Hyperglycemia in pregnancy.

Diagnostics, biomarkers, follow-up, and monitoring of glycemic control

Johanne Holm Toft

Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment and funding

The present work was carried out at the Department of Obstetrics and Gynecology, Stavanger University Hospital (SUS) in affiliation with the Department of Clinical Science, University of Bergen (UiB) in the period 2016–2022.

My main supervisor has been Inger Økland, MD PhD, obstetrician, Associate Professor II at the University of Stavanger (UiS), and previous Head of Research (SUS). My co-supervisors has been Inger Hjørdis Bleskestad, MD PhD, endocrinologist, Department of Internal Medicine (SUS), and Lasse Gunnar Gøransson, Professor, Department of Clinical Medicine (UiB), and nephrologist, Department of Internal Medicine (SUS).

We collaborated with Christina Furskog Risa, PhD, Associate Professor (UiS), Ingvild Dalen, PhD, biostatistician, Associate Professor II (UiS), Section of Biostatistics, Department of Research (SUS) and Øyvind Skadberg, MD, Department of Medical Biochemistry (SUS). I have been a member of the research group at the Department of Obstetrics and Gynecology (SUS).

I started my scientific carrier at the Medical Student Research Programme, Norwegian University of Science and Technology (NTNU) in the years 2004–2009. I fulfilled the PhD program at The Department of Cancer Research and Molecular Medicine, and the late Professor Rigmor Austgulen was my principal supervisor in that period.

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Abbrevations

AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
CLSI	Clinical and Laboratory Standards Institute
CV	Coefficient of variation
DIP	Diabetes in pregnancy
DOHaD	Developmental Origin of Health and Disease
EDD	Estimated date of delivery
FIGO	International Federation of Gynecology and Obstetrics
FPG	Fasting plasma glucose
GA	Glycated albumin
GDM	Gestational diabetes mellitus
GP	General Practitioner
HAPO	Hyperglycemia and Adverse Pregnancy Outcome
HbA1c	Glycated hemoglobin A1c
HIP	Hyperglycemia in pregnancy
IADPSG	International Association of Diabetes and Pregnancy Study Groups
IDF	International Diabetes Federation
IFCC	International Federation of Clinical Chemistry
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LGA	Large for gestational age
NCD	Non-communicable disease
OGTT	Oral glucose tolerance test
OR	Odds ratio
RI	Reference interval
ROC	Receiver operating characteristics
SD	Standard deviation
SGA	Small for gestational age
SMBG	Self-monitoring of blood glucose
SVD	Svangerskapsdiabetes
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
WHO	World Health Organization

Sammendrag

Diabetes mellitus er blant de største globale folkehelseutfordringene i vår tid. Hyperglykemi affiserer ett av seks svangerskap og svangerskapsdiabetes (SVD) er den vanligste årsak. Gravide med hyperglykemi har økt risiko for de fleste svangerskapskomplikasjoner og kvinner med SVD har en tidoblet risiko for å utvikle diabetes mellitus type 2. Barn født av mødre med diabetes i svangerskapet har økt risiko for overvekt og diabetes. Det er kjent at god glykemisk kontroll reduserer risiko for både mor og barn, på kort og lang sikt. I dag benyttes HbA1c som markør på glykemisk kontroll, selv om metoden har kjente svakheter i svangerskap.

Glykert albumin (GA) gjenspeiler blodsukkeret siste 2–3 uker. I Asia er bruken av GA utbredt, og GA er anbefalt brukt hos gravide. Ved Stavanger universitetssjukehus (SUS) er det utviklet en ny analysemetode for GA basert på væske kromatografi-massespektrometri (LC-MS/MS).

Mål for denne avhandlingen var: å etablere referanseområdet for GA hos friske gravide ved LC-MS/MS; evaluere bruk av GA og HbA1c i diagnostikk av SVD; undersøke forekomsten av SVD etter ulike retningslinjer; undersøke norske kvinners erfaringer med oppfølging av SVD; kartlegge assosiasjonen mellom GA og kontinuerlig vevsglukose (CGM) data hos gravide med pre-gestasjonell diabetes; og studere GA og HbA1c i monitorering av glykemisk kontroll ved bruk av CGM data som referanse. Doktorgradsarbeidet inkluderer tre kliniske studier utført ved SUS i perioden 2016–2020, kvantitative og kvalitative studiedesign er benyttet.

Referanseintervallet for GA i svangerskap ble etablert. Vi fant en tredobling i forekomst av SVD, men når vi sammenlignet forekomsten etter nye og gamle diagnostiske kriterier, var det en liten nedgang. Verken GA eller HbA1c egnet seg i diagnostikk av SVD. De fleste kvinnene påpekte manglende oppfølging av SVD etter fødsel. Glykemisk kontroll bedret seg under svangerskapet hos kvinner med pre-gestasjonell diabetes, samtidig med lavere glykemisk variabilitet og fallende GA-nivå. GA korrelerte med CGM data og analyser viste at GA var bedre enn HbA1c til å avdekke tid utenfor anbefalt målområde for CGM data.

Konklusjoner er at verken GA eller HbA1c bør brukes til å diagnostisere SVD. GA kan benyttes i monitorering av glykemisk kontroll hos gravide med pre-gestasjonell diabetes og avdekket dårlig glykemisk kontroll bedre enn HbA1c. Forekomsten av SVD var 14%. Oppfølging av kvinner med SVD bør bli bedre.

Abstract

Diabetes mellitus is among the largest public health concerns of our time. Hyperglycemia affects one in six pregnancies, the majority due to gestational diabetes mellitus (GDM). Women with hyperglycemia have increased risk of most pregnancy complications, and women with prior GDM have a tenfold increased risk of diabetes mellitus. Offspring of mothers with GDM are more likely to develop diabetes mellitus and obesity. It is well known that good glycemic control reduces the risks for mothers and children, in the short and long run. Today, HbA1c is used to monitor glycemic control, even its known limitations in pregnancy.

Glycated albumin (GA) reflects short-term glycemia (2–3 weeks). In Asia, GA is used frequently, also during pregnancy. Recently, a new method for GA measurement using LC-MS/MS was developed at Stavanger University Hospital (SUS).

The aims of the thesis were to: Establish a reference interval (RI) for GA in healthy pregnancies analyzed by LC-MS/MS; evaluate the accuracy of GA and HbA1c in the diagnosis of GDM; explore the prevalence of GDM using different diagnostic criteria; elucidate Norwegian women's experiences of GDM follow-up; explore the association between GA and continuous glucose monitoring (CGM) metrics across gestation in diabetic pregnancies; and investigate the accuracy of GA and HbA1c to detect poor glycemic control using CGM metrics as the reference. The thesis includes three clinical studies conducted at SUS in the years 2016–2020, quantitative and qualitative study designs have been utilized.

The RI for GA in pregnancy was established. An almost threefold increase in GDM prevalence was found. However, when comparing the old and new diagnostic criteria, the prevalence declined slightly. Neither GA nor HbA1c differentiated between those with or without GDM. Most women experienced a lack of follow-up for GDM after delivery. Glycemic control improved across gestation in women with pre-gestational diabetes coinciding with decreased glycemic variability and lower mean GA level. GA correlated with CGM metrics, and GA was more accurate than HbA1c to detect time outside the recommended range for CGM metrics.

In conclusion, neither GA nor HbA1c should be used in GDM diagnostics. GA may be used in monitoring glycemic control in women with pre-gestational diabetes, and was more accurate than HbA1c to detect poor glycemic control. The prevalence of GDM was 14%. Improvements in GDM follow-up after delivery are required.

List of Publications

Paper I

Toft JH, Dalen I, Skadberg Ø, Gøransson LG, Økland I, Bleskestad IH. **Glycated albumin and continuous glucose monitoring metrics across pregnancy in women with pre-gestational diabetes.** Endocrinol Diab Metab. 2022;00:e376.

Paper II

Toft JH, Bleskestad IH, Skadberg Ø, Gøransson LG, Økland I. **Glycated albumin in pregnancy: LC-MS/MS-based reference interval in healthy, nulliparous Scandinavian women and its diagnostic accuracy in gestational diabetes mellitus.** Scand J Clin Lab Invest. 2022;82(2):123-131.

Paper III

Toft JH, Økland I, Risa CF**. Gestational diabetes mellitus follow-up in Norwegian primary health care: a qualitative study.** BJGP Open. 2022;6(1).

What this research is about

The overall rationale for this thesis was a wish to improve pregnancy outcomes and reduce the burden for women with hyperglycemia in pregnancy. There were many questions yet to be answered. Would this alternative biomarker properly reflect glycemia and glycemic excursions in women with pre-gestational diabetes? What about GDM diagnostics, could the use of GA reduce the need for the cumbersome OGTTs? What about the introduction of the new GDM guideline? Did more women get the GDM diagnosis?

We wanted to assess the use of GA analyzed by LC-MS/MS in monitorering glycemic control in women with pre-gestational diabetes. Thus, we designed a prospective study to collect blood glucose data across gestation along with repeated measurements of GA and HbA1c.

Before assessing the clinical potential of GA in pregnancy, establishment of a reference interval (RI) in a healthy population is warranted. The reference population should be as similar as possible to the population to which the test will be applied, with the exception of the presence of disease. Therefore, we planned a cross-sectional study to establish the RI of GA and invited women with healthy pregnancies to participate. Coinciding, the Norwegian guideline for GDM was published (2017). Thus, to explore the prevalence of GDM according to the new diagnostic criteria, we invited pregnant women to OGTT. We included nulliparous pregnant women >25 years. The age-criterion was among the criteria being most discussed.

In comparison with reports from the Medical Birth Registry of Norway, our results showed an almost threefold increase in the prevalence of GDM. However, when we compared the old and new diagnostic criteria, the prevalence was almost unchanged. However, different women were diagnosed with GDM using the various guidelines.

Women with GDM are recommended close follow-up in primary health care throughout pregnancy and after delivery. According to the Norwegian GDM guideline,

measurement of HbA1c is recommended at 4 months after birth, then annually. Lifestyle changes and weight loss are important to reduce the risk of recurrent GDM and development of type 2 diabetes mellitus (T2DM) in the future.

Few reports exist on Norwegian women's experience of GDM follow-up. Worldwide, several studies have reported a lack of follow-up after delivery. My experience from the outpatient clinic was that many women in Rogaland also suffered from inadequate follow-up, both in pregnancy and after delivery. Therefore, we conducted a qualitative interview study with the women diagnosed with GDM during the cross-sectional study, to explore these women's experiences.

This PhD thesis includes three clinical studies. Quantitative and qualitative design are being used. The research assesses different aspects of hyperglycemia in pregnancy, the use of GA in monitoring of glycemic control, and in the diagnostics of GDM. Moreover, the prevalence of GDM with old and new criteria are assessed along with Norwegian women's experiences of GDM follow-up.

1. Introduction

1.1 Historical aspects

Although descriptions of diabetes mellitus are found in ancient Egyptian papyrus, the first reference to diabetes mellitus in pregnancy is as recent as in 1824. In his thesis, Dr Bennewitz described a complicated delivery of a 5 kg stillborn in a multiparous German woman with extensive thirst and glucosuria [1]. In 1882, maternal mortality rates of 50% in British women with diabetes mellitus were reported [2]. The discovery of insulin in 1921 revolutionized the prognosis for people living with diabetes. Before access to insulin, women with diabetes mellitus rarely reached childbearing age, and the chances to conceive and have a successful pregnancy, were low. With insulin available, the clinical scenario of diabetes mellitus in pregnancy became a fact. Following improved glycemic control, the risk of ketoacidosis was reduced and the prognosis improved.

Over time, it became apparent that pre-gestational diabetes was associated with increased risk of macrosomia. In 1952, Jørgen Pedersen from Denmark proposed that maternal hyperglycemia causes fetal hyperglycemia resulting in hypertrophy of fetal pancreatic islet tissue [3]. This in turn causes hypersecretion of insulin, leading to increased fetal utilization of glucose and subsequent fetal overgrowth. The Pedersen hypothesis has made the basis for our understanding of fetal overgrowth in diabetic pregnancies.

During the 1960s, the first reports describing high incidence of congenital anomalies in newborns of mothers with diabetes mellitus were published [2]. Hyperglycemia in early pregnancy was proposed as the underlying mechanism.

In 1972, a linear relationship between glycemic control and perinatal mortality was reported [4]. Today, obtaining glycemic control is still recognized as the most important factor to avoid maternal and fetal complications.

Back in the 1950s, when the Pedersen hypothesis was established, the majority of pregnant women with hyperglycemia had type 1 diabetes mellitus (T1DM), whereas today, most women have GDM, and increasing numbers have T2DM. The underlying pathophysiological mechanisms differ. β-cell failure and lack of insulin are hallmarks of T1DM, contrasting β-cell dysfunction and insulin resistance in GDM and T2DM [5].

Historically, obstetrical concerns about large fetuses have focused mainly on women with diabetes mellitus in pregnancy. In light of the growing epidemic of obesity, one has questioned whether it is time to rethink our beliefs related to fetal growth [6]. Pregnant women today are older, have higher pre-pregnancy BMI, and gain more weight during gestation. Fetal growth is complex, and the causes to fetal overgrowth include both genetic and environmental factors. Through the last 2–3 decades, there has been an overall 15–25% rise in women giving birth to large for gestational age (LGA) neonates worldwide, and the rapid increase has environmental causes [7]. There is growing evidence that the obesogenic environment with hyperlipidemia along with hyperglycemia, is contributing to fetal adiposity and metabolic dysfunction [7].

In the St. Vincent Declaration initiated by the World Health Organization (WHO) and the International Diabetes Federation (IDF), published in 1989, one of the 5-year targets was to *achieve a pregnancy outcome in the diabetic woman that approximates that of the non-diabetic woman* [8]. Today, 33 years later, although improved prognosis, diabetic pregnancies are still considered high-risk with increased risk for maternal-fetal complications across pregnancy, during delivery, and postpartum.

1.2 Hyperglycemia in pregnancy

1.2.1 Definitions and epidemiology

Worldwide, one in six live births occur to women with hyperglycemia during pregnancy [9]. Thus, hyperglycemia is among the most common medical complications women encounter during gestation.

Hyperglycemia in pregnancy (HIP) is classified as either *diabetes in pregnancy* (DIP) or *gestational diabetes mellitus* (GDM) [9]. DIP is either pre-existing diabetes mellitus, mostly T1DM or T2DM, or hyperglycemia that meets the WHO criteria for diabetes mellitus in the non-pregnant state, diagnosed during pregnancy, and often referred to as overt diabetes [10].

GDM is hyperglycemia diagnosed for the first time during pregnancy [9]. GDM may occur any time across pregnancy, but most likely after 24 weeks. The diagnostic criteria for GDM include lower cut-off values for plasma glucose than DIP. With GDM, the glucose levels returns to normal after delivery. Overall, hyperglycemia during pregnancy is associated with maternal, perinatal and neonatal morbidity and mortality, as well as long-term consequences for mothers and children [11].

The IDF estimates that the global prevalence of pre-gestational diabetes has doubled from 1990 to 2020, but that the overall prevalence is still low ca 1% [12]. In contrast, the estimated 2021 global prevalence of GDM was 14%, ranging from around 7% in North America and Europe, to 27% in Middle East and North Africa [13].

According to the Medical Birth Registry of Norway, the prevalence of pregnancies complicated by pre-gestational diabetes has been stable around 0.7% for the last decade, whereas the prevalence of GDM has tripled and was 6.3% in 2021 [14]. However, in a recent study, merging data from four Norwegian cohort studies, a GDM prevalence around 10% was reported [15].

1.2.2 Metabolic adaptations in the normal pregnancy

In a normal pregnancy, multiple metabolic alterations occur to ensure a continuous supply of metabolites to support the growth and development of the fetus. The composite of changes are dynamic and evolve throughout gestation. Glucose is the primary energy source, although fatty acids also play a critical role in fetal development, and as a secondary, key energy source [16].

Insulin and glucagon are the major hormones regulating fuel mobilization and storage. Insulin orchestrates the metabolism of not only glucose, but also lipids and amino acids [17]. In the liver, insulin promotes glycogen and fat synthesis while suppressing glycogenolysis and ketogenesis. In muscle tissue, insulin promotes glycolysis, glycogen and protein synthesis, and suppresses proteolysis. In adipose tissue, insulin promotes fat storage and glycerol synthesis, while suppressing lipolysis [17]. Glucagon is the major counter-regulatory hormone of insulin.

During pregnancy, the alterations in maternal lipid metabolism are characterized by an anabolic state in the first and second trimester, switching to a catabolic state in the third trimester [16].

Maternal insulin resistance is increasing in all pregnancies, especially from the second trimester. Insulin sensitivity, defined as the ability of insulin to increase glucose uptake in muscle and adipose tissue, decreases as much as 50% in late gestation [18]. As a compensatory mechanism, there is a two- to three-fold increase in maternal insulin secretion from the pancreatic β-cells, resulting in blood glucose within the normal ranges. The switch from net anabolic to net catabolic state during pregnancy has been attributed to the alterations in maternal insulin sensitivity [16].

The level of maternal fasting glucose decreases during a normal pregnancy, even if the endogenous glucose production increases with 30% [18]. Factors contributing to the lower concentrations of fasting glucose are most likely the high utilization of glucose by the fetal-placental unit, as well as the rise in maternal plasma volume.

1.2.3 Diabetes in pregnancy

Summary of the risks during pregnancy and delivery

Women with pre-gestational diabetes mellitus or overt diabetes have increased risk of most pregnancy complications. There are risk of miscarriage, fetal anomalies, placental failure, hypertensive disorders and preterm delivery, both spontaneously and induced [19]. Moreover, fetal distress, small for gestational age (SGA), LGA, shoulder dystocia,

perinatal and sphincter injuries, operative deliveries and stillbirth, are more common. In addition, higher neonatal morbidity and mortality are observed [19].

In addition, women with DIP have higher level of emotional stress and anxiety in comparison with women with healthy pregnancies [20]. Furthermore, women with established nephropathy and retinopathy are at risk of deterioration, and if serum creatinine is elevated, there is an increased risk of permanent loss of renal function [19].

Finally, maternal hypoglycemia is frequent during pregnancy, and repetitive hypoglycemic excursions may lead to a temporary increase in hypoglycemia unawareness, a condition where the signals of hypoglycaemia are detected less well and/or at a lower glucose level [21].

The risk of fetal anomalies

In a background population, the rate of congenital malformations is around 2%. In women with DIP, the risk is increased around two- to fivefold [22]. Hyperglycemia in the period around conception/early pregnancy is probably the major teratogen, but obesity and other factors associated with metabolic dysfunction may contribute [22].

The risk of anomalies increases markedly with poor glycemic control; from 5% when HbA1c is in the range 62–86 mmol/mol to 25% when HbA1c is >86 mmol/mol [19]. A reduction in HbA1c by 11 mmol/mol reduces the risk of malformations by around 50% [22]. In a nationwide population-based study including all births in Norway during 1999–2004, the risk of anomalies was 5.7% in offspring of women with T1DM [23].

The risk of hypertensive disorders

Hypertensive disorders in pregnancy constitute four major groups: Essential hypertension, gestational hypertension, preeclampsia, and preeclampsia superimposed on hypertension, all of them being more common in women with hyperglycemia in pregnancy [24].

Preeclampsia is around four to five times more frequent in women with T1DM [25, 26], and the risk increases with poor glycemic control (odds ratio (OR) 1.65 for each 11 mmol/mol increase in HbA1c) [19]. A recent Norwegian population-based study reported ORs of 5.0, 10.2, and 2.7 for developing early (<34 weeks), intermediate (34–36 weeks) and late preeclampsia (>36 weeks) respectively, in women with T1DM [27].

The risk of stillbirth and perinatal deaths

There is an increased risk of early spontaneous fetal loss and miscarriage, often because of non-viable, severe malformations [22]. The OR for stillbirth in Norwegian women with T1DM was 3.6, whereas the OR of perinatal and infant death were 2.9 and 1.9, respectively [26].

Antenatal care in Norway

In Norway, antenatal care of women with DIP is primarily organized in secondary healthcare with antenatal visits every 2–4 weeks [28]. In accordance with international recommendations, most consultations are multidisciplinary where the woman meets an obstetrician, an endocrinologist and a midwife during the same visit.

To reduce the risk of congenital defects, women with T1DM or T2DM planning pregnancy, are recommended good glycemic control (HbA1C <53 mmol/mol). For the majority, the first ultrasound examination is in early first trimester to confirm intrauterine, vital pregnancy and to assess gestational age. At pregnancy week 12, a complete ultrasound examination of the fetal anatomy is performed. In study I, participants were followed-up in accordance with these recommendations.

Throughout the study period of study I (2016–2018), women with pre-gestational diabetes and otherwise uncomplicated pregnancies, labour was induced at the estimated date of delivery (EDD). However, during the last years, and in accordance with recent recommendations in the national guideline for obstetrics [28], at Stavanger University Hospital, labour is now induced at pregnancy week 38–39 for most women with DIP.

1.2.4 Gestational diabetes mellitus

Pathophysiology of GDM

In women developing GDM, both excessive insulin resistance and insufficient insulin production contribute to the hyperglycemia [18]. In women with risk factors for developing GDM, these changes are probably present prior to gestation. An overview of the pathophysiological mechanisms in GDM are presented in Figure 1.

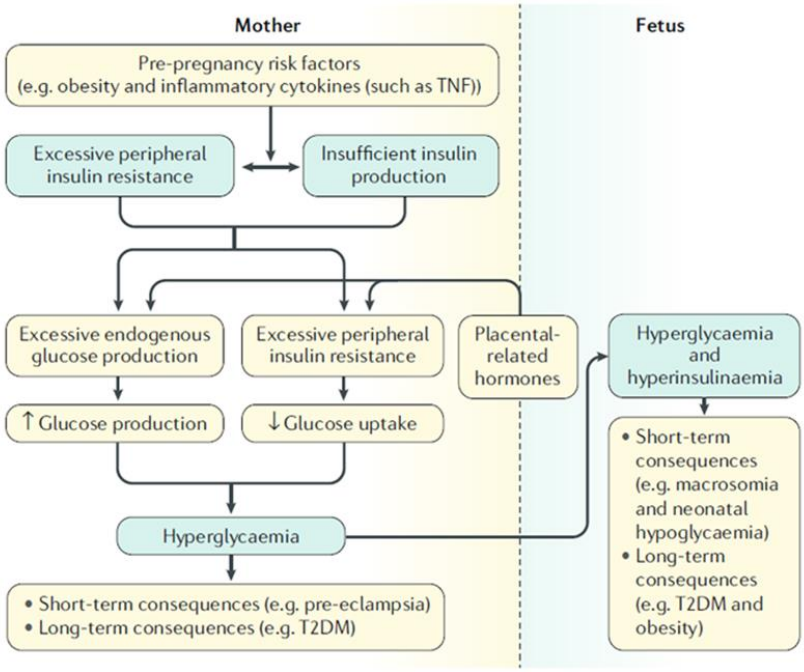


Figure 1. Pathophysiology of GDM. McIntyre et al. [18]. Reprinted with permission

Risk factors for GDM

There are several risk factors for GDM, some of them modifiable. Maternal risk factors include older age, high parity, overweight, excessive weight gain in pregnancy as well as weight gain between pregnancies, polycystic ovarian syndrome, ethnicity and a family history of diabetes [9, 18, 29]. In addition, preeclampsia, macrosomia (in

previous or index pregnancy), and a history of GDM, are well-known risk factors for GDM [9, 25].

In a recent Norwegian population-based study, the risk of GDM varied substantially between maternal country of birth, highest in women from Bangladesh (OR 8.4), Sri Lanka (OR 7.6) and Pakistan (OR 5.5) compared to women with Norwegian descent [30]. Moreover, the risk of GDM appeared to increase with longer time of residence in certain immigrant groups [30].

As many of the risk factors for GDM are increasingly common (older age, overweight, family history), and since there are fewer pregnant women with no risk factors, the International Federation of Gynecology and Obstetrics (FIGO), WHO and IDF support universal screening for GDM [9].

Modifiable lifestyle factors

Overweight and obesity are the most important modifiable risk factors [31]. In addition, cigarette smoking increases the risk of GDM, independent of pre-pregnancy BMI or other factors. According to the Medical Birth Registry of Norway, among the 55 892 deliveries in 2021, maternal BMI was ≥25 in 38.6%, whereas 1.9% and 1.1% were smokers in early vs late pregnancy, respectively [14]. Healthy dietary habits along with physical activity both before and across pregnancy reduce the risk of GDM [18].

Short and long-term risks

During pregnancy, women with GDM have risk of the same pregnancy complications as women with DIP [9], described in chapter 1.2.3. In addition, women with a history of GDM have a tenfold increased risk of being diagnosed with T2DM later on [32], and within 15 years postpartum, one third of women with GDM have been diagnosed with T2DM [33]. Moreover, there are findings indicating a twofold higher risk of cardiovascular disease (CVD) in women with prior GDM, and this risk is independent of development of T2DM [34]. In a systematic review and metaanalysis, the CVD risk was apparent within ten years after pregnancy [34].

For the offspring of women with GDM, there are risk of overweight, metabolic syndrome and pre-diabetes or diabetes [18]. In a Danish study, 21% of the offspring (18–27 years old) had diabetes or pre-diabetes, an eightfold greater risk compared with the background population [35].

Treatment of GDM

To reduce the risks associated with GDM, the blood glucose level should be within a certain range. The Norwegian GDM guideline recommends fasting glucose <5.3 mmol/l, and glucose two hours postprandial <6.7 mmol/l [36]. To achieve this, most women with GDM have to adjust dietary habits and increase physical activity. Lifestyle modification is the cornerstone of GDM treatment. If several glucose measurements are above target, medication (insulin and/or metformin) may be necessary.

Follow-up of GDM

According to the Norwegian GDM guideline from 2017, women diagnosed with GDM should be followed-up in primary healthcare by a general practitioner (GP). They should be taught self-monitoring of blood glucose (SMBG) and be offered lifestyle counselling [36]. Women with several glucose measurements above the target range during a two-week period should be referred to secondary healthcare. The endocrinologist will then consider anti-diabetic therapy and the obstetrician will assess the growth and well-being of the fetus through an ultrasound examination.

4–6 months after delivery, the Norwegian guideline recommends a GP consultation with HbA1c measurement, lifestyle counselling and individualized risk assessment. Moreover, women are advised to check their HbA1c level annually and before a new pregnancy.

Despite the well-documented elevated diabetes risk in women with a history of GDM and the growing evidence that lifestyle intervention and metformin effectively reduce the risk, long-term follow-up still appears challenging worldwide [37-39].

Women's experiences with GDM

Through the last decades, increasing numbers of qualitative studies exploring women's experiences with GDM have been published. A common finding is the high emotional burden and stigma of GDM, and the lack of postpartum follow-up [40-42]. Few studies have explored Norwegian women's experiences of GDM, and to my knowledge, no studies to date have explored the short- and long-term follow-up of GDM following implementation of the Norwegian guideline from 2017.

1.3 Evolving diagnostic criteria

In 1964, O'Sullivan and Mahan proposed the first set of diagnostic criteria for GDM. The criteria were validated on their ability to predict subsequent maternal diabetes mellitus later in life [43]. The O'Sullivan and Mahan criteria included an OGTT using 100 gram glucose. Venous whole blood samples were taken fasting, and at 1, 2 and 3 hour after the glucose ingestion. The criteria made the basis for the GDM diagnosis in the USA. Interestingly, at that time about 2% of pregnant American women fulfilled the criteria [44].

Along with improved analytical methods, there has been a shift towards venous plasma or serum samples. Traditionally, the WHO has supported the use of uniform diabetes mellitus criteria, within and outside pregnancy [44]. In the WHO-1999 criteria, based on increased risk of diabetic microvascular complications, the GDM criteria were fasting plasma glucose (FPG) >7.0 mmol/l or 2 hour glucose level >7.8 mmol/l [45]. Most women were diagnosed with GDM on the latter 2 hour criterion.

In 2008, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study showed the association between maternal hyperglycemia and a linearly increased risk of perinatal complications with no obvious threshold value [46]. Moreover, the HAPO study addressed the importance of having all three glucose values (fasting, 1 hour, and

2 hour post glucose load) in the OGTT since none of the glucose values were significantly correlated, and no single value was better in predicting a GDM diagnosis.

Consequently, The International Association of Diabetes and Pregnancy Study Groups (IADPSG) proposed new diagnostic criteria and universal GDM screening with a one-step 75 gram OGTT at pregnancy week 24–28 for all pregnant women [47]. For the first time, the diagnostic criteria for GDM were based on perinatal outcomes.

The IADPSG-criteria were criticized. Applying the criteria retrospectively to the HAPO-cohort, would result in 18% prevalence of GDM [44]. Many argued that such a high prevalence was unlikely, whereas others stated that it was in line with the rising prevalence of obesity and increasing rate of glucose intolerance. The economic aspects, cost-effectiveness and medicalization have also been part of the debate.

In 2013, the WHO published an updated guideline, which adopted the IADPSG diagnostic criteria, but did not conclude on screening strategy [48].

Table 1. Diagnostic threshold values for gestational diabetes mellitus

Criteria	Fasting plasma glucose (mmol/l)	1 hour glucose, OGTT (mmol/l)	2 hour glucose, OGTT (mmol/l)	3 hour glucose, OGTT (mmol/l)	Number of elevated results (≥)
O'Sullivan and Mahan, 1964	5.0*	9.2	8.1	7.0	2
WHO, 1999	7.0	-	7.8	-	1
IADPSG, 2010	5.1	10.0	8.5	-	1
WHO, 2013	5.1	10.0	8.5	-	1
NICE, 2015	5.6	-	7.8	-	1
Norwegian guideline, 2017	5.3	-	9.0	-	1

*venous whole blood

In 2017, the current Norwegian GDM guideline was published [36]. Until then, the WHO guideline from 1999 had been used in Norway. A change in screening policy from selected high-risk women to a nearly comprehensive screening of close to 70% of the pregnant population was presented. In addition, new diagnostic criteria were introduced,

which included FPG 5.3–6.9 mmol/l and 2 hour glucose level 9.0–11.0 mmol/l. Thus, the Norwegian glucose criteria differed from WHO-2013, as the cut-offs were based on an OR of 2.0 for adverse outcomes derived from the HAPO-study, whereas the WHO-2013 used an OR of 1.75. The various GDM criteria included in the different guidelines mentioned above are included in Table 1.

The Norwegian GDM debate

In Norway, the introduction of the GDM-guideline in 2017 led to a long-lasting debate about cost-benefit, medicalization and, in particular, the lack of evidence supporting widespread GDM screening [49]. Two years later, in 2019, the Norwegian Directorate of Health announced that they would revise the screening criteria.

In 2021, Oslo Economics published a health economic analysis evaluating the screening criteria [50]. The analysis was done on behalf of the Directorate of Health, and concluded that offering screening for the most 'restrictive target population' (BMI ≥25 and age >30 years in addition to high-risk groups), probably represented the alternative being most in line with the national recommendation for priority setting in healthcare [51]. To date, no revisions in the screening criteria have been included in the Norwegian GDM guideline. In summary, there is still a lack of international consensus on the diagnosis of GDM as both the diagnostic and screening criteria differ.

1.4 Oral glucose tolerance test

The OGTT is the gold standard test for diagnosing GDM. FIGO, IDF, and the WHO support the one-step procedure utilizing a 75 gram glucose load after an overnight fast [9]. In contrast, the American College of Obstetricians and Gynecologists (ACOG) recommends the two-step approach that includes an initial nonfasting glucose challenge test followed by a full 3 hour, 100 gram OGTT if the glucose value exceed threshold on the challenge test [52].

Despite the two approaches, the varying glucose loads and duration of the OGTTs, different diagnostic cut-offs, and number of glucose values needed to exceed threshold, the OGTT remains the gold standard test in the diagnosis of GDM. Another drawback with the OGTT includes the fasting, which may be challenging during pregnancy. Additionally, the OGTT is time-consuming for the women and the healthcare system. Moreover, for decades there have been raising concerns about the reproducibility of the OGTT [53]. Overall reproducibility of 66–78% are reported in pregnant women [53]. However, the IADPSG predicts that simpler and more cost-effective strategies as FPG or biomarkers will replace the OGTT in the future [47].

1.5 Life-course approach

The major cause of global premature mortality is no longer the communicable diseases such as infections, but chronic diseases, among them diabetes mellitus [54]. Today, the non-communicable diseases (NCDs), including CVD, chronic respiratory disease, cancer, and diabetes mellitus account for more than 70% of all deaths globally [55].

NCDs are chronic conditions, tending to be of long duration, and treatable, but seldom curable. NCDs are the result of a combination of genetic, physiological, environmental and behavioral factors [56]. In addition, the risks for NCDs start from early fetal life and increase cumulatively along the trajectory of the life-course [57].

The life-course can be visualized as a circle including the various stages of life: embryonic and fetal life, infancy, childhood, adolescence and reproductive age, where positive and negative events at any stage may have an impact on subsequent stages and even across generations [58]. The life-course approach aims to prevent disease and promote health across generations. Figure 2 presents the life-course view of NCD risk.

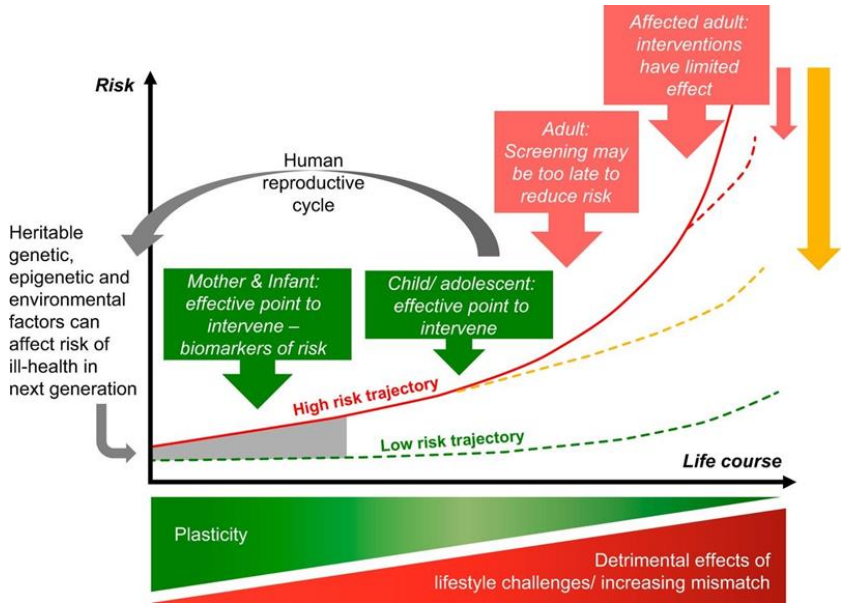


Figure 2. Life-course view of non-communicable disease risk. Risk increases in a nonlinear way because of declining plasticity and accumulative damage from lifestyle-imposed or other factors. Hanson et al. [59]. Reprinted with permission.

The Developmental Origins of Health and Disease (DOHaD) concept is complementary to the life-course approach, and suggests that events before birth can have life-long consequences, and that prevention in early life could improve future health [60]. After the rise of epidemiological data from the 1944–1945 Dutch famine cohort showing that maternal starvation during gestation correlated with CVD and metabolic disease in the offspring, the DOHaD concept gained momentum [61]. Although initially focusing on CVD, DOHaD now includes the other NCDs. To address the increasing global burden of NCDs, a key focus is to consider early life factors and to limit the passage of NCD risks to the next generation [60].

In 2018, FIGO published a global declaration on hyperglycemia in pregnancy [11]. Among the aims were to address the link between maternal health, obesity, and diabetes mellitus as a public health priority. Moreover, to increase public awareness about HIP

and its impact on maternal and children's health, encourage preconception counselling, antenatal care, and postpartum follow-up.

In 2020, the FIGO Pregnancy and Non-Communicable Diseases Committee published a guideline on management of pre-pregnancy, pregnancy, and postpartum obesity [62]. The guideline highlights that clinicians should assess and discuss nutrition and healthy weight with women of reproductive age, making the best out of every contact with this group. By doing this, outcomes may be improved and the burden on healthcare systems reduced.

The Norwegian GDM guideline from 2017 also endorses the life-course approach [36].

1.6 Markers of glycemic control

1.6.1 Glycated hemoglobin A1c

The most common biomarker of glycemia is glycated hemoglobin A1c (HbA1c). The formation of HbA1c occurs through a glycation process, i.e. glucose adds to an amino acid in the hemoglobin molecule within the red blood cell. There are many different glycation sites in the hemoglobin molecule, but the amino-terminal valine of the β-chain (HbA1c), is the most common site [63].

HbA1c was included as a diagnostic criterion for diabetes mellitus in 2011 [64], following a standardization process of the HbA1c assays [65]. HbA1c reflects mean glycemia over the last 8–12 weeks [66]. However, the most recent glycemia level (last 4 weeks), accounts for 50% of the HbA1c value [63].

In pregnancy, there is a linear relationship between average glucose and HbA1c, but the change in HbA1c reflects a smaller difference in mean glucose compared with that found in the non-pregnant state [67]. Moreover, altered erythrocyte turnover (decreased erythrocyte life span and increased erythrocyte production) and iron deficiency may alter HbA1c, making it less accurate during pregnancy [68, 69]. Even in healthy,

pregnant women without diabetes mellitus, the HbA1c level is lower from early first trimester compared with non-pregnant women [70]. Despite these limitations, HbA1c is used worldwide to monitor glycemic control during pregnancy in women with DIP.

The Norwegian diabetes guideline from 2016 recommends HbA1c measurements at least every 4 weeks through gestation in women with pre-gestational diabetes mellitus [71]. Ideally, the HbA1c level should be in the range 38–42 mmol/mol during third trimester.

To identify women with overt diabetes in pregnancy (HbA1c ≥48mmol/mol), the Norwegian GDM guideline from 2017 recommends HbA1c measurement before pregnancy week 16 in women with certain risk criteria [36]. Elevated HbA1c level is not included in the diagnostic criteria for GDM. However, women with an HbA1c level in the upper range (41–47 mmol/mol) are considered high-risk for developing GDM, and should be referred to secondary healthcare [36]. For all practical purposes, at Stavanger University Hospital, these women have been followed-up as women diagnosed with GDM at the OGTT.

1.6.2 Glycated albumin

Glycated albumin (GA), a biomarker reflecting short-term glycemia (2–3 weeks), is suggested to supplement HbA1c [72]. Especially in clinical situations where HbA1c has limitations as in pregnancy, GA could be useful. Moreover, in diabetic pregnancies where glycemic control is crucial to reduce the risk of adverse outcomes, a marker reflecting recent glycemic status is preferable.

Albumin is the most abundant protein in plasma, and because of its high concentration, albumin is highly sensitive to glycation. GA is the final product of a non-enzymatic glycation process of circulating albumin and is expressed as a percentage of total albumin. The rate of albumin glycation in vivo is around nine times that of hemoglobin [73]. In addition, the albumin glycation reaction occurs ten times more quickly [73].

Albumin contains many potential glycation sites, but the main glycation site (lysine, 525K), accounts for 33% of overall glycation [74].

GA can be measured in serum and plasma by various methods [75]. Offering robust quantification, and being easy to use, the enzymatic method is common [76]. A new method for GA measurement developed at Stavanger University Hospital, was used in the GA analyses in this thesis [77]. The method is described in more details in 4.3.

Clinical usefulness

Recent studies have shown that GA is a better indicator of glucose fluctuations in patients with diabetes mellitus than HbA1c [72]. Moreover, GA ables to predict diabetes mellitus in the general population [78-80], and has been associated with microvascular complications and cardiovascular outcomes [81, 82].

There is a negative association between GA levels and BMI. The reasons remain unexplained, but may be due to increased albumin turnover related to inflammation in obese [83]. GA levels are also affected by serum albumin metabolism. Thyroid hormones is known to promote albumin catabolism. In accordance with this, studies have shown inverse correlations between thyroid hormone levels and GA levels [84].

Glycated albumin in pregnancy

Several studies have reported the reference interval (RI) for GA in the general population [85, 86]. In pregnancy, a few reports exist, most of them based on Asian populations [87]. In healthy Japanese pregnant women, an RI of 11.5–15.7% was found [88], whereas in Chinese pregnant women, an RI of 9.2–14.6% is reported [89]. In the first European study, Agnello et al found an RI of 10.2–15.4% in healthy, Italian pregnant women. In addition, they found significantly decreasing GA levels throughout gestation, with lowest levels in third trimester [90]. The latter is also found by others [87, 88].

It has been suggested that the decline in GA level observed in pregnancies, is explained by the physiological increased estimated glomerular filtration rate (eGFR) [90]. Recently, Palerari et al. showed preliminary results investigating the time course of GA (%), GA (g/l), albumin (g/l) in healthy pregnant women [91], and found a marked decline during pregnancy for all three measurands. However, the extent of GA (g/l) decrease calculated from the differences between early and late pregnancy was much higher in respect to the fall in albumin concentration. They concluded that the decrease of GA (%) is not caused by the dilution effect due to increased plasma volume, but that the higher decrease of GA (g/l) may be due increased turnover of albumin, and/or increased selective loss of GA to albumin through the glomerular filtration.

Elevated GA levels are seen in pregnancies complicated by pre-gestational diabetes mellitus and GDM, and has been associated with adverse outcomes [89, 92, 93]. However, the role of GA in monitoring glycemic control in diabetic pregnancies, and as a diagnostic test of GDM is still controversial [87, 94, 95].

1.7 Continuous glucose monitoring

Traditionally, self-monitoring of glycemia has been carried out by measuring capillary blood glucose obtained by finger stick, referred to as self-monitoring of blood glucose (SMBG). In contrast, monitoring of urine glucose level was the routine method until 1975 [96].

The most recent method for measuring glucose levels is by the continuous glucose monitoring (CGM) technology [54]. In 1999, the first CGM device was approved, and this represented a new era in diabetes care [97]. From then on, most glucose fluctuations, hypo- and hyperglycemia, were possible to detect, providing the users an opportunity to respond to the fluctuations as they occur. The most recent devices send alerts when the glucose level is out of range. Novel devices being connected to an insulin pump, may adjust the glucose level automatically. Moreover, users may download applications on their mobile phone to have easy access to the CGM data.

With CGM, a sensor is placed directly under the skin. The CGM device measures the interstitial glucose level every 2 to 5 minutes, thus being an indirect method to assess blood glucose, as compared with SMBG. The interstitial level generally reflects venous blood or capillary glucose levels, but there may be lag time when blood glucose levels are changing rapidly [96]. However, the accuracy has improved with the novel generations of CGM sensors [98].

By the recent international consensus for CGM monitoring in pregnancy, the pregnancy glucose target for T1DM was set to 3.5–7.8 mmol/mol. Women are recommended >70%, <25% and <4% of time within, above and below the pregnancy glucose target, respectively [99]. The terms 'time in range' (TIR), 'time above range' (TAR) and 'time below range' (TBR) were introduced. To date, there are not provided CGM targets for pregnant women with GDM or T2DM, due to lack of evidence and limited data.

According to a recent Cochrane review investigating different techniques (SMBG vs. CGM) for monitoring maternal blood glucose and their impact on pregnancy outcomes, the authors concluded that CGM may reduce hypertensive disorders, but they did not find a clear reduction in the occurrence of preeclampsia [100]. Moreover, there was no evidence of a difference in other primary outcomes.

In Norway, the use of CGM in pregnancy has increased markedly through the last years. According to the national diabetes guideline from 2016, CGM should be offered to pregnant women with poor glycemic control or additional challenges such as impaired awareness of hypoglycaemia [71]. The impression from clinical work is that most pregnant women with T1DM have CGM today, and increasing numbers of women with T2DM.

2. Aims

The overall aim of this thesis was to assess hyperglycemia in pregnancy, aspects on diagnostics, biomarkers, follow-up, and monitoring of glycemic control.

The specific objectives were:

Paper I

In a study population of women with pre-gestational diabetes:

- To explore the association between GA and CGM metrics across gestation.
- To investigate the accuracy of GA and HbA1c to detect poor glycemic control using CGM metrics as the reference standard.

Paper II

In an unselected population of healthy pregnant women:

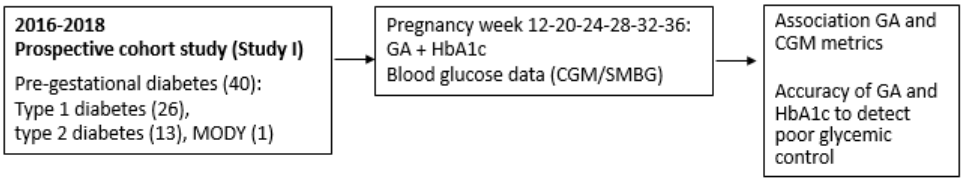
- To establish the RI for GA, analyzed by LC-MS/MS.
- To evaluate the diagnostic accuracy of GA and HbA1c in the diagnosis of GDM, using the OGTT as the gold standard.
- To explore the prevalence of GDM using the diagnostic criteria from three guidelines: WHO-1999, WHO-2013 and the Norwegian guideline from 2017.

Paper III

Among women with a history of GDM in first pregnancy:

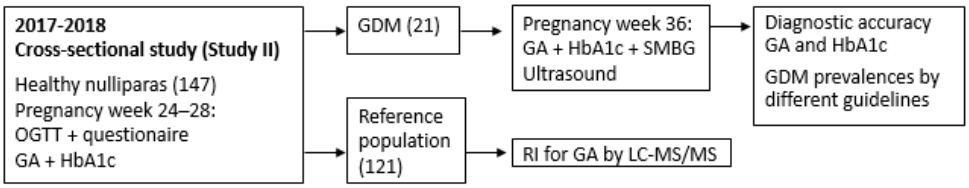
- To elucidate women's experiences of GDM follow-up, both in pregnancy and until 30 months after delivery.
- To explore thoughts of future diabetes risk and motivation for lifestyle changes.

3. Overview of studies



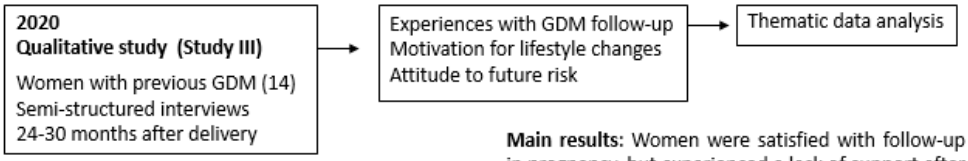
Paper I: Glycated albumin, and continuous glucose monitoring metrics across pregnancy in women with pre-gestational diabetes.

Main results: GA correlated well with most CGM metrics. High GA level was associated with less time in target range and high glycemic variability. GA was more accurate than HbA1c to detect poor glycemic control.



Paper II: Glycated albumin in pregnancy: LC-MS/MS-based reference interval in healthy, nulliparous Scandinavian women and its diagnostic accuracy in gestational diabetes mellitus.

Main results: RI for GA: 7.1–11.6%. Low diagnostic accuracy of GA and HbA1c in GDM diagnostics. GDM prevalence varied from 14.4% to 24.7%.



Paper III: Gestational diabetes mellitus follow-up in Norwegian primary health care: a qualitative study.

Main results: Women were satisfied with follow-up in pregnancy, but experienced a lack of support after delivery. To maintain the healthy lifestyle, women want improved support and tailored information.

4. Material and methods

4.1 Study design and participants

4.1.1 Prospective cohort study – Study I

The prospective study was conducted at Stavanger University Hospital in 2016–2018. All women with pre-gestational diabetes mellitus and singleton pregnancies were eligible for inclusion. At the first antenatal visit in first trimester, women were asked to participate. In all, 42 women were eligible, and 41 women were included in the study. One woman withdraw during the study period, resulting in a total study population of 40 women. Among these women 26 (65%), 13 (32.5%) and one (2.5%) had T1DM, T2DM, and maturity onset diabetes of the young (MODY), respectively.

All participants were followed-up according to the current clinical guideline with visits every 2 to 4 weeks until pregnancy week 38. Women with otherwise uncomplicated pregnancies, had an additional consultation at pregnancy week 39. Labour were induced no later than the EDD. For the women, participation in the study involved blood sampling at pregnancy week 12, 20, 24, 28, 32, and 36, as well as registration of blood glucose data and clinical data.

4.1.2 Cross-sectional study – Study II

The cross-sectional study was conducted at Stavanger University Hospital in 2017–2018. Inclusion criteria were nulliparous women >25 years with singleton pregnancies, not previously diagnosed with diabetes mellitus or GDM. Women were asked to participate when they met for the routine second-trimester ultrasound examination around pregnancy week 18. A one-step 75 gram OGTT was performed at the Clinical Trial Ward at pregnancy week 24–28 [36]. In addition to GA and HbA1c, thyroid and iron status were assessed.

Women diagnosed with GDM were informed about the diagnosis and advised to contact their GP for follow-up. Within two weeks after the diagnosis, all women diagnosed with GDM, attended a GDM workshop at Stavanger University Hospital with an endocrinologist, diabetes nurse and clinical nutritionist. Moreover, they were offered a follow-up consultation, including ultrasound examination and blood sampling at gestational week 36. In all, 147 women were included. One woman diagnosed with diabetes mellitus in pregnancy was excluded from all further analyses.

4.1.3 Qualitative interview study – Study III

The qualitative study was conducted in 2020. All Norwegian-speaking women diagnosed with GDM in the cross-sectional study, were invited to participate. This resulted in an eligible study population of 18 out of the 21 women. To achieve a maximum variety sampling all 18 women were invited.

Information letters describing the aims and method of the study, as well as an informed consent form, were sent in September and October 2020. 14 women consented to participate, and an interview was scheduled within two weeks. Participants could choose between telephone- and face-to-face interviews, and they could choose time and place. All women preferred telephone interviews, probably due to the ongoing corona pandemic. The majority were of Norwegian descent whereas four women had other background. Most of the women had a master's or bachelor's degree.

4.2 Collection of clinical data

In all studies, data on pregnancy outcome (weight gain in pregnancy, preeclampsia, and hypertension, induction of labor, operative vaginal delivery, cesarean section, birth weight, Apgar score, and admission to the neonatal intensive care unit) were collected from medical records after delivery.

In study I (prospective cohort study), all participants received routine clinical care as described in 4.1.1. Blood pressure and maternal weight were measured at all visits along with analyses of microalbuminuria and protein-creatinine ratio.

In study II (cross-sectional study), all participating women answered a questionnaire in which age, ethnicity, height, pre-pregnancy weight, weight gain in pregnancy to date, family history of diabetes, smoking and tobacco use, chronic illnesses, medication, and supplement use were recorded. Weight and height were used to calculate BMI (kg/m^2).

In study III (qualitative study), most clinical data were already registered in the study database from their participation in the cross-sectional trial. During the interviews, women were asked about their current situation (educational level, occupation, social status, place of living and weight) and whether they had been diagnosed with recurrent GDM or T2DM.

4.3 Collection of blood samples. Laboratory analyses

In study I and II, blood sampling were done at the Clinical Trial Ward and all analyses were performed at Department for Medical Biochemistry, SUS.

Blood samples for GA were collected in serum gel tubes, stored at room temperature for 30 minutes, centrifuged at 2500g to obtain serum, and stored at -75◦C. A recently developed LC-MS/MS method was used for GA measurement [77]. This methodology combines the physical separation capabilities of liquid chromatography (LC) with the mass analysis qualities of tandem mass spectrometry (MS/MS).

Relative glycation is measured at a specific amino acid (lysine, 525K) in the albumin molecule, which is the most frequently reported glycation site on human serum albumin [74]. The method is in clinical use at Stavanger University Hospital to supplement the HbA1c assay in diabetes diagnostics and monitoring outside pregnancy.

HbA1c was analysed using BioRad Variant II Turbo, high-performance liquid chromatography, standardized by the International Federation of Clinical Chemistry (IFCC) reference method (analytical variation ≤ 3%), and Abbott Architect c16000 was used for analysis of glucose.

4.4 Collection and management of blood glucose data

In study I, all available glucose data from SMBG and/or CGM were downloaded from the internet-based Diasend system (Glooko) at every visit. Diasend is used in routine clinical care at Stavanger University Hospital, and is easy to use for both patients and health personnel. Blood glucose data are uploaded from the glucometer and Diasend provides an overview of the SMBG (Figure 3) and/or CGM data (Figure 4), diagrams and graphs, as well as mean glucose, time in ranges and CGM metrics. For the user of Medtronic CGM system, raw data were downloaded from CareLink (Medtronic).

From the CGM data, we calculated several statistical CGM metrics including mean glucose level and the percentage of time spent within (TIR), above (TAR), and below (TBR) the pregnancy glucose target range (3.5–7.8 mmol/l). The time below 3.0 mmol/l was also included in the analyses, denoted TBR2. Although the Norwegian diabetes guideline recommends 3.4 mmol and 7.1 mmol/l as the lower and upper cut-offs, we used 3.5 mmol/l and 7.8 mmol/l in the analyses to align with international recommendations [99]. Measures of glycemic variability included coefficient of variation (CV) and glucose standard deviation (SD).

According to recent consensus on CGM use, we required at least 70% coverage (percentage of time CGM is active) for inclusion in the analysis. We included CGM data from the 14 days leading up to each blood sampling at pregnancy week 12, 20, 24, 28, 32, and 36.

In study II, SMBG data from time of diagnosis (pregnancy week 24–28) until follow-up (pregnancy week 36), were provided from Diasend.

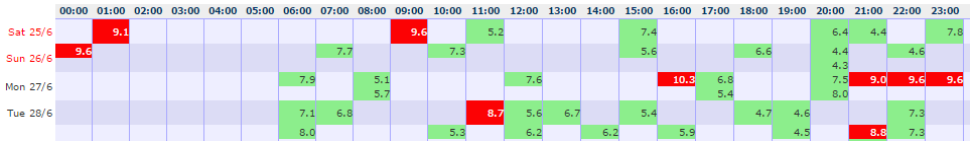


Figure 3. Self-monitoring of blood glucose data as presented in Diasend. This overview shows all glucose measurements during four days. Glucose values within target range are marked with green colour, whereas glucose values above target are marked in red colour.

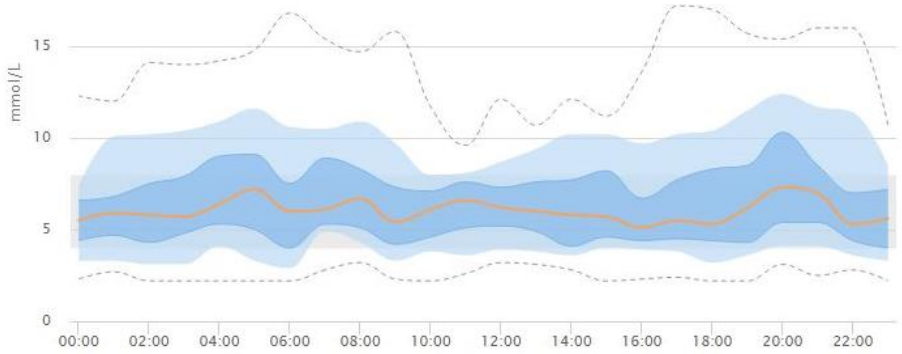


Figure 4. Continuous glucose monitoring data as presented in Diasend. This overview shows the glucose data during 24 hours. Orange line, median; dark blue area, interquartile range; light blue area, 10/90 percentile; dotted line, minimum and maximum glucose values.

4.5 Collection of qualitative data

The qualitative data in paper III were collected using a semi-structured interview guide to explore women's experiences of the GDM follow-up in pregnancy and after delivery. The interview guide (Appendices) consisted of open-ended questions about follow-up, understanding of, and attitude to future diabetes risk and motivation for lifestyle changes.

All interviews were digitally audio-recorded and transcribed verbatim by the PhD candidate in October 2020, resulting in 99 pages (50 059 words). Each transcript was anonymized and compared with the complete original audio recording to ensure

reliability. The interviews lasted between 19 and 41 minutes with an average of 30 minutes.

4.6 Thematic data analysis

In the qualitative study, a thematic analysis inspired by Braun and Clarke was performed [101]. All transcripts were read several times to gain deeper insight of the data set, thus being an inductive approach [102]. Text relevant to the research questions were highlighted and discussed among the authors. Thereafter, transcripts were coded line-by-line by the PhD candidate. Accordingly, 205 codes were consecutively sorted into the following four categories, all being in the interview topic guide and equal to the research questions: *experience of being diagnosed with GDM*, *follow-up*, *motivation* and *future diabetes risk*.

Table 2. Example from the data analysis of transforming transcripts to codes and themes.

Transcript	**Code**	**Theme**
I actually felt ashamed. Are my dietary habits so bad? I felt as a bad mother.	Ashamed of getting GDM. Feeling as a bad mother.	Stigma and shame
Suddenly, gestational diabetes was very serious. Had my GP and I been too laid-back?	Adequate self-management and follow-up?	Uncertainty
I was frightened, how could gestational diabetes affect my baby's health?	Frightened, worried about the baby.	Uncertainty
After the initial shock, my stress level decreased. I had to do what was possible, no panic of missing one measurement.	Shock getting GDM, stress level decreased gradually.	Gaining control and finding balance

GDM; gestational diabetes mellitus, GP; general practitioner.

Throughout the last two interviews, data saturation was achieved, indicating that no new knowledge relevant to the research questions was obtained. Examples of the analyses from transcript to themes are provided in Table 2.

In the next phase, all codes were sorted into broader overarching themes representing repeated patterns across the data set. Through thorough team discussions, a common understanding of the themes was developed. Afterwards, a revision and refining of the themes checking their relation to the coded extracts were performed. Finally, after agreement among all three authors, an overall interpretation was established.

This study was reported in accordance with the Standards for Reporting Qualitative Research (SRQR) [103], a standard highlighted by the EQUATOR network [104].

4.7 Statistics

Throughout the PhD period, the statistical analyses has been carried out in collaboration with Ingvild Dalen, biostatistician and associate professor II. The advanced statistical methods (adjustments for repeated measures design and clustering) used in paper I, was performed by Dalen. Likewise, in paper II, for the establishment of the RI for GA, Øyvind Skadberg did the statistical analysis.

4.7.1 Establishing a reference interval

The most commonly used definition of a reference interval (RI) is the interval of values containing the central 95% of a healthy population, thus the reference limits are the values at the 2.5 and 97.5 percentiles, respectively [105]. For establishment of an RI, the Clinical and Laboratory Standards Institute (CLSI) recommends the non-parametric approach using a reference population including at least 120 individuals [106]. Thus, a sample size of 150 pregnant women was chosen in the cross-sectional trial to ensure that at least 120 healthy individuals were included.

From the total study population, we excluded the women who were diagnosed with GDM and T2DM according to the Norwegian-2017 guideline. Moreover, we excluded four women using medication possibly interfering with their blood glucose level, resulting in a total reference population of 121 healthy pregnant women. All these women had normal liver, kidney and thyroid function. The RI for GA was calculated using Analyse-it, version 5.65 for Microsoft Excel, based on the 2.5 and 97.5 percentiles and corresponding 90% CI in the reference population. The Dixon method was used for outlier detection [106].

4.7.2 Diagnostic accuracy analyses

Receiver operating characteristics (ROC) curve analysis was presumably developed during the Second World War to differentiate noise from signal in radar detection. Later on, the methodology has been adapted to improve medical decision making. The ROC analysis is a statistical method to assess the diagnostic accuracy of a biomarker that has a continuous spectrum of test results [107]. The diagnostic accuracy of a test relates to its ability to differentiate between clinically relevant groups.

To evaluate diagnostic accuracy, there are three basic classifications: 'Diseased/not diseased' referring to the status of the patient; 'positive/negative' referring to the test result; and finally, 'true/false' referring to the correctness to an individual application of the test [108].

Sensitivity and specificity are measures of a test's ability to classify an individual as having the condition investigated or not, correctly. Thus, sensitivity corresponds to the 'true positive rate' whereas specificity, the 'true negative rate'. Ideally, a test should be both highly sensitive and highly specific, however, mostly there is a trade-off.

The ROC curve is created by plotting all possible combinations of true positives (sensitivity) and false positives (1-specificity) at various threshold settings [109]. The aim of the ROC curve is to find the 'optimal value' giving most true positives and fewest false positives. An advantage with the ROC analysis is the ability to test accuracy across

a range of scores, not requiring a predetermined cut-off. Moreover, the ROC analysis is independent of the outcome prevalence [108].

Area under the curve (AUC) is the measure of overall diagnostic accuracy, and allows the cut-off value providing the highest sensitivity and specificity to be calculated [108]. An AUC value of 0.5 indicates no predictive ability or random chance, whereas a value of 1.0 indicates perfect discrimination. Thus, the closer the curve is to the left upper corner, the more accurate the test.

In paper I, ROC analyses were used to compare the accuracy of GA and HbA1c to detect poor glycemic control defined as non-achievement of the clinical targets for CGM metrics, thus, TIR <70%, TAR>25% and TBR >4% for the pregnancy glucose target 3.5–7.8 mmol/l. Similarly, we also presented the ROC curve for time below range <3.0 mmol/l >1%, denoted TBR2.

The optimal GA cut-offs for detecting TIR <70% and TAR >25% were estimated using the Youden index, and corresponding sensitivities and specificities were estimated in logistic regression models.

In paper II, ROC analyses were used to assess the accuracy of GA and HbA1c in the diagnosis of GDM using the OGTT as the reference diagnostic test.

4.7.3 Analyses of blood glucose data

In paper I, mean values of GA and HbA1c at different time points were estimated in mixed linear models. Comparison of levels between time points were performed with paired samples t-tests. Correlation coefficients were used to assess relationships between GA, HbA1c and CGM metrics. The correlation coefficients were estimated allowing for the repeated measures design using the approach outlined by Hamlett [110].

4.8 Ethics

All three studies were carried out in accordance with the Declaration of Helsinki [111]. Informed written consent was obtained from all women included in all three studies.

The Regional Committee for Medical and Health Research Ethics (REC) Western Norway (REK 2016/563) approved the prospective cohort study that collected data for paper I. An extension of the project period was approved by REC Western Norway in a project amendment in May 2021 (reference number 29950). The study was registered in Clinical Trials with identifier NCT03330951.

REC South-Eastern Norway (REK 2017/771) approved the cross-sectional study collecting data for paper II. REC South-Eastern Norway gave an approval for a project amendment including the qualitative study collecting data for paper III in May 2020 (reference number 8402). The cross-sectional study was registered in Clinical Trials with identifier NCT03372824.

5. Main results

The results are described in detail in the papers, and only a summary of the main results are presented here.

5.1 Paper I

In total, 17 women were CGM users before pregnancy. Out of the four women offered CGM during pregnancy, one of them had a preterm delivery one week later. For another woman the CGM-raw data were lost, resulting in CGM data from 19 women. The majority in the CGM group had T1DM, whereas the non-CGM group was more heterogeneous. All insulin-pump users were in the CGM group. In contrast, most women used insulin pens in the non-CGM group. Moreover, women in the CGM group were younger and had longer diabetes duration compared with women in the non-CGM group. Pre-pregnancy HbA1c level, pre-pregnancy BMI and weight-gain in pregnancy were comparable between the two groups.

Regarding pregnancy outcomes, in the total study population (n =40) almost one in five women developed preeclampsia, two thirds had a vaginal delivery and one third delivered an LGA newborn. Induction of labour and vaginal delivery was more frequent in the non-CGM group (85% vs 55%, and 80% vs 40%, respectively), whereas the mean birthweight centile was significantly higher in the CGM group (88 vs 71, respectively).

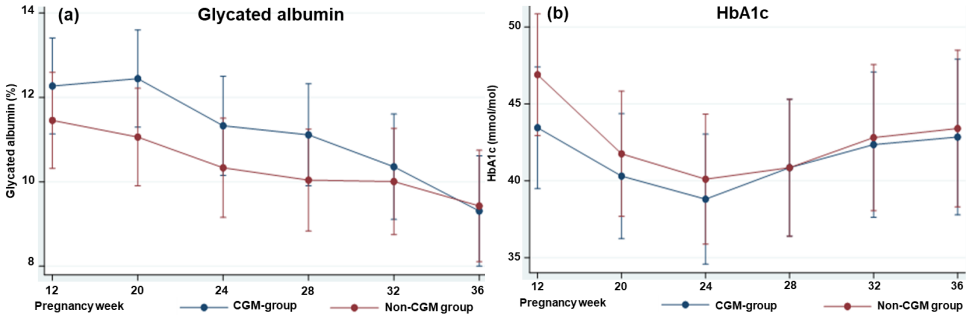


Figure 5. Glycemic markers across gestation in the CGM and non-CGM group. a) Glycated albumin (%). b) HbA1c (mmol/mol). Data presented as mean with 95% confidence intervals. CGM: continuous glucose monitoring; HbA1c: glycated hemoglobin A1c. Toft et al. [112]. Reprinted with permission.

The mean GA level decreased throughout gestation in both the CGM (n =20) and non-CGM group (n=20) (Figure 5a), whereas the mean HbA1c level decreased from first trimester until pregnancy week 24, and increased towards pregnancy week 36 (Figure 5b).

Glycemic control improved across gestation with more time spent in target range and less time spent above and below range areas (Figure 6a-c). Mean glucose varied slightly across gestation (Figure 6d), whereas glycemic variability decreased markedly towards pregnancy week 36 (Figure 6e and 6f). However, in total, only 25 of the 14-days periods (24%) achieved the international recommendation of >70% TIR for the pregnancy glucose target 3.5–7.8 mmol/l. For TAR <25%, TBR <4% and TBR2 <1%, the corresponding percentages were 38%, 28% and 19%, respectively.

We observed positive associations between GA and mean glucose, TAR, glucose CV and SD, a negative association with TIR and no association with TBR. Correlations were found between GA and mean glucose, TIR, TAR and glucose SD. For HbA1c, correlations were found with mean glucose, TAR, TBR and TBR2.

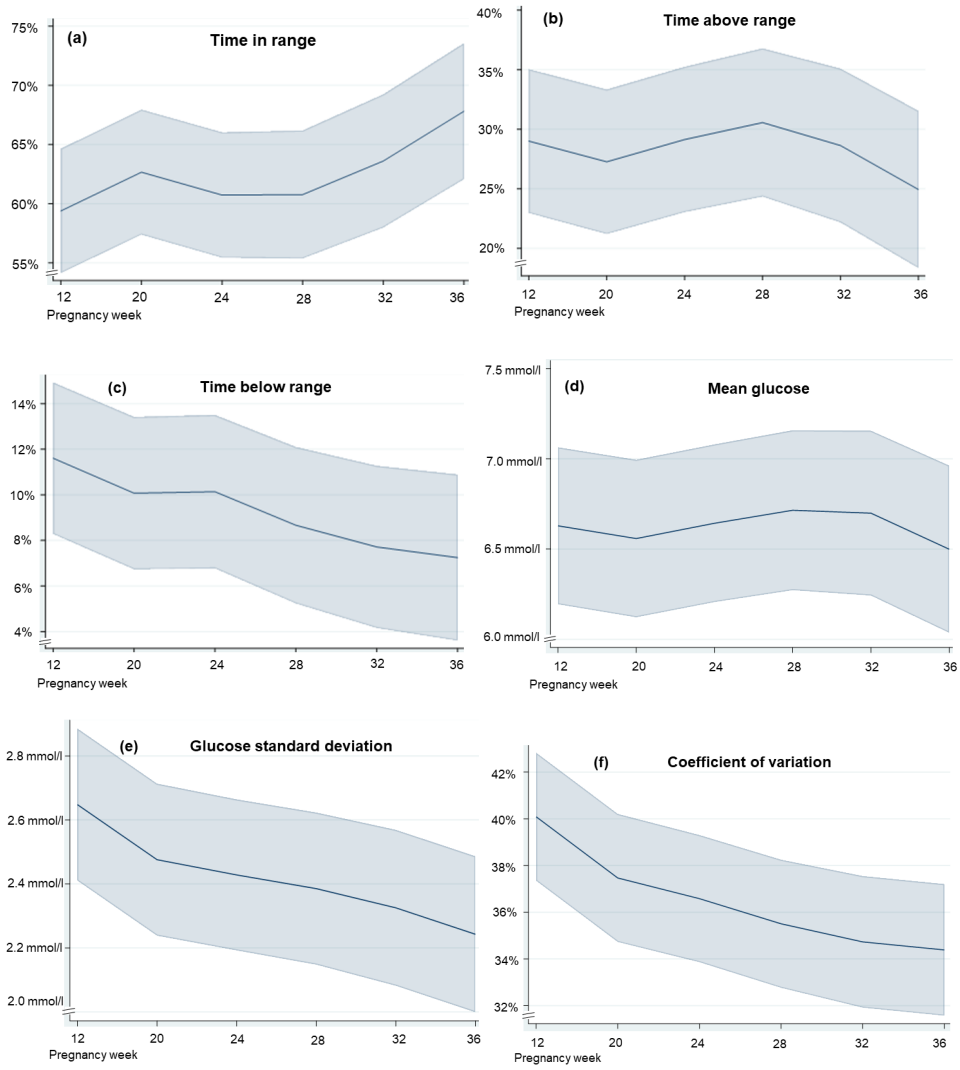


Figure 6. CGM-metrics across gestation. a) Time in range: 3.5–7.8 mmol/l. b) Time above range: >7.8 mmol/l. c) Time below range: <3.5 mmol/l. d) Mean glucose. e) Glucose standard deviation. f) Coefficient of variation. Calculations based on 103 14-days periods with >70% coverage. Data presented as mean with 95% confidence intervals, adjusted predictions. CGM: continuous glucose monitoring. Toft et al. [112]. Reprinted with permission.

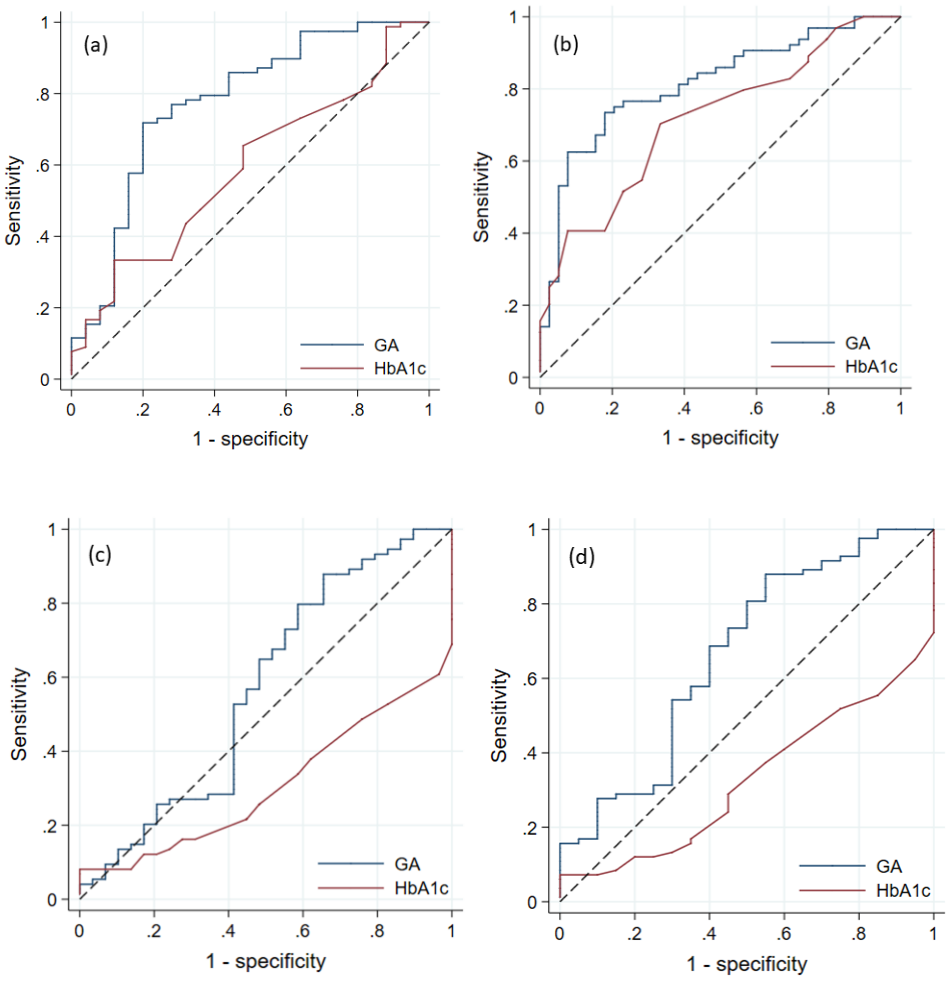


Figure 7. Receiver operating characteristic (ROC) curves to assess the ability of GA and HbA1c to detect poor glycemic control. a) Time in range <70%. b) Time above range >25%. c) Time below range >4%. d) Time below range 2 >1%. Continuous glucose monitoring metrics are calculated from 103 14-days periods with >70% coverage. Toft et al [112]. Reprinted with permission.

In the ROC analyses, the adjusted AUC for GA in detecting TIR <70%, TAR >25%, TBR >4% and TBR2 >1% was 0.78 (95% CI 0.60–0.95), 0.82 (95% CI 0.70–0.94), 0.56 (95% CI 0.31–0.82) and 0.66 (95% CI 0.42–0.90), respectively.

For HbA1c, the adjusted AUCs for detecting TIR <70%, TAR >25%, TBR >4% and TBR2 >1% was 0.60 (95% CI 0.41–0.78), 0.72 (95% CI 0.54–0.90), 0.30 (95% CI 0.13–0.47) and 0.32 (95% CI 0.13–0.52), respectively. The ROC-curves are presented in Figure 7.

The optimal GA cut-off value for detecting TIR <70% was GA >10.5%, with corresponding sensitivity 68% (95% CI 52–83%) and specificity 73% (95% CI 51–95%). Similarly, the optimal GA cut-off value for detecting TAR >25% was GA >11% (sensitivity 70% (95% CI 54–87%), specificity 79% (95% CI 62–96%). The CGM targets for glycemic control in pregnancy are presented in Figure 8a, whereas the optimal GA cut-off values for detecting TIR <70% and TAR >25% are given in Figure 8b.

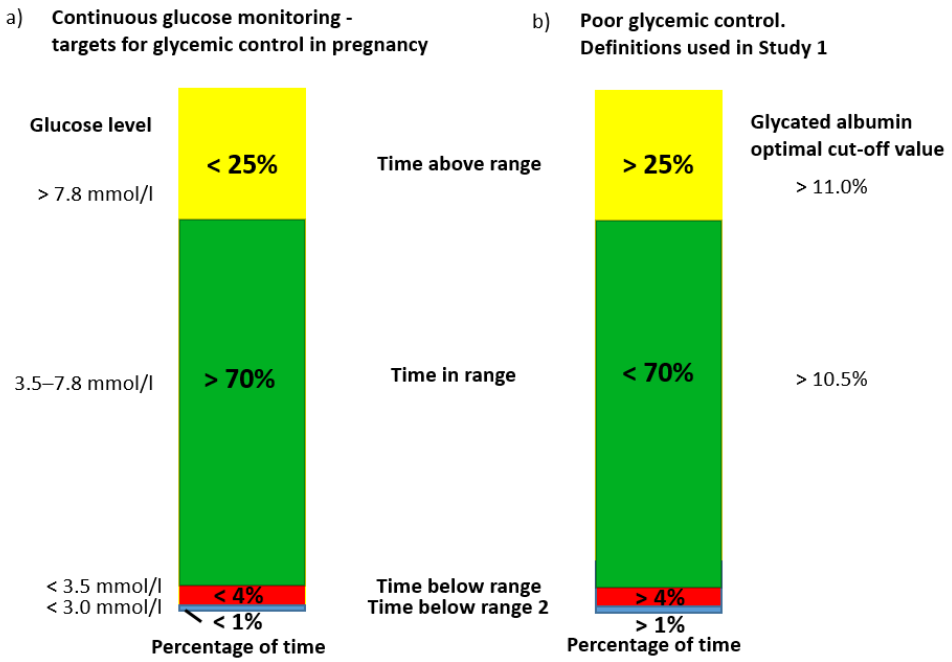


Figure 8. a) Continuous glucose monitoring targets during pregnancy according to international consensus [99]. b) Glycated albumin cut-off values for detecting time above range >25% and time in range <70%.

5.2 Paper II

The RI for GA in healthy pregnant women was 7.1–11.6%. The mean GA level decreased with increasing BMI. The diagnostic accuracy of GA and HbA1c in the diagnostics of GDM using the OGTT as the reference diagnostic test, are presented in Figure 9. The AUC of GA was 0.53, whereas AUC of HbA1c was 0.63. Thus, the results did not support the use of these markers in the diagnosis of GDM.

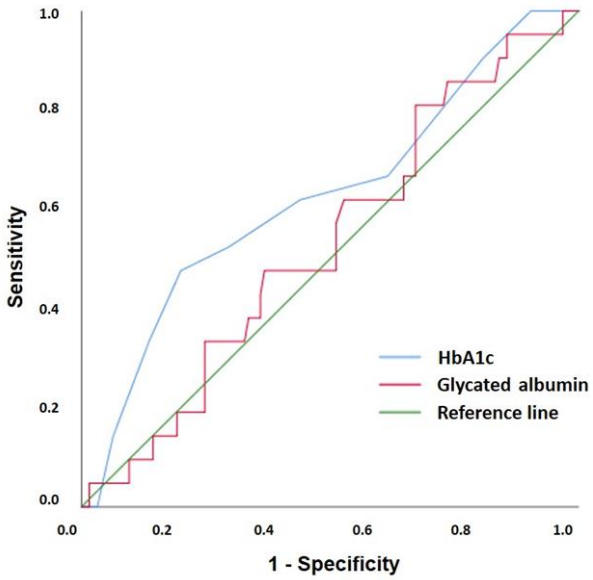


Figure 9. ROC curves to assess the accuracy of GA and HbA1c in the diagnosis of GDM in pregnancy week 24–28 using the oral glucose tolerance test as the reference standard. Toft et al. [113]. Reprinted with permission.

The prevalences of GDM were 16.4%, 24.7% and 14.4% according to WHO-1999, WHO-2013 and the Norwegian-2017 guideline, respectively. Only nine women (6%) fulfilled the GDM-criteria of all guidelines. Figure 10 shows an Euler diagram illustrating the number of women diagnosed by each guideline.

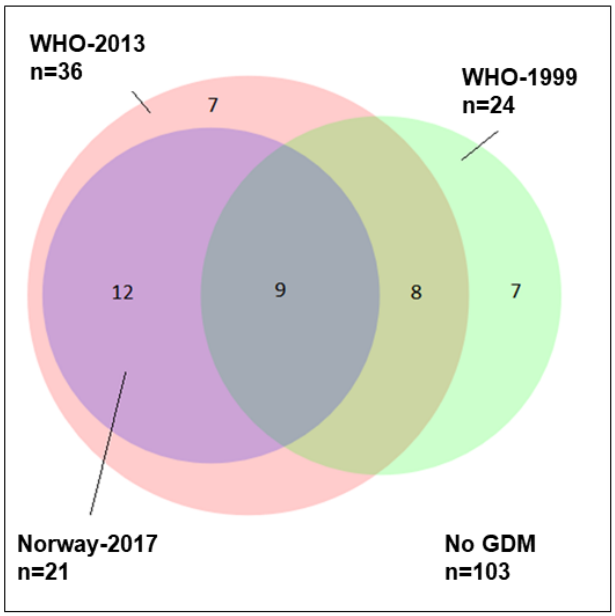


Figure 10. Euler diagram showing the relationship between GDM diagnoses according to the three different guidelines WHO-1999, green circle (n=24), WHO-2013, pink circle (n=36) and the Norwegian guideline from 2017, violet circle (n=21). Toft et al [113]. Reprinted with permission.

Among the 21 women diagnosed with GDM according to the Norwegian-2017 guideline, 15 (71.4%) had FPG ≥5.3 mmol/l as the only diagnostic criterion. In contrast, elevated 2 hour plasma glucose ≥7.8 mmol/l was the only diagnostic criterion for all women diagnosed with GDM according to WHO-1999.

There was no significant difference in mean GA level nor HbA1c level between women with and without GDM, diagnosed by the Norwegian-2017 guideline at pregnancy week 24–28. 18 women with GDM (86%) met for follow-up consultation around pregnancy week 36, and in these, the mean GA level was significantly lower than at the time of diagnosis: 9.1% vs 9.6%, whereas mean HbA1c level was significantly higher: 33.4 mmol/mol vs 31.9 mmol/mol.

Blood glucose data registered from women with GDM showed good glycemic control with mean plasma glucose 5.3 mmol/l from time of diagnosis until follow-up. The majority achieved glycemic control through healthy eating and physical activity only, whereas 3 of 21 women with GDM (14.3%) needed anti-diabetic medication.

5.3 Paper III

Most women were satisfied with the follow-up for GDM during pregnancy. In contrast, the majority experienced a lack of follow-up after delivery. Only two women were followed-up in accordance with the guideline after delivery, including tailored information, HbA1c measurement and lifestyle counselling. In most encounters with the GPs after delivery, GDM was not mentioned.

Following the thematic analysis, four main themes emerged: 'stigma and shame', 'uncertainty', 'gaining control and finding balance' and 'a need for support to sustain change'.

The first theme summarizes the feelings of stigma and shame that most of the women associated with GDM. The majority associated the diagnosis with unhealthy dietary habits, leading to self-blame for putting the fetus at risk. Several measured blood glucose in discrete to avoid questions. Some of them stated that getting GDM would have been less stigmatic if they had been told about various risk factors for developing GDM, such as family history.

Among the participants with non-Scandinavian descent, a common finding was that the feeling of stigma associated with GDM predominantly was related to their background, resulting in less self-blame at the individual level. Additionally, for some of these women, this impaired their motivation for lifestyle changes after birth, as they thought they would develop T2DM anyhow. In contrast, the women with Scandinavian descent associated the diagnosis with unhealthy lifestyle, causing more self-blame at the personal level.

Early in the data analysis process, the theme ‘uncertainty’ became clear. Uncertainty affected women’s reactions to the diagnosis, expectations of follow-up, and influenced their thoughts of maternal-fetal risk.

The third theme ‘gaining control and finding balance’ describes the process many of the women went through: the initial feelings of shock after being diagnosed, to the stressful first weeks where they had to incorporate SMBG in daily life, adjust dietary habits and physical activity, to a new balance finally was reached.

The fourth theme ‘a need for support to sustain change’ summarizes the experiences most participants had, regarding a lack of follow-up after delivery. The majority stated that the GP did not address GDM at all in the encounters after delivery, contrasting the close follow-up during pregnancy. Most women were concerned about the increased diabetes risk, and thought of this as a motivator to regain pre-pregnancy weight and maintain the healthy lifestyle adopted in pregnancy. However, several requested tailored information regarding their individual risk and more than half of the participants had gained weight.

A comprehensive understanding of the four main themes described, could be included in two broader overarching themes. The first is women’s internal emotions relating to the GDM diagnosis, and the second is the experiences of contrasting follow-up (during and after pregnancy) affecting women’s health seeking behavior to mitigate future risk. The relation between the overarching themes and the main themes along the time course is shown in Figure 11.

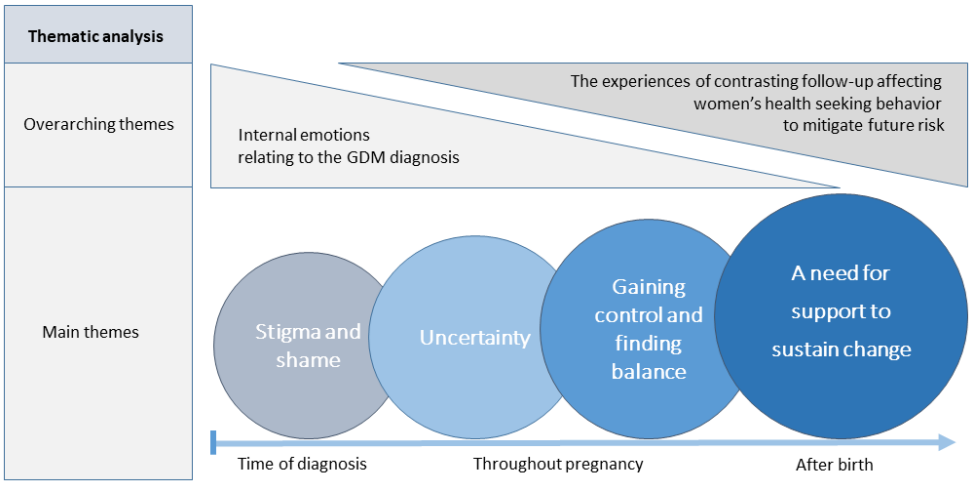


Figure 11. The relation between the overarching themes and main themes along the time course. Toft et al. [114]. Reprinted with permission.

6. Discussion

6.1 Metodological considerations

This thesis includes three clinical studies, in which both quantitative and qualitative study designs have been used. The two quantitative studies assessed different aspects of the use of glycated albumin in pregnancy; establishment of an RI, monitoring of glycemic control, and GA in the diagnostics of GDM. The qualitative study explored women's experiences of GDM follow-up, attitudes to diabetes risk and motivations for lifestyle changes. In the following section, I will reflect on the strengths and weaknesses related to study design, data collection, potential biases and statistical and ethical considerations. Furthermore, for the qualitative interview study, I will discuss how we aimed to ensure trustworthiness.

The word 'valid' is derived from the Latin 'validus' meaning strong. In research, validity extents to which the experiments are well founded, and whereas the results obtained answer the research questions. The internal validity of a study refers to whether the conclusions are likely to be correct given the circumstances for that particular study [115]. External validity refers the ability to generalise from the study to other situations or populations [115].

Study participants

In 2017, there were 4616 deliveries at Stavanger University Hospital, making the hospital among the largest birth centers in Norway [14]. Moreover, the hospital is the only delivery unit in the region South-Rogaland, and is therefore a suitable location for clinical studies. All women with pre-gestational diabetes in the region are followed-up at the antenatal outpatient clinic.

In the prospective cohort study (study I), all eligible women throughout the study period over two years were asked to participate, and only 1 out of 42 women declined.

In the cross-sectional study (study II), women were unselected with various socioeconomic status, age, and BMI, representative of the pregnant population. Most of them were of Norwegian descent, although 9.6% had Non-European background.

In study II, the mean pre-pregnancy BMI in the total study population was 23.9 kg/m^2, thus being a little lower than the registered mean pre-pregnancy BMI both in Norway and Rogaland (24.1 kg/m^2) in 2017 [14]. Among the study participants, self-reported pre-pregnancy weight and height were registered for all participants, whereas in the Medical Birth Registry pre-pregnancy BMI was registered for 86% of all births, and for 98% of the births in Rogaland in 2017. Regarding self-reported weight and height, others have shown that it is a tendency of under-reporting weight and over-reporting height [116].

Moreover, in study II, the mean maternal age was 30.8 years. In contrast, the mean maternal age for primiparous women in both Norway and Rogaland were lower (29.2 and 28.6 years, respectively) [14].

Higher maternal age in our study population (study II) is a risk factor for GDM. Moreover, 22.6% had a family history of diabetes, defined as first-degree relative with diabetes mellitus, which also contributes to the GDM risk. However, the lower mean pre-pregnancy BMI could indicate a lower GDM risk. Our findings of relatively high GDM prevalence should be considered in light of these factors.

In the qualitative study (study III), we included the Norwegian-speaking GDM women, only. From the eligible women (n =18), two declined to participate whereas two did not respond after a reminder, resulting in a sample size of 14. In qualitative in-depth interviews, a sample size of 10 to 15 is common. However, as described by Malterud: a shift in attention from numerical input to the contribution of new knowledge from the analysis may be beneficial [117]. Furthermore, information power indicates that the more information the sample holds, relevant for the study, the lower number of

participants is needed [117]. I will discuss methodological considerations regarding the qualitative study in more detail below.

In a recent Norwegian study, language challenges were among the factors contributing to sub-optimal maternal care among recently migrated pregnant women born in low- or middle-income countries [118]. If the non-Norwegian speaking women had been included in study III, would they have reported the same as their Norwegian-speaking counterparts? Most likely, our main conclusions would have been the same.

A strength with the study population in study III is that the participants represented the pregnant population with different ages, various pre-pregnancy BMIs, living in both rural and urban parts of our region, and being followed-up by different GPs. As we chose to conduct the interviews in Norwegian with Norwegian-speaking women, the participants spoke fluently and freely, and gave vivid descriptions of their experiences during the interviews. In contrast to other qualitative studies on GDM, the majority of the study participants had a master's or a bachelor's degree. Thus, our findings may not be applicable to other sosioeconomic groups. Women with higher education level are more likely to attend postpartum screening/follow-up after a pregnancy complicated by GDM than women with lower education level [119].

In conclusion, regarding study participants and the possibilities of selection bias: In study I, the study population most probably is representative. In study II, the study population was unselected, however, the increased maternal age may have influenced our results regarding GDM prevalence. In study III, our main finding (lack of GDM follow-up after delivery) most likely would have been the same if the non-Norwegian speaking women had been included.

Study design – the prospective study

In study I, we chose a prospective, longitudinal design to explore the association between GA and blood glucose in pregnancy, and included eligible women consecutively. Before we started the inclusion, a search in the hospital's journal system

indicated that the annual numbers of women with pre-gestational diabetes having their follow-up at the antenatal clinic were somewhat higher, around 30 per year, than we experienced throughout the study period. Factors contributing to a lower total number of eligible women in our study were inclusion in first trimester and of singleton pregnancies, only. Several women were not eligible for inclusion due to overt diabetes later in pregnancy, referral after first trimester, or twin pregnancies.

Among the included women in study I, half of them were users of CGM prior to gestation or got CGM during pregnancy. Ideally, to study the association between GA and blood glucose during pregnancy, the CGM group should have been larger. In paper I, for the non-CGM group, we explored the time course of GA and HbA1c throughout gestation. As the amount of SMBG data differed substantially between the women in the non-CGM group, it was difficult to perform proper analyses of the association between blood glucose and laboratory glycemic markers in this group.

In the analyses, we included CGM data from the last 14 days before each blood sampling. This was a way to organize the huge amount of data. Moreover, this recent 2 weeks' period is both relevant and important for clinicians in the meeting with these women. Good glycemic control is pivotal in these pregnancies, and it may be challenging to achieve the recommended targets, as the glucose levels are more fluctuating during gestation.

Our primary aim of study I was to explore the association between GA and blood glucose. As GA represents recent glycemic control over the last 2–3 weeks [72], the inclusion of CGM data from the last 2 weeks was suitable. However, the results of HbA1c and the corresponding associations and correlations with CGM data, should be considered in light of this as HbA1c represents mean glycemia over the past 8–12 weeks [54]. However, the recent 4 weeks contributes to 50% of the HbA1c value [63].

Strengths of the study design (study I) includes the real-life setting, the prospective design, repeated measurements of GA and HbA1c six times across pregnancy, and the

quantity of CGM data. Moreover, trained study nurses at the Clinical Trial Ward performed the blood samplings and preparation of samples. Limitations are the sample size and the use of different CGM devices.

Study design – the cross-sectional study

In study II, a cross-sectional design was chosen, as the primary aim was to establish the RI for GA in pregnancy. The reference population should be as similar as possible to the population on which the test will be applied, with the exception of the disease, i.e. hyperglycemia in pregnancy [105]. Thus, we included women independent of pre-pregnancy BMI and with different descent. We established the RI of GA at pregnancy week 24–28, as this is the recommended screening period for GDM. Moreover, we chose maternal age 25 years as an inclusion criterion, as these women were recommended an OGTT in the Norwegian-2017 guideline, which was published a few months earlier. The age-criterion for primiparous women was among the subjects highly debated. In light of the ongoing debate, we wanted to explore the prevalence of GDM according to the Norwegian guideline, in a study population of primiparous women 25 years of age.

Other RI-studies have shown that age-related changes are less associated with GA [120], thus, excluding pregnant women younger than 25 years from our study population, most likely did not influence the reference interval. Furthermore, mean maternal age for primiparous women in Norway (2021) was 30.0 years, thus women younger than 25 years anyhow constituted a minority.

We aimed to enroll 150 women in this study, to ensure that at least 120 healthy women were included for establishment of the RI population [106]. Based on a previous Norwegian study, we expected a prevalence of GDM around 10% [121], although the last reports from the Medical Birth Registry indicated a considerably lower prevalence of 4% in Rogaland (2016 data). Surprisingly, our results showed a GDM prevalence as high as 14% according to the Norwegian-2017 guideline. After excluding these women (n=21), and others using medication possibly interfering with their blood glucose level

e.g. prednisolone (n=4), and the woman diagnosed with overt diabetes in pregnancy, the reference population included 121 women.

Strengths of the study design (study II) is the implementation of the OGTT and blood sampling at the Clinical Trial Ward. Only 1 out of 147 women had to repeat the OGTT due to vomiting. Others have reported a failure rate of 10% with OGTT in pregnant women, mostly because of vomiting [122]. Contributing factors for the high success rate in our study may have been the calm surroundings at the Clinical Trial Ward in contrast to a busy GP's office, or that the glucose-solution was served ice cold with two droplets of lemon juice. Finally, the well-characterized reference population and the analysis of GA by LC-MS/MS contributes to the strengths of study II.

Limitations include that the study design did not allow for establishing trimester-specific RI for GA. In addition, multiparous women and women with multiple gestations were not included. Finally, the sample size was too small to conclude on pregnancy outcome.

Study design – the qualitative study

To get a comprehensive understanding of the research questions in study III (*women's experience of being diagnosed with GDM, their experience with GDM follow-up, attitude to diabetes risk, and motivation for lifestyle changes),* we chose a semi-structured interview approach. This approach is suitable when addressing sensitive topics. The participants could choose between face-to-face or telephone interviews, however, likely due to the ongoing corona pandemic, all of them preferred telephone interviews.

The interviews were conducted 24–30 months after delivery. This might have caused recall bias. However, my impression was that the women gave detailed descriptions on their experiences.

Missing data

In the prospective study (study I), the majority (82.5%) completed all six blood samples for GA and HbA1c, whereas five women (12.5%) missed one blood sample and two women (5%) missed two blood samples. The main reason for not completing all blood samples was preterm delivery. Two women missed one and two blood samples respectively, due to moving from Rogaland during third trimester.

Through searches in medical records, pre-pregnancy HbA1c levels were obtained for 34 out of the 40 participants in study 1. Among these, 21 women (62%) had good glycemic control (HbA1c <53 mmol/mol) in first trimester. For most, the HbA1c level was measured within two months prior to gestation. Among the six women missing pre-pregnancy HbA1c, half had good glycemic control in first trimester (mean HbA1c level 46 mmol/mol), whereas the other half had poor glycemic control (mean HbA1c level 97 mmol/mol).

The clinical outcome variables were available for most participants through their medical records (study I and II). For the women no longer living in Rogaland, some of the outcome info were provided by the women in a follow-up telephone call some weeks after delivery.

Regarding the CGM data, as recommended by the recent consensus [99], we only included periods with at least 70% coverage. After exclusion of six 14-days periods with coverage below 70%, 103 periods were available for analyses. For the included periods, the mean coverage was as high as 92.6%.

In study II, the questionnaire was completed by all participants (n=147). Only three women with GDM were lost to follow-up for repeated blood tests at pregnancy week 36.

However, blood glucose data from time of GDM diagnosis until follow-up was available for only 67%. I had access to SMBG data from the majority, but unfortunately, it turned

out that some of them also had measured the blood glucose level of family and friends using the same glucometer, thus, the data could not be included.

Trustworthiness – the qualitative study

Similar to reliability and validity in quantitative studies, trustworthiness needs to be evaluated in qualitative research. The following four criteria are used to establish trustworthiness [123]:

Credibility – whether the findings accurately and fairly represents the data.

Transferability – whether the findings can be applied to other settings.

Confirmability – whether the findings are biased by the researcher.

Dependability – whether the findings are consistent and sustainable over time.

To ensure credibility I took part in all steps involving the qualitative study, conducted all the interviews and transcribed the audio files into text. The technical quality of the audio files was very good, so although it was a time-consuming transcription process, I had no problems with hearing what the participants said. The participants already knew me from participation in the cross-sectional study, and I knew their background and the outcomes in their first pregnancy. This common knowledge, likely improved the quality of the data. The participants gave detailed descriptions of their experiences.

Transferability refers to which extent the results can be transferred to other settings or within the same context on a later occasion. That our sample represented the pregnant population with different ages, descent, various pre-pregnancy BMIs, living in the cities and in the countryside, contributes to transferability. However, not only the context, but also the researchers preunderstanding may influence the process. I was aware of my role, and tried to be open towards the participants' views and experiences throughout the interviews.

Transferability also concerns the aspect of applicability [124]. As described by Korstjens and Moser; it is the researcher's responsibility to provide a '*thick description*' of the participants and the research process, to enable the readers to assess whether the findings are transferable to their own settings [124]. In paper III, we aimed to give detailed descriptions of both the participants and the process.

Confirmability was ensured by involving all authors of paper III in the data analysis process, to ensure inter-subjectivity of the data. The final interpretation was grounded in the data. Christina Furskog Risa experienced with qualitative studies and thematic analyses had an important role in these discussions.

Finally, dependability is whether the findings are consistent over time. As described by Korstjens and Moser: dependability includes the aspect of consistency [99]. Thus, the researcher need to check whether the analysis is in line with accepted standards for the particular design. We followed the recommended standards for reporting qualitative research [103], aiming to improve transparency. In addition, as recommended by Malterud, a set of notes (project log) was undertaken throughout the whole study process with study III [125]. The notes included decisions made during the research process, team meetings, reflective thoughts and emergence of the findings contributing to transparency.

Statistical considerations

Because of repeated measurements of GA and HbA1c, advanced statistical methods including linear mixed models, were applied in paper I. In addition, the correlation coefficients were estimated using the approach by Hamlett [110], allowing for repeated measures.

ROC-analyses were used in both paper I and II. An important issue when using ROC curves is that the measurements of interest and the reference diagnostic test should be independent of each other [126].

When working with the analyses in paper II, I realized that several papers using ROC-curves to assess the accuracy of GA and HbA1c in the diagnosis of GDM also included FPG in the analyses [87, 94, 127]. These papers used the OGTT as the gold standard test. The highest AUCs were reported for FPG. As FPG is a substantial part of the OGTT, including FPG in a ROC curve using OGTT as the reference diagnostic test for GDM, is not appropriate [128]. A woman may be diagnosed by elevated FPG and/or elevated 2 hour glucose on the OGTT.

In paper I, we used the CGM metrics as the reference standard. We explored the accuracy of GA and HbA1c to detect poor glycemic control, which we defined as non-achievements of the targets for CGM-metrics.

Ethical considerations

Several ethical aspects have been taken into consideration in planning and conducting the three studies included in this PhD project. All women were given verbal and written information before they signed the consent form. They were informed about their right to withdraw from the study anytime without any explanation. They were also given my contact information if they had further questions. Several women contacted me throughout the study period.

In the cross-sectional study, midwives included the participants, whereas I included women to the prospective and the qualitative study. Participation in the cross-sectional and prospective study included standard clinical care, but for women in the cross-sectional study, the OGTT was performed at the Clinical Trial Ward rather than at their GP's office, for some resulting in a longer travel distance.

Women diagnosed with GDM were offered an additional workshop with an endocrinologist, clinical nutritionist and diabetes nurse at Stavanger University Hospital within two weeks from the time of diagnosis. All women attended the workshop. Several described the workshop as informative, whereas others stated that they already knew

most of the information. One of the participant described that she felt stigmatized attending the workshop.

Women with pre-gestational diabetes have close follow-up in secondary healthcare throughout their pregnancies. To reduce the burden of study participation, blood sampling was coordinated with their clinical appointments. To ensure continuity throughout the study period, I had all the consultations for all women with hyperglycemia in pregnancy weekly from 2016 to 2018. Several of the study participants with pre-gestational diabetes appreciated the continuity of care and the close follow-up.

For many women a GDM diagnosis is challenging, and there may be a shift from positive feelings and expectations to worries and stress [129]. An in-depth interview exploring women's experiences of a pregnancy complicated by GDM may bring back some tough memories. Additionally, it could be difficult to reflect around future risk. I was aware of these concerns when conducting the interviews. To acknowledge our gratitude for their time, all participants received a 50 EUR gift card.

The studies included in this thesis are funded by Stavanger University Hospital, The Norwegian Diabetes Association, Johan Selmer Kvanes Foundation, and Dr. Nils Henrichsens and wife Anna Henrichsen Foundation. For the two latter, the application processes were through the Norwegian Medical Association and the University of Bergen, respectively. None of the funding sources participated in the planning of the studies, nor in the interpretation of the results. The PhD grant was provided by Stavanger University Hospital.

6.2 Discussion of the main findings

6.2.1 Paper I

Overall glycemic control

Overall glycemic control improved throughout pregnancy with more time spent in target range. Mean glucose varied slightly, whereas glycemic variability decreased markedly. Albeit an increase in mean percentage of time in target range from 59% in first trimester to 68% in third trimester, most women were far from achieving the recommended target (>70%). Actually, only 25 of the 14-days periods (24%) achieved the international recommendation of >70% for TIR. For TAR <25%, TBR <4% and TBR2 <1%, the corresponding percentages were 38%, 28% and 19%, respectively.

Our results are comparable with others. In the CONCEPTT study, a randomized controlled trial examining the effectiveness of CGM on maternal glycemic control and obstetric and neonatal outcomes, time in range improved from 52% in the first trimester to 68% in the third trimester [130]. In contrast, they reported markedly lower TBR (3%) and slightly higher TAR (27%) than that found in our study (7% and 25%, respectively). Of note, their results were from pregnancy week 34, whereas our results from pregnancy week 36.

In a Swedish cohort study of 186 women with T1DM, corresponding proportions for TIR, TAR and TBR in the third trimester were 60%, 34% and 7%, respectively [131]. In addition, the mean glucose level and glycemic variability measures were higher in all trimesters. Taken together, these results indicate that it is challenging to obtain the targets for glycemic control during pregnancy.

Association between laboratory glycemic markers and CGM metrics

The mean GA level decreased throughout gestation in both the CGM and the non-CGM group, whereas the mean HbA1c level decreased from first trimester until pregnancy

week 24, and increased towards pregnancy week 36 (Figure 5). In the CGM group, the mean HbA1c level was 44 mmol/mol, both at pregnancy week 12 and 36.

We found statistically significant correlations between GA level and mean glucose, TIR, TAR and glucose SD. Whereas for HbA1c, statistically significant correlations with mean glucose, TAR, TBR and TBR2 were found. Furthermore, we observed positive associations between glycated albumin level and TAR, mean glucose, SD, and CV, a negative association with TIR and no association with TBR.

The improving glycemic control observed in our study using CGM metrics as the reference standard was not reflected in decreasing HbA1c levels, whereas GA levels decreased throughout pregnancy.

ROC-curves

In the ROC analyses, GA was more accurate than HbA1c to detect time in range <70% and time above range >25% with adjusted AUCs of 0.78 and 0.82, whereas adjusted AUCs of 0.60 and 0.72 were found for HbA1c, respectively.

For the hypoglycemic measures, TBR >4% and TBR2 >1%, the adjusted AUCs for GA was 0.56 and 0.66 with CI including 0.5, thus not statistically significant. In contrast, for HbA1c, the AUCs for TBR >4% and TBR2 >1% were 0.30 and 0.32 (statistically significant for TBR >4% with CI 0.13-0.47). These findings suggest that high HbA1c levels indicate a reduced risk for these two CGM metrics.

GA and HbA1c – different qualities in monitoring glycemic control

Our findings support the use of GA to assess glycemia in pregnant women with pre-gestational diabetes. Furthermore, our findings illustrate that GA and HbA1c have different qualities in the monitoring of glycemic control. More studies with larger sample sizes are needed to further explore the association between GA and glycemic excursions. The optimal GA cut-off values for detecting poor glycemic control (TIR <70% and TAR >25%) were found. More analyses including more glucose data are needed to assess the optimal GA cut-off value for TBR.

Our findings of a statistically significant correlation between GA and glucose SD, and although not statistically significant, the positive correlation between GA and glucose CV, and the AUCs >0.5 for TBR >4% and TBR2 >1%, are in further support of previous findings indicating that high GA may detect glycemic variability, including the hypoglycemic fluctuations [132].

Pregnancy outcome

Study I was not designed to explore differences in pregnancy outcome between the CGM and the non-CGM group. However, it is still interesting to assess the outcome. The mean pre-pregnancy HbA1c was 51.5 mmol/mol in the total study population, indicating overall good glycemic control in accordance with clinical recommendations.

In our study population, about one in five women developed preeclampsia (18%), one third delivered an LGA neonate (33%), and about one in seven women (15%) had a preterm delivery. In the CGM group, where the majority had T1DM, some of the above-mentioned outcome were more frequent (preeclampsia 25%, and LGA 40%), whereas preterm birth was less frequent (10%).

In the CONCEPTT trial, exploring the use of CGM in pregnant women with T1DM, HbA1c at enrollment was higher (57–58 mmol/mol) [130] than in our study. In their CGM group, 9% developed preeclampsia, 38% had a preterm delivery, and 53% delivered an LGA neonate, whereas the corresponding percentages in the non-CGM control group were 18% preeclampsia, 42% preterm delivery, and 68% LGA.

In the Swedish cohort study by Kristensen et al., mean HbA1c level at first trimester was 52.4 mmol/mol among women with T1DM (88% nulliparas) [131]. In comparison, we found lower mean HbA1c level in first trimester of 44 mmol/mol and 47 mmol/mol in the CGM group and non-CGM group, respectively. They reported lower prevalence of preeclampsia/pregnancy induced hypertension (18%), and higher prevalence of both preterm birth (28%) and LGA (53%) as compared with our CGM group.

6.2.2 Paper II

The RI for GA in healthy pregnant women

The reference interval for GA in pregnant women analyzed by LC-MS/MS was 7.1–11.6%, which is slightly lower than the RI reported from our laboratory for non-pregnant women (7.8–12.4%). Also in comparison with other RI studies for GA in pregnancy [88, 89], our RI was lower. Direct comparisons are difficult as different methods are applied, women with pre-pregnancy BMI >25 were excluded in one of the studies, and the study populations includes women with different descent. As previously reported [83, 120], we found lower GA levels in higher BMI categories.

The accuracy of GA and HbA1c in GDM diagnostics

With a reported AUC of only 0.53, our study did not support the use of GA as a diagnostic tool for GDM. The finding is also in agreement with previous studies reporting AUCs comparable with ours, and in the range 0.53–0.57 [94, 127, 133]. For HbA1c the AUC was higher (0.63) than the AUC of GA, but still not statistically significant. Moreover, we found no correlation between GA and HbA1c in our dataset, although a strong correlation has been found outside pregnancy [77]. The differences may be explained by a more homogeneous dataset and less spread in the pregnant population, as correlations are relative [134].

The prevalence of GDM, using different diagnostic criteria

The prevalence of GDM according to the different guidelines was 16.4% (WHO-1999), 24.7% (WHO-2013), and 14.4% (Norwegian-2017 guideline). Only 6.2% fulfilled the GDM criteria in all three guidelines. When comparing WHO-1999 and Norway-2017, which represent the previous and present diagnostic criteria used in Norway, a slightly decreased prevalence was observed (16% vs 14%). As discussed previously (paragraph 6.1), higher maternal age in our study population may be a contributing factor to the high GDM prevalence observed.

In a recent study merging data from four Norwegian cohort studies, the prevalence of GDM among European women was 10.7%, 16.9%, and 10.3% applying the WHO-1999, WHO-2013, and the Norwegian-2017 criteria. The corresponding prevalence's for non-European women were much higher (14.5%, 37.7% and 27.0%, respectively). In our study population, only 9.5% had non-European background.

Another Norwegian study reported GDM prevalence in Scandinavian women of 13.4%, 24.8%, and 9.2% according to WHO-1999, WHO-2013, and the Norwegian-2017 guideline [135]. Their study population is more comparable with ours, likewise their reported GDM prevalences. In a recent Dutch study applying the WHO-2013 criteria in a high-risk population, the GDM prevalence increased from 22% to 32% when compared with WHO-1999 [136].

In our study, among the 21 women diagnosed with GDM with the Norwegian-2017 guideline, 71.4% had FPG ≥5.3 mmol/l as the only diagnostic criterion. In contrast, all women diagnosed applying the WHO-1999 criteria (n=24) had elevated 2 hour glucose ≥7.8 mmol/l.

Taken together, in our study population of healthy primiparous women, a GDM prevalence of 14.4% was found. Interestingly, when comparing the old and new diagnostic criteria in Norway, there was a slightly decrease (from 16% to 14%) and other women were diagnosed with GDM when applying the new criteria.

The 'rule out–rule in' strategy

In Switzerland, GDM screening includes a simplification of the IADPSG consensus. At the OGTT, glucose ingestion is only performed in women with FPG in the range 4.4–5.0 mmol/l. Women with FPG ≥5.1 mmol/l are diagnosed with GDM ('rule-in'), whereas those with FPG <4.4 mmol/l are 'ruled-out'. The diagnostic performance of this strategy was evaluated in a Swiss population with a GDM prevalence of 10.9% [137]. The authors reported a sensitivity of 78.5%, and that 63.8% would have avoided the OGTT. This finding is in contrast to Agarwal et al., who reported a high sensitivity

(95.4%) in Arab women using the same simplification [138]. The conflicting results have several explanations, one being the prevalence of GDM (10.9% vs 37.7%), another the distribution of abnormal values on the OGTT.

In our study, only 11 women (7.5%) had FPG <4.4 mmol/l. Using the 'rule-out/in' strategy with cut-off values of FPG <4.4 and ≥5.3 mmol/l respectively, only 26 women (18%) would have avoided the OGTT and none of the women with GDM according to the Norwegian-2017 guideline would have been missed. However, our sample size is limited, including low total numbers of GDM women.

6.2.3 Paper III

Most women were satisfied with the follow-up for GDM during pregnancy. In contrast, the majority experienced a lack of follow-up after delivery. Only two women were followed-up in accordance with the guideline after delivery, including tailored information, HbA1c measurement and lifestyle counselling. In most encounters with the GPs after delivery, GDM was not mentioned.

Among the 14 participants, nine had measured HbA1c one or more times after the GDM pregnancy. Interestingly, eight of these women stated that the HbA1c measurement was done by their own initiative (not the GP's initiative), and that the blood sampling was done when they visited the GP's office for other reasons, e.g. with a sick child. Thus, the HbA1c measurement did not lead to a conversation about lifestyle and future diabetes risk.

All but one woman stated that the experience with GDM would affect lifestyle and diet in the next pregnancy. Likewise, all but two women were aware of or thinking about future diabetes risk. However, more than half had gained weight. To sustain the healthy lifestyle established in pregnancy, awareness of future risk was a motivational factor, but the women asked for tailored information on individual risk and improved support.

Following the thematic analysis, four main themes emerged: *stigma and shame; uncertainty; gaining control and finding balance; and a need for support to sustain change.* The themes are discussed below.

Stigma and shame

Many participants described initial feelings of shame and embarrassment. Most of the women associated GDM with unhealthy dietary habits, leading to self-blame for putting the fetus at risk. Among the participants of non-Scandinavian background, the stigma was predominantly related to their ethnic group, resulting at less self-blame at the individual level. Additionally, for some of these women, this impaired their motivation for lifestyle changes after birth, as they thought they would develop T2DM anyhow.

A recent scoping review examining the current evidence on stigma and GDM, reports that women may experience stigma in the form of overt discrimination from healthcare personnel and relatives, and in the form of internalised stigma, such as guilt and shame [41]. Participants in our study described both these types of stigma. Some of the participants stated that getting GDM would have been less stigmatic if they had been told about various risk factors, such as family history.

Uncertainty

Uncertainty affected women's reactions to the diagnosis and expectations of follow-up, and influenced their thoughts of maternal and fetal risk. A recent review exploring factors affecting uncertainty in high-risk pregnancies summarized that personal, pregnancy-related, demographic, and healthcare-related factors were involved [139]. Uncertainty was associated with less support and lack of information, and closely tied to appraisal of maternal and fetal risk, as also found in our study.

Contrasting our findings of high levels of uncertainty in a study population with high education level, Schmuke et al. reported lower levels of uncertainty among women with higher education level [139]. Furthermore, uncertainty may affect coping-strategies in

high-risk pregnant women. High levels of uncertainty are associated with emotion-focused rather than problem-focused coping [140].

The burden of treatment is described as 'the workload of healthcare and its effect on patient functioning and wellbeing' [141]. Most participants in our study reported that the burden of GDM was high, and medicalisation of pregnancy was apparent. Uncertainty contributed to the overall burden of GDM.

Gaining control and finding balance

Gaining control was a dominant theme, involving dietary planning, meals, SMBG, and clinical follow-ups. Most women reported that self-management such as incorporating SMBG in daily life, planning diet and activity were most challenging; though achieving glycemic control also gave mastery and stress relief. However, for several women the burdens of treatment were overwhelming, and two participants described the feeling of having an eating disorder. Others felt obsessed with having a well-controlled diet, with the 'numbers', and that the blood glucose management took all their time.

The cornerstone of GDM treatment includes healthy eating and physical activity: So easy, although so challenging. Diet modification in GDM management may include emphasis on carbohydrate intake and calorie counting, as well as SMBG. Both these factors may depend on health literacy and numeracy [142]. Health literacy is defined as 'the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions', whereas numeracy is defined as 'the ability to use and understand numbers in daily life' [142].

Health literacy and numeracy are both positively correlated with education [143]. Among the participants in our study, we observed a high health literacy level. Could this have contributed to their experience of overwhelming burden of treatment or feelings of having an eating disorder described above?

Some weeks after the GDM diagnosis, many participants described that their stress level decreased, and they realised that finding the right balance in measurements and diet became most important. Several emphasised the emotional support from health personnel.

A need for support to sustain change

Overall, most women contrasted their lack of follow-up after birth with the healthcare they received for GDM during pregnancy. The sense of lack of interest felt like an abandonment, as several requested a need to discuss tailored information regarding their personal risk. Women asked for improved support to sustain change and maintain the healthy lifestyle. Several women suggested a GP consultation including HbA1c measurement as part of their maternity care 4–6 months after delivery.

To sustain a healthy lifestyle, patient empowerment is important. In patient empowerment, the goal is to encourage the patients to make informed decisions in order to achieve goals [144]. The role of health personnel is to encourage patients to make informed decisions, and ensure sufficient support.

In light of our findings, a potential key to successful management of GDM must ensure ongoing support by the providers, both in primary and secondary healthcare. Furthermore, to reduce uncertainty from the beginning, at time of diagnosis, across gestation, and postpartum. Finally, to empower the women to be responsible for their own health, as this most likely also will influence and improve the health of the whole family.

7. Conclusions

- Glycemic control improved throughout gestation in women with pre-gestational diabetes, time in range increased from 59% to 68%, whereas glycemic variability decreased. Overall, women were far from achieving the recommended targets for glycemic control.
- The mean GA level decreased throughout gestation, and correlated with mean glucose, TIR, TAR and glucose SD. In contrast, the mean HbA1c level decreased until pregnancy week 24, and increased towards pregnancy week 36.
- In the ROC analyses, GA was more accurate than HbA1c to detect TIR <70% and TAR >25% with adjusted AUCs of 0.78 and 0.82.
- Our findings support the use of GA to assess glycemia in pregnant women with diabetes. Furthermore, our findings illustrate that GA and HbA1c have different qualities in the monitoring of glycemic control.
- The RI for GA in pregnant women analysed by LC-MS/MS was 7.1–11.6%.
- With a reported AUC of only 0.53, our study did not support the use of GA as a diagnostic tool for GDM.
- The prevalence of GDM according to the different guidelines was 16.4% (WHO-1999), 24.7% (WHO-2013), and 14.4% (Norwegian-2017 guideline) in our study population of unselected primiparous women. Only 6.2% fulfilled the GDM criteria in all three guidelines.
- Women experienced a lack of support for GDM after delivery. To maintain the healthy lifestyle, women suggest improved support.
- Awareness of future diabetes risk was a motivational factor for lifestyle changes, but women ask for tailored information on personal risk.

8. Clinical implications and future perspectives

The overall aim of this thesis was to assess hyperglycemia in pregnancy, and to bring new insight into diagnostics, biomarkers, follow-up, and monitoring of glycemic control. Our results support the use of GA in monitoring glycemic control in women with pre-gestational diabetes. Moreover, we demonstrated that GA did better than HbA1c to capture poor glycemic control defined as time in range <70% and time above range >25%. Unfortunately, there were no differences in mean GA level, nor HbA1c level at pregnancy week 24–28 in women with GDM in our cross-sectional study. Thus, are findings do not support the use of these biomarkers in the diagnostics of GDM. Despite all limitations and drawbacks, the OGTT remains the gold standard test.

Today, the use of CGM is increasing, especially in developed countries. In the future, CGM technology will continue to improve, and hopefully access to CGM for all pregnant women with pre-gestational diabetes will be a reality. Until then, a biomarker as GA could be a supplement to assess recent glycemic control in women with pre-gestational diabetes. We hope our results will contribute to a better understanding of the monitoring of glycemia in pregnant women, moreover, that HbA1c and GA have different qualities in this aspect.

In future studies, we would like to explore glycemic variability and fluctuations in more detail. It would be interesting to assess whether there are differences in GA level between those with stable and more fluctuating glucose levels. Moreover, we would like to perform new analyses to examine the association between fetal growth, GA level and fetal weight percentiles. Finally, we are planning a methodology paper with analyses comparing GA measurements done by our LC-MS/MS method and the more widespread enzymatic assay.

The prevalence of diabetes mellitus is escalating worldwide, and hyperglycemia is among the most common medical complications throughout gestation. During this PhD period, the reported prevalence of GDM from the Medical Birth Registry has been

increasing every year. Likewise, the amount of pregnant women with overweight and obesity.

It is necessary with increased awareness on the life-course perspective, and that the risks for NCDs start in utero. Diabetes begets diabetes. We need to focus more on the importance of healthy pregnancies, improving maternal and fetal health, in the short and long run. In Norway, introduction of the GDM guideline in 2017 and the following debate culminated, without much attention on the life-course perspective.

The PhD period is ending, and I can look back on an academic journey. My impression after weekly encounters with women having their pregnancies complicated by hyperglycemia, as well the in-depth interviews with the women in study III is that the hyperglycemia highly affects the pregnancies for these women. Wanting the best for their offspring, most of these women make an effort, struggling to keep the blood glucose in range. For the majority, medicalization is apparent.

After delivery, women with GDM suffer from a lack of follow-up, as we found in the qualitative study. The window of opportunity impairs. Women with a history of GDM deserve a proper follow-up after delivery. These women are at high risk of recurrent GDM, as well as development of T2DM and CVD within few years. In line with the life-course approach, more studies are needed, focusing on how to improve the follow-up of these women. In Norway, the continuity of care ensured by the GPs is of importance, and probably a part of the key to succeed.

The overall rationale for this thesis was a wish to improve pregnancy outcomes and reduce the burden for women with hyperglycemia in pregnancy. I hope that the findings may be small steps towards a better understanding of hyperglycemia in pregnancy and monitoring of glycemic control. Finally, that follow-up of women with a history of GDM will be improved.

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10. Erratum

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RESEARCH ARTICLE

Glycated albumin and continuous glucose monitoring metrics across pregnancy in women with pre-gestational diabetes

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Abstract

Introduction: Glycated albumin (GA), a biomarker reflecting short-term glycaemia, may be useful to assess glycaemic control in pregnancy. We examined the association between GA and continuous glucose monitoring (CGM) metrics across gestation.

Methods: In this prospective cohort study including 40 women with pre-gestational diabetes, blood samples for analysis of GA and glycated haemoglobin A1c (HbA1c) were collected at pregnancy week 12, 20, 24, 28, 32 and 36. In the CGM-group (n = 19), CGM data were collected from first trimester until pregnancy week 36. Receiver operating characteristic (ROC) curves were used to assess the accuracy of GA and HbA1c to detect poor glycaemic control, using CGM metrics as the reference standard. This study was conducted at Stavanger University Hospital, Norway, in 2016–2018.

Results: Glycaemic control improved across gestation with more time spent in target range, coinciding with decreased glycaemic variability and lower mean GA level. There was statistically significant correlation between GA and most CGM metrics. The area under the ROC curves (AUC) for detecting time in range <70% and time above range >25% for the pregnancy glucose target 63–140 mg/dl (3.5–7.8 mmol/L) were 0.78 and 0.82 for GA, whereas AUCs of 0.60 and 0.72 were found for HbA1c, respectively.

Conclusions: Higher GA levels were associated with less time spent in target range, more time spent in the above range area and increased glycaemic variability. GA was more accurate than HbA1c to detect time above range >25% and time in range <70%.

KEYWORDS
continuous glucose monitoring, glycated albumin, glycated haemoglobin A1c, pregnancy, type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

In women with pre-gestational diabetes, the risk of adverse pregnancy outcomes correlate with the level of glycaemia.[1] In Norway, the prevalence of pregnancies complicated by pre-gestational diabetes has been stable around 0.7% for the last decade.[2] Corresponding numbers are reported in Australia (0.6%) and in the United States (0.9%).[3,4] However, due to increasing obesity, earlier onset of type 2 diabetes (T2D) and higher maternal age, the prevalence of pre-gestational diabetes is expected to rice globally.

Continuous glucose monitoring (CGM) enables users to monitor their glucose level, providing the opportunity to respond to glucose fluctuations as they occur.[5] With randomized controlled trials showing that CGM is associated with improvements in maternal glycaemic control and neonatal outcomes,[6] the use of CGM in antenatal care is increasing.[7] By recent international consensus for CGM monitoring, the pregnancy glucose target range for type 1 diabetes (T1D) was set to 63–140 mg/dl (3.5–7.8 mmol/L). Women should strive to achieve >70% of time within target range.[8] Currently, there are not provided CGM targets for pregnant women with T2D, due to the lack of evidence and limited data. However, access to CGM for all pregnant women with diabetes is still limited.

Glycated albumin (GA), a biomarker reflecting short-term glycaemia (2–4 weeks) has been suggested to supplement glycated haemoglobin A1c (HbA1c) in monitoring glycaemic control.[9] In diabetic pregnancies where strict glycaemic control is important to reduce adverse maternal/foetal outcomes, a marker reflecting recent glycaemic status is preferable. Moreover, GA may be better than HbA1c to detect glucose variability and fluctuations, which have been associated with increased risk of developing large for gestational age (LGA) foetuses.[10] Furthermore, elevated maternal GA levels may predict perinatal complications.[11] Thus, GA may be a useful tool for detecting and monitoring recent glycaemic control in diabetic pregnancies, and in particular, the glucose fluctuations, not provided by HbA1c.

Haemoglobin A1c is recognized as the gold standard of diabetic survey[12] and was included as a diagnostic criterion for diabetes mellitus in 2011.[13] HbA1c reflects mean glycaemia over the preceding 8–12 weeks.[14] There is a linear relationship between average glucose and HbA1c in pregnancy, but the change in HbA1c reflects a smaller difference in mean glucose compared with that found in non-pregnant adults.[15] Moreover, altered erythrocyte turnover and iron deficiency may influence HbA1c, making it less accurate during pregnancy.[16,17] Despite these limitations, HbA1c is used worldwide in clinical practice to monitor glycaemic control during pregnancy.

Recently, a new high-throughput method for GA measurement using liquid chromatography–tandem mass spectrometry (LC–MS/MS) was developed in our laboratory.[18] Subsequently, the reference interval for GA in healthy pregnant women was established.[19]

The primary aim of this study was to explore the association between GA and CGM metrics across gestation in women with pregestational diabetes. Secondly, we investigated the accuracy of GA and HbA1c to detect poor glycaemic control using CGM metrics as the reference standard.

2 | METHODS

2.1 | Study population

This prospective cohort study was conducted at Stavanger University Hospital, Norway, in 2016–2018. Women were asked to participate in the study when they met at the antenatal diabetic outpatient clinic in first trimester. All women with pregestational diabetes and singleton pregnancies were eligible for inclusion. In Norway, antenatal care of women with pre-existing diabetes is primarily organized in specialist health care where the woman meets an obstetrician, a midwife and an endocrinologist at every visit. All participants received current routine clinical care, with antenatal visits every 2–4 weeks until pregnancy week 38. Women with otherwise uncomplicated pregnancies, had an additional consultation at pregnancy week 39 and labour was induced no later than the due date. In addition, the consenting women had blood samples for analysis of GA and HbA1c taken at Stavanger University Hospital's Clinical Trial Ward around pregnancy week 12, 20, 24, 28, 32 and 36, coordinated with the clinical appointments.

Blood samples for GA were collected in serum gel tubes, stored at room temperature for 30 min, centrifuged at 2500*g* to obtain serum, and stored at −75°C until used. GA was analysed by LC–MS/MS as previously described.[18] HbA1c was analysed on BioRad Variant II Turbo, high-performance liquid chromatography, standardized to the International Federation of Clinical Chemistry reference method (analytical variation ≤3%). All analyses were performed at the Department for Medical Biochemistry, Stavanger University Hospital.

2.2 | Blood glucose data

According to recommendations in the Norwegian guideline, the HbA1c level should be <53 mmol/mol (<7%) in the preconception period and <42 mmol/mol (<6%) from second trimester. Throughout pregnancy, treatment goals for glucose are fasting plasma glucose 63–99 mg/dl (3.5–5.5 mmol/L) and <128 mg/dl (<7.1 mmol/L) 2 h postprandial.[20] CGM were offered to women with poor glycaemic control, or additional challenges such as impaired awareness of hypoglycaemia. Otherwise, self-monitoring of blood glucose with frequent daily measurements (7–10 times a day) was advised. In Norway, the use of CGM during pregnancy has markedly increased over the past years. Seventeen women in the study were already users of CGM before pregnancy, whereas four participants were offered CGM during pregnancy.

2.3 | CGM system

Among the CGM users, the majority had Dexcom G4 (Dexcom Inc), whereas one had Freestyle Libre (Abbott) and another used the Medtronic CGM system (Medtronic). The Dexcom G4 device, measures subcutaneous interstitial glucose concentration every 10 s and generates a glucose value every 5 min, available for the user real time. Dexcom G4 requires calibration by the user against capillary plasma glucose twice daily. With the Freestyle Libre system, known as a 'flash' glucose monitor, no calibration is required. The interstitial glucose level is measured every 60 s, a glucose value is generated

every 15 min, but the results are available only retrospectively when the sensor is scanned with a reading device. The Medtronic CGM system is also a real time system, generating a glucose value every 5 min.

2.4 | Glucose data management

At every visit, available data from self-monitored blood glucose and/or CGM were downloaded from the internet-based Diasend system (Glooko). For the user of Medtronic CGM system, glucose data were downloaded from CareLink (Medtronic). We included CGM data from the 14 days leading up to each blood sampling at pregnancy week 12, 20, 24, 28, 32 and 36. According to recent consensus on CGM use, we required at least 70% coverage (percentage of time CGM is active) for inclusion in the analysis.[8]

From CGM data, we calculated mean glucose level and the percentage of time spent in target range (time in range, TIR), time below range (TBR) and time above range (TAR) for the pregnancy glucose target range 63–140 mg/dl (3.5–7.8 mmol/L).[8] We also calculated time below range <54 mg/dl (<3.0 mmol/L), denoted TBR2. Measures of glycaemic variability included glucose standard deviation (SD) and coefficient of variation (CV).[8]

2.5 | Obstetric data and outcomes

Information concerning pregnancy outcome was collected from medical records after delivery. Frequencies of small for gestational age and large for gestational age were calculated using the 10th and 90th percentile according to Gjessing et al.[21] In addition, birth weight centiles and percentage birth weight deviations from the median birth weight for gestational age, were calculated.[21]

2.6 | Ethical considerations/approval

The study was carried out in accordance with the Helsinki Declaration and was approved by the Regional Committees for Medical and Health Research Ethics, Western Norway (May 2016, REK 2016/563). The study was registered in Clinical Trials with identifier NCT 03330951. All included women received written information about the study and gave informed consent.

2.7 | Statistical analyses

Categorical data are shown as percentages. Continuous variables are presented as mean with SD, or median with interquartile ranges (IQR) for skewed distributions. Differences in clinical characteristics between the CGM and non-CGM group were assessed using independent samples *t*-test (normal distribution) and Mann–Whitney test (skewed distribution) for continuous data, whereas Chi-squared test was performed for categorical data. A p-value $< .05$ was considered statistically significant.

Mean values of GA and HbA1c at different time points were estimated in mixed linear models with random intercepts and random effects of time points. Comparison of levels between time points was performed with paired samples *t*-tests.

Correlation coefficients were used to assess relationships between GA, HbA1c and CGM metrics. The correlation coefficients were estimated allowing for the repeated measures design using the approach outlined by Hamlett et al.[22] Confidence intervals (CI) were bias-corrected percentile bootstrap intervals based on 1000 resamples of the 19 participants in the CGM group.

Receiver operating characteristics (ROC) analyses were performed to compare the accuracy of GA and HbA1c to detect poor glycaemic control defined as TIR <70%, TAB >25%, TBR >4% and TBR2 >1%. The area under the ROC curve (AUC) for each glycaemic marker was calculated as the Harrell's C statistic and presented with 95% CI adjusted for clustering. Optimal cut-offs were estimated based on the Youden Index, and corresponding sensitivities and specificities were estimated in logistic regression models with random intercepts to allow for clustering. The statistical analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp.) and Stata/SE for Windows, version 17.0 (StataCorp LLC).

3 | RESULTS

In all, 42 women were asked to participate in the study and 41 were included. One participant withdrew during the study period, resulting in a total study population of 40 pregnant women. Among these, 26 (65%), 13 (32.5%) and one (2.5%) had type 1 diabetes, type 2 diabetes and maturity onset diabetes of the young (MODY), respectively.

In total, 17 women were CGM-users before pregnancy. Out of the four women offered CGM during pregnancy, one delivered prematurely a week later. For another woman, the CGM raw data were lost, resulting in 19 women with available CGM-data from first trimester to pregnancy week 36. The majority in the CGM group had T1D, whereas the non-CGM group was more heterogeneous. All insulin-pump users were in the CGM group, and most had Animas vibe pumps (Animas Corporation), while three women had either a Paradigm 715 (Medtronic), Minimed 640G (Medtronic) or an Omnipod (Insulet) pump. In contrast, most women used insulin pens in the non-CGM group. Moreover, women in the CGM group were younger and had longer diabetes duration compared with the non-CGM group. Pre-pregnancy HbA1c level, BMI and weight-gain in pregnancy were comparable between the two groups.

Almost one in five women developed preeclampsia, one third delivered an LGA-newborn and two thirds had a vaginal delivery. The clinical characteristics of the total study population, CGM group and non-CGM group are summarized in Table 1.

The majority (82.5%) completed all six blood samples for analyses of GA and HbA1c, whereas five women (12.5%) missed one blood sample and two women (5%) missed two blood samples. The

TABLE 1 Maternal and neonatal characteristics in the total study population, CGM-group and non-CGM group.

	Total study population ($n = 40$)	CGM group ($n = 20$)	Non-CGM group ($n = 20$)	*p*-value
Age, years	30.9 ± 5.5	29.2 ± 5.0	32.6 ± 5.5	.049*
Pre-pregnancy BMI, kg/m^2	25.8 (8.0)	25.8 (6.3)	25.8 (11.3)	.99
Pre-pregnancy HbA1c, %	6.9 (1.3)	7.0 (1.3)	6.6 (1.3)	.99
Pre-pregnancy HbA1c, mmol/mol	51.5 (15)	55.5 (15)	49.0 (15)	.78
Weight-gain in pregnancy, kg	14.3 (8.9)	14.3 (8)	14.5 (9.7)	.78
Diabetes duration, years	10.5 ± 7.4	15.3 ± 6.5	5.0 (6)	<.001**
Nulliparous	35	40	30	.51
Retinopathy	33	50	15	.018*
Nephropathy	-	-	-	-
Chronic hypertension	5	10	-	.15
Gestational age at inclusion (weeks)	12.4 ± 0.9	12.3 ± 0.7	12.6 ± 1.1	.27
Ethnic background				
European	78	90	65	.058
Middle Eastern	5	-	10	.15
Asian	10	10	10	1.00
African	8	-	15	.072
Diabetes type				
Type 1 diabetes	65	95	35	<.001**
Type 2 diabetes	33	5	60	<.001**
MODY diabetes	3	-	5	.31
Anti-glycaemic therapy in pregnancy				
Insulin	90	90	90	1.00
Metformin	5	5	5	1.00
Insulin and Metformin	5	5	5	1.00
Insulin pump	30	60	-	<.001**
Pregnancy outcome				
Gestational age, weeks	38.9 (1.9)	38.9 (1.3)	38.9 (2.4)	.84
Preeclampsia	18	25	10	.21
Gestational hypertension	3	5	-	.31
Preterm delivery	15	10	20	.38
Induction of labour	70	55	85	.038*
Vaginal delivery	60	40	80	.010*
Shoulder dystocia	-	-	-	-
Elective caesarean section	3	5	-	.31
Acute caesarean section	38	55	20	.022*
Neonatal characteristics				
Birthweight, g	3794 (697)	3865 (726)	3683 (862)	.13
Birthweight, percentile	83.9 (42.2)	88.2 (28.7)	70.9 (42.8)	.040*
Large for gestational age	33	40	25	.31
Small for gestational age	5	-	10	.15
NICU admission	43	50	35	.34

Note: Continuous variables are reported as mean ± SD or median (IQR) as appropriate, categorical data as percent.

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin A1c; MODY, maturity-onset diabetes of the young; NICU, neonatal intensive care unit.

*$p < .05$, **$p < .001$.

TABLE 2 Glycated albumin, HbA1c and CGM metrics across gestation.

	12 weeks	20 weeks	24 weeks	28 weeks	32 weeks	36 weeks
CGM metrics						
Mean glucose, mg/dl	119 (112, 128)	119 (110, 126)	119 (112, 128)	121 (114, 130)	121 (112, 130)	117 (108, 128)
Mean glucose, mmol/L	6.6 (6.2, 7.1)	6.6 (6.1, 7.0)	6.6 (6.2, 7.1)	6.7 (6.3, 7.2)	6.7 (6.2, 7.2)	6.5 (6.0, 7.0)
TIR, %	59 (54, 65)	63 (57, 68)	61 (55, 66)	61 (55, 66)	64 (58, 69)	68 (62, 74)
TAR, %	29 (23, 35)	27 (21, 33)	29 (23, 35)	31 (24, 37)	29 (22, 35)	25 (18, 32)
TBR, %	12 (8, 15)	10 (7, 13)	10 (7, 14)	9 (5, 12)	8 (4, 11)	7.2 (4, 11)
TBR2, %	7 (4, 10)	5 (3, 7)	6 (3, 9)	5 (3, 7)	4 (1, 7)	4 (2, 6)
Coefficient of variation, %	40 (37, 43)	38 (35, 40)	37 (34, 39)	36 (33, 38)	35 (32, 38)	34 (32, 37)
Glucose SD, mmol/L	2.7 (2.4, 2.9)	2.5 (2.2, 2.7)	2.5 (2.2, 2.7)	2.4 (2.2, 2.6)	2.3 (2.1, 2.6)	2.2 (2.0, 2.5)
Laboratory glycaemic markers						
CGM-group ($n = 20$)						
Glycated albumin, %	12.1 (11.3, 13.0)	12.4 (11.5, 13.3)	11.3 (10.4, 12.2)	11.0 (10.1, 11.9)	10.2 (9.3, 11.1)	9.3 (8.4, 10.3)
HbA1c, %	6.1 (5.8, 6.4)	5.8 (5.6, 6.1)	5.7 (5.4, 6.0)	6.2 (5.6, 6.3)	6.1 (5.8, 6.4)	6.1 (5.8, 6.5)
HbA1c, mmol/mol	44 (40, 47)	40 (37, 44)	39 (36, 42)	44 (38, 45)	43 (40, 47)	44 (40, 47)
Non-CGM group ($n = 20$)						
Glycated albumin, %	11.6 (10.2, 12.9)	11.1 (9.7, 12.5)	10.3 (8.9, 11.8)	10.0 (8.6, 11.5)	10.0 (8.5, 11.5)	9.2 (7.6, 10.8)
HbA1c, %	6.4 (6.0, 6.9)	6.0 (5.5, 6.4)	5.8 (5.4, 6.3)	5.9 (5.4, 6.4)	6.1 (5.5, 6.7)	6.1 (5.6, 6.7)
HbA1c, mmol/mol	47 (42, 52)	42 (37, 47)	40 (35, 45)	41 (35, 46)	43 (37, 49)	44 (37, 50)

Note: Data presented as mean with 95% confidence intervals, adjusted predictions. CGM metrics were calculated from 103 14-days periods across gestation with >70% coverage.

Abbreviations: CGM, continuous glucose monitoring; HbA1c, glycated haemoglobin A1c; SD, standard deviation; TAR, time above range >140 mg/dl (>7.8 mmol/L); TBR, time below range <63 mg/dl (<3.5 mmol/L); TBR2, time below range <54 mg/dl (<3.0 mmol/L); TIR, time in range 63–140 mg/dl (3.5–7.8 mmol/L).

main reason for not completing all blood samples was premature delivery. In total, 231 blood samples across gestation were available for analyses of GA and HbA1c.

After exclusion of six 14-days periods with <70% coverage, 103 14-days periods throughout gestation were available for the analysis of CGM-data (mean coverage 92.6%, SD 4.9). The CGM metrics and laboratory markers of glycaemia varied across gestation (Table 2). We found correlations between GA and mean glucose, TIR, TAR and glucose SD (Table 3). For HbA1c, correlations were found with mean glucose, TAR, TBR and TBR2 (Table 3).

The mean GA level decreased throughout gestation in both the CGM and non-CGM group (Figure 1A), whereas the mean HbA1c level decreased from first trimester until pregnancy week 24, and increased towards pregnancy week 36 (Figure 1B), all changes statistically significant ($p < .05$).

Glycaemic control improved across gestation with more time spent in target range (Figure 2A) and less time spent above range and below range areas (Figure 2B,C). Mean glucose varied slightly (Figure 2D), whereas glycaemic variability decreased markedly (Figure 2E,F). However, in total, only 25 of the 14-days periods (24%) achieved the international recommendation of >70% TIR for the pregnancy glucose target 63–140 mg/dl (3.5–7.8 mmol/L). For TAR <25%, TBR <4% and TBR2 <1%, the corresponding percentages were 38%, 28% and 19%, respectively.

We observed positive associations between GA and TAR, mean glucose, SD and CV (Figure 3B,D–F), a negative association with TIR (Figure 3A) and no association with TBR (Figure 3C). Corresponding scatterplots showing the association between HbA1c and CGM-metrics are presented in Figure S1.

Receiver operating characteristic curves were used to assess the accuracy of GA and HbA1c to detect poor glycaemic control defined as non-achievement of the clinical targets for CGM metrics, thus, TIR <70%, TAB >25%, TBR >4% and TBR2 >1% for the pregnancy glucose target 63–140 mg/dl. The adjusted AUCs for GA in detecting TIR <70%, TAB >25%, TBR >4% and TBR2 >1% were 0.78 (95% CI 0.60–0.95), 0.82 (95% CI 0.70–0.94), 0.56 (95% CI 0.31–0.82) and 0.66 (95% CI 0.42–0.90), respectively.

For HbA1c, the adjusted AUCs for detecting TIR <70%, TAB >25%, TBR >4% and TBR2 >1% were 0.60 (95% CI 0.41–0.78), 0.72 (95% CI 0.54–0.90), 0.30 (95% CI 0.13–0.47) and 0.32 (95% CI 0.13–0.52), respectively. The ROC-curves are presented in Figure 4.

The optimal GA cut-off value for detecting TIR <70% was >10.5%, with corresponding sensitivity (SE) 68% (95% CI 52%–83%) and specificity (SP) 73% (51%–95%). Similarly, the optimal cut-off for detecting TAR >25% was a GA level >11% (SE 70 [54%–87%], SP 79 [62%–96%]).

4 | DISCUSSION

In this prospective study of pregnant women with pre-gestational diabetes, overall glycaemic control improved across gestation with

	Glycated albumin	HbA1c
Time in range (TIR)	**−0.58 (−0.77, −0.27)**	−0.41 (−0.66, 0.09)
Time above range (TAR)	**0.56 (0.35, 0.71)**	**0.58 (0.22, 0.77)**
Time below range (TBR)	−0.09 (−0.47, 0.25)	**−0.44 (−0.64, −0.14)**
Time below range 2 (TBR2)	−0.05 (−0.41, 0.26)	**−0.38 (−0.58, −0.11)**
Mean glucose	**0.49 (0.28, 0.62)**	**0.63 (0.32, 0.79)**
Standard deviation (SD)	**0.58 (0.24, 0.77)**	0.38 (−0.14, 0.66)
Coefficient of variation (CV)	0.36 (−0.09, 0.65)	−0.07 (−0.43, 0.22)

Note: Correlation coefficients for repeated measures design with 95% confidence intervals. CGM metrics were calculated from 103 14-days periods across gestation with >70% coverage. Significant correlations are marked in bold.

Abbreviations: CGM, continuous glucose monitoring; HbA1c, glycated haemoglobin A1c.

TABLE 3 Correlation coefficients with 95% confidence intervals for laboratory glycaemic markers and CGM metrics across gestation in diabetic pregnancies.

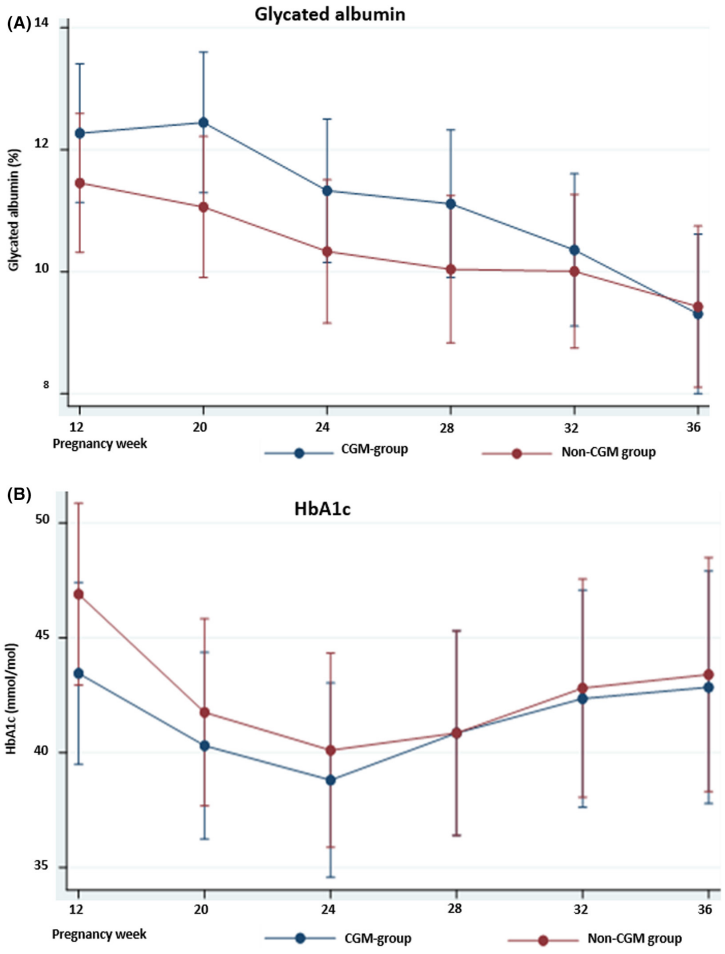

FIGURE 1 Glycaemic markers across gestation in the CGM and non-CGM group. (A) Glycated albumin (%). (B) HbA1c (mmol/mol). Data presented as mean with 95% confidence intervals. CGM, continuous glucose monitoring; HbA1c, glycated haemoglobin A1c

more time spent in target range, whereas glycaemic variability decreased. Glycated albumin level decreased throughout pregnancy and correlated significantly with CGM metrics. In the ROC analysis, GA was markedly better than HbA1c to detect TIR <70% and TAB >25% with AUC values of 0.78 and 0.82.

Our findings support the use of GA as a biomarker of glycaemia in pregnant women with diabetes. As long as CGM is not available for all pregnant women, a short-term biomarker to supplement self-monitoring of blood glucose is useful. With the known limitations of HbA1c, this biomarker should not be used

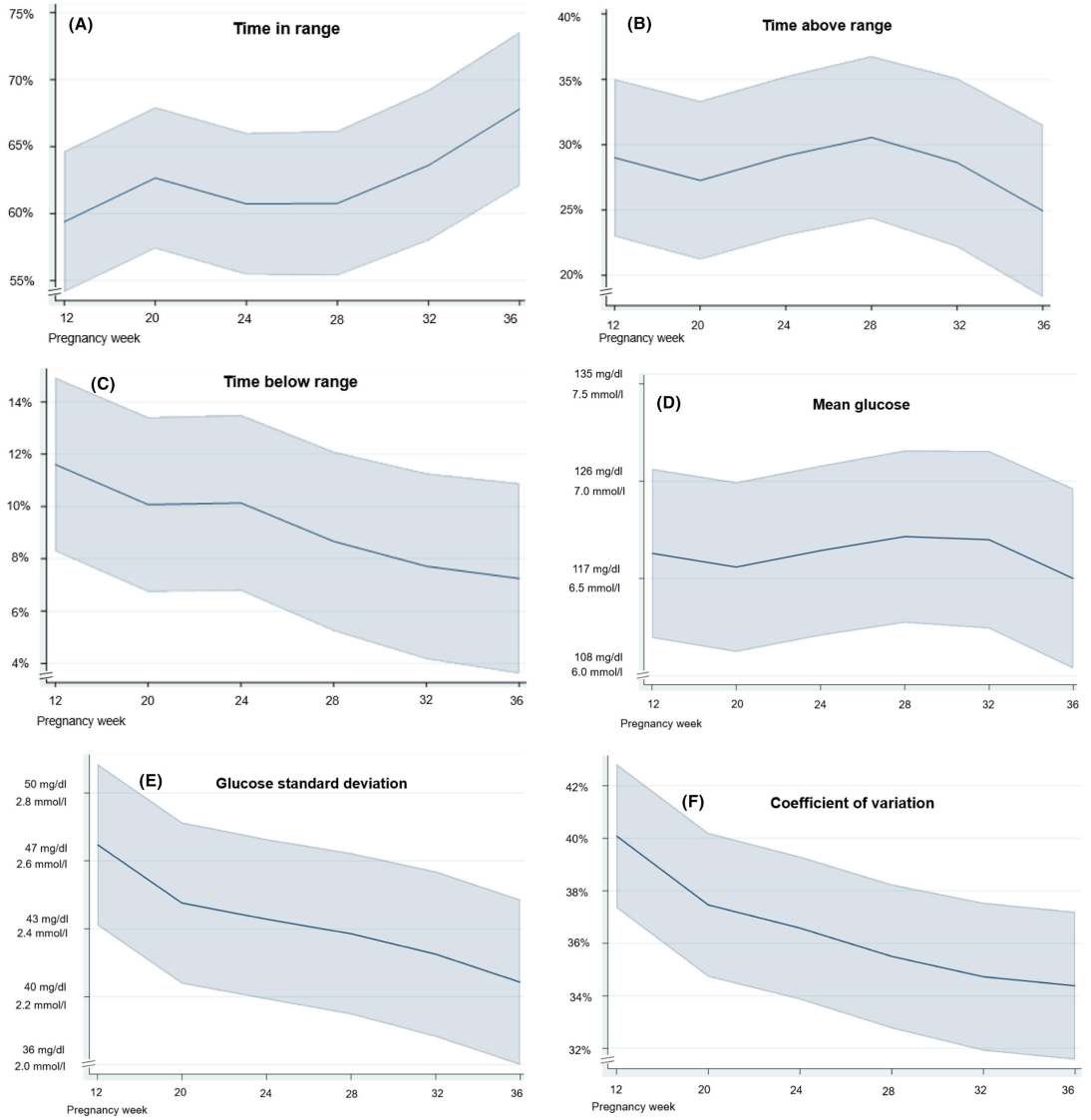

FIGURE 2 CGM-metrics across gestation. (A) Time in range: 63–140 mg/dl (3.5–7.8 mmol/L). (B) Time above range: >140 mg/dl (>7.8 mmol/L). (C) Time below range: <63 mg/dl (<3.5 mmol/L). (D) Mean glucose. (E) Glucose standard deviation. (F) Coefficient of variation. Calculations based on 103 14-days periods with >70% coverage. Data presented as mean with 95% confidence intervals, adjusted predictions. CGM, continuous glucose monitoring

to assess glycaemia in pregnant women.[23] The improving glycaemic control throughout pregnancy observed in our study using CGM-metrics as the reference standard, was not at all reflected in lower HbA1c levels, in contrast, GA levels decreased throughout the pregnancy. We found high, statistically significant correlation between GA and glucose SD. Although not statistically significant, the positive correlation between GA and glucose CV and an AUC >0.5 for TBR >4% and TBR2 >1%, are in further support of previous findings indicating that high GA may also detect glycaemic variability,[10] including hypoglycaemic fluctuations.

Others have shown that the GA level also decreases during gestation in women with healthy pregnancies.[24,25] The reasons remain unexplained, but might be due to increased turnover of albumin and/or increased selective loss of GA through glomerular filtration.[25] Although the GA-values are not directly comparable due to different methods for GA-analysis, the observed decrease in mean GA level in

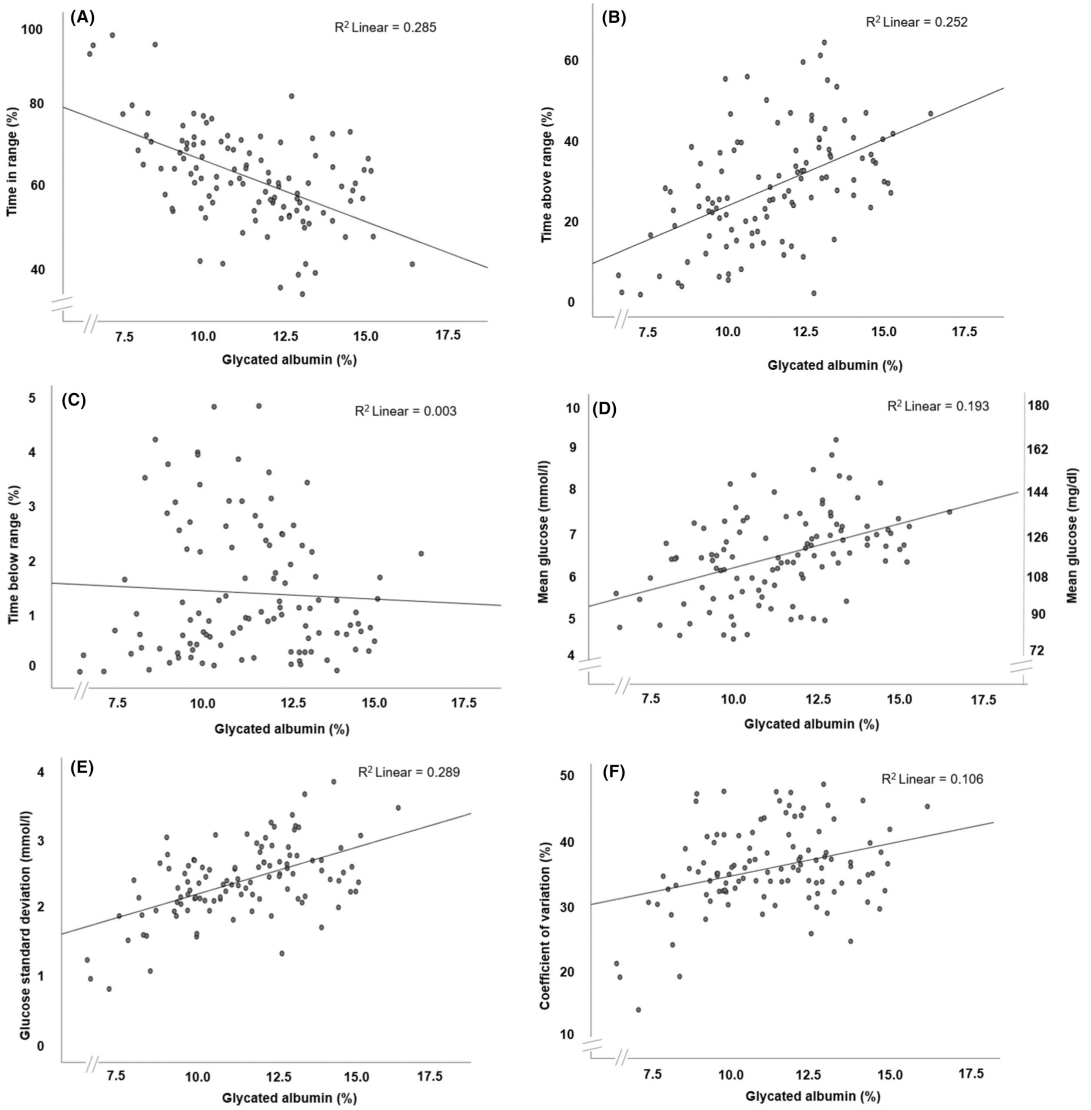

FIGURE 3 Scatterplots indicating the association between glycated albumin with CGM metrics. (A) Time in range: 63–140 mg/dl (3.5–7.8 mmol/L). (B) Time above range: >140 mg/dl (>7.8 mmol/L). (C) Time below range: <63 mg/dl (<3.5 mmol/L). (D) Mean glucose. (E) Glucose standard deviation. (F) Coefficient of variation. CGM metrics are calculated from 103 14-days periods with >70% coverage. CGM, continuous glucose monitoring; R^2, coefficient of determination

our study is more prominent (from 12.1% to 9.3%). In comparison, the mean GA level in healthy pregnant women was 9.5% at pregnancy week 24–28 in our previous study,[19] whereas a mean GA level of 11.3% and 10.3% was found in the CGM and non-CGM group at pregnancy week 24 the present study.

Another population where HbA1c has limitation, haemodialysis patients with diabetes, Divani et al.[26] found higher accuracy for GA than HbA1c to detect TIR <50%. None of the glycaemic markers were able to detect TBR. In the current study, for GA, the AUC of 0.66 for TBR2 >1% was not statistically significant, however suggesting that high GA levels may detect hypoglycaemic excursions. In contrast, HbA1c detected TBR and TBR2 above thresholds with AUCs of 0.30 and 0.32 (the latter not statistically significant), that is high HbA1c levels indicate reduced risk for these CGM metrics.

Albeit an increase in mean percentage of time spent in target range from 59% in first trimester to 68% in third trimester, most

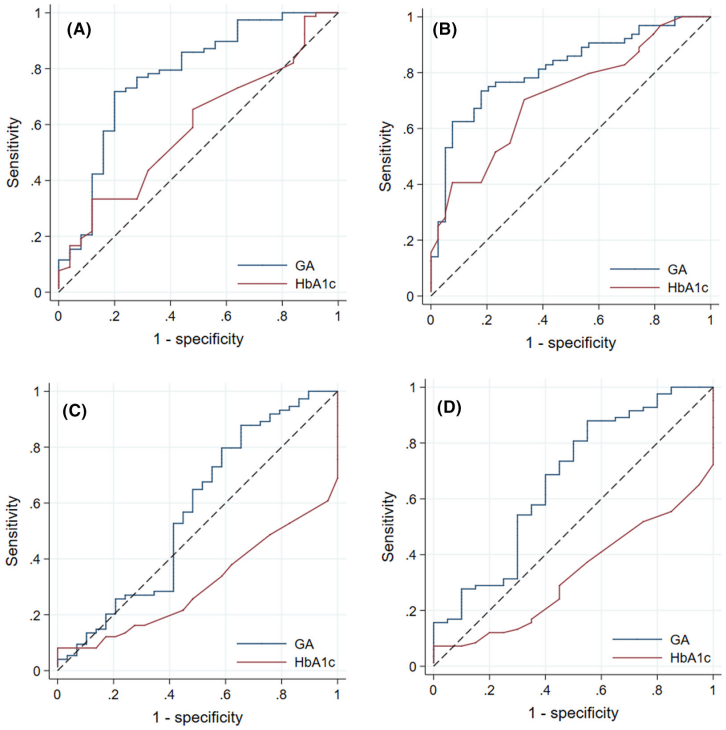

FIGURE 4 Receiver operating characteristic (ROC) curves to assess the ability of GA and HbA1c to detect poor glycaemic control. (A) Time in range <70%. (B) Time above range >25%. (C) Time below range >4%. (D) Time below range 2 >1%. Continuous glucose monitoring metrics are calculated from 103 14-days periods with >70% coverage.

women in our study were far from achieving the recommended target >70% for TIR. Only 24% of the analysed 14-days periods achieved TIR >70%, while 38% of the periods were within the target <25% for TAR. This is despite close follow-up according to clinical guidelines during pregnancy. Moreover, the mean pre-pregnancy HbA1c for the total study population was 51.5 mmol/mol, suggesting adequate glycaemic control.

In the CONCEPTT study, a multicentre randomized controlled trial on CGM use in pregnancy, time in target range reached 68% in the third trimester, similar to our study.[6] In contrast, they reported markedly lower TBR (3% vs. 7%) and slightly higher TAR (27% vs. 25%) in third trimester. In a Swedish cohort study of 186 women with type 1 diabetes, corresponding proportions for TIR, TAR and TBR in the third trimester were 60%, 34% and 7%, respectively.[27] In addition, the mean glucose level and glycaemic variability measures were higher in all trimesters. Taken together, these results indicate that it is challenging to obtain the targets for glycaemic control during pregnancy. Closed-loop insulin therapy have shown promising results to improve glycaemic control but is not yet included in clinical guidelines.[28]

Strengths of the current study include the real-life setting, the prospective design and the quantity of CGM data, continuously collected from first trimester until pregnancy week 36. In contrast, other studies report CGM data from notably shorter time periods of pregnancy, even as short as 3-days.[29] Moreover, repeated measurements of GA and HbA1c were performed and CGM metrics according to international consensus were reported.[8] Among eligible women, all except one wanted to participate in the study and only one woman withdrew during the study period. Blood sampling and preparation of samples were performed by trained study nurses at the Clinical Trial Ward, and all samples were analysed at the same laboratory. Limitations include the limited sample size. Most CGM-users in the present study had the Dexcom G4 device. Novel generations of CGM sensors such as Dexcom G6 may be more accurate.[30] Moreover, three women had different CGM systems, possibly influencing the results. Due to the current absence of CGM-criteria for women with T2D, we included the only CGM-user with T2D in the analyses.

In this longitudinal study on pregnant women with pre-gestational diabetes, GA level correlated well with CGM metrics. The improved glycaemic control observed was reflected in lower GA levels, but not in lower HbA1c levels. Higher GA levels were associated with less time spent in target range, more time spent in the above range area and increased glycaemic variability. Moreover, our results support previous findings that GA detects glycaemic variability better than HbA1c. Despite close follow-up during pregnancy in line with clinical guidelines, most women in our study did not achieve the clinical targets for CGM metrics. In the ROC-analysis, GA was more accurate than HbA1c to detect TIR <70% and TAR >25%. Thus, our findings support the use of GA to assess glycaemia in pregnant women with diabetes. Finally, our findings illustrate that GA and HbA1c have different qualities in the monitoring of glycaemic control. More studies,

with larger sample sizes are required to better understand the role of GA in diabetic pregnancies, and for establishing optimal cut-off values for detecting poor glycaemic control.

AUTHOR CONTRIBUTIONS

Johanne Holm Toft: Conceptualization (equal); data curation (lead); formal analysis (equal); funding acquisition (lead); investigation (lead); methodology (equal); project administration (lead); resources (equal); software (equal); supervision (supporting); validation (equal); visualization (equal); writing – original draft (lead); writing – review and editing (lead). **Ingvild Dalen:** Conceptualization (equal); data curation (equal); formal analysis (lead); investigation (equal); methodology (lead); project administration (supporting); software (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (supporting); writing – review and editing (supporting). **Øyvind Skadberg:** Conceptualization (equal); investigation (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal). **Lasse Gunnar Gøransson:** Conceptualization (equal); formal analysis (equal); investigation (equal); project administration (equal); resources (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Inger Økland:** Conceptualization (equal); data curation (equal); funding acquisition (equal); investigation (equal); project administration (equal); supervision (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Inger Hjørdis Bleskestad:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); project administration (equal); supervision (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Glycated albumin in pregnancy: LC-MS/MS-based reference interval in healthy, nulliparous Scandinavian women and its diagnostic accuracy in gestational diabetes mellitus

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ORIGINAL ARTICLE

Glycated albumin in pregnancy: LC-MS/MS-based reference interval in healthy, nulliparous Scandinavian women and its diagnostic accuracy in gestational diabetes mellitus

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ABSTRACT

Glycated albumin (GA) may be a useful biomarker of glycemia in pregnancy. The aim of this study was to establish the reference interval (RI) for GA, analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS), in healthy, nulliparous pregnant women. In addition, we assessed the accuracy of GA and glycated hemoglobin A1c (HbA1c) in the diagnosis of gestational diabetes mellitus (GDM). Finally, we explored the prevalence of GDM in healthy nulliparas, comparing three diagnostic guidelines (WHO-1999, WHO-2013 and the Norwegian guideline). The study was carried out at Stavanger University Hospital, Norway, and included a study population of 147 pregnant nulliparous women. An oral glucose tolerance test (OGTT) was performed and used as the gold standard for GDM diagnosis. Blood samples for analysis of GA and HbA1c were collected at pregnancy week 24–28. A nonparametric approach was chosen for RI calculation, and receiver operating characteristic (ROC) curves were used to evaluate the diagnostic performance of GA and HbA1c. The established RI for GA in 121 pregnant women was 7.1–11.6%. The area under the ROC curves (AUCs) were 0.531 (GA) and 0.627 (HbA1c). According to the WHO-1999, WHO-2013 and the Norwegian guideline, respectively, 24 (16%), 36 (24%) and 21 (14%) women were diagnosed with GDM. Only nine women (6%) fulfilled the GDM-criteria of all guidelines. In conclusion, we established the first LC-MS/MS-based RI for GA in pregnant women. At pregnancy weeks 24–28, neither GA nor HbA1c discriminated between those with and without GDM. Different women were diagnosed with GDM using the three guidelines.

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Introduction

Hyperglycemia is among the most common medical complications in pregnancy and is classified as either diabetes in pregnancy (DIP) or gestational diabetes mellitus (GDM) [1]. In Europe, GDM prevalence is around 5–10%, depending on screening strategy, diagnostic criteria and study population [2]. GDM is associated with adverse maternal-fetal outcomes in the short and long term [3].

Since 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) have advocated universal GDM screening of all pregnant women [4]. There is, however, no international consensus on the diagnosis [5]. In 2017, a Norwegian GDM guideline was published [6], recommending almost universal screening with an oral glucose tolerance test (OGTT) during pregnancy weeks 24–28. New criteria for GDM diagnosis were established, with fasting plasma glucose (FPG) 5.3–6.9 mmol/l and/or 2 h plasma glucose (2hPG) 9.0–11.0 mmol/l. Until 2017, selective screening of high-risk women and the GDM diagnostic criteria according to the WHO-1999 guideline was used in Norway [7].

Despite low reproducibility and high coefficients of variation (CV) [8,9], the OGTT remains the gold standard test for diagnosing GDM. However, the IADPSG predicts that simpler and more cost-effective strategies as FPG or markers of short-term glycemia will replace the OGTT in the future [4]. Glycated hemoglobin A1c (HbA1c) reflects mean glycemia over the preceding 8–12 weeks [10] and has been the principal diagnostic test for diabetes mellitus for the last decade [11]. Other factors than glycemia, e.g. altered erythrocyte turnover [12], may influence HbA1c level. In addition, there are clinical settings, among them pregnancy, where HbA1c has limitations [13]. In a recent meta-analysis

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exploring the accuracy of HbA1c in diagnosing GDM, the authors concluded that HbA1c has high specificity, but low sensitivity [14].

Glycated albumin (GA), a biomarker of glycemia reflecting short-term (2–4 weeks) glycemic control, has been suggested as a supplement to HbA1c [15]. In diabetic pregnancies, where strict glycemic control is important to reduce the risk of adverse maternal/fetal outcomes, a marker reflecting recent glycemic status is preferable. Elevated GA level is seen in pregnancies complicated by GDM and has been associated with adverse outcomes [16,17]. However, the role of GA in monitoring glycemic control in diabetic pregnancies and as a diagnostic test of GDM, is still controversial. The reference interval (RI) for GA in healthy pregnant women is not well defined. A few studies have reported the RI for GA (using enzymatic methodology) in Asian pregnant women [18,19]. To our knowledge, only one study has established a RI for GA in a healthy Caucasian pregnant population [20]. Recently, a new high-throughput method for GA measurement utilizing liquid chromatography-tandem mass spectrometry (LC-MS/MS) was developed in our laboratory [21]. Prior to assess the potential clinical role of GA as a biomarker of glycemia in pregnancy, establishment of a RI in a pregnant population is mandatory.

The aim of this study was to establish the RI for GA, analyzed by LC-MS/MS, in healthy, nulliparous pregnant women at pregnancy weeks 24–28. In addition, we evaluated the diagnostic accuracy of GA and HbA1c in the diagnosis of GDM, using the OGTT as the gold standard. Finally, we explored the prevalence of GDM among healthy nulliparas using the diagnostic criteria from three different GDM-guidelines: WHO-1999, WHO-2013 and the newer Norwegian guideline (Norway-2017).

Materials and methods

Study setting

This cross-sectional study was conducted at Stavanger University Hospital, Norway, in 2017–2018. Women were asked to participate in the study when they met for routine second-trimester ultrasound examination around pregnancy week 18. Inclusion criteria were nulliparous women $>$ 25 years with singleton pregnancies, not previously diagnosed with diabetes. According to the Norway-2017 guideline, these women are recommended to have an OGTT at pregnancy weeks 24–28. A one-step 75 g OGTT was performed at the Clinical Trial Ward in the morning after an overnight fast [6]. In addition to GA and HbA1c, thyroid and iron status were assessed, as abnormal thyroid function is known to influence GA [15] and iron deficiency may increase HbA1c [12].

All participating women answered a questionnaire in which age, ethnicity, pre-pregnancy weight, height, weight gain in pregnancy to date, family history of diabetes, smoking and tobacco use, chronic illnesses, medication and supplement use were recorded. Weight and height were used to calculate BMI (kg/m^2). Information concerning pregnancy outcome, such as weight gain in pregnancy, preeclampsia, hypertension, induction of labor, operative vaginal delivery, cesarean section, birth weight and Apgar score, and admission to the neonatal intensive care unit were collected from medical records after delivery. Frequencies of small for gestational age and large for gestational age babies were calculated using the 10th and 90th percentile according to Gjessing et al. [22].

The women diagnosed with GDM according to the Norway-2017 guideline were informed about the diagnosis and advised to contact their general practitioner for follow-up. Within two weeks of the OGTT, all women with GDM attended a workshop with an endocrinologist, clinical nutritionist and diabetes nurse at Stavanger University Hospital. The target for glycemic control throughout the remainder of pregnancy was FPG $<$ 5.3 mmol/L and 2 h postprandial glucose $<$ 6.7 mmol/L. In cases were glycemic control was not achieved by diet or lifestyle changes, anti-diabetic medication was initiated by an endocrinologist. All women with ferritin level $<$ 15 ug/L were recommended iron substitution. Women with GDM were offered a follow-up consultation at the hospital, including ultrasound examination and repeat blood tests at gestational weeks 36–38. Their blood glucose measurements from time of diagnosis until follow-up were retrieved from Diasend (Glooko Inc., Mountain View, CA).

The prevalence of GDM in our study population was assessed using the three different diagnostic guidelines; WHO-1999 (FPG $\geq$ 7.0 mmol/L or 2hPG $\geq$ 7.8 mmol/L), WHO-2013 (FPG 5.1–6.9 mmol/L, 1 h plasma glucose (1hPG) $\geq$ 10.0 mmol/L and/or 2hPG 8.5–11.0 mmol/L) and finally, the Norway-2017 guideline.

LC-MS/MS analysis

Blood samples for GA were collected in serum gel tubes, stored at room temperature for 30 min, centrifuged at 2500 *g* to obtain serum, and stored at −75 °C until used. A recently developed LC-MS/MS method was used for GA measurement [21]. GA is measured by the relative degree of glycation of the N-terminus lysine (K) of KQTALVELVK, a proteotypic peptide of human serum albumin obtained by enzymatic digestion with trypsin. The glycation of lysine (525 K) is the most frequently reported glycation site on human serum albumin [23]. The percentage of GA is estimated by neat peak area response of glycated peptide divided by the sum of glycated and non-glycated peptide using full scan nano-LC-MS.

Since 2016, this method has been implemented in routine use for complementing the HbA1c assay and assisting in diabetes detection and monitoring. The method is applied as previously published, but with a few modifications. Robot pipetting is now with an EVO Freedom 150 liquid handling robot (Tecan, Männedorf, Switzerland) and basically 2 µL serum is mixed with 450 µL TRIS-formate buffer (50 mM, pH 7.6) followed by mixing and discarding 400 µL. To this diluted sample the following was added: 10 µL of trypsin (0.05–0.06 µg/µL with 25–30 mM Ca) mg/mL) and 190 µL

Table 1. Characteristics of the reference population ($n = 121$).

Variable	Mean (SD) or %
Age (years)	30.6 (3.7)
European ethnicity	91.7
Non-European ethnicity	8.3
First-degree relative with diabetes mellitus	20.7
Smoking	0.8
Pre-pregnancy BMI (kg/m^2)	23.7 (4.6)
Creatinine (umol/L)	49.5 (7.4)
eGFR (mL/min/1.73 m^2)	125.7 (8.0)
TSH (mIU/L)	1.7 (0.9)
fT4 (pmol/L)	10.9 (1.0)
HbA1c (mmol/mol)	30.5 (2.7)
CRP (mg/L)	5.4 (5.2)
Glycated albumin (%)	
Total reference population ($n = 121$)	9.5 (1.1)
Pre-pregnancy BMI < 20 ($n = 21$)	9.7 (1.2)
Pre-pregnancy BMI 20–24 ($n = 68$)	9.7 (1.0)
Pre-pregnancy BMI 25–29 ($n = 22$)	9.3 (1.1)
Pre-pregnancy BMI ≥ 30 ($n = 10$)	8.1[a] (0.7)

[a]$p < .05$ comparing the mean glycated albumin level with the mean glycated albumin level in the other BMI-categories.
SD: Standard deviation; BMI: body mass index; eGFR: estimated glomerular filtration rate using CKD-EPI Creatinine Equation; TSH: thyroid-stimulating hormone; fT4: free thyroxine; HbA1c: glycated hemoglobin A1c; CRP: c-reactive protein.

acetonitrile. The plate was capped and incubated for one hour at 37 °C, followed by 11 min centrifugation, 4000 *g* at 4 °C, and direct analysis by LC-MS/MS.

Method calibration was performed by using a commercial quality control sample (Seronorm Liquid Level 1, Sero, Norway) with an in-house assigned level of 13.5% GA. A different in-house quality control sample (HK) with a mean level of 8.91% GA was applied to monitor long-term precision, resulting in a CV of 4.0% (12 months, $n = 57$). The level specific CV for a batch analysis was 2.0% (mean GA level 12.1%). The normal reference range was established by analysis of Nobida biobank serum samples and was found to be 7.8–12.4% GA, which most likely is specific for the laboratory of Stavanger University Hospital. Instrumental method files for the robot pipetting and instrumental analysis, as well as an example of processed results are provided in Supplementary material.

HbA1c was analyzed using BioRad Variant II Turbo, high-performance LC, standardized by the International Federation of Clinical Chemistry (IFCC) reference method (analytical variation $\leq$ 3%), and Abbott Architect c16000 was used for analysis of glucose. All analyses were performed at Department for Medical Biochemistry, Stavanger University Hospital.

Statistical analysis

To calculate the RI by the nonparametric approach, as recommended by the Clinical and Laboratory Standards Institute (CLSI) [24], a sample size of 150 pregnant women was chosen to ensure at least 120 healthy individuals were included. The RI for GA was calculated using Analyse-it version 5.65 for Microsoft Excel (Analyse-it Software Ltd, Leeds, United Kingdom), based on the 2.5 and 97.5 percentiles and corresponding 90% CI in the reference population. The Dixon method was used for outlier detection [24].

For the diagnostic-accuracy analyses, sample size calculations were carried out with MedCalc for Windows version 17.6 (MedCalc Software, Ostend, Belgium). We estimated a prevalence of GDM of 10%, as found in previous Norwegian studies [25]. Previous receiver operating characteristics (ROCs) analyses in the general population have shown that the accuracy of GA is comparable to that of HbA1c with an expected area under the ROC curve (AUC) about 0.8 [26,27]. In women with GDM, an AUC of 0.757 for HbA1c is reported [28]. Based on these calculations, specifying a significance level of 5%, power of 80%, GDM prevalence of 10% and an AUC of 0.757, a sample size of at least 110 was needed. ROC analyses were performed to compare the diagnostic values of GA and HbA1c, considering the OGTT as the reference diagnostic test. The diagnostic-accuracy analyses are in accordance with the 2015 Standards for reporting of diagnostic checklist (STARD) [29].

The statistical analyses were performed using IBM SPSS Statistics for Windows version 26 (IBM Corp., Armonk, NY). Continuous variables are presented as mean with standard deviation (SD), while categorical data are presented with number and percentage. Of 95% confidence intervals (CIs) or SDs are given. Q–Q-plots were used to assess data distribution and Welch's t-interval was used in situations where SD in one group was > 1.5 times the SD in the other group. Student's t-test was used to examine differences between women with and without GDM and paired samples t-test was performed where appropriate. A two-tailed p value $< .05$ was considered statistically significant. Pearson's test was used for correlation analysis. One woman with pre-pregnancy BMI 47 and 10-kg weight loss in pregnancy prior to the OGTT was considered an outlier in the analyses of pre-pregnancy BMI and weight gain in pregnancy, and was removed from these analyses.

Results

In all, we included 147 women. One woman diagnosed with diabetes mellitus in pregnancy (FPG > 7.0 and 2hPG > 11.0) was excluded from all further analyses. To establish the RI for GA in pregnancy we followed the recommendation by the CLSI [24] and excluded women diagnosed with GDM ($n = 21$) and DM ($n = 1$) according to Norway-2017. Furthermore, we excluded four women using medication possibly interfering with their blood glucose level (e.g. prednisolone), resulting in a total reference population of 121 women. All these women had normal liver, kidney and thyroid function.

The characteristics of the reference population are shown in Table 1. In the reference population, the mean GA level was significantly lower among women with pre-pregnancy BMI ≥ 30 compared with GA level in women in the other BMI categories (BMI < 20, BMI 20–24 and BMI 25–29), $p < .05$ (Table 1) whereas the mean CRP level increased in the higher two BMI categories. The RI for GA was 7.1–11.6% (Table 2). There were no outliers detected.

Table 2. Glycated albumin reference interval in pregnant women.

	n	Mean	2.5 percentile (90% CI)	97.5 percentile (90% CI)	Range (minimum–maximum)
Total reference population	121	9.5	7.1 (6.9–7.7)	11.6 (11.4–12.5)	6.9–12.5

Glycated albumin, %; CI: confidence interval.

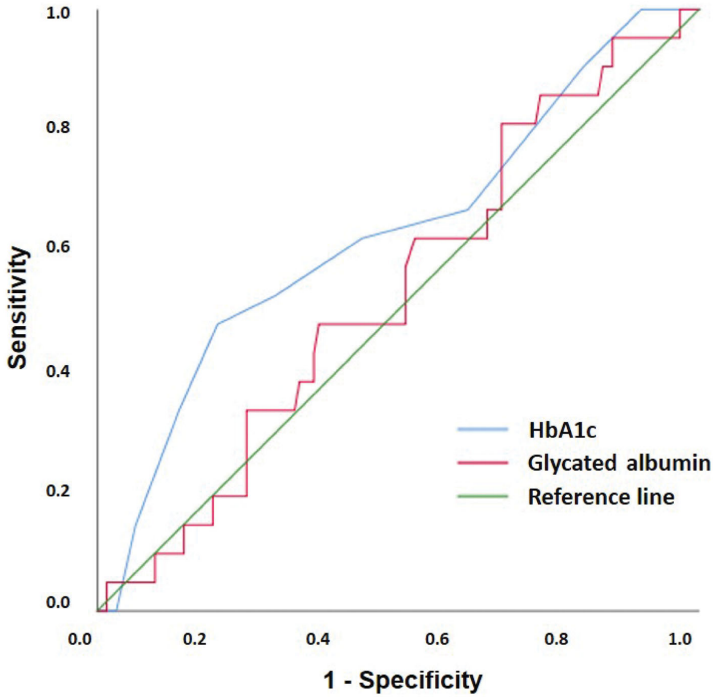

Figure 1. Receiver operating characteristics (ROC) curves to assess the suitability of GA and HbA1c in the diagnosis of GDM in pregnancy weeks 24–28 using the oral glucose tolerance test as the reference standard. The AUC value of GA was 0.531 (SE 0.065, 95% CI 0.405–0.658) and HbA1C was 0.627 (SE 0.069, 95% CI 0.492–0.762). GA: glycated albumin; HbA1c: glycated hemoglobin A1c; GDM: gestational diabetes mellitus; AUC: area under the ROC curve; SE: standard error; CI: confidence interval.

The performance of GA and HbA1c in the diagnosis of GDM, using the OGTT as the reference diagnostic test, is presented in Figure 1. ROC analysis showed AUC of GA was 0.531 ($p = .649$), whereas AUC of HbA1c was 0.627 ($p = .063$). The correlation coefficient between GA and HbA1c was $r = -0.073$ ($n = 146$).

The numbers of women diagnosed with GDM were 24 (16.4%, 95% CI 10.4–22.5), 36 (24.7%, 95% CI 17.7–31.6) and 21 (14.4%, 95% CI 8.6–20.2) according to WHO-1999, WHO-2013 and Norway-2017, respectively. Among the 21 women diagnosed with GDM according to Norway-2017, 15 (71.4%) had FPG $\geq$ 5.3 mmol/L as the only diagnostic criterion. In contrast, the 24 women diagnosed using WHO-1999 criteria had elevated 2hPG $\geq$ 7.8 mmol/L. The characteristics of women with and without GDM diagnosed by Norway-2017 are presented in Table 3, while characteristics of women with and without GDM according to WHO-1999, WHO-2013 and Norway-2017 are provided in Supplemental Table 1.

Figure 2 shows an Euler diagram illustrating the number of women diagnosed by each guideline. Only nine women (6.2%) fulfilled the GDM criteria in all three guidelines. In these nine women, hyperglycemia was more pronounced and all glucose values at the OGTT were higher compared with those for the rest of the study population ($n = 137$). Comparing these two groups, the mean FPG, 1hPG and 2hPG were 5.1 mmol/L (SD 0.4) *vs.* 4.8 mmol/L (SD 0.3), 9.8 mmol/L (SD 0.9) *vs.* 6.8 mmol/L (SD 1.6) and 9.0 mmol/L (SD 0.8) *vs.* 5.9 mmol/L (SD 1.3), respectively (all $p < .05$). There was no significant difference in mean GA level or HbA1c level between these two groups.

There was no significant difference in mean GA level or HbA1c level between women with and without GDM, diagnosed by Norway-2017 at the OGTT. 18 of 21 women with GDM met for follow-up consultation around pregnancy week 37, and in these, the mean GA level was significantly lower than at the time of diagnosis: 9.1% (SD 0.95) *vs.* 9.6% (SD 0.97), whereas mean HbA1c level was significantly higher: 33.4 mmol/mol (SD 2.6) *vs.* 31.9 mmol/mol (SD 3.5) (Figure 3(A,B)). In addition, the mean hemoglobin level increased from 11.6 g/dL (SD 0.7) to 12.4 g/dL (SD 0.8), whereas the mean ferritin level remained low and showed

Table 3. Characteristics of women with and without gestational diabetes mellitus (GDM).

	NoGDM ($n = 125$)	GDM ($n = 21$)	Difference (95% CI)
Clinical characteristics	Mean (SD)	Mean (SD)	Mean diff (95% CI)
Age at OGTT (years)	30.6 (3.8)	31.6 (4.1)	0.9 (−0.9, 2.7)
Pre-pregnancy body mass index (kg/m^2)	23.5 (4.0)[a]	24.7 (4.3)	1.2 (−0.7, 3.1)
Weight gain in pregnancy prior to OGTT (kg)	7.8 (3.0)[a]	8.8 (4.0)	1.0 (−0.5, 2.4)
	Count (%)	Count (%)	RR (95% CI)
Non-European ethnicity	10 (8.0)	4 (19.0)	2.4 (0.8, 6.9)
First-degree relative with diabetes mellitus	26 (20.8)	7 (33.3)	1.6 (0.8, 3.2)
OGTT (24–28 weeks)	Mean (SD)	Mean (SD)	Mean diff (95% CI)
Fasting plasma glucose (mmol/L)	4.7 (0.3)	5.3 (0.3)	0.6 (0.4, 0.7)
1 h plasma glucose (mmol/L)	6.6 (1.6)	8.9 (1.5)	2.3 (1.5, 3.0)
2 h plasma glucose (mmol/L)	5.8 (1.3)	7.6 (1.5)	1.8 (1.2, 2.4)
HbA1c (mmol/mol)	30.5 (2.7)	31.8 (2.7)	1.3 (0.0, 2.5)
Glycated albumin (%)	9.5 (1.1)	9.6 (1.0)	0.1 (−0.4, 0.6)
Pregnancy outcome	Count (%)	Count (%)	RR (95% CI)
Preeclampsia	4 (3.2)	0	–
Hypertension	5 (4.0)	3 (14.3)	3.6 (0.9–13.8)
Preterm delivery	7 (5.6)	0	–
Induction of labor	29 (23.2)	8 (38.1)	1.6 (0.9, 3.1)
Elective cesarean section	5 (4.0)	3 (14.3)	3.6 (0.9, 13.8)
Emergency cesarean section	13 (10.4)	3 (14.3)	1.4 (0.4, 4.4)
Small for gestational age	20 (16.0)	2 (9.5)	0.6 (0.2, 2.7)
Large for gestational age	8 (6.4)	2 (9.5)	1.5 (0.3, 6.5)
Neonatal intensive care unit	11 (8.8)	3 (14.3)	1.6 (0.5, 5.3)

Characteristics of women with and without gestational diabetes mellitus (GDM). Total study population $n = 146$ women. Data given as mean (SD) with mean differences (95% CI) for continuous variables and number (%) with relative risk (RR) (95% CI) for categorical data.

[a]One outlier is removed from the analysis.

SD: Standard deviation; CI: confidence interval; diff: difference; OGTT: oral glucose tolerance test; HbA1c: glycated hemoglobin A1c.

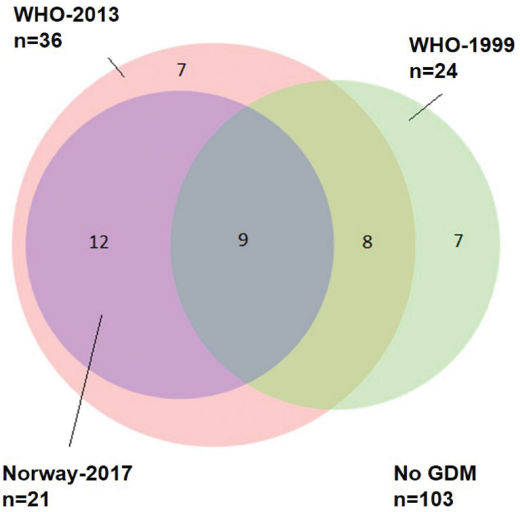

Figure 2. Euler diagram showing the relationship between GDM diagnoses according to the three different guidelines WHO-1999, green circle ($n = 24$), WHO-2013, pink circle ($n = 36$) and Norway-2017 and violet circle ($n = 21$). Numbers in the three circles indicate how many women were diagnosed with GDM according to each guideline, in both single and multiple guidelines. Total study population $n = 146$. GDM: gestational diabetes mellitus; WHO: World Health Organization.

no significant difference from initial measurement (Figure 3(C,D)) despite 12 of the women being recommended iron substitution at the OGTT. Neither did we observe any difference between mean reticulocyte count or mean reticulocyte hemoglobin level at pregnancy weeks 24–28 compared to pregnancy week 37 (data not shown).

Blood glucose data registered from women with GDM showed good glycemic control with mean PG 5.3 mmol/l (SD 0.4) from time of diagnosis until follow-up at pregnancy week 37 (Supplemental material). Only 3 of 21 women with GDM (14.3%) needed anti-diabetic medication during pregnancy.

Discussion

This study established the first LC-MS/MS-based RI for GA in a population of healthy women at pregnancy weeks 24–28. Before assessing the clinical potential of a biomarker, establishment of a RI in a healthy population similar to the population on which the biomarker is to be applied, is the first step. In pregnancy, GA could be a supplement in the diagnostics of GDM and in monitoring of glycemic control. According to CLSI, the best means to establish a RI is to collect a minimum of 120 samples from qualified reference individuals [24]. Thus, the sample size was estimated for this main purpose and not to assess differences between women with and without GDM. The reference population should be as similar as possible to the population to which the test will be applied, with the exception of the presence of disease [30]. Thus, we included women with various pre-pregnancy BMIs and different ethnicities, although this was not done in other RI studies for GA in pregnancy [18,19]. According to the Medical Birth Registry of Norway, one out of three pregnant women has pre-pregnancy BMI > 25 [31]. Therefore, excluding this group from the reference population would not reflect the 'normal' pregnant population. We established the RI of GA in pregnancy weeks 24–28, as this is the recommended screening period for GDM.

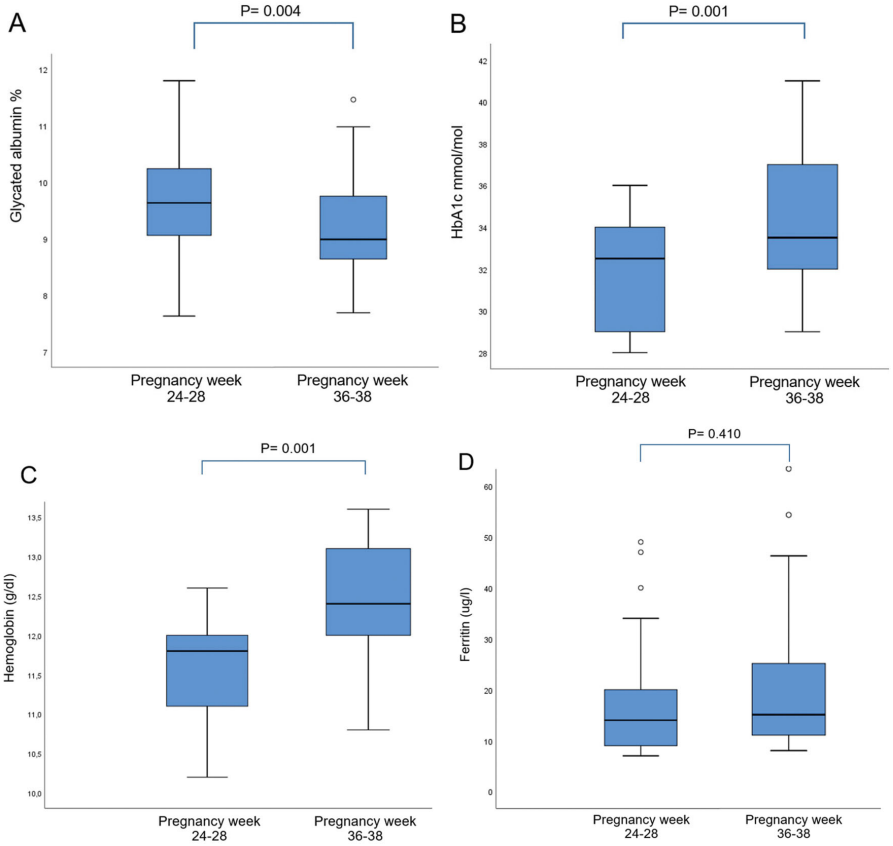

Figure 3. Box plot of glycated albumin level (A), HbA1c level (B), hemoglobin level (C) and ferritin level (D) in women with gestational diabetes mellitus at pregnancy weeks 24–28 and 36–38 ($n = 18$). HbA1c: glycated hemoglobin A1c.

In this study, the RI for GA in pregnant women analyzed by LC-MS/MS was 7.1–11.6%, which is somewhat lower than the RI reported from our laboratory in non-pregnant women (7.8–12.4%). Hiramatsu et al. showed that the RI for GA in healthy Japanese pregnant women was 11.5–15.7% [18], whereas in Chinese pregnant women, a GA RI of 9.2–14.6% is established [17]. Both these studies used an enzymatic method for GA analysis [32], and women with pre-pregnancy BMI > 25 were excluded in the Japanese study. Other studies have shown that GA level is lower in higher BMI categories [33]; the reasons remain unexplained, but might be due to increased albumin turnover related to inflammation [34]. In accordance with this, a lower GA level was also seen in the obese group in our study population (Table 1).

With a reported AUC of only 0.531, our study does not support the use of GA as a diagnostic tool for GDM, which is also in agreement with previous studies finding AUCs for GA comparable with ours, and in the range 0.531–0.568 [35–37].

There was no correlation between GA and HbA1c ($r = 0.073$) in our data set, although a strong positive correlation was found outside pregnancy ($r = 0.84$) [21]. The difference may be explained by a more homogeneous dataset and less spread in the pregnant population, as correlations are relative [38]. Another explanation may be the differences between GA and HbA1c, detecting short-term and long-term glycemia, respectively.

In our study population, the prevalence of GDM varied from 14.4% (Norway-2017) to 24.7% (WHO-2013), and only 6.2% fulfilled the GDM criteria in all three guidelines. When comparing WHO-1999 and Norway-2017, which represent the previous and present diagnostic criteria used in Norway, a corresponding prevalence was observed (16 *vs.* 14%). However, only nine women were diagnosed with GDM using both guidelines (Figure 2). In a recent Dutch study, applying the WHO-2013 criteria in a high-risk population increased the number of GDM diagnoses from 22 to 32% (as compared to WHO-1999) [39]. Moreover, they observed that women diagnosed on the WHO-2013 FPG-

threshold of 5.1 mmol/L had increased risk of adverse outcomes, supporting the use of this criterion.

The WHO-2013 criteria are based on an estimated increased risk of adverse outcomes, using an odds ratio (OR) of 1.75, based on the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [40]. The diagnostic criteria in Norway-2017 use a cut-off of OR 2.0. In our study population, an almost doubled prevalence of GDM was observed with the use of WHO-2013 criteria compared with the use of the Norway-2017 criteria. Unfortunately, our sample size is too small to compare the risk of adverse outcomes using the different guidelines. To avoid the high WHO-2013-calculated prevalence of GDM, some have supported the use of OR 2.0 [41], which is also in agreement with the evidence from the Maternal-Fetal Medicine Units Network randomized trial of treatment of mild GDM [42].

In Switzerland, GDM screening includes a simplification of the IADPSG consensus, and glucose loading in OGTT is only performed in women with FPG in the range 4.4–5.0 mmol/L. Women with FPG $\geq$ 5.1 mmol/L are diagnosed with GDM ('rule-in'), whereas those with FPG $<$ 4.4 mmol/L are 'ruled-out'. The diagnostic performance of this strategy was evaluated in a Swiss population with a GDM prevalence of 10.9% [43]. The authors reported a sensitivity of 78.5%, and that 63.8% would have avoided the OGTT. This finding is in contrast to Agarwal et al. who reported a high sensitivity (95.4%) in Arab women using the same simplification [44]. The conflicting results have several explanations, one being the prevalence of GDM (10.9 *vs.* 37.7%), another the distribution of abnormal values on the OGTT. In our study, only 11 women (7.5%) had FPG $<$ 4.4 mmol/L. Using the 'rule-out/in' strategy with cut-off values of FPG $<$ 4.4 and $\geq$ 5.3 mmol/L respectively, 26 women (18%) would have avoided the OGTT and none of the women with GDM according to Norway-2017 would have been missed.

As in two Chinese studies [19,36], we did not find any difference in mean GA when comparing women with and without GDM at pregnancy weeks 24–28. At follow-up around pregnancy week 37, the mean GA level was significantly reduced from the time of diagnosis (Figure 3(A)), in contrast to Zhu et al., who found a higher GA level in the third trimester [36]. Exploring the role of GA in monitoring glycemic control was not among the aims of our study; however, a lower GA level at follow-up may reflect the good glycemic control achieved by these women as shown in their daily glucose monitoring (mean glucose 5.3 mmol/L). Conversely, the HbA1c level increased in the same period, and one might speculate whether this was because of iron deficiency. The mean ferritin level was low both at the OGTT and at follow-up, however, the mean hemoglobin level increased slightly.

Others have shown that GA level is stable or decreases throughout gestation in healthy pregnant women [18,19,36]. Unfortunately, our study design did not allow for comparison of GA level among women with and without GDM in late third trimester.

Limitations to our study include that the study design did not allow establishing trimester-specific RIs for GA. Moreover, this was a single-center study with a limited sample size including only women $>$ 25 years of age with singleton pregnancies. Multiparous women and women with multiple gestations were not included. The majority of the women were of Scandinavian heritage, with only 9.5% having a non-European background, thus our findings may not apply to all ethnicities. In addition, our sample size is too small to conclude on pregnancy outcome.

Strengths of this study include the well-characterized pregnant reference population, the implementation of the OGTT on a Clinical Trial Ward, and the analysis of GA by LC-MS/MS. This high-throughput method has shown good reproducibility (analytical variation $\leq$ 4% and a strong correlation between GA and HbA1c ($r = 0.84$)) [21]. Although the study was carried out at Stavanger University Hospital, the women included were unselected, living in both rural and urban parts of our region with various socio-economic status, representative of the pregnant population. Only three women with GDM were lost to follow-up for repeat blood tests.

In conclusion, the established LC-MS/MS-based RI for GA in pregnant women was 7.1–11.6%. At pregnancy week 24–28, neither GA nor HbA1c discriminated between those with and without GDM, thus this study does not support the use of these biomarkers in GDM diagnosis. Finally, the prevalence of GDM among healthy nulliparas in our study population differs from 14.4 to 24.7% according to the various diagnostic guidelines and only 6.2% of the women fulfilled the GDM criteria in all three guidelines. It is time to reach international consensus for the diagnostic criteria of GDM.

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Ethical approval

The study was carried out in accordance with the Helsinki Declaration and was approved by the Regional Committee for Medical and Health Research Ethics (REC) South-Eastern Norway (May 2017, REK 2017/771). The study was registered in Clinical Trials with identifier NCT03372824. Informed consent was obtained from all women included in this study.

Author contributions

All authors were responsible for study design and interpretation of data. ØS was responsible for analysis of GA and establishment of the RI. JHT has carried out the study, followed-up the study participants and did the data analysis. JHT and IØ drafted the manuscript, and all authors contributed to the revision of the manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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III

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RESEARCH

Gestational diabetes mellitus follow-up in Norwegian primary health care: a qualitative study

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Abstract

Background: Women with gestational diabetes mellitus (GDM) have a tenfold increased risk of developing diabetes, and a high risk of recurrent GDM. Endorsing the life-course approach, aiming to prevent disease and promote health across generations, the Norwegian GDM guideline recommends follow-up in primary care after delivery, with information on the increased risks, lifestyle counselling, and annual diabetes screening. Few reports exist on Norwegian women's experiences of GDM follow-up.

Aim: To elucidate women's experiences with follow-up of GDM in pregnancy and after delivery, and to explore their attitudes to diabetes risk and motivation for lifestyle changes.

Design & setting: Qualitative study in primary care in the region of Stavanger, Norway.

Method: Semi-structured in-depth interviews were conducted 24–30 months after delivery with 14 women aged 28–44 years, with a history of GDM. Data were analysed thematically.

Results: Most women were satisfied with the follow-up during pregnancy; however, only two women were followed-up according to the guideline after delivery. In most encounters with GPs after delivery, GDM was not mentioned. To continue the healthy lifestyle adopted in pregnancy, awareness of future risk was a motivational factor, and the women asked for tailored information on individual risk and improved support. The main themes emerging from the analysis were as follows: stigma and shame; uncertainty; gaining control and finding balance; and a need for support to sustain change.

Conclusion: Women experienced a lack of support for GDM in Norwegian primary care after delivery. To maintain a healthy lifestyle, women suggested being given tailored information and improved support.

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How this fits in

Despite being at high risk, most women with GDM experience insufficient follow-up after delivery. In Norway, continuity of care is ensured by the GPs being responsible for follow-up before, during, and after pregnancy, as implemented in a new national guideline. However, in the present study, most women experienced a lack of follow-up until 30 months after delivery. Stigma and shame and uncertainty were among the feelings associated with GDM. The participants asked for improved support to sustain change and maintain the healthy lifestyle adopted in pregnancy.

Introduction

Hyperglycaemia, affecting one in six live births worldwide, is a common medical complication in pregnancy and should be classified as either diabetes mellitus in pregnancy (DIP) or GDM.[1] In Norway,

the prevalence of GDM is now around 6%, after a threefold increase over the past decade.[2] Among women of non-Scandinavian ethnicity, the prevalence of GDM is higher than in Norwegian women, and the risk of GDM increases with years of residence.[3]

GDM is associated with adverse maternal and fetal outcomes in the short and long term.[4] Women with prior GDM have a tenfold increased risk of being diagnosed with type two diabetes mellitus (T2DM) later on,[5] and within 15 years postpartum, one-third of women with GDM have been diagnosed with T2DM.[6] Moreover, the recurrence rate of GDM is high. For example, in a recent Scandinavian study, the overall recurrence risk of GDM in the second pregnancy was 39%.[7] As lifestyle intervention reduces the risk of both recurrent GDM and future T2DM, the interconception period is considered as a window of opportunity to improve current and future health of mothers and children.[8]

International guidelines seem to agree on recommending long-term follow-up of women with prior GDM, although the specific tests and schedules vary between countries.[9] In 2017, a Norwegian GDM guideline was implemented,[10] implying that follow-up of women with GDM should be done by GPs in primary care, whereas women with poor glycaemic control should be referred to specialist health care. The guideline recommends measurement of HbA1c at 4 months after birth, then annually. Moreover, the GPs should give tailored information about future diabetes risk and offer lifestyle counselling. Most Norwegian citizens are registered with an individual GP, and maternity care is free of charge.

In Norway, introduction of the guideline led to a long-lasting debate about cost-benefit, medicalisation, and in particular, the lack of evidence supporting widespread GDM screening.[11]

Despite diverse guidelines and evidence supporting the effectiveness of early detection of T2DM, long-term follow-up of women with a history of GDM appears challenging worldwide.[12,13] In England, annual rates of long-term follow-up stayed consistently around 20%,[14] whereas in the US, rates up to 54% have been reported.[15] In Australia a national GDM register sends reminders to both mothers and GPs, and the screening rates at 6-week postpartum ranged from 43%–58%, and the annual screening rates were even lower.[16] In a recent Danish study, women experienced limited initiative from their healthcare providers in supporting them to engage in a healthy lifestyle postpartum.[17]

The life-course approach, which aims to prevent non-communicable diseases (NCDs) such as diabetes and promote health across generations, emphasises pregnancy as an important transition period where there might be unique opportunities to make a positive shift in the trajectory of a generation.[18,19] Recently, the urgent need to focus on maternal health to prevent NCDs was outlined in a global statement by the International Federation of Gynacology and Obstetrics (FIGO). The importance of preconception counselling, and antenatal and postpartum care was underlined.[20]

To the authors' knowledge, no studies have explored how Norwegian women experience the short- and long-term follow-up of GDM following implementation of the Norwegian guideline. Hence, the aims of this study were to elucidate women's experiences of GDM follow-up, both in pregnancy and until 30 months after childbirth, and to explore thoughts of future diabetes risk and motivation for lifestyle changes.

Method

Study setting

In 2017–2018, 147 nulliparous women aged >25 years with singleton pregnancies participated in a cross-sectional study at Stavanger University Hospital, Norway.[21] The women had a 75 g oral glucose tolerance test (OGTT) in pregnancy at week 24–28, diagnosing 21 (14%) with GDM. They were informed about the diagnosis, and advised to contact their GP for further follow-up. All women diagnosed with GDM attended a 3-hour workshop, and were offered an ultrasound examination in pregnancy at week 36. According to the Norwegian guideline, women were followed-up in primary care and were referred to secondary health care if glycaemic control was not achieved.

Sampling and recruitment

The qualitative study included all the Norwegian-speaking women, resulting in an eligible study population of 18 women with a history of GDM. To achieve a maximum variety sampling, all 18 women were invited. Information letters describing the aims and method of the study, as well as an informed consent form, were sent in September and October 2020. Women who did not reply within a couple

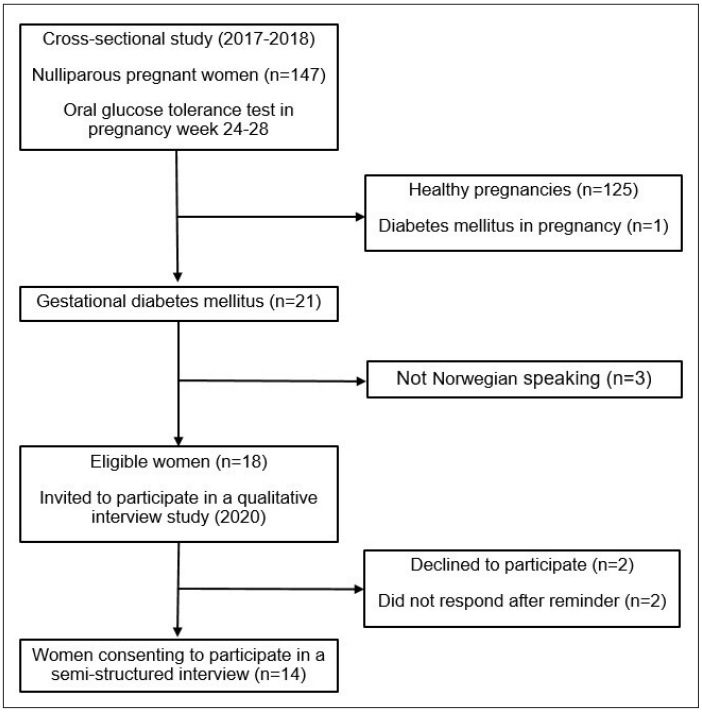

Figure 1 Flowchart of the study population

of weeks got a reminder on short message service (SMS). The 14 women consenting to participate signed the informed consent and an appointment for interview was made within 2 weeks. Participants could choose between telephone and face-to-face interviews, and they could choose time and place. Probably owing to the COVID-19 pandemic, they all preferred telephone interviews. A flowchart of the study population is presented in ***Figure 1***.

The current qualitative study was conducted in 2020 and included 14 of the 21 women diagnosed with GDM in the cross-sectional study.[21]

Data collection

Data were collected using a semi-structured interview guide to explore women's experiences of the GDM follow-up in pregnancy and after delivery. The interview guide (see Supplementary Appendix S1) consisted of open-ended questions about follow-up, understanding of, and attitude to future diabetes risk, and motivation for lifestyle changes. All interviews were conducted digitally, audio-recorded, and transcribed verbatim by the first author in October 2020, resulting in 99 pages (50 059 words). Each transcript was anonymised and compared with the complete original audio-recording to ensure reliability. The interviews lasted between 19 and 41 minutes, with an average of 30 minutes. All participants received a 50 EUR gift card to acknowledge the authors' gratitude.

Data analysis

A thematic analysis inspired by Braun and Clarke was conducted on the entire dataset.[22] An inductive approach was used, where two authors individually read all transcripts several times to gain deeper insight of the material.[23] Meaningful text relevant to the research questions were highlighted and discussed. Transcripts were then coded line by line by the first author. Accordingly, 205 codes were consecutively sorted into the following four categories, which were in the interview topic guide: experience of being diagnosed with GDM; follow-up; motivation; and future diabetes risk. Next,

Table 1 Example from the data analysis of transforming transcripts to codes and themes

Transcript	Code	Theme
After the initial shock, my stress level decreased. I had to do what was possible, no panic of missing one measurement. Suddenly, gestational diabetes was very serious. Had my GP and I been too laid-back?	Shock getting GDM, stress level decreased gradually. Adequate self-management and follow-up?	Gaining control and finding balance Uncertainty
I was frightened, how could gestational diabetes affect my baby's health?	Frightened, worried about the baby	Uncertainty

GDM = gestational diabetes mellitus.

the codes were collated into broader overarching themes representing repeated patterns across the dataset. Through thorough team discussions a common understanding of the themes was developed. Then a revision and refining of the themes, checking their relation to the coded extracts, was performed by the first author. Finally, after agreement among all authors, an overall interpretation was developed.

Data saturation was achieved during the last two interviews, indicating that no new knowledge relevant to the research questions was obtained. Examples of the analysis from transcript to themes are provided in ***Table 1***. This study is reported in accordance with the Standards for Reporting Qualitative Research (SRQR),[24] a standard highlighted by the EQUATOR Network (https://www.equator-network.org).

Results

Demographics

The majority of the 14 women included in the study had a Scandinavian background and almost half had a family history of diabetes. Five women had given birth again, one of these had been diagnosed with recurrent GDM, whereas three women were pregnant. None of the participants had been diagnosed with T2DM. Characteristics of the study population are presented in ***Table 2***.

Table 2 Characteristics of the study population (n = 14)

Characteristic	Mean (range)	*n* (%)
Age, years	33.7 (28–44)	
Ethnic background		
Scandinavian		11 (79)
Mediterranean or Middle Eastern		3 (21)
Educational level		
Master's degree		7 (50)
Bachelor's degree		4 (29)
Student		3 (21)
First-degree relative with diabetes mellitus		6 (43)
Pre-pregnancy BMI (kg/m^2)[a]	25.4 (20–36)	
Weight gain in pregnancy until OGTT (kg)[a]	10.0 (3–18)	
Insulin use in pregnancy[a]		2 (14)
Interview time-point[b]	27.4 (24–30)	

[a]In first pregnancy. [b]Months after birth. BMI = body mass index. OGTT = oral glucose tolerance test.

Main themes

Following the thematic analysis, four main themes emerged: stigma and shame; uncertainty; gaining control and finding balance; and a need for support to sustain change. The themes are discussed in more detail below.

Stigma and shame

The majority reported that the GDM diagnosis was surprising, as they did not consider themselves to be at risk. Many described initial feelings of shock, embarrassment, and shame. Some women with obesity and/or family history of diabetes stated that getting GDM was somewhat expected, although it felt tough. Most of the participants associated the diagnosis with unhealthy dietary habits, leading to self-blame for putting the fetus at risk:

> *'I felt it was hard, what to say, am I that unhealthy? I did not think so. I actually felt ashamed. Are my eating habits so bad? I felt as a bad mother.'* (Participant [P]9)

Several of the participants described situations where they got hurtful comments from others regarding what they ate. The diabetic management made the diagnosis visible to others, and women measured blood glucose in discrete to avoid questions. One of the participants on insulin therapy stated that the feeling of shame increased when she *'could not control'* (P3) her blood glucose without insulin, and the multiple injections throughout the day made the diagnosis even more visible to colleagues.

The majority reported a lack of knowledge about GDM. Together with concern for the fetus, this led to anxiety and a call for updated knowledge. Several participants reported difficulties finding reliable information and appreciated the counselling they got from health profesionals. Some of them stated that getting GDM would have been less stigmatic if they had been told about various risk factors for developing GDM, such as family history. Among the participants with a non-Scandinavian background, a common finding was that the feeling of stigma associated with GDM predominantly was related to their ethnic group, resulting in less self-blame at the individual level. Additionally, for some of these women of non-Scandinavian ethnicity, this impaired their motivation for lifestyle changes after birth, as they thought they would develop T2DM anyhow. In contrast, the Scandinavian women associated the diagnosis with unhealthy lifestyle, causing more self-blame at the personal level.

> *'I know I will get diabetes in the future anyway. All in my family do.'* (P3)

Despite the emotional distress following the diagnosis, concerns for the fetus and wishing to avoid a macrosomic baby seemed to be main motivational factors for lifestyle changes during pregnancy. Other motives were a desire to avoid insulin therapy or induction of labour, or being allowed to stay at the hospital's low-risk unit.

> *'A combination of pressure and fear gave me my motivation. I did it for my own health, but of course, also for my baby's health.'* (P5)

Uncertainty

The initial response to the diagnosis was anxiety, partly owing to lack of knowledge and unpredictable implications for the pregnancy. Others became more conscious throughout the pregnancy and after delivery as they learnt more about the increased risks. However, uncertainty affected women's reactions to the diagnosis, expectations of follow-up, and influenced their thoughts of maternal and fetal risk:

> *'During pregnancy I had control because I measured my blood sugar, I knew everything about what to eat and how different food would affect my values. But after pregnancy, I have no idea, how much will it take to develop diabetes in the future?'* (P6)

Whether they actually had GDM was another aspect of uncertainty raised by several participants, as their self-glucose monitorings were within target range, or because of threshold glucose value on the OGTT. Others had become aware of the discussion in the media about the guideline, as well the lack of consensus in GDM-diagnostic criteria among countries. For women experiencing a lack of informational and emotional support, the sense of uncertainty became more manifest.

Overall, women's glycaemic control was very good, with most values within target range. Nevertheless, induction of labour was decided for one woman because of macrosomia, whereas others were frequently checked owing to fetal growth restriction, cementing their understanding of strict glycaemic control as the most important factor to avoid complications. One woman could not understand why she needed insulin *'to avoid a macrosomic baby'* (P3) as her child was small for gestational age:

> *'At least, I did not get any explanation why these insulin injections would do anything good for my baby being too small. How insulin would help her, I never got an answer. It was very frustrating taking these injections.'* (P3)

Most women presumed they would be diagnosed with GDM in their next pregnancy. A few stated that not getting the diagnosis again felt illogical as they now had a less healthy diet and were more inactive. Moreover, they had not regained pre-pregnancy weight before the second pregnancy.

Gaining control and finding balance

Gaining control was a dominant and ongoing theme, involving dietary planning, meals, blood glucose measurements, and clinical follow-ups including ultrasound examinations. Most women reported that self-management, such as incorporating blood glucose measurements in daily life, planning diet, and activity, were most challenging, although achieving glycaemic control also gave mastery and stress relief. However, for several women the burdens of treatment were overwhelming, and two participants described the feeling of having an eating disorder. Others felt obsessed with having a well-controlled diet, with the *'numbers'* (several participants) and their blood glucose management dominating their thoughts:

> *'I got very upset with the blood sugar measurements. Exercise, eat, and measure. I was obsessed, the measurements should all be good. I talked to my GP about it, and I understood that it could be a big problem for those being too obsessed with this.'* (P12)

Some weeks after the GDM diagnosis, many participants realised that finding the right balance in measurements and diet became the most important goal. Others emphasised the emotional support from health professionals to be reassuring.

> *'I suddenly realised my life was all about nutrition and table of contents. I got very cautious and strict. I had to remind myself of common sense.'* (P14)

A need for support to sustain change

Overall, most women contrasted their lack of follow-up after birth with the health care they received for GDM during pregnancy. Most of them stated that the GP did not address the topic of GDM in the encounters after pregnancy. The sense of lack of interest felt like an abandonment, as several requested a need to discuss tailored information regarding their personal risk. Only two women experienced that their GP encouraged them to maintain a healthy lifestyle after pregnancy and had received information about diabetes risk and/or the importance of controlling weight.

> *'It has been no talk about GDM. I think when the diagnosis caused all that stress during pregnancy, I was surprised that it has not been mentioned nor followed-up after delivery. I could of course have done more myself, but you know, everyday life continues.'* (P14)

Although to a varying degree, most women were aware of the increased diabetes risk and reported that this continuously influenced their lifestyle choices. The majority were concerned about the risk, and thought of this as a motivator to regain pre-pregnancy weight, and maintain a healthy lifestyle for themselves and their family. However, more than half of the participants had gained weight.

> *'When I got the diagnosis, I read about the increased diabetes risk, but I am not that worried because I think my food habits are OK and I do exercise; however, by all means, I do think about it and I am aware.'* (P17)

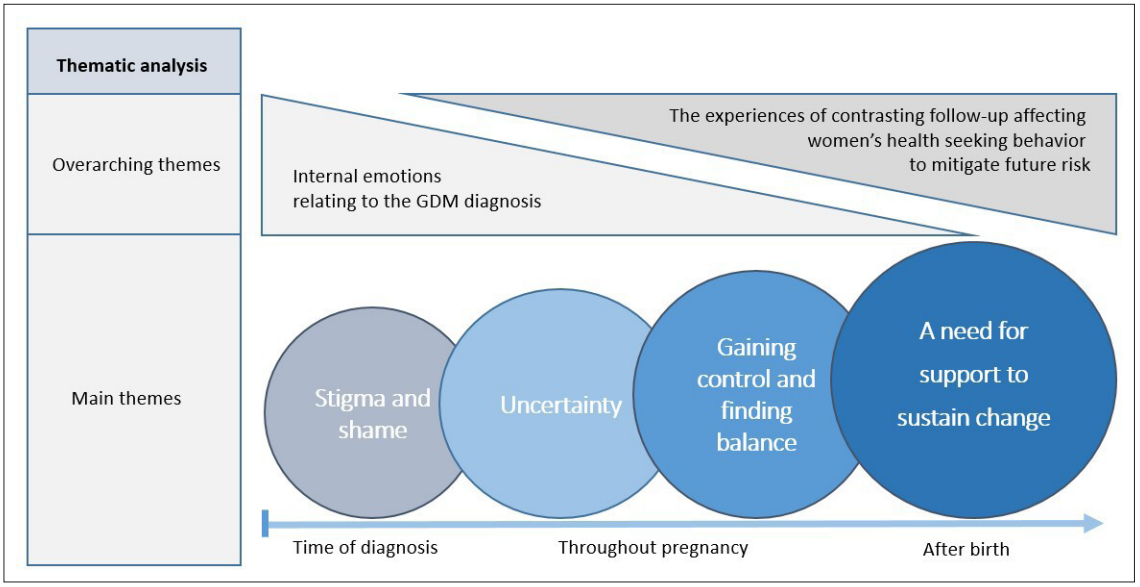

Figure 2 Relationship between overarching themes and main themes along the time course. GDM = gestational diabetes mellitus

Several participants continued to measure blood glucose sporadically after delivery and in the next pregnancy, just to be aware. A few ignored the risks, or thought that their individual risk was low owing to good glycaemic control, a healthy diet, and/or a normal body mass index (BMI).

Nine out of 14 women had measured HbA1c one or more times after their first pregnancy, and all but one stated that this was self-initiated, mostly done when visiting their GP for other reasons. Some reported they were not aware of the recommendation to measure HbA1c, while others had forgotten.

There were different opinions among the participants about the preferred time to receive information about diabetes risk; for example, some wanted all information during pregnancy, whereas others stated that the burden of disease and treatment was enough. Moreover, they assumed they would be more receptive after delivery, and several women suggested a GP consultation including HbA1c as part of their maternity care 4–6 months postpartum. A comprehensive understanding of the four main themes described could be included in two broader overarching themes. The first is women's internal emotions relating to the GDM diagnosis, and the second is the experiences of contrasting follow-up (during and after pregnancy) affecting women's health-seeking behaviour to mitigate future risk. The relationship between the overarching themes and the main themes along the time course is illustrated in ***Figure 2***, and findings of women's experiences of GDM follow-up and attitudes to future diabetes risk are summarised in ***Table 3***.

Discussion

Summary

This study explored women's experiences of GDM follow-up and attitudes to future risk in Western Norway. The findings indicated that the majority had a positive experience of health care during pregnancy, while most participants stated that they received little or no support for GDM after delivery. Women's worries about their own and their baby's health were the major motivational factors for lifestyle changes in pregnancy, and all but one woman noted that their GDM experience would promote a healthy lifestyle in future pregnancies. The majority were aware of being at risk of diabetes and considered this as a motivation to maintain a healthy lifestyle, promoting weight loss after delivery. However, more than half had gained weight. Stigma and shame and uncertainty were among the

Table 3 Study participants' experiences of GDM follow-up, weight development, and attitudes to future diabetes risk (*n* = 14)

Category	*n* (%)
Follow-up in pregnancy[a]	
Good	8 (57)
Middle	3 (21)
Not good	3 (21)
Follow-up after pregnancy[a]	
Good	2 (14)
Middle	2 (14)
Not good	10 (71)
HbA1c measurement after pregnancy	
Participant's initiative	8 (57)
GP's initiative	1 (7)
Not measured	5 (36)
Weight development after pregnancy[b]	
Weight gain	8 (57)
Weight loss	6 (43)
The experience with GDM will affect lifestyle and diet in next pregnancy	
Yes	13 (93)
No	1 (7)
Aware of or thinking about future diabetes risk	
Yes	12 (86)
No	2 (14)

[a]Participants were asked to select a response.
[b]Compared with pre-pregnancy weight in first pregnancy. GDM = gestational diabetes mellitus.

feelings associated with GDM, and the women asked for improved support to sustain change and maintain a healthy lifestyle.

Strengths and limitations

This qualitative study has several strengths. First, the participants represent the pregnant population with different ages, various pre-pregnancy BMI, living in both rural and urban parts of the region, and having their follow-up from different GPs. Although the majority were ethnic Norwegians, four women had other ethnic backgrounds. Second, all participants spoke Norwegian fluently, they spoke freely, and gave vivid descriptions of their experiences during the interviews. Third, all interviews were conducted by an experienced resident working at a university hospital's outpatient clinic for women with complicated pregnancies, who also performed the cross-sectional study from which the participants were recruited.[21] This background likely improved the quality of the data. Finally, trustworthiness was ensured by involving all authors in the data analysis, a team that was experienced with qualitative studies and thematic analysis.[25,26]

One limitation is that the participants were interviewed 24–30 months after delivery. This might have caused recall bias on participants' experiences. On the other side, eight of the women were pregnant or had given birth again, giving an opportunity to elucidate their follow-up in the second pregnancy. A semi-structured interview approach was chosen to get a comprehensive understanding of the research questions. This approach is suitable when addressing sensitive topics. All the interviews were conducted by telephone, as preferred by the participants. A limitation with telephone interviews is the miss of facial expressions; however, this does not necessarily influence findings.[27] Owing to participation in the 2017–2018 study,[21] detailed information was available on the women's first pregnancy, including background, blood test results, and maternal and fetal outcomes. However, as with other qualitative studies, the present findings rely on self-report, and social desirability bias may have influenced the answers. Finally, the majority of the participants had a master's or bachelor's degree, thus, the findings may not be applicable to other socioeconomic groups.

Comparison with existing literature

Despite the well-documented elevated diabetes risk among women with a history of GDM[5] and the growing evidence that lifestyle intervention and metformin effectively reduce the long-term risk,[28] follow-up after delivery appears challenging worldwide.[13,14,29–31] In the present study, most participants reported that GDM had not been a topic in the encounters with their GPs after delivery, contrary to the recommendations.[10] As GPs' experiences of GDM care were not investigated, the findings rely on women's reports only. In a recent review, women being lost to follow-up and lack of communication between healthcare professionals are barriers mentioned by the providers.[12] The Norwegian model of

care with the GPs being responsible for follow-up before, during, and after pregnancy could facilitate continuity of care for these high-risk women. However, to improve perceived care, women suggest a consultation 4–6 months after birth, including HbA1c, lifestyle counselling, and individualised risk assessment, which is according to the current guideline.[10]

The women in the study got the GDM diagnosis 9–15 months after publication of the guideline. It is well known that guideline implementation and adherence might take several years to fulfil.[32] However, no difference was observed between women's satisfaction of follow-up between the start and the end of the study period.

A gap in the quality between recommended and actual care is well documented, also for patients diagnosed with T2DM.[33] In Norwegian general practice, major gaps in complication screening among patients with diabetes are shown,[34] and a recent study found large variations in GPs' performance of care, with patient reminders being one factor associated with better performance.[35]

The Norwegian GDM guideline seems to align with international guidelines in taking the life-course approach. However, regarding GDM, the findings may indicate that some GPs still work within the acute-care paradigm.[36] To succeed with the life-course perspective a shift in priorities is required. The healthcare systems have traditionally focused on short-term fixes and acute health care. Thus, involvement of policymakers and stakeholders is necessary.[37] Unfortunately, as observed in other developed countries, Norwegian general practice faces several challenges including growing workload and pressures on funding.[38]

The burden of treatment is described as the workload of health care and its effect on patient functioning and wellbeing.[39] In accordance with others,[40] most participants in the present study reported that the burden of GDM was high and medicalisation of pregnancy was apparent. Data analysis revealed 'uncertainty' as one of the main themes affecting women's reactions to the diagnosis, expectations of follow-up, and their attitudes to the increased risk. A recent review evaluating factors affecting uncertainty in high-risk pregnancies concluded that personal, pregnancy-related, demographic, and healthcare-related factors were involved.[41] Uncertainty was associated with less support and lack of information, and closely tied to appraisal of maternal and fetal risk, as also found in the present study. A further study has reported that uncertainty also affects coping strategies in high-risk pregnant women, and that high levels of uncertainty are associated with emotion-focused rather than problem-focused coping.[42]

The theme 'gaining control and finding balance' resonates with others describing the process of being diagnosed and living with GDM as a process from stun to gradual balance.[43] In a British study, the initial concerns after being diagnosed eased as the women learnt how they could control and manage GDM.[44]

A finding contributing to the burden of disease observed in the present study was women's awareness of risk and then the following experience of a lack of follow-up, and that they had to request the HbA1c tests themselves. Maybe the motivation for maintaining a healthy lifestyle disappears as the window of opportunity closes? In a recent Scottish study, a lack of aftercare and the need to arrange postnatal testing themselves led some women to question how serious the increased diabetes risk was.[44]

Implications for research and practice

To reduce the risk of T2DM among women with previous GDM, effective behavioural change interventions are crucial to encourage sustainable change and maintain healthy lifestyles.[45] A key to successful behavioural change is patient empowerment, where ongoing support helps patients to be responsible for their own health.[46] In patient empowerment, the health professional's role is to encourage patients to make informed decisions in order to achieve their goals, and providers need to ensure they can support patients to become effective self-managers.

In England, brief, low-cost training of midwives and nurses in healthy conversation skills in a primary care setting was appreciated, and encouraged many women to set goals for behavioural change.[47] This is in line with the FIGO vision making the best of every contact with women in the reproductive age group.[20] The FIGO nutrition checklist is another tool for clinicians.[48] It is approved to be acceptable in routine care, helping to flag-up nutritional at-risk women. Future studies should explore how this could be implemented in a Scandinavian healthcare setting.

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Ethical approval

The Regional Committees for Medical and Health Research Ethics (REC) South-Eastern Norway approved the study (reference number: 2017/771; date of approval: 31 May 2017). An approval for a project amendment including the qualitative study was given by REC South-Eastern Norway on 25 May 2020 (reference number: 8402). The cross-sectional study, from which the participants in the current qualitative study were recruited, was registered in Clinical Trials with identifier NCT03372824.

Provenance

Freely submitted; externally peer reviewed.

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Appendices

The following documents are included in the Appendices:

- Ethical approvals (study I–III)
- Questionnaire (study II)
- The interview-guide (study III)

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Øyvind Straume	55978496	09.05.2016	2016/563/REK vest
			Deres dato:	Deres referanse:
			30.03.2016	

Vår referanse må oppgis ved alle henvendelser

Johanne Holm Toft
Kvinneklinikken

2016/563 Glykemisk kontroll og jernomsetning i diabetessvangerskap - en studie av nye markører

Forskningsansvarlig: Helse Stavanger HF
Prosjektleder: Johanne Holm Toft

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK vest) i møtet 21.04.2016. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektomtale
Formålet med studien er å sammenligne dagens markør for langtidsblodsukker, HbA1c, med glykosylert albumin. Glykosylert albumin er foreslått som ny og bedre markør, men få studier foreligger.

Vurdering

Forsvarlighet
Studien innebærer at det tas ekstra blod ved planlagt prøvetaking og innsamling av enkelte helseopplysninger til prosjektet. REK vest anser opplysningene som relevante for forskningsspørsmålet, og vurderer dette som en forsvarlig studie å gjennomføre.

Ny prosjektspesifikk biobank
Søknaden innebærer opprettelse av en ny prosjektspesifikk forskningsbioank. Tittelen på denne er «Glykosylert albumin i svangerskap» og ansvarshavende er Johanne Holm Toft. REK vest har ingen innvendinger til dette. Biobanken er prosjektspesifikk og REK vest godkjenner dermed også opphør av biobanken og destruksjon av eventuelle restprøver ved prosjektslutt 01.12.2021.

Informasjonsskrivet
Informasjonsskrivet mangler informasjon om forsikring. REK vest setter som vilkår for godkjenningen at dette utbedres, og at revidert skriv sendes til REK.

Prosjektslutt og håndtering av data
Prosjektslutt er satt til 01.12.2021. I følge søknaden så vil «Data vil bli slettet eller anonymisert ihht gjeldende rutiner 5 år etter prosjektslutt.» REK vest har ingen innvendinger til dette, men presiserer at lagringen etter prosjektslutt er for etterkontroll.

Vilkår

- Informasjonsskrivet skal revideres i tråd med ovennevnte merknad og ettersendes REK vest.

Besøksadresse:
Armauer Hansens Hus (AHH), Tverrfløy Nord, 2 etasje. Rom 281. Haukelandsveien 28

Telefon: 55975000
E-post: rek-vest@uib.no
Web: http://helseforskning.etikkom.no/

Vedtak
REK vest godkjenner prosjektet på betingelse av at ovennevnte vilkår tas til følge.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK vest på eget skjema senest 01.06.2022, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK vest dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Ansgar Berg
Prof. Dr.med
Komiteleder

Øyvind Straume
sekretariatsleder

Kopi til:forskning@sus.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Camilla Gjerstad	55978499	18.05.2021	29950

Johanne Holm Toft

Prosjektsøknad: Glykemisk kontroll og jernomsetning i diabetessvangerskap - en studie av nye markører
Søknadsnummer: 2016/563
Forskningsansvarlig institusjon: Helse Stavanger HF - Stavanger universitetssjukehus

Prosjektsøknad: Endring godkjennes av REK

Søkers beskrivelse

Hos pasienter med diabetes måles langtidsblodsukker (HbA1c) regelmessig for å følge blodsukkernivå og sykdomsutvikling. Studier har vist at HbA1c har svakheter ved samtidig jernmangel, noe som er utbredt blant gravide. Det er viktig med god blodsukkerkontroll for å unngå komplikasjoner for mor og barn. Vi ønsker å sammenligne HbA1c med en annen markør på blodsukkerkontroll (glykosylert albumin) hos gravide med diabetes. Glykosylert albumin er foreslått som ny og bedre markør, men få studier foreligger. Vi vil undersøke dagens rutineprøver på jernstatus og hormonet hepcidin som trolig vil inngå i rutinediagnostikk av jernmangel innen få år. Diabeteskvinnene tar i dag blodprøve for HbA1c regelmessig i svangerskapet. Vi vil ta studieblodprøvene sammen med HbA1c, kvinnene trenger dermed ikke komme til ekstra prøvetaking. Så vidt vi vet har ingen studier kartlagt glykosylert albumin og hepcidin hos gravide kvinner i Norge.

Vi viser til endringssøknad mottatt 18.05.2021.

Endringssøknaden er behandlet av REK vest ved sekretariatet på delegert fullmakt fra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

REKs vurdering

Prosjektendring
Nåværende prosjektslutt er 01.12.2021. Det søkes om ny prosjektslutt der ny prosjektsluttdato vil være 31.12.2024. Endringen skyldes forsinkelser i studien av flere grunner (permisjon, corona og endret rekkefølge på gjennomføring av studiene inkludert i doktorgraden).

Vurdering
REK vest har vurdert endringsmeldingen og har ingen merknader.

Vedtak

REK vest godkjenner prosjektendringen, med hjemmel i helseforskningsloven § 11.

Sluttmelding
Prosjektleder skal sende sluttmelding til REK på eget skjema via REK-portalen senest senest 6 måneder etter sluttdato 31.12.2024, jf. helseforskningsloven § 12. Dersom prosjektet ikke starter opp eller gjennomføres meldes dette også via skjemaet for sluttmelding.

Søknad om endring
Dersom man ønsker å foreta vesentlige endringer i formål, metode, tidsløp eller organisering må prosjektleder sende søknad om endring via portalen på eget skjema til REK, jf. helseforskningsloven § 11.

Klageadgang
Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar av dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Med vennlig hilsen

Camilla Gjerstad
rådgiver

Kopi til:

Helse Stavanger HF - Stavanger universitetssjukehus

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Tor Even Svanes	22845521	31.05.2017	2017/771/REK sør-øst C
			Deres dato:	Deres referanse:
			28.03.2017	

Vår referanse må oppgis ved alle henvendelser

Johanne Holm Toft
Helse Stavanger HF - Stavanger universitetssjukehus

2017/771 Glukosebelastning, HbA1c eller glykert albumin? Kan glykert albumin redusere behovet for glukosebelastning hos gravide?

Forskningsansvarlig: Helse Stavanger HF - Stavanger universitetssjukehus
Prosjektleder: Johanne Holm Toft

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 04.05.2017. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10.

Prosjektomtale
Diagnosen svangerskapsdiabetes stilles ved glukosebelastningstest. Det er ventet ny nasjonal retningslinje for svangerskapsdiabetes, høringsutkastet ble publisert av Helsedirektoratet våren -16. Det legges opp til økt screening, anslagsvis vil 70 % av gravide komme i kategorien hvor glukosebelastning anbefales i svangerskapsuke 24-28. Glukosebelastning krever faste i 8-14 timer, inntak av sukkeroppløsning, blodsukkermåling fastende og etter to timer. Testen er ressurskrevende for helsevesenet, kan være ubehagelig for den gravide (faste, kvalme, oppkast), samt testen har lav reproduserbarhet. Det er ønskelig med enklere diagnostikk. Vi vil undersøke om glykert albumin i en blodprøve kan redusere behovet for glukosebelastning. Vi vil teste 150 gravide som etter høringsutkastet anbefales glukosebelastning. Vi vil etablere referanseintervall for glykert albumin i svangerskap. Gravide som oppfyller kriterier for svangerskapsdiabetes vil bli fulgt opp etter dagens retningslinjer.

Vurdering
Komiteen har ingen innvendinger til designet i studien, men påpeker at prosjektleder står oppført med graden cand. med. i søknaden, og således ikke innehar den formelle prosjektlederkompetansen som kreves etter helseforskningslovens § 4. Komiteen krever derfor at prosjektlederrollen overføres en person med forskerkompetanse. Av tekniske grunner må denne overføringen meldes REK på skjema for prosjektendring, for at vårt system skal kunne oppdateres.

Forskningsbiobank
Det søkes om å opprette en spesifikk forskningsbiobank med navn *Glykert albumin og glukosebelastning* i prosjektet.

Ansvarshavende for forskningsbiobanken er Johanne Holm Toft.

Forskningsbiobanken vil bestå av fullblod og serum.

Biobankens varighet følger prosjektperioden. Deretter skal materialet behandles i henhold til

helseforskningslovens § 30.

Det vil ikke være aktuelt med utførsel av materialet til utlandet. Dersom slik utførsel blir aktuell vil dette kreve søknad til REK, jf. Helseforskningslovens § 29.

Ut fra dette setter komiteen følgende vilkår for prosjektet:

1. Prosjektlederansvaret må overføres til en person med tilstrekkelig forskerkompetanse.

Vedtak
Prosjektet godkjennes under forutsetning av at ovennevnte vilkår oppfylles, jf. helseforskningslovens §§ 9 og 33.

Komiteen godkjenner opprettelse av forskningsbiobanken *Glykert albumin og glukosebelastning*, i tråd med det som er angitt i prosjektsøknaden. Biobankregisteret vil bli underrettet ved kopi av dette brev.

I tillegg til vilkår som fremgår av dette vedtaket, er tillatelsen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 31.12.2022. Av dokumentasjonshensyn skal prosjektopplysningene likevel bevares inntil 31.12.2027. Opplysningene skal lagres atskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Komiteens avgjørelse var enstemmig.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. Forvaltningslovens § 28 flg. Eventuell klage sendes til REK Sør-Øst. Klagefristen er tre uker fra mottak av dette brevet.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK sør-øst på eget skjema senest 30.06.2023, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK sør-øst dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Med vennlig hilsen

Britt-Ingjerd Nesheim
prof. dr. med
leder REK sør-øst C

Tor Even Svanes
seniorrådgiver

Kopi til:svein.skeie@sus.no
Stavanger universitetssjukehus HF ved øverste administrative ledelse: post@helse-stavanger.no

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst C	Anders Strand		25.05.2020	8402
			Deres referanse:	

Inger Hjørdis Bleskestad

8402 Glukosebelastning, HbA1c eller glykert albumin? Kan glykert albumin redusere behovet for glukosebelastning hos gravide?

Forskningsansvarlig: Helse Stavanger HF - Stavanger universitetssjukehus

Søker: Inger Hjørdis Bleskestad

REKs vurdering

REK viser til endringsmelding mottatt 22.04.2020, for prosjekt 2017/771 «Glukosebelastning, HbA1c eller glykert albumin? Kan glykert albumin redusere behovet for glukosebelastning hos gravide?». Komiteleder har vurdert meldingen på fullmakt fra REK sør-øst C, med hjemmel i helseforskningsloven §11.

Den omsøkte endringen består i at prosjektet skal utvides for å gjennomføre en intervjubasert oppfølging av de deltagerne som fikk påvist svangerskapsdiabetes. 21 av deltagerne i det opprinnelige prosjektet skal forespørres om deltagelse i oppfølgingen, og deltagelse i oppfølgingen dekkes av et separat samtykke. Videre søkes det om:

- Utvidet prosjektperiode, slik at ny sluttdato blir 31.12.2025.
- Christina Furskog Risa (Universitetet i Stavanger) inkluderes som prosjektmedarbeider.

Vennligst oppgi vårt referansenummer i korrespondanse.

Med vennlig hilsen,

Britt Ingjerd Nesheim
Prof. Dr.med
Komiteleder, REK sør-øst C

Anders Strand
Rådgiver

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK sør-øst C. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst C, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering.

Stavanger Universitetssjukehus
Helse Stavanger HF

SPØRRESKJEMA FOR FORSKNINGSPROSJEKT

Dato:	Studienummer:

Takk for at du fyller ut dette spørreskjemaet!

Forskningsprosjekt: Glukosebelastning, HbA1c eller glykert albumin? Kan glykert albumin redusere behovet for glukosebelastning hos gravide?

Din alder (år):	Høyde (cm):	Ultralydtermin:
Din vekt før svangerskapet (kg):		
Vektoppgang til nå i svangerskapet (antall kg):		
Diabetes i nær familie? Foreldre ☐, Søsken ☐, Besteforeldre ☐, Andre:		
Etnisitet: Nord-Europa ☐, Sør-Europa ☐, Midtøsten ☐, Asiatisk ☐, Afrikansk ☐ Annen etnisitet (skriv ned):		
Røyking i svangerskapet (Ja/Nei):	Hvis ja: antall sigaretter daglig:	
Snusing i svangerskapet (Ja/Nei):		
Eventuelle sykdommer: Nyresykdom ☐, Leversykdom ☐, Stoffskiftesykdom ☐, Blodsykdom ☐ Høyt blodtrykk før svangerskap ☐, Høyt blodtrykk i svangerskap ☐ Andre sykdommer (skriv ned):		
Dine faste medisiner (skriv ned):		
Kosttilskudd: Jern ☐, Vitaminer ☐, Andre tilskudd:		

Stavanger Universitetssjukehus
Helse Stavanger HF

29.09.2020

INTERVJUGUIDE- KVALITATIV DELSTUDIE

Kvinners erfaring med å få diagnosen svangerskapsdiabetes- om oppfølging og motivasjon for livsstilsendringer etter fødsel.

INTRODUKSJON

Mål: introduksjon og målsetning.

Presentere meg. Du fikk påvist svangerskapsdiabetes i ditt første svangerskap og har sagt ja til å være med i et forskningsintervju. Dette intervjuet har som mål å finne ut **hvordan det er å få diagnosen svangerskapsdiabetes, hvordan du opplevde oppfølgingen i svangerskapet og etter fødsel**, **og om din motivasjon for livsstilsendringer i svangerskapet og etter fødsel.**

Det er ingen rette eller gale svar, jeg er opptatt av **dine erfaringer**. Kom gjerne med eksempler underveis.

Som det sto skrevet i samtykkeskjemaet vil dette intervjuet bli tatt opp som en lydfil. Lydfila vil bli lagret anonymisert på en forskningsserver mens studien pågår. Lydfila vil bli slettet når dataanalysen er over.

Takk for at du stiller opp.

ERFARINGER MED Å FÅ DIAGNOSEN SVANGERSKAPSDIABETES

Mål: kartlegge kvinnens opplevelse med å få diagnosen:

> Vi ønsker å høre fra deg **hvordan du opplevde å få diagnosen** svangerskapsdiabetes i ditt første svangerskap. Kan du fortelle om det?
>
> Hvordan følte du deg? Hva tenkte du?
>
> «Det må ha vært tøft for deg» - var det noe som hjalp deg med å takle all bekymringen?
>
> Noe mer du vil tilføye om det å få diagnosen svangerskapsdiabetes?
>
> Har du vært gravid igjen etter ditt første svangerskap?
>
> (Fikk du evt. påvist svangerskapsdiabetes på ny? Hvordan har det vært?)

OPPFØLGING I SVANGERSKAPET

Mål: kartlegge hvordan kvinnen opplevde oppfølgingen av svangerskapsdiabetes i graviditeten

> Vi ønsker kartlegge oppfølgingen av svangerskapsdiabetes mens du var gravid. Kan du fortelle om det?
>
> Hvilken oppfølging fikk du (både fra jordmor og fastlege)?
>
> Følte du deg trygg? Hvorfor/hvorfor ikke?

Du fikk tilbud om et gruppebasert kurs om svangerskapsdiabetes, deltok du på kurset? Hvordan var det?

Hva mener du skal til for at kvinner med svangerskapsdiabetes skal føle seg godt i varetatt?

SVANGERSKAPSDIABETES, OPPFØLGING FRA FASTLEGE ETTER FØDSEL

Mål: kartlegge oppfølging etter fødsel.

Vi ønsker kartlegge fastlegens oppfølgingen av din svangerskapsdiabetes etter (din første) fødsel. Kan du fortelle litt om det?

Hvordan har du opplevd oppfølgingen?

Ble du innkalt til time eller tok du selv kontakt?

Var svangerskapsdiabetes et tema på 6-ukers kontrollen?

Hvilke råd har du fått? Plan for oppfølging videre?

Har du kontrollert langtidsblodsukker (HbA1c)? En eller flere ganger? Resultat?

Hva har vært fokus for oppfølgingen? (f.eks kosthold, aktivitet eller vekt)

Har du tanker om hvordan oppfølgingen kunne vært bedre?

KOST OG TRENINGSVANER I SVANGERSKAPET OG ETTER FØDSEL

Hvilken informasjon fikk du om kost og aktivitetsråd i svangerskapet?

Var det noe informasjon du savnet?

Visste du fra tidlig i svangerskapet at du skulle gjennomføre glukosebelastningen i uke 24-28? Påvirket det i såfall kost og treningsvaner i svangerskapet fram til du tok testen?

Klarte du følge rådene om kost og fysisk aktivitet i svangerskapet? Hvorfor/hvorfor ikke? Hva er de største barrierene?

Hvilken informasjon har du fått om kost og aktivitetsråd etter fødsel?

Hvordan er kost og treningsvanene dine i dag? Hva er evt de største barrierene for at du ikke får gjennomført kost og aktivitetsrådene?

Hvilke muligheter finnes for fysisk aktivitet i ditt nærmiljø? Barseltrening?

MOTIVASJON

Mål: kartlegge type motivasjon (indre eller ytre)

Å få diagnosen svangerskapsdiabetes krever ofte både omlegging av kosthold og økt fysisk aktivitet for å nå behandlingsmålene. I tillegg må man måle blodsukker hyppig. Dette kan være krevende.

Kan du fortelle om din motivasjon for å følge rådene om sunt kosthold og fysisk aktivitet i svangerskapet?

Hvordan har det vært med motivasjonen for å opprettholde et sunt kosthold/trene etter fødsel?

Var motivasjonen din et resultat av press utenfra eller egen motivasjon?

Hva styrker din motivasjon for å klare å spise sunt og være fysisk aktiv?

VEKT

Mål: kartlegge vekt

Når du deltok i glukosebelastningstudien, skrev du at din vekt før svangerskapet var XX kg.

Hva er din vekt i dag?

Ved vektoppgang: har du forsøkt å gå ned i vekt?

Hva er de største barrierene for at du ikke har klart å gå ned i vekt?

FRAMTIDIG DIABETESRISIKO - FOLKEHELSEPERSPEKTIVET

Mål: kartlegge tanker om framtidig diabetesrisiko

Hva tenker du om din risiko for å utvikle diabetes i framtida?

Er det noe som bekymrer deg og påvirker det livsførselen din i dag?

Hvilken informasjon har du fått om din risiko for å utvikle diabetes?

Når tenker du er det beste tidspunktet å informere kvinner om dette?

Hva tenker du om dine barns risiko for diabetes i framtida?

FRAMTIDIGE SVANGERSKAP

Mål: kartlegge tanker om neste svangerskap

Hva tenker du om neste svangerskap og sjansen for å få svangerskapsdiabetes igjen?

Det at du har hatt svangerskapsdiabetes i ditt første svangerskap, vil det påvirke livsførselen i ditt neste svangerskap?

Hvordan er motivasjonen din for å følge kost og aktivitetsrådene i neste svangerskap?

TILLEGGSINFORMASJON

Høyeste fullførte utdanning?

Hva gjør du i dag? (i arbeid, permisjon, studerer, hjemmeværende)

Sivil status, samboer, gift, enslig?

Bor du i byen eller på landet?

OPPSUMMERING

Mål: oppsummere, åpne for andre tanker

Avslutningsvis, har du andre tanker du vil dele om din opplevelse av svangerskapsdiabetes?

Du har kommet med mange gode innspill. Tusen takk for dine svar. Hvis noe viser seg å være uklart når jeg skal skrive dette intervjuet ned, er det greit at jeg kontakter deg?

REGISTRERE MOBILNUMMER, GAVEKORT

Som takk for at du stilte opp vil du få et gavekort på 500kr. Gavekortet kan blant annet brukes på Kvadrat, Amfi Madla, Amfi Vågen, Amfi Ålgård og Jærhagen. Jeg vil sende deg gavekortet på en sms. Hva er ditt telefonnummer:

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