Administrative information

Changing diagnostic criteria for gestational diabetes in Sweden - a stepped wedge national cluster randomised controlled trial - the CDC4G SAP

Trial registration number: ISRCTN41918550 (15/12/2017)
SAP version: 8, 20220923
Study Protocol: Fadl H, Saeedi M, Montgomery S, Magnuson A, Schwarcz E, Berntorp K, et al. Changing diagnostic criteria for gestational diabetes in Sweden-a stepped wedge national cluster randomised controlled trial-the CDC4G study protocol. *BMC pregnancy and childbirth. 2019;19(1):398.*

SAP revisions

Version Number	Reason for Update	Updated By:	Date
1	Creation of a draft statistical analysis plan	Maryam de Brun	2020-12-01
2	Comments from steering group including statistician	Maryam de Brun	2021-02-23
3	Steering group meeting with SAP planning	Maryam de Brun	2021-12-08
4	Steering group meeting with SAP planning	Maryam de Brun	2022-04-27
5	M de Brun, A Magnuson, D Simmons, H Backman statistical clarification	Helena Backman	2022-06-15
6	Clarifications	Helena Backman	2022-08-31
7	Comments and steering group meeting with finalisation	Maryam de Brun	2022-09-20
8	Finalised SAP	Helena Backman, Anders Magnuson, Scott Montgomery and Maryam de Brun	2022-10-28

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Table of content

List of abbreviations

CDC4G	Changing Diagnostic Criteria for Gestational Diabetes
CS	Caesarean Section
eCRF	electronic Case Report Form
FPG	Fasting Plasma Glucose
GDM	Gestational Diabetes Mellitus
GROW	Gestation Related Optimal Weight
IADPSG	International Association of the Diabetes and Pregnancy Study Group
LGA	Large for Gestational Age
MBR	Medical Birth Register
NPR	National Patient Register
OGTT	Oral Glucose Tolerance Test
PG	Plasma Glucose
RPG	Random Plasma Glucose
SAE	Serious Adverse Events
SCB	Statistics Sweden
SNBHW	Swedish National Board of Health and Welfare
SNQ	Swedish Neonatal Quality register
SPR	Swedish Pregnancy Register
SW-CRT	Stepped Wedge Cluster Randomised Controlled Trial
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organisation

1. Introduction

1.1 Background and rationale

Gestational diabetes mellitus (GDM) or hyperglycaemia during pregnancy is one of the most common medical complications during pregnancy with a growing prevalence globally. Hyperglycaemia during pregnancy is associated with several long- and short-term adverse outcomes for the mother and offspring. There is a strong linear association between the level of hyperglycaemia during pregnancy and the child´s birth weight. There is an increased risk for gestational hypertension, preeclampsia and caesarean section (CS) as well as large for gestational age (LGA) neonates, neonatal hypoglycaemia, birth trauma and shoulder dystocia (1). In the long term, an association with metabolic disease such as obesity, development of type 2 diabetes mellitus (T2DM) and cardiovascular disease has been shown among women with previous GDM (2-4). The offspring have been shown to have a higher risk of obesity and impaired glucose tolerance (5, 6).

There is clinical importance of finding women with GDM since several short-term adverse outcomes (e.g. LGA, primary CS) have been shown to be reduced with GDM treatment (lifestyle and diet, metformin, insulin) (7-9).

Internationally, the prevalence of GDM varies extensively from 1-28% depending on characteristics such as age, ethnicity, overweight/obesity, lifestyle (physical activity, diet) and T2DM prevalence in the background population (10-15). Further variation is due to local GDM screening strategies and diagnostic criteria that have made global comparison of GDM prevalence and outcomes problematic (16, 17).

In order to progress towards a universal standard approach to GDM diagnosis, the World Health Organisation (WHO) adopted the International Association of the Diabetes and Pregnancy Study Group (IADPSG) criteria in 2013, using a 2-h 75 g oral glucose tolerance test (OGTT) with three time points blood testing (fasting, 1- and 2-h) (18). These 2013 WHO criteria define GDM as ≥5.1 mmol/L, ≥10.0 mmol/L and/or ≥ 8.5 mmol/L fasting, 1-h and/or 2-h thresholds respectively. These cut-off values are based on a ≥ 75% adjusted excess risk of adverse neonatal outcomes (e.g. LGA, foetal hyperinsulinemia) based on data from the Hyperglycaemia and Adverse Pregnancy Outcomes study involving 23,316 women from nine countries (19).

The debate over the merits of these new GDM criteria including the expected 2-11-fold increase in prevalence (10, 19-22) has raised concerns over their cost and clinical effectiveness. There is an uncertainty concerning the clinical relevance of GDM treatment based on the IADPSG criteria and the associated risk of developing T2DM later in life (23-27). The consensus based WHO 2013 criteria were developed using available large-scale epidemiological data and randomised control trials, but uniform worldwide application might not be suitable as associations with adverse outcomes might vary between different populations (28).

In Sweden, there is national variation in GDM screening, diagnostic criteria, and sampling method (29, 30). The older Swedish GDM criteria were based on a 2-hour 75 g OGTT. If a fasting threshold was used (not used in one region), then ≥7.0 mmol/L was considered diagnostic for GDM. The 2-h criteria ranged from 9.0–11.1 mmol/L, using either capillary or venous samples (30). Before 2018, 1–3% of the 115,000 births were complicated by GDM annually (31). In June 2015 the Swedish National Board of Health and Welfare (SNBHW) recommended a move to the 2013 WHO diagnostic criteria (32) based on venous sampling. The SNBHW made no recommendations in relation to the screening (e.g. universal vs risk factor) due to limitations in the available evidence, and did not make recommendations on capillary OGTT thresholds. The Swedish national health and population registers offer a practical possibility to assess the national impact of introducing the new GDM criteria on pregnancy outcomes and long-term health for both mother and child.

With the current variation in GDM diagnostic practice across Sweden and the debate over the criteria, there was a recognition that the transition to the recommended new guidelines could be either by an ad hoc, or planned and structured way, to minimise clinical variation. A stepped wedge cluster randomised controlled trial (SW-CRT) was designed to evaluate the clinical and health economic impacts of

Changing the Diagnostic Criteria for GDM in Sweden (CDC4G) and to create a prospective cohort to compare the many long-term outcomes in mother and baby under the old and new diagnostic approaches.

1.2 Objectives

Our hypothesis is that there will be a reduction in adverse neonatal and maternal outcomes following the implementation of the new GDM criteria, hence leading to less healthcare costs.

Our objective is to through SW-CRT answer the question whether the implementation of the new SNBHW GDM criteria will

- Lead to a reduction in LGA rates (primary outcome)?
- Lead to reduction in adverse maternal pregnancy outcomes?
- Lead to reduction in adverse neonatal outcomes?
- Lead to any difference in costs and cost-effectiveness?

2. Study Methods

2.1 Trial design

The CDC4G study is a national prospective, unblinded, SW-CRT (allocation ratio of 1:1 controlled cluster groups) of the switch from the former Swedish diagnostic criteria (control) to the SNBHW 2015 criteria for GDM (intervention) involving a 3-point OGTT with venous fasting plasma glucose, 1-h and/or 2-h diagnostic thresholds of ≥5.1, ≥10.0, ≥8.5 mmol/L, respectively. The SW-CRT involves randomly allocated times for clusters to introduce the intervention, allowing participants before and after any change to serve as control and intervention groups, respectively.

All delivery units in Sweden (n=40) were offered to join, and 17 delivery units entered the study. Each participating delivery unit was assigned into a cluster, in which the patients continued to undergo screening for GDM following their usual approach throughout the trial period, see Table 1. The time of transition to the new criteria was randomised and subsequently rolled out until all 11 clusters implemented the new GDM regimens during 2018.
During the national preparation phase (September–December 2017), prior to the commencement of the trial, all clusters shifted to a uniform approach to GDM management and agreed that no local policies including GDM screening would change during the study period, Appendix Table 1-2. Clusters using capillary sampling for GDM diagnosing were to change to venous sampling, which is the approach recommended by the SNBHW (18, 19, 32).
The trial started on the 1st of January 2018 with 1 month of baseline data collection when no randomisation occurred. Subsequently, at periodic time points called “steps”, clusters changed to the new GDM criteria in a randomised order over a 10-month period. By December 2018 all clusters had introduced the SNBHW criteria for GDM.

Details of the screening criteria at booking for undergoing an 2-h 75 g OGTT and sampling method are listed in Table 1 and the previously published study protocol (30). Women with overt diabetes (according to definitions in Table 1) are diagnosed and treated as GDM but with rapid management by specialist care unit in contrast to usual maternal healthcare.

Cluster inclusion criteria:

- All clusters that had changed clinical management guidelines according to study protocol, including performing venous OGTT for diagnosis of GDM.

Cluster exclusion criteria:

- Clusters that did not adhere to study protocol procedures from the beginning.

2.2 Randomisation

A stratified randomisation by cluster size was conducted using two strata, as the expected number of births varies across the delivery units. The first strata included the two largest populated clusters (Stockholm and Gothenburg) which were randomised to change GDM criteria in June or August of 2018, respectively. The second strata with the nine remaining clusters changed, one cluster per month, in a randomised order from February to July and September to November of 2018, respectively. The randomisation allocation was performed using computer-generated, random allocation sequences using SPSS version 22 (Armonk, NY: IBM Corp) by the study statistician at Clinical Epidemiology and Biostatistics, Region Örebro County. The randomisation was concealed from the participating centres and the list was stored in a safe at Örebro University Hospital. Randomisation details have been previously published in the study protocol (30).

2.3 Sample size

With 11 clusters participating and an intra cluster correlation of 0.0026 a minimum sample size of 47,916 pregnant women (23,958 before change and 23,958 after changing to the new SNBHW GDM criteria) the trial has 90% statistical power with a 5% significance level to detect an absolute reduction in LGA by 1.5% on a population level (from the existing 10 to 8.5%). The Intraclass Correlation Coefficient was estimated from the variation in LGA incidence in year 2012 between participating clusters, which varied between 7.7 and 13.3% (0.077–0.133). The sample size calculation for this SW-CRT design was made using STATA release 14 by a statistician (33) and has previously been published in the study protocol (30).

2.4 Framework

The CDC4G study is a Swedish multicentre superiority SW-CRT comparing the implementation of the SNBHW 2015 criteria to the old GDM criteria used in Sweden. The study includes a health economic analysis.

2.5 Statistical interim analyses and stopping guidance

Serious Adverse Events (SAEs) and GDM prevalence were reported each month through the website (www.cdc4g.com) by local Principal Investigators. The data was compiled every month by the study coordinator to identify any safety or protocol breaches. Any sign of deviation was discussed with the chief investigator and/or steering group. There were no pre-specified formal stopping rules. The Data and Safety Monitoring Board was available to determine whether any safety issues warranted termination of the trial such as SAEs.

2.6 Timing of final analysis and outcome assessments

The main results for CDC4G study will begin to be analysed during 2022 with all outcomes analysed collectively. The primary and secondary outcome with time point for measurement are stated in 5.1 Outcome definitions.

3. Statistical Principles

3.1 Confidence intervals and P values

All significance tests will be two sided and conducted at the 5% significance level. Significance tests will be accompanied by 95% confidence intervals for estimated effect sizes, measures of association, or other parameters of interest.

3.2 Adherence and protocol deviations

Every month each cluster reported their monitoring according to a checklist on the website to make sure that the guidelines for the CDC4G study (e.g. GDM treatment, blood sampling methods, obstetric surveillance, and switch to the new criteria) were followed at each step of the study. In addition, the number of women with GDM diagnosed every month and SAEs during the study period were registered. Any sign of deviation was discussed with the chief investigator and/or steering group.

3.3 Analysis populations

The statistical analysis will be based on all the eligible pregnancies in the clusters randomised into the trial. All relevant data available from each participant will be included.

3.3.1 The intention to treat population

The intention to treat population will consist of all eligible pregnancies in randomised clusters.

3.3.2 The per-protocol population

The per-protocol population will consist of all pregnancies in the randomised clusters having commenced the study until exclusion due to protocol violation.

4. Trial Population

All delivery units in Sweden were invited to participate over the 12-month study period. 17 delivery units in Sweden agreed to participate (approximately 66 000 births during 2018). All women within the participating delivery units (including within both primary and secondary care) across Sweden are included in the study, unless they opt out from the Swedish Pregnancy Register (SPR) or Medical Birth Register (MBR).

4.1 Population definition

4.1.1 The study population definition

- All pregnancies with an OGTT performed during 2018-01-01—2018-12-31
- All pregnancies diagnosed with GDM during 2017, but not passed 23+6 gestational weeks 2018-01-01
- All pregnancies without an OGTT from 28+0 gestational weeks on 2018-01-01 up to 2018-12-31 (per month and cluster defining allocation of pregnancies each month).See 4.1.2 and figure 1.

4.1.2 Period cluster group definition

Every pregnancy is allocated to a period based on the month of the OGTT date or the date of achieving 28+0 gestational weeks if no OGTT was performed during pregnancy. Every pregnancy is allocated to a cluster based upon delivery unit or the unit where the OGTT was performed. The period cluster group is allocated according to the period and cluster.

- **OGTT population**: The first OGTT date during 2018 will define if the woman belongs to pre or post intervention group, unless the indication for the OGTT is polyhydramnios, suspected LGA or OGTT ≥ 36+0 without information on indication, in which case the original group is maintained. If previous OGTT was done during 2017 (when the study guidelines were not implemented), and repeated OGTT was done during the study period (2018) the women is allocated according to 2018 OGTT, see 4.1.1.
- **Non-OGTT population**: All pregnant women achieving 28+0 gestational weeks during the period (month) even if she has a later OGTT.

4.2 Screening data, eligibility and recruitment

All pregnant women within the participating delivery units (primary and secondary care) across Sweden during 2018 were included in the study, unless they opted out from the SPR.

Women with pre-existing diabetes, gastric bypass surgery and multifetal pregnancies are excluded. Women were recruited de facto by being under the care of a participating health service. Women always had an option to decline testing and, if GDM was diagnosed, to decline treatment. Informed consent was not requested beyond the routine invitation to opt out of the SPR with the option at any time to refuse any aspect of management.

4.3 Withdrawal/follow-up

Withdrawal/loss to follow-up will be reported in the study flowchart.

4.4 Baseline patient characteristics

Demographics and patient characteristics at baseline and data source will be listed. Pregnancies will be grouped by intervention (SNBHW 2015 criteria) and no intervention (old GDM criteria).

4.4.1 Maternal characteristics

Data is retrieved from SPR, National Patient Register (NPR), Statistics Sweden (SCB) or MBR.

- Age at childbirth (years)
- Maternal height at first antenatal visit (cm)
- Maternal weight at first antenatal visit (kg)
- BMI at first antenatal visit (kg/m^2) (Calculated from height and weight variables above)
- Parity (numbers of previous deliveries; stillbirths or live births)
- Chronic hypertension, blood pressure ≥140/90 mmHg before gestational week 20 (mmHg) (ICD-10 I10-15, I10.9, O10.0)
- Smoking at first antenatal visit (0 = No, 1 = 1-9 cig/day, 2 = 10 or more cig/day, 3 = not stated)
- Swedish oral moist snuff ("snus") at first antenatal visit (-1 = null, 0 = No, 1 = Yes, -2 = Unknown)
- Country of birth (grouped according to IDF Diabetes Atlas except for having an extra category for Sweden (34)) (Nominal, Western Pacific, South & Central America, Europe except Sweden, Africa, Middle East & North Africa, South East Asia, North America and Caribbean, Sweden)
- Highest educational level (years) (school education < 9, 9, 10-11, 12, collage/university <3, doctoral studies)

4.4.2 Neonatal characteristics

- Sex at birth (male/female)

4.4.3 Maternal OGTT group data

Data are retrieved from electronic Case Report Form (eCRF) at the time of OGTT unless stated otherwise. Indication for OGTT during pregnancy will be reported according to Appendix Table 4.

- Venous blood glucose
    - Fasting (mmol/L)
    - 1-hour (mmol/L)
    - 2-hour (mmol/L)

4.4.4 GDM group

- HbA1c at first visit (mmol/mol)

5. Analysis

5.1 Outcome definitions

Timing of outcome measures are at birth/post-partum unless stated otherwise. Secondary outcomes for the mother and neonate are defined according to the proposed core outcome sets (35) and/ or outcomes reported in major studies in the research field for comparison reasons. Pre-defined secondary outcomes

for the mother and neonate are listed in Appendix Table 5. Data is retrieved from SPR, NPR, SCB, MBR, Swedish neonatal quality register (SNQ), Cause of death register, National Prescribed Drug Register or eCRF, either manually entered data or ICD codes.

5.1.1 Primary Outcome

- LGA is defined as birth weight above the 90th percentile in the Swedish reference population (36) corrected for gestational age and sex, measured at birth (kg).

5.1.2 Secondary maternal outcomes

- Mother's treatment during pregnancy
  - Diet only
  - Metformin only
  - Insulin only
  - Metformin and insulin
- Gestational hypertension, blood pressure ≥140/90 mmHg, measured two times with at least 4 hour interval during pregnancy after gestational week 20 (37) (mmHg) (ICD-10 O13.9)
- Pre-eclampsia, gestational hypertension defined as above and newly onset proteinuria ≥ 300mg/24 hours after gestational week 20 (37) (ICD-10 O14.0-1A, 1B,1X, 2, 9+ O15.0-2,9, O11.9)
- Gestational weight gain (kg) (weight at first visit and last noted weight with date)
- Emergency CS (ICD-10 O82.1-2, 8-9)
- Elective CS (ICD-10 O82.0)
- Instrumental delivery (ICD-10 O81.0-5, 3A-B, 3W,3X,4A-B, 4W,4X, O83.0-2, 8-9)
- Composite maternal outcomes
  - Shoulder dystocia (ICD-10 O66.0)
  - Perineal trauma, 3rd and 4th degree tears (ICD-10 O70.2, 2C-F, X+O70.3+MBC33)
  - Post-partum bleeding, bleeding ≥ 1000ml (ICD-10 O72.0-3, 1A,B,X, O67.8)

5.1.3 Secondary neonatal outcomes

- Preterm birth (<37 weeks) (ICD-10 O60, SNQ 316,317)
- Small for Gestational Age, birth weight < 10th percentile in the Swedish reference population (36) corrected for gestational age and sex.
- Composite variable for severe child morbidity and mortality
  - Respiratory distress, defined as needing at least 4 hours' respiratory support with supplemental oxygen, continuous positive airway pressure, or intermittent positive pressure ventilation in the 24 hours after delivery (ICD-10 P24.0+P22.0-1,8-9, SNQ 1102-1105 + 1247, 1250, 1253, 1256)
  - Birth trauma, according to IADPSG criteria (38)
    - Spinal cord injury (ICD-10 P11.0,1,2,3,4,9)
    - Peripheral nerve injury/brachial plexus (ICD-10 P14.0, P14.1-3,8-9)
    - Basal skull fracture or depressed skull fracture (ICD-10 P13.0, P13,1)
    - Clavicular fracture (ICD-10 P13.4)
    - Long bone fracture (humerus, radius, ulna, femur, tibia or fibula) (ICD 10 P13.3,8-9)
    - Cranial haemorrhage (Subdural or intracerebral of any kind [confirmed by cranial ultrasound, computerised tomography scan, or magnetic resonance imaging) (ICD 10 P10.0-4+8,9, P52.0-6+8,9)
  - Stillbirth (foetal death at ≥22 + 0 gestational weeks (ICD-10 Z37.1, 1B, 1C, O36.4, P95.9B,C,X) or neonatal death (death of neonate within first 28 days (SNQ 1732,1733,1804,1805, 1809-1818+1901-1903)
  - Need of therapeutic cooling (ICD 10 P21.1B,0,9, P90.9, P91.6+8, P94.2, SNQ 1332)

5.1.4 Exploratory outcome variables

5.1.4.1 Maternal outcomes

- Maternal death up to 42 days after delivery (deaths due to accidents are excluded) (ICD-10 O95.9, O97)

5.1.4.2 Neonatal outcomes

- Birth length (cm)
- Macrosomia defined as birthweight ≥4000g or ≥4500g
- LGA defined as birth weight above the 90th percentile, corrected for gestational age and sex, measured at birth, using reference curves of
    - Intergrowth-21 population (39)
    - Updated Swedish intrauterine growth reference (40)
    - Gestation Related Optimal Weight (GROW) (https://www.gestation.net/)
- LGA defined as birth weight above the 97th percentile (+2 SD) corrected for gestational age and sex, measured at birth, using reference curves of
    - Marsal et al. classification (36)
    - Intergrowth-21 population (39)
    - Updated Swedish intrauterine growth reference (40)
    - GROW (https://www.gestation.net/)

5.1.4 Outcomes for health economic evaluation

Costs are assessed by

- Identifying relevant resource use,
- Measuring each resource for each individual, and
- Valuing each resource by unit costs.

Identify and measure resource use, using the same data sources stated in headline 5.1 Outcome definitions.

- Visits to midwife
- Ultrasound visits
- Visits to physician
- Laboratory blood sampling
- Visits to other healthcare personnel
- Pharmaceutical use
- Mother's and infant's admissions to hospital related to pregnancy, delivery and birth

Valuing resource use by unit costs (Resources are valued by best available cost data, primarily from the Cost per patient database and/or inter-regional price contracts).

- Unit costs for each type of resource

5.2 Analysis methods

For this stepped wedge design, mixed effect logistic models will be used to evaluate the primary outcome, LGA. Mixed effect logistic models will include clusters as random effects and the intervention as a fixed effect and with adjustment for time.

As the randomisation is on the cluster level and not on the participant level, we will adjust for important prognostic predictors for birthweight, including mother´s age, chronic hypertension, smoking or snuff, country of birth and parity. Adjusted and unadjusted data will be analysed.

Because of the stepped wedge study design, design-specific analyses will be conducted such as stratifying by clusters. The secondary adverse neonatal and maternal outcomes will be analysed using the same type of methods and considerations as for the primary outcome.

5.2.1 Sensitivity analysis

Sensitivity analysis excluding different pregnancies from the same women, only including the first pregnancy.

5.2.2 Subgroup analyses

Subgroup analysis on primary and secondary outcomes for the mother and neonate on the population who were untreated before randomisation and treated after intervention i.e. the cohort of women with fasting and 2-hour blood glucose cut off between the SNBH 2015 criteria and previous GDM criteria (Fasting Plasma Glucose (FPG) 5.1-6.9 and/or 2-h Plasma Glucose (PG) 8.5-8.8/8.9/9.9 mmol/L according to definitions in Table 1).

5.2.3 Health economic evaluations

The health economic aspects of the trial will be analysed in three different health economics evaluations: a short-term cost analysis, a short-term cost-effectiveness analysis (CEA) and a long-term model-based CEA. The health economic evaluations will compare the new GDM diagnostic criteria (2013 WHO criteria) to the old GDM criteria (i.e. standard practice for screening, diagnostic criteria and sampling method with variations across regions), in the setting of the Swedish public health services. The evaluations will take a health care perspective, including costs and consequences within the health care sector. Costs are assessed by

- identifying relevant resource use
- measuring each resource for each individual
- Valuing each resource by unit costs.

5.2.3.1 Cost analysis

The cost analysis will include resource use and costs associated with the treatment of GDM, the mother's healthcare utilisation during pregnancy and delivery, and the infant's healthcare utilization after birth. The cost analysis will take a time horizon from first maternal healthcare visit and 28 and 90 days after delivery/birth. Discounting will not be applicable due to the short time horizon. Results will be presented as incremental costs. As a secondary analysis, costs will be related to the study's primary outcome LGA, presented as an incremental cost effectiveness ratio of costs per LGA averted. Parameter uncertainties will be assessed by deterministic and/or probabilistic sensitivity analysis.

5.3 Missing data

Missing data will be handled by multiple imputation if needed.

5.4 Harms

5.4.1 Serious adverse outcomes

SAEs were reported during the study to the Data and Safety Monitoring Board. In addition, SAEs were included in monthly checklist on the website.
SAE were defined as:

- Maternal death. Death of mother included in the study during the study period.
- Serious maternal hypoglycaemia: low blood glucose levels resulting in cognitive impairment that requires assistance from another person to treat
- Lactic acidosis in metformin treated women

5.5 Statistical software

STATA, StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC)
SPSS, IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp

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Table 1. List of included clusters and methods for diagnosing GDM (30)

Cluster	**Number of births/ year**[a]	**Indication for diagnostic 75 g OGTT**									**Diagnostic criteria prior to switch (mmol/L)**	**Overt diabetes** [f] **(mmol/L)**	**Method for glucose analysis**
		History of previous				Clinical indication							
		GDM	**Macrosomia**[b]	**LGA**[c]	**IUFD**	**BMI**	**FH**[d]	**Polyhydramnios**	**Accel growth**	**RBG**			
Gotland[g]	538	24-28	24-28	-	-	≥35	24-28	Yes	Yes	RPG[e] ≥9.0 mmol/L at enrollment week 25, 29, 32/33, 37/38.	FPG <7.0 and 2-h PG 8.9–11.0	FPG ≥7.0 and/or 2-h PG ≥11.1	HemoCue AB HemoCue 201 RT (glucose dehydrogenase)
Västerås[h]	3 120	24-28	24-28	24-28	-	≥35	-	Yess	Yes	RPG[e] ≥9.0 mmol/L at booking week 25, 30, 35.	FPG <7.0 and 2-h PG 8.9–11.0	FPG ≥7 .0 and/or 2-h PG ≥11.1	Beckman Coulter Au (hexokinase)
Stockholm[i]	28 602	T1& 24-28	24-28	24-28	-	≥35	-	Yes	Yes	RPG[e] ≥9 mmol/L at booking, week 25, 29, 32/33, 37/38.	FPG <7.0 and 2-h PG 8.9–11.1	FPG ≥7 .0 and/or 2-h PG ≥11.2	Roche Cobas Beckman Coulter Au. Siemens Advia (hexokinase)
Halland[j]	4 446	12/ 24-28	-	24-28	24-28	≥30	24-28	Yes	Yes	RPG[e] ≥8.0 mmol/L at enrollment, week 12, 28/29, 32, 37	FPG <7.0 and 2-h PG 9.0–11.1	FPG ≥7 and/or 2-h PG ≥11.2	HemoCue AB HemoCue 201 RT (glucose dehydrogenase)
Gothenburg[k]	9 550	25-29	25-29	25-29	-	≥35	25-29	Yes	-	Within one week if RPG[e] 8.0–12.1 mmol/L at first antenatal care visit, week 25, 28–29, 35–36.	FPG ≥7.0 and/or 2-h PG ≥10.0 RPG[e] ≥12.2	Not defined	Nova Biomedical StatStrip TM Multi-Well™ (glucose oxidase)
Örebro[l]	3 565	T1 & 24-28	24-28	24-28	-	≥35	24-28/40	Yes	Yes-within 3 days	RPG[e] ≥9 mmol/L at booking, week 24, 28/29, 33, 37.	FPG <7.0 and 2-h PG 8.9–11.0	FPG ≥7 .0 and/or 2-h PG ≥11.1	Siemens Advia (hexokinase)
Uppsala[m]	4 200	12-14/24-28	24-28/40	24-28/40	-	≥30	24-28	Yes	Yes	RPG[e] ≥8.8 mmol/L at booking, week 25, 28/29, 33, 37	FPG ≥7.0 and/or 2-h PG ≥10.0	Not defined	Abbott Architect (hexokinase)
Dalarna[n]	3 232	12-14/24-28	24-28/40	24-28/40	-	>35	24-28/40	Yes	Yes	RPG[e] ≥9.0 mmol/L at booking, week 24, 28/29, 33, 37.	FPG <7.0 and/or 2-h PG ≥8.9	FPG and/or 2-h PG ≥11.1	Siemens Advia (hexokinase)
Malmö[o]	4 944	10-12	10-12	-	-	≥35	10-12	Yes	No	Capillary 75g OGTT week 28 in all women. FBG[e] ≥7 and/or 2-h PG[e] ≥10.0 mmol/L indication for a	FPG ≥7.0 and/or 2-h PG ≥9.0	Not defined	Roche Cobas (hexokinase)
Lund[p]	3 703	10-12	10-12	-	-	≥35	10-12	Yes	No				
Kristianstad[q]	2 085	10-12	10-12	-	-	≥35	10-12	Yes	No				

	diagnostic OGTT

When not otherwise stated, glucose measurement is based on venous plasma.
BMI, body mass index; FH, family history; FPG, fasting plasma glucose; IUFD, intrauterine foetal death; LGA, large for gestational age, OGTT, oral glucose tolerance test; PG, plasma glucose; RPG, random plasma glucose; T1, trimester 1.
[a]Number of births per year based on data from the SPR 2017
[b]Defined as birth weight ≥ 4.5 kg
[c]Defined as birth weight ≥ +2 standard deviations above the Swedish reference curve (36)
[d]In Dalarna, Malmö, Lund, Kristianstad, Uppsala, Gotland, Halland defined as first degree relative with type 1 or type 2 diabetes, otherwise first degree relative with type 2 diabetes.
[e]Based on capillary samples
[f]Diagnosed and treated as GDM but with rapid management by specialist care unit in contrast to usual maternal healthcare
[g] Gotland (Visby Hospital)
[h] Västerås (Västerås Central Hospital)
[i] Stockholm (Stockholm South General Hospital, Danderyds Hospital, Karolinska University Hospital, Huddinge BB Stockholm, Karolinska University Hospital, Solna, Södertälje Hospital.)
[j] Halland (Varberg Hospital)
[k] Gothenburg (Gothenburg Sahlgrenska Universitetssjukhuset)
[l] Örebro (Örebro University hospital, Karlskoga Hospital)
[m] Uppsala (Uppsala University Hospital)
[n] Dalarna (Falun Hospital)
[o] Malmö (Skåne University Hospital, Malmö)
[p] Lund (Skåne University Hospital, Lund)
[q] Kristianstad (Kristianstad Central Hospital)

Figure 1. Pregnancies included in the CDC4G trial based on gestational week, OGTT dates and GDM status.

Pregnancies	**2017**	**Study period (2018)**	**2019**
Non- OGTT		No OGTT and ≥ 28+0 GW[b]	2018 population followed
OGTT	GDM and ≤ 23+6 GW[a]	OGTT[c]	90 days post-partum[d]

OGTT oral glucose tolerance test, GDM gestational diabetes, GW gestational week
[a]All pregnancies diagnosed with GDM during 2017, but not passed 23+6 gestational week 2018-01-01 are included in the OGTT population in January 2018. If previous OGTT was done during 2017 (when the study guidelines were not implemented), and repeated OGTT was done during the study period (2018) the women is allocated according to 2018 OGTT.
[b] All pregnancies without an OGTT from 28+0 gestational weeks on 2018-01-01 up to 2018-12-31 are included in the non- OGTT group
[c] All pregnancies with an OGTT during 2018-01-01—2018-12-31 are included in the OGTT group unless the indication for the OGTT is polyhydramnios, suspected LGA or OGTT ≥ 36+0 without information on indication, in which case the original group is maintained.
[d] Pregnancies included in the study during the later study periods (months) will be followed until 90 days.

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Appendix for the Statistical Analytical Plan for the CDC4G study

Table 1. Algorithm for starting (A), titration (B), maximum dose (C) for treatment (lifestyle advice, metformin and insulin) in the CDC4G study.

	Dose (mg/IU)
Lifestyle advice [a]	Dietitian
Metformin[b]	
A. Start dose	500x1
B.Titration dose	500x/3rd day
C. Maximum dose	1gx3
Insulin[c]	
A. Start dose (mmol/L)[d]	
Fast acting insulin. 1 hour postprandial cPG	
8–10	4
>10	6
Intermediate acting insulin. Fasting cPG	
5.3–6.0	6
> 6.0	8
B.Titration dose (mmol/L)[e]	
FPG	
<4	- 2
4.0–5.3	± 0
5.3–6	+ 2
>6	+ 4
Postprandial glucose	
<6	- 2
6–8	± 0
8–10	+ 2
>10	+ 4

cPG, Capillary plasma glucose. FPG, Fasting plasma glucose

[a] All women diagnosed with GDM were offered lifestyleadvice. If ≥3 glucose values above target during 1 week led to pharmacological treatment.

[b] Overweight or high fasting and basal glucose levels.

[c] When metformin is not expected to bring hyperglycaemia rapidly under control or considered inappropriate for clinical reasons or declined by the patient. If fasting blood glucose above the target, intermediate acting insulin was the first lineofchoice. Longactinganalogueinsulins if the blood glucose targets were not reached. Rapid acting insulin analogues was added when elevated postprandial glucose levels.

[d] Starting doses are 4–8 units depending on the glycaemia and other clinical factors (e.g. BMI).

[e] Evaluation of glucose values and titration of insulin dose twice a week initially, after which titration is performed once a week. Changes in insulin doses if ≥3 glucose values above target during 1 week.

Table 2. Target glucose during pharmacological treatment.

Timing[a]	**Target for cPG (mmol/L)**
Fasting	<5,3
Before other meals	<6
1-h after meal	<8
Before bedtime	<7

cPG, capillary plasma glucose

[a] Blood glucose is measured 4 times/day in lifestyle treatment group and 7 times/day in pharmacological treated group. Self-measurement of plasma glucose.

Table 3. The minimal requirements on obstetrical surveillance during 2018 for participating centers

All	**Dietary treatment**	**Metformin/insulin treatment**
Written information about diet and exercise	If blood glucose within goal levels no other controls except weight estimation week 38 for pre-delivery assessment.	Ultrasound weight estimation at least 2 times, week 28-32 and latest at week 38.
Conventional maternal healthcare controls	Induction when indicated according to current guidelines at the clinic (provided that weight estimation is normal)	Induction if not delivered, at the latest week 40+6

Table 4. OGTT indications during pregnancy pre-and post-intervention

BMI above threshold (kg/m^2) (≥ 30 or 35)
Previous LGA, +2SD
Previous macrosomia (gram) (≥ 4000 or 4500)
Previous GDM
History of 1st degree relative with Diabetes Mellitus
Accelerated foetal growth (cm)
Polyhydramnios (amniotic fluid index ≥24 or deepest vertical pocket ≥8 (cm)
Random blood glucose during pregnancy (mmol/L)
Previous IUFD
Other reasons

BMI body mass index, IUFD intrauterine fetal demise, LGA large for gestational age, OGTT oral glucose tolerance test, GDM Gestational diabetes mellitus

Table 5. Pre-defined secondary outcomes and sources for mother and neonate either from register data or based on ICD codes

Secondary maternal outcomes
• Induction of labor (SPR, ICD-10 O61.0,1,8,9,0A, 0B,0X, 1A, 1B, 1X)
• Length of maternal stay from delivery to discharge (SPR, PR, eCRF)
• Breastfeeding at hospital discharge (SPR)
• SRH during and after pregnancy (SPR) (ordinal,1 = Very good, 2 = Good, 3 = nor good or bad, 4 = Bad, 5 = Very bad, 6 = Don't know)
• Satisfaction with childbirth (SPR) (VAS 1-10)
Secondary neonatal outcomes
• NICU days (>24h (3)) (eCRF, SNQ 913,914,1701,1704,1712)
• Erbs palsy (NPR, ICD-10 P14.0, P14.1, P14.3 SNQ 2401)
• Metabolic acidosis, pH <7.05 and base excess >12 mmol/L in umbilical artery or pH <7.00 in umbilical artery (SPR, SNQ 401,404)
• 5 min Apgar score < 4 (SPR, SNQ 329, 330, 331)

• Hypoxic ischemic encephalopathy II-III (SNQ 1308-1310, NPR ICD-10 P91)
• Intracranial haemorrhage (SNQ 1311-19 +1321, NPR ICD-10 P10, P52+P11.0-3, 9)
• Meconium aspiration syndrome (SNQ 1104, NPR ICD-10 P24.0)
• Mechanical ventilation (SPR, SNQ 1148, 1151, 1169, 1172, ICD-10 DG021, DG022, DG002)
• Fractured clavicle/humerus (SPR, NPR ICD-10 P13)
• Blood glucose in infants <2.6 (mmol/L) (SNQ, eCRF, P70.4, 4A-B)
• Hypoglycaemia needing IV therapy (eCRF, SNQ 1401-1403, NPR ICD-10, P70.4, P70.4A, P70.4B)

SRH self-rated health, SPR Swedish pregnancy register, NICU neonatal intensive care unit, SNQ Swedish national quality register, eCRF electronic case report form, NPR national patient register

1. Women's NCCf, Health Cs. Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. 2010;NICE Clinical Guidelines, No. 107.
2. Maršál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta paediatrica. 1996;85(7):843-8.
3. Definitions IAoDiPSGWGoO, Feig DS, Corcoy R, Jensen DM, Kautzky-Willer A, Nolan CJ, et al. Diabetes in pregnancy outcomes: a systematic review and proposed codification of definitions. Diabetes/metabolism research and reviews. 2015;31(7):680-90.