The Effectiveness of Real-Time Continuous Glucose Monitoring to Improve Glycaemic Control and Pregnancy Outcome in Patients with Gestational Diabetes Mellitus

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Synopsis

Introduction: Real-time continuous glucose monitoring (rt-CGM) systems provide users with information about current interstitial glucose levels and alert the patient before the upper or lower glucose threshold is reached or when glucose levels change rapidly. Hence, glycaemic excursions can be early identified and accordingly adapted by behavioural change or pharmacologic intervention. Randomized controlled studies adequately powered to evaluate the impact of long-term application of rt-CGM systems on the risk reduction of adverse obstetric outcomes are missing.

Study Design: Open-label multicentre randomized controlled trial with two parallel groups including a total of 372 female patients with recent diagnosis of GDM: n=186 with rt-CGM (Dexcom G6), n=186 with self-monitored blood glucose (SMBG). Following the recommendations for the evaluation of complex interventions, a health economic evaluation will be performed.

Visits: Women with GDM will be consecutively recruited at their first appointment after diagnosis (V1) and randomized to either treatment (rt-CGM augmented glucose monitoring) or control group (routine care SMBG) after a run-in period of 6-8 days at the second visit (V2). The third visit (V3) will be scheduled 8 to 10 days after V2 and further follow-up visits every two weeks. At every visit glucose measurements (SMBG or rt-CGM) will be evaluated by the medical staff and all patients will be treated according to the standard of care for patients with GDM. From V2 to V3 as well as once for ten days between gestational week 36+0 and 38+6 the control group will receive blinded CGM. Cord blood will be sampled immediately after delivery (VPP0). A postpartum examination will be scheduled within 48 hours after delivery (VPP1) for assessment of neonatal biometry and maternal HbA1c, as well as between 8 weeks to 12 months after delivery (VPP2) in all patients for a detailed re-examination of glucose metabolism including blinded CGM for 8 to 10 days in both groups.

Outcomes: Differences in the proportion of LGA newborns (birth weight >90. pct) in women with GDM using rt-CGM as compared to women with GDM using SMBG will be assessed as the primary outcome. Differences in neonatal hypoglycemia, rate of caesarean section, shoulder dystocia and neonatal anthropometry will be assessed as secondary outcomes. Further secondary outcomes are: differences in neonatal hyperinsulinemia, CGM measures such as mean interstitial glucose, glucose variability, time in range as well as time spent in hyper- and hypoglycemia (day- and night-time), duration and frequency of postprandial hyperglycaemic excursions, start and amount of glucose lowering therapy, HbA1c, change in bodyweight during pregnancy and after delivery, glucose disposal at postpartum (markers of insulin sensitivity, insulin secretion and β-cell function assessed by a postpartum OGTT), as well as health-related quality of life, and patients' risk- and time preferences and its association with adherence to dietary and exercise recommendations.

1. General Conditions

1.1. Scientific background of the study

The incidence of obesity and diabetes is rising worldwide even in younger populations. With a rise in maternal obesity also gestational diabetes mellitus (GDM) becomes more prevalent with a prevalence of up to 18% of pregnancies[1,2]. Previous studies found hyperglycaemia in pregnancy to be associated with gestational complications including macrosomia and neonatal hyperinsulinaemic hypoglycaemia[3] and an increased long-term risk for obesity or diabetes in the offspring's later life[4]. Large interventional trials provided evidence that obstetric and neonatal complications such as large for gestational age offspring (LGA, defined as birthweight >90 pct.) or shoulder dystocia can be significantly reduced through intensified treatment of even mild forms of maternal hyperglycaemia (e.g. by lifestyle modification or pharmacotherapy)[5–7].

Continuous Glucose Monitoring (CGM) has been shown to improve glycaemic control without increasing the risk of hypoglycaemia in patients with type 1 and 2 diabetes[8,9]. However, only a small number of studies evaluated the use of CGM in pregnancies affected by GDM: In the setting of a larger non-randomized observational study Yu et al.[10] found that mothers in the CGM group (using CGM for 72 hours every 2 to 4 weeks) had improved glycaemic control as well as a lower amount of glycaemic variability as compared to a control group using self-monitored blood glucose (SMBG). In addition, the CGM group showed lower birth weight percentiles associated with a lower risk for LGA offspring (13.7% vs. 25.8) or neonatal hypoglycaemia (5.5% vs. 14%). Also a second observational study including 57 pregnancies with GDM indicated that CGM was more effectively detecting hyperglycaemic episodes as well as nocturnal hypoglycaemia as compared to SMBG[11]. A study in 73 pregnant women with GDM, randomly assigned to either SMBG or CGM for a duration of 48h after diagnosis, found that CGM detected a markedly higher proportion of women requiring glucose lowering pharmacotherapy (31% vs 8%)[12]. Another randomized controlled trial on 106 women with GDM observed significantly lower weight gain associated with CGM. LGA cases were more often observed in the SMBG group (52.7% vs. 35.3%), however, the difference failed statistical significance as the study was not powered for obstetric outcomes[13].

Unfortunately, both randomized controlled studies used older versions of a blinded CGM device, where glucose values are not directly visible for patients. In contrast, more recently developed "real-time" CGM (rt-CGM) systems provide users with information about current glucose levels and alert the patient before the upper or lower glucose threshold is reached or when glucose levels change rapidly. Hence, glycaemic excursions can be rapidly identified and accordingly adapted by behavioural change or pharmacologic intervention. A number of studies including non-pregnant patients have shown superiority of rt-CGM over

older blinded CGM versions in order to effectively empower and educate patients with diabetes to better understand how dietary habits, exercise or pharmacotherapy affects their glucose levels[14]. A beneficial effect of rt-CGM in pregnancy was also supported by the CONCEPTT trial for pregnant women with type 1 diabetes[15]. Only one recent study compared SMBG with rt-CGM in women with GDM using a single application for 3–7 days within two weeks after diagnosis but it failed to demonstrate improvements in HbA1c or pregnancy outcomes, which was, however, likely due to the sample size and the short duration of intervention (single application)[16].

Taken together, larger randomized controlled studies adequately powered to evaluate the impact of long-term application of rt-CGM systems on the risk reduction of adverse obstetric outcomes are missing[17]. Of note, such studies are of high clinical relevance because of their guideline-changing potential. In addition, rt-CGM has the potential to reduce reported barriers to SMBG (such as inconvenience, pain or stigma of testing in public places) in order to improve poor reliability and adherence to glucose monitoring, which is a non-negligible problem in the treatment of GDM[18].

1.2. Specific Hypotheses

The main hypothesis of the proposed study is that rt-CGM can effectively reduce the risk for neonatal and obstetric complications. It is further hypothesized that rt-CGM can improve maternal glycaemic control, body weight gain during pregnancy and (as rt-CGM potentially improves self-management strategies) has beneficial long-term effects on maternal metabolism after pregnancy.

1.3. Primary and secondary outcomes

Primary objective: To assess differences in the proportion of LGA newborns (birth weight >90. pct) in women with GDM using rt-CGM as compared to women with GDM using SMBG.

Secondary objectives: To assess differences in further obstetric or neonatal complications, neonatal hypoglycaemia, rate of caesarean section, shoulder dystocia and neonatal anthropometry will be assessed as secondary objectives. Further secondary outcomes are: differences in neonatal hyperinsulinemia, rt-CGM measures such as mean interstitial glucose, glycaemic variability, time in range (65 to 140 mg/dl [3.6 to 7.8 mmol/l]) as well as time spent in hyper- and hypoglycaemia (day-time: 07.01 to 22.59hr and night-time: 23.00 to 07.00hr), duration and frequency postprandial hyperglycaemic excursions, start and amount of glucose lowering therapy, HbA1c, glycosylated fibronectin, hsCRP, proBNP, Troponin T, change in bodyweight during pregnancy and after delivery as well as glucose disposal at postpartum (markers of insulin sensitivity, insulin secretion and β-cell function assessed by a postpartum OGTT). Health-related quality of life (HRQoL) is a patient-reported outcome which has become

as important in the evaluation of interventions as patient-relevant clinical outcomes. Therefore, HRQoL will be elicited. In addition, a health economic evaluation in terms of cost-effectiveness and cost-utility analysis will be performed.

1.4. Expected effects on the advancement of clinical practice

The aim of this proposal is to assess the ability of rt-CGM to improve glycaemic control (reduction of mean glucose, hyperglycaemic episodes and duration, improvement of glycaemic variability) in order to prevent adverse pregnancy outcomes and neonatal complications in women with GDM. The results of this study will contribute to:

- the improvement of clinical monitoring and management of glucose metabolism during pregnancy with GDM
- increased knowledge about possible limitations of SMBG (routine care), such as undetected hyper- or hypoglycaemia, as well as to determine if comprehensive glucose data (as derived from CGM) results in more or fewer women needing pharmacotherapy
- possible improvement of adverse perinatal outcome and particularly fetal macrosomia in offspring of mothers with GDM

1.5. Cooperation arrangements relevant to the study

This study comprises international research cooperation:

- Dr. Andrea Tura from the Metabolic Unit, Institute of Neuroscience, National Research Council (CNR), Padova, Italy, will provide intellectual support, and perform analyses of metabolic data assessed from CGM and oral glucose tolerance tests.
- Prof. Dr. Michael Roden, Director of the German Diabetes Center, the Leibniz Center for Diabetes Research and of the Division of Endocrinology and Metabolic Diseases at the Heinrich-Heine University, Düsseldorf, Germany, and his team will provide intellectual support as well as input in design and data analysis and will be responsible for supervision of patient recruitment and management.
- Prof. Dr. Tanja Fehm, Director of the Department of Obstetrics and Gynaecology at the Heinrich-Heine University, Düsseldorf, Germany, and her team will provide intellectual support and will be responsible for supervision of patient recruitment and management.
- Ass.-Prof. Dr. Petra Rust, Department of Nutritional Sciences, University of Vienna and her team will perform dietary assessments during the trial.
- Prof. Dr. Irene Hösli, Director of the Division of Obstetrics, Department of Obstetrics and Gynaecology, University Hospital Basel, Basel, Switzerland and Dr. Evelyn Huhn, Dr. Katharina Redling, Dr. Katharina Geissler, will provide intellectual support and will be responsible for supervision of patient recruitment and management at their Department.

- Prof. Johan Jendle, MD PhD, Senior Consultant at Örebro University Hospital, Örebro, Sweden and his team will provide intellectual support as well as input in design and data analysis and will be responsible for supervision of patient recruitment and management.
- Prof. Andrea Icks MD PhD MBA, Director of the Institutes of Health Sevices Research and Health Economics at the German Diabetes Center and the Heinrich Heine University Düsseldorf, and her team will provide intellectual support and will perform analyses of HRQoL and preference data as well as the health economic evaluation.
- Prof. Dr. Wolfgang Henrich, Director of the Clinic of Obstetrics, Charité Berlin and his team will provide intellectual support and will be responsible for supervision of patient recruitment and management at his clinic.
- Prof. Dr. Tanja Groten, Director of the Clinic of Obstetrics, University Hospital Jena and her team will provide intellectual support and will be responsible for supervision of patient recruitment and management at her clinic.
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2. Research Design and Methods

2.1. Participants and recruitment; Exclusion criteria

This study is designed as an open-label multicentre randomized controlled trial with two parallel groups including a total of 372 female patients (n=186 with rt-CGM, n=186 with SMBG) with recent diagnosis of GDM. Diagnosis of GDM (i.e. diabetes first diagnosed in second and third trimester and not clearly type 1 or type 2 diabetes[19]) is made in accordance with the IADPSG criteria after 24+0 weeks of gestation by a 2h 75g OGTT[20]. If the GDM diagnosis is made before 24+0 weeks of gestation in accordance with the local guideline (i.e. when IADPSG cut-offs for fasting and post-load glucose are exceeded) patients can be included if no insulin treatment was started until 24+0 [21]. The study will be conducted at four tertiary referral centres in Austria, Switzerland, Sweden and Germany. All pregnant females (aged between 18 and 55 years) will be consecutively recruited after diagnosis of GDM until 31+6 weeks of gestation among women visiting the pregnancy outpatient departments (Division of Obstetrics and feto-maternal Medicine, Medical University of Vienna; Division of Obstetrics, University Hospital Basel, Clinic of Obstetrics, Charité Berlin, Clinic of Obsetrics, University Hospital Jena) or the diabetes outpatient departments (Division of Endocrinology and Metabolic Diseases at the Heinrich Heine University, Düsseldorf; Department of Medicine, University Hospital, Örebro).

Exclusion criteria are:

Overt diabetes (i.e. pregestationally known type 1 or type 2 diabetes or fasting plasma glucose during the OGTT ≥126 mg/dl [7.0 mmol/l] or HbA1c ≥6.5% [44 mmol/l] or 2h post-load OGTT levels ≥200 mg/dl [11.1 mmol/l] assessed before 24+0 weeks of gestation, whereby results need to be confirmed by repeated testing in case of unequivocal hyperglycemia according to the ADA standards[19]); History of bariatric surgery or other surgeries that induce malabsorption; Long-term use (>2 weeks) of systemic steroids prior to enrolment; Multiple pregnancy; Patients already using glucose lowering medications (metformin or insulin) before study entry; fetal growth restriction due to placental dysfunction at study entry; Inpatient psychiatric treatment up to 1 year before enrolment; Participation in this study in previous pregnancy;

2.2. Study visits pregnancy

A broad risk evaluation will be performed in participating females at the initial contact (V1) including: evaluation of maternal age, parity, history of GDM in previous pregnancies, detailed family history, ethnicity, preconceptional diseases, obstetric history. Height (stadiometer measured to the nearest centimeter) and actual weight (calibrated scales, no clothes) will be additionally assessed. Moreover, an evaluation of preconceptional weight (self-reported) and BMI as well as measurement of blood pressure will be performed. All patients receive medical nutrition therapy (isocaloric diet containing 40-50% carbohydrates, 20% proteins and 30-35% fat, divided into three meals and three snacks) and lifestyle advice for 30 minutes following international recommendations and are advised on capillary blood glucose measurement (fasting as well as 1h after starting each meal) at the initial visit (V1). Randomisation will be done after a run-in period of 6 to 8 days (V2). The run-in period is omitted for patients who had a diagnosis of GDM before 24+0 according to the local guidelines and already received medical nutrition therapy, lifestyle intervention and advices on capillary blood glucose measurements. The third visit (V3) will be scheduled 8 to 10 days after V2 and further follow-up visits every two weeks (i.e. 12 to 16 days after each visit). HbA1c and glycosylated fibronectin, hsCRP, proBNP, Troponin T, will be assessed at V2 as well as at the first visit between 36+0 and 38+6 weeks of gestation (12 ml, non-fasting state) (V4). Detailed fetal ultrasound examinations, a detailed examination of dietary intake as well as a blinded CGM (control group only) will be performed at V2 and V4. Body weight change and use of glucose lowering medications (amount of insulin units) will be examined at every visit. At every follow-up visit glucose measurements (SMBG or rt-CGM) and routine ultrasound examinations (fetal biometry and umbilical artery doppler) will be evaluated by the medical staff and all patients will be treated according to the standard of care for patients with GDM. This includes lifestyle modification and insulin therapy if recommended thresholds are exceeded. Both groups will be treated to be in the target range between 65 to 140 mg/dl [3.6 to 7.8 mmol/l] with at least 8h fasting glucose levels equal or below 95 mg/dl [5.3 mmol/l] and 1h postprandial glucose

measurements equal or below 140 mg/dl [7.8 mmol/l] in accordance with the CONCEPTT study[15] and the ADA recommendations[22], respectively. Intermediate acting neutral protamine Hagedorn (NPH) insulin is started in the evening if ≥2 measurements of fasting glucose are equal or above 95 mg/dl [5.3 mmol/l] in a period of one week and rapid acting insulin analogues (Aspart or Lispro) if ≥2 measurements of 1h postprandial glucose (either after breakfast, lunch or dinner) are equal or above 140 mg/dl [7.8 mmol/l] in a period of one week. NPH is started with 6 to 10 IU and increased by 4 IU (or in case of higher doses i.e. >25 IU by 20%) and rapid acting insulin is started with 2 to 4 IU and increased by 2 to 4 IU if thresholds are not achieved within three days. Long acting insulin analogues such as glargine (U100/U300) or detemir can be used as an alternative to NPH if necessary. Patients are trained on insulin management and titration according to their glucose levels. Metformin can be used according to local practice guidelines (recommended in Sweden but not in Austria, Germany or Switzerland as first-line pharmacological intervention).

2.3 Study visits postpartum

Cord blood will be sampled and stored (at -80°C) immediately after delivery (VPP0). A postpartum examination will be scheduled within 48 hours after delivery (VPP1) for assessment of neonatal parameters and maternal HbA1c and glycosylated fibronectin, hsCRP, proBNP, Troponin T, (12 ml, non-fasting state), as well as between 8 weeks and 12 months after delivery (VPP2) in all patients for a detailed re-examination of glucose homeostasis at postpartum (including lifestyle and dietary pattern as well as HbA1c, glycosylated Fibronectin, hsCRP, proBNP, Troponin T, as well as a blinded CGM for 10 days and an OGTT to assess the presence of prediabetic conditions after pregnancy with GDM). The postpartum OGTT is further used to provide estimates of insulin sensitivity, β-cell function and hepatic insulin extraction, the major physiological components of impaired glucose tolerance.

2.4. Randomisation

Participants will be randomized to either treatment (rt-CGM augmented glucose monitoring) or control group (routine care SMBG) in a 1:1 ratio. The minimisation method[23] with a 0.85 assignment probability will be used to minimize the imbalance between the groups according to week of gestation at study entry i.e. at V1 (three strata: 24+0 to 25+6, 26+0 to 27+6, 28+0 to 29+6, 30+0 to 31+6), previous pregnancy with GDM (two strata: yes or no) and preconceptional overweight/obesity status with three strata: i. normal weight (i.e. BMI below 25.0 kg/m²); ii. overweight (BMI 25.0 – 29.9 kg/m²); iii. obesity (BMI equal or above 30.0 kg/m²). Randomisation will be performed at the second study visit (V2) by using the “MUW Randomizer” software.

2.5. Intervention

Patients randomized to the intervention group will be equipped with a rt-CGM sensor (Dexcom G6 sensor, a small flexible device that records interstitial glucose levels every five minutes) at V2. The sensor will be inserted into the subcutaneous tissue of the anterior abdomen wall (if this location is not tolerated by the pregnant patients, the upper buttock or posterior upper arm may be used instead). Additionally, patients will be advised to record capillary blood glucose values if glucose alerts or readings do not match with symptoms or expectations. Participants will be educated how to exchange the sensor (has to be exchanged every ten days) and will be equipped with a real-time CGM monitor and instructed in its use. The monitor provides the user with information about current glucose levels and notifies the patient before she reaches her upper or lower glucose threshold and when glucose levels change rapidly. All patients in the intervention group will specifically trained how to use the system. As an alternative to the real-time monitor the patients' smart phone with an anonymized access to the CLARITY® mobile app can be used (details see below: "Intervention: Device description").

2.5.1. Intervention: Device description

The Dexcom G6 intended use is for the management of diabetes in persons aged 2 years and older. The Dexcom G6 System is intended to replace fingerstick blood glucose testing for diabetes treatment decisions. Interpretation of the Dexcom G6 System results should be based on the glucose trends and several sequential readings over time. The Dexcom G6 System also aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments. The Dexcom G6 System can be used alone or in conjunction with these digitally connected medical devices for the purpose of managing diabetes.

The system consists of a sensor, transmitter, receiver, and mobile app. The sensor is a small, flexible wire inserted into subcutaneous tissue where it converts glucose into electrical current. The sensor incorporates an interferent layer that minimizes the effect of potential electroactive interferents, such as acetaminophen, by preventing it from reaching the sensor wire surface. The benefit of this interferent layer in blocking the effects of acetaminophen prevents falsely high glucose readings. Thus, users may ingest acetaminophen while wearing the G6 CGM system. The transmitter, which is connected to the sensor and worn on the body, samples the electrical current produced by the sensor and converts the measurement into a glucose reading using an onboard algorithm. The receiver and/or the app displays the glucose reading along with a rate of change arrow and a trend graph. Additionally, the receiver and/or app issues alarms and alerts to notify the patient of glucose level changes and other important system conditions. The app provides the additional capability to share data with "followers"

using the Dexcom Share service. The receiver can be put into a blinded mode using CLARITY® software. In this mode, users are unable to see the CGM data or receive CGM alerts.

CGM Ancillary Devices Dexcom CLARITY® is an accessory to users of the Dexcom CGM system. It is a software program that allows the transfer of glucose data from the CGM system to Dexcom remote servers for data management to allow use of the CGM data by the user and study clinicians. Target ranges of 60 to 140 mg/dl [3.3 to 7.8 mmol/l] will be set and the patients will be introduced in the use of alarm settings. Both participants and study sites will use CLARITY® to transfer glucose data between user and study site, whether CGM is used in blinded or real-time mode. A CLARITY® mobile app can be used for retrospective review of glucose data on the smart device and can also be set up to allow receipt of push notifications of CGM data facilitating weekly data review. For all patients (intervention and control group) an anonymized CLARITY® account will be created by using a sequential study number which is allocated at randomization (sex will be female and birth date for each account will be set to 1.1.1990 for all accounts).

2.5.2 Intervention: Study proceedings

1. For participants that have a supported phone, the G6 CGM app will be installed on participant's smart phone.
2. An anonymized CLARITY® mobile account will be set up and linked to the research site.
3. Participants will use CGM data for their diabetes management.
5. A high alert threshold will be set at 140 mg/dl [7.8 mmol/l]. Low alert threshold and urgent low soon alerts will be turned off. If participants require insulin, the low alert will be turned on and the threshold set at 65 mg/dl [3.6 mmol/l]. In addition, the urgent low alert (55 mg/dl [3.1 mmol/l]), the urgent low soon alert (when glucose levels are falling fast and will be below 55 mg/dl [3.1 mmol/l] in less than 20 min) as well as alerts for rise and fall rate (3 mg/dl [0.17 mmol/l]) in addition to alerts for signal loss and no readings for more than 20 min will be enabled.
6. Participants with applicable smart phones may have CLARITY® push notifications on the CLARITY® mobile app about weekly time in range comparison enabled during the study.
7. For app users, the "Share and Follow" functionality will be discussed and encouraged (i.e. the study participants are able to invite followers to review their glucose levels).
8. For participants using the receiver only, the receiver will be downloaded into the CLARITY® clinic account at each visit.
9. For participants using real-time CGM data summary will be downloaded for documentation at V3 and V4 (between 36+0 and 38+6) as well as after delivery (VPP1)
10. The research team will review the CGM in CLARITY® to inform lifestyle and therapy recommendations.

11. The Dexcom G6 system will not be calibrated during the study period.

2.5. Control group

The control group participants will perform self-monitored blood glucose testing with a study-provided blood glucose meter, including testing supplies. They will perform capillary blood glucose monitoring as routinely used for patients with GDM, i.e., at least four capillary blood glucose values daily including measurements at fasting as well as 1h after starting each meal by using a routinely available blood glucose measurement device. The study participants will keep a log book of their glucose values, which will be reviewed by clinicians from the study team at each visit and used for lifestyle and dietary recommendations as is routinely done in clinical practice. From V2 to V3 as well as once for ten days between 36+0 and 38+6 the control group receive blinded CGM; neither patients nor the treating medical staff will have access to the data recorded by the CGM sensor at this point in time. Instead, patients will control blood glucose levels based on SMBG, as is the routine procedure in current GDM treatment. Otherwise, the control group will receive the same study assessments as the intervention group. The blinded CGM will be removed and returned to Dexcom after the 10 day wear period after CGM data is uploaded to CLARITY® by an unblinded investigator who must not communicate about the results with patients or medical staff.

Each participant in the control group will be assigned a study blood glucose meter to measure and store their blood glucose values during the study. Therefore, the Contour® Next One system will be used. The meter has CE Mark clearance and is commercially available in Europe. Participants will receive an ample supply of meter test materials based on quantities routinely used. A commercially available desk-top software (Diabass® Pro), used in conjunction with Contour® Next One system glucose meter for blood glucose monitoring, will be utilized for downloading the meter data by the sites at V3 and V4 after checking that dates and times are correct.

Blood glucose meters used by the control group will be assessed to establish frequency of testing (overall and per week) as well as percentage of days with lower than four measurements per day.

2.6. Analyses of CGM data

CGM data allows a detailed examination of the percentage of time in which glucose levels are in target range (65 to 140 mg/dl [3.6 to 7.8 mmol/l]), hyperglycaemic episodes (glucose ≥140 mg/dl [7.8 mmol/l]) as well as mild (<65 mg/dl [3.6 mmol/l]), moderate (≤54 mg/dl [3.0 mmol/l]) or severe hypoglycaemic episodes (requiring third party assistance) and their duration. To this purpose, several indices of the glucose control quality will be calculated, such as GRADE (Glycaemic Risk Assessment Diabetes Equation), some indices of hypoglycaemia and

hyperglycaemia, and indices assessing the risk associated to both low and high glycaemic values, such as IGC (Index of Glycaemic Control) and ADRR (Average Daily Risk Range)[24]. Glycaemic variability will be also assessed, which can be quantified by standard deviation of the CGM data, or by more sophisticated indices, such as MAGE (Mean Amplitude Glucose Excursions), CONGA (Continuous Overlapping Net Glycaemic Action), Lability Index[24], as well as further indices that we developed internally, such as the Shape Index[25]. These will be compared between real-time CGM users and controls (i.e. from data obtained during the blinded CGM wear).

2.7. Assessment of dietary patterns

Dietary patterns will be assessed in all patients at V1, VPP1, and VPP2 via a published and validated Food-Frequency-Questionnaire (FFQ) proposed by the German Robert Koch Institute[26]. It was also previously used for the German DEGS project (www.degs-studie.de). Information from the FFQ will be analyzed quantitatively or summarized by eating scores proposed in the literature (such as the Healthy Eating Index 2010 or Alternate Healthy Eating Index 2010) reflecting diet quality based on actual guidelines[27,28]. In addition, all patients will be advised to conduct a nutritional protocol (seven days) from V2 to V3 as well as once at V4 (between 36+0 and 38+6 weeks of gestation). In a subgroup (only study site Vienna) dietary intake will also be assessed by performing 24-h-recalls by trained interviewers at V2, V4 and postpartum (VPP2): one face-to-face interview (approx. one hour) and the others as telephone interviews (approx. 30 minutes) during which data are entered simultaneously in GloboDiet. GloboDiet is a computerized program which was developed by the International Agency for Cancer Research (IARC) within the framework of the European Prospective Investigation into Cancer and Nutrition Study (EPIC-Study) for the conduction of harmonized and standardized 24-h-recalls[29]. This open-ended software was used in numerous previous studies and was validated within the EFCOVAL project[30–32]. In brief, GloboDiet is an interview-based dietary assessment instrument that allows obtaining a very detailed description and quantification of foods, recipes, and supplements consumed in the course of the preceding day and thus standardising data within and between countries. Probing questions and entering consumed foods in chronological order support the respondent's memory. The standardized structure prescribes – on the food group level – possibilities of description and quantification of food items to choose from. Quantification of consumed foods is supported by the GloboDiet picture book that comprises coloured photographs of foods in different portion sizes, photographs of familiar household measures and schematic displays of forms (e.g. bread, cake). The software provides an automatic coding of food items and recipe ingredients as well as a rough calculation of nutrient intake meant for quality control of the interview. GloboDiet is characterised by the obtained standardization of dietary data within Europe, a large number of

available foods and recipes, and a very detailed description of consumed foods. Currently, GloboDiet is one of the few dietary instruments providing comparable nutritional data within Europe. After finalisation of the interviews, GloboDiet will be linked to the local nutrition database – the Bundeslebenmittelsschlüssel (BLS) enhanced by the Austrian Nutrition Table (Österreichische Nährwerttabelle, ÖNWT), containing typical Austrian foods and recipes – allowing analyses on food ingredients level and to conduct risk assessment.

2.8. Assessment of physical activity

Physical activity will be assessed at V1, VPP1, and VPP2 via the International IPAQ (Physical Activity Questionnaire, long form). The IPAQ represents a well-accepted, validated instrument for monitoring population levels of physical activity in different settings and countries[33]. It will be analysed via published guidelines for data processing and analysis at the IPAQ homepage Guidelines for data processing and analysis of the international physical activity questionnaire (IPAQ)[34]: In short, collected data will be summarized as median MET (metabolic equivalent of task) minutes per week, representing a continuous score for walking, moderate intensity activities, vigorous intensity activities and total activities, as recommended. In addition, the Pregnancy Physical Activity Questionnaire (PPAQ) will be performed to capture information on physical activity participation and sedentary behaviour during pregnancy[35].

2.9. Assessment of maternal intramyocellular and intrahepatocellular lipids

Intramyocellular (IMCL), and intrahepatocellular lipids (HCL) will be measured in a subgroup of 40 patients (20 rt-CGM, 20 SMBG) at V3 and after delivery (VPP2) based on previously described methods[36–38]. The participants will be studied in supine position within the nuclear magnetic resonance (NMR) spectrometer. For IMCL measurements the calf muscle (right leg) will be positioned in a quadrature bird cage ^{1}H volume coil. A circular ^{1}H surface coil will be positioned over the liver for HCL measurement. Patients will be positioned with a left pelvic tilt to avoid pressure on the inferior vena cava according to other studies in pregnancy[39]. Magnetic resonance measurements will be performed on a 3.0-T Siemens or Philips System. NMR spectrometry is a non-invasive technique to evaluate metabolic physiology and was shown to be safe and well tolerated by pregnant women in previous studies[39,40].

2.10. Fetal biometry

Parameters of fetal anthropometry as determined by ultrasound as well as neonatal data including length, weight, gestational age at delivery will be included in the final analysis. A detailed fetal ultrasound examination will be performed at V2 and repeated at V4 (between 36+0 to 38+6 weeks of gestation) to assess fetal growth parameters including head circumference, biparietal diameter and abdominal circumference and abdominal fat thickness,

femur length (measured and expressed as standardized gestational age related fetal growth percentiles [41]), amnion fluid index as well as size and location of the placenta and fetal subcutaneous tissue thickness. Moreover, fetal growth symmetry will be assessed by fetal head to abdomen circumference ratio and fetal doppler measurements (mainly umbilical artery and middle cerebral artery[42] and ductus venosus). Furthermore, fetal hepatic size (all hepatic diameters, such as area and volume) and umbilical venous volume flow and an echocardiac examination of the fetus will be performed in a subgroup (only study site Vienna).

2.11. Obstetric Outcome

Obstetric outcome (caesarean section, birth injury, preterm birth before 37 completed weeks of gestation) stillbirth, small for gestational age (birth weight <10. Pct), large for gestational age infant (birth weight >90. Pct), shoulder dystocia, admitted to neonatal intensive care unit umbilical cord blood pH, APGAR score) will be recorded immediately after delivery. Length of hospital stay for mothers and offspring as well as duration of high-level neonatal care, respiratory distress, fetal hyperbilrubinemia and neonatal death ≤28 days will be further assessed. Calculations of age and sex adjusted percentiles will be performed by using international anthropometric standards according to those used in the CONCEPTT study[43]. Neonatal hypoglycaemia is defined as local blood glucose ≤31 mg/dl [1.7 mmol/l] in the first 24h after delivery and ≤45 mg/dl [2.5 mmol/l] after the first 24h after delivery or treatment with glucose infusion according to the HAPO study[3]. Additional anthropometric measures of the offspring include: head, shoulder and abdominal circumference, length, upper and lower arm and leg circumference and skin fold measurements (suprailiac and subscapular, triceps, quadriceps) in accordance with previous studies[44–46]. Thereby Skinfold measurements will be performed by using a validated instrument (Harpenden Skinfold Caliper) within 48h after delivery (VPP1).

2.12. Assessment of cord blood

17 ml cord-blood (1x8 ml serum and 1x9 ml EDTA) will be taken immediately after delivery to examine cord-blood glucose, insulin and C-peptide.

2.13. Postpartum OGTT

The OGTT will be performed at VPP2 (i.e. 8 – 16 weeks after delivery): after collecting blood samples for measurements of glucose (2 ml blood), insulin and C-peptide (3 ml blood) in the fasting state (at least 8 hours), participating females will receive a standardized 300 ml 75g glucose. Further blood samples of glucose, insulin and C-peptide measurements will be taken at 30, 60, 90, and 120 minutes. Insulin sensitivity during the OGTT will be assessed by the oral glucose insulin sensitivity index (OGIS) according to[47]; this quantifies dynamic glucose

clearance per unit change of insulin. The more recently developed PREDIM index will be used in addition[48]. As an approximation for hepatic insulin resistance the homeostasis model assessment of insulin resistance (HOMA-IR) will be used. Insulin secretion will be calculated by using the C-peptide deconvolution method[49]. β-cell function parameters, such as pancreatic glucose sensitivity and rate sensitivity, and potentiation of insulin secretion, will be computed through mathematical modelling[49].

2.14. Assessment of health-related quality of life and patients' preferences

Health-related quality of life will be elicited using the SF36 and the EQ-5D-5L[50]. It can be expected that adherence to life style and dietary recommendations are associated with risk and time preferences. Hence, risk and time preferences will be elicited based on lottery approaches[51,52]. Regarding risk preferences, participants will be asked to choose between two hypothetical lotteries that differ in expected outcomes which enables us to derive an individual classification of the risk type, i.e. risk-averse, risk-neutral or risk-loving. Time preferences will be elicited in a similar lottery framework whereat participants are faced with a trade-off between lower benefits now or higher benefits later on. Time preferences allow us to classify participants according to present-biased individuals and patient ones. Quality of life as well as risk and time preferences will be assessed at V1, VPP1, and VPP2. Obstetrical patient's satisfaction will be additionally assessed at VPP1 by using the Wijma score[53].

2.15. Health economic evaluation

For the evaluation of a complex intervention, a health economic evaluation is recommended as well [54,55]. In this study, a cost-effectiveness and a cost-utility analysis will be performed from the perspective of the health insurance. Effect measures will be avoided cases of LGA newborns as well as quality-adjusted life-years (QALYs). QALYs will be calculated using the SF36 assessment and the SF-6D[56] that derives preference-based scores from the SF-36 by using population-based preferences (utilities) for the SF-36 health states. Intervention costs as well as health care costs (direct costs) will be calculated. For the elicitation of health care use a validated instrument will be used[57]. Health care use will include e.g. clinical visits for the mother and associated procedures during trial and after delivery, inpatient stays, office-based visits, medication, glucose monitoring supplies and devices. Costs will be estimated and considered from the perspective of the health insurance. Since the evaluation covers only the observation period alongside the trial, costs and effects will not be discounted. Outcomes are incremental cost-effectiveness and cost-utility ratios (ICER/IUCR: additional cost per additional LGA newborn avoided or per quality-adjusted life year gained).

3. Sample Size and Statistical Analysis

3.1. Sample size

With a sample size of n=338 (169 women per group) we will be able to detect a difference between two independent proportions of LGA of 13.7% vs 25.8% (according to the results of a previous study[10]) with a power of 80% and a two-sided type 1 error of α=0.05 (calculated for Pearson's chi-square test). Considering a drop-out rate of 10% a total sample size of n=372 (186 women per group) is necessary for this study. This is in line with the sample size suggested by Kestilä et al.[12]. A blinded sample size review (the proportion of LGA cases in the sample is reviewed) and adaptation is planned after 50% of the patients have been investigated. The sample-size calculation was performed by using the software G*Power (V3.1.9.2)[58].

3.2. Analysis plan

Analyses should be conducted on the intention-to-treat principle. Categorical variables will be summarized by counts and proportions; continuous variables data will be summarized by means and standard deviations (SD) or by median and interquartile range in the case of strong deviations from the normal distribution. Pearson's chi-square test will be used to compare differences in the primary outcome (difference in proportion of LGA newborns) and for binary secondary outcomes (such as caesarean section rate, shoulder dystocia and neonatal hypoglycaemia). Bernard's test will be used as an alternative if an expected frequency in contingence tables is equal or less than 5 and the Cochran-Mantel-Haenszel method will be used as sensitivity analysis to adjust for possible center specific effects. Continuous secondary outcome parameters (such as mean glucose, duration and amount of hyperglycaemia, glycaemic variability and other CGM measures, postpartum OGTT data, HbA1c, glycosylated fibronectin, hsCRP, proBNP, Troponin T, or anthropometric data of the newborn) will be compared by student's t-test. Rank based inference (such as the Brunner-Munzel test[59]) will be used as an alternative in case of skewed distributed parameters. The association between HbA1c, CGM measures and delivery and risk of LGA offspring will be assessed by binary logistic regression. There are many possible objectives for which analysis could be performed in this study (e.g. functional principal components analysis for CGM data). Hence, the present analysis plan represents only a selection of methods, which will be used for analysing the main objectives. Risk and time preferences will be analysed by non-parametric and parametric methods. In particular, we plan to fit the choice data to a CRRA (constant relative risk aversion) utility function. Associations between risk and time preferences and behaviour (dietary patterns and physical activity) will be investigated. For the health economic evaluation, incremental cost-effectiveness and cost-utility ratios (ICER/IUCR: additional cost per additional LGA

newborn avoided or per quality-adjusted life year gained) will be calculated. 95% confidence intervals will be analysed using bootstrap procedures[60]. To consider uncertainty, univariate and probabilistic sensitivity analyses will be performed and cost-acceptability curves will be created[61]. A two-sided p-value ≤0.05 is considered statistically significant. All analyses will be performed by using the statistic software R and contributing packages[62]. No further adjustment for multiplicity is planned for this study.

4. General rules and provisions

4.1. Ethical aspects

The present study will be performed in accordance with the current guidelines of the Declaration of Helsinki following the criteria of Good Scientific Practice. The study protocol will be evaluated and approved by the local ethics committees. Subsequent amendments to the Protocol will be submitted to the Ethics Committee for review. All participating patients will be informed about possible complications. Their consent to participate in the study is noted by the signature (and date) on the consent form.

4.2. Legal regulations and provisions relevant to the study, in particular the requirements of good clinical practice (GCP), good manufacturing practice (GMP), as well as good laboratory practice (GLP), Quality assurance and Data security and Monitoring

The principle investigators will be regularly informed about the progress of the study and will be instructed immediately in cases of problems and uncertainties. Any complication with possible connection to study participation will be declared to the Ethical Commission within 24 hours. Statistical analyses are based on the allocation of a continuously registered individual number, which is indirectly personalized and can only be decoded by the principle investigators. Every investigator is bound to secrecy. An electronic CRF will be provided by the KKS (Koordinationszentrum für Klinische Studien), the Medical University's monitoring facility. In addition, the KKS will support the project by providing, quality control, query management, data close out.

4.3. Data protection

A transfer of the data, in particular to the contractual partner (Dexcom, Inc., California, USA), takes place only in encrypted or anonymous form. For any publications, only the encrypted or anonymized data will be used. The manufacturer of the medical device (Dexcom) has access to anonymised encrypted clinical data, such as glucose readings, therapy, or size and weight. As well as insight into clinical data of the study participant's child (height, weight,

Task	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Sample Acquisition																			
Data Collection																			
Data analysis																			
Dissemination of results																			

measurements of the head, arm, forearm, thigh and calf of your child or complications at birth). However, identification is not possible on the basis of this data.

5. Timeline

Gantt chart of timeline and assigned tasks in the 48 months of the project. Colors represent individual contributors of principal investigator and co-applicants. CSG (yellow); MR (blue); AT (red)

6. References

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