Diabetes after pregnancy - a long-term follow-up in women with normal OGTT

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Research Article

Keywords: Oral glucose tolerance test, diabetes mellitus, follow-up, risk factors, cohort, gestational diabetes mellitus

Posted Date: February 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1345808/v1

Abstract

Purpose. Our aim was a follow-up off a cohort of women screened for GDM with normal oral glucose tolerance test in pregnancy, to investigate the incidence and time of diagnosis of manifest diabetes mellitus and to identify the risk factors for later development of diabetes.

Methods. A follow-up study of a cohort with normal oral glucose tolerance test (OGTT) in 1991/1992. Of the original 352 only five women were lost to follow up.

Results. In total 64 women (18%) had manifest diabetes with median age of 57 years after 28 years of follow-up. This amounts to three times the expected rate compared to the background population. The rate of manifest diabetes rises 10 - 20 years after pregnancy and after the age of 40. A normal fasting glucose at OGTT as well as borderline OGTT during pregnancy were associated with risk of manifest diabetes ($p<0.001$), also after adjustment for age, BMI, non-Danish origin and smoking during pregnancy ($p<0.002$).

Conclusion. The incidence of diabetes is higher in women with various risk factors for DM and a previous normal OGTT in pregnancy compared to the background incidence. On this background our results are useful in identifying the time where women may benefit from the effective implementation of evidence-based treatment to postpone and advert manifest DM, even though they had a normal OGTT during pregnancy.

Introduction

Gestational diabetes mellitus (GDM) has a prevalence ranging from 2 to 22% worldwide depending on the population and type of diagnostic test; later on these women are at risk of impaired glucose tolerance (IGT), metabolic syndrome and manifest diabetes mellitus (1-3). Kjos et al. advocated use of early postpartum screening to rule out manifest diabetes (DM) debut during pregnancy and found that any degree of glucose intolerance after pregnancy was as strong a predictor for future diabetes as GDM itself (4). However, most women are not diagnosed with GDM and their risk of diabetes later in life depends on several factors like weight gain, concomitant dyslipidemia, tobacco use, physical inactivity and dietary habits. The impact to the health system of this majority of women cannot be underestimated and the challenge is to seek out those with a medium risk of diabetes. The diagnostic work-up and the potential preventive interventions would benefit from knowing the time at follow-up and risk factors that most likely predispose for diabetes in these women.

Major randomized trials with lifestyle intervention were met with major challenges at implementation to prevent diabetes postpartum (5-8), due to low participation rate, programs that lack evidence-based guidelines for modification and motivation for populations without diabetes and very limited knowledge of the risk of later onset of diabetes in low-to medium risk populations (8-10). Firstly, the proper time for enrollment for such intervention is not known and, secondly, if an optimal time is ascertained whether effective intervention exists, and what effect the participation rates play in order to be cost-effective (9).

To balance the cost of such programs, the magnitude and timing of potential diabetes needs to be outlined and updated. The risk awareness of later development of DM even after GDM is surprisingly low, so the need is apparent to address this lack in knowledge and identify risk in view of a worldwide diabetes epidemic. A review by Nielsen et al found that only a minority of women with previous GDM was conscious of their risk of developing diabetes later in life. These women had high intention to maintain a healthy lifestyle after pregnancy but most women did not, and only one in three reported a sufficient level of daily physical activity (11).

The aim of this study was to follow up on a cohort of women with normal OGTT during pregnancy, who had various risk factors for DM that caused the screening in the first place. We, hereby, gained information on prevalence, timing and type of diabetes manifestation later in life in relation to their risk factors early in life. This study is a continuation of this group's studies on GDM women and later development of DM and metabolic syndrome.

Methods

A follow-up was performed in spring 2021 on a cohort women who had an oral glucose tolerance test (OGTT) in 1991/1992. In total 352 women had a normal OGTT result of which five were lost to follow-up due to emigration with no data recorded. The screening indications were maternal pre-pregnancy body mass index (BMI) ≥ 27 kg/m^2, family disposition of diabetes, previous GDM, multiple pregnancy, previous macrosomia (birth weight ≥ 4500 gram), stillbirths and glucosuria. The OGTT was performed with seven point measurements with the diagnostic threshold values of 6.4 mmol/l (fasting), 13.6 mmol/l (30 min.), 13.7 mmol/l (60 min.), 11 mmol/l (90 min.), 10.2 mmol/l (120 min.), 9.7 mmol/l (150 min.), and 8.5 mmol/l (180 min.); GDM was diagnosed if two capillary plasma glucose values exceeded the thresholds. The OGTT was performed first early 2nd trimester and repeated in week 28-32. The women were grouped into two groups, normal and borderline OGTT group; the latter was characterized as borderline if just one value exceeded the threshold at any time.

Hospital data were collected previously on the 352 women in 1991/92 from the hospital charts together with laboratory data. We registered age, height, pre- and post-pregnancy weight, co-morbidity, and parity. Further on, screening indication, gestational age, birth weight, length, and head circumference. Blood samples were registered: HbA1c, mean glucose, 2-h glucose at 75 g OGTT and fasting blood glucose at the time of screening during pregnancy.

At follow-up the medical and laboratory charts were reviewed including medications and prescriptions in current or previous use together with the date of commencement. In women with no diabetes the most recent glucose evaluation was registered and, for those with diabetes at follow-up, the date and values at diabetes diagnosis were used. Birth weight ratio was calculated by dividing observed birth weight by expected birth weight for the same gestational age and gender. The expected weights were calculated according to the charts endorsed and distributed by the Danish Health and Medicines Authority. Ponderal index was calculated as birth weight / length^3. In the recent follow-up on the 347 women the electronic

charts were studied for the total of glucose measurements available and the national prescription registry, which is updated daily and contains information on current and previous prescription. Seven had died and 3 had emigrated since delivery. The diabetes status was ascertained in the 10 women and two were diagnosed with type 2 diabetes, none of the other eight had abnormal glucose values or had any prescription on anti-diabetes drugs. Their status was locked to the last known date, which was either date of death or emigration. We categorized a woman with manifest diabetes if fasting glucose was above 7.0 mmol/l, 2-h OGTT value ≥ 11.1 mmol/l, HbA1c ≥ 48 mmol/mol (IFCC) or former levels 6.5 % (DCCT).

The Regional Ethics Committee and Data Protection Agency approved the project (nos. 1-16-02-824-17, 1-16-02-825-17, and 1-16-02-180-17), which was conducted in accordance with the Helsinki Declaration and the guidelines for Good Clinical Practice.

Statistical analysis

To test for difference between two variable means, the Student's t-test was applied if data followed a Gaussian distribution; otherwise Mann-Whitney's U-test was used. Proportions were tested in χ^2 test and 95% confidence intervals (95 % CI) were calculated using http://vassarstats.net/. The continuous variables age, glucose at OGTT (fasting and 2-h glucose), follow-up time were subjected to Kaplan-Meier analysis with the OGTT result (normal/borderline), and DM diagnosis after pregnancy as group variable. Log-rank test was applied for significance testing. Cox regression analysis was performed on the outcome of manifest diabetes with age, BMI, smoking and parity as continuous covariates and the categorical variables of OGTT result (normal/borderline), screening indications and non-Danish origin. Statistical analyses were conducted using the statistical software program IBM SPSS Statistics 20. Data are given as mean ± SD if they followed a Gaussian distribution; if not, median (range) are indicated. Follow-up times are given as median (range). A two-sided p value of < 0.05 was chosen as the level of significance.

Results

Of the original 352 women where obstetrical data were collected we managed to follow-up on medicine prescriptions, blood samples and diagnosis in 347 women. A borderline OGTT was found in 74 women during pregnancy and we could aggregate data on 73 (99 %) of these women. The other 278 women had a normal OGTT during pregnancy and 274 (99%) were followed-up. The initial data showed that the women with borderline OGTT were shorter (Table 1) and delivered heavier neonates than those with normal OGTT (Table 2). Besides these anthropometrics, no difference was found in the screenings indications, basal characteristics and obstetrical outcome except that the borderline women had their last OGTT later in pregnancy and higher fasting glucose than the women with normal OGTT. The weight at delivery was apparently higher in women with normal OGTT; however, in 31 % the weight record was absent. Those women who were screened due to GDM in a previous pregnancy (n=19) had similar risk of subsequent diabetes, at similar age (p=0.66) and at similar years of follow-up (p=0.6) compared to the women with history of GDM. In 8% of women no further OGTT was performed after week 22 (Table 2)

Follow-up was performed median 28 years after pregnancy at an age of 57 years (Table 3); we found that 18 % of the women had manifest diabetes, diagnosed at a median age of 50 years (33-66). They, too, had more likely other endocrine and cardiovascular disorders; nearly 20 % of those with manifest DM had concomitant thyroid disease, ¾ hypercholesterolemia and cardiovascular disorders (women with manifest DM vs. other women, $p<0.01$, Table 4). Contemporary data was similar in women with no manifest DM with respect to with previous normal and borderline OGTT; however, the fasting glucose during pregnancy was still higher in the borderline OGTT group compared to the women with normal OGTT (Table 4)

Figure 1 and 2 displays the age and the time after pregnancy when manifest diabetes was diagnosed in the women with normal and borderline OGTT, respectively. The latter developed diabetes faster after pregnancy and at an earlier age than those with normal OGTT ($p<0.0001$). Twenty percent of women with borderline OGTT had manifest DM within 22 years after pregnancy at 50 years of age (Fig.1 and 2). In women with normal OGTT 15 % had DM 28 years after pregnancy and 20 % at 61 years of age. At regression analysis fasting glucose stayed associated with developing manifest diabetes ($p<0.001$) even after adding for adjustment age, height, smoking, parity, ethnicity and various screening indications ($p<0.002$).

Discussion

Our main result is that nearly one in five of women with various risk factor for DM and normal OGTT in pregnancy were diagnosed with manifest diabetes. This is more than three times the expected rate of 6 % registered in the Danish population at 50-60 years of age (12). As GDM was excluded during pregnancy the high incidence may come as a surprise for these women. A similar but shorter study found almost 6 % had progressed to type 2 diabetes with a follow up period of 10 years in women where GDM was excluded (13). When extrapolated further up to nearly 30 years in our follow-up, this result matches the incidence we found. Another long-term study with 23 years of follow-up, however, did only diagnose type 2 diabetes in 5.5 % of women after normal pregnancy (14). An Iranian study had 15 years of follow up study and found a yearly progression rate of 0.4 % per year with a mean age at follow-up of 36. This translates into 12 % after 30 years when women were at their mid- to end-of-forties years of age (15). They could report that family history and BMI were significant risk factors when repeatedly checking up on the women. The only significant hint of what may lie behind is that fasting glucose stayed with a strong association to later development of DM when adjusted for covariates, similar to our findings. An important caveat in comparison, is of course the different ethnicities and DM prevalence in the discussed studies (13-15). The point is that even in a Scandinavian population with low incidence of type 2 DM, the risk of manifest DM is also a potential outcome when classical risk factors are present.

We find that our high incidence rate of DM is an overlooked issue; nevertheless, this is validated in the registries ascertaining the diagnosis. Our long-term follow-up is resonated in recent systematic reviews and meta-analysis that pointed at the length studies; even shorter studies (<5 years) of DM after GDM showed higher rates just after pregnancy than comparing to those with longer follow-up. It is also known

that a history of GDM leads to faster development to DM compared to those with a family history of DM and obesity alone. The challenge of the late debut is to look for DM after normo-glycemic pregnancies, which was the aim of this study (16).

The number of pathological OGTT threshold values also has an impact on developing type 1 or type 2 diabetes. The probability of remaining diabetes-free decreases linearly even with one pathological value when followed for more than 15 years (14). In our study one single abnormal value (i.e. borderline OGTT) increased the risk of DM profoundly together with known risk factors when looking at DM after pregnancy with risk factors for DM and differentiating on borderline OGTT. Herath et al showed that maternal age ≥ 30 years and neonatal weight above 3.5 kg increased the risk for later DM but not so family history, previous GDM or parity (13). Abnormal fasting glucose, which is suggestive of a beta cell dysfunction, had high risk of later being diagnosed with type 2 diabetes, similar to our findings. Inactive lifestyle with smoking and weight gains adds more to peripheral glucose intolerance and is rightfully blamed for diabetes epidemic worldwide. However, early testing by fasting glucose has the strongest predictive value and not necessarily with diagnosed GDM. This may help to explain why some of these apparently normal women, but with risk factors for DM, later are diagnosed with DM (14). At follow-up, the fasting glucose during pregnancy was lower in the normal OGTT group without DM and HbA1c similar compared to the other groups, i.e. the borderline and manifest DM group (Table 4). This indicates what is in wait for the borderline group as the fasting glucose is an indicator for beta cell function ‘at rest’ like a thermostat set at a particular homeostasis level, while HbA1c is a mirror of fluctuating glucose levels over days and weeks. The slightly higher fasting glucose indicates a higher risk of manifest DM.

As some of the women had previous GDM as indication for screening with OGTT this could cause some misclassification (Table 1); however, we decided not to exclude them from the cohort, as they were screened diabetes-negative at OGTT in the index period and had similar risk of DM displaying the variation on this issue. The other morbidities present at follow-up point at a potential concern of the endocrine health in these women. However, we have no record on pre-pregnant morbidity like hypertension or obstructive sleep apnea, which are associated with the development of diabetes. While the prevalence of the latter probably is negligible in our women with a mean of 29 years, the blood pressure may exert an impact as a risk factor. The prevalence of 35 to 77% cardiovascular disorders indicates that this is in fact an issue.

The major strengths of this study are a long follow-up and few missed cases. Virtually no DM was detected in the first 10 years of follow-up after borderline OGTT and almost 15 years after the initial screen-negative OGTT (Fig 2), both of which may be due to detection bias in a low-to medium risk population. Correspondingly, studies with shorter follow-up period show higher incidences after normal pregnancies (13). Even though the diagnosis itself was ascertained in repeated blood analyses and medication we cannot rule out that a certain delay has occurred, either in registration or diagnostic work-up as our results depend on the electronic medical charts and registries with no patient contact. We presume that this delay is a systematic occurrence in these women with risk factors after a normal pregnancy. When diabetes was first ruled out during pregnancy, any health professional would not expect

to apply diagnostic tests for diabetes in women less than 40 years old with 'just' risk factors. Additionally, our primary selection of women for the cohort could be affected by several factors. The delivery rate in the years 1990/91 was 6000 and 406 women (6.8%) were screened due to risk for diabetes. This resulted in a GDM rate of only 0.9% (n=54), which is a low incidence rate by current standards. This is, in part, due to different diagnostic criteria or fewer risk factors 30 years ago as the most important factor for screening is body weight. Obesity rates have steadily increased in a few past decades and 17 % of adults in Denmark were obese in 2017 (17). Obesity, thus, has more than doubled; up from 7.5 in 1994 and 9.5 % in 2000 (18). This would, too, affect incidence rates of DM, as obesity increased during the follow up period and added new risks, for which we have no data and, thus, cannot substantiate. In comparison to this mega-trend in the Western world, other risk factors seem less important, like the diagnostic criteria, efficacy in the diagnostic work-up, breast feeding, smoking and life style changes. One tenth of the women did not have a second OGTT to confirm that they did not have GDM despite having diabetes risk factors. Thus, in these women GDM may have been overlooked and biased the follow-up with an increased the risk of manifest DM. The issue of non-compliance within screening programs is a well-known, even to-day when screen positive rates are 3-5 times higher (1,2,6,10,11,13).

In conclusion, the incidence of diabetes is higher in women with a previous normal OGTT in pregnancy compared to the background incidence. Follow-up on women with risk factors for diabetes, even after a pregnancy without GDM, may identify women with manifest diabetes earlier to prevent possible complications. On this background our results are useful in identifying the time where women may benefit from the effective implementation of evidence-based treatment to postpone and advert manifest DM, even though they had a normal OGTT during pregnancy.

Abbreviations

BMI: body mass index

GDM: gestational diabetes

IGT: Impaired glucose tolerance

OGTT. Oral glucose tolerance test

SD: standard deviation

T1DM: Type 1 diabetes mellitus

T2DM: Type 2 diabetes mellitus

Declarations

Ethical approval: The Danish Data Protection Agency approved the project (Nos. 1-16-02-824-17, 1-16-02-825-17 and 1-16-02-180-17) and the ethical standards were in compliance with the 1964 Helsinki

declaration and its later amendments or comparable ethical standards. The original approvals included permission to add of data from one cohort study to the other, which is covered by the running permission no. 621549 and belongs to the approval no 1-16-02-824-17. The regions umbrella permission further covers retrospective follow-up studies as long as no single person is identifiable and thus anonymous. The handling of data is conforming with the personal data law and further expressed by the data handling agreement no. 509 with the National Health Authority.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors. According to the approval by law n. 509 no persons need to give consent to access or publication of the registered data.

Data are anonymized and cannot by law be transferred out Denmark.

Disclosure of interests: The authors report no conflict of interest.

Funding: This study was not funded by any grants

Role of the funding source: None

Authors' contribution:

GD: Data verification and qualification, manuscript writing

FFL: Project idea and implementation, registration and legal applications, data analysis and manuscript editing

AVG: Data evaluation and verification, manuscript editing

KK: Data evaluation and manuscript editing

MFN: Data evaluation and manuscript editing

Acknowledgements: None

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Tables

Table 1: Baseline characteristics of the 352 pregnant women with normal and borderline OGTT

	Total n = 352	Normal OGTT n = 278	Borderline OGTT n = 74	Borderline vs. normal OGTT p-value
Height (cm)	168 ±6	169 ±6	166 ±5	0.001
Weight pre-pregnancy (kg)	78 ±16	79 ±17	76 ±15	0.14
BMI pre-pregnancy (kg/m^2)	27.6 ± 6	27.7 ± 5.7	27.5 ± 5.3	0.82
Overweight (>25 kg/m^2) no (%)	219 (62)	168 (60)	50 (68)	0.28
Obesity (>30 kg/m^2) no. (%)	106 (30)	86 (31)	20 (27)	0.57
Severe obesity (>35 kg/m^2) no. (%)	32 (9)	27 (10)	5 (7)	0.5
Parity[a] (no.)				
0	159	126	33	
1	107	81	26	0.97
≥2	63	48	15	
Age at delivery (yrs)	29 (19-47)	29 (19-43)	30 (20-47)	0.08
Age >38 years no. (%)	15 (4)	11 (4)	4 (5)	0.74
Smoking no. (%)	64 (18)	47 (17)	17 (23)	0.15
Ethnicity non-Danish no. (%)	11 (3)	8 (3)	3 (4)	0.71
Screening criteria				
Pre-pregnant BMI >27 kg/m^2 no. (%)	209 (59)	161 (58)	48 (65)	0.29
Family history of DM	70 (20)	53 (19)	17 (23)	0.41
Previous GDM no. (%)	19 (5)	12 (4)	7 (9)	0.08
Glycosuria no. (%)	38 (11)	27 (10)	11 (15)	0.21
Previous macrosomia no. (%)	15 (4)	12 (4)	3 (4)	1
Stillbirth no. (%)	4 (1)	4 (1)	0	-

All data following Gaussian distribution are given as mean ± SD, DM: diabetes mellitus, GDM: Gestational diabetes; [a]: data on parity was missing in 23 cases

Table 2: Pregnancy data and neonatal outcome in 352 women with normal and borderline OGTT

	Total n = 352	Normal OGTT n = 278	Borderline OGTT n = 74	Borderline vs. normal OGTT p-value
OGTT data				
Weight (kg)	87 (53-136)	87 (53-136)	85 (58-132)	0.21
BMI (kg/m^2)	30 (20-40)	29 (20-40)	31 (22-40)	0.65
last OGTT (week)[a]		30 (13-39)	32 (22-40)	0.005
Fasting glucose (mmol/l)		4.9 (3.4-5.9)	5.1 (4.3-7.8)	0.001
Weight at delivery (kg)[b]	94 (55-140)	96 (55-140)	90 (60-134)	< 0.05
Gestational hypertension / preeclampsia no. (%)	18 (5)	13 (5)	5 (7)	0.55
Hematoma no.	2	1	1	n.s.
Anal Sphincter rupture no.	3	2	1	n.s.
Neonatal anthropometrics				
Gestational age (weeks)	40±1	40±1	40±1	0.57
Birth weight (g)[c]	3749±540	3720±514	3852±611	0.07
Birth weight ratio[c]	1.08 ±0.14	1.07 ±0.13	1.12 ±0.15	0.017
Child length (cm)[c]	53±2	53±2	53±2	0.42
Ponderal index (g/dm^3)[c]	25.6±2.5	25.5 ±2.4	26±2.8	0.15
Head circumference (cm)[c]	36±2	36±1	36±2	0.6
Shoulder dystocia no.	2	1	1	n.s.
Fetal malformation no.	4	4	0	0.58
Perinatal demise no.	2	1	1	n.s.
Preterm delivery (> 3 weeks ante term no.	5	5	0	0.37

All data following Gaussian distribution are given as mean ± SD, n.s. : non-significant

[a]: In 27 women no further testing was performed after week 22, [b]: Data for 242 women only, [c]: 24 birth weights were unavailable

Table 3: Follow-up data in women with normal and borderline OGTT during pregnancy

	Total n = 347	Normal OGTT n = 274	Borderline OGTT n = 73	Borderline vs. normal OGTT p-value
Follow-up all women (years)	28 (7.5-28)	28 (7.5-28)	28 (10-28)	0.14
Age at follow-up on women without diabetes diagnosis (years)[a]	57 (47-70)	57 (47-70)	57 (48-68)	0.28
Follow-up of women until diabetes diagnosis (years)[b]	20 (10.5-25)	20 (10.5-25)	19 (11-25)	0.12
T2DM+T1DM in no. (%)	61+3 (18)	38+3 (15)	23+0 (32)	0.001[c]
T1DM in %	4.7	7.3	0	0.01

All data are given as median (range); follow-up time is given as years after pregnancy.

Crude diabetes rate is calculated as no. of women diagnosed with diabetes / women followed-up; T1DM: Type 1 diabetes, T2DM: Type 2 diabetes; [a]: n=283, [b]: n=64, [c]: T2DM+T1DM combined

Table 4: Endocrine and cardiovascular data post-partum and most recent data

	Non-DM at latest follow-up[a]		Manifest diabetes[a]
	Normal OGTT n = 233	Borderline OGTT n = 50	n = 64
Hypercholesteremia no. (%)	37 (16)	9 (18)	47 (73)*
Thyroid disorder no. (%)	22 (9)	4 (8)	12 (19)*
Osteoporosis no.	3	1	1
Treatment of diabetes (n)			
Diet			6
Tablets			47
Insulin (hereof T1DM)			11 (3)
OGTT gestational week	30 (14-40)	31 (22-40)**	32 (18-39)
Fasting glucose at OGTT in pregnancy (mmol/l)	4.9 ±0.7**	5.1 ±0.5	5.1 ±0.6
Cardiovascular disorders no.(%)	81 (35)	19 (38)	49 (77)*
Most recent measurements			
			Borderline vs. normal. OGTT; p-value
HbA1c (mmol/mol)	37 ±4	38±5	0.39

All data following Gaussian distribution are given as mean ± SD, non-Gaussian data are given as mean (range). a: 347 of 352 women had follow-up

*: Manifest diabetes vs. the other groups p<0.01; **: normal OGTT vs. the other groups, p< 0.01

Figures

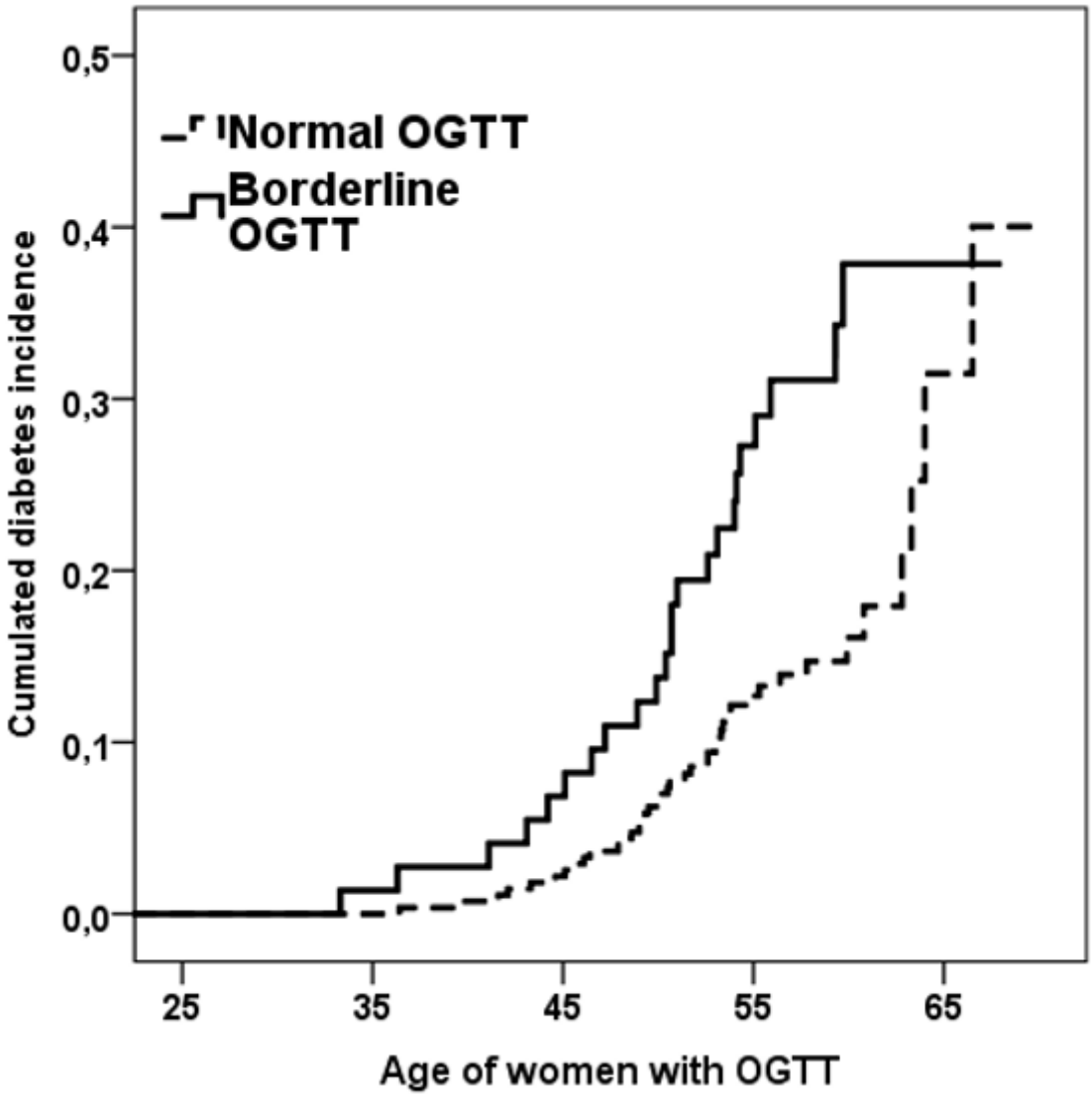

Figure 1

Cumulated diabetes incidence by age of the women with normal and borderline OGTT result during pregnancy Women with normal vs. borderline OGTT during pregnancy, p<0.0001

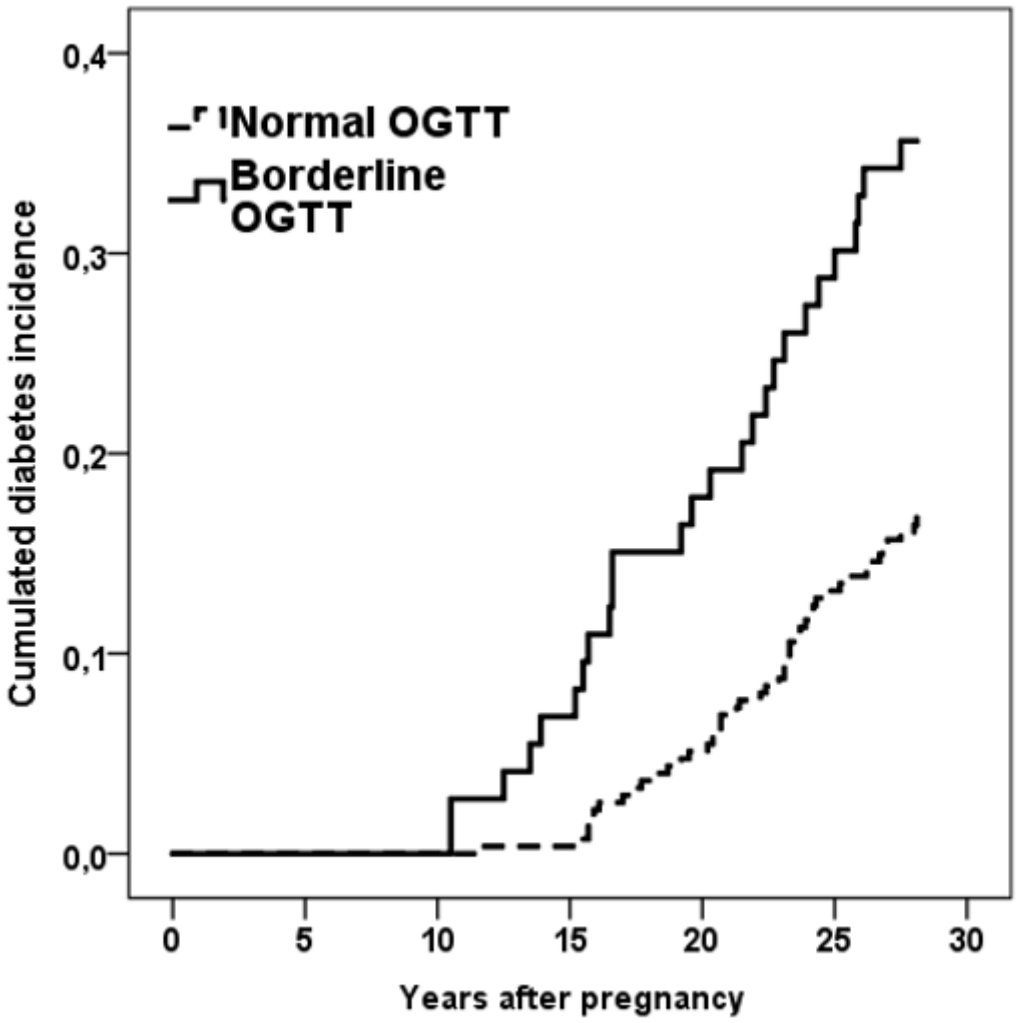

Figure 2

Cumulated diabetes incidence after normal pregnancy by OGTT result during pregnancy Women with normal vs. borderline OGTT during pregnancy, p<0.0001