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Adherence to screening guidelines for gestational diabetes in pregnancy

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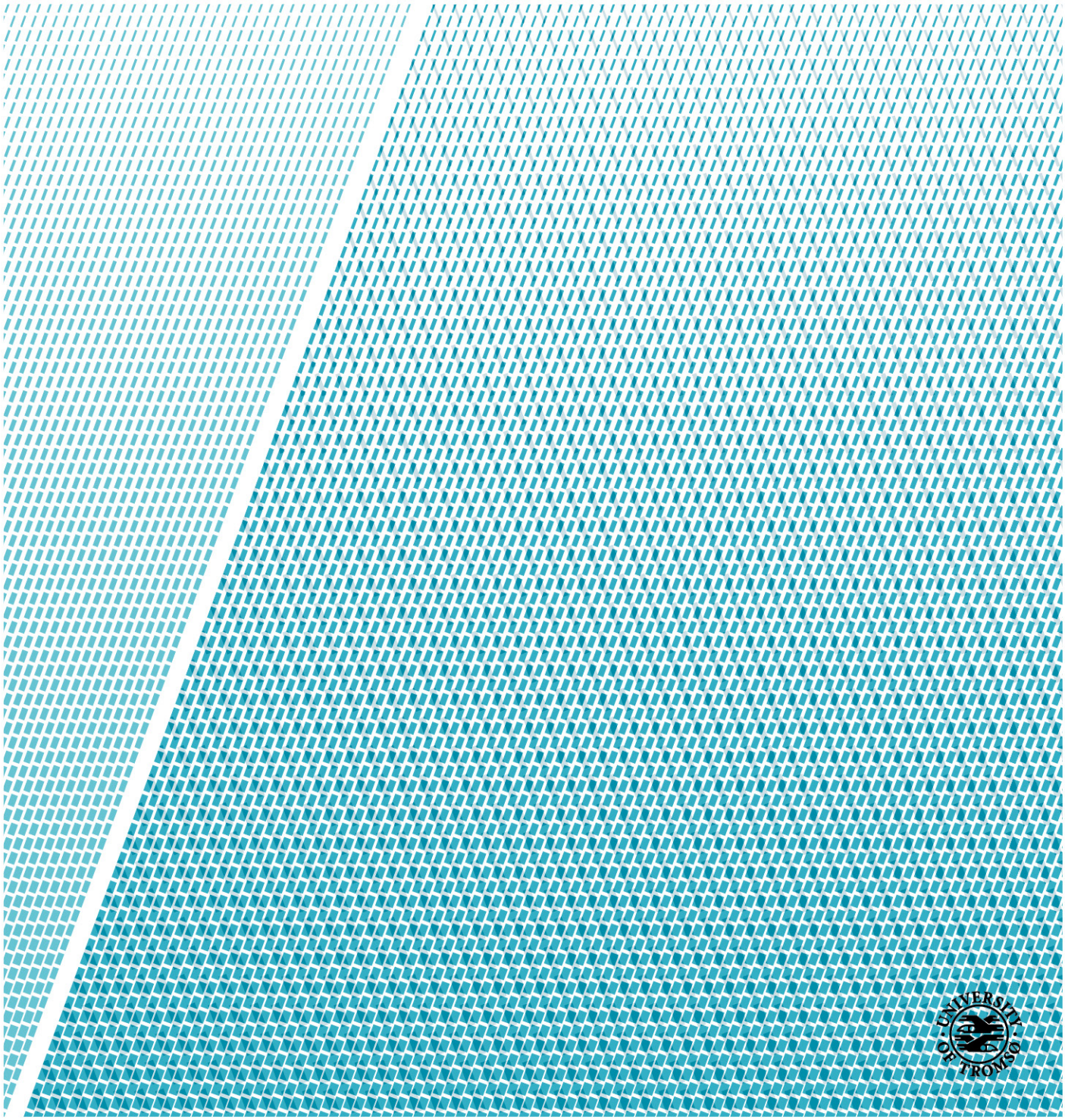

Preface

My interest in obstetrics and gynaecology was evoked in the 7:th semester and confirmed during my clinical rotation. I firmly believe that women's health is an area where more research and education is crucial. I contacted Finn Egil Skjeldestad, The Department of Community Medicine (ISM), UiT The Arctic University of Norway, Tromsø and Åse Torunn Revholt Pettersen, Consultant Obstetrician and Gynaecologist at University Hospital of Northern Norway (UNN), Tromsø in the autumn of 2018 and we discussed potential topics. The new national guidelines on screening, diagnosis and follow up on gestational diabetes mellitus had recently been published and was a topic of debate. We decided to evaluate adherence to screening guidelines, size of screening population and follow up before and after implementation of the new guidelines.

In October 2018 I searched for relevant literature, graded articles and wrote my project description. In May 2019 I joined a meeting in Oslo with a multidisciplinary working group were revision of the new guidelines were discussed on the initiative of The Norwegian Directorate of Health. Both the primary and specialist health care services were represented, and this gave me more knowledge on the working process behind the guidelines, the criticism and the workload on different levels of health care.

Through the summer and my fifth year of clinical training I collected data for analysis. Due to the COVID-19 pandemic all further supervision was performed through mail and phone contact. Skjeldestad and I agreed on the final plan for analysis and he helped me to clean the datafile. Skjeldestad then performed the analysis and I drafted the results, formed tables/figures and discussed the findings.

I want to express my gratitude to my supervisor Finn-Egil Skjeldestad for his great commitment, countless hours of work in helping me with my thesis and excellent guidance through a demanding, exciting and educational process. I would also like to thank my co-supervisor Åse Torunn Revholt Pettersen for her inspiration, knowledge and help with the final data.

Tromsø 08.08.20, Lina Grönvall

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Abbreviations

BW	Birth Weight
DM	Diabetes mellitus
GDM	Gestational diabetes mellitus
IADPSG	The International Association of Diabetes and Pregnancy Study Groups
LGA	Large for gestational age
OGTT	Oral Glucose Tolerance Test
T2D	Type 2 Diabetes
UNN	University Hospital of North Norway
WHO	World Health Organization

Abstract

Background/Objective: There are major controversies in screening and diagnostic criteria for gestational diabetes. In 2017, new national guidelines were implemented in Norway. The aim of this study is to evaluate change in size of risk population for GDM, adherence to screening guidelines and follow up before and after implementation of the new guidelines.

Method: This study is a retrospective case-series study. Data from women giving birth at the University Hospital of North Norway and the local maternity wards in Troms during first half-years of 2013 and 2018 was collected from the electronic medical record PARTUS and the antenatal fact sheet. Included were women giving birth after 29 weeks' gestation, with singleton fetus and no pre-pregnancy DM (N=1349). Categorical variables were age (17-24, 25-34, 35-39 and 40 through highest), pre-pregnancy BMI (lowest thru 24.99, 25.00-26.99, 27.00 thru highest), parity (nulliparous/parous), ethnicity (high risk/low risk), follow up (neglected/lifestyle intervention/metformin/insulin), obstetric risk assessment (yes/no). Primary outcomes were change in size of risk population across guidelines, adherence to screening guidelines and prevalence of GDM. Statistical analyses were done using IBM SPSS with Chi-square test. P-values < 0.05 were considered statistically significant.

Results: After changing the screening guidelines in 2017, the population at risk for GDM increased from 46.4% to 67.6% ($p<0.01$). However, only 28.7% in 2013 and 49.2% in 2018 were actually exposed to OGTT ($p<0.01$). Of those correctly screened 16.7% (15/90) of the women were diagnosed with GDM in 2013, respectively 10.7% (24/224) in 2018. Overall 2.2% (15/676) of the cohort was diagnosed with GDM in 2013 and 3.6% (24/673) in 2018. In 2018 41.7% of the women were diagnosed with GDM based on the fasting plasma glucose test solely. Among the women diagnosed with GDM, follow up was neglected in 13.3% in 2013, and in 20.8% in 2018. Of the remaining women, all women eligible for obstetric risk assessment in week 36 were followed-up as scheduled in the guidelines.

Conclusion: With the introduction of new, broader criteria far more women were screened, resulting in a slightly higher prevalence of GDM. Adherence to screening guidelines remained poor across study populations. The national authorities in charge of screening for GDM need to consolidate quality measures that increase focus on screening and follow-up of women diagnosed with GDM.

1 Introduction

1.1 Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is defined as hyperglycaemia with onset during pregnancy (1). Screening and diagnostic criteria to treatment and follow-up for GDM have been subjects for great controversy in the past decades (2).

During the normal pregnancy a progressive insulin resistance develops in the second half of the pregnancy due to circulating placental hormones and adipokines including human placental lactogen, tumour necrosis factor (TNF) - alfa, and human placental growth hormone (3). As a compensation for the peripheral insulin resistance, the insulin secretion from the beta cells of the pancreas increases. Compared to women with normal pregnancies, the women who develop GDM have reduced levels of insulin secretion in relation to the changes in insulin sensitivity.

The most reported contributing risk factors for GDM are maternal pre-pregnancy body mass index (BMI), excess maternal weight gain during pregnancy, ethnicity, family history of diabetes, higher maternal age, prior history of GDM and previous adverse pregnancy outcome (e.g. fetal macrosomia and congenital malformation). The risk of developing GDM increases by cumulative number of risk factors (4, 5).

Gestational diabetes is a topic of great interest mainly because of three reasons. First and foremost, it represents the most frequent metabolic problem in pregnancy; secondly, it is associated with adverse pregnancy outcomes; and, third, appropriate treatment can lead to prevention of perinatal morbidity and mortality (6).

1.2 Epidemiology

Because of the heterogeneity in screening methods and diagnostic criteria, but also the underlying characteristics of the population that is being studied, it is difficult to compare the GDM burden between countries (7). Studies have shown that the prevalence varies widely,

from 1% to 28% (8-10) . Despite these challenges in estimating the burden of GDM, it is generally accepted that it has emerged to be a global public health concern (11).

In Norway, the latest data from the Medical Birth Registry reported an incidence of gestational diabetes to 5.1% in 2019 (9). In 2012 the STORK study, comprising all pregnant women in Groruddalen, Oslo, found that more than 10% had gestational diabetes (8, 12). This difference can be due to ethnicity, but also to the fact that women registered in the Medical Birth Registry are underscreened (12). The Norwegian Directorate of Health has reported a near five-fold increase in the prevalence of GDM from 2005 to 2014, but according to the STORK study these numbers are too low (12, 13).

Several reasons for the global increase of GDM has been described. The most important include the trend toward higher maternal age at first and subsequent deliveries, epidemic of obesity and diabetes, and reduced level of physical activity (13).

1.3 Adverse short-term outcomes

Gestational diabetes is associated with short-term and long-term adverse outcomes for both the mothers and the neonates (14). Commonly described maternal short-term outcomes are preeclampsia, hypertension in pregnancy, and delivery-related morbidity (e.g. shoulder dystocia). Fetal macrosomia (birth weight (BW) > 4000 g), large for gestational age (LGA) which corresponds to a birthweight ≥ 90th percentile (15), and hypoglycaemia are some of the reported short-term neonatal outcomes (16).

1.3.1 Preeclampsia

Preeclampsia is a complication of pregnancy, characterized by hypertension, proteinuria and oedema, which can lead to increased fetal and maternal morbidity and mortality (16). Endothelial dysfunction, oxidative stress, dyslipidaemia and angiogenic imbalance are maladaptation to pregnancy that are seen in both preeclampsia and GDM. Studies in Canada and Sweden have stated that gestational diabetes mellitus is an independent risk factor for preeclampsia and hence, increased rate of preeclampsia can be expected to be seen in mothers with GDM (17). Globally, there is an increasing trend of preeclampsia in line with the

increase in maternal age, obesity and other predisposing comorbidities (18). In Norway the reported incidence of preeclampsia decreased from 3.7% in 2006 to 2.7% in 2016 (19).

1.3.2 Neonatal Hypoglycaemia

Neonatal hypoglycaemia is an important metabolic complication of new-born that can lead to severe long-term neurological lesions, and even death, if not recognized and treated correctly (20). Maternal glucose passes freely over the placenta and hyperglycaemia associated with GDM lead to increased levels of glucose in the foetus, which in turn causes fetal hyperinsulinism. At birth, the glucose supply from the mother ceases, but there are still elevated levels of neonatal insulin. This may lead to hypoglycaemia and inhibition of the normal metabolic compensation mechanisms (e.g., gluconeogenesis) that usually occur during birth (21).

1.3.3 Fetal macrosomia and LGA

Excessive fetal growth can be described either by «macrosomia» or as «LGA» (15). The later term allows identification of premature neonates with an excess growth. According to the Pedersen-Freinkel's hypothesis fetal overgrowth is a result of transplacental transfer of maternal glucose, leading to increased release of insulin from the fetal pancreas. This in turn leads to an up-regulation in the insulin-like growth factor system which is a major component in fetal growth, providing the link between GDM and excessive fetal growth (22).

1.3.4 Shoulder dystocia

Shoulder dystocia represents an obstetric emergency and is defined as a delivery where additional obstetric manoeuvres are required to release the shoulders after failure of gentle downward traction of the fetal head (23). A study by Young et al. concluded that women with GDM are at increased risk of shoulder dystocia (OR:3.2) even after controlling for birthweight (24).

1.4 Adverse long-term outcomes

Evidence show that GDM in pregnancy also has effects after birth. Type 2 diabetes and cardiovascular disease is more common in women with GDM, and the offspring are reported to have higher rates of obesity, metabolic syndrome and development of type 2 diabetes later in life (25).

1.4.1 Type 2 diabetes

In a large meta-analysis of 20 cohort studies published in The Lancet in 2009, where 675 455 women where followed through and after pregnancy, it was demonstrated that women with gestational diabetes had an increased risk (RR 7.4; 95% CI: 4.8-11.5) of developing diabetes type 2 later in life in comparison with women without gestational diabetes. A recent systemic review published in March 2020 suggested that women with a history of GDM are 10 times more likely to develop T2D than healthy controls, confirming existing evidence (26, 27). GDM is associated with similar metabolic abnormalities to those seen in type 2 diabetes, including lacking β-cell compensation for the insulin resistance. Most women return to a euglycemic state after giving birth, but the affected women remain at high risk of progressing to overt type 2 diabetes in the future (28). The risk increases the first 5 years after delivery and according to a recent study it plateaus after 10 years (28). Since GDM is a forerunner of type 2 diabetes preventive strategies like lifestyle and pharmacological interventions aimed at the affected women can delay or prevent the development of type 2 diabetes and contribute to the prevention of the current epidemic of diabetes (28, 29).

1.4.2 Cardiovascular disease

A retrospective cohort study of over a million Canadian women giving birth between 1989 and 2013 showed that women with GDM had a 70% increased risk for cardiovascular disease later in life (30). To determine the long-term impact these women were followed for up to two decades after delivery. A higher cumulative incidence of hospitalization for ischemic heart disease, myocardial infarction, coronary angioplasty and coronary artery bypass graft was observed in the woman with GDM compared with woman having a normoglycemic pregnancy (30).

This increase in cardiovascular disease can partly be explained by the development of type 2 diabetes (31), but other mechanisms are also possible. GDM is associated with both acute and chronic effects on the cardiovascular system, such as endothelial changes. Impaired endothelial vasodilation, a reduction in coronary flow reserve and increased thickness of intima media in the common carotid artery are some of the changes that have been observed (30).

1.4.3 Epigenetics

Epigenetics involves changes of the heritable phenotype without alterations in the individual's DNA sequence (31). DNA methylation, histone modification and heterochromatization are some of the mechanisms involved in these heritable changes of gene expression or repression (31). Recent studies have shown that intrauterine hyperglycaemia can lead to epigenetic modifications in the offspring, influencing metabolism, neuroendocrine functions and energy homeostasis (32). This in turn, can lead to lifelong increased morbidity. In a study on epigenetics and GDM by Lehnen et al. gestational diabetes mellitus is said to be an impressive example for the «fetal origins of adult disease» (32). Foetal overnutrition should be regarded as a great risk factor for phenotypic changes having consequences in later life. Offspring to mothers with GDM have epigenetic changes making them vulnerable for development of metabolic diseases. It is important to break this cycle in order to prevent metabolic diseases later in life (32). Epimutations, in contrast to genetic mutations, are in principle reversible and therefore there is a possibility to compensate for the adverse intrauterine environment after birth through pharmacological or behavioural interventions (32).

1.5 Why screen for gestational diabetes?

WHO (World Health Organization) defines screening as « the presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests, examinations or other procedures that can be applied rapidly and easily to the target population » (33). In 1968 Wilson and Jungner described the principles of screening, and they defined the gold standard criteria of screening assessment. These include that the condition

has to be an important health problem, that there is an acceptable treatment, that there's an suitable screening test and that the case-finding is cost-effective (34, 35).

Prevalence studies have concluded that there is an increasing global burden of gestational diabetes (7) and that this is associated with an significant risk of adverse maternal and perinatal outcomes in addition to the ‹‹two generation risk ›› due to epigenetic changes (14). The gold standard for testing GMD is Oral Glucose Tolerance Test (OGTT). The test is time-consuming, and the women must meet fasting, but these disadvantages are considered minor in relation to the possible complications for pregnant women who remain undiagnosed (36).

The treatment of gestational diabetes is dietary counselling, increased physical activity and when indicated pharmacological treatment with insulin or metformin. The number needed to treat is low (33). When taking these different aspects in consideration one can state that it is important to screen for GDM to enable early diagnosis and treatment (14). However, screening of GDM is a controversial topic and there are different views on whether the screening should be universal or based on risk factors, and which diagnostic criteria that are most sensitive for disease prevention (33).

1.6 Guidelines on GDM: a global perspective

The diagnostic criteria for GDM presented by WHO in 1999 has been revised in the light of new available knowledge (33). The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study has been referred to as the landmark study of hyperglycemia during pregnancy and adverse perinatal outcomes. The women underwent a blinded 2-hour, 75-g OGTT at 24-32 weeks' gestation. The HAPO study found a linear relationship between the glucose values and adverse pregnancy outcomes (2).

As a result of the HAPO study and other recent research, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) panel recommended a single step 75 g 2-h OGTT to be performed in all pregnant women at 24-28 weeks' gestation, except for those women who had already been diagnosed with overt diabetes or GDM through earlier testing (2, 36, 37). They used an odds ratio of 1.75 of having adverse outcomes as seen in the HAPO study and defined the diagnostic criteria in OGTT as displayed in table 1 (38).

Table 1 Diagnostic criteria on GDM

Guideline	OGTT	Fasting plasma glucose (mmol/l)	1- Hour plasma glucose (mmol/l)	2-hour plasma glucose (mmol/l)
WHO 2013	75 g 2 hours	≥5.1	≥10.0	≥8.5
Norway 2008	75 g 2 hours	<7.0		7.8 – 11.0
Norway 2017	75 g 2 hours	>5.3		9.0 – 11.0

In 2013, WHO adopted the IADPSG criteria, and other societies like Australian Diabetes in Pregnancy Society (ADIPS), Endocrine Society, International Federation of Gynaecology and Obstetrics (FIGO) and American Diabetes Association (ADA) have done the same, to name a few (37, 39). The response to the IADPSG recommendations vary widely and there is still a widespread use of regional and institutional criteria, but the aim is to broaden the use of the one-step IADPSG criteria to achieve an international uniform approach to GDM (39).

Universal screening is practiced in many countries, while other uses risk factor-based screening. For example, in Norway, Italy and the UK a risk-based screening is practised, while universal screening is the standard in the US (38).

1.7 National guidelines on GDM in Norway

In 2017 the Norwegian Directorate of Health presented updated guidelines on gestational diabetes in the light of the work by IADPSG (39).

1.7.1 Changes in guidelines

In the old screening-criteria, all women > 35 were recommended screening. In the new criteria, screening is recommended among all nulliparous women > 25 years and multiparous woman > 40 years of age. Regarding BMI, the old criteria stated that all women with BMI >

27 kg/m^2 should be screened, while the new criteria include all women with an BMI > 25 kg/m^2. In addition, glucosuria has been eliminated as screening-criteria in the new guidelines and some changes has been made in the criteria for conditions in previous and current pregnancies (11, 40) (table 2).

Table 2 Clinical risk factors for GDM used as screening criteria according to old and new clinical guidelines

Criteria:	**Guidelines**	
	2008	**2017**
In general		
Age and parity	> 35 years regardless of parity	> 25 years and nulliparous > 40 years and multiparous
BMI	BMI > 27.0 kg/m^2	BMI >25.0 kg/m^2
Ethnicity	From North Africa and the Indian subcontinent.	From Asia and Africa.
Family history	First degree relative.	First degree relative.
Glucose intolerance	Occasionally detected FPG between 6.1 - 7,0 mmol/l.	Impaired glucose tolerance.
Previous pregnancy		
Prior GDM	Yes	Yes
Previous macrosomia	Yes	Yes
Pre-Eclampsia	No	Yes
Shoulder dystocia	No	Yes
Current pregnancy		
Glucosuria	Yes	No
Polyhydramnios	Yes	No
Rapid fetal growth	Yes	No

These changes may lead to screening of nearly 70% of pregnant woman as these women fulfil one or more of the risk factors (11, 41). The new guidelines will according to the Directory of Health identify the pregnant woman who will benefit most from early treatment. Furthermore, it has been estimated that 50% of women with GDM are being missed with the use of the old criteria (11). Disbelievers of the new guidelines argue that this may lead to overdiagnosis and an increased burden on the health system, and that there is lacking evidence of harms and benefits for such wide screening criteria (42).

The new Norwegian diagnostic criteria differ from the criteria that was presented by IADPSG and later accepted by WHO. The cut-off values of fasting plasma glucose and 2 hour plasma glucose are higher in the Norwegian guidelines (11). The values presented by IADPSG are derived from the glucose values that reach an odds ratio (OR) of 1.75 for adverse outcomes compared to mean glucose values. The values presented by the Norwegian Directorate of Health are based on OR of 2.0 for adverse outcomes (Table 1).

Everyone who is diagnosed with GDM should receive diet and exercise counselling. Lifestyle interventions alone can be enough to control 70-85% of the cases (43). If glycaemic goals are not met (FPG: < 5.3 mmol/l or two-hour postprandial glucose: < 6.7 mmol/l), then pharmacotherapy should be initiated. Insulin has been the gold standard medication for a long time but recent studies show that insulin and metformin are equally effective in treating GDM (11).

Women with GDM treated by lifestyle interventions can be followed up in primary care, but according to the latest recommendations an obstetric risk assessment should be performed in gestational week 36. When medical treatment is indicated, the women should be referred to an obstetric outpatient clinic where they in principle are followed up in the same manner as patients with pre-existing diabetes (44).

1.7.2 Timing of delivery

Decreased perinatal mortality, prevention of macrosomia and associated perinatal complications such as birth trauma, caesarean delivery and shoulder dystocia are some of the arguments favouring planned delivery in women with GDM (45). In the new guidelines there is a more detailed approach to induction of labour in women with GDM. It is suggested that

women with GDM managed with diet and exercise in primary health service should go through an obligatory obstetric risk assessment in 36 weeks of gestation to evaluate if there is indication for induction. If there are no signs of complications, a new evaluation should be made at a gestational age of 286 +/- 2 days. Induction should be realized from gestational week 38 in women with medically treated GDM (11).

2 Materials and methods

2.1 Study design and data sources

This study is a retrospective case-series study where women giving birth in the first half-year of 2013 represents the "old" screening population, and women giving birth in the first half-year of 2018 represents the "new" screening population (table 3). The electronic medical record PARTUS and the antenatal fact sheet ("Helsekort for gravide") were utilized to obtain data from women giving birth at the maternity clinic of UNN (University Hospital of North Norway) including the local maternity wards at Finnsnes and Nordreisa.

2.2 Selection of study population

In total, 1453 women gave birth in the two periods being studied. Excluded were women with diabetes type 1 or 2 diagnosed before pregnancy (n=18), twin pregnancies (n=37), women giving birth before 29 weeks' gestation (n=16) and women with incomplete data or missing medical records (n=33) leaving us with a study population comprising 1349 women in total, 676 in 2013 (old study group) and 673 in 2018 (new study group).

The study was restricted to focusing on BMI, high maternal age and ethnicity since these risk factors have demonstrated profound effects on the incidence of GDM and since high pre-pregnancy BMI and age constitute the risk factors that have undergone revision in the 2017 guideline (table 2).

2.3 Variable specification

Age was categorized in line with the screening criteria into 4 groups (17-24, 25-34, 35-39 and 40 through highest). Pre-pregnancy BMI was defined as weight divided by the square of the body weight (kg/m^2) and categorized into 3 groups (lowest thru 24.99, 25.00-26.99, 27.00 thru highest). Parity was categorized into 2 groups (nulliparous/parous) and ethnicity was categorized as "high risk ethnicity" including women with Asian or African origin and "low risk ethnicity", compromising all other women.

2.4 Primary endpoints

This study has 3 primary endpoints as summarized in the PICO table (Table 3). First, change in size of risk population across guidelines. This was measured as the number of women with at least one of the screening exposures. Furthermore, adherence to screening guidelines was evaluated as the number of exposed women screened with a 2-hour, 75-g OGTT. Finally, the prevalence of GDM was measured using following diagnostic criteria: fasting plasma glucose < 7 mmol/l and 2-hour glucose between 7,8 – 11,0 mmol/l in the 2013 study group and fasting plasma glucose > 5,3 mmol/l and/or 2-hour glucose between 9,0 – 11,0 in the 2018 study group.

2.5 Secondary endpoints

Secondary endpoints were follow up in the women diagnosed with GDM and onset of labour. Follow up was further categorized as neglected/lifestyle intervention/metformin/insulin and whether obstetric risk assessment was done in 36 weeks of gestation (yes/no). Neglected follow up was defined as no follow up even though pathological fasting and/or 2-hour glucose values were documented on the antenatal fact sheet. The outcome of the obstetric risk assessment was categorized as planned induction/ no induction and delivery method as elective CS/vaginal delivery.

2.6 Statistics

Statistical analyses were done using IBM SPSS with Chi-square test. P-values < 0.05 were considered statistically significant.

2.7 Formal approvals

The Patient Ombudsman at the University Hospital of Northern Norway, Tromsø, authorized the study as a specific quality assurance study (reference 20197697; project no. 02223)

3 Results

3.1 Characteristics of study population

There were no significant differences in distribution of age, parity or ethnicity by time-period (Table 4). The women studied in 2013 had a significantly higher pre-pregnancy BMI compared with women studied in 2018 ($p < 0.01$). With the implementation of new national screening guidelines for gestational diabetes the BMI-criteria changed from including all women with a BMI > 27.0 kg/m2 in the screening program to all women with a BMI > 25.0 kg/m2. The prevalence of women with a BMI ranging from 25.00 – 26.99 kg/m2 was far higher in 2013 compared to 2018, there were no difference in the number of women with BMI ranging from 27.0 – 29.99 kg/m2 , whereas there were significantly more women with a BMI > 30 kg/m2 in 2013 (table 4).

3.2 Size of screening population

Figure 1 summarizes the screening process and the outcomes of screening. Among 676 women in 2013, 314 (46.4%) women fulfilled at least one screening criteria for GDM, respective 455 out of 673 (67.6%) in 2018 ($p<0.01$). This summarizes to a 46% increase in the number of women eligible for GDM screening in 2018 relative to 2013. Pre-pregnancy BMI was the most common clinical risk factor accounting for 27.5% (2013) and 37.7% (2018). Age as a risk factor (based on parity in 2018) was reported in 14.5% (2013) and 25.9% (2018) while high risk ethnicity was found in 4.6% (2013) and 4.0% (2018).

3.3 Adherence to screening guidelines

In 2013, screening was realized in accordance with guidelines for 28.7% (90/314) of the women who fulfilled at least one criterion for performing OGTT. In 2018, the proportion of women who were screened correctly increased to 49.2% (224/455).

In the 2013 population screening was performed in the recommended time window at 24-28 weeks' gestation in 62.2% relative to 71.3% in 2018. When expanding the "window" of screening to week 23-29, 74.4% were included in 2013, and 82.5% in 2018.

3.4 Prevalence of GDM

Among the women who were correctly exposed to OGTT, 16.7% (15/90) of the women were diagnosed with GDM in 2013 respectively 10.7% (24/224) of the women in 2018. Overall 2.2% (15/676) of the cohort was diagnosed with GDM in 2013 and 3.6% (24/673) in 2018.

In 2013 all women were diagnosed based on the 2-hour glucose test including 3 women with a fasting glucose value above threshold. The proportion of women diagnosed with GDM based on the fasting glucose value solely increased in 2018, accounting for 41.7% of the women.

3.5 Follow up

In 2013, follow up was neglected in 2 (13.3%) women with GDM, 8 (53.3%) women were treated with lifestyle intervention and 5 (33.3%) women with insulin. No women were treated with metformin. In 2018, follow up was neglected in 5 (20.8%) women, 13 (54.1%) women were treated with lifestyle intervention, 3 (12.5%) with metformin and 3 (12.5%) with insulin.

One woman gave birth before week 36 in 2013 leaving 12 women eligible for obstetric risk assessment in week 36. All 12 women were followed up in week 36 in a maternity outpatient clinic (or private practice specialist) as advised in the guidelines. One woman gave birth before week 36 in 2018, leaving 18 women eligible for obstetric risk assessment in week 36. All cases were followed up according to guidelines.

3.6 Mode of delivery

In 2013, induction was planned at the risk assessment visit at week 36 in 5 women, 4 (33.3%) of these underwent induction whereas 1 (8.3%) had an emergency CS. All the woman who had elective CS were planned at the 36-week visit. One more woman had an emergency CS

while the remaining 5 (41.6%) women gave birth spontaneously. All women were follow up was neglected delivered vaginally, with spontaneous onset. In 2018, all seven (38.9%) women who had an induction were planned at the 36-week visit. Two (11%) women had emergent CS, two women elective CS, and 7 (38.9%) women delivered spontaneously. Out of the women were follow up was neglected, all had a vaginal delivery with spontaneous onset.

4 Discussion

4.1 Summary of findings

There were no significant differences in distribution of age, parity or ethnicity by study population. However, the 2013 study population had a significant higher pre-pregnancy BMI compared with the 2018 study population ($p<0.01$). After changing the screening guidelines in 2017, the screening population for GDM increased from 46.4% in 2013 to 67.6% in 2018 ($p<0.01$). However, only 28.7% in 2013 and 49.2% in 2018 were actually exposed to OGTT ($p<0.01$). Of those correctly exposed to screening, 16.7% (15/90) of the women were diagnosed with GDM in 2013, respectively 10.7% (24/224) in 2018. In 2018 41.7% of the women were diagnosed with GDM based on the fasting plasma glucose test solely. Among the women diagnosed with GDM, follow up was neglected in 13.3% in 2013, and 20.8% in 2018. Of the remaining women, all women eligible for obstetric risk assessment in week 36 were followed-up as scheduled in the guidelines.

4.2 Size of screening population

The present study was restricted to focusing on BMI, high maternal age and ethnicity as risk factors for GDM, since high pre-pregnancy BMI and age comprised the risk factors that were revised in the 2017 guideline, while the population of immigrants still increases in Norway. First degree relative with DM, prior GDM, previous macrosomia, shoulder dystocia and pre-eclampsia are other risk factors indicating screening in the national guideline. In previous literature the prevalence of all these risk factors are low, except for first degree relative with DM, among which the prevalence varies from 13-36% (46, 47).

When the new national guidelines on gestational diabetes was introduced in Norway in April 2017, there was a discussion on whether this would lead to a massive over-screening and over medicalization of healthy pregnant women (41). Especially, The Norwegian Association for General Medicine criticized screening of all women > 25 years, since the average age at first pregnancy is 29 years and hence, the majority of pregnant women would fulfil at least one screening criteria (48). It was estimated that over 70% of pregnant Norwegian women would be candidates for screening (41). We found that 67.7% fulfilled at least one criterion for screening in 2018 and that the entire increase in size of risk population from 2013 was attributed to changes in the BMI and maternal age criterions. The increase in size of risk population has, to our knowledge, only been addressed in one previous study. This study reported that the women at risk for GDM, using the new criteria, was 68.2% which is in line with the findings in the current study (49).

4.3 Adherence to screening guidelines

This study demonstrates that the adherence with screening guidelines is unsatisfactory, with an adherence rate of 28.7% in 2013 and 49.2% in 2018. There has been increasing attention to GDM as a growing public health concern and there is controversy on how to screen and diagnose GDM (50). This, together with the implementation of the new guidelines in 2017 and the discussion that followed may have contributed to the improved adherence to guidelines that was observed between the two time periods. But still, the adherence rate is too low.

Few studies have reported adherence with screening guidelines. In a recent retrospective analysis of 2432 nulliparous women in UK and Ireland Murphy et al. found that 60.8% of the women that had identifiable risk factors for GDM were appropriately screened (51), demonstrating higher adherence compared to our study. Similar studies conducted in the largest hospital in Thailand and in the French Rhône‐Alpes region showed compliance rates of 78% and 80%, respectively (52, 53). These studies were conducted in hospital and private clinic settings and had slightly different screening approaches. For instance, the study conducted in UK and Ireland only assessed screening for GDM in relation to obesity, family history of diabetes and ethnic risk, while the other studies used a broader approach (46, 51, 52). In a Swedish study with 822 participants, 257 fulfilled at least one screening criteria but

only 79 (30.7%) of these women were screened (54). The majority of the OGTTs were performed within the midwifery services and the local health care centre, few in hospitals, which is in line with screening practice in the present study.

A non-randomized interventional study from France that compared adherence to guidelines before and after implementation of the WHO guidelines in 2000 demonstrated that the adherence to guidelines increased significantly, indicating that information and attention to new guidelines might improve screening practices (53). In agreement with this study we observed an increase in adherence after implantation of new guidelines.

Few studies have analyzed the difference in compliance between various risk factors for GDM. Ruengkhachorn Et al. demonstrated that adherence with risk factors differed. Maternal age, family history of DM and obesity had adherence rates of 80%, 50%, 13% respectively. Previous history of macrosomia, unexplained fetal death and GDM had a compliance rate as low as 3%. A significant higher compliance-rate was demonstrated in those who had > 2 risk factors compared to those with only one (52).

The present study did not investigate potential causes explaining the low adherence to national guidelines. Barriers to screening might include failure among health care workers to identify risk factors either on the first antenatal visit, or that the risk factors are being overlooked at the time when the OGTT should be arranged. Another contributing factor might be that some pregnant women refuse to undergo OGTT (55). Other barriers that could affect adherence to clinical practical guidelines is the characteristics of the test. How easy the test is to administer, and the intrinsic quality of the test might have an impact. The screening test recommended in Norway consists of a plasma glucose determination while fasting, and at 2 hours after a 75-g oral glucose load. This test has shown to have lower rates of false-positive than the 50-g or the 100-g OGTT (56). This is desirable due to the social and financial consequences of treating women who are in low risk for developing fetal or maternal complications (56) . However, the OGTT costs around 150 NOK per test, without taking the socioeconomic costs in account (41) and women have reported it to be both unpleasant and time-consuming (56).

Screening within the recommended gestation time frame was satisfying in most of the cases. 74.4% in the old study population and 84.5% in the new were screened between week 23-29,

which is high compared to 50% screened in the correct time frame in a previous study (51). This is important since insulin resistance mediated by placental hormones increase as the pregnancy advance and testing too early might fail to identify many women at risk (50). Performing the test too late in the third trimester reduces the time where interventions can take place and benefit the women.

4.4 Prevalence of GDM

The prevalence presented in this study is based on the women who fulfilled the pre pregnancy BMI, maternal age and ethnicity-criteria indicating screening for GDM. In a recently published systemic review on risk factor-based screening to identify GDM, BMI and high maternal age as criteria for screening alone was as good as more complex risk prediction models (10). This is in line with a study published by Benhalima et al who demonstrated that using age and BMI alone as cut-offs for screening yielded a positive detection rate of 69.9%, when adding other risk factors such as previous GDM, history of high birth weight and first-degree family history of diabetes, the positive rate increased to 70.5% (57). This demonstrates the strength of maternal age and BMI to predict GDM. However, previous literature does not present enough evidence on at what maternal age and at which pre-pregnancy BMI the risk for developing GDM is sufficient to justify screening (57).

The WHO-report that summarize the findings from the HAPO study (2) assessed the evidence as “very low” for the new guidelines (33). The effect of wider screening criterions and lower diagnostic thresholds has increased the prevalence of GDM by 2-3 fold over existing levels of 2-6% (58). A systematic review published in 2019 found a prevalence of 4.4% regardless of type of screening threshold, when using the new IADPSG criteria the overall prevalence was 10.6% (59). The wide variations in the approach to screening and diagnosing GDM has made global comparisons of prevalence and outcomes problematic. The heterogeneity in the identification of GDM has impacted the estimation of prevalence of GDM, health outcomes and use of resources (60).

In our study 16.7% (15/90) in 2013 and 10.7% (24/224) in 2018 of the women who were correctly exposed to OGTT were diagnosed with GDM, overall 2.2% (15/676) of the entire study population was diagnosed with GDM in 2013 and 3.6% (24/673) in 2018. Numbers

from the Medical Birth Registry show that nationally, the prevalence of GDM increased from 3.0% in 2013, to 5.0% in 2018. In Troms/Finnmark the prevalence increased from 2.3% in 2013 to 2.8% in 2018. These findings stand in contrast to previous literature stating that the new guidelines would double or triple the prevalence of GDM. Since the adherence to screening guidelines was poor, the true prevalence in the present study population is most likely higher than demonstrated.

With the implementation of the new guidelines for screening and diagnosing GDM in 2017 the number of women being screened in our study population increased from 90 to 240, but only 7 more cases of GDM was diagnosed, implying poor case finding and ineffective use of resources. A Finish study published in 2016 evaluated maternal and neonatal outcomes before and after implementation of the new screening guidelines. They concluded that OGTT tests were performed twice as often, the prevalence increased from 7.2% to 11.3%, but this comprehensive screening did not improve pregnancy or neonatal outcomes (61).

The HAPO study found continuous associations between maternal glucose levels and perinatal outcomes such as increased birth weight and neonatal hyperinsulinemia (2). A recent meta-analysis concluded that women with GDM appear to have a nearly 10-fold increase in risk for developing type 2 diabetes later in life (27). Through large volumes of congruent observational epidemiologic data, the relationship between hyperglycemia and adverse maternal and neonatal outcomes are well documented (2, 7, 24, 26). However, there are major controversies in screening and diagnostic criteria for GDM. There are debates concerning the relevance of treating milder forms of GDM and whether this is cost effective (55). In agreement with the present study, a recent meta-analysis concluded that risk factor-based screening methods are poor predictors of which pregnant women will be diagnosed with GDM (10). Cundy et al argue that the diagnostic changes following the HAPO study are unjustified since they are based on results from an observational study and since the screening test have poor reproducibility (58). They further claim that despite the increase in diagnosis, there are no evidence from randomized controlled trials that outcomes are improved (58).

In the current study we found that all women in 2013 were diagnosed based on the 2-hour glucose value, and 3 of these women had elevated fasting glucose values too. In 2018, after implementation of reduced diagnostic thresholds, the majority of the women were diagnosed

based on the fasting glucose value solely. Can we be enough confident that these women have a significant glucose intolerance? Since the observational epidemiologic data that is available shows a continuous increase in adverse outcomes with increasing levels of maternal glycemia the decision on diagnostic threshold values will be arbitrary and based on the view on which level of risk that is sufficient to merit identification and treatment of GDM (62). The cut-off values recommended by the IADPSG panel following the HAPO – study did not concord with any prior OGTT values used in wide range. The diagnostic criteria used in Norway are based on glucose values that reach an OR of 2.0 for adverse outcomes demonstrated in the HAPO study. The reliability of odds ratios derived from observational data is poor, and the fact that only one abnormal value (fasting or 2-hour) is required further elucidate this problem (58). Fasting plasma glucose has low specificity which limit its usefulness as a screening test (63). A systemic review on the OGTT test concluded that "caution should be exercised when interpreting a single test result " (64). Results from our study show that if double positive test was required for GDM to be diagnosed only 3 (20%) women would qualify in 2013, and 7 (29%) in 2018, and hence the prevalence would be minimal.

4.5 Follow up

Out of the women screened correctly and diagnosed with GDM, follow up was neglected in 13.3% (2/15) in 2013, and 20.8% (5/24) in 2018. In all these cases pathological values were documented in the antenatal fact sheet but the mother was not diagnosed with GDM and hence not followed-up in the primary nor secondary care. Since the former diagnostic criteria had a much higher threshold for fasting glucose and a lower threshold for the two-hour glucose value, health care providers might have failed to identify these women due to poor adaptation to the new criteria.

Among the women who were correctly diagnosed with GDM, all eligible women were followed up in week 36 in a maternity outpatient clinic as directed in the guidelines. Few studies have analysed the compliance to follow-up in primary or specialist antenatal care following a GDM-diagnosis. Most studies focus on treatment, outcome and post-partum follow up. A systemic review on the determinants and barriers for GDM services found that there were serious barriers to satisfying GDM services and management even in high-income

countries and across study settings, from screening to post-partum follow up (65). In the current study adherence to screening guidelines and correct diagnosis of GDM is unsatisfactory, but the follow up in week 36 with ultrasound and plan for delivery was considered satisfying.

With a larger study population, it would have been possible to analyse mode of delivery in the women diagnosed with GDM and correctly managed vs. those who were neglected. However, there was a significant trend ($p < 0.01$) towards increase in induction-rates in the group of women who had at least one of the risk factor (maternal age, BMI, ethnicity) for GDM (n=769) compared to the group of women who had none (n=580) (data not shown). This finding is not controlled for confounding factors that could contribute to the increase in inductions. It would be interesting though, to do a follow-up study comparing outcomes in three different groups: the women were screening wasn't indicated, the women were screening was indicated but not performed and the group of women who were correctly screened.

4.6 Effectiveness of current guidelines

This study of pregnant women in a Norwegian setting demonstrated that adherence to risk-based screening guidelines for GDM was poor both before and after implementation of the new guidelines, in line with literature (51-54).With the new guidelines there was a great increase in the number of women subjected to screening, followed by a little increase in prevalence of GDM. This stand in contrast to the argument that 50 % of the GDM cases would be missed with the old screening-criteria presented by the Norwegian Directory of Health (11). The findings correspond with the assumptions made by detractors of the new national guidelines. The new screening criteria have major impact on costs and infrastructure capacity, and there is no clear evidence of the benefits of such broad screening (55). Another perspective to have in thought is the impact of labelling asymptomatic pregnant women, in a time where they might be particularly receptive to stress, guilt and anxiety (58).

The evidence on which the new criteria are based on are of moderate quality. There is no evidence on whether the different screening alternatives improves patient-important outcomes (11). With the new guidelines there will be a significantly higher proportion of OGTTs´ to be

performed in the primary health service. In total, the costs associated with broader screening for GDM and follow-up/treatment as a consequence will be approximately 16 million NOK (11). No cost-benefit analyses have been made by the Norwegian Directory of Health. The benefit effect, i.e. the costs saved by preventing and treating unfortunate outcomes are difficult to estimate particularly due to ambiguities related to short- and long-term perspectives (11). Present research provides few answers to this. Two studies have analysed the cost effectiveness of implementing the new criteria (based on IADPSG recommendations). One concluded that it would be cost effective only if detection of GDM reduced the rate of subsequent type 2 diabetes (66). The long-term risk of developing type 2 diabetes in women with mild hyperglycaemia identified with the new criteria is unknown. The second study found that the new criteria only would be cost effective if they reduced the number of CS which is unlikely since diagnosis of GDM is associated with an increase in CS rate even if the birth weight is normalized through treatment (67). A systemic review on the cost effectiveness of controlling GDM published in 2019 concluded that neither screening nor treating mild GDM was convincingly cost-effective (68). One can raise questions on whether it was too early to develop new guidelines when it is clear that more research (cost-benefit analyses, randomised controlled clinical trials on outcomes) is needed in this field.

4.7 Strengths and limitations

Strengths of this study include the population-based design with data collection from the electronic medical record PARTUS and the antenatal fact sheet, which reflect screening how it is practised. Only few cases were excluded due to missing information. The study provides new insight in adherence to guidelines since this is poorly covered in existing literature.

The low number of women diagnosed with GDM provides low statistical power with inclusive outcome data. Another possible limitation is that not all risk factors recommended for screening in the guidelines were included.

5 Conclusions

The new broad screening criteria resulted in a large increase in study population at risk, an increase in adherence to screening reaching nearly 50% in 2018, resulting in a slight increase in prevalence of GDM. There may be concerns around the diagnosis of GDM as 41% were diagnosed with GDM in 2018 based on the fasting plasma glucose value solely. Follow up was neglected in more women after the new guidelines were introduced. All women eligible for obstetric assessment in week 36 were followed up as advised in the guidelines. In order to increase several aspects of screening for GDM we recommend national authorities to initiate a set of activities for education of health care professional and pregnant women, systems for identifying the population at risk and increase adherence to guidelines and follow-up of diagnosed GDM cases.

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7 Tables

Table 3 PICO table

Screening population: Selection criteria	Study groups		Outcome	Study design	Ethics
• Maternal age • Parity • BMI • Ethnicity	"Old" 2013	"New" 2018	P1: Change in size of risk population P2: Adherence to guidelines P3: Prevalence of GDM	Case – series	None

Table 4 Baseline characteristics of the study population

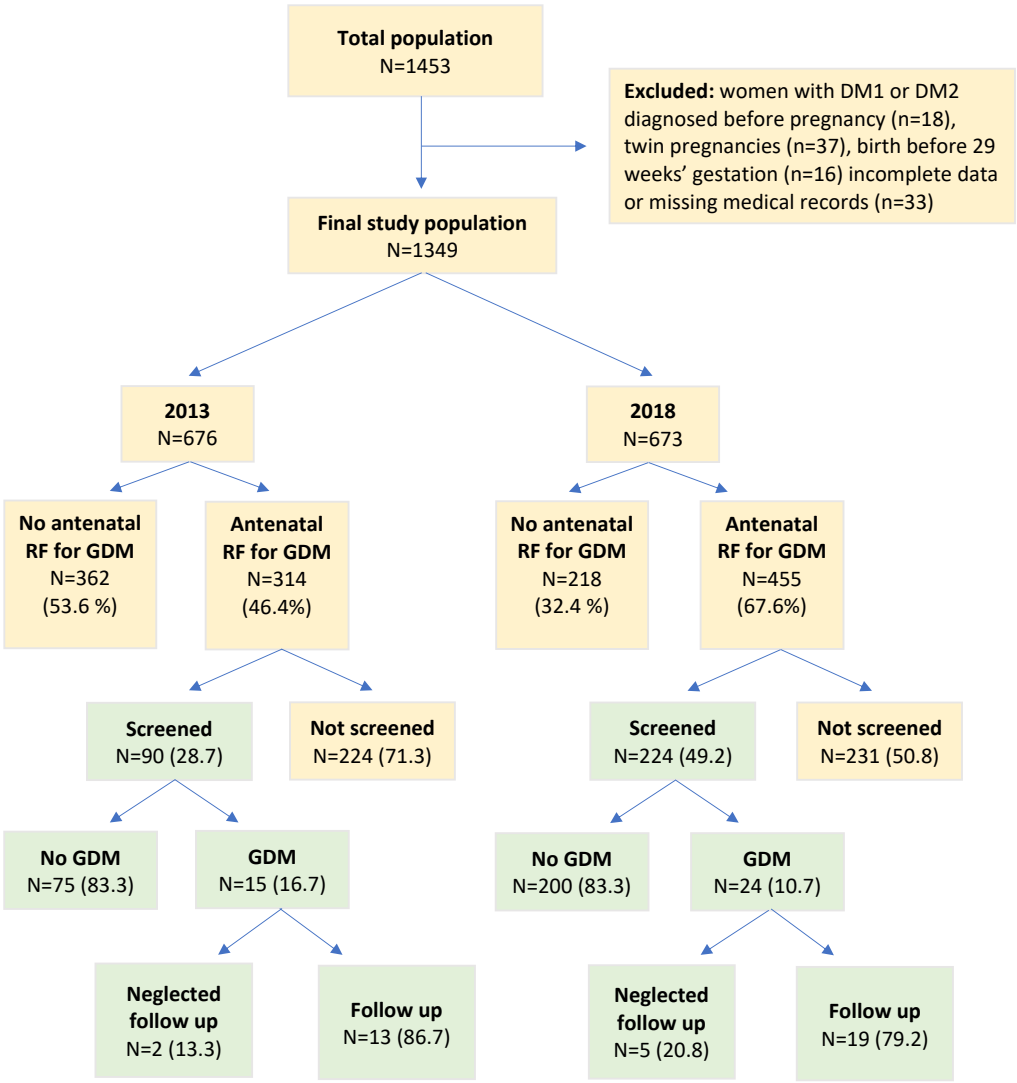
Variables	Time period		P-value
	2013 N=676 (%)	**2018 N=673 (%)**	
Maternal age (years)			0.504
17-24	104 (15.4)	78 (11.6)	
25-34	415 (61.4)	445 (66.1)	
35-39	119 (17.6)	114 (19.6)	
40-47	38 (5.6)	36 (5.3)	
Parity			0.956
Nulliparous	306 (45.3)	303 (45.0)	
Parous	370 (54.7)	370 (55.0)	
Pre-pregnancy BMI (kg/m²)			0.000
≤ 24.99	338 (50.0)	419 (62.3)	
25.00- 26,99	122 (18.0)	76 (11.3)	
27.00 – 29,99	92 (13.6)	87 (12.9)	
≥ 30,00	124 (18.3)	91 (13.5)	
Ethnicity			0.255
Europe	622 (92.0)	604 (89.7)	
Asia	23 (3.4)	36 (5.3)	
Africa	29 (4.3)	28 (4.2)	
Others	2 (0.3)	5 (0.7)	

Table 5 Primary exposures for GDM

Exposures	**Time period**	
	2013 N=676 %	2018 N=673 %
None	53.6	32.4
Age	14.5	2.4
Age and parity	0	23.5
BMI	27.5	37.7
Ethnicity	4.4	4.0

8 Figures

Figure 1 Flowchart: Outcome of screening



9 GRADE-evaluation

Referanse:
Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358(19):1991-2002.2

Studiedesign: Case series

Grade - kvalitet II - III

Formål

To clarify risks of adverse outcomes associated with degrees of maternal glucose intolerance less severe than overt diabetes mellitus.

Konklusjon

Results indicate strong, continous association of maternal glucose levels below those diagnostic of diabetes with increased birth weight and increased cord-blood serum C-peptide levels.

Land

9 countries

År data innsamling

2000-2006

Materiale og metode

Study setting:
15 centres in 9 countries.

Inclusion:
Pregnant women.

Exclusion:
- Mat.age < 18 years
- Uncertain LMP, no USG
- Plan to deliver at another hospital
- OGTT not performed within 32 weeks
- Multiple pregnancy
- Conception through IVF or gonadotropin ovulation induction
- Earlier diagnosis of DM, or during current pregnancy
- HIV/HBV/HCV
- Participation in interfering study
- Need of interpretor

25,505 pregnant woman underwent 75-g OGTT testing at 24-28 weeks of gestation.

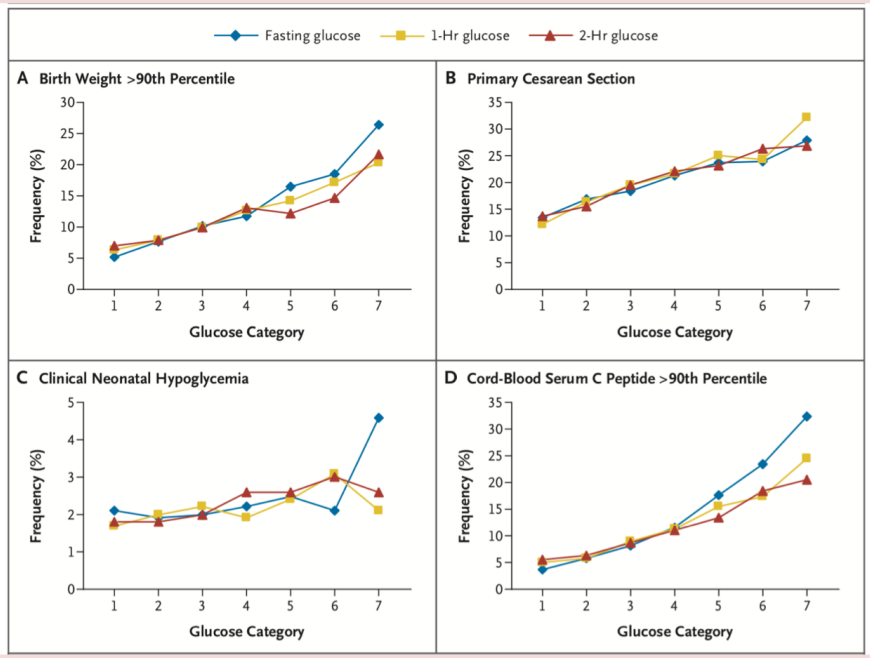
Main exposure:
- Various degrees of mat. glucose intolerance less severe than that in overt diabetes mellitus.

Primary outcome:
- BW >= 90 perce
- Primary CS
- Neonatal Hypoglycemia
- Cord-blood serum C-peptide > 90 perce

Statistical analysis:
Mean and standard deviaton reported for continuous variables, number and percentage reported for categorical variables. Pearson product-moment correlations were used to assess associations among glucose measures.

Resultater

Figure 1. Frequency of Primary Outcomes across the seven Glucose Categories.



With increasing maternal glucose levels, the frequency of each primary outcome increased, although less so for clinical neonatal hypoglycemia than for the other outcomes. There where no obvious thresholds at which risks increased.

Diskusjon/kommentarer/sjekkliste

Sjekkliste:
- **Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe?** NO. All participants gave consent.
- **Var det sikret at utvalget ikke var selektert?** YES. Difference in age and education level were small between those who agreed to participate and those who did not.
- **Var inklusjonskriteriene klart definert?** YES
- **Var svarprosenten høy nok?** NO. Aim: min. 60 %, in this study: 54 %.
- **Var alle pasientene i samme stadium av sykdommen?** Not relevant.
- **Var oppfølgningen tilstrekkelig (type/omfang) for å få endepunkt?** YES
- **Ble det brukt objektive kriterier for å vurdere/validere endepunktene?** YES
- **Ved sammenligninger av pasientserier, er seriene tilstrekkelig beskrevet?** YES
- **Er prognostiske/konfunderende faktorer beskrevet?** YES
- **Var registreringen prospektiv?** YES

Strengths:
- Double-blinding of glucose levels
- Broad inclusion critera.
- Large study population
- Geographic distribution

Limitations:
- Nutritional status and gestational weight gain of the participants could affect outcomes.
- Causality cannot be concluded due to study design
- Confounders influencing choice of rute of delivery (previous GDM, mat. BMI, previous macrosomia)
- Difference in follow up of pregnant women between countries.

Reference: Ellenberg A, Sarvilinna N, Gissler M, Ulander VM. New guidelines for screening, diagnosing, and treating gestational diabetes-evaluation of maternal and neonatal outcomes in Finland from 2006 to 2012. Acta Obstet Gynecol Scand. 2016;96:372–81.

Design: Cohort | **Grade assessment II**

Checklist, comments

Aims

To assess the changes in pregnancy outcomes following the implementation of national guidelines for gestational diabetes mellitus (GDM) - Current Care Guidelines (CCG) in 2008, which changed the screening policy from risk-based to comprehensive screening.

Conclusion

Glucose tolerance tests were performed twice as often as a result of the implementation of the national GDM guidelines, but this comprehensive screening practice did not improve pregnancy and neonatal outcomes.

Country

Finland

Year data collection

- 2006-2008
- 2012-2012

M&M

Study setting:
Retrospective register-based cohort study based on the data from the Finnish Medical Birth Register and Hospital Discharge Register including 34 794 singleton births in 2006-2008 and 36 488 in 2010-2012.

Inclusion criterias:
All singleton births to wmn ≥18 y/o in all three Helsinki metropolitan area hospitals, from jan 2006-june 2008 and from Jul 2012 until Dec 2012.

Exclusion:
- Mat.age < 18 years
- Prepregnancy diabetes type 1 or 2
- Discrepancies in their reported OGTT status/uncertain status

Main exposure:
Various degrees of mat. glucose levels less severe than in overt DM and GDM-riskfactors during pregnancy. OGTT-testing and intervention when indicated.

Outcomes:
- Gestational age
- Delivery characteristics (Inductio/Episiotomy/Oxytocin)
- Delivery mode (vag/CS, vac/)
- Complications (perineal rup/post.part blood transfusion)
- Children (BW/macrosomia/apgarscore < 7 at 5 min/pH < 7,05)
- Children. comp (NICU/respirator/resuscitation/asphyxia /shoukder dystocia/hypoglycemia/phototherapy)
- Perinatal mortality

Statistical methods:
Continuous variables were compared using a two-tailed Student's t-test. Pearson's chi-square test and tests for relative proportions were used for categorical variables. Values of p <0.05 were considered statistically significant.

Results

- OGTT number multiplied (29.6% in 2006-2008 compared with 59.7% in 2010-2012)
- The prevalence of GDM increased from 7.2 to 11.3% (57 % increase) and was highest among obese women (body mass index ≥30 kg/m2)
- The main pregnancy outcomes for the women with GDM were the increased usage of oxytocin (19.5/40.0%, p < 0.001), increased number of inductions (27.2/33.0%; p < 0.001) and reduced birthweight (mean ± SD: 3647 ± 575 g/3567 ± 575 g). Healthy and unscreened women displayed similar results.
- Children of both women with GDM and healthy screened women had fewer admissions to the neonatal intensive care unit (16.3%/12.1%; p < 0.001) and less asphyxia (11.3%/6.3%; p < 0.001).
- The rates of cesarean delivery (26.5%/25.4%, p = 0.31), resuscitation (2.6%/2.0%; p = 0.12), and perinatal mortality (1.2‰/3.1‰, p = 0.11) among women with GDM **did not change**, whereas the number of hypoglycemia cases **increased** (2.3%/5.2%; p < 0.001).
- Obese women without GDM gave birth to children with higher birthweights than women in the same obesity class diagnosed with GDM.
- The most important changes following the CCG have been the doubling of the number of women being tested and the increased prevalence of the disease resulting in increased maternal stress and use of healthcare resources.

Is the aim(s) clearly defined? Yes

The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation? Yes

Are non-responders/responders in both cohorts alike? Not relevant.

Was the study prospective? No.

Validated measures of exposue and outcome similar in both groups? Yes: risk factors and glucose values were defined after current criteria. Outcome was measured according to guidelines.

Follow-up time long enough/sample size large enough? Yes**.** All women were followed until birth.

Exposure level or prognostic factor is assessed more than once (during f-up)? No.

The main potential confounders are identified and taken into account in the design and analysis. No. F.ex. etnicity was not taken into account.

Are investigators blinded for exposure? Less relevant due to hard outcomes.

Are the results of this study directly applicable to the patient group targeted in this guideline? Yes

Author discussion - strength:
- Broad inclusion criteria
- Large sample size

Author discussion - limitations:
- Not geographic distribution
- Solely register-based

Supporting literature? Yes
Plausible explanations? Yes
Applicable to "real life"? Yes

Referanse:
Persson M, Winkvist A, Mogren I. Surprisingly low compliance to local guidelines for risk factor based screening for gestational diabetes mellitus - A population-based study. BMC Pregnancy Childbirth. 2009;9:53.

Studiedesign: Case series

Grade – kvalitet II

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer/sjekkliste

Formål

To investigate: 1) the compliance with local guidelines of screening for GDM and
2) the outcomes of pregnancy and birth in relation to risk factors of GDM and whether or not exposed to oral glucose tolerance test (OGTT).

Konklusjon

Low compliance with local clinical guidelines for screening for GDM during pregnancy was found. The prevalence of risk factors for GDM was almost doubled compared to previous Swedish studies. Pregnant women developing risk factors of GDM during pregnancy were found to be at substantially increased risk of giving birth to an macrosomic infant.

Land

Sweden

År data innsamling

2002

Materiale og metode

Study setting:
2 local hospitals

Inclusion:
Pregnant women giving birth after 23 gestational weeks and proficiency in the Swedish language.

Exclusion:
- No consent
- Emigration, unknown adress, protected identity
- Prepregnancy DM1 or DM2

Main exposure:
- RF for GDM

Primary outcome:
- Adeherence to screening guidelines
- Outcomes of pregnancy and birth in relaiton to RF for GDM and whether screened/not screened.

Statistical analysis:
For analyses of categorical variables, the Chi square-test was performed. Smal samples: Fischer's exact test. Continuous variables: Student's t-test and ANOVA. For association between exposure annd outcome univariate and stepwise multiple logistic regression analyses were used.

Resultater

Of the 822 participants, 257 (31.3%) women fulfilled at least one criterion for being exposed to screening for GDM according to the local clinical guidelines. However, only 79 (30.7%)of these women were actually exposed to OGTT and of those correctly exposed for screening, seven women were diagnosed with GDM. Women developing risk factors for GDM during pregnancy had a substantially increased risk of giving birth to an infant with macrosomia.

Table 2: Statistical comparisons of outcomes of pregnancy and birth for women in study groups

	Risk factors for GDM in medical history (n = 170)		*No risk factors for GDM in medical history (n = 652)*		*P value*
	Risk factor group 1, R1† (n = 45)	**Risk factor group 2, R2† (n = 125)**	**Risk factor group 3, R3† (n = 87)**	**Normal group, NG† (n = 565)**	
Maternal weight gain in kg during pregnancy, mean (± SD)	11.0[1] (± 7,3)	12.4 (± 5,5)	13.8[2] (± 5,7)	12.8 (± 4,8)	0.028
Highest systolic blood pressure (mm Hg), median (25 - 75 quartiles)	140[2] (125-147)	130[2] (120-140)	130[2] (120-135)	125 [2] (120-133)	< 0.001
Highest diastolic blood pressure (mm Hg), median (25 - 75 quartiles)	87 [3] (80-95)	80 (75-85)	80 (75-85)	80 (73-84)	< 0.001
Highest random blood glucose value (mmol/l), median (25 - 75 quartiles)	6.7 [4] (5,7-8,0)	5.7 (5,3-6,2)	6.7 [4] (5,6-7,7)	5.6 (5,1-6,2)	< 0.001
Proteinurea during pregnancy	18 (40%)	25 (20%)	18 (21%)	112 (20%)	0.017
Preeclampsia, ICD-10 codes O14+O15	5 (11%)	6 (5%)	4 (5%)	22 (4%)	0.172
Gestational weeks at birth, mean (± SD)	39.1 (± 1.89)	39.0 (± 2.22)	39.1 (± 2.24)	39.0 (± 2.16)	0.964
Birth weight of child (g), mean (± SD)	3958[5] (± 673)	3570[5] (± 709)	3773[5] (± 703)	3469 (± 600)	< 0.001
Weight of placenta (g), median (25-75 quartiles)	692[6] (609-800)	632[6] (520-705)	670[6] (600-790)	585[6] (509-660)	< 0.001
Birth experience*, mean (± SD)	7.36 (± 2,3)	7.69 (± 2,5)	7.74 (± 2,4)	8.04 (± 1.9)	0.064

† R1: Women with risk factors for GDM in medical history and developing additional risk factors during pregnancy, R2: Women with risk factors for GDM in medical history and not developing additional risk factors during pregnancy, R3: Women with no risk factors for GDM in medical history and developing additional risk factors during pregnancy and NG: Women with no risk factors for GDM in medical history nor during pregnancy

Diskusjon/kommentarer/sjekkliste

Sjekkliste:
- **Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe?** No. All participants gave consent.
- **Var det sikret at utvalget ikke var selektert?** Statistical comparisons of maternal characteristics of study groups showed only small differences.
- **Var inklusjonskriteriene klart definert?** Yes.
- **Var svarprosenten høy nok?** Yes. Aim: min. 60 %, in this study: 73.8 %.
- **Var alle pasientene i samme stadium av sykdommen?** Not relevant.
- **Var oppfølgningen tilstrekkelig (type/omfang) for å få endepunkt?** Yes
- **Ble det brukt objektive kriterier for å vurdere/validere endepunktene?** Yes
- **Ved sammenligninger av pasientserier, er seriene tilstrekkelig beskrevet?** Yes
- **Er prognostiske/konfunderende faktorer beskrevet?** Yes.
- **Var registreringen prospektiv?** No.

Strengths:
- Population-based study design
- Internal and external validity of the questionnaire
- Internal validity of data from medical cords
- Study population accurately reflect the population.

Limitations:
- Recall-bias
- Few participants
- Causality cannot be concluded due to study design

Jenum AK, Mørkrid K, Sletner L, Vangen S, Torper JL, Nakstad B, et al. Impact of ethnicity on gestational diabetes identified with the WHO and the modified International Association of Diabetes and Pregnancy Study Groups criteria: a population-based cohort study. Eur J Endocrinol. 2012;166(2):317-24.

Design: Cohort	Grade assessment	II-III

Checklist, comments

Aims	M&M	Results	-Is the aim(s) clearly defined? Yes.

To compare prevalence rates, risk factors, and the effect of ethnicity on GDM using the WHO criteria and the modified IADPSG criteria.

Conclusion

GDM prevalence was overall 2.4-times higher with the modified IADPSG criteria compared with the WHO criteria. The new criteria identified many subjects with a relatively mild increase in FPG, strongly associated with South Asian origin and prepregnant overweight.

Country

Norway

Year data collection

May 2006– May 2010

Study setting: The study was conducted at three public Child Health Clinics in Groruddalen, Oslo, Norway.

Inclusion criterias:
Women were eligible if they i) lived in the districts, ii) planned to give birth at one of the two study hospitals, iii) were <20 weeks pregnant, iv) could communicate in Norwegian or any of the languages that the material and information had been translated to and v) were able to give a written consent to participate.

Exclusion:
Wmn with:
- Pregestational diabetes
- Diseases necessitating intensive hospital follow-up during pregnancy

Final study population: N=759.

Data collection: Data from questionnaires, anthropometric measurements and venous fasting blood samples drawn after an overnight fast, were collected.

Exposure: Ethnic minority originn

Outcomes:
Prevalence of GDM and its risk factors with the WHO and the IADPSG diagnostic criteria, incl. association between ethnic origin and these criteria after adjusting for covariates (education, BMI, DM1/DM2 i family history).

Statistical methods:
Differences in characteristics between groups: one-way ANOVA for continous and χ2 tests for categorical variables. Effect of ethnic origin on GDM: Univariate and multiple logistic regression analyses. Statistical significance level was set to P<0.05.

	WHO-criteria FPG ≥7.0 or 2-h PG ≥7.8 mmol/l	IADPSG criteria FPG ≥5.1 or 2-h PG ≥8.5 mmol/l.
Prevalence of GDM	13.0%	31.5 %
Prevalence rates by ethnicity	No significant differance	Highly significant differance:western european (24.0 %), ethnic minority (36.8 %).
Effect of ethnicity on GDM	Independent predictor when adjusted for mat. age, prepregnancy BMI and parity Eliminated independence when adjusted for education and body height.	Significantly increased OR for GDM for ethnic minority women even after adjusting for confounding factors.
RF independently associated with GDM	• Age (OR:1.2) • Parity (OR: 2.33) • Body height (OR: 0.92) • Family history (OR:1.89) • Boarderline significant: Prepregnant BMI, education.	• Ethnic minority origin (OR: 1.56-4.13) • Prepregnant BMI (per unit change; OR: 1.09)

The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation: Pregnant women. A slight selection toward lower parity (South Asians) and age (Africans) was found.

Are non-responders/responders in both cohorts alike? Not relevant-

Was the study prospective? Yes.

Validated measures of exposure and outcome similar in both groups? Yes.

Follow-up at end of study – high enough in both groups? Yes: 74 %

Attrition analysis – do those that completed the study differ from those that were lost-to-f-up/premature f-up? No analysis of those lost to follow-up (4 %) has been performed.

Follow-up time long enough/sample size large enough? Yes.

The main potential confounders are identified and taken into account in the design and analysis.
Yes.

Are investigators blinded for exposure? No.

Are the results of this study directly applicable to the patient group targeted in this guideline? Yes.

Strengths: Population-based study cohort, high attendance rate, low loss to follow-up (4%), good response rate (74 %), multi-ethnic population.

Limitaitons: Small numbers in some ethnic minority groups, higher proportion of ethnic minorities than for Norway as whole, absence of 1-h PG measurements.

Referanse:
Murphy NM, McCarthy FP, Khashan AS, Myers JE, Simpson NA, Kearney PM, et al. Compliance with National Institute of Health and Care Excellence risk-based screening for Gestational Diabetes Mellitus in nulliparous women. Eur J Obstet Gynecol Reprod Biol. 2016;199:60-5.

Studiedesign: Case series

Grade - kvalitet	II

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer/sjekkliste
To investigate compliance with risk-based screening for Gestational Diabetes Mellitus (GDM) in a nulliparous cohort. **Konklusjon** This study highlights poor compliance with risk factor screening for GDM in nulliparous women. The risk factor missed most often was ethnic group. **Land** England, Ireland. **År data innsamling** May 2007 - February 2011.	**Study setting:** A retrospective analysis of nulliparous women recruited to a prospective cohort in Ireland and UK centres where risk factor screening is performed. The population included 2428 healthy nulliparous women with singleton pregnancies **Inclusion:** Pregnant women. **Exclusion:** • Multiparous • Twin pregnancy • Underlying medical conditions (hypertension requiring antihypertensive drugs, DM, renal disease, SLE, HIV, sickle cell disease, antiphospholipid syndrome) • Major fetal anomaly or abn. karyotype • Previous cone biopsy • Three or more abortions or misscarriages • Intervention that could modify outcome of pregancy (e.g. aspirin, cerivical suture) **Main exposure:** • Risk factors associated with GDM **Primary outcome:** • Size of populatiton at risk • Compliance with risk-based screening • Prevalence of GDM **Statistical analysis:** Descriptive statistics were presented for the various baseline characteristics using numbers and percentages. Cross tabulation was used to compare relevant groups. When comparing group distributions Chi-square test was used. Stat. sign. p <0.05.	**Characteristics of study population**: Primarily Caucasian (94 %) and aged between 25-34 (75 %). **Risk factors for GDM:** 650 (26.7%) women had identifiable risk factors according to the NICE guidelines . **Adherence to guidelines:** 395 (60.8%) were appropriately screened. 253 (38.9%) women had risk factors but were not screened. 261 (14.6%) had no NICE risk factors but were screened with a GTT. **Prevalence of GDM:** 8.9% prevalence of GDM in women that had a risk factor and were screened. 2% (n = 54) of the cohort had a diagnosis of GDM. **Timing for screening:** 50% (n = 29) were assessed at 24–28 weeks' gestation as recommended.	**Sjekkliste:** • **Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe?** No, all participants provided written informed consent • **Var det sikret at utvalget ikke var selektert?** No. • **Var inklusjonskriteriene klart definert?** YES. • **Var svarprosenten høy nok?** YES. Data for analysis were available on 99.9% of wmn. • **Var alle pasientene i samme stadium av sykdommen?** Not relevant. • **Var oppfølgningen tilstrekkelig (type/omfang) for å få endepunkt?** YES • **Ble det brukt objektive kriterier for å vurdere/validere endepunktene?** YES • **Ved sammenligninger av pasientserier, er seriene tilstrekkelig beskrevet?** YES • **Er prognostiske/konfunderende faktorer beskrevet?** YES • **Var registreringen prospektiv?** YES **Strengths:** • High completeness of data in participants (99%) • All RF for GDM included • Large study population • Geographic distribution **Limitations:** • Poor generalisability due to nulliparous, primarily caucasian cohort • Inability to assess why wmn with NO risk factor (14.6 %) were screened or why wmn with RF were missed