among the women who submitted diet records in 3rd trimester, 7 delivered macrosomia babies, and 8 mothers delivered non-macrosomia babies. No differences in dietary intake between the groups were observed.

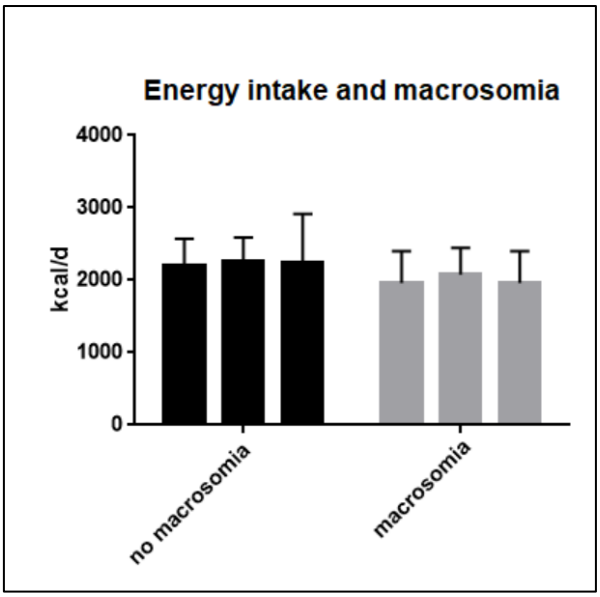

Figure 9. Energy intake in 1st 2nd 3rd trimester with women who had macrosomia & non- macrosomia babies.

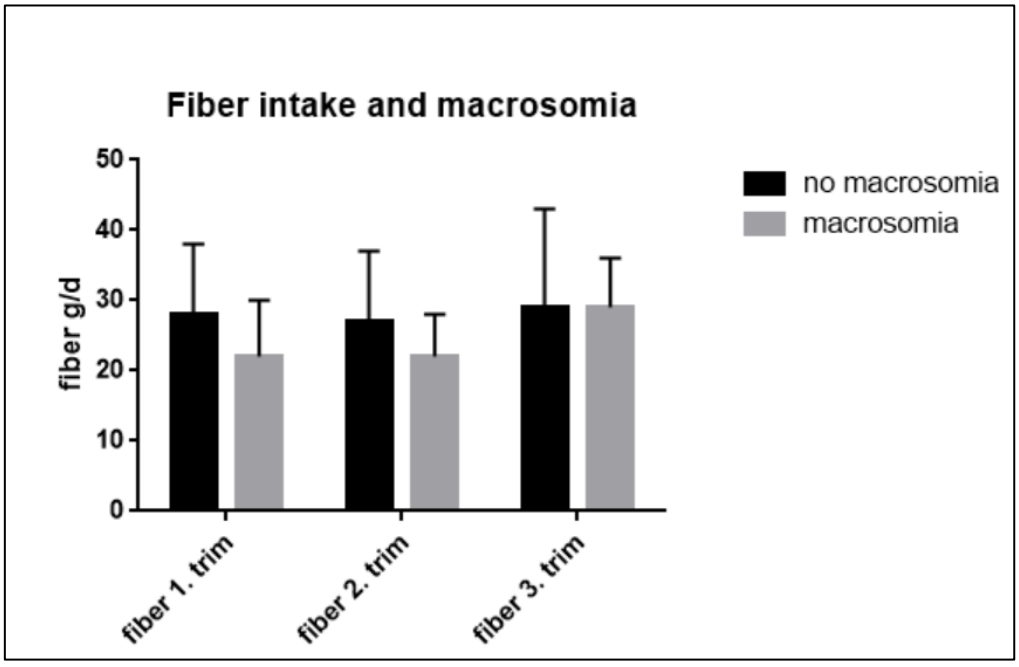

Figure 10. Fiber intake in 1st 2nd 3rd trimester with women who had macrosomia & non- macrosomia babies.

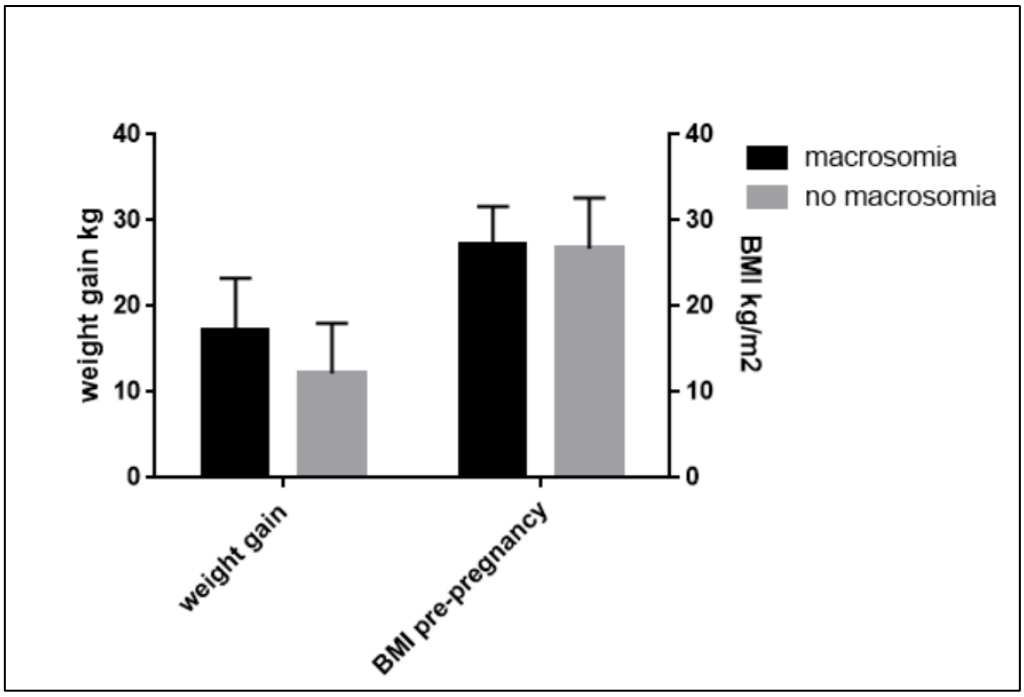

Figure 11. Pre- pregnancy BMI & gestational weight gain in women who had macrosomia & non- macrosomia babies.

Weight gain was significantly different.

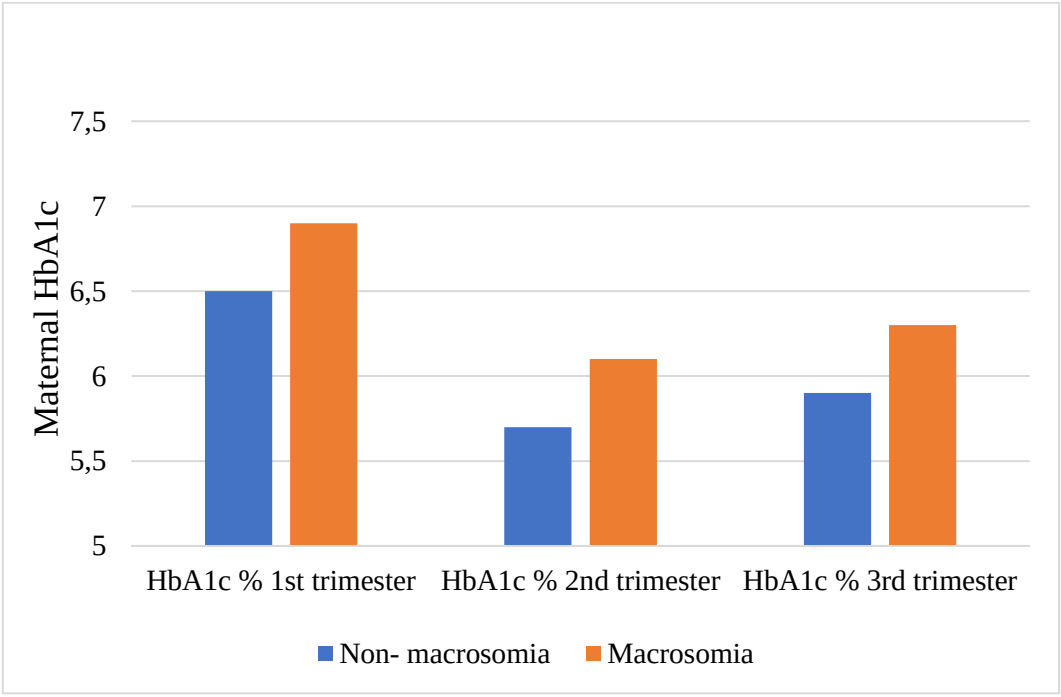

Figure 12. Mean maternal HbA1c in each trimester in mothers to macrosomia & non macrosomia.

3.9 Fat and pregnancy outcomes

Table 9a: Macrosomia

	Non macrosomia (n=15) Mean (SD)	Macrosomia (n=11) Mean (SD)	T test
Trimester 1			
SFA g/d	32.1 ± 7.2	29.5 ± 10.5	0.448
MUFA g/d	30.9 ± 7.3	25.5 ± 10.3	0.132
PUFA g/d	10.3 ± 4.3	10.9 ± 3.9	0.156
Omega 3 FA g/d	3.1 ± 1.3	3.0 ± 1.5	0.903
Omega 6 FA g/d	10.6 ± 3.6	7.5 ± 3.0	**0.027**
Trimester 2	(n= 11)	(n= 13)	
SFA g/d	35.2 ± 3.3	34.5 ± 13.3	0.863
MUFA g/d	30.6 ± 7.2	29.5 ± 10.8	0.777
PUFA g/d	15.5 ± 7.4	14.3 ± 7.8	0.717
Omega 3 FA g/d	4.0 ± 2.2	2.7 ± 1.7	0.118
Omega 6 FA g/d	11.5 ± 5.2	11.5 ± 6.5	0.973
Trimester 3	(n=10)	(n=9)	
SFA g/d	30.8 ± 9.6	34.7 ± 12.6	0.459
MUFA g /d	34.9 ± 15.7	31.0 ± 11.4	0.548
PUFA g/d	16.2 ± 9.9	12.9 ± 4.9	0.380
Omega 3 FA g/d	3.4 ± 1.8	3.0 ± 2.0	0.650
Omega 6 FA g/d	12.7 ± 7.9	9.6 ± 3.8	0.297

Table 10a: Fat and pregnancy outcomes – Macrosomia.

SFA- saturated fatty acids, MUFA - monounsaturated fatty acids, PUFA - polyunsaturated fatty acids, E%- energy percent, Omega 3 FA - Omega 3 fatty acids, Omega 6 FA - Omega 6 fatty acids

Diet records of 1st trimester show that there was no significant difference in intake of SFA, MUFA, PUFA, or omega 3 fatty acids between the groups. There was a significant difference in the intake of omega 6 fatty acids in 1st trimester. No significant differences in dietary were observed in 2nd and 3rd trimester.

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Table 9b: Prematurity

	Term (n=19) Mean (SD)	Prematurity (n=7) Mean (SD)	T test
Trimester 1			
SFA g/d	29.9 ± 8.9	33.9 ± 7.9	0.318
MUFA g/d	29.2 ± 8.2	27.3 ± 11.2	0.645
PUFA g/d	12.4 ± 3.9	12.4 ± 3.9	0.828
Omega 3 g/d	3.3 ± 1.4	2.4 ± 0.9	0.164
Omega 6 g/d	9.4 ± 3.2	8.9 ± 4.9	0.735
trimester 2	(n= 18)	(n=6)	
SFA g/d	37.8 ± 8.6	25.8 ± 8.2	**0.007**
MUFA g/d	32.2 ± 9.3	23.5 ± 4.7	0.410
PUFA g/d	15.8 ± 8.4	11.8 ± 1.6	0.265
Omega 3 g/d	3.7 ± 2.2	2.2 ± 0.4	0.119
Omega 6 g/d	12.3 ± 6.5	9.0 ± 1.4	0.231

Table 11b: Fat and pregnancy outcomes – Prematurity.

SFA- saturated fatty acids, MUFA - monounsaturated fatty acids, PUFA - polyunsaturated fatty acids, E%- energy percent, Omega 3 FA - Omega 3 fatty acids, Omega 6 FA Omega 6- fatty acids

No significant differences were observed in dietary intake in the 1st trimester according to the prematurity was observed.

In the 2nd trimester there was a significant difference in the intake of SFA.

4. Discussion

In this study involving 49 pregnant women with PGDM, we observed significant associations of metabolic control with birth outcomes (z score of birth weight and gestational age at birth). Among 26 women who submitted dietary records in the 1st trimester, we observed few significant associations of dietary intake with birth weight, but no significant differences according to macrosomia. Macrosomia was associated with gestational weight gain, but not with dietary intake.

Women with preterm delivery had low intakes of energy, fat, and protein in the 2nd trimester.

4.1 Strengths and limitations

One strength of the study is that the design is a longitudinal observational one. This study is part of a larger project which was done by a multidisciplinary team of a tertiary unit. The study had a low dropout rate and good compliance of study visits with voluntary participation. The participants in this study were well educated, 93% of participants have above 13 years of education including 44% of participants have 17 years of education. Dietary intake data were obtained from dietary records, which is regarded as the gold standard method. Measurement of dietary intake was repeated during each trimester, and there were very few studies that performed this. Participants were unaware of the outcome of pregnancy when they took food records, so pregnancy outcome could not affect the reporting.

The obvious limitation of this study is the size of the study group. Out of 49 participants, 53% in 1st trimester 49% in 2nd trimester and 39% in 3rd trimester submitted food records. Due to circumstances beyond our control, we could not get 100% data collection. The pre-pregnancy BMI was calculated from the self-reported pre-pregnancy weight.

The study group consists of type 1 and type 2 DM participants. Type 1 and type 2 DM differ in many ways. Pre-gravid BMI, gestational weight gain and metabolic control are significantly associated with pregnancy outcomes. Pre-pregnancy BMI is usually higher in type 2 DM than type 1 DM. Even though both types have similar treatment, poorer neonatal outcomes occur more commonly in babies of type 1 DM mothers (81).

4.2 Discussions of results

Pregnant women with DM have been related to numerous maternal and fetal complications. Therefore, the cesarean section is high in these mothers. Cesarean birth in Norway in 2018 is 15.9% but in this study group, 45% of birth were cesarean birth, which is much higher. All cesarean birth in Hordaland region is only 11.6% (6). Macrosomia affects 3-15% of all pregnancies in the population (68) but in this study, it affects around 39% of babies. Macrosomia is associated with difficult delivery results in trauma to the mother and the fetus and increased risks of cesarean section (88).

Studies have shown that Hb1Ac % in at conception, 1st trimester (82), 2nd trimester (83), and 3rd trimester (84) of pregnancy were associated with macrosomia. According to the Pederson hypothesis, maternal high blood glucose results in transplacental diffusion of a higher amount of glucose to the fetus, resulting in increased fetal insulin secretion. This leads to fetal macrosomia (92). However, despite good glycemic control, the incidence of fetal macrosomia in Type I diabetic women was high (84,85,). Anyway, there is not enough investigation done about birthweight and its association with maternal diet during pregnancy.

The mean birth weight of this study group was higher (3591± 892 g) than the average birth weight of Norway in 2018 (3490±585g). Pre-pregnancy BMI was 26.8 ± 5.4 kg/m^2 in this study which is higher than the average pre-pregnancy BMI in Norway in 2018 which was 24.5 ± 4.8 kg/m^2 (6, 86). Pre-gravid BMI and maternal weight gain are positively associated with birth weight in a study from Australia involving with 1617 mothers with diabetes (87). In our study, pre-pregnancy BMI was not different between women who had a child with or without macrosomia. This may be due to a low number of participants or good pre-pregnancy awareness. Even though pre-gravid BMI between women with macrosomia baby and women with non-macrosomia baby is no significant difference, gestational weight gain was significantly higher in women with macrosomia baby (p: 0.012). A study showing that Type 1 diabetes women with higher gestational weight gain was associated with macrosomia independent of pre-pregnancy BMI and glycemic control in late pregnancy (97).

There are guidelines for appropriate maternal weight gain with pre-pregnancy BMI. What extent is it compatible to women with PGDM?

Pregnant women with diabetes are recommended to restrict their intake of carbohydrates which may result in improved maternal glycemia. However, carbohydrates have a very varied effect on blood glucose levels and metabolic control, which is usually expressed by the glycemic index. Diabetic women are advised to consume carbohydrate containing food with low glycemic index (95). Unfortunately, we do not have any data on the GI of carbohydrates in our study.

Anyway, it seems to be better to include high quality carbohydrates with lower glycemic index and food containing lower fat. Replacement of lower glycemic index carbohydrates reduces the need for insulin and improves post-meal glycemia and maternal glucose and lowers infant birthweight in diabetic mother (94). The type of carbohydrate intake would be a factor in glycemic control rather than the amount of carbohydrate consumed. The carbohydrate should be distributed to maintain optimal glycemic control and to avoid hypoglycemia and ketonemia (95).

Intake of dietary fiber in the 1st and 2nd trimester was lower in mothers who delivered macrosomia babies in this study. Intake of 44 to 50 g/d of fiber in diet reported to improve glycemia, but usual fiber intake (up to 24 g/d) in the diet has not shown positive effects on glycemia (95).

Intake of omega 6 fatty acids during the 1st trimester was significantly low in women who had macrosomia babies (P: 0.027). According to a study in Korea, despite sufficient levels of omega-3 fatty acids, women who had high levels of omega-6 fatty acids delivered infants at low birth weight. Birth weight was inversely correlated with maternal omega-6 FA intake (93).

Premature birth in Norway is 5.5% but, in our study, it is 31%. We had no information for the reasons for premature birth in the cohort, it has been reported that polyhydramnios (excess amniotic fluid) is an independent risk factor for spontaneous premature birth in pre-gestational diabetes women (89). The mean z-score of birth weight was higher in premature babies than in babies who delivered at term. Women who delivered preterm babies had a higher mean HbA1c level than women who delivered term babies. Mean z-score birth weight could be higher due to worse metabolic control indicated by higher HbA1c level in preterm delivered mothers. Strict glycemic control during pregnancy reduces the risk of spontaneous preterm delivery (101).

Nutrition during pregnancy is the only way to provide the essential nutrients for fetal growth. An imbalance diet during pregnancy may be a vital factor linked with preterm birth (106). In our study, energy intake in 2nd trimester was significantly lower in preterm delivery mothers compared to normal delivery mothers (p- value: 0.003). Dietary intake in 2nd trimester was much lower than recommended by IOM and NNR (78). Low dietary intake in 2nd trimester was associated with preterm delivery, indicating that dietary intake may have been inadequate in these women. There is a case-control study in India suggests that low protein and energy intake during pregnancy is possibly associated with preterm delivery (102).

In addition to the total energy intake and carbohydrates, also the intake of saturated fatty acids in 2nd trimester was significantly lower in women who delivered preterm babies than women who delivered term babies (P: 0.007). This could be due to the restriction of fat intake to reduce maternal weight.

A case control study from China showed that women in preterm infants had lower intake of fat than women in full-term infants (107). Dietary intake of fat plays a role in preventing preterm births. A study of Poland found this result already (109).

Dietary fiber intake in 1st trimester in mothers with preterm delivery was significantly lower than mothers with at term delivery (p- value: 0.041). Increased soluble fiber improves blood glucose control and promotes regularity in diabetes mellitus and enhances insulin sensitivity (44). There are consistent but limited evidence indicates that certain food patterns during pregnancy are related with a lower risk of preterm birth. These protective food patterns are higher in fruits, vegetables, salad, whole grains. nuts, legumes, seeds, and fish and lower in red meat and processed meat products and fried foods. (108)

In general, the maternal diet must give an adequate supply of energy to support the mother's requirements as well as those of the growing fetus. While preventing maternal obesity is important to reduce the risk of macrosomia infants, and maternal and childbirth complications benefits of energy restriction must be judged against possible harms including intrauterine growth retardation.

Besides diet, other factors affect gestational weight gain and birth weight. Pregnant women who do regular exercise are expected to have an appropriate gestational weight gain and healthy birth weight infant. Regular physical activity reduces circulating blood glucose level. Proper energy intake, hydration is important before, during and after activity (103). There are many factors affecting weight gain during pregnancy including pre-pregnancy BMI, age,

parity, dietary practices, physical activity, physiological, social, and psychological factors (61).

The average intake of carbohydrates and added sugars were within recommended levels in this study. This may reflect the participant's awareness of carbohydrates and effects on blood glucose. Anyway, the mean intake of dietary fiber is of the lower limit of the recommended range (25-35 g /day) in 1st trimester, lower than the recommended requirement in 2nd trimester according to the guideline. According to this study, adequate intake of dietary fiber particularly during the 1st and 2nd trimester was associated with a lower z score of birth weight and increased gestational age at birth. Inadequate intake of dietary fiber is closely related to premature birth and large for gestational age babies. If enough fiber was eaten during the 1st and 2nd trimester, it would have reduced the chance of macrosomia baby. Dietary fiber slows the absorption of sugar and helps improve blood sugar levels, decreasing the chance of constipation, lower total blood cholesterol levels by lowering low-density lipoprotein, reducing weight by law calorie value (1-2kcal/ g), fibrous foods can also contain antioxidants (e.g.- oats, beans) (90). Adequate fiber intake in obese significantly promotes weight loss (44).

Intake of SFA E% is high, even though the intake of energy proportion of total fat was within the recommended range, the proportion of SFA exceeded the dietary recommendations in each trimester. Intake of PUFA was the lower half of the recommended range. A high intake of SFA is associated with high LDL - cholesterol concentrations. (99,78) There is strong evidence that replacing dietary SFA with unsaturated fatty acids, both MUFA and PUFA and carbohydrates from fiber-rich whole grains, protein from plant sources benefit cardiovascular health. (100)

Generally, mothers' weight, Hb1Ac is positively correlated with Z-score birth weight & negatively correlated with gestational age at birth. Hb1Ac is an indicator of average blood glucose level, but it may not reflect daily blood glucose variation that may reflect on pregnancy outcomes, such as hypo and hyperglycemia. Even though we have good health status, still there is a challenge for nutritionists and health staff to change the diet and lifestyle of women with PGDM. Pre-pregnancy care including planned pregnancy, controlling other diseases, glycemic control, and appropriate weight should be achieved to get a healthy pregnancy outcome. Pre-gravid and early prenatal dietary counselling encouraging healthy

dietary intake could improve pregnancy outcomes (104). Well-designed interventions and studies on how to implement the existing recommendations are most likely needed.

5. Conclusion

This study, one of the first to investigate dietary intake longitudinally during pregnancy. Even though the number of women were small, it is striking that the women did on average not increase their dietary intake from the 1st to 2nd trimester, and that the increase in 3rd trimester was much lower than recommended. Low dietary intake in 2nd trimester was associated with prematurity, which is an important pregnancy outcome. We propose that the dietary intake of women with pregestational diabetes should be better investigated and the focus should be on sufficient energy intake with maintaining metabolic control at the same time. More studies are required that investigate dietary intake in pregnant women with pre-gestational diabetes.

6. Recommendations

More research is required to understand the association of pre-conception dietary intake with birth weight, gestational age at birth in pre- gestational diabetic women.

A study of dietary intake, maternal lifestyle (especially physical activity) and glycemic control with pregnancy outcome in PGDM mothers will give interesting results.

A study of appropriate weight gain for women of PGDM with pre-pregnancy BMI.

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Appendix 1: List of Figures

Appendix 2: List of Tables