Hyperglycemia in pregnancy – diagnostics and duration of labor

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Sofia Nevander
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2023-11-06 The thesis was first published online. The online published version reflects the printed version.
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Errata

Paper I:

Table 1:

Indication for OGTT – previous IUFD: wrong percentage number, the correct percentage is 0.6%.

Paper III:

Material and methods:

Additional information regarding the definition of the variable gestational weight gain (GWG):

GWG was defined as maternal weight gain from the early pregnancy baseline visit to measured weight on admission to the delivery unit. The study population was sub-classified into below, within or above recommended GWG according to the American Institute of Medicines guidelines on GWG during pregnancy, in relation to pre-pregnancy BMI.

Table 1:

Additional information below the table:

BMI = Body Mass Index, GWG = Gestational Weight Gain, CS = Caesarean Section, VE = Vacuum Extraction SGA = Small for Gestational Age, LGA = Large for Gestational Age

Definition of gestational weight gain: a According to American Institute of Medicine´s recommendations on gestational weight gain during pregnancy.
Revised flow chart, figure 9. (Figure 1 in paper III)

All primiparae women, singleton pregnancy, ≥34+0 gestational weeks and delivered between Jan 1 2014 and May 30 2020
n=243537

Excluded: Gestational diabetes mellitus n = 4935

Excluded from analysis of time in active labour: Elective caesarean section n = 6262

Included in the analyses of indications of elective cesarean section

Women with pre-pregnancy diabetes n=115
Women with no diabetes n=6147

Data restricted to primiparae with trial of labour (emergency section included)

n=232340

Excluded due to missing value or faulty data on start of active labour n= 64690

Women with pre-pregnancy diabetes n=599
Women with no diabetes n=64091

Final study population for analyses of time in active labour n=167650

Women with pre-pregnancy diabetes n=832
Women with no diabetes n=166818

Included in the subanalysis of indications of emergency cesarean section:

Pre-pregnancy diabetes n=420
No diabetes n=16304
Hyperglycemia in pregnancy -
diagnostics and duration of labor

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Department of Biomedical and Clinical Sciences
Linköping University, Linköping, Sweden
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In loving memory of my incredibly wise mother,

Lena Nevander Friström

1954 - 2008

who loved life and who taught me that the only one directing the path in your own life, is you.
ABSTRACT

Objectives
The overall aim of this thesis was to evaluate the impact of maternal hyperglycemia in pregnancy on the duration of active labor, to evaluate indications for cesarean section and further, to examine cut-offs for gestational diabetes mellitus diagnosis based on capillary sampling.

Material and methods
Study I was a cross-sectional study on diagnostic accuracy performed at an antenatal care clinic at the University Hospital in Linköping, Sweden. The study included 175 women undergoing an oral glucose tolerance test (OGTT) and aimed to compare capillary and venous sampling in the diagnosis of gestational diabetes mellitus (GDM) using Accu-Chek Inform II.

Studies II and III were population-based, nationwide, Swedish register studies using data from the Swedish Pregnancy Register (SPR). In these, 247 524 primiparous women who delivered a singleton fetus, ≥34+0 (completed gestational weeks + additional days) with a cephalic presentation between 1 January 2014 and 30 May 2020 and had their data available in the SPR were included. Time in active labor was compared between women with GDM and women without diabetes (study II) and between women with type 1 diabetes and women without diabetes (study III) using Kaplan-Meier survival analysis and Cox regression analysis.

In study III, we also evaluated indications for elective and emergency cesarean section (CS) in women with type 1 diabetes and women without diabetes.

Results
In study I, the cut-offs for a GDM diagnosis using capillary samples were corrected from 5.1 to 5.3 mmol/L for the fasting sample, from 10.0 to 11.1 mmol/L for the 1 h sample and from 8.5 to 9.4 mmol/L for the 2 h sample using half of the dataset. Applying these cut-offs to the remaining dataset resulted in a sensitivity, specificity and accuracy of 85.0%, 95.0% and 90.3% respectively, with a positive predictive value (PPV) of 83%, a negative predictive value (NPV) of 96% and a positive likelihood ratio (LHR) of 16.4 using capillary sampling for the GDM diagnosis at fasting and 2-h.

In study II, women with GDM had a significantly longer time in active labor, both with a spontaneous onset and induction of labor compared to women without diabetes. Women with GDM also had a decreased chance of vaginal delivery at a certain time-point compared to women without diabetes, with an
adjusted hazard ratio (aHR) of 0.92 (0.88-0.96) and 0.83 (0.76-0.90) for those with spontaneous onset and induction of labor respectively.

Women with GDM had an increased risk for time in active labor ≥12 h both in spontaneous labor onset (adjusted odds ratio (aOR) 1.14 (1.04-1.25)) and in induction of labor (aOR 1.55 (1.28-1.87)).

Women with type 1 diabetes had a significantly longer time in active labor, both in spontaneous onset and induced labor compared to women without diabetes. They also had a decreased chance of vaginal delivery at a certain time-point compared to women without diabetes with an aHR of 0.65 (0.60-0.70). The total rate of CS was 34.6% in the group of women with type 1 diabetes and 9.5% in the group of women without diabetes (both elective and emergency CS).

The most common indication for elective CS among women with type 1 diabetes was suspected macrosomia (50.4%) whereas the corresponding number was 8.7% among women without diabetes. For emergency CS, the most common indication was fetal distress in women with type 1 diabetes (31.9%) and the corresponding number in women without diabetes was 35.9%.

Conclusions
Regarding the diagnosis of GDM, we propose that capillary fasting and 2-hour post-prandial glucose samples, analyzed using the Accu-Chek Inform II system, could be used for the diagnosis of GDM during pregnancy. This approach would involve the use of adjusted cut-off values and demonstrates an acceptable level of accuracy within an antenatal care setting. It is imperative to obtain duplicate samples in order to maintain adequate precision. Furthermore, it is advisable to continue with the OGTT when the fasting samples fall within the normal range, as this leads to a greater number of women receiving a GDM diagnosis.

Regarding time in active labor, both women with GDM and type 1 diabetes seemed to spend a longer time in active labor and were less likely to have a vaginal delivery at any given time compared to their non-diabetic counterparts. In order to customize and individualize intrapartum care, it is imperative to conduct further investigations that illustrate the influence of hyperglycemia in pregnancy on the duration of active labor and on the outcomes during childbirth. In subsequent studies, it will be determined whether the observed difference in the duration of active labor, as indicated in the current studies, remains consistent when employing new definitions of active labor and labor progression.

Suspected fetal macrosomia is the main reason for elective CS among women with type I diabetes and needs to be addressed further.
LIST OF SCIENTIFIC PAPERS

I  Comparison of Venous and Capillary Sampling in Oral Glucose Testing for the Diagnosis of Gestational Diabetes Mellitus: A Diagnostic Accuracy Cross-sectional Study using Accu-Chek Inform II

Sofia Nevander, Eva Landberg, Marie Blomberg, Bertil Ekman, Caroline Lilliecreutz

*Diagnostics. 2020; 10(12):1011.

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II  Gestational diabetes mellitus and time in active labor: a population-based cohort study

Sofia Nevander, Sara Carlhäll, Karin Källén, Caroline Lilliecreutz, Marie Blomberg


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III  Type 1 diabetes in pregnancy - time in active labor and indications of cesarean sections: a population based cohort study

Sofia Nevander, Sara Carlhäll, Karin Källén, Caroline Lilliecreutz, Marie Blomberg

Submitted

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During the period of completing this thesis, I also contributed as a co-author in the following published articles:

**Evaluation of venous plasma glucose measured by point-of-care testing (Accu-Chek Inform II) and a hospital laboratory hexokinase method (Cobas c701) in oral glucose tolerance testing during pregnancy - a challenge in diagnostic accuracy.**

Eva Landberg, Sofia Nevander, Mohammed Hadi, Marie Blomberg, Anna Norling, Bertil Ekman, Caroline Lilliecreutz


**Success rate of external cephalic version in relation to the woman's body mass index and other factors-a population-based cohort study.**

Emelie Svensson, Daniel Axelsson, Marie Nelson, Sofia Nevander, Marie Blomberg

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<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOG</td>
<td>American College of Obstetricians and Gynecologists</td>
</tr>
<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CS</td>
<td>Cesarean section</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variation</td>
</tr>
<tr>
<td>DAG</td>
<td>Directed acyclic graph</td>
</tr>
<tr>
<td>DIP</td>
<td>Diabetes in pregnancy</td>
</tr>
<tr>
<td>FFA</td>
<td>Free fatty acids</td>
</tr>
<tr>
<td>FIGO</td>
<td>International Federation of Gynecology and Obstetrics</td>
</tr>
<tr>
<td>GDM</td>
<td>Gestational diabetes mellitus</td>
</tr>
<tr>
<td>GW</td>
<td>Gestational week</td>
</tr>
<tr>
<td>HAPO</td>
<td>Hyperglycemia and Adverse Pregnancy Outcomes</td>
</tr>
<tr>
<td>HIP</td>
<td>Hyperglycemia in pregnancy</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>IADPSG</td>
<td>International Association of Diabetes and Pregnancy Study Groups</td>
</tr>
<tr>
<td>IOL</td>
<td>Induction of labor</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>LGA</td>
<td>Large for gestational age</td>
</tr>
<tr>
<td>NDDG</td>
<td>National Diabetes Data Group</td>
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<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PE</td>
<td>Preeclampsia</td>
</tr>
<tr>
<td>POCT</td>
<td>Point-of-care testing</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SGA</td>
<td>Small for gestational age</td>
</tr>
<tr>
<td>SPR</td>
<td>Swedish Pregnancy Register</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
BACKGROUND

HYPERGLYCEMIA IN PREGNANCY

Hyperglycemia is the most common medical complication during pregnancy. It has been estimated that in 2021, 21.1 million live births, accounting for 16.7% of all births worldwide, were associated with this condition. The majority of these cases, 80.3%, were attributed to gestational diabetes mellitus (GDM). Additionally, 10.6% were linked to pre-pregnancy type 1 or type 2 diabetes mellitus, while 9.1% were the result of type 1 or type 2 diabetes first identified during pregnancy.

The most commonly accepted definition for what constitutes hyperglycemia in pregnancy (HIP) is the one suggested by the International Federation of Obstetrics and Gynecology (FIGO) in 2015 covering all degrees of severity of hyperglycemia. Diabetes in pregnancy (DIP) includes both pre-pregnancy diabetes and diabetes that are characterized by glucose levels consistent with overt diabetes that is first detected during pregnancy. Pre-pregnancy diabetes includes type 1 diabetes, type 2 diabetes, and other types of diabetes such as cystic fibrosis-related diabetes, steroid/medication-induced diabetes, and monogenic diabetes.

Figure 1. Hyperglycemia in pregnancy - definition
HIP is associated with increased rates of adverse maternal and neonatal outcomes, including both short-term complications during pregnancy and delivery as well as long-term complications for both mother and offspring \(^5\)\(^8\). The severity of hyperglycemia is generally correlated with an increased likelihood of immediate complications for mother and child. The prevalence of HIP is known to be on the rise globally, mirroring the simultaneous epidemics of obesity and diabetes that are affecting populations worldwide \(^5\)\(^9\).

**TYPE 1 DIABETES**

**Historical summary**

Before the discovery of insulin, pregnancies in women with diabetes were rare, infertility was high and very few conceptions were reported. Insulin was discovered in 1921 by Banting and Best and was given with a life-saving effect to the first patient with diabetes at the beginning of 1922. The discovery led to a Nobel prize in physiology or medicine in 1923 \(^10\). The arrival of insulin in 1922 made it possible for women with diabetes to successfully complete pregnancy and give birth to healthy babies. Soon after the initiation of insulin therapy, the pregnancy rate increased seven-fold \(^11\). However, there were notable complications for both the mother and the baby. While the mortality rate for mothers improved significantly, there was only a slight enhancement in perinatal mortality and morbidity. In 1933, Skipper \(^12\) released a comprehensive analysis of the literature following the implementation of insulin until the year 1933. He examined 136 pregnancies in 118 women and compared the findings with his own set of 37 pregnancies in 33 women. The fetal mortality rate in the compiled cases was 45.2\%, while in his series it stood at 40.5\%. 
The conclusions from this study, shown in Figure 2, are surprisingly durable to this date.

- The use of insulin has lower maternal mortality, but has led to no reduction in the fetal mortality
- Diabetic women usually lose tolerance during the latter months of pregnancy
- Hypoglycemia during puerperium is almost invariably in patients receiving insulin and may lead to hypoglycemia coma
- With adequate treatment, pregnancy is not harmful to the diabetic woman
- Ketonuria is common in pregnancy and is a special liability to diabetic coma in the badly treated case
- The most important cause of fetal death is poor control of the diabetes. Other causes are overdevelopment of the fetus and congenital malformations
- Because diabetes may commence during pregnancy, every woman with glycosuria should be investigated as possibly having diabetes
- During treatment, constant supervision and rigid control of the blood sugar are of great importance
- Cesarean may be necessary when the fetus is of excessive size
- Breast feeding is not contraindicated; it should always be tried

**Figure 2. Skipper’s conclusions from 1933**

In the year 1949, Priscilla White published a comprehensive account of her 15-year involvement in 439 cases of diabetic women who gave birth to infants weighing more than 960 g. This study served as the foundation for the renowned White’s classification of diabetes and pregnancy which is still in use in clinical practice today. The medical and obstetric team responsible for the study consistently cared for each patient, ensuring uniformity in treatment. The resulting conclusions were widely adopted as guidelines by numerous medical institutions throughout the USA, and remained so for an extended period of time.
Figure 3 illustrates an overview of the maternal and perinatal mortality at that time (late 1940s and early 1950s) and how White\textsuperscript{13} and Pedersen\textsuperscript{14} predicted the development would continue for the years to come.

The introduction of ultrasound in obstetrics came in the late 1960s. Also during this period, a variety of different tests were tried, focusing on matters like glycemic control, ways to determine fetal-placental function and ways to assess fetal lung maturity\textsuperscript{11}.

In the early 1970s, studies were able to establish a correlation between glycemic control and perinatal mortality and neonatal complications\textsuperscript{15-18}. Congenital anomalies emerged as a recognized complication; nevertheless, the etiology remained poorly comprehended. It was suggested that optimal glycemic control before conception could reduce this complication\textsuperscript{19}. During the later part of the 1970s, malformations were found to be associated with HbA1c levels, a diagnostic examination that had recently been introduced in clinical medicine\textsuperscript{20}.

In the 1970s and 1980s, synthetic insulin, blood glucose meters, and insulin pumps were developed, which improved the glucose control and quality of life for pregnant women with diabetes\textsuperscript{21}.

Since that time, there have been ongoing advancements in technology and medicine. However, even with the current extensive knowledge and persistent efforts, achieving the best possible metabolic control before conception still remains suboptimal and women who have diabetes before pregnancy still face significant increased risks for adverse maternal and neonatal outcomes.
Prevalence and incidence of pre-pregnancy diabetes

Today, Finland and Sweden have the highest incidence of type 1 diabetes in the world with incidence rates of 52.2 and 44.1 per 100 000 population per year. Regarding the prevalence of pre-pregnancy diabetes, a recent systematic review and meta-analysis aimed to describe the global prevalence of pre-existing diabetes in pregnancy, based on studies from January 2010 to December 2020. The prevalence of pre-existing diabetes doubled from 0.5% to 1.0% during the period 1990–2020 with the prevalence of pre-existing diabetes in pregnancy ranging from 0.5% to 2.4% in different countries. The pooled prevalence of pre-existing type 1 and type 2 diabetes were 0.3% (95% CI 0.2–0.4) and 0.2% (95% CI 0.0–0.9) respectively. The authors concluded that, while this is still a low prevalence, pre-existing diabetes appears to have doubled during the period 1990–2020. Considering the ongoing rise in the prevalence of obesity-related type 2 diabetes, the prevalence of pre-existing diabetes in pregnancy is also likely to increase.

![Figure 4. Pooled prevalence of pre-existing diabetes in pregnancy per country.](image)


A Swedish study from 2016 investigated trends in diabetes in pregnancy in Sweden, finding a prevalence of 0.5% in women with type 1 diabetes and 0.1% in women with type 2 diabetes, with both type 1 diabetes and type 2 diabetes during pregnancy increasing over the 15-year period studied.
**Diagnostic criteria** for pre-pregnancy diabetes are well established. The following diagnostic criteria are widely accepted and used:23:

- HbA1c ≥ 48 mmol/mol (≥ 6.5%)
- Fasting plasma glucose ≥ 7.0 mmol/l
  
  Or

- 2-hour plasma glucose ≥ 11.0 mmol/l following a 75 g oral glucose load
  
  Or

- Random plasma glucose ≥ 11.0 mmol/l and diabetes symptoms

Unless a clear clinical diagnosis is present (for example, a patient in a hyperglycemic crisis or displaying classic symptoms of hyperglycemia with a random plasma glucose level of ≥ 11.1 mmol/L [200 mg/dL]), two abnormal test results from the same sample or two separate test samples are required for the diagnosis.24
GESTATIONAL DIABETES MELLITUS

GDM is one of the most common medical complications of pregnancy and is currently defined as hyperglycemia that is first diagnosed during pregnancy, with glucose levels below those considered diagnostic of overt diabetes outside of pregnancy.

GDM has long been known to be associated with obstetric and neonatal complications and is increasingly being acknowledged as a substantial risk factor for long term complications like type 2 diabetes, obesity, and cardiovascular disease in both mother and offspring.

Perinatal complications due to GDM are significantly reduced by treatment, which make the diagnosis and detection of GDM important. However, there is a lack of international consensus regarding diagnostic criteria, screening and management of GDM.

In 2022, Wang et al estimated the pooled global standardized prevalence of GDM to be 14.0% (95% confidence interval: 13.97–14.04%) 

In Sweden, the prevalence of women diagnosed with GDM varies between 1.4-17.9% between different regions.

Figure 5. Gestational diabetes mellitus – an overview
Historical summary

In a historical context, the first record of diabetes in pregnancy was initially made by Bennewitz in Germany in 1824 when he described a woman with recurrent glycosuria and intensive thirst in three consecutive pregnancies. In 1909, Williams published a comprehensive review of the current global literature, detailing a total of 66 pregnancies. The focus of the review was on the interpretation and diagnostic significance of glycosuria during pregnancy, which was the basis of the diagnosis of diabetes during that time.

Later, the term gestational diabetes then first attracted attention in 1957 after the work of Carrington, but gained a wider recognition after 1964 when O’Sullivan and Mahan defined diagnostic criteria for gestational diabetes using a 100-g 3-hour OGTT.

The World Health Organization (WHO) formally defined gestational diabetes for the first time in 1965, based on the work of O’Sullivan and Mahan. They described it as “hyperglycemia of diabetic levels occurring during pregnancy” and recommended the diagnosis of GDM using either a 50-gram or 100-gram OGTT using the 2-hour post load glucose value. The same thresholds used for diagnosing diabetes in the nonpregnant population were applied.

The National Diabetes Data Group (NDDG) redefined GDM in 1979 as “glucose intolerance that has its onset or recognition during pregnancy” and published updated conversions for the original O’Sullivan and Mahan 100-g 3-hour OGTT diagnostic criteria for GDM, reflecting the shift from analyzing venous whole blood glucose to plasma blood glucose analysis.

In 1982, Carpenter and Coustan suggested lowering the levels used for the diagnostic criteria recommended by the NDDG, reflecting newer enzymatic methods that were more specific to plasma glucose levels.

The definition of GDM was further revised in 1985 at the Second International Workshop-Conference on Gestational Diabetes. It was described as “carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy”, and this remained the most commonly used definition until the current recommended definition from FIGO.

In 2000, the American Diabetes Association (ADA) recommended the modified Carpenter and Coustan diagnostic glucose thresholds for GDM. Additionally, from 2003, the ADA recommended the 1-step 75-g 2-hour OGTT for the diagnosing GDM based on the modified Carpenter and Coustan fasting, 1- and
2-hour glucose thresholds for the 100-g 3-hour OGTT. This was particularly recommended for high-risk women.

**Diagnostic criteria and screening – controversy and lack of consensus**

The historical absence of agreement regarding the diagnosis of GDM is demonstrated by the progression of the definition and the diagnostic criteria for GDM. The determination of disease presence or absence has been found to vary upon expert consensus. Furthermore, the overall reasoning behind the diagnosis of GDM has gradually evolved to focus more on identifying perinatal risk rather than the risk of future maternal diabetes.

The current diagnostic criteria for GDM originates from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study in 2008 where the association between maternal glucose levels on the 75-g 2-hour OGTT, performed in 24 to 32 weeks gestation in over 25000 pregnant women, and maternal and fetal outcomes were studied. The primary perinatal outcomes included birthweight > 90th percentile for gestational age, primary CS, neonatal hypoglycemia, and cord blood serum C-peptide > 90th centile and secondary outcomes were preeclampsia, preterm delivery (defined as delivery before 37 weeks’ gestation), shoulder dystocia or birth injury, hyperbilirubinemia, and neonatal intensive care admission. The results showed a continuous positive linear relationship between maternal fasting; 1- and 2-hour plasma glucose levels obtained on the OGTT and risk of primary outcomes without obvious cut-off points.

Based on the findings in the HAPO-study and further supported by the results of two large randomized controlled trials that stated that treatment of GDM is effective in reducing or preventing maternal and fetal short-term complications even in “milder” degrees of maternal hyperglycemia, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) revised its diagnostic criteria for GDM in 2010.

Despite the absence of a definitive diagnostic glucose threshold in the HAPO-study, the IADPSG reached a consensus on establishing diagnostic thresholds for GDM using venous sampling in fasting, 1-hour, and 2-hour glucose values during the 75-gram 2-hour OGTT.

These thresholds were chosen to reflect the average glucose values at which adjusted odds ratio (aOR) was 1.75 for birth weight ≥90th percentile, cord C-peptide ≥90th percentile, and percent body fat ≥90th percentile (in the infant) compared to the mean glucose levels observed in the HAPO-study. Consequently, the primary objective of the diagnostic criteria for GDM
following the HAPO study was to specify the degree of risk associated with increased perinatal complications.

The IADPSG consensus also concluded that only one single elevated glucose level during the OGTT was sufficient for diagnosing GDM, as each threshold represented a similar level of risk. The recommended screening strategy was universal testing of all pregnant women between 24 to 28 weeks of gestation using the 75-g 2-hour OGTT.

The recommendations from IADPSG were then accepted and recommended by the WHO in 2013. 43

Post-HAPO and the subsequent recommendations of IADPSG and WHO, several different screening and testing approaches exist for the diagnosis of GDM worldwide, which are highlighted in Table 1.
Table 1. A selection of diagnostic criteria for the diagnosis of GDM

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Selective vs universal testing</th>
<th>Fasting plasma glucose (mmol/l)</th>
<th>1-hour glucose (mmol/l)</th>
<th>2-hour glucose (mmol/l)</th>
<th>3-hour glucose (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IADPSG/ADA WHO/FIGO</td>
<td>Universal</td>
<td>≥ 5.1</td>
<td>≥ 10.0</td>
<td>≥ 8.5</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>One abnormal value needed for diagnosis</td>
</tr>
<tr>
<td>Carpenter-Coustan criteria (ACOG primary recommendation)</td>
<td>Universal</td>
<td>≥ 5.3</td>
<td>≥ 10.0</td>
<td>≥ 8.6</td>
<td>≥ 7.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Two abnormal values needed for diagnosis</td>
</tr>
<tr>
<td>NDDG criteria (ACOG alternative)</td>
<td>Universal</td>
<td>≥ 5.8</td>
<td>≥ 10.6</td>
<td>≥ 9.2</td>
<td>≥ 8.0</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Two abnormal values needed for diagnosis</td>
</tr>
<tr>
<td>CDA (Canada)</td>
<td>Universal</td>
<td>≥ 5.3</td>
<td>≥ 10.6</td>
<td>≥ 9.0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>One abnormal value needed for diagnosis</td>
</tr>
<tr>
<td>NICE (UK)</td>
<td>Selective</td>
<td>≥ 5.6</td>
<td></td>
<td>≥ 7.8</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>One abnormal value needed for diagnosis</td>
</tr>
<tr>
<td>WHO 1985</td>
<td></td>
<td>≥ 7.8</td>
<td></td>
<td>≥ 7.8</td>
<td></td>
</tr>
<tr>
<td>WHO 1999</td>
<td></td>
<td>≥ 7.0</td>
<td></td>
<td>≥ 7.8</td>
<td></td>
</tr>
</tbody>
</table>

Most countries and organizations recommend that the diagnosis of GDM should be made using a 75 g OGTT, conducted between 24 and 28 weeks of pregnancy. Furthermore, some countries only screen women with risk factors for GDM, while most countries use universal screening. When selective screening is applied, women who are considered to have risk factors for GDM are screened for the diagnosis using the OGTT.
Risk factors for GDM include maternal overweight and obesity, maternal age, previous history of GDM, family history of type 2 diabetes and ethnicity. In Sweden, the pattern mimics the global situation with a lack of consensus in regard to the mode of screening and diagnostic criteria. Throughout the 21 different regions in the country, there are currently 19 different diagnostic and screening strategies. During 2018, there was a stepped-wedge cluster randomized trial in Sweden, involving 11 clinics, called Changing Diagnostic Criteria for Gestational Diabetes (CDC4G). This study aims to compare pregnancy outcomes before and after the switch in GDM criteria, but the results remain to be published.

**Diagnostics and laboratory methods**

The diagnosis of GDM is solely reliant on the evaluation of plasma glucose levels, and it is often determined or ruled out based on a single measured glucose concentration that exceeds or falls below a specific threshold. Thus, the dependability of analytical techniques used for assessing plasma glucose has great importance.

Laboratory measurements of glucose are based on enzymatic reactions that involve one of four enzymes: glucose 1-dehydrogenase, glucose oxidase, glucokinase, or hexokinase. Among these enzymes, glucose oxidase, glucokinase, or hexokinase are most commonly used. Glucose oxidase exhibits the highest specificity and exclusively reacts with D-glucose, however, the glucokinase or hexokinase methods are regarded as more precise compared to the glucose oxidase method. For point-of-care tests, either glucose oxidase or glucose 1-dehydrogenase are typically used.

The current recommended mode of sampling for the diagnosis of GDM is venous sampling. However, capillary sampling and the use of a point-of-care testing (POCT) instrument for diagnostic purposes could be especially practical in pregnancy. The rapid POCT result during an oral glucose tolerance test (OGTT) is an advantage and can be used to decide if fasting P-glucose is above the diagnostic cut-off for GDM and if the OGTT has to be continued or not. Additionally, women who receive the GDM diagnosis can get an immediate follow-up plan and management. Another advantage of POCT is that the sample will be analyzed without any delay and thus there will be no artifacts due to storage or in vitro glycolysis.

Previous studies regarding the use of POCT for the diagnosis of GDM show various results. O’Malley et al. compared POCT-corrected capillary glucose results versus laboratory venous plasma glucose results in OGTT for the diagnosis of GDM. They recommend the use of laboratory analysis when strict
adherence to pre-analytical sample handling can be applied; otherwise, POCT may be used for the diagnosis of GDM. On the other hand, Daly et al. concluded that POCT capillary maternal glucose tests were superior to customary laboratory practices for diagnosing GDM and that adjusted point-of-care glucose measurements have potential in the diagnosis of GDM.

When it comes to capillary and venous sampling in measuring glucose, studies suggest that the levels of glucose in capillary and venous plasma cannot be used interchangeably, particularly in the non-fasting state.

**OBSTETRIC AND NEONATAL OUTCOMES IN RELATION TO HYPERGLYCEMIA IN PREGNANCY**

Hyperglycemia in pregnancy is associated with increased rates of adverse maternal and neonatal outcomes, including both short-term and long-term complications for both mother and offspring.

Short-term complications include: Stillbirth, macrosomia, infants being large for gestational age (LGA), respiratory distress syndrome (RDS), neonatal hypoglycemia, neonatal intensive care unit (NICU) admission, congenital anomalies, preeclampsia (PE) and gestational hypertension, CS and preterm birth. In the long-term, both mothers and their offspring have an increased risk of metabolic disease.

Women with GDM have about a seven times higher risk of developing type 2 diabetes mellitus after pregnancy and additionally face a four-fold increased risk of developing cardiovascular disease.

Pre-pregnancy diabetes predisposes women to develop diabetes-related complications such as retinopathy and nephropathy or accelerating the course of these complications if they already exist.

**Comparing adverse outcomes in GDM and pre-pregnancy diabetes**

It is well documented that all types of maternal diabetes are associated with pregnancy complications. However, adverse outcomes are more common in women with pre-pregnancy diabetes compared to women with GDM.

Poor glycemic control during pregnancy and the critical period of organogenesis in the first trimester are closely associated with adverse pregnancy outcomes. It is believed that preconception hyperglycemia and prolonged exposure to hyperglycemia in utero may play a role in the complications linked to pre-pregnancy diabetes.
A recent, large systematic review from 2022 compared adverse outcomes in women with pre-pregnancy diabetes and women with GDM and concluded that adverse pregnancy outcomes such as CS, PE, macrosomia, neonatal hypoglycemia, LGA, stillbirth and NICU admission were more common in women with pre-pregnancy diabetes compared to women with GDM.

Maternal and neonatal complications of GDM

Maternal hyperglycemia in both pre-pregnancy diabetes and GDM leads to perinatal consequences whose mechanisms are schematically shown in Figure 6.

Figure 6. Perinatal consequences of gestational diabetes mellitus. Reprinted from: Sweeting, Arianne et al. “A Clinical Update on Gestational Diabetes Mellitus.” Endocrine reviews vol. 43,5 (2022): 763-793. doi:10.1210/endrev/bnac003 by permission of Oxford University Press

The HAPO study stated that there is an independent and graded linear correlation between maternal hyperglycemia and increased risks of PE, preterm delivery, CS, the birth of LGA infants, shoulder dystocia, neonatal hypoglycemia, hyperbilirubinemia and admission to neonatal special care units. Regarding long-term complications in both mother and offspring, a follow-up study from the HAPO study demonstrated that GDM diagnosed using the IADPSG criteria is associated with a long-term risk of type 2 diabetes in the mother and a risk of obesity in offspring.

The risks of short-term and long-term complications from the HAPO-study and the HAPO-follow-up-study (HAPO-FUS) are shown in Table 2.
Table 2. A summary of outcomes from the HAPO-study and the HAPO-FUS (follow-up-study)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>GDM (%)</th>
<th>Non-GDM (%)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perinatal outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preclampsia</td>
<td>9.1</td>
<td>4.5</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Preterm delivery (&lt;37 weeks)</td>
<td>9.4</td>
<td>6.4</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Primary cesarean delivery</td>
<td>24.4</td>
<td>16.8</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Shoulder dystocia or birth injury</td>
<td>1.8</td>
<td>1.3</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Birthweight greater than ninetieth percentile</td>
<td>16.2</td>
<td>8.3</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Neonate percentage body fat greater than ninetieth percentile</td>
<td>16.6</td>
<td>8.5</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Cord blood C-peptide level greater than ninetieth percentile</td>
<td>17.5</td>
<td>6.7</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Clinical neonatal hypoglycemia</td>
<td>2.7</td>
<td>1.9</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Admission to newborn intensive care</td>
<td>9.1</td>
<td>7.8</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td><strong>Long-term outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal diabetes</td>
<td>10.7</td>
<td>1.6</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Maternal pre-diabetes</td>
<td>41.5</td>
<td>18.4</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Offspring overweight or obesity</td>
<td>39.5</td>
<td>28.6</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Offspring obesity</td>
<td>19.1</td>
<td>9.9</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Offspring percentage body fat greater than eighty-fifth percentile</td>
<td>21.7</td>
<td>13.9</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Offspring impaired fasting glucose (ADA threshold of ≥5.6 mmol/l)</td>
<td>9.2</td>
<td>7.4</td>
<td>Not significant</td>
</tr>
<tr>
<td>Offspring impaired glucose tolerance</td>
<td>10.6</td>
<td>5.0</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Offspring diabetes</td>
<td>0.3</td>
<td>0.2</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

*Women classified post hoc as having GDM by IADPSG criteria

*b Outcomes from the HAPO study

*c Outcomes from the HAPO-FUS

A summary of the maternal and neonatal short-term and long-term complications in women with GDM is shown in Table 3.

Table 3. Maternal and neonatal short-term and long-term complications in women with GDM

<table>
<thead>
<tr>
<th>Complications</th>
<th>Maternal</th>
<th>Neonatal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term</strong></td>
<td>Preeclampsia, Gestational hypertension, Polyhydramnios, Urinary tract/vaginal infections, Instrumental delivery, Cesarean delivery, Traumatic labor/perineal tears, Postpartum hemorrhage, Difficulty initiating and/or maintaining breastfeeding</td>
<td>Stillbirth, Neonatal death, Preterm birth, Congenital malformations, Macrosomia, Cardiomyopathy, Birth trauma: Shoulder dystocia, Bone fracture, Brachial plexus injury, Hypoglycemia, Hyperbilirubinemia, Respiratory distress syndrome</td>
</tr>
<tr>
<td><strong>Long-term</strong></td>
<td>Recurrence of GDM, Type 2 diabetes mellitus, Hypertension, Ischemic heart disease, Nonalcoholic fatty liver disease, Dyslipidemia, Chronic kidney disease</td>
<td>Metabolic syndrome, Hyperinsulinemia, Childhood obesity, Excess abdominal adiposity, Higher blood pressure, Possible earlier onset cardiovascular disease, Possible attention-deficit hyperactivity disorder, Autism spectrum disorder</td>
</tr>
</tbody>
</table>

ONSET OF LABOR AND LABOR PROGRESSION

Stages of labor
The stages of labor include:
First stage
- Latent first stage/latent phase
- Active first stage/active phase
Second stage:
- The time from full cervical dilation until the birth of the neonate
Third stage:
- Begins with the birth of the neonate and ends with the delivery of the placenta.

Onset of active labor
The definition of onset of the active phase of labor varies globally and has gradually evolved throughout history. In the 1950s, Emanuel Friedman provided a description of the criteria that determined normal progression of labor. These criteria have since been used for the assessment and management of labor for many years. His findings indicated a labor curve that accelerates from 3-4 cm, with an expected rate of labor progression of 1 cm dilation of the cervix per hour. Based on the labor curve proposed by Friedman, Philpott and his associates then established a set of guidelines aimed at overseeing the progress of labor and identifying any deviation from normal progress.

In 1994, the World Health Organization (WHO), influenced by the work of both Friedman and Philpott, made the recommendation that the active phase of labor should commence when the cervical dilatation reaches 3 cm and the WHO partograph was introduced. The implementation of alert and action lines was also advised for the purpose of labor management. Subsequently, in 1995, the American College of Obstetricians and Gynecologists (ACOG) established the initiation of the active phase of labor based on Friedman’s criteria. According to this, the onset of the active phase is indicated by a sudden change in the slope of the curve when plotting cervical dilatation against time. Typically, this change occurs when the cervix reaches a dilatation of 3 to 4 cm. However, in 2017, ACOG proposed that for many women, the onset of active labor may not take place until the cervical dilatation reaches 5 to 6 cm. In 2019, the recommendations from ACOG were altered once again in order to reduce the emphasis on the duration of labor. It was advised that expectant management is
a reasonable approach for women who are at 4 to 6 cm of dilatation, as long as the well-being of both the mother and the baby has been assured.

Similarly, in 2018, the WHO proposed that the active phase of labor begins when the cervix is dilated to 5 cm. Additionally, following the ACOG's decision to move away from time-based estimates, the WHO also stopped recommending the use of the 1 cm per hour cervical dilatation threshold for assessing the progress of normal labor.

**Labor progression and duration of labor**

A complete understanding of the characteristics of normal labor progression is still lacking and continues to be a topic of discussion. For decades, the work of Friedman and Philpott, the WHO guidelines and the WHO partograph from 1994 have influenced intrapartum care and the view of what is normal labor progression. Since 2010 however, several studies have assessed the normal progress of labor to establish more contemporary criteria.

Studies conducted by Zhang and Oladapo have demonstrated that labor may have a longer duration and exhibit slower progress until the point of 5-6 cm cervical dilatation, after which it tends to accelerate. These contemporary criteria differ from those described by Friedman stating that the active phase can start at a more advanced cervical dilation, and cervical dilatation can be slower than originally described and still be normal and hence, associated with a high chance of vaginal birth and normal newborn outcome.

A recent investigation on labor progress conducted in Sweden revealed, in accordance with the research conducted by Zhang and Oladapo, a hastening of cervical dilation at 5-6 cm; however, it was observed that the median time for the first stage of labor was faster.

In a comprehensive study carried out in Norway, the labor outcomes of nulliparous women with spontaneous onset of labor were compared. The management of these women was based on either the partogram using Friedman's data or Zhang's findings. No significant differences were found in adverse outcomes, including the rate of cesarean section, but regarding the duration of labor, women who delivered by intrapartum cesarean delivery had a prolonged labor duration compared with those who delivered vaginally in both study groups. Both groups being studied also showed a decrease in the number of CS during labor when compared to before the study. This finding supports the idea that by paying more attention to the progress of labor, the rate of CS during labor can be reduced.

A recent large prospective, observational cohort study from the USA by Tilden et al. studied the duration of spontaneous active and pushing phases of labor.
among 75,243 US women when intervention was minimal and found labor
durations that were often longer than previous findings, especially in nulliparous
women. A summary of the findings in a selection of studies concerning the duration of
the active first stage and second stage in nulliparous women is given in Table 4 and Table 5.
Table 4. A selection of studies on the duration of the active phase of the first stage in in
nulliparous women after spontaneous onset of labor with a term, singleton, fetus in a
cephalic presentation

<table>
<thead>
<tr>
<th>Study</th>
<th>Population/region/country</th>
<th>Number</th>
<th>Definition of active phase</th>
<th>Duration of active phase of the first stage in hours Median (90th percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedman66, 1955</td>
<td>United States</td>
<td>500</td>
<td>cervical dilation from 2.5 - 10 cm</td>
<td>4.9±3.4 (mean±SD)</td>
</tr>
<tr>
<td>Bergsjo et al83, 1979</td>
<td>Norway</td>
<td>497</td>
<td>cervical dilation from 4–10 cm</td>
<td>2.4 (5.0)</td>
</tr>
<tr>
<td>Zhang et al75, 2010</td>
<td>United States</td>
<td>6096</td>
<td>cervical dilation from 3-3.5 cm to 10 cm</td>
<td>6.9 (17.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5550</td>
<td>cervical dilation from 4-4.5 cm to 10 cm</td>
<td>5.3 (16.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2764</td>
<td>cervical dilation from 5-5.5 cm to 10 cm</td>
<td>6.9 (17.4)</td>
</tr>
<tr>
<td>Laughon et al84, 2012</td>
<td>United States</td>
<td>43756</td>
<td>cervical dilation from 6–10 cm</td>
<td>2.2 (10.0)</td>
</tr>
<tr>
<td>Oladapo et al73, 77, 2018</td>
<td>Nigeria, Uganda</td>
<td>715</td>
<td>cervical dilation from 4–10 cm</td>
<td>5.9 (14.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>316</td>
<td>cervical dilation from 5–10 cm</td>
<td>4.3 (11.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>322</td>
<td>cervical dilation from 6–10 cm</td>
<td>2.9 (9.3)</td>
</tr>
<tr>
<td>Lundborg et al99, 2020</td>
<td>Sweden</td>
<td>11520</td>
<td>cervical dilation from 4–10 cm</td>
<td>5.0 (14.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8201</td>
<td>cervical dilation from 5–10 cm</td>
<td>3.7 (12.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5843</td>
<td>cervical dilation from 6–10 cm</td>
<td>2.7 (10.7)</td>
</tr>
</tbody>
</table>
In February 2018, WHO published new recommendations on intrapartum care for a positive childbirth experience, which included updated definitions and durations for the first and second stages of labor, based on the evidence from systematic reviews. This is a summary of the recommendations from WHO:

- Due to the very low certainty of evidence on the duration of the latent phase of the first stage of labor, resulting in part from the difficulty in ascertaining the actual onset of labor, WHO chose not to establish a standardized duration for the latent first stage for the purpose of decision making during
labor. Women should be informed that a standard duration of the latent first stage has not been established and can vary widely from one woman to another.

- The active first stage is a period of time characterized by regular painful uterine contractions, a substantial degree of cervical effacement and more rapid cervical dilatation from 5 cm until full dilatation for first and subsequent labors.
- The duration of active first stage (from 5 cm until full cervical dilatation) usually does not extend beyond 12 hours in first labors, and usually does not extend beyond 10 hours in subsequent labors.
- The expected duration of the active phase of the first stage of labor depends on the reference threshold used for its onset. The established boundaries for the active first stage were rounded 95th percentile values from evidence on the duration of the progress of cervical dilatation from 5 cm to 10 cm.
- The median duration of the active first stage is 4 hours in first labors and 3 hours in second and subsequent labors, when the reference starting point is 5 cm cervical dilatation.
- The decision to intervene when the first stage of labor appears to be prolonged must not be taken on the basis of duration alone.
- Health care professionals should support pregnant women with spontaneous labor onset to experience labor and childbirth according to each individual woman’s natural reproductive process without interventions to shorten the duration of labor, provided the condition of the mother and baby is reassuring, there is progressive cervical dilatation, and the expected duration of labor is within the recommended limits.
- Health care professionals should advise healthy pregnant women that the duration of labor is highly variable and depends on their individual physiological process and pregnancy characteristics.

In 2020, WHO released its new guidelines, the WHO Labour Care Guide (LCG) as a tool to use in intrapartum care in line with the WHO recommendations.
CESAREAN SECTION

Cesarean section is a potentially life-saving medical procedure that can greatly enhance the safety of obstetric care. Nonetheless, CS is a major abdominal operation that carries significant risks, while vaginal birth provides important physiological cues that contribute to the well-being and health of both the mother and the newborn. The advantages of vaginal birth encompass a reduction in postpartum pain, an improvement in the bonding between the mother and the newborn, an increase in the rate of breastfeeding, and a decrease in the occurrence of childhood asthma, allergies, and obesity. Furthermore, CS imposes increased risks of surgical complications, bleeding, venous thromboembolism, postoperative infections, and future pregnancy complications, such as uterine rupture, abnormal placentation, ectopic pregnancy, and stillbirth.

In 2015, the WHO stated that cesarean rates higher than 10–15% were not associated with a reduction in maternal and newborn mortality rates. The global prevalence of CS is progressively on the rise, and the escalating cesarean delivery rate is accompanied by reports of increased maternal morbidity due to pathological placentation, peripartum hysterectomy, and significant obstetric hemorrhage.

In Sweden, the total rate of CS is also gradually increasing from 17.3% in 2014 to 19.1% in 2022. Labor dystocia is the most common indication for primary CS worldwide, followed by abnormal fetal heart rate tracing, fetal malpresentation, multiple gestation and suspected fetal macrosomia. A study from 2019 investigated the indications of CS in a tertiary hospital in Sweden and found that the most common indication for elective CS in 2015 was maternal request (41.2%) and that the most common indications for emergency CS were prolonged labor (51.2%) followed by imminent fetal asphyxia (23.1%).
HYPERGLYCEMIA IN PREGNANCY AND DURATION OF LABOR

Hyperglycemia in pregnancy, as mentioned previously, is associated with various adverse perinatal outcomes, including an increased risk for CS \(^5,8,9\).

The exact mechanisms that cause the increased risk for CS are not fully understood, but some research suggests that it may be due to obesity, while other studies have found diabetes to be an independent risk factor \(^{100,101}\).

Fetal distress and macrosomia also contribute to the overall increase in emergency CS rate, but studies on women with GDM\(^{102}\) and studies that include both women with pre-pregnancy diabetes and GDM\(^{101}\) indicate that reducing macrosomia does not lead to a corresponding decrease in CS rate.

Studies regarding hyperglycemia in pregnancy and duration in labor have had various results. In a study examining both women with GDM and women with pre-pregnancy diabetes, Hawkins et al. \(^{103}\) examined progress and outcomes in 122 women with diabetes who underwent prostaglandin labor induction. They found that women with diabetes experienced a significantly prolonged time to reach active labor and time to delivery and had lower rates of delivery within 36 or 48 h due to a prolonged latent phase, but that the time in active labor was similar compared to women without diabetes. Timofeev et al. demonstrated that active labor progression and duration were similar in 458 nulliparous and 1079 multiparous women with pre-existing diabetes mellitus and GDM compared to normal controls matched by neonatal birth weight, parity and maternal BMI \(^{104}\). However, only vaginal deliveries with normal neonatal outcome were included. When examining only women with GDM, Sheiner et al. compared obstetric risk factors for failure to progress in the first (1197 women) vs the second stage (1154 women) of labor and noted that GDM was an independent risk factor for failure of labor to progress during the first stage \(^{105}\).

In vitro studies on myometrium from humans \(^{106}\) and from mice \(^{107}\) comparing individuals with and without diabetes (both pre-pregnancy diabetes and GDM) suggest that diabetes may lead to changes in the myometrium reflecting impaired uterine contractility. Therefore, it is possible that impaired myometrium contractility and/or labor may play a role in certain adverse outcomes observed in women with hyperglycemia in pregnancy.
SPECIFIC BACKGROUND TO THE PRESENT STUDIES

In summary, hyperglycemia in pregnancy is the most common medical complication in pregnancy and is associated with adverse outcomes, both short-term and long-term, for both mother and child. Management of this group in pregnancy and delivery occurs in the clinical setting on a daily basis. Despite this, the diagnostics and diagnostic criteria and management during pregnancy and delivery of this continuously growing group, are beset with uncertainties and lack of consensus. The diagnostics and diagnostic criteria of GDM remain unclear and are used with an extreme variation worldwide. It is therefore important to investigate ways to make diagnostics easier and manageable in every-day clinical practice, which was the reason we conducted study I.

As a clinician in obstetrics, I have seen many women with different kinds of hyperglycemia in pregnancy on the delivery ward. It has puzzled me as to why it seems that these women often get into some sort of obstructive, prolonged labors and are subjected to various forms of obstetric interventions like CS. This led to the question of whether these women indeed have increased risk for longer duration of labor. It also led to further consideration of the possibility that dysfunctional labor could play a role in some of the adverse outcomes seen in women with hyperglycemia in pregnancy. Therefore, it is imperative to conduct studies on a population level to comprehensively assess the duration of labor in women with GDM and pre-pregnancy diabetes and the effects of hyperglycemia during pregnancy on childbirth outcomes. This could allow for an optimized and personalized obstetric management and approach for this continuously increasing group of women who are facing increased risks in pregnancy and delivery.

Furthermore, the especially marked increased risk for CS seen in the group of women with type 1 diabetes raised the question of how the indications for CS in this population are distributed in a high resource setting.
AIMS

OVERALL AIM

The overall aim of this thesis was to evaluate the impact of maternal hyperglycemia in pregnancy on the duration of active labor, to evaluate indications for cesarean section and further, to examine cut-offs for GDM diagnosis based on capillary sampling.

SPECIFIC AIMS

- To examine whether plasma glucose cut-offs for GDM diagnosis based on venous sampling can be replaced by cut-offs based on capillary sampling in an antenatal setting without compromising diagnostic accuracy. (Study I)

- To evaluate the necessity to continue OGTT after taking fasting samples and to investigate the additional number of women who receive the diagnosis of GDM at 1 h and 2 h after OGTT. (Study I)

- To evaluate the impact of gestational diabetes in primiparous women on time in active labor, in both women with spontaneous onset and induced labor. (Study II)

- To evaluate the impact of type 1 diabetes in primiparous women on time in active labor and to analyze indications and rates for elective and emergency CS compared to women without diabetes. (Study III)
MATERIAL AND METHODS

An overview of the three studies included in the thesis is presented in Table 6.

Table 6. Overview of the three studies included in the thesis

<table>
<thead>
<tr>
<th>Study</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Prospective cross-sectional study</td>
<td>Population-based (retrospective) cohort study</td>
<td>Population-based (retrospective) cohort study</td>
</tr>
<tr>
<td>Data sources</td>
<td>Medical record: Obstetrix®</td>
<td>The Swedish Pregnancy Register</td>
<td>The Swedish Pregnancy Register</td>
</tr>
<tr>
<td>Laboratory method</td>
<td>Accu-Chek Inform II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting</td>
<td>Antenatal care clinic at the university hospital in Linköping, Sweden</td>
<td>National, Sweden</td>
<td>National, Sweden</td>
</tr>
<tr>
<td>Participants</td>
<td>175 pregnant women undergoing an OGTT</td>
<td>Primiparous women, singleton pregnancy, cephalic presentation, ≥34+0 gestational weeks and delivered between Jan 1 2014 and May 30 2020 n=247524</td>
<td>Primiparous women, singleton pregnancy, cephalic presentation, ≥34+0 gestational weeks and delivered between Jan 1 2014 and May 30 2020 n=243537</td>
</tr>
<tr>
<td>Exposures</td>
<td></td>
<td>Gestational diabetes mellitus</td>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td>Primary outcome measures</td>
<td>Plasma glucose cutoffs for GDM diagnosis based on capillary sampling</td>
<td>Time in active labor</td>
<td>Time in active labor and indications for cesarean section</td>
</tr>
<tr>
<td>Statistics</td>
<td>Descriptive statistics, Passing-Bablock regression analysis, Bland-Altman plots, Spearman’s rank correlation coefficient (r), sensitivity, specificity, positive and negative predictive values, accuracy, likelihood ratios, coefficient of variation</td>
<td>Descriptive statistics, Mann-Whitney U-test, Kaplan-Meier survival analysis, Cox regression analysis, logistic regression analysis</td>
<td>Descriptive statistics, Mann-Whitney U-test, Kaplan-Meier survival analysis, Cox regression analysis</td>
</tr>
</tbody>
</table>

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DATA SOURCES

The Swedish Pregnancy Register

Data in studies II and III were retrieved from the Swedish Pregnancy Register (SPR) \(^{30}\). The SPR is a national quality register established in 2013. The register collects data on pregnancy and childbirth, from the first visit at the antenatal care clinic to the follow-up visit, which usually occurs around 6-12 weeks postpartum. The SPR contains information on maternal characteristics, pregnancy complications, and data on labor and birth. In 2022, 98.7% of all deliveries in Sweden were registered in the SPR. The coverage rate in 2014 was 85%. The majority of the variables included in the register are continuously transferred electronically from the medical antenatal and labor records. Some variables are registered manually by the midwives at the antenatal care clinics \(^{30}\).

Medical records

For study I, background data was collected from the Obstetryx\(^{®}\) Cerner, an electronic medical record system used by midwives, obstetricians and pediatricians working in prenatal, delivery and perinatal care. The records include maternal demographic and health data, prenatal maternal diagnoses and prospectively registered information from early pregnancy until after delivery. The data include both documentation in free text and documentation using standardized prewritten checkboxes to fill in.
STUDY DESIGN, POPULATION AND OUTCOMES

Comparing venous and capillary sampling in oral glucose testing for the diagnosis of GDM using Accu-Chek Inform II (Study I)

Design and population

Study I was a cross-sectional study on diagnostic accuracy conducted at an antenatal care clinic in Linköping, Sweden between March 2017 and January 2019.

The study participants were 175 pregnant women, who had been recommended to take an OGTT.

The criteria for undergoing an OGTT in gestational week (GW) 28-29 were body mass index (BMI) ≥ 30, previously neonate with a birth weight of ≥ 4500 g, family history of type 2 diabetes, previously intrauterine fetal death, polyhydramnios, accelerated fetal growth according to the symphysis-fundal height, and non-European origin. Also, if random capillary P-glucose in GW 10, 25, 29 or 32 was >8.9 to <12.2 mmol/L, the woman was recommended to have an OGTT within the following seven days.

Oral and written information were given and if oral consent was obtained inclusion took place. Women with surgery due to obesity or an inability to understand both spoken and written Swedish were excluded.

Data concerning the women’s age, pre-pregnancy BMI, weight, parity, GW at the time of OGTT and indication for OGTT were manually extracted from an electronic medical record system (Obstetrix, Cerner).

Data were divided into two parts with similar distribution concerning time for inclusion and with similar proportions of samples collected in different sampling orders. The first data-set (n = 88) was used to calculate a conversion factor between venous and capillary P-glucose at fasting, 1 hour and 2 hours after per oral glucose load which was used to correct the capillary P-glucose cut-offs for the GDM diagnosis. The second data-set (n = 87) was used to evaluate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and positive and negative likelihood ratios (LHR).

Outcomes

- Mean differences between capillary and venous sampling using Accu-Chek Inform II to find corrected cut-offs for a GDM diagnosis using capillary samples.

- Evaluation of the corrected cut-offs looking at the sensitivity, specificity, PPV, NPV, accuracy, and positive and negative LHRs.
Blood sample collection and method for analysis

The sampling was carried out in the following sequence: after an overnight fast, duplicate blood samples were collected both by capillary sampling from the side of the third or fourth fingertip and by venous puncture of the ante-cubital vein. The women were numbered from 1–175. For women with odd numbers, capillary samples were taken before the venous samples and for women with even numbers the process was the other way around. The venous samples were collected in vacuum tubes spray-coated with K2 EDTA (Vacutainer™, Becton-Dickinson) and were mixed 10 times by vertical inversion. Within 10 min blood was absorbed on two test strips and immediately analyzed on the Accu-Chek Inform II (Roche Diagnostics Scandinavia AB). A sample volume of 0.6 µL was required. Capillary samples were collected after wiping off two to three drops of blood from the side of the fingertip and measured using an Accu-Chek Inform II. Duplicate samples were taken. Subsequently, 75 g anhydrous glucose dissolved in 200 mL water was given for oral ingestion within five minutes. The sampling and measurement procedures were then repeated after 1 h and 2 h.

Figure 7. Accu-Chek Inform II

The Accu-Chek Inform II is a hand-held device approved for diagnostic use that determines plasma glucose concentration by means of glucose test strips with a measuring range of 0.6–33.3 mmol/L. The glucose results of both the capillary and the venous determination are reported in mmol/L. The test principle of the Accu-Chek Inform II is based on the direct measurement of glucose in the plasma phase using glucose dehydrogenase and pyrroloquinoline quinone as a coenzyme. After further reaction steps, this leads to the formation of electrons which are measured amperometrically by the instrument. The analysis is not dependent on oxygen saturation in the sample and gives reliable results in the hematocrit interval of 0.10–0.65. The calibration of each test strip lot is traceable to the
National Institute of Standard and Technology standards and the reference method is based on isotopic dilution gas chromatography-mass spectrometry (IDGC-MS).

A total of four Accu-Chek Inform II instruments were used. Analytical quality was regularly checked by analysis of internal controls on two levels. The coefficient of variation (CV) calculated for all these instruments during a 12-month period was 4.1% (level: 2.4 mmol/L, \( n = 178 \)) and 2.8% (level: 16.0 mmol/L, \( n = 171 \)). New lots of test strips were checked on three mentor instruments which were also included in an external control program. In this program, results from individual laboratories are compared to values determined by a replicate of analyses on a reference method (IDGC-MS) or a reliable hospital laboratory method. The mean bias during the study period was \(-2.6\%\) (\( n = 50 \)) and all but one sample differed by less than 10% against the reference value. Upon introduction of Accu-Chek Inform II and prior to this study, validation was performed against IDGC-MS at Linköping University Hospital. Thirty plasma samples with different levels of glucose were analyzed on four different meters using one lot of test strips. Analyses were made in duplicates on each glucose meter and by the reference method. The method is based on derivatisation of glucose to its aldonitrile pentaacetate and \(^{13}\)C-glucose is used as an internal standard. Briefly, analysis was performed on a gas chromatograph equipped with a CP-Sil-13 CB WCOT fused silica column (Chrompack International, BC, Middleburg, The Netherlands) and a HP MSD 5970 mass spectrometer (Hewlett-Packard, Palo Alt, CA). Glucose was quantified using the acquisition of ions at \( m/z \) 314.0 and 242.1 for unlabeled glucose and ions at \( m/z \) 319.0 and 246.1 for \(^{13}\)C-labeled glucose.
Time in active labor and indications of cesarean section (Studies II and III)

Design and population

Studies II and III are nationwide population-based (retrospective) cohort studies based on data from the SPR.

Data was collected between 1 January 2014 and 30 May 2020, and all primiparous women who delivered a singleton fetus, \(\geq 34+0\) (completed gestational weeks + additional days) with a singleton pregnancy with a cephalic presentation and had their data available in the SPR were included in the extraction of data.

From the raw SPR data set, we first extracted the data to use in study II. Later, for study III, we did a new extraction of data from the raw SPR data set based on the aims of study III.

In study II, 172,380 women were included in the final study population for analyses of time in active labor and 2978 (1.7%) of these women had GDM after the exclusion of women delivered by elective CS, women with pre-pregnancy diabetes and women with missing or faulty data on start of active labor.

In study III, a total of 167,650 women were included in the final study population for analysis of time in active labor, and 832 (0.5%) of these women had type 1 diabetes. In the study population of elective CS, a total of 6262 women were included, and in this population 115 (1.9%) women had type 1 diabetes.

Flowcharts of how the study populations in study II and III were derived are provided in Figure 8 (study II) and Figure 9 (study III).

Outcomes

- Time in active labor (studies II and III)
- Indications for elective and emergency CS (study III).
Figure 8. Flowchart of the study population in study II
Figure 9. Flowchart of the study population in study III
Time in active labor was defined as the time between the start of active labor and the time of delivery.

The start of active labor was, during the first part of the study period (Jan 2014-March 2015), defined as a cervix dilated three centimeters or more in women with painful regular uterine contractions. During the remainder of the study period, the onset of active labor was defined according to the Swedish nationally recommended definition, which states that at least two out of three of the following criteria must be fulfilled: spontaneous rupture of the membrane, regular painful contractions (2-3/10 minutes), and a cervix dilated four centimeters or cervix effaced and dilated more than one centimeter. In addition to these criteria, the labor should progress within the subsequent two hours. The exposure in study II was the presence of GDM and in study III the presence of type 1 diabetes (pre-pregnancy diabetes).

Since some women have several indications for a CS, two hierarchies of indications were constructed, both for elective and emergency CS, in collaboration with experienced obstetricians at Linköping University Hospital. The aims of the hierarchies were to reflect the clinical relevance of the CS indications for women with type 1 diabetes, ensuring that each woman was counted only once for her most relevant CS indication and to get a clearer view of how the indications are distributed. The clinical relevance of the indication was assessed in regard to women with type 1 diabetes.

The number of CS in each indication group includes CS with that specific indication, but without the indications listed above in the hierarchy. For example, all women with a diagnosis of macrosomia were included in the macrosomia group (as macrosomia was deemed the most clinically relevant indication for CS). Preeclampsia was deemed the second most important indication for CS and the preeclampsia group included women with a diagnosis of preeclampsia but without a diagnosis of macrosomia, and so on.

Table 7. Hierarchies of elective and emergency cesarean section

<table>
<thead>
<tr>
<th></th>
<th>Elective cesarean section</th>
<th>Emergency cesarean section</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fetal macrosomia</td>
<td>Fetal asphyxia</td>
</tr>
<tr>
<td>2</td>
<td>Preeclampsia</td>
<td>Labor dystocia</td>
</tr>
<tr>
<td>3</td>
<td>Small for gestational age (SGA)</td>
<td>Preeclampsia</td>
</tr>
<tr>
<td>4</td>
<td>Placenta previa</td>
<td>Chorioamnionitis</td>
</tr>
<tr>
<td>5</td>
<td>Maternal request</td>
<td>Failed induction</td>
</tr>
<tr>
<td>6</td>
<td>None of the above</td>
<td>None of the above</td>
</tr>
</tbody>
</table>
STATISTICS

Sample size estimation

Study I

To detect a difference in fasting plasma glucose at a minimum of 0.15 mmol/L with a correlation coefficient of 0.7, a standard deviation of 0.9, alpha <0.05 and a power of 0.8, the sample size was determined to be 172 individuals.

Studies II and III

Given that studies II and III are population-based studies, sample size estimation was not necessary.

Descriptive and comparative statistics

Study I

Normal distribution was checked using a Kolmogorov-Smirnov test. Normally distributed data are reported as mean ± SD. The significance of differences between capillary and venous samples was examined by a two-sided paired Student’s T-test. A p-value <0.05 was considered significant. Capillary and venous P-glucose were further compared by a Passing-Bablock regression analysis. Bland-Altman plots were used to assess the analytical performance of the POCT device. Spearman’s rank correlation coefficient (r) was used for calculating the correlation between all venous and capillary P-glucose values. The use of capillary sampling compared to venous sampling was assessed by calculating the sensitivity, specificity, PPV, NPV, accuracy and likelihood ratios based on true positive, false negative, true negative and false positive values. Venous P-glucose was considered as the standard (true positive) since recommended cut-offs are based on venous sampling. The imprecision of P-glucose measured in capillary and venous samples was calculated from the values of duplicate samples using Dahlberg’s formula, and it is presented as relative standard deviation (CV%).

Study II and III

Categorical data was presented as number and percent. Continuous, not normally distributed, data was presented as median with quartiles and inter quartile ranges IQR. The descriptive, overall differences in time in active labor were evaluated using the Mann-Whitney-U-test.
The outcome time in active labor was assessed using Kaplan-Meier survival analyses in women with spontaneous labor onset and women with induced labor, respectively. Graphs were produced to illustrate the association between GDM (study II) or type 1 diabetes (study III) and time in active labor, taking censoring due to emergency CS into account when applicable. Cox regression analyses were performed, and graphs were produced to illustrate the association between GDM (study II) or type 1 diabetes (study III) and time in active labor taking censoring due to emergency CS into account (when applicable) and adjusting for confounding factors. Several factors were considered possible confounders and mediators and were assessed using a directed acyclic graph. Figure 10 illustrates the directed acyclic graph (DAG) used in study II:

![Directed Acyclic Graph](image)

**Figure 10.** Gestational diabetes mellitus and time in active labor – a directed acyclic graph to define and display confounders (purple) and mediators (green)

Adjustments were made for maternal BMI in early pregnancy, smoking in early pregnancy, maternal age at delivery and gestational week at delivery in study II. Birthweight was considered a mediator. Furthermore, the impact of maternal height was evaluated in study II. In study III, adjustments were made for maternal BMI in early pregnancy, smoking in early pregnancy, maternal age at delivery, gestational week at delivery and induction of labor. From the Cox regression analyses, we calculated the hazard ratio (HR) and adjusted hazard ratio (aHR) for the risk of an event i.e., vaginal delivery at a specific time-point. In study II, time in active labor was also studied using multivariable logistic regression analyses to estimate the crude (OR) and adjusted (aOR) odds ratio for time in active labor ≥12 h compared with <12 h in women with GDM and
women without diabetes. In these multivariable analyses, adjustments were made for BMI, maternal age at delivery, smoking and gestational week at time of delivery. Drop-out analyses on trial of labor deliveries were made to compare women with and without available data on the start of active labor. Chi-2 analyses were used to calculate the overall heterogeneity within each domain. A p-value <0.05 was considered statistically significant. Data were obtained from the SPR and de-identified, with no direct participation of patients; hence, informed consent was waived.

**Software used**
The statistical analyses in study I-III were performed using IBM SPSS version 28 (IMB Inc, Armonk, NY).

**ETHICAL APPROVAL AND CONSIDERATIONS**
The studies in this thesis were approved by the Regional Ethical Review Board in Linköping, Sweden (Study I: Dnr 2016/498-32 and Study II and III: Dnr 2018/464-31).

Every research endeavor necessitates ethical contemplation and consideration according to the Helsinki Declaration, particularly in cases where human subjects are involved.

Before commencing a study, it is crucial to take into account another ethical aspect, which is the significance and worth of the conducted studies. Study I was believed to contribute valuable knowledge that could have immediate clinical implications. As for Studies II and III, they could be regarded as providing pieces of information that is anticipated to have future clinical implications. In every study, it is crucial to protect the confidentiality of the individuals involved in the research and to reduce potential intrusion into the privacy of those individuals. The studies included in this thesis presented different kinds of ethical considerations.

In study I, all participants were provided with comprehensive written and verbal information, and upon giving oral consent, they were enrolled in the study. All women who were included in the study had already been scheduled to undergo an oral glucose tolerance test (OGTT) and consequently, had their blood samples collected. Nonetheless, in the context of the comparison between capillary and venous sampling in study I, a greater number of blood samples were obtained compared to the usual routine. Furthermore, it is not possible to rule out the risk
that a patient who consented to take part in the study felt a sense of duty toward the researchers to take part.

Data in studies II and III were obtained from the SPR and de-identified, with no direct participation of patients; hence, informed consent was waived. In general, research on personal health using data maintained in large registers does not require informed consent. Inclusion of data in the SPR does not require consent from the patients and participation in the register is voluntary.
RESULTS

COMPARING VENOUS AND CAPILLARY SAMPLING IN ORAL GLUCOSE TESTING FOR THE DIAGNOSIS OF GDM USING ACCU-CHEK INFORM II (STUDY I)

Capillary P-glucose measured by the Accu-Chek Inform II was significantly higher than venous P-glucose at fasting (4.99 ± 0.41 vs. 4.77 ± 0.41, p < 0.001), 1 h (8.38 ± 1.71 vs. 7.26 ± 1.70, p < 0.001), and 2 h (7.11 ± 1.61 vs. 6.21 ± 1.61, p < 0.001). The glucose values represent means from duplicate measurements and were normally distributed.

Using the first data set, the differences between venous and capillary P-glucose at all-time points were determined by Bland-Altman plots. The mean differences were 0.22 mmol/L (95% CI: 0.18–0.27) at fasting, 1.12 mmol/L (95% CI: 0.99–1.26), at 1 h and 0.87 mmol/L (95% CI: 0.76–0.98) at 2 h after OGTT. Based on these findings, the cut-offs for a GDM diagnosis using capillary samples were corrected from 5.1 to 5.3 mmol/L, 10.0 to 11.1 mmol/L, and from 8.5 to 9.4 mmol/L for the fasting, 1 h, and 2 h samples, respectively.

The Bland-Altman plots are seen in Figure 11 a-c.
Figure 11. Bland Altman Plots of capillary and venous P-glucose in the first data. (a) set in fasting (n = 88); (b) set at 1 h (n = 87); (c) set at 2 h (n = 87).
The second data set was used to evaluate the corrected cut-offs obtained from the first data set by calculating the sensitivity, specificity, PPV, NPV, accuracy, and positive and negative LHRs, which are shown in Table 8.

Table 8. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and positive and negative likelihood ratios (LHR) for corrected cut-offs in capillary sampling with venous sampling considered as the standard (true positive).

<table>
<thead>
<tr>
<th>Test Corrected Cut-offs for Capillary Samples</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
<th>LHR (positive)</th>
<th>LHR (negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting*</td>
<td>81.0</td>
<td>95.4</td>
<td>85.0</td>
<td>94.0</td>
<td>92.0</td>
<td>17.8</td>
<td>0.2</td>
</tr>
<tr>
<td>1 h²</td>
<td>71.4</td>
<td>97.4</td>
<td>71.4</td>
<td>97.4</td>
<td>95.2</td>
<td>27.5</td>
<td>0.3</td>
</tr>
<tr>
<td>2 h³</td>
<td>100</td>
<td>98.7</td>
<td>85.7</td>
<td>100</td>
<td>98.8</td>
<td>77</td>
<td>0.0</td>
</tr>
<tr>
<td>Fasting, 1 hour* and 2 hours²</td>
<td>88.1</td>
<td>92.5</td>
<td>78.7</td>
<td>96.1</td>
<td>91.4</td>
<td>16.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Fasting* and 2 hours²</td>
<td>85.0</td>
<td>95.0</td>
<td>83.0</td>
<td>96.0</td>
<td>90.3</td>
<td>16.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

* ≥5.3 mmol/l; h; ≥11.1 mmol/l; * ≥9.4 mmol/l.

Passing–Bablock regression applied on venous and capillary P-glucose found a positive intercept for capillary samples at all time points in accordance with calculated mean differences. The number of women diagnosed with GDM in relation to different sampling methods and time points is seen in table 9.

Table 9. Number of women diagnosed with gestational diabetes mellitus in relation to sampling method and OGTT time points (n = 175).

<table>
<thead>
<tr>
<th></th>
<th>Fasting Sample n (%)</th>
<th>One-hour Sample n (%)</th>
<th>Two-hour Sample n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous samples</td>
<td>36</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Capillary samples*</td>
<td>35</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Cumulative number venous samples</td>
<td>36 (20.6)</td>
<td>40 (22.9)</td>
<td>44 (25.1)</td>
</tr>
<tr>
<td>Cumulative number capillary samples*</td>
<td>35 (20.0)</td>
<td>44 (25.1)</td>
<td>47 (26.9)</td>
</tr>
<tr>
<td>Cumulative number venous samples *</td>
<td>36 (20.6)</td>
<td>X</td>
<td>40 (22.9)</td>
</tr>
<tr>
<td>Cumulative number capillary samples *</td>
<td>35 (20.0)</td>
<td>X</td>
<td>41 (23.4)</td>
</tr>
</tbody>
</table>

* Corrected cut-offs were used for capillary samples; †Not taking the 1 hour sample in to account.
When looking at using both capillary and venous sampling with the corresponding cut-offs for the diagnosis, 30 women in fasting + 3 women at 1-h + 4 women at 2-h, in total 37 women, exceeded both the corresponding cut-offs. This shows the unique individuals who would have received the diagnosis of GDM using both capillary and venous sampling using the corresponding cut-offs.
TIME IN ACTIVE LABOR (STUDIES II AND III)

In study II, 172 380 women were included in the final study population for analyses of time in active labor after the exclusion of women delivered by elective CS, women with pre-pregnancy diabetes and women with missing or faulty data on start of active labor. In the final study population, 2978 (1.7%) women had GDM.

More women with GDM were obese (33.3% versus 8.9%), had induced labor (21.2% versus 10%) and gave birth to an LGA infant (7.3% versus 2.0%) compared to women without diabetes.

In study III, a total of 167 650 women were included in the final study population for analyses of time in active labor, and 832 (0.5%) of these women had type 1 diabetes. In the group of women with type 1 diabetes going into trial of labor, 26.2% gave birth to an LGA infant as compared to 2.0% in the group of women without diabetes. In the study population of elective CS, a total of 6262 women were included, and in this population, 115 (1.9%) women had type 1 diabetes.

Time in active labor, both in spontaneous onset of labor and in induction of labor of the study populations in both studies II and III are seen in Table 10.

Table 10. Time in active labor in study II and study III

<table>
<thead>
<tr>
<th></th>
<th>Women with GDM (study II) n= 2347</th>
<th>Women without diabetes (study II) n= 152508</th>
<th>Women with pre-pregnancy diabetes (study III) n= 546</th>
<th>Women without diabetes (study III) n= 150283</th>
</tr>
</thead>
</table>

Women with GDM had an increased risk for a time in active labor ≥12 h compared to women without diabetes, both in spontaneous onset of labor (aOR 1.14 (1.04-1.25)), and in induction of labor (IOL) (aOR 1.55 (1.28-1.87)).
The Cox regression analyses in study II, adjusted for confounders and taking censoring due to emergency CS into account, showed that women with GDM had a significantly longer time in active labor compared to women without diabetes. This applied both to women with a spontaneous onset and induced labor. (Figure 12 and Figure 13).

Figure 12. Cox regression analysis of time in active labor in women with gestational diabetes mellitus compared to women without diabetes in spontaneous labor onset
Adjustments were made for maternal body mass index, maternal age, smoking in early pregnancy and gestational week at delivery

\[ aHR = 0.92 \ (0.88-0.96) \]
Figure 13. Cox regression analysis of time in active labor in women with gestational diabetes mellitus compared to women without diabetes in induction of labor
Adjustments were made for maternal body mass index, maternal age, smoking in early pregnancy and gestational week at delivery

In study III, the Kaplan-Meier survival curves, taking censoring due to emergency CS into account, showed that women with type 1 diabetes had a significantly longer time in active labor compared to women without diabetes. This applied for both spontaneous onset and induced labor (Figure 14 and Figure 15).
The Cox regression analyses, adjusted for confounders and taking censoring due to emergency CS into account, also showed that women with type 1 diabetes had a significantly longer time in active labor (Figure 16).
Figure 14. Kaplan-Meier survival analysis of time in active labor in women with pre-pregnancy diabetes compared to women without diabetes in spontaneous labour onset

Figure 15. Kaplan-Meier survival analysis of time in active labor in women with pre-pregnancy diabetes compared to women without diabetes in induction of labour
Figure 16. Cox regression analysis of time in active labor in women with pre-pregnancy diabetes compared to women without diabetes

Adjustments were made for maternal body mass index, maternal age, smoking in early pregnancy, gestational week at delivery and induction of labor

\[ aHR = 0.65 \ (0.60-0.70) \]
The total rate of CS (both elective and emergency) was 34.6% in the group of women with type 1 diabetes and 9.5% in the group of women without diabetes. The most common indication for elective CS was suspected fetal macrosomia in the group of women with type 1 diabetes (50.4%) whereas the corresponding elective CS rate for suspected fetal macrosomia among women without diabetes was 8.7%. For emergency CS, the most common indication was fetal distress in the group of women with type 1 diabetes (31.9%) and the corresponding CS rate for fetal distress in the group of women with no diabetes was 35.9%. The indications and rates for elective and emergency CS are seen in Table 11 and Table 12 and are reported based on the constructed hierarchies.

Table 11. Indications and rates of elective cesarean section in women with pre-pregnancy diabetes and women without diabetes (only cephalic presentation)

<table>
<thead>
<tr>
<th></th>
<th>Pre-pregnancy diabetes N=1546 n (%)</th>
<th>No diabetes N=237056 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective cesarean section</td>
<td>115 (7.4)</td>
<td>6147 (2.6)</td>
</tr>
<tr>
<td>Indications for elective cesarean section</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrosomia</td>
<td>58 (50.4)</td>
<td>535 (8.7)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>15 (13.0)</td>
<td>266 (4.3)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>2 (1.7)</td>
<td>186 (3.0)</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>1 (0.9)</td>
<td>334 (5.4)</td>
</tr>
<tr>
<td>Maternal request</td>
<td>24 (20.9)</td>
<td>3571 (58.1)</td>
</tr>
<tr>
<td>Other indications than above*</td>
<td>15 (13.0)</td>
<td>1255 (20.4)</td>
</tr>
</tbody>
</table>

* For example: Previous surgery to the uterine wall, pelvic reservoir, non-reassuring fetal heart rate, unstable fetal position, or other intercurrent illness as indications for CS
Table 12. Indications and rates for emergency cesarean section in women with pre-pregnancy diabetes and women without diabetes (only cephalic presentation)

<table>
<thead>
<tr>
<th></th>
<th>Pre-pregnancy diabetes N=1546 n (%)</th>
<th>No diabetes N=237056 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency cesarean section</td>
<td>420 (27.2)</td>
<td>16304 (6.9)</td>
</tr>
<tr>
<td><strong>Indications for emergency cesarean section</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal distress</td>
<td>134 (31.9)</td>
<td>5858 (35.9)</td>
</tr>
<tr>
<td>Obstructive labor/Labor dystocia</td>
<td>91 (21.7)</td>
<td>5620 (34.5)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>103 (24.5)</td>
<td>1341 (8.2)</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>1 (0.2)</td>
<td>88 (0.5)</td>
</tr>
<tr>
<td>Failed induction</td>
<td>8 (1.9)</td>
<td>229 (1.4)</td>
</tr>
<tr>
<td>Other indications than above*</td>
<td>83 (19.8)</td>
<td>3168 (19.4)</td>
</tr>
</tbody>
</table>

*For example; maternal request, placental abruption, umbilical cord prolapse, insufficient pain relief
DISCUSSION

METHODOLOGICAL CONSIDERATIONS

Systematic and random errors

In observational cohort studies, the internal validity (the degree to which the results of a study are correct for the specific study patients included) can be affected by two types of errors: systematic errors (bias) and random errors (chance). The risk for random errors can be reduced by increasing the sample size/study population, whereas systematic errors (bias) still persist. Common types of bias in observational studies include selection bias, information bias and confounding bias.

Selection bias

Selection bias occurs when individuals or groups in a study differ systematically from the population of interest, leading to a systematic error in an association or outcome. In study I, women who did not understand Swedish in speech or writing were excluded from the study. These women represent a group with marked increased risk of GDM, and not including these women could indicate selection bias in this study. Including these women probably would have led to a higher prevalence of GDM in the study population with a subsequent effect on PPV and NPV. The population-based designs with large study populations in studies II and III decrease the likelihood of selection bias. Women going into trial of labor who were delivered by emergency CS were censored and contributed with their time in active labor until censoring, hence avoiding the selection bias of only investigating time in active labor of women who reached vaginal delivery.

Information bias

Information bias occurs when any data or information collected in a study is measured or recorded inaccurately. It is also affected by the degree of missing data in the study population. Common types of information bias are misclassification bias, observer bias, recall bias and reporting bias.

In large registers, like the SPR used in studies II and III, there is always a risk of errors in recorded data and missing values. In our studies, 27.8% (study II) and 27.9% (study III) of the women had missing data on the start of active labor and were therefore also excluded from the final study population for analysis of time in active labor. The variable start or onset of active labor is a variable that is
manually registered in the electronic charts and then automatically transferred to SPR. However, there is no reason to suspect that the degree of underreporting of this variable changes depending on whether you have GDM/type 1 diabetes or not. Speculatively, the variable of time of start of active labor could be reported in a lesser extent among women who come to the delivery ward already far progressed in labor.

Drop-out analyses and characteristics of the women who had missing data on the start of active labor were made in both studies to avoid attrition bias, e.g. systematic differences between the ones who “leave” the study and those who continue. The drop-out analyses did not show any clinically relevant demographic difference.

**Confounding and colliding bias**

A confounding variable increases the probability of the exposure and independently alters the outcome, thereby creating the illusion of an association between the exposure and the outcome when there is none or concealing a true association. It is important to reduce the effects of known possible confounders, although the possibility of unknown confounders always remains, as they cannot be accounted for.

When a third variable is caused independently by both an exposure and an outcome, it is referred to as a collider. The act of inappropriately controlling for a collider variable, whether through study design or statistical analysis, leads to what is known as collider bias. This bias can result in a distorted association between the exposure and outcome, even in the absence of any actual association. This type of bias is primarily observed in observational studies.

A causal DAG can be helpful in identifying possible sources of bias. A causal DAG is a graph with arrows indicating the direction of hypothesized causal effects. The absence of cycles in causal DAGs is due to the fact that causality implies a time order from cause to effect (for instance, the presence of GDM may impact the duration of active labor, but the duration of active labor cannot subsequently affect the presence of GDM before that time). Thus, causal DAGs are directed and acyclic.

Causal DAGs serve to visually represent potential causal pathways that can potentially influence the relationship between patient exposures or treatments and clinical outcomes. These graphs aid in identifying sources of bias, such as confounders and colliders, as well as methods to adjust for them.
The effect of $E$ on $O$, which is being estimated, is represented by the directed paths. To eliminate bias, one can reduce it by adjusting or controlling for confounders in order to close the nondirected path. On the contrary, if the nondirected path includes a collider and is left uncontrolled, it is closed and does not introduce bias. However, if one controls for a collider, it opens that path and may introduce bias.

Causal DAGs offer an illustration of assumptions that may or may not be accurate; nevertheless, they provide researchers with the chance to determine which possible effects should be taken into account. Causal DAGs do not reveal the extent of biases or how they interact with random errors. Moreover, causal DAGs can become very intricate and complex, as a reflection of the real-life concerns about potential sources of bias.

In studies II and III, we used Kaplan-Meier survival analysis to investigate the crude cumulative survival between exposure groups. However, Kaplan-Meier survival analysis does not allow for adjustments of confounders. To adjust for confounders in the survival curves, we used Cox regression analysis. Cox proportional hazard regression attempts to find a hazard ratio that is independent of time. The hazard rate can be thought of as the probability of transitioning at time $t$, given that you made it to $t$. The hazard ratio is a contrast between two hazard rates.

Figure 17. Example of a directed acyclic graph including directed and nondirected paths
The founders adjusted for in studies II and III, maternal BMI, maternal age and smoking, all have known effects on both exposure (GDM/type 1 diabetes) and on the outcome time in active labor. Furthermore, the study population was restricted to nulliparous women to rule out the effect of parity and to ensure that each woman contributed only once in the Cox regression models.

In studies II and III we also decided to adjust for gestational week at delivery, even though it was considered to be a mediator. Mediators are part of a directed path, and thus, controlling for them in the analysis removes part of the effect of exposure. We chose to make this adjustment anyway because we wanted some kind of estimate on the fetal effect on the time in active labor, even though considered a mediator.

**Random errors**

Random errors are caused by variations in the data as a result of chance. Statistics can be employed to approximate the degree to which chance contributes to the outcomes observed in a study.

A type I error means concluding that there is a difference between groups when in fact there is no difference (=false positive). The probability or risk of making a type I error is equivalent to the significance level (alpha or \( \alpha \)), or p-value, which is usually set to \(<0.05\)\(^{116}\).

A type II error occurs when we conclude that there is no difference, when in fact there is a difference (=false negative). The probability or risk of making a type II error (beta or \( \beta \)) is usually set to 20% (0.2) which means that the probability of a test not being able to detect a true difference is 20%. The statistical power derives from the type II error rate (1- \( \beta \)) and describes to which extent a test can correctly detect a difference when there in fact is one. A power of minimum 80% is usually considered adequate\(^{116}\).

In order to minimize the risk of random errors, it is important to make sure you have an adequate sample size. To calculate the appropriate sample size for a study, the type I error rate (\( \alpha \)), the type II error rate (\( \beta \)) or statistical power (1-\( \beta \)), the smallest effect size or difference of clinical interest and the nature of the data need to be addressed. Nature of data could include the variability of the outcome (often estimated and expressed as standard deviation) and the frequency of the expected outcome.

Large study populations, as in studies II and III, reduce the risk of random errors, but on the other hand small differences can turn out to be statistically significant but lack clinical relevance.
In study I, we calculated the sample size to 172 individuals to detect a difference in fasting plasma glucose at a minimum of 0.15 mmol/L with a correlation coefficient of 0.7, a standard deviation of 0.9, alpha <0.05 and a power of 0.8. If we had increased the sample size, we would have reduced the risk of random errors even further, but from an ethical point of view in means of recruiting patients, this was not applicable.

**External validity**

External validity refers to the generalizability of a study or how the results may be applied to other individuals or settings. The results from study I suggest that the method of capillary sampling using Accu-Chek Inform II can be used in a similar setting, and also in low-resource settings where the means of minimizing glycolysis are small.

As study II and study III consist of large cohorts, the findings from these studies can be applied to the Swedish population or similar populations and settings. The definition of active labor was not the same during the study period, although in clinical practice there are no huge differences between these definitions of start of active labor. However, we cannot exclude the possibility that the different definitions influenced the results. Our definition of start of active labor may also affect the generalizability of the present study, especially in light of new definitions of the onset of active labor and labor progression. Hence, these findings cannot be generalizable to other populations and countries that have different criteria for determining the start of active labor.

In regards to analyzing the effect of GDM on time in active labor, one must take into account that, as described earlier, the definition and diagnostics of GDM have great variation worldwide. On the other hand, the heterogeneity of our population of women with GDM in study II could be seen as a strength in terms of generalizability.
DISCUSSION OF FINDINGS IN STUDY I-III

Diagnostics

A significant cause of pre-analytical error in the measurement of glucose is the loss of glucose from blood samples due to glycolysis \(^{117}\). The rate at which glucose is lost from whole blood samples at room temperature is estimated to be approximately 5%–7% per hour \(^{117}\).

In 2011, the American Association for Clinical Chemistry and ADA provided a guideline on laboratory testing in diabetes and recommended that samples be immediately immersed in an ice slurry and analyzed within 30 min of collection \(^{117}\). These guidelines were updated in 2023 and the new recommendations concerning pre-analytical handling to minimize glycolysis includes using a tube containing a rapidly effective glycolytic inhibitor such as granulated citrate buffer (citrate/fluoride/EDTA (CFE)) for collecting the sample. If this cannot be achieved, the sample tube should immediately be placed in an ice-water slurry and subjected to centrifugation to remove the cells within 15 to 30 min. Tubes with only enolase inhibitors such as sodium fluoride should not be relied on to prevent glycolysis and are not recommended \(^{46}\).

The authors did not recommend portable glucose meters to be used in the diagnosis of diabetes, including gestational diabetes mellitus \(^{46}\).

In connection to conducting study I, in addition to collecting capillary and venous samples for analysis on Accu-Chek Inform II, we also retrieved venous samples for analysis using the hospital laboratory method, Cobas c701. In this “spin-off” study from study I, we aimed to evaluate the accuracy of the POCT instrument Accu-Chek Inform II compared to the central laboratory instrument Cobas c701 for measurement of venous P-glucose in OGTT during pregnancy. The study also included evaluation of the impact of sampling tubes with EDTA, used for analysis on Accu-Chek Inform II, and sampling tubes with citrate/fluoride/EDTA mix tubes, used for analysis on Cobas c701. A further aim was to compare the rate of GDM diagnosis for the two diagnostic procedures \(^{118}\).

Surprisingly, the bias between methods was 8%, resulting in a large discrepancy in the proportion of women diagnosed with GDM; 25% based on glucose results from Accu-Chek Inform II compared to 55% based on Cobas c701. The way the women diagnosed with GDM were distributed in relation to analytical method and OGTT time points is seen in Table 13.
Table 13. Number of women diagnosed with gestational diabetes mellitus in relation to analytical method and OGTT time points (according to WHO 2013 cut-offs)

<table>
<thead>
<tr>
<th>Methods</th>
<th>Fasting sample</th>
<th>1-h Sample</th>
<th>2-h Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accu-Chek Inform II</td>
<td>36 (20.6)</td>
<td>11 (6.3)</td>
<td>11 (6.3)</td>
</tr>
<tr>
<td>Cobas c701</td>
<td>88 (50.3)</td>
<td>27 (15.4)</td>
<td>26 (14.9)</td>
</tr>
<tr>
<td>Cumulative incidence</td>
<td>36 (20.6)</td>
<td>46 (26.9)</td>
<td>44 (25.1)</td>
</tr>
<tr>
<td>Accu-Chek Inform II</td>
<td>88 (50.3)</td>
<td>94 (53.7)</td>
<td>96 (54.9)</td>
</tr>
<tr>
<td>Cobas c701</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative incidence</td>
<td>36 (20.6)</td>
<td>X</td>
<td>40 (22.9)</td>
</tr>
<tr>
<td>Accu-Chek Inform II (not taking the 1-hour sample in to account)</td>
<td>88 (50.3)</td>
<td>X</td>
<td>92 (52.6)</td>
</tr>
</tbody>
</table>

Using venous blood from pregnant women, the POCT system Accu-Chek Inform II showed a satisfactory imprecision and trueness. However, the Cobas c701 showed a bias of approximately 5% against the reference method, which is far more than the desirable bias of <2.6%. The lack of accuracy has great implications for over- or under-diagnosing GDM.

The implementation of more stringent and lower thresholds of P-glucose in the diagnosis of GDM raises concerns about the dependability of analytical techniques. One might question if the laboratory methods, whether they are hospital-based or point-of-care methods, could meet the requirements of accuracy and precision necessary for identifying pregnant women with GDM. It is imperative that the accuracy of the glucose method used for diagnostic purposes is validated, regardless of whether it is employed in a POCT or hospital setting.

There are several advantages to capillary sampling, as it is easier to perform and requires simpler equipment. By using POCT, errors caused by glycolysis due to delayed measurement at a laboratory are reduced. The test result is also instantly available to facilitate further decision-making and to allow the possibility of starting treatment at once.\textsuperscript{119}

When using a selective screening approach based on risk factors, there is a relatively high chance of detecting GDM in the women who undergo screening. It is crucial not to miss any cases since the perinatal risks associated with GDM are reduced by treatment. The drawback of receiving a false-positive diagnosis can be considered minor since the treatment is based on advice and recommendations regarding a healthy lifestyle and eating habits.

Sensitivity and specificity reveal the ability of a test to identify true positives (sensitivity) and true negatives (specificity). From a clinical point-of-view and patient-centered perspective, likelihood ratios can be a more clinically relevant way to look at diagnostic tests. A test’s ability to rule-in (using positive LHR) or
rule-out (using negative LHR) a disease are determined by both the sensitivity and the specificity. In study I, the ability to rule-in the diagnosis of GDM was high using the fasting sample and the 2 h sample given the positive LHR of 16.4, which means the impact of a positive result is strong. The negative LHR of 0.2, indicates a moderate impact of a negative result. Since the likelihood ratios remained unchanged when including only fasting values and 2-h values compared to when using fasting, 1 h and 2 h samples, this could implicate that using the approach of fasting samples in combination with the 2 h sample could be a reasonable option. Further, the accuracy for using the fasting and 2 h samples with corrected cutoffs for capillary samples in study I is high, and the number of women receiving the diagnosis of GDM is almost identical in both sampling methods (40 versus 41 women).

**Hyperglycemia in pregnancy and duration of labor**

In our studies, both women with GDM and women with type 1 diabetes seem to spend longer time in active labor than their non-diabetic counterparts. Previous studies regarding hyperglycemia in pregnancy and duration of labor are limited and show conflicting results. Additionally, it is hard to extrapolate these results since women with GDM and pre-pregnancy diabetes have often been studied together and women undergoing emergency CS have been excluded. One might speculate that the prolonged duration of active labor we have seen in studies II and III could be part of the intricate explanation for the increased risk for CS seen in women with hyperglycemia in pregnancy.

Al Qathani et al. studied myometrial contractility on lower uterine segment biopsies from women with and without diabetes (both pre-pregnancy diabetes and GDM) undergoing elective CS. They found that women with diabetes had less uterine muscle mass, reduced calcium channel expression, reduced intracellular calcium and a decreased contraction amplitude and duration in vitro, which may be translated into inferior uterine contractility. The authors conclude that these factors significantly contribute to the increased emergency CS rate in patients with diabetes.

An alternative possibility is that metabolic disturbances associated with diabetes, such as hyperglycemia, may impede labor progression by affecting arachidonic acid metabolism. Hyperglycemia is known to affect levels of arachidonic acid, as well as several prostaglandin metabolites. The regulation of arachidonic acid metabolism is thought to be critical for labor progression, with differential expression during gestation and parturition for arachidonic acid and its prostaglandin metabolites.

Factors affecting labor duration present a picture of great complexity that goes beyond just the four Ps (power, passage, passenger, and psyche). Regarding women with type 1 diabetes, who bear the highest risks for adverse outcomes of
women with hyperglycemia in pregnancy, several researchers have studied factors affecting the mode of delivery. Kruijt et al suggested that planned vaginal delivery was associated with a lower rate of adverse perinatal outcomes compared to elective CS, with no difference in the rates of adverse maternal outcome, and that IOL could be a viable option. Another study found that pre-pregnancy body weight, gestational weight gain, and the accuracy of the prediction of fetal macrosomia were considered potentially modifiable risk factors for cesarean delivery. Fisher et al studied 204 women (118 women with type 1 diabetes, 86 with type 2 diabetes) and found that nulliparity, the presence of a hypertensive disorder, previous CS and a shorter maternal height were predictors of emergency CS in women with a planned trial of labor. Women scheduled for a elective CS were characterized by poorer glycemic control and higher estimated fetal size than those offered a trial of labor.

Indications for cesarean section

Suspected fetal macrosomia was the most common indication for elective CS among women with type 1 diabetes in study III. However, we do not know if the neonates born after CS performed due to this indication in fact had macrosomia at birth. The definition of fetal macrosomia varies between 4000 and 4500 g internationally, and is different from the term LGA which reflects the fetal growth in relation to gestational week. In Sweden, LGA is defined as birth weight above two standard deviations in relation to gestational week and sex using the Swedish growth charts. The prediction of fetal macrosomia has proved to be difficult. In term pregnancies, estimated fetal weight by ultrasound over-diagnosed macrosomia up to 70% of the time in one study. In the same study, over 80% of the neonates delivered by CS for the indication of suspected macrosomia weighed less than 4500 g, suggesting that some of the CS were unnecessary or the indication of macrosomia was incorrect.

It is also noted, that in the group of women with type 1 diabetes going in to trial of labor in our study III, 26.2% of the neonates were born LGA and 27.9% weighed more than 4000 g. The corresponding figures in women without diabetes in study III was 2.0% (LGA) and 13.1% (≥ 4000 g). The management of women with type 1 diabetes with suspected fetal macrosomia and/or LGA represents a difficult challenge in contemporary obstetrics, especially when it comes to the mode of delivery.

In the absence of more effective indicators for predicting the success of vaginal delivery, ACOG suggested that elective CS should only be considered for estimated fetal weights exceeding 5000 g or 4500 g in diabetic patients. The decision to plan for cesarean delivery in cases of fetal macrosomia is primarily based on expert opinion and necessitates a thorough discussion with the patient.
regarding the risks and benefits of both vaginal and cesarean delivery\textsuperscript{127}. According to the currently available evidence, the most reliable way to assess feto-pelvic adequacy is through a proper trial of labor\textsuperscript{127,130}. 
CLINICAL IMPLICATIONS

Based on the studies in this thesis, the following clinical implications may be drawn:

- The findings from study I using capillary sampling using Accu-Chek Inform II and corrected cut-offs, have led to a change in clinical practice in the region of Östergötland, Sweden. Currently, in the antenatal care units in Östergötland, women undergoing an OGTT are subjected to capillary sampling and the consequent diagnosis of GDM is based on the corrected cut-offs found in study I.

- Women with GDM seemed to have a longer time in active labor than women without diabetes. When looking at the extra time in active labor per woman the difference might seem small from a clinical perspective. However, looking at it from the perspective of the potential total clinical impact of the entire, continuously increasing, group of women with GDM, the difference becomes more clinically relevant.

- Women with type 1 diabetes also spend a longer time in active labor than their non-diabetic counterparts which should be considered in the total context when making clinical decisions during delivery.

- Fetal macrosomia was the main reason for elective CS in women with type 1 diabetes, but the prevalence of LGA and neonates with a birthweight ≥4000 g was also high in the group of women with type 1 diabetes going into trial of labor. These findings highlight the clinical challenge that suspected fetal macrosomia in diabetic patients presents in contemporary obstetrics, and needs to be addressed further.
CONCLUSIONS

Based on the studies included in this thesis the following conclusions may be drawn:

- We suggest that capillary fasting and 2 h P-glucose samples analyzed on the Accu-Chek Inform II could be used for the diagnosis of GDM during pregnancy using corrected cut-offs with acceptable accuracy in an antenatal care setting. Duplicate samples are necessary to maintain adequate precision. It is also worth continuing with OGTT when the fasting samples are within a normal range, since more women will receive the diagnosis of GDM.

- Women with GDM seem to have a longer time in active labor, both in spontaneous labor onset and in IOL compared to women without diabetes. To be able to individualize care intrapartum, there is a need for more studies demonstrating the impact of hyperglycemia during pregnancy on outcomes during childbirth. Future studies will show whether the difference in time in active labor between women with GDM and those without diabetes found in the present study persists with new definitions of active labor as well as labor progression.

- Women with type 1 diabetes seem to have a longer time in active labor, both in labor with spontaneous onset and induced labor and were less likely to have a vaginal delivery at any given time compared to women without diabetes. The prolonged time in active labor in women with type 1 diabetes should be considered in the overall assessment when managing women with type 1 diabetes in active labor. Also, to improve the obstetric management of women with type 1 diabetes future studies are needed to investigate factors contributing to the increased risk of CS among this group.

- Among women with type 1 diabetes,macrosomia and fetal distress were the main reasons for elective and emergency CS respectively and needs to be addressed further.

- The results from study III, indicating that type 1 diabetes in pregnancy itself could be a risk factor for a longer time in active labor, could be of interest to all involved professionals to optimize the care of this high-risk group of women before and during pregnancy and in labor.
FUTURE PERSPECTIVES

DIAGNOSTICS

“What is the best test to diagnose diabetes in pregnant women?” was named one of the top 10 research priorities in diabetes and pregnancy according to women, support networks and healthcare professionals in a recent study. The study recognized a need for a more convenient, single, non-fasting test to replace the OGTT in the diagnosis of GDM. As an example, studies have been made concerning the potential of plasma glycated CD59 (pGCD59) as a biomarker for GDM screening. In a study by Bogdanet et al., the authors found that pGCD59 could predict elevated fasting glucose levels with reasonable accuracy in a general population, but had excellent accuracy in the subgroup of women with very high BMI.

A recent randomized control study compared the use of lower glycemic criteria for the diagnosis of GDM to higher glycemic criteria, the primary outcome being the birth of an LGA infant. The criteria for the low glycemic group was a fasting plasma glucose level of ≥5.1 mmol/L, a 1-hour level of ≥10.0 mmol/L, or a 2-hour level ≥8.5 mmol per liter. The criteria in the higher glycemic group was a fasting plasma glucose ≥5.5 mmol/L or a 2-hour level of ≥9.0 mmol/L. The use of the lower glycemic threshold led to a higher percentage of women receiving the diagnosis of GDM (15.3% in the lower glycemic group vs 6.1 % in the higher glycemic group), which in turn led to a greater use of healthcare services in this group. However, the use of lower glycemic criteria was not associated with a lower risk of adverse events or LGA infants.

It is noted, that among the women who had glucose test results that ranged between the lower and the higher glycemic criteria, those who received treatment for gestational diabetes, in comparison to those who did not, there were positive health outcomes for both the mother and infant, such as a reduced number of infants born LGA and less preeclampsia.

In summary, the search for clarity and consensus regarding diagnostics and diagnostic criteria for GDM continues.

HYPERGLYCEMIA IN PREGNANCY AND DURATION OF ACTIVE LABOR

The findings in studies II and III indicate that women with hyperglycemia in pregnancy spend a longer time in active labor. This inevitably raises the
question of whether the hyperglycemia itself has an effect on the myometrial contractility on a cellular level. If so, could this be part of the explanation for the increased risk for CS in women with hyperglycemia in pregnancy? As mentioned in the discussion, Al Qathani et al\textsuperscript{106} studied myometrial contractility on lower uterine segment biopsies from women with and without diabetes (both pre-pregnancy diabetes and GDM) undergoing elective CS. Based on their data and their findings of reduced calcium channel expression, less uterine muscle mass, reduced intracellular calcium and a decreased contraction amplitude and duration in vitro, they suggest that in labor, myometrial activity will be poorer in diabetic patients and this might lead to an increased risk of CS even when controlling for other factors such as obesity and hypertension. The findings remained consistent even when comparing insulin-treated patients with diet-controlled gestational diabetic patients in the analysis of diabetic patients. Whether it occurred spontaneously, with oxytocin, or high K+, the diabetic samples had poorer contractility. The reduction in contractility was probably due to reduced calcium channel expression and signaling. Oxytocin had a similar effect on myometrial force and calcium transients in both non-diabetic and diabetic patients. A study by Liu et al\textsuperscript{133} showed that hyperglycemia induced oxytocin receptor suppression in vitro in human neuron progenitor cells and that this suppression remained during subsequent normoglycemia. Furthermore, their in vivo mouse study showed that maternal diabetes induces oxytocin receptor suppression\textsuperscript{133}. Although this study examined the effect of maternal hyperglycemia on the oxytocin receptor in neuron progenitor cells, theoretically this suppression of the oxytocin receptor could also be the case in myometrial cells. Could maternal hyperglycemia induce oxytocin receptor suppression in the myometrium? All previous studies on different aspects of myometrial contractility have used myometrial biopsies taken during CS\textsuperscript{106,134-136}. One might argue that women undergoing CS, especially elective CS, represent a selected group concerning uterine contractility and that the results might not be generalizable to most women who deliver vaginally. Currently, there is an ongoing pilot study at the University Hospital of Linköping to examine the possibility of taking myometrial biopsies after vaginal delivery. Being able to do this could lead to interesting future perspectives. It could enable comparisons on different aspects of myometrial contractility and oxytocin receptor expression between groups for example non-diabetic vs diabetic, obese vs normal weight or CS vs vaginal delivery, and so on. This could be a complement to further studies regarding the duration of labor.

In light of the new guidelines for intrapartum care released by the WHO in 2018, more studies are indeed needed to evaluate time in active labor, both in low-risk women and in women with higher risks for adverse outcomes to be able to individualize care intrapartum, possibly reduce the risks for adverse events.
and perhaps reach a deeper understanding of labor progression and labor dystocia. Given the wide range of variations in the definition of the start of active labor and the pattern of labor progression, one might argue that the definition of abnormal labor may not be based on an idealized or average labor curve. An upper limit of a distribution of labor duration to determine abnormally slow labor has been suggested \(^{74}\), but this too has its limitations. The WHO recommendations are based on relatively few studies regarding normal labor progression which, in a way, reflects the complexity of the subject. There is a requirement for additional objective indicators and tools to detect the onset of active labor, track labor advancement, and determine when labor duration is associated with maternal and neonatal risk.

One tool to be evaluated for this purpose is the Labour Care Guide (LCG) released by WHO in 2020. The 2020 LCG has not been subjected to any RCT, unlike the WHO 1994 partograph. However, even with its publication and the recommendation for universal implementation, the impact it may have on maternal and neonatal outcomes is still uncertain. The LCG has mainly been developed for women with low-risk pregnancies in low- and middle-income country settings, and it has yet to be tested in high-income settings. The PICRINO-study, a Swedish national, multicenter, stepped-wedge cluster, and randomized trial will start in late 2023 \(^{137}\). This study aims to evaluate the implementation and impacts of using two different guidelines (the LCG and the currently used standard care guideline) and compare outcomes for mother, child, obstetrical complications, birth experience and health economics with respect to neonatal and maternal outcomes.

Women with increased perinatal risks in labor, such as women with diabetes, need to be addressed individually and cannot be expected to fall in to the same category of low-risk women who are included in the studies that constitute the foundation of the new WHO guidelines. However, it is important not only to consider risks, but also to see and consider the positive, healthy factors in women who carry high risks in pregnancy and delivery. On the other hand, low-risk women should also be addressed individually during labor and should not be treated as high-risk when they are not.

It would be interesting to perform further studies regarding labor progression and labor duration under the umbrella of the PICRINO-study and the LCG. An interesting scoop would be to combine studies on the duration of labor and to include myometrial biopsies; however, only the future will reveal if this proves possible.
Diabetes under graviditet – diagnostik samt betydelsen av diabetes för den totala tiden i aktiv förlössning

Högt blodsocker, s.k. hyperglykemi, under graviditet innebär ökade risker för både mor och barn. Riskerna är ökade både i samband med graviditet och förlössning men även på längre sikt. Under graviditet har man ett ökat insulinbehov pga. nedsatt glukostolerans. Om man inte klarar av att öka insulinproduktionen tillräckligt mycket för att svara upp till det ökade behovet så uppstår hyperglykemi. Hyperglykemi under graviditet delas in i diabetes under graviditet samt gestationell diabetes, även kallad graviditetsdiabetes. I begreppet diabetes under graviditet ingår typ 1 och typ 2 diabetes som man vet om redan innan graviditet samt de fall av typ 1 och typ 2 diabetes som upptäcktes under graviditet.

Globalt så uppskattar man att 21.1 miljoner (16.7%) av förlössningarna med levande barn under 2021 var associerade med någon form av diabetes hos mamman. Av dessa var 10.6% p.g.a. diabetes (typ 1 och typ 2) som var känd redan innan graviditeten, 9.1% p.g.a. typ 1 diabetes och typ 2 diabetes som upptäcktes under graviditeten och 80.3% var p.g.a. graviditetsdiabetes.

Graviditetsdiabetes är en av de vanligaste graviditetskomplikationerna över hela världen som ökar i takt med de globala epidemierna av fetma och typ 2 diabetes.

Det är viktigt att diagnostisera graviditetsdiabetes på ett bra och korrekt sätt då riskerna för mor och barn minskar med behandling.


Syftet med den här avhandlingen var att undersöka om det finns en skillnad i förlössningstid mellan förstföderskor med diabetes under graviditet jämfört med
förstföderskor utan diabetes samt att titta på olika orsaker till planerade och akuta kejsarsnitt i gruppen av kvinnor med typ 1 diabetes. Syftet var även att undersöka om det är säkert att använda kapillär provtagningsmen för att ställa diagnosen graviditetsdiabetes för att göra diagnostiken snabb och lättillgänglig för de gravida kvinnorna.

Jämförelse av kapillär och venös provtagningsmen för diagnos av graviditetsdiabetes

Studie I var en tvärsnittsstudie där syftet var att undersöka om man kan använda kapillär provtagningsmen (med stick i fingret) för att diagnostisera graviditetsdiabetes på ett säkert och noggrant sätt. Vi inkluderade 175 kvinnor på en mödrablösovårdscentral i Linköping som hade planerad att genomgå en s.k. glukosbelastning. På alla kvinnor togs både kapillära prover samt venösa prover (stick i armvecket) både fastande samt 1 h och 2 h efter själva glukosbelastningen. Alla prover analyserades på en apparat som mäter blodsocker som heter Accu-Chek Inform II, en så kallad patientnära metod (proverna behöver inte skickas till något laboratorium utan kan analyseras direkt).

Utifrån resultaten på alla prover vi fick in kunde vi korrigera gränsvärdena för diagnosen graviditetsdiabetes. Gränserna för GDM-diagnos med kapillär provtagningsmen korrigerades från 5.1 till 5.3 mmol/L för fastandeprovet, från 10.0 till 11.1 mmol/L för 1 h provet, och från 8.5 till 9.4 mmol/L för 2-h provet. Sedan testade vi den diagnostiska noggrannheten för hur dessa gränsvärden fungerade jämfört med venös provtagningsmen, vilket var standardmetoden (golden standard). Den totala diagnostiska noggrannheten, d.v.s. andelen sant positiva och sant negativa prov jämfört med referensmetoden, var mellan 90.3 – 98.8 % beroende på vilket eller vilka provtagningsstillfällen man tittade på.

Slutsats: Kapillär provtagningsmen med korrigerade gränsvärden kan användas för att diagnostisera graviditetsdiabetes med bibehållen noggrannhet vid användning av Accu-Chek Inform II.

Diabetes hos mamman och hur tiden i aktiv förlossning påverkas


Syftet var att undersöka om det finns en skillnad i förlossningstid mellan förstföderskor med diabetes under graviditet jämfört med förstföderskor utan diabetes samt att titta på olika orsaker till planerade och akuta kejsarsnitt i gruppen av kvinnor med typ 1 diabetes. Tiden i aktiven förlossning definierades som tiden från start av aktiv förlossning tills barnet är fött.

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I studie II jämförde vi kvinnor med och utan graviditetsdiabetes avseende förlossningstid. Vi fann att kvinnor med graviditetsdiabetes spenderar längre tid i aktiv förllossning jämfört med kvinnor utan diabetes och att kvinnor med graviditetsdiabetes har en ökad risk för att spendera ≥12 timmar i aktiv förllossning.


Den vanligaste orsaken till planerat kejsarsnitt i gruppen med kvinnor med typ 1 diabetes var misstänkt stort barn vilket angavs som orsak i 50.8% av fallen. Som jämförelse så var misstänkt stort barn angett som orsak till planerat kejsarsnitt i 8.7% av fallen hos kvinnor utan diabetes.

**Slutsats:**
Både kvinnor med graviditetsdiabetes och kvinnor med typ 1 diabetes spenderade längre tid i aktiv förlössning och hade en minskad chans för vaginal förlössning vid varje given tidpunkt jämfört med kvinnor utan diabetes. Risken för att genomgå kejsarsnitt var 3-4 gånger högre i gruppen kvinnor med typ 1 diabetes jämfört med kvinnor utan någon form av diabetes och den vanligaste orsaken till planerat kejsarsnitt hos kvinnor med typ 1 diabetes var misstänkt stort barn.

**Vilken kunskap och nytta bidrar avhandlingen med?**
Avhandlingens första studie ger ny kunskap om användningen av kapillär provtagningsmetod för att ställa diagnosen graviditetsdiabetes. Denna studie har legat till grund för den rutin vi har för att ställa diagnosen graviditetsdiabetes i Östergötland sedan en tid tillbaka och används dagligen.

De två sista studierna som ingår i avhandlingen ger ny kunskap om hur diabetes hos mamman påverkar tiden kvinnor spenderar i aktiv förlössning. Resultaten skulle, i kombination med mer forskning och kunskap, kunna leda till ett mer individualiserat omhändertagande av kvinnor med diabetes under förlossning för att förhoppningsvis kunna öka förutsättningarna för en normal förlossning för dessa kvinnor. Resultaten skulle också kunna vara av värde för andra personer inom sjukvården som tar hand om kvinnor med diabetes för att optimera förutsättningarna med bra kontroll på blodsockret innan och under graviditet.
Resultaten kan också användas i framtida forskning för att öka förståelsen kring de olika ökade riskerna kvinnor med diabetes har under graviditet och förlossning och förhoppningsvis kunna förbättra dessa.
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PAPERS I-III
Papers

The papers associated with this thesis have been removed for copyright reasons. For more details about these see:

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Hyperglycemia in pregnancy – diagnostics and duration of labor

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