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Early *vs.* standard screening and treatment of gestational diabetes in high-risk women – An attempt to determine relative advantages and disadvantages

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Abstract *Background and aims:* Screening for Gestational Diabetes (GDM) is usually recommended between 24 and 28 weeks of pregnancy; however available evidence suggests that GDM may be already present before recommended time for screening, in particular among high-risk women as those with prior GDM or obesity. The purpose of this retrospective study was to evaluate whether early screening (16–18 weeks) and treatment of GDM may improve maternal and fetal outcomes.
Methods and results: In 290 women at high-risk for GDM, we analyzed maternal and fetal outcomes, according to early or standard screening and GDM diagnosis time. Early screening was performed by 50% of high-risk women. The prevalence of GDM was 62%. Among those who underwent early screened, GDM was diagnosed at the first evaluation in 42.7%. Women with early diagnosis were more frequently treated with insulin and had a slightly lower HbA1c than women with who were diagnosed late. No differences were observed in the prevalence of Cesarean section, operative delivery, gestational age at the delivery, macrosomia, neonatal weight, Ponderal Index and Large-for-Gestational-Age among women with early or late GDM diagnosis or NGT. However, compared to NGT women, GDM women, irrespective of the time of diagnosis, had a lower gestational weight gain, lower prevalence of macrosomia (3.9% vs. 11.4%), small (1.7% vs. 8.3%) as well as large for gestational age (3.3% vs. 16.7%), but higher prevalence of pre-term delivery (8.9% vs. 2.7%).
Conclusion: Early vs. standard screening and treatment of GDM in high-risk women is associated with similar short-term maternal-fetal outcomes, although women with an early diagnosis were treated to a greater extent with insulin therapy.

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Introduction

The screening for Gestational Diabetes (GDM) is usually recommended between 24 and 28 weeks of pregnancy [1–4] as a compromise between time of detection of GDM and potential for subsequent treatment and risk containment [5]. However, available evidence suggests that GDM may be already present before recommended time for screening, in particular among high risk women as those with prior GDM or obesity [6–8]. Unfortunately, there is no available information regarding the impact of an earlier (16–18 gestational weeks) screening and treatment of GDM on maternal and fetal outcomes. The purpose of the present study was to evaluate some short-term maternal and fetal outcomes among women at high risk for GDM who performed early (16–18 gestational weeks) or standard screening (24–28 gestational weeks) receiving comparable real world care of GDM.

Methods

This retrospective study included a total of 290 high-risk pregnant women as indicated by prior GDM or pre-pregnancy-BMI $\geq$30 kg/m^2 or fasting plasma glucose (FPG) 5.55–6.94 mmol/L at the first prenatal visit, who attended the Diabetes Clinic of the University Hospital of Pisa between January 2013 and December 2016 for the screening of GDM, according to the Italian National Guidelines [9,10]. Based on these guidelines and according to risk stratification, high risk women should be screened between the 16th-18th gestational week to be repeated at 24th-28th week in case of normal glucose tolerance (NGT). However, out of 290 women, 145 (50%) underwent oral glucose tolerance test (OGTT) at 16th-18th gestational week and received a further OGTT at 24th-28th week if the results were normal, according to our guidelines, while the remaining 145 (50%) of the women recruited disappointed the guidelines and performed only the standard screening at 24th-28th week of gestation [11]. Therefore, we compared a group of women who, according to guidelines performed early screening, with those who did not. On the morning of the screening day, consent for the processing of personal data was obtained from each woman. Body weight and height were measured and an 75-g OGTT was performed after an overnight fast for the measurement of basal, 1 h- and 2 h plasma glucose using a glucose-oxidase standard technique. The diagnosis of GDM was based on IADPSG/WHO criteria [1,2]. For all women, standardized medical history and fasting plasma glucose (FPG) level during the first trimester were recorded. All women with a diagnosis of GDM received medical information by the Diabetologist, a personalized diet by the dietitian and were encouraged to monitor their blood glucose by collecting fasting and 1 h post-meal capillary glucose values. Insulin treatment was prescribed in case of fasting glucose values >5.1 mmol/L or 1 h plasma glucose >7.2 mmol/L in at least 20% of the evaluations carried out within two weeks. Both GDM groups, early and standard diagnosis, were equally treated according to the best practice care; the only difference was the time at which the treatment for GDM started: 16–18 gestational weeks (defined as *early*) *vs*. 24–28 gestational weeks (defined as *late*). Obstetric surveillance was performed in all women in accordance with national guidelines [9]. HbA1c (measured by high-performance liquid chromatography) was determined at 30–32 weeks of pregnancy. Maternal body weight at the end of pregnancy, mode of delivery and maternal and fetal outcomes were obtained from hospital discharge records. Pre-pregnancy-BMI (kg/m^2) was calculated from height and self reported pre-pregnancy body weight. Gestational weight gain was calculated as the difference between body weight at delivery and self-reported pre-pregnancy weight. The study complies with the Declaration of Helsinki and was approved by the local Ethical Committee. Statistical analysis was performed using the SPSS program. Continuous measures are expressed as mean $\pm$ standard deviation (SD), while discrete variables are reported as count and/or percentage. Statistical significance was tested by ANOVA, LSD Fisher's test or X^2 test as appropriate.

Results

The main features of the study population are shown in Table 1. As many as 87.1% of pregnant women were Caucasian. There was no difference in any of the parameters assessed between women with early screening versus those with standard screening, with the exception of the prevalence of prior GDM that was more common among women who performed early screening (42.3% vs. 20.6%; $p < 0.01$). Among those undergoing early screening, GDM

Table 1 Main characteristics of women included in the study.

	All	Early screening (16–18 weeks of pregnancy)	Late screening (24–28 weeks of pregnancy)	p
Women	290	145	145	
Age (years)	34.6 $\pm$ 5.1	34 $\pm$ 5	35 $\pm$ 5	n.s.
FPG at first prenatal visit (mmol/L)	4.77 $\pm$ 0.56	4.82 $\pm$ 0.56	4.77 $\pm$ 0.67	n.s.
Pre-pregnancy-BMI (Kg/m^2)	30.2 $\pm$ 6.1	29.9 $\pm$ 6.4	30.5 $\pm$ 5.7	n.s.
FPG 5.55–6.94 mmol/L at first prenatal visit	15.2%	13.7%	16.1%	n.s.
Pre-pregnancy-BMI $\geq$30 kg/m^2	62.7%	59.0%	66.4%	n.s.
Previous GDM	31.2%	42.3%	20.6%	<0.01
Family history of diabetes	37.8%	41.4%	34.1%	n.s.

FPG: Fasting Plasma Glucose. BMI: Body Mass Index. GDM: Gestational diabetes Mellitus.

was diagnosed in 62 women (42.7%) while this prevalence was higher among those with standard screening (n = 92; 63.4%). Among NGT women at early screening, repeat late OGTT led to GDM diagnosis in 26 of them (31.3%), for a total of 88 women with GDM (60.7%) among those who performed early screening, and overall GDM prevalence of 62% (180 women) in the whole cohort (Fig. 1). When women with GDM diagnosed at 16–18 gestational weeks were compared to those with GDM diagnosed at 24–28 gestational weeks, the former had higher FPG at the first prenatal visit, but no difference in prior GDM (Table 2). Women with early diagnosis of GDM were more frequently treated with insulin (48 vs. 29%, $p < 0.01$) and had lower HbA1c than women with late diagnosis (34 ± 3 vs. 36 ± 3 mmol/mol, $p < 0.05$). No differences were observed between women with early *vs.* late diagnosis in mean capillary glucose values, measured fasting and 1 h post-meals, as well as in the rate of women achieving glucose target at 35–37 gestational weeks (Table 3); only women with early screening and late diagnosis reached the post-meal glucose target at the lower rate. Moreover, no difference between early *vs.* late diagnosis was observed in rate of weight gain by the starting of GDM treatment (at the time of diagnostic OGTT) to the delivery (data not shown). Table 4 reports typical outcomes of interest for mothers with diabetes and their newborns. Neither maternal nor newborn outcomes differed between women with early *vs.* those with late diagnosis (Table 4). When compared to NGT women, GDM women, irrespective of the time of diagnosis, had a paradoxical lower gestational weight gain (Table 2), lower prevalence of macrosomia (3.9% *vs.* 11.4%; $p = 0.02$), and lower small (1.7% *vs.* 8.3%; $p = 0.02$) as well as large for gestational age (3.3% *vs.* 16.7%; $p < 0.0001$). However, women with GDM

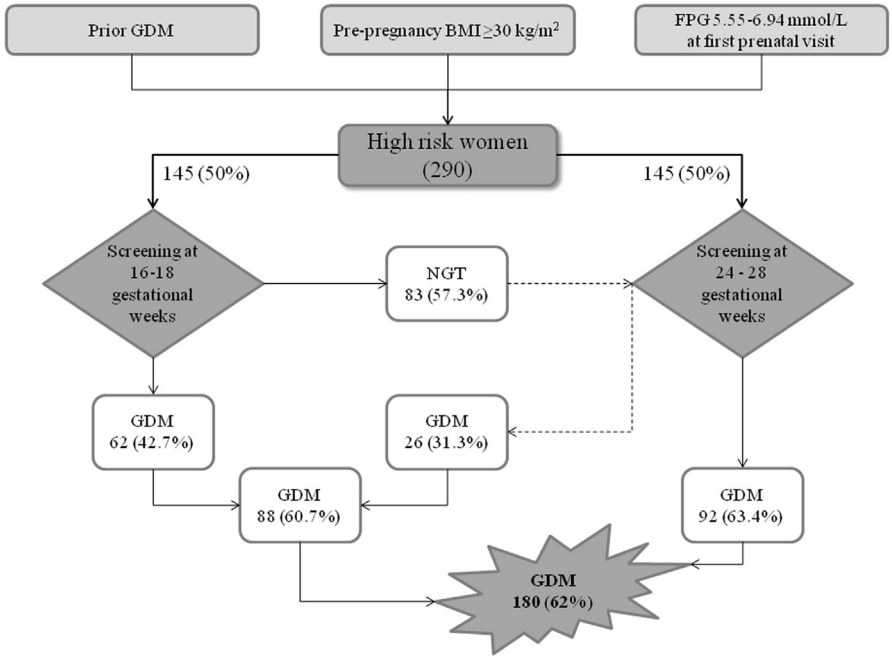

Figure 1 Screening time and diagnosis of GDM in the pregnant women of the study cohort. FPG: Fasting Plasma Glucose. BMI: Body Mass Index. GDM: Gestational Diabetes Mellitus. NGT: Normal Glucose Tolerance.

Table 2 Main characteristics of women according to timing of GDM screening and diagnosis.

	Normal Glucose Tolerance	Early screening Early diagnosis	Early screening Late diagnosis	Late screening Late diagnosis	p
Women	110	62	26	92	
Age (years)	34 ± 5	34 ± 6	35 ± 5	35 ± 5	n.s.
FPG at first prenatal visit (mmol/L)	4.61 ± 0.44	5.16 ± 0.61	4.83 ± 0.44	4.72 ± 0.61	<0.01[a]
Pre-pregnancy -BMI (Kg/m^2)	28.7 ± 6.3	31.2 ± 6.4	30.9 ± 40.8	30.2 ± 7.1	<0.05[b]
FPG 5.55–6.94 mmol/L at first prenatal visit	7.1%	36.7%	0%	13.2%	0.001[a]
Pre-pregnancy-BMI ≥30 kg/m^2	57.4%	58.1%	61.5%	71.7%	n.s.
Previous GDM	28.6%	37.5%	57.9%	22.7%	n.s.
Family history of diabetes	37.1%	45.9%	45.8%	31.1%	n.s.
Gestational Weight Gain (Kg)	13.2 ± 5.2	10.1 ± 4.7	10.8 ± 4.9	12.0 ± 5.4	0.01[b]

FPG: Fasting Plasma Glucose. BMI: Body Mass Index. GDM: Gestational diabetes Mellitus.
[a] Early screening Early diagnosis vs. Normal Glucose Tolerance and vs. Late screening Late diagnosis.
[b] Normal Glucose Tolerance vs. Early screening Early diagnosis and vs. Late screening Late diagnosis.

Table 3 Mean value of fasting and 1 h post-meal glucose value and rate of women achieving glucose target at 35–37 gestational week, registered at the time of last visit at Diabetes Clinic before delivery.

	All GDM	Early screening Early diagnosis	Early screening Late diagnosis	Late screening Late diagnosis	p
Women	180	62	26	92	n.s.
Fasting glucose (mmol/L)	4.9 ± 0.4	4.9 ± 0.4	4.9 ± 0.4	4.8 ± 0.4	n.s.
1 h-post-brackfast glucose (mmol/L)	6.4 ± 0.7	6.4 ± 0.7	6.6 ± 0.6	6.3 ± 0.7	n.s.
1 h-post-lunch glucose (mmol/L)	6.6 ± 0.7	6.7 ± 0.6	6.3 ± 0.8	6.5 ± 0.7	n.s.
1 h-post-dinner glucose (mmol/L)	6.6 ± 0.8	6.8 ± 0.6	6.5 ± 0.7	6.6 ± 0.9	n.s.
Fasting glucose <5.1 mmol/L	51.1%	41.9%	42.3%	59.8%	n.s.
1 h-post-meal glucose <7.2 mmol/L	84.4%	88.7%	65.4%	87.0%	0.014[a]

GDM: Gestational diabetes Mellitus.
[a] Early screening Late diagnosis *vs.* other groups.

had higher prevalence of pre-term delivery in comparison with NGT (8.9% *vs.* 2.7%; p = 0.04).

Discussion

By this analysis we have shown that in high-risk women for GDM, detection and treatment of diabetes early in the course of pregnancy (16–18 weeks) is not associated with any specific advantage in terms of maternal and newborn outcomes, despite the achievement of similar glycemic control in women with early and late GDM diagnosis. However, the early use of insulin therapy in women with early diagnosis is itself a factor that influenced the good glycemic control and therefore may positively impact on outcomes of pregnancy.

The importance of strict metabolic control before and during pregnancy is widely regarded as essential to prevent complications in women with pre-gestational diabetes mellitus [12,13]. Similarly, effective management of GDM is also essential to minimize adverse outcomes (macrosomia, prematurity and neonatal hypoglycemia) and cesarian section delivery [14,15]. Because of these clear-cut advantages, greater attention has been paid with respect to prompter GDM diagnosis and treatment. In fact, up to 25% of cases of GDM could be detected at a much earlier stage during pregnancy [6] ensuring timely treatment. In spite of these expectations, there are no studies directly assessing the usefulness of early glucose screening after the first antenatal visit and consequent earlier treatment.

To date, international guidelines suggest GDM screening to be performed at 24–28 weeks of gestation [1–4]. However, in some countries an earlier screening is recommended in high risk women. For instance, the NICE guidelines [16] recommend that women with prior GDM should be offered an OGTT at 16–18 weeks and a repeat OGTT at 28 weeks if the results are normal. Similarly, the Italian National Health System [9,10] recommends early screening between 16 and 18 gestational weeks in women with prior GDM, or obesity or impaired fasting plasma glucose (FPG 5.55–6.94 mmol/L) during the first trimester of pregnancy. However, addressing the questions about who should be screened and when screening should be performed, would be benefits from data determining the risks and the advantages of early GDM screening.

Some data suggest that in women with an early-onset (first trimester) of GDM, the maintenance of a good metabolic control, started early in the pregnancy, may improve maternal and fetal outcomes [17–19]. However, all these outcome studies performed the glucose screening at the first prenatal visit, and the authors concluded that these women probably had previously undiagnosed overt diabetes discovered during pregnancy. Similarly, a very recent retrospective cohort analysis by Feghali et al. [20] showed that GDM diagnosed before 24 weeks was associated with an increased risk for macrosomia and was not associated with other adverse outcome. However, also in this study, screening for pre-existing diabetes was not universally performed, therefore it is possible that some cases of overt diabetes were missed. Moreover, GDM

Table 4 Main short-term maternal and fetal outcomes according to timing of GDM screening and diagnosis.

	Normal Glucose Tolerance	Early screening Early diagnosis	Early screening Late diagnosis	Late screening Late diagnosis	p
Women	110	62	26	92	
Cesarian Section	43.8%	40.9%	40.8%	47.6%	n.s.
Operative delivery	6.3%	2.3%	0%	2.6%	n.s.
Gestational age at the delivery	39.4 ± 1.5 weeks	38.8 ± 2.2 weeks	38.7 ± 1.6 weeks	39.1 ± 2.1 weeks	n.s.
Pre-term delivery	2.5%	6.8%	9.5%	10.5%	n.s.
Macrosomia	11.4%	4.5%	0%	3.9%	n.s.
Ponderal Index	2.61 ± 0.36	2.66 ± 0.25	2.62 ± 0.23	2.58 ± 0.24	n.s.
Small-for-Gestational-Age	8.3%	0%	0%	3.1%	n.s.
Large-for-Gestational-Age	16.7%	4.5%	0%	3.1%	n.s.
Apgar (5 min) ≤ 8	7.3%	11.3%	12.0%	0%	n.s.

screening was performed according to Carpenter-Coustan protocol.

To our knowledge, this is the first report exploring the impact of early screening and treatment of GDM in high-risk women, previously screened to exclude overt diabetes, on maternal and newborn outcomes. Although the study finds strength in the application of the recent IADPSG/WHO criteria for the diagnosis of GDM and in the treatment uniformity in a "real world" care, the results should be interpreted with caution due to the small number of women included. However, the present data suggest that screening and effective treatment of GDM early in pregnancy does not lend any specific advantage above and beyond what is provided by diagnosis and effective intervention at 24–28 weeks, raising doubt about the cost effectiveness of early screening. This becomes of even greater concern given the fact that women with NGT at an early OGTT still have to undergo a second test later. Moreover, early GDM diagnosis may increase treatment-related costs and use of medical infrastructure and has the potential to "medicalize" more pregnancies, sometimes with untoward psychological consequences in frailer women. Our data suggest that late GDM diagnosis and treatment were not associated with worse pregnancy outcomes. Therefore, implementation of just the standard screening even in high risk women could potentially save resources. However, since all treatment-related costs may represent a preventative investment for the future health of the mother and her offspring, careful cost-to-benefit analysis will be necessary in larger studies. Although no differences in the fetal and maternal outcomes were observed in our study between women with early and those with late GDM diagnosis, women with early GDM diagnosis had higher FPG at the first prenatal visit and more frequently needed insulin during pregnancy, in agreement with the results of a recent meta-analysis [21], suggesting a "worse" GDM that could potentially benefit from early treatment. However, at screening time, there was no difference in any of the parameters assessed between women with early *vs.* those with late screening, with the exception of the prevalence of prior GDM, which was more common among women performing early screening (Table 1). Therefore, it is not easy to identify which women could really benefit from an early screening and treatment or at higher risk of "worse" GDM, suggesting that also among those who performed standard screening at 24–28 gestational weeks there could be some with "worse" GDM. However, in our study late GDM diagnosis and treatment were not associated with worse pregnancy outcomes. Moreover, it should be considered that the difference between the beginning of treatment is very short (about 8 weeks) and probably may not significantly impact on perinatal outcomes.

Furthermore, it should be considered that the cut-off points used for the diagnosis of GDM were chosen on the basis of the incidence of adverse outcomes in women who performed OGTT at 24–32 gestational weeks [22] and therefore are not automatically transferable to an earlier stage of pregnancy. Insulin resistance increases during the second trimester and glucose levels rise in women who do not have the ability to produce enough insulin to counteract this resistance, therefore different cut-off points should be evaluated in early pregnancy, underlining the need for randomized controlled trials in order to investigate benefits and possible treatment of early-onset GDM.

The prevalence of GDM in our cohort is higher than those published in the literature in other cohorts of high risk women [6,23–25]. For example, in the epidemiological evaluation of GDM prevalence conducted during the European multicenter DALI study [6], which recruited obese women (pre-pregnancy BMI $\geq$29 kg/m^2) before 20 weeks of gestation, the GDM prevalence in early pregnancy was 24%, ranging from 10% in UK to 43% in Denmark. The Italian prevalence of early GDM in this study was 11%. However, this difference in GDM prevalence may be due to the higher risk profile of our cohort, as shown by the baseline characteristics of the two cohorts [23]. Women of our study were older (34.6 $\pm$ 5.1 years *vs.* 32.0 $\pm$ 5.4 years), had higher prevalence of prior GDM (31% *vs.* 6%) and family history of diabetes (37.8% *vs.* 23%) and 15.2% of them had FPG 5.55–6.94 mmol/L at the first prenatal visit; conversely, in the DALI study, women with high FPG levels before 20 weeks of gestation were excluded. Similar clinical differences may be observed comparing our cohort with those recruited in other clinical studies [24,25].

Of interest, GDM women, irrespective of the time of diagnosis, tended to have outcomes that were slightly better than NGT women. This may sound paradoxical, but it must be kept in mind that these are all high-risk women and we tend to account for these differences on the basis of lower gestational weight gain in the GDM than in NGT women. Therefore, irrespective of glucose tolerance, special care should be paid in all high-risk women with respect to all potential risk factors and in particular gestational weight gain [26]. In other words, the lack of GDM diagnosis in high risk women should not result in a relaxation of care, but calls for antenatal counseling aiming to reduce pre-pregnancy obesity and adequate gestational weight gain.

Finally, the extremely high prevalence of Caesarean sections observed in this study deserves to be discussed. This high rate is due to the obstetricians' decisions, who tend to be more often interventionists in women with multiple risk factors. Moreover, our University Hospital is a reference center for complicated pregnancies and the only one with neonatal intensive care unit in our geographical area. Therefore, this could be explain the high rate of Cesarian sections observed.

In conclusion, the results of this survey show that early *vs.* standard screening and treatment of GDM in high-risk women is associated with similar short-term maternal-fetal outcomes, although women with an early diagnosis were treated to a greater extent with insulin therapy, leading to a potential risk reduction and thus to similar outcomes in the two groups. However, before casting doubts about the utility and cost-effectiveness of early GDM screening in high-risk pregnant women, this paper calls for larger surveys and careful analyses of accurately collected data in order to gain stronger evidence that may

guide in selecting those women in whom earlier screening and treatment should be implemented.

Conflict of interest

None declared.

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