CLINICAL STUDY PROTOCOL

Effect of intensive nutrition training, education, and support versus standard care in reducing the need for insulin therapy in gestational diabetes (INTENSE-GDM): A randomised controlled trial

Short title: The INTENSE-GDM Trial

Trial site
Steno Diabetes Center Copenhagen (SDCC)
Borgmester Ib Juuls Vej 83, 2730 Herlev
Denmark

Version 2.0

The study protocol has been prepared according to the National Ethics Committee's guidelines for clinical trials

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3 Abbreviations and definitions of terms

BMI	Body Mass Index
Clinically relevant differences	Definitions of clinically relevant differences for all hypothesis-related outcomes will be reported in a statistical analyses plan (SAP). The SAP will be written and uploaded to clinicaltrials.gov before the statistical analyses will be conducted.
DDQOL	Diabetes Diet-related Quality of Life
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EMR	Electronic Medical Record
GA	Gestational age
GDM	Gestational Diabetes Mellitus
HbA1c	Glycosylated haemoglobin A1c
HCCQ	Health Care Climate Questionnaire
Jaundice	Neonatal jaundice or neonatal hyperbilirubinemia is defined as elevated total serum bilirubin (TSB) (>68-137 µmol/l) and clinically manifests as yellowish discoloration of the skin, sclera, and mucous membrane.
LGA	Large for gestational age
Macrosomia	Macrosomia or foetal overgrowth is defined as birth weight >4,500 g
Neonatal hypoglycaemia	Neonatal hypoglycaemia is defined as plasma glucose level < 2.5 mmol/l after the first 2 postnatal hours.
NICU	Neonatal Intensive Care Unit
Non-white ethnic minority background	Non-white ethnic minority groups are defined as groups belonging to minority populations of non-European origin characterised by their non-white status. These include Asian (Indian, Pakistani, Bangladeshi, Chinese, any other Asian background), Caribbean, Black, African, Middle East, Hispanic/Latino, and any mixed or multiple ethnic background (1).
OGTT	Oral Glucose Tolerance Test.
PCDS	Perceived Competence in Diabetes Scale
PPAQ	Pregnancy Physical Activity Questionnaire
Preeclampsia	Preeclampsia is defined as new-onset gestationel hypertension (with a blood pressure ≥140/90 mmHg after 20 weeks of gestation in combination with proteinuria (≥0.3 g protein in 24-hour urine specimen or (≥0.1 g protein in a midstream urine spot), pulmonary oedema and/or specific symptoms of significant end-organ dysfunctions (e.g., headache, nausea, vomiting).
Preterm birth	Preterm birth is defined as GA less than 37 completed weeks
SD	Standard deviation
SGA	Small for gestational age
SOP	Standard operational procedure
Telemedicine	Telemedicine consultations are defined as tele- or video consultation
V	Visit
White ethnic background	White origin is defined as people with European ancestral origins who identify, or are identified, as white (also called European, or in terms of racial classifications, the group known as Caucasian). The term derives from the concept of race but is used as an indicator of ethnicity(1).
WHO-5	The WHO-Five Wellbeing Index (WHO-5) to assess wellbeing

4 Introduction

4.1 Background

4.1.1 Prevalence and ethology

The prevalence of gestational diabetes (GDM) is increasing in parallel with the global epidemic of obesity, both worldwide and in Denmark. GDM now affects around 6% of all pregnancies in Denmark (2), and 14% of pregnancies worldwide (standardised estimation) ranging from 8% in North America and Europe, 10% in South and Central America, 14% in Africa, 21% in South-East Asia to 28% in Middle East and North Africa (3). Higher risks of GDM have been reported in immigrants from Non-Western countries living in Denmark , reflecting ethnic differences in the prevalence of GDM (4).

GDM is defined as glucose intolerance with onset or first recognition during pregnancy (5). The disease is characterized by hyperglycaemia and a marked insulin resistance secondary to placental hormonal release (6). Risk factors for developing GDM in pregnancy include obesity, excessive gestational weight gain, previous GDM, glucosuria, family history of diabetes, ethnicity, and hypertension (6). Hyperglycaemia is associated with serious short- and long-term complications for mother and child including delivering large-for-gestational-age (LGA) babies, macrosomia (birth weight >4,500 g), preterm birth, caesarean section, preeclampsia, birth injury (e.g., shoulder dystocia), respiratory distress syndrome, neonatal hypoglycaemia, jaundice, and increased admission to neonatal intensive care unit (NICU) (7). Finally, hyperglycaemia during pregnancy also increases the long-term risk of obesity, type 2-diabetes (T2D), and cardiovascular disease both in the mother and the offspring later in life (6).

4.1.2 Dietary therapy

First-line treatment in GDM after diagnosis is dietary therapy including a systematic and detailed dietary assessment to identify relevant areas for adjusting the diet and overall lifestyle (e.g., increasing physical activity). The overall goals with dietary therapy are 1) To provide adequate calories and micro- and macronutrients to meet the needs of pregnancy consistent with maintaining normoglycaemia, 1) To improve glycaemic control; and 3) To secure appropriate gestational weight gain and avoid excessive weekly gestational weight gain (6, 8). In addition to dietary therapy, women are trained in self-monitoring blood glucose (SMBG) to assess if glycaemic targets are met. The American Diabetes Association (ADA) recommends continuous dietary adjustments based on the women's regularly measured blood glucose, appetite, weight-gain patterns, changes in dietary preferences, exercise patterns, and overall life situation (e.g., work and leisure time versus maternity leave changes affecting diet and physical activity) (6).

The majority of pregnant women are screened and diagnosed with GDM between 24-28 weeks of gestation. This leaves a very short window for dietary intervention to improve blood glucose control and limit body weight gain during pregnancy. Currently, no evidence exists for specific recommendations concerning the optimal frequency, intensity, or duration of visits with a dietitian for improving maternal, foetal, or neonatal outcomes (6, 9). National clinical guidelines for treatment of GDM recommends up to three visits with a dietitian depending on the time of diagnosis (10). However, in the latest national clinical guidelines under review this has been changed to only one visit (11). Real-world data show that women with GDM are only seen once by a dietitian during pregnancy at Danish

hospitals (unpublished data). In some international clinics, dietitians review women with GDM again prior to starting insulin (the second-line treatment in GDM) to see whether any dietary modifications can be made so that insulin therapy may be averted (12). ADA also recommends telehealth visits including feedback systems for women with GDM to improve outcome compared with standard in person care based on high evidence(6, 13).

Kurtzhals et al. found that women with GDM with a lower weekly gestational weight gain from time of diagnosis and throughout dietary therapy, reflecting higher dietary adherence, was associated with improved maternal and neonatal outcomes including lower late-pregnancy HbA1c and healthier foetal growth (14). Based on clinical experiences most women with GDM are highly motivated for behavioural changes to protect the health of their unborn child (14). But with only one visit with a dietitian after diagnosis, the women are left much on their own to assess when, where, and how to adjust their diet most appropriately to meet targets for glycaemic control and body weight management while securing sufficient intake of micro- and macronutrients. In semi-structured interviews with 20 women with GDM of different ethnicity conducted in the Department of Obstetrics, Herlev Hospital, Autumn 2022, most of the women experienced being left much on their own after diagnosis and missed having more intensive dietary support (unpublished data).

4.1.3 Insulin therapy

In most cases dietary improvements are sufficient to achieve glycaemic goals but in some cases insulin therapy is needed (6, 10). The need for initiating insulin therapy is assessed by the obstetrician at regular visits based on the woman's pre- and postprandial blood glucose, and ultrasonographic evaluation of foetal growth/abdominal circumference (10). The exact proportion of women with GDM requiring insulin therapy is not well-described due to lack of valid register-based data (incorrect use of diagnosis codes, and supply of insulin directly from the hospitals). One Danish cohort study found that the proportion of women with GDM requiring insulin therapy to be 27% during the reported period 2004 – 2016 (15). Another Danish cohort study reported that 32% of women with GDM were treated with insulin during the reported period 2011 – 2017 (14). No changes in diagnostic criteria for GDM have been made in Denmark during the reported periods. Based on data from Herlev Hospital, we found that 30% of women with GDM had been treated with insulin in 2019 – 2022 (unpublished data).

Several studies have tried to identify patient characteristics and predict failure of dietary therapy and need for insulin therapy (12, 14, 16-18). Factors include higher pre-pregnancy BMI; BMI at diagnosis; previous GDM; higher haemoglobin A1c (HbA1c) at diagnosis and in late pregnancy; higher 2-hour glucose level on an oral glucose tolerance test (OGTT); lower gestational age (GA) at diagnosis; and higher weekly weight gain during pregnancy. The percentages starting insulin therapy also vary significantly according to ethnicity as shown in a retrospective review of five ethnic groups (South-East Asian, South Asian, Middle Eastern, Anglo-European and Pacific Islander) (19).

Insulin therapy can improve glycaemic control and has been shown to be effective in reducing the rate of macrosomia in GDM (20). But use of insulin during pregnancy is also associated with several clinical implications (e.g., increased risk of maternal hypoglycaemia) (6, 14, 21), increased hospital costs (endocrinologist visits, extra visits to other health care professionals, additional ultrasonographic examinations depending on the time of insulin initiation), and medical costs (insulin) (22) as well as higher costs in relation to delivery (e.g., induction of labor, pre-term delivery) (14) , and neonatal care (increased risk of neonatal hypoglycaemia) (23, 24). Finally, the personal burden associated with insulin

use (e.g., extra worries, additional SMBG measurements, and insulin injections every day) also affects women with GDM (25). Only one smaller case-control study has looked at quality of life (QoL) in GDM and found no differences between the diet-treated vs. insulin-treated group (26).

4.1.4 Nutrition recommendations

There is no clear consensus on an ideal dietary composition in GDM. A Cochrane review from 2014 examined the evidence for different dietary approaches and ended up concluding that all the studies for comparisons of maternal and infant health outcomes were too small for reliable conclusions about which type of dietary recommendations are most suitable for women with GDM (27). In a systematic review and meta-analysis for maternal glucose control and neonatal outcomes in GDM, it was found that modified dietary interventions (including low glycaemic index diets; low- versus high-carbohydrate diets; fibre-enriched diet; Dietary Approaches to Stop Hypertension (DASH)-diet; moderate energy restriction diet; high monounsaturated/polyunsaturated fatty acids diets; soy protein diets; personalised diet; ethnic meal plan diet) were associated with lower infant birth weight and less macrosomia. These associations were found despite a high heterogeneity between studies indicating that several methods can be used, and that dietary education and support should be individualised (28).

Since carbohydrate is the main energy-contributing nutrient in our diet with the highest impact on postprandial blood glucose levels (and a significant impact on the total energy balance), awareness concerning the intake of carbohydrate-rich food sources constitutes an important aspect of dietary therapy in GDM. Carbohydrates make up approx. 45% of total daily energy intake (E%) in the traditional Danish diet (29) which is in the lower end of the range of recommended intake in GDM (46-60 E%) (8). Institute for Medicine (IOM) and ADA recommends a minimum of 175 g of carbohydrates daily (≈35% of 8,400 kJ/2,000 kcal per day) for normal pregnant women and for women with GDM to ensure appropriate glucose for normal foetal growth and cerebral development and function (6). However, the amount, type and distribution of carbohydrate intake varies greatly between different ethnic and cultural groups with the highest carbohydrate intake (>60 E%) in traditional South-Asian, East-Asian, and African diets (30).

The total amount of carbohydrates consumed in a meal is a major predictor of the postprandial glucose response. However, both the quantity and quality (i.e., intake of dietary fibre, added sugar and glycaemic index) of carbohydrates influence blood glucose levels (6, 8). Thus, monitoring the dietary intake of carbohydrates continuously is important to control postprandial glucose fluctuations. This may lead to clinical benefits such as a reduction in the need for insulin, limit gestational weight gain, and potentially reduce foetal overgrowth, neonatal hypoglycaemia, and admission to NICU.

Health literacy especially among women from non-White ethnic minority groups are highly variable, and this may have a significant impact on GDM management including adherence to dietary therapy (31). Furthermore, migrants in Western society may also face huge challenges in managing their GDM due to language barriers. For example, some studies have shown that women living in English-speaking countries predominantly speaking other languages than English, have lower rates of dietary understanding compared with their English-speaking counterparts. This may also affect dietary adherence (32). Thus dietary recommendations must be culturally sensitive (4) and not based on Western ideas of what ideal meals should include to support dietary adherence and glycaemic control.

In summary, the most optimal way to deliver dietary therapy to women with GDM is not known. The possibility that intensive dietary therapy may reduce the need for initiating insulin treatment without increasing hospital service costs for these women in comparison with women receiving standard dietary care needs to be explored.

4.2 Objective

The overall objective is to investigate the effectiveness and hospital service costs of implementing an intervention with intensive dietary counselling and support during pregnancy in women with GDM.

4.3 Specific objectives

The overall objective is to investigate differences in clinical, cost-related, and patient-reported outcomes between women with GDM randomised to either intensive dietary therapy or standard dietary care.

The specific objectives are:

1. To investigate the effect of intensive dietary therapy on the likelihood of remaining treated with diet only vs. needing insulin therapy based on a hypothesis hierarchy (main objective)
2. To investigate the effects on maternal outcomes: changes in gestational weight gain; glycaemic control (HbA1c); gestational age at insulin initiation and prescribed insulin dose
3. To investigate the effects on neonatal outcomes: changes in birth weight; birth weight standard deviation score; neonatal hypoglycaemia; and admission to NICU
4. To describe changes in other pregnancy outcomes: number of cases of preeclampsia; preterm birth; mode of birth (caesarean section); jaundice; and macrosomia
5. To describe changes in patient-reported outcomes: treatment satisfaction; well-being; diet-related quality of life; autonomy support; and health competencies
6. To describe changes in dietary intake and physical activity
7. To describe if the intervention was conducted as planned, including number and type of visits
8. To describe hospital service costs related to the intensive dietary intervention compared with standard care in a cost-analysis.

4.4 Hypotheses

1. Hypothesis hierarchy for the primary outcome (objective 1):
   The type I error will be controlled in the strong sense using the following hierarchical (fixed sequence A-C) testing procedure. This is based on priority ordering of the hypotheses and testing them in this order until an insignificant result appears:
   A. We hypothesise that intensive dietary therapy is superior to standard dietary care (control group) in reducing the need for initiating insulin therapy in women with GDM. Superiority will be claimed if the difference between the two groups is equal to, or surpass, the minimal important difference (defined as 50% reduction in need for initiating insulin therapy in the intervention group compared with the control group) in favour of the intensive treated group, and if the P-value is < 0.05.
   B. We hypothesise that intensive dietary therapy is superior to standard dietary care (control group) in reducing the need for insulin therapy in women with a white ethnic background with GDM. Superiority will be claimed if the difference between the two groups is equal

to, or surpass, the minimal important difference (defined as 50% reduction in need for initiating insulin therapy in the intervention group compared with the control group) in favour of the intensive treated group, and if the P-value is < 0.05.

C. We hypothesise that intensive dietary therapy is superior to standard dietary care (control group) in reducing the need for initiating insulin therapy in women with GDM with a non-white ethnic minority background. Superiority will be claimed if the difference between the two groups is equal to, or surpass, the minimal important difference (defined as 50% reduction in need for insulin therapy in the intervention group compared with the control group) in favour of the intensive treated group, and if the P-value is < 0.05.

2. Hypotheses for secondary outcomes (objective 2 and 3):
   - We hypothesise that an intensive dietary intervention in comparison with standard dietary care will induce:
     - a clinically relevant limitation in gestational weight gain
     - a clinically relevant improvement in HbA1c
     - a clinically relevant delay in insulin therapy initiation
     - a clinically relevant limited maximal insulin dose (units per kg body weight)
     - a clinically relevant reduction in birth weight at delivery at term
     - a clinically relevant reduction in birth weight SD at delivery
     - a clinically relevant reduction in neonatal hypoglycaemia
     - a clinically relevant reduction in new-borns admitted to NICU
3. Objectives 4-7 are regarded descriptive
4. Hypothesis for hospital care costs related to the intensive dietary intervention (objective 8):
   - We hypothesise that an intensive dietary intervention in comparison with standard dietary care will have a positive effect on the net hospital costs, or at least be cost neutral (non-inferiority) if insulin therapy can be prevented for some of the women. The reason being that insulin therapy is associated with more cost intensive GDM treatment during pregnancy, higher expenses for inducement of labour, and higher cost of adverse events for mother and child as caesarean section and NICU stay, and length of hospital stay. The cost will be estimated from referral with GDM to discharge of mother and offspring.

4.5 Study endpoints

4.5.1 Primary endpoint

The primary endpoint is the percentage of women with GDM treated with insulin therapy in the intervention group and the control group at delivery.

4.5.2 Secondary endpoints

Secondary endpoints include the following measures:

- Maternal endpoints
  - Changes in body weight (kg) from referral to delivery
  - Changes in HbA1c (mmol/mol) from referral to delivery
  - Time to insulin treatment onset (days) from study inclusion until prescription or delivery if insulin therapy is not initiated

    - Mean prescribed initial and maximal insulin dose (units/kg body weight)
- Neonatal endpoints
    - Percentage of LGA new-borns
    - Percentage of new-borns small for gestational age (SGA)
    - Percentage of new-borns with macrosomia (birth weight >4,500 g)
    - Percentage of new-borns with neonatal hypoglycaemia (see definition in section 3)
    - Percentage of new-borns admitted to NICU

4.5.3 Descriptive/exploratory endpoints

Descriptive/exploratory endpoints include changes in the following study inclusion until delivery:

- Maternal endpoints
    - Percentage of cases of preeclampsia (see definition in section 3)
    - Percentage of cases of preterm births (see definition in section 3)
    - Percentage of cases of acute caesarean sections
    - Percentage of cases of planned caesarean sections
- Neonatal endpoints
    - Number of cases of neonatal jaundice (see definition in section 3)
- Questionnaires
    - Diabetes Diet-related Quality of Life (DDQOL)
    - Well-being (WHO-5)
    - Health Care Climate Questionnaire (HCCQ)
    - Perceived Competence in Diabetes Scale (PCDS)
    - Diabetes Treatment Satisfaction Questionnaire (DTSQ)
    - Pregnancy Physical Activity Questionnaire (PPAQ)

4.5.4 Endpoints related to intervention and adherence

- Adherence to intervention (number of no shows for planned visits)
- Number and types of visits (face-to-face, video and telephone)
- Changes in dietary intake with focus on carbohydrate intakes (total intake and meals)
- Adverse events

4.5.5 Endpoints related to hospital costs

Hospital costs will be analysed for the two study groups (intensive dietary therapy vs. standard care) including costs from referral with GDM to discharge after delivery divided into the categories:

- Outpatient contacts and costs related to the treatment of GDM
- Delivery costs
- Inpatient costs after delivery for mother and offspring separately, including NICU costs
- Total net costs

5 Investigational study design

5.1 Study design

The INTENSE-GDM trial is a randomised controlled parallel group open-label effectiveness trial including 232 women with GDM (Figure 1). Participants will attend one consultation with a dietitian in the standard care group and up to 5 consultations with a dietitian in the intensive dietary counselling group. Both groups will receive one end-of-intervention telephone call. Each study visit is described in detail in section 5.4.

Study visits
V0: Screening
V1: Baseline visit including one dietary consultation max 2 days after screening (both groups)
V2: Follow-up 1 with the dietitian max 2-3 days after V1 (only in the intensive group)
V3: Follow-up 2 with the dietitian a week after V2 (only in the intensive group)
V4: Follow-up 3 with the dietitian only if needed (only in the intensive group)
V5: Follow-up 4 with the dietitian only if needed (only in the intensive group)
V6: Telephone visit 2 weeks before delivery (both groups)

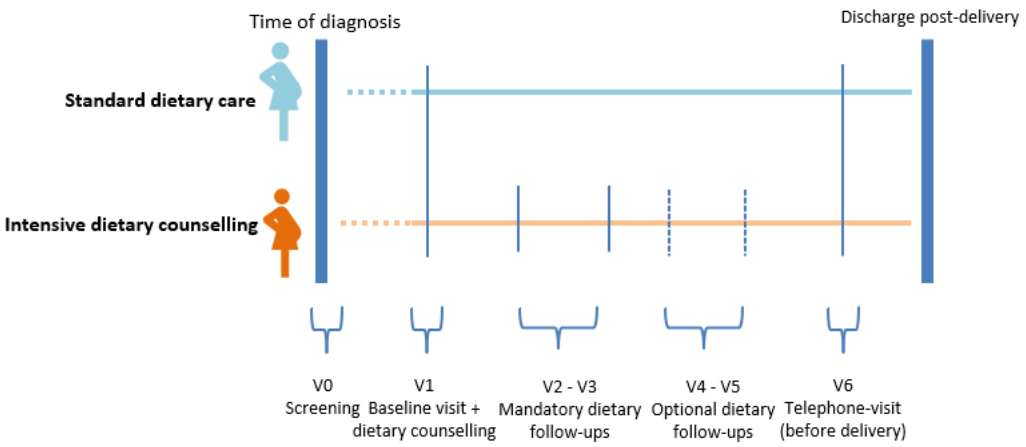

Figure 1 Study design. Depending on GA at GDM diagnosis and time of delivery the intervention duration will be 5 – 20 weeks. Min. two follow-up consultations are provided in the intensive group.

5.2 Randomisation

Participants eligible for inclusion in the study according to the screening will have their baseline measurements collected followed by a randomisation at V1. Participants will be randomised to either an intensive dietary counselling group or a usual dietary care group (control group) in a 1:1 ratio. Randomisation will be performed by the research dietitian using the randomisation module in the software program REDCap. The randomisation list will be made by a researcher/statistician not involved in the trial, who will be the only person to access the randomisation list during the trial. Should this person be unable to continue this function, a new person not involved in the trial will be appointed to store and access the sequence.

5.3 Intervention

5.3.1 Intensive dietary counselling

Women randomised to the intensive dietary intervention group will receive one initial dietary counselling consultation, and two mandatory follow-up consultations with a dietitian. In addition, participants in this group will be offered 1-2 follow-up consultations if needed (see figure 1).

Intervention

- 1 x 60 min initial dietary counselling (in-person)
- 2 x 30 min follow-up dietary consultations (phone/video/in-person according to preference)
- 1-2 x 15-30 min follow-up dietary consultations if needed (phone/video)

The initial dietary counselling includes setting personal dietary goals for behavioural change according to individual challenges with the diet, patient preferences and the overall goal for weight and glycaemic control. Women will be educated in basic carbohydrate counselling. This includes identifying carbohydrates, learning how to count carbohydrates e.g., by calculating the carbohydrate content from food labels, carbohydrate food tables, or apps for smartphones and use of a personalised carbohydrate plan with guiding suggestions for daily intake of carbohydrates at meals based on the personal dietary history. An app from the Danish Diabetes Association (*Diabetes og Kulhydrattælling*®. The Danish Diabetes Association's app, Pragma soft A/S, available in Google Play® and App Store® 12/2014, Free) will be introduced to support calculation of carbohydrates if the patient is able to understand and use this app. In addition, attention concerning carbohydrate quality (dietary fibre intake, and glycaemic index principles) and overall calorie intake will be introduced.

Follow-up consultations will include feedback on postprandial plasma glucose measurements and foods eaten, and adjustments of dietary plan until delivery.

5.3.2 Standard dietary care (control)

Women randomised to the standard dietary care group will receive one dietary counselling consultation according to the initial dietary counselling described in section 5.3.1 without any follow-up consultations with a dietitian. Participants are encouraged to follow their dietary plan until delivery.

- 1 x 60 min dietary counselling (in-person)

5.3.3 General instructions

All study participants will be encouraged to obtain and maintain a moderate-intensity aerobic activity level such as brisk walking during their pregnancy and achieving the best possible sleep. Additionally, all study participants will be instructed to follow their usual care at the Department of Obstetrics at Herlev Hospital and at SDCC if referred to an endocrinologist eventually. The medical doctors at the Department of Obstetrics will assess the need for initiating insulin therapy and referral to an endocrinologist.

5.3.4 Adherence

Dietary adherence will be measured by the dietitian using the dietary history method for data collection. A dietary history is a structured interview methods consisting of questions about habitual dietary intake of foods from core food groups, in this study with particular focus on collecting data on carbohydrate sources and estimation of carbohydrate portions sizes (in grams) distributed throughout the day before and after the intervention. Dietary data will be collected at V1 and V6.

5.4 Study visits

The following section describes all visits included in the study. An overview of the data collection procedures is presented in table 1. The visits will be conducted by the research dietitians including the principal investigator. Examinations are described in section 7. Windows are allowed for all study visits during the study period. However, we aim to carry out the initial dietary counselling within the first week after referral to Herlev Hospital for both groups, and the first follow-up consultation within the first 2-3 days after the initial dietary counselling in the intensive dietary intervention group. An outline of the protocol is detailed in Figure 2.

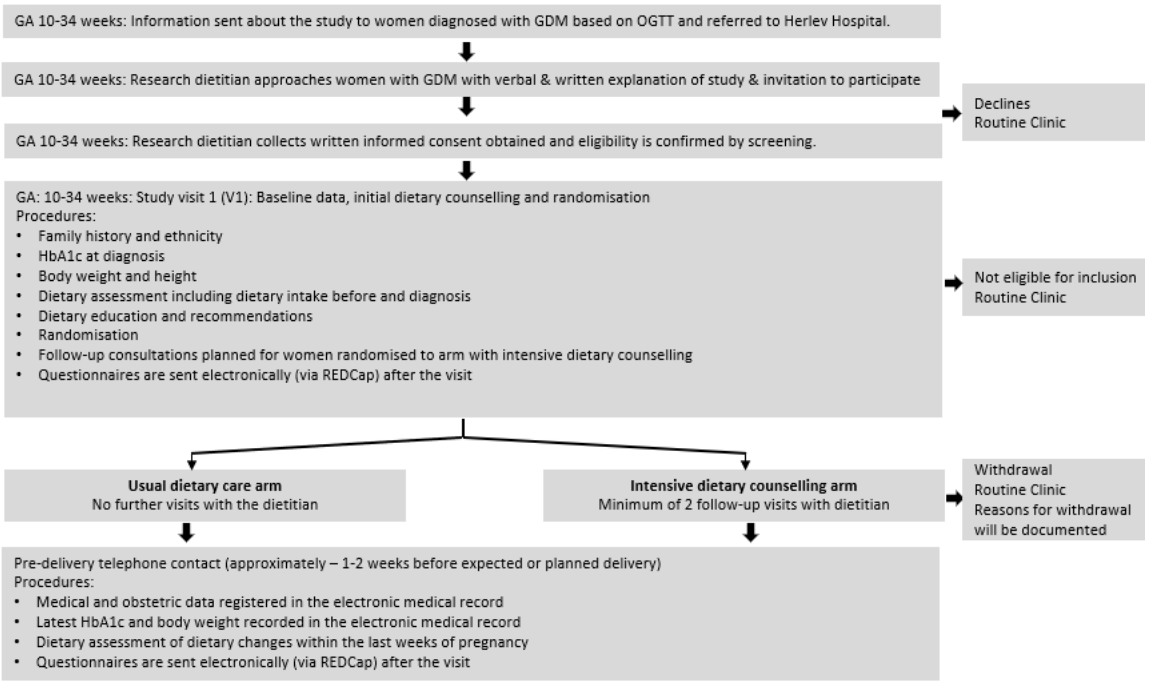

Figure 2 INTENSE-GDM protocol summary
GA, gestational age; GDM, gestational diabetes; HbA1c, haemoglobin A1c; OGTT, oral glucose tolerance test.

5.4.1 Screening (V0)

The screening visit (V0) will take place in quiet surroundings at SDCC. After information about the study, and signing of an informed consent, information on medical history (medication, previous and current diseases) will be collected, and in- and exclusion criteria will be assessed by a research dietitian. If the patient fulfils all inclusion criteria and none of the exclusion criteria, the patient will be included in the study. If the patient needs additional time to consider, a new date for a screening visit will be scheduled. If the patient is not eligible for study inclusion the cause of screening failure will be recorded. Patients eligible for inclusion will be registered with an ID code.

5.4.2 Baseline (V1) – both groups

At the baseline visit (V1) participants will meet with a research dietitian in the clinic at SDCC. The following procedures and assessments will be performed: A clinical examination with measurement of body weight and height; HbA1c after diagnosis will be collected from the patient's medical record; and information about family history and ethnic origin will be collected.

A diet history interview will be performed as part of the dietary counselling focusing on carbohydrate intake before and after diagnosis. The dietitian assesses the diet, and a balanced dietary plan will be prescribed with emphasis on appropriate nutritional intake and distribution especially of carbohydrates, and low glycaemic index diet. Dietary recommendations will be culturally adapted and tailored to the individual.

Randomisation will be performed before the participant is sent home to plan follow-up consultations for women randomised to the intensive dietary group. Questionnaires will be sent electronically through REDCap after the visit.

5.4.3 Intervention – intensive dietary group (V2)

V2 is a mandatory follow-up visit with the dietitian either in person or remote as telemedicine based on the participant's preference. The visit will take place ±2-3 days after the initial dietary counselling (V1). Focus will be on dietary adherence, carbohydrate distribution and amounts of carbohydrates eaten at each meal in relation to 7-point SMBG measurements in this dietary consultation.

5.4.4 Intervention – intensive dietary group (V3)

V3 is a mandatory follow-up visit with the dietitian either in person or remote as telemedicine based on the participant's preference. The visit will take place ±7 days after V2. Focus will be on dietary adherence, in relation to 7-point SMBG measurements. Evaluation of the need for a dietary follow-up visit.

5.4.5 Intervention – intensive dietary group (V4)

Optional follow-up telemedicine consultation with the dietitian. The visit can take place up to 3 weeks before delivery.

5.4.6 Intervention – intensive dietary group (V5)

Optional follow-up telemedicine consultation with the dietitian. The visit can take place up to 3 weeks before delivery.

5.4.7 Pre-delivery visit (V6) – both groups

A telephone visit will be carried out 1-2 weeks before the planned delivery with both groups. A diet history interview will be performed focusing on the carbohydrate intake during the intervention period. Obstetric history, changes in medication, HbA1c, body weight and 7-point SMGB measurements registered in the participant's medical record will be recorded in REDCap. Questionnaires will be sent electronically through REDCap after the telephone visit.

Table 1. Data collection procedures in the INTENSE-GDM Trial

Variable	Measurement	Participant	Screening	Baseline	Pre-delivery	Post-delivery
			V0	V1	V6	No visit
Ethnicity and socio-economic, status	Self-constructed questions	W		•		
Medical history	EMR	W	•	•		
Dietary history	Personal interview	W		•	•	
Alcohol, sleep, and smoking	Self-constructed questions	W		•	•	
Obstetric history	EMR	W		•	•	•
Medication	EMR	W		•	•	
Glycose control	HbA1c	W		•	•	
	7-point SMGB	W		•	•	
	Neonatal hypoglycaemia	N				•
	Admission to NICU	W, N				•
Anthropometry	Height, BW, BMI	W		•	•	
	Delivery weight (EMR)	N				•
	LGA (EMR)	N				•
	SGA (EMR)	N				•
	Macrosomia (EMR)	N				•
Delivery complications	Preterm birth (EMR)	W				•
	Preeclampsia (EMR)	W				•
	Caesarean section (EMR)	W				•
	Jaundice (EMR)	N				•
Well-being	The WHO-Five Wellbeing Index (WHO-5)(33)	W		•	•	
Diet-Related Quality of Life	Diabetes Diet-Related Quality of Life (DDRQOL) (34)	W		•	•	
Autonomy support	Health Care Climate Questionnaire (HCCQ) (35)	W		•	•	
Perceived competences	Perceived Competence in Diabetes Scale (PCDS) (35)	W		•	•	
Treatment satisfaction	Diabetes Treatment Satisfaction Questionnaire (DTSQ) (36, 37)	W		•	•	
Physical activity	Pregnancy Physical Activity Questionnaire (PPAQ) (38)	W		•	•	
Adherence	EMR data	W				•
Hospital costs	EMR and registry data	W, N				•
Safety	Adverse events	W			•	•

BMI, Body Mass Index; BW, Body weight; EMR, Electronic Medical Record; HbA1, Haemoglobin A1c; W, Woman with GDM; N, neonate delivered by women with GDM in the study; NICU, neonatal intensive care unit.

5.5 Recruitment and informed consent

We plan to recruit at least 232 women and, if possible, up to 304 women with GDM from the Department of Obstetrics at Herlev-Gentofte Hospital. Written informed consent will be obtained from both the pregnant women and their partner (the unborn child's father/co-parent with whom the woman is planning joint custody with, hereafter referred to as the woman's partner) prior to entry into the study.

Participants will be recruited when they are newly diagnosed with GDM and referred to the Department of Obstetrics at Herlev Hospital for GDM management. A written participant information in Danish and English will be sent together with the brochure "*Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt"* through E-boks together with the invitation to the initial consultation with a dietitian (standard procedure). The right to bring a relative is mentioned in the written information. Women are encouraged to bring their partner so that written informed consent can be obtained from both parents. If the identity of the unborn child's father is doubtful and the woman is planning full custody, only written informed consent will be collected from the woman for study inclusion. There will be allocated plenty of time for the oral study information at the first appointment with one of the research dietitians (who also perform the routine dietitian visits with all women with GDM). The research dietitian will start by asking the woman and her partner if they have read the participant information and if they are still interested in oral information about the clinical trial. If they have read the information and are still interested, the research dietitian will provide an oral information (either in Danish or English or together with an interpreter) study including information about study objectives, significance, content, and requirements including risks implications and principles for randomisation with allocation to one of two groups. In particular, the woman and the partner will be informed about: 1) the possibility of withdrawing from the study at any time without giving any reason; 2) how personal health-related data will be collected and used and processed in accordance with the data protection legislation in the study; and 3) that all personal and health-related data will be anonymised.

The woman and her partner will be given time to discuss any questions and will be offered a minimum of 24 hours to consider before signing the informed consent. If the woman and her partner decide to participate in the study right away, the women, her partner and the research dietitian will sign the written informed consent (in Danish or English), and the research dietitian will perform a screening (V0) to assess if the woman is eligible for inclusion in the study. Women eligible for study inclusion where both the woman and her partner have signed the informed consent will subsequently be offered an initial dietary counselling, performance of baseline measurements, and randomisation (in the mentioned order) (V1) by the research dietitian. Alternatively, the patient will be booked for a visit (V1) within 48 hours after the screening visit. If the woman and her partner need more time to decide if they want to participate in the study, or have not read the participant information, the research dietitian will schedule for a new meeting after 24 hours. If the partner is not participating in the initial consultation where the oral information is given, and the woman gives her written informed accept to participate and is eligible for inclusion, a visit with the partner and the research dietitian at one of the coming ultrasound visits with the woman is planned to provide oral information and obtain written informed consent from the partner to collect data from the child's medical record after delivery.

6 Participants

6.1 Inclusion criteria

- Newly diagnosed women with GDM referred to Department of Obstetrics Herlev Hospital
- Women diagnosed with GDM based on a 2-hour OGTT plasma glucose value ≥ 9.0 mmol/l
- Women diagnosed with GDM based on at least 2 plasma glucose measurements above targets (either pre-prandial ≥6.0 mmol/l, or 2-hours postprandial ≥8.0 mmol/l)
- GA at GDM diagnosis ≤ 34
- Provided voluntary written informed parental consent in Danish or English or after translation by an interpreter for non-Danish and non-English speaking parents

6.2 Exclusion criteria

- Bariatric surgery
- Other intercurrent illness (e.g., cancer, ulcerative colitis) as judged by the medical experts
- Uncontrolled medical issues, as judged by the investigators
- Concomitant participation in other clinical trials that could interfere with the INTENSE-GDM trial as evaluated by the investigators
- Unable to understand the informed consent and procedures regardless of the language spoken

6.3 Criteria for withdrawal

One or more of these criteria will result in withdrawal of the participant from the study:

- A participant withdraws the informed consent
- A participant's general condition contraindicates continuing the study as judged by the investigators or medical experts
- Other reasons determined by the investigator

7 Examinations

All patients found eligible for inclusion in the study will be invited to a first study visit (V1) for collection of baseline measurements according to study specific SOPs. Subsequently, all participants will be randomised to one of the two study groups. All examinations will be performed in the outpatient diabetes clinic at SDCC. Study visits and examinations are described in detail in table 2 below, in the current section and section 5.4.

Table 2: Schematic overview of study visits

Visit	V0	V1	V6
Patient-related information			
Informed consent	X		
Assessment of in- and exclusion criteria	X		
Medical history	X		
Dietary history		X	X
Medication use		X	X
Randomisation	X		
Clinical efficacy outcomes			
Insulin use			X
Insulin dose (IE per kg body weight)			X
Time to insulin (days) from study allocation until prescription			X
Diet history interview		X	X
HbA1c		X	X
Body weight and height (height only at V1)		X	X
7-point SMGB		X	X
Questionnaires			
Socio-economic and ethnic characteristics		X	
Well-being (WHO-5)		X	X
Diabetes Diet-Related Quality of Life (DDRQOL)		X	X
Health Care Climate Questionnaire (HCCQ)		X	X
Perceived Competence in Diabetes Scale (PCDS)		X	X
Diabetes Treatment Satisfaction Questionnaire (DTSQ)		X	X
Pregnancy Physical Activity Questionnaire (PPAQ)		X	X

Abbreviations: SMBG, Self-Monitored Blood Glucose; V0, Screening, V1, data collected at baseline; V6, data collected pre-delivery.

7.1 Clinical examination

Body weight and height will be measured to the nearest 0.1 kg and 0.1 cm, respectively with calculation of BMI (kg/m^2) at the baseline visit (V1). Body weight will be measured with the participant wearing light indoor clothes and no shoes after emptying the bladder. Height is measured using a wall-mounted stadiometer with the participants not wearing shoes and with the heels, buttocks and upper part of the back remaining in contact with the wall/back of the stadiometer. Body weight at V6 will be recorded based on data from the patients' medical records. GA at the time of the registered body weight measurement in EMR will be recorded.

7.2 Blood samples

HbA1c will be measured in a non-fasting condition. The routine HbA1c measurement performed shortly after referral to Department of Obstetrics at Herlev Hospital will be recorded at V1, and HbA1c measured closest to delivery (GA recorded) will be recorded at V6. Laboratory analyses of blood samples will be performed in the laboratory at Herlev-Gentofte Hospital by skilled laboratory technicians.

7.3 Electronic medical record data

The written consent provides the trial investigators, the sponsor, the sponsor's representatives, and regulatory authorities direct access to obtain information from the patient's medical records, including electronic records, with the purpose of reviewing information regarding the participant's health condition. This access is necessary for conducting the research project and for regulatory oversight, including self-regulation, quality control, and monitoring, which they are obligated to perform. According to planned and described procedures, the research dietitians will access the participant's medical record to collect information relevant to the study as described under screening (assessment of in- and exclusion criteria), collection of medical history, concomitant medications, and clinical outcomes from referral until discharge after delivery. The purpose of obtaining information from the medical records is to assess whether the women is eligible for inclusion, to describe the study population, and report study outcomes related to pregnancy and child delivery.

The following data from the mother's and infant medical records and The National Patient Register will be collected (see Table 1 for details about data sources):

Background data
Age
GA at GDM diagnosis and referral to the Department of Obstetrics
Method for diagnosing GDM (OGTT or 3-days SMBG monitoring)
OGTT value, mmol/l at diagnosis
Number of pregnancies, n
Multiple pregnancy
Previous GDM
Pregestational BMI, kg/m^2
Hypertensive disorders of pregnancy
Pregestational hypertension
Pregestational dyslipidaemia
Diet-affecting diseases e.g., gastroparesis, kidney disease, coeliac disease

Prenatal care data
Number and types of visits in each study group from referral to discharge after delivery:

- Type and number of visits with a dietitian (initial 60 min visit, 15-30 min follow-up visits, face-to-face, telephone or video)
- Number of visits with a midwife
- Number of visits with a nurse (individually)
- Number of visits with a nurse (in a group)
- Number of visits with an endocrinologist

Number of telephone contacts with an endocrinologist

Number of visits with an obstetrician
Number of visits for ultrasonographic examination
Number of visits including an interpreter (face-to-face, telephone or video)
Body weight, kg at diagnosis and until delivery
HbA1c, mmol/mol measured at diagnosis and until delivery
Insulin-treated
Time to insulin (days):
- from study allocation until insulin prescription
- from maternal GA
Prescribed insulin, type, and dose (units/kg body weight)
Prescribed antihypertensive medication, type, and dose
Hospital admissions before delivery due to GDM
Registered blood glucose measurements
Preeclampsia

Labor data
Induction of labour (yes vs no) and what weeks of gestation
Preterm birth (defined as <37 weeks of gestation)
Mode of delivery (vaginal delivery or caesarean section)

Post-natal care
Neonatal gestational age at birth
Neonatal delivery weight, gram
LGA
SGA
Macrosomia
Jaundice
Hospital days after delivery
Neonatal hypoglycaemia
Admission and number of days in NICU
Stillbirth/neonatal death

7.4 Socioeconomic baseline data

The following self-administered questions on baseline demographics for background information will be sent out electronically after V1:

- Educational level
- Main occupation
- Civil status
- Household composition

8 Sample size determination

A 50% difference in the incidence of insulin therapy between the two study groups during the study period was defined as the minimally important difference for the primary outcome. The sample size estimation was based on a logistic regression model (outcome = group) and the following assumptions: An allocation ratio of 1:1; alpha = 0.05; 0.8 power, an incidence of insulin therapy of 30% in the usual care group and 15% in the intervention group in need of insulin therapy. The expected incidence in the standard care group is based on register data from Herlev Hospital in the period 2019-2022 showing that approximately 30% of the women with GDM referred to the hospital had been prescribed insulin therapy. This resulted in a total number of participants required to complete the trial of 191. To account for potential uncertainties in the assumptions used for the power calculation, the total number or participants was multiplied by 1.1 and then by 1.1 to account for potential dropouts, resulting in 232 participants to be included. If the rate of inclusion permits, we aim for including 304 participants to attain a statistical power of 0.9 based on the abovementioned assumptions and uncertainties.

8.1 Study feasibility

Register data show that 200-300 women are diagnosed with GDM and treated in the Department of Obstetrics at Herlev Hospital yearly based on the current OGTT cut off value of ≥ 9,0 mmol/l for GDM in pregnancy (10). A high proportion of these women are expected to meet the criteria for study inclusion. Thus, it is realistic to expect that the study can recruit and include up to 304 women with GDM during the planned study recruitment period of approximately 1.5 years from October 2023 to April 2025.

9 Data management

9.1 Data handling

The study will comply with the Danish Data Protection Agency and the General Data Protection Regulation. All health-related matters and sensitive personal data will be handled in accordance with the Danish "Act on Processing of Personal Data". Adequate blinding of all personal data during data processing and publication will be ensured. Data will be stored in coded form for 10 years after last participant has attended the last visit after which it will be fully anonymised.

All data will be entered directly into electronic case report forms (CRFs) using the software system REDCap licensed by the Capital Region in Denmark. Errors and corrections are logged as provided by the REDCap interface. It is possible to transport validated data from REDCap to e.g., a statistical program (e.g., SAS) for further statistical analysis. When data have been entered, reviewed, and verified the data will be frozen to prevent editing.

9.2 Data reporting and protection

Before initiating the study, acceptance from the Danish Data Protection Agency will be secured. All health-related matters and sensitive personal data will be handled in accordance with the Danish "Act on Processing of Personal Data". All health-related matters and sensitive personal data (blood test result etc.) will be depersonalized. All participants will be given a study number referring to their personal

information, which will be stored securely and separately. Adequate blinding of all personal data during data processing and publication will be ensured. Data will be stored in coded form in 10 years after last participant has attended the last visit, where after the data will be fully anonymised.

9.3 Source data identification and verification

All study-related information will be recorded, handled, and stored in a way that allows accurate reporting, interpretation, and verification. All questionnaire data will be collected electronically using the software system REDCap according to local standards for research projects in the capital region of Denmark. In addition, source data will be registered in REDCap on an ongoing basis and at the end of study. Data is stored in coded form for 10 years from last participant last visit. Hereafter, data will be fully anonymised.

9.4 Data reporting and protection

All information on study participants is protected according to the General Data Protection Regulation and the Danish Data Protection Agency ("Databeskyttelsesloven" and "Datatilsynet"), and the law of health and it will not be possible to identify any participant. None of the study-related blood samples or data will be stored or analysed in countries outside Denmark.

9.5 Protocol changes

Substantial amendments to this protocol may be implemented only after a favourable opinion of the Ethics Committee of the Capital Region, Copenhagen has been obtained. Amendments to the protocol are regarded as substantial if they have a significant impact on the safety, physical health, and mental integrity of the participants. If an event occurs related to the conduct of the study which may affect the safety of the participants, the study investigators may take appropriate measures to protect the participants against immediate hazards. The investigator will inform Ethics Committee of the Capital Region, Copenhagen of the new events and the measures taken as soon as possible.

10 Publication

Positive, negative, or inconclusive study results will be published by the investigators in international peer-reviewed journals. the study results. Positive, negative, or inconclusive study results will be published by the investigators in international peer-reviewed scientific journals. Principal investigator Bettina Ewers will be first and corresponding author. All co-authors must comply with the international committee of medical journal editors (ICMJE) guidelines. The author order depends on the different authors' contributions to the study. Co-authorship also requires that all co-authors have approved the final manuscript and confirmed that they wish to be co-authors.

11 Study timeframe

The active study period will begin with recruitment of participants from October 2023 and expected to be finalised by April 2025.

12 Financing

The study is initiated by the principal investigator Bettina Ewers and co-investigators at SDCC and Herlev-Gentofte Hospital. In 2022, Bettina Ewers received funding from the Novo Nordisk Foundation as part of the non-standard initiatives ("Supplerende behandlingsinitiativer") primarily to cover salary for research dietitians, postdoc, and administration at SDCC (DKK 1.8 mill) to conduct the study. The funding is administered through the Management, Secretariat and Research Administration at SDCC. The sponsor and investigators have no economic interest in the results of the study. If external funding is obtained, the Ethics Committee of the Capital Region, Copenhagen will be notified.

12.1 Conflicts of interest

SDCC is a hospital in the Capital Region of Denmark providing health services for individuals with diabetes for the public health care system. The trial is funded by the Novo Nordisk Foundation through unrestricted grants. Thus, the Novo Nordisk Foundation has no economic interests in the study. The Novo Nordisk Foundation will not have influence on 1) The study design; 2) The collection, analysis, and interpretation of data; 3) The writing of the study report, or any publication; and 4) The decision to submit the paper for publication. The investigators employed at SDCC will not benefit economically from conducting the study.

13 Compensation of participants

The study covers interpreter expenses. Travelling expenses related to study visits will not be reimbursed. Participants will not receive financial compensation for participating in the study.

14 Ethics and regulations

14.1 Independent ethics committee and regulatory authority

The study protocol will be submitted for approval by the Ethics Committee of the Capital Region, Copenhagen and the study will be registered for approval of data storage at the Danish Data Protection Agency. After obtaining approvals from all authorities the study will be registered at clinical trials.gov and before study commencement.

14.2 Ethical considerations

The study will be conducted in accordance with the ethical principles in the Declaration of Helsinki and to the regulations for Good Clinical Practice (GCP) to the extent that this is relevant for a non-pharmacological study. The study will deliver important new insights on the effects of an intensive dietary intervention for reducing insulin needs during pregnancy as well as improving other relevant clinical maternal and neonatal outcomes in women with GDM. Additionally, this study will provide a cost-benefit analyses to assess if implementing more intensive dietary support in a clinic is cost neutral or even cost saving. To our knowledge this has not previously been done in our study population. The findings from the study may also have direct patient-related implications for future national guidelines.

Thus, there is great need for studies investigating the effectiveness of a more intensive dietary regime for management of GDM.

The study has no obvious ethical concerns for the participants, and only minor potential risks in relation to participation (described in the next section) which are compensated by the expectable advances of conducting the study. The anticipated benefits for the participants are high including improved glycaemic control for both mother and child reducing the risk of pregnancy complications.

14.3 Risks related to participation

Overall, limited risks are expected with the current study. Obstetricians will assess the need for initiating insulin therapy according to standard procedure based on current national guidelines for management of GDM. Only a minor disadvantage associated with delayed onset of dietary guidance can be expected when women with newly diagnosed GDM are referred to a dietitian due to time needed for informed consent and screening in the study. Rapid education and support to improve dietary habits and thereby glycaemic control are crucial components after diagnosis. However, the standard procedure at the Department of Obstetrics at Herlev Hospital has been up to one week of waiting time until deliverance of dietary support. It is regarded as realistic to be able to match this procedure or and even improve time until dietary support in the study despite time used on informed consent and screening procedures.

15 Insurance

The patients are covered by the Patient Insurance Act according to the Danish Act on the Right to Complain (Lov om klage- og erstatningsadgang inden for sundhedsvæsenet, lov nr. 1113 07/11/2011). and Receive Compensation within the Health Service.

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