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MATERNAL-FETAL MEDICINE

Clinical implications of the 100-g oral glucose tolerance test in the third trimester

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Abstract

Purpose The clinical implications of gestational diabetes mellitus (GDM) diagnosed in the third trimester are not well established and controversy continues regarding the performance of diagnostic tests beyond 28-week gestation. This study aimed to evaluate the incidence of abnormal third trimester oral glucose tolerance test (OGTT) results in women at high risk and to compare the obstetric and neonatal outcomes with those of women with normal OGTT results.

Methods The study included 372 women who completed late (>29 weeks) 100-g OGTT due to suspected fetal macrosomia, polyhydramnios or a personal risk factor for GDM, diagnosed according to the Carpenter & Coustan criteria. Women with only one abnormal OGTT value were diagnosed with GDM by abnormal glucose follow-up and analyzed separately. Obstetric and neonatal outcomes were compared between the GDM and the non-GDM groups.

Results GDM was diagnosed in 85/372 (22%) women, including 35 (59.3%) women with one abnormal OGTT value who were later diagnosed with GDM. Of 200 women who had a normal 1-h 50-g glucose challenge test at 24–28 weeks, late GDM was diagnosed in 33 (16.5%). Seventy-six (89.5%) of those with GDM were treated by dietary therapy and 9 (10.5%) by pharmacological therapy. Among women with GDM, large-for-gestational-age fetuses, labor induction and elective cesarean section were more prevalent than for those without GDM. Significant differences were not found between the groups in macrosomia and neonatal outcomes.

Conclusions The performance of OGTT in women with risk factors during the third trimester should be considered following further prospective trials.

Keywords Gestational diabetes · Late diagnosis · 100-g oral glucose tolerance test · Large for gestational age · Polyhydramnios

Introduction

Gestational diabetes mellitus (GDM) is a glucose intolerance disorder that is first diagnosed during pregnancy [1, 2]. The prevalence of GDM in central Europe is 5–7% and 10% in Asia [3, 4]. Among women with risk factors for GDM, such as family history of DM, Hispanic/Indian/Asian ethnicity, obesity, advanced maternal age, and a previous pregnancy with GDM or macrosomia [5], the rates range from 18 to 25% [6].

Among risk factors for GDM are a history of GDM in a previous pregnancy, previous pregnancy without GDM yet complicated by hypertensive disorders, maternal obesity and fetal macrosomia [7]. GDM is associated with increased maternal and neonatal morbidity, as well as a long-term impact on both the gravida and the offspring [8–12]. Fetal hyperinsulinemia increases risks of complications, such as macrosomia, birth injuries, shoulder dystocia, caesarean sections, neonatal hypoglycemia and respiratory distress [8].The long-term risks for the offspring include endocrine morbidity [10], obesity [11], and increased risk for cardiovascular complications in childhood, adolescence and adulthood [12]. GDM-associated

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maternal complications include metabolic syndrome and cardiovascular disease later in life [9]

GDM screening is recommended at 24–28-week gestation. During this period, insulin resistance increases substantially, and leads to hyperglycemia in women with insufficient insulin secretory capacity to maintain euglycemia [5, 13]. The one-step approach simplifies screening by performing only a diagnostic test, typically a fasting 75-g oral glucose tolerance test (OGTT) in all women. However, the two-step test is the most widely used approach. This consists of a 1-h 50-g glucose challenge test (GCT), after which screen-positive individuals undergo a fasting 100-g OGTT; the latter is a diagnostic test for GDM [5]. A recently published randomized clinical trial showed that twice as many women in the one-step group were diagnosed with GDM, while clinical outcomes such as large-for-gestational-age (LGA), perinatal composite outcome and primary cesarean section (CS) were similar for the two groups [14]. There is no consensus among national and international organizations regarding the optimal approach, and the choice generally depends on local protocols [14].

Controversy continues regarding screening test performance beyond 28-week gestation. Some consider macrosomia and polyhydramnios indications for performing third-trimester OGTT [15]. However, others claim that GDM diagnosed in the last trimester, especially in women who do not require pharmacological therapy, represents a physiological change in glucose metabolism during pregnancy, rather than the feature of a pathological entity [16].

The clinical implications of late GDM diagnosis are also a matter of debate. GDM diagnosed at term was reportedly associated with a twofold increase in CS rate [17] and increased neonatal complications, such as longer hospitalization [16]. However, others found that late diagnosis of GDM was not associated with significant increase in CS rate and adverse neonatal outcomes [17, 18].

Our aim was to evaluate the incidence of abnormal third trimester OGTT results in women at high risk and to compare the obstetric and neonatal outcomes with those of women with normal OGTT results.

Methods

Study design

This is a retrospective cohort study of late OGTT diagnosis (beyond 29 weeks) due to various indications, in women hospitalized in the maternal fetal unit of a tertiary hospital, between January 2017 and September 2020. The study was approved by the medical center's ethics committee.

Study population

Women were included if they had undergone late OGTT during their hospitalization due to suspected LGA, polyhydramnios and/or other factors predisposing them for GDM, such as BMI > 30 kg/m^2, family history of DM and personal history of GDM in a previous pregnancy. Women were also included if they had a pathological GCT during 24–28 weeks of pregnancy that was not followed by an OGTT. Exclusion criteria were pre-gestational DM, twin pregnancy and fetal congenital malformations. In addition, women who underwent late OGTT in our unit but delivered elsewhere were excluded from the analysis.

Interpretation of OGTT results

Interpretation of the diagnostic 100-g OGTT was according to the Carpenter–Coustan criteria [19]. The test was performed in the morning after overnight fasting of at least 8 h. Two abnormalities above the threshold: fasting—95 mg/dL; 1-h—180 mg/dL; 2 h—155 mg/dL and 3 h—140 mg/dL were considered as positive for GDM. Women with one abnormal value were further screened. Accordingly, those with risk factors for GDM such as GDM in a previous pregnancy or obesity were directly diagnosed with GDM. Following the protocol of our unit, the other women were followed with thorough capillary blood glucose tests daily (7 times per day: at fasting state, before each meal and 2 h after each meal). These women did not receive a special diet and were diagnosed with GDM if the follow-up curve was considered abnormal.

Women with newly diagnosed late GDM were instructed by the fetal–maternal unit team to start diet control. Pharmacological therapy was initiated when 30% of capillary blood glucose tests were above goal [20].

Data collection

We searched our computerized database for women who underwent OGTT beyond 29 weeks and retrieved data that included demographic details, such as age and parity, and indication, timing and results of the test. In addition, we collected information regarding GCT and OGTT performance earlier in pregnancy. There was no information regarding first trimester fasting glucose values. Gestational age (GA) at the time of testing was calculated by the last menstrual period or crown-to-rump length if a discrepancy of 7 days was found in the first trimester [21]. Estimated fetal weight was calculated by the Hadlock formula using ultrasonography, and LGA was defined as birthweight more than the 90th percentile for GA. We used the global intergrowth-21

reference of percentile distributions of birth weight adjusted for gender and GA [22]. Polyhydramnios was defined as amniotic index fluid above 25 cm.

Data analysis

Obstetric and perinatal outcomes were stratified by GDM status. Obstetrical complications included pre-eclampsia, pre-term labor, induction of labor and delivery mode. Birth complications included emergent CS, the incidence of shoulder dystocia, and third- or fourth-degree perineal tear. Neonatal outcomes included Apgar score at 5 min < 7, arterial cord pH < 7.1 and neonatal intensive care unit admission.

Three distinct groups were compared: women with no abnormal OGTT value, women with one abnormal OGTT value yet without GDM in further investigation, and women with one abnormal OGTT value and subsequent confirmation of GDM.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), or as median and range values, according to the distribution shapes of the variables. Qualitative variables are presented as frequencies and percentages. Continuous variables were compared between the two groups using either the independent sample *t* test or the Mann–Whitney test, according to the sample sizes of the groups and the distribution shapes of the variables. Categorical variables were analyzed using Pearson's chi-squared test or Fisher's exact test.

The sample size was calculated using the formula for comparing two groups (paired design), based on the findings of two other studies. Accordingly, Eran Zilberberg et al. [15] reported incidence of adverse neonatal outcomes as 4% in the non-GDM group, and 13% in the late GDM group. De Wit et al. [23] reported a GDM prevalence of 22% based on third-trimester OGTT. With a power of 80% and alpha 0.05, we calculated a sample size of 370.

A two-tailed *p* value of < 0.05 was considered statistically significant.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

During the study period, late OGTT (>29 weeks) was performed in 415 women who were admitted to the maternal–fetal medicine unit due to preterm contractions, cervical shortening, antepartum bleeding or trauma. The 21 women who had twin pregnancies and the 22 who delivered elsewhere were excluded from the statistical analysis. Of the total sample, 279 women had undergone previous GCT or OGTT during 24–28-week pregnancy. Those tests showed normal GCT values in 200, abnormal GCT in 49 and normal OGTT values in 30.

GDM diagnosis

The final sample included 372 women who underwent third trimester OGTT. Among them, 263 (70.7%) had a normal result and 50 (13.4%) had two or more abnormal values. Of the 59 (15.9%) with one abnormal value, 35 (59%) were eventually diagnosed with GDM, according to risk factors and glucose curves. Two (6%) required pharmacological treatment. The total number of women with newly diagnosed late GDM was 85/372 (22%); 9 (10.5%) required either insulin or metformin, while 76 (89.5%) required only dietary intervention (Fig. 1).

Statistically significant differences were not observed in maternal age, parity, family history of DM and GA at OGTT performance between those newly diagnosed with GDM during the third trimester and those without GDM. Women diagnosed with GDM were more likely to have had GDM in a previous pregnancy ($p < 0.001$) and were more likely to be obese ($p = 0.040$) (Table 1).

GDM diagnosis, stratified by indications and GCT status

Of 372 women, 200 (53.7%) had a normal GCT result in the second trimester and presented with risk factors for GDM in the third trimester. We stratified the results by GCT status.

Among the 372 women, indications for performing the OGTT included: polyhydramnios (37.6%), suspected LGA (33.9%), pathological GCT (13.2%), personal history of GDM (3%), first-degree family history of DM (9.9%) and obesity (2.4%) (Table 2). GDM was more frequently diagnosed when the OGTT was performed due to personal history of GDM (54.5%), followed by the following indications: pathological GCT (28.6%), suspected LGA (24.6%), polyhydramnios (19.3%) and first-degree family history of DM (18.9%) (Table 2).

Normal GCT at 24–28-week pregnancy

Overall, the probability of GDM diagnosis was 16.5%. The most common reason for performing late OGTT after a normal second trimester GCT was polyhydramnios (47%), followed by suspected LGA (42%), family history of DM (6.5%), obesity (2.5%) and personal history of DM (2%). Among the 200 women with a normal second trimester GCT, 16% of those with polyhydramnios and 13% of those with suspected LGA were diagnosed with third trimester GDM (Table 2).

Fig. 1 Flow-chart

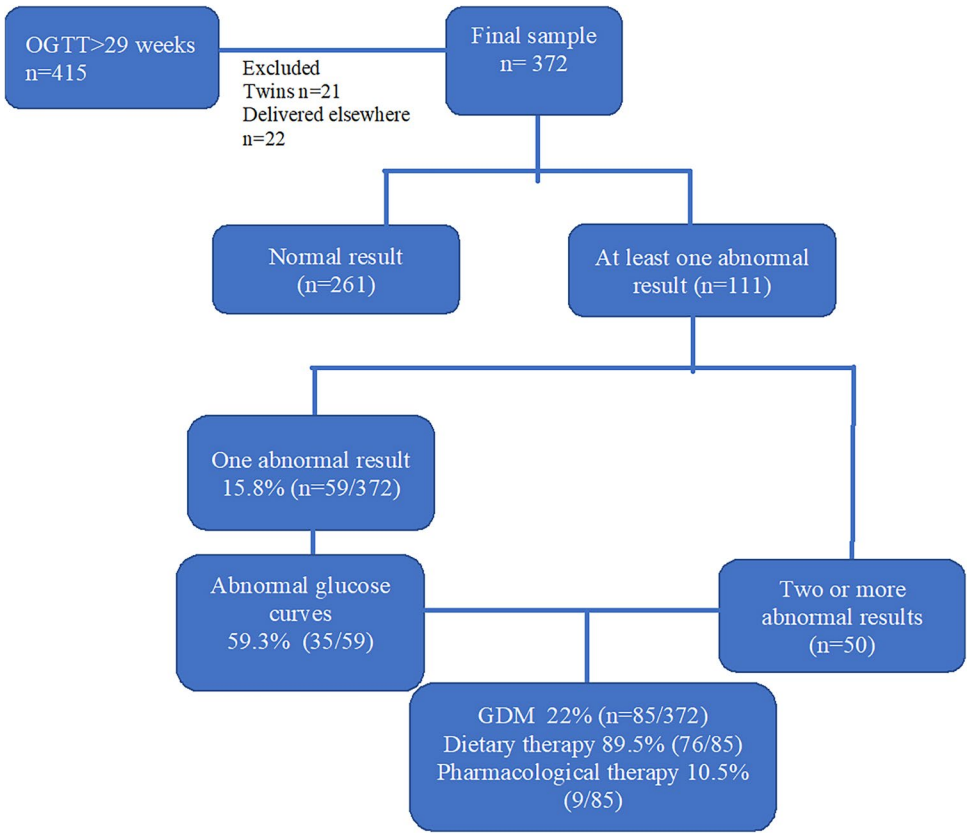

Table 1 Characteristics of the sample, according to GDM and non-GDM

Characteristics	Total sample ($N=372$)	GDM ($N=85$)	Non-GDM ($N=287$)	P value
Maternal age, mean ± SD	32.45 ± 5.4	33.35 ± 6.0	32.18 ± 5.2	0.106
Parity, median [min–max]	2 [1–11]	2 [1–8]	2 [1–11]	0.870
Gestational age at OGTT	37 (29–41.1)	36.5 (29–41.4)	37.1 (29–41.6)	0.066
Obesity, *n* (%)	38 (10.2%)	14 (16.5%)	24 (8.4%)	0.040
Family history of DM, *n* (%)	93 (25%)	26 (30.6%)	67 (23.3%)	0.199
Personal history of GDM, *n* (%)	14 (3.8%)	11 (12.9%)	3 (1.0%)	<0.001
Personal history of macrosomia, *n* (%)	53 (14.2%)	16 (18.8%)	37 (12.9%)	0.215

GDM gestational diabetes mellitus, *SD* standard deviation, *OGTT* oral glucose tolerance test, *DM* diabetes mellitus

Women who did not undergo GCT

In total, 113 women missed their GCT at 24–28 weeks and presented with risk factors for GDM in the third trimester. These women underwent OGTT as a first screening method for GDM. The most common indication for late OGTT in this group was polyhydramnios (35.4%), followed by suspected LGA (31.0%) and family history of DM (21.2%). GDM was more commonly diagnosed among women with suspected LGA (45.7%).

Late GDM diagnosis and obstetrical outcomes

Compared to women not diagnosed with GDM, those diagnosed with late GDM had higher rates of LGA (49.4% vs. 30.7%, $p=0.002$), overall labor induction (34.1% vs. 20.9%, $p=0.014$) and labor induction at >39-week

Table 2 GDM prevalence according to third trimester 100 g-OGTT in high-risk women (total sample and women with normal GCT)

Indications	Total sample ($n=372$)		Women with normal GCT ($n=200$)		Women who did not undergo GCT ($n=113$)	
	Prevalence	Diagnosis of GDM	Prevalence	Diagnosis of GDM	Prevalence	Diagnosis of GDM
Polyhydramnios	140 (37.6%)	27/140 (19.3%)	94 (47%)	15/94 (16%)	40 (35.4%)	9/40 (22.5%)
Suspected LGA	126 (33.9%)	31/126 (24.6%)	84 (42%)	11/84 (13.1%)	35 (31.0%)	16/35 (45.7%)
GCT > 140 mg/dL	49 (13.2%)	14/49 (28.6%)				
Family history of DM	37 (9.9%)	7/37 (18.9%)	13 (6.5%)	3/13 (23.1%)	24 (21.2%)	4/24 (16.7%)
Personal history of GDM	11 (3%)	6/11 (54.5%)	4 (2%)	3/4 (75%)	6 (5.3%)	2/6 (33.3%)
BMI > 30 kg/m^2	7 (2.4%)	0/9 (0%)	5 (2.5%)	1/5 (20%)	8 (7.1%)	0/8 (0.0%)
Total	$N=372$	85/372 (22%)	$N=200$	33/200 (16.5%)	$N=113$	31/113 (27.4%)

GCT glucose challenge test, *LGA* large for gestational age, *DM* diabetes mellitus, *GDM* gestational diabetes mellitus

gestation (45.4% vs. 25.9, $p<0.01$) (Table 3). Overall, CS was not performed more frequently among those diagnosed vs. not diagnosed with GDM (44.7% vs. 39.3%, $p=0.369$), although elective CS was more frequent (22.5% vs. 11.6%, $p=0.018$). Birthweight (3591 vs. 3473 g, $p=0.116$), delivery week (39.3 vs. 38.80, $p=0.072$), the proportion of pre-term birth (5.0% vs. 9.8%, $p=0.259$) and the proportion of male newborns (66.3% vs. 56.6%, $p=0.155$) did not differ significantly between women with and without GDM. Significant differences were not found between these groups in incidences of polyhydramnios (35.3% vs. 42.5%, $p=0.260$), macrosomia (21.1% vs. 16.7%, $p=0.328$), shoulder dystocia (1.3% vs. 0.4%, $p=0.4$), pre-eclampsia (1.2% vs. 2.4%, $p=0.688$) and neonatal intensive care unit admission (5.0% vs. 2.5%, $p=0.276$), nor in Apgar score or cord pH (Table 3). Women with third trimester GDM were more likely to undergo induction of labor, odds ratio (OR) = 1.95 (95% confidence interval [CI] = 1.15–3.33, $p=0.013$) and elective CS, OR = 2.214 (95% CI 1.17–4.20, $p=0.015$) (Table 4).

Table 3 Obstetrics and perinatal outcomes according to the diagnosis of GDM in late pregnancy

Characteristics	100-g OGTT in third trimester		
	GDM	Non-GDM	*P* value
Polyhydramnios	30 (35.3%)	122 (42.5%)	0.260
Gestational age at delivery	39.3 (29.1–42.1)	38.80 (30–41.6)	0.072
Macrosomia (birthweight > 4000 g)	18 (21.1%)	48 (16.7%)	0.328
Birthweight (grams)	3591.2 ± 575.2	3473.5 ± 592.74	0.116
LGA at delivery	40 (49.4%)	84 (30.7%)	0.002
Apgar 5 < 7	0 (0%)	4 (1.4%)	0.579
pH < 7.1	0 (0%)	0 (0%)	NS
Male fetus	53 (66.3%)	155 (56.6%)	0.155
Shoulder dystocia	1 (1.3%)	1 (0.4%)	0.400
NICU admission	4 (5%)	7 (2.5%)	0.276
Pre-eclampsia	1 (1.2%)	7 (2.4%)	0.688
Pre-term birth (<37w)	4 (5%)	27 (9.8%)	0.259
Induction of labor	29 (34.1%)	60 (20.9%)	0.014
Induction of labor > 39 weeks (of 39w + births)	20 (45.4%)	44 (25.8%)	<0.01
Total CS	38 (44.7%)	113 (39.3%)	0.369
Elective CS	18 (22.5%)	32 (11.6%)	0.018

GDM gestational diabetes mellitus, *OGTT* oral glucose challenge test, *LGA* large for gestational age, *NICU* neonatal intensive care unit, *CS* cesarean section

Table 4 Logistic regression of the association of late diagnosed GDM with obstetric outcomes

	OR (95% CI)	*P* value
Induction of labor	1.95 (1.15–3.33)	0.013
Pre-eclampsia	0.467 (0.06–3.92)	0.491
CS due to suspected macrosomia	2.214 (1.17–4.20)	0.015

OR odds ratio, *CI* confidence interval, *GDM* gestational diabetes mellitus, *CS* cesarean section

Comparison between women with one abnormal OGTT value and no abnormal OGTT values

Subgroup analysis revealed that compared with women who had no abnormal OGTT values, women with one abnormal value who were later diagnosed with GDM had a higher rate of LGA (55.9% vs. 31.6%, $p=0.007$) and mean birthweight (3787 g vs. 3595 g, $p=0.029$) (Table 5). Among those with one abnormal OGTT value, we compared those who were later diagnosed with GDM to those who were not diagnosed with GDM. Comparing the former to the latter, the rate of LGA (55.9% vs. 13.6%, $p=0.02$) and the mean birthweight were higher (3787 vs. 3215 g, $p<0.001$), as was the rate of elective CS due to suspected macrosomia (23.5% vs. 0%, $p=0.017$).

Discussion

Among women who underwent late OGTT in the third trimester due to various indications, the GDM rate was 22%. The most frequent indication for performing late OGTT was polyhydramnios, followed by suspected LGA. Factors associated with late GDM diagnosis were obesity and a personal history of GDM in a previous pregnancy. Among women with a previous normal GCT, the diagnosis of third trimester GDM was lower (16.5%). However, according to the guidelines of the Israel Association of Obstetrics and Gynecology, women with risk factors for GDM (BMI > 30 kg/m^2, GDM in a previous pregnancy, previous macrosomia) should undergo OGTT at 24–28 weeks [24].

Our findings corroborate studies reporting that repeat GDM-screening in the third trimester, independent of clinical indications, yields an additional 5.2–23.5% GDM diagnosis [18, 23, 25]. Among GDM and normoglycaemic women in our cohort, the median GA at the OGTT test was 36.5 and 37.1 weeks, respectively. This compares to 33.3 and 33.1 weeks, respectively, as reported in another analysis of women with normal OGTT at 24–28 weeks of pregnancy who repeated the test in the third trimester due to risk factors [23]. Similar to our study, following the second OGTT, 23.5% of the women in that study were subsequently diagnosed with GDM, and the most common indication was related to fetal growth. A prospective study by Kurtbas et al. [25] evaluated GDM screening during 24–28-week gestation by GCT and diagnostic tests. The protocol was repeated at least 1 month after the first screening, at 30–34 gestational weeks, in all women, regardless of risk factors. This resulted in an additional 5.2% diagnosis of late GDM. We report one abnormal OGTT value out of 15.8% of the study cohort, and two abnormal values or more out of 13.4%. This compares with one abnormal OGTT value found in 9.9% reported by a retrospective cohort study [18], that included women with normal GCT at 24–28-week gestation, followed by a third trimester OGTT at 30 weeks. In that study, two or more abnormal values were found in 4.3%.

Our study showed a lower probability for GDM diagnosis when the test was performed after a normal GCT. The rate of additional GDM diagnosis in the third trimester was 13–16% for women with suspected LGA or polyhydramnios when the GCT was normal. Among women who underwent OGTT at 32-week gestation without a prior GCT due to suspected LGA or polyhydramnios, both these indications showed a positive predictive value of 40% for GDM diagnosis [26]. De Wit et al. [23] reported that repetition of the test after a normal OGTT yielded positive predictive values for GDM diagnosis of 7% among those with polyhydramnios and 23% among those with suspected LGA. Our study showed a lower GDM diagnosis rate when the indication was

Table 5 Obstetric outcomes for one abnormal OGTT value (with GDM and without GDM) compared with no abnormal OGTT values

Obstetric 9 Outcomes	1 no abnormal OGTT	One abnormal OGTT value		*P* values for comparing different groups		
		2 without GDM	3 with GDM	1 vs. 2	1 vs. 3	2 vs. 3
Macrosomia	46 (18.3%)	1 (4.5%)	6 (17.6%)	0.140	1.00	0.226
Total CS	108 (43.0%)	5 (22.7%)	16 (47.1%)	0.073 (two sided)	0.714	0.092
Elective CS	32 (12.7%)	0 (0%)	8 (23.5%)	0.088	0.111	0.017
LGA	79 (31.6%)	3 (13.6%)	19 (55.9%)	0.092	0.007	0.02
Birthweight (gram)	3595 (891–4692)	3215 (2278–4510)	3787 (1540–4492)	0.004	0.029	<0.001

GDM gestational diabetes mellitus, *CS* cesarean section, *LGA* large for gestational age statements and declarations

suspected LGA, and a higher GDM diagnosis among those with polyhydramnios.

Interestingly, we found that the most predictive indication for a late GDM diagnosis is a personal history of GDM. This yielded 54.5% with late GDM diagnosis. This result supports the previously reported recurrence rate of 40–50% in future pregnancies [27, 28]. Thus, once diagnosed with GDM in previous pregnancy, preventive measures should be considered in future pregnancy, with adequate-diet quality and exercise considered first line choices for GDM prophylaxis. However, several clinical studies have demonstrated the effectiveness and tolerability of inositols, mainly myo-Inositol, in GDM prevention in a future pregnancy [29]. A recent review showed that myo-Inositol, which is considered safe during pregnancy, can lower GDM rates and improve gestational glycemia and lipid and insulin resistance parameters, as well as reduce the need for insulin therapy should GDM develop later [30, 31]

We report significant increases in labor induction at >39-week gestation, and in elective CS due to suspected macrosomia in women with vs. without GDM. We demonstrated an increase in elective CS rate in accordance with previous studies [16, 32]. This might reflect a lower threshold for performing CS in these women. According to the American College of Obstetricians and Gynecologists (ACOG), for women with GDM treated by diet alone, induction of labor is usually not indicated before 39 weeks; if the fetal status is reassuring, expectant management until 40 6\7 weeks is appropriate [5]. However, for those with GDM treated pharmacologically, induction of labor is appropriate between 39 weeks and 39 6\7. Despite the increased CS rate among our patients with late GDM diagnosis, the rate of macrosomia was not increased, in accordance with previous studies [32]. However, among those with and without GDM, the rate of macrosomia (21.1% and 16.7%, respectively) was higher than the rate of 7.8% reported by the ACOG for the general population [33]. This is probably because the OGTT was performed in a high-risk population with excessive fetal growth and maternal obesity. Fetal macrosomia is a common adverse outcome in unrecognized or untreated GDM [34]. In our study, adequate GDM treatment might explain the similar macrosomia rates between the women treated by a dietary intervention (89.5%) and those who required pharmacological therapy (10.5%). This might also explain the similar rates, in the two groups, of shoulder dystocia and third- or fourth-degree perineal tears. Although other studies reported higher pre-eclampsia rates in women diagnosed with third trimester GDM [16], our study found no significant difference, possibly due to a small sample size.

A strength of our study is the subgroup analysis of women with one abnormal OGTT value. We showed that when personal risk factors were the indications for undergoing late OGTT, one abnormal OGTT value was associated with more than 50% GDM diagnosis, mostly GDM treated by diet. To our best knowledge, we are the first to report this relatively high rate. Simsek et al. [35] showed that women with a single elevated OGTT value had a higher risk of maternal and neonatal complications, similar to women with GDM. They suggested classifying these women as "borderline GDM" and advised further intervention for them, with dietary and lifestyle changes. We showed that GDM diagnosis in this particular subgroup leads to higher rates of CS and LGA, and higher birthweight. No difference was found in the rate of macrosomia, probably because these women were treated briefly after diagnosis, mostly by dietary intervention, while a minority required insulin or metformin for optimal glucose control (5.7%). The higher LGA rate associated with one abnormal OGTT value was similar to that reported by Langer et al. [36]. We suggest that one abnormal OGTT value in the third trimester should be further investigated.

This study has some limitations, including its retrospective design. Since the OGTT test was performed in high-risk women, the conclusions do not apply to all pregnant women. In addition, we do not have follow-up data on postpartum screening results. Previous studies have demonstrated the long-term sequalae of GDM: up to 10% with GDM are diagnosed with type 2 DM soon after delivery and 40–60% during a 10-year follow-up [37, 38]. A recent Danish study by Aagaard et al. [39] showed that the risk of manifesting diabetes after 25 years of follow-up was six times higher in women with previous GDM compared with non-GDM (RR = 6; 95% CI 4–11). Interestingly, an Israeli study by Yefet et al. [40] showed that women with OAV in OGTT are also at increased risk for Type 2 DM; after 12 years of follow-up, the cumulative risk shown was 18%. Women with GDM generally demonstrate higher levels of insulin resistance in the puerperium and/ or later in life, which reflects pancreas B-cell dysfunction, and suggests that GDM is a transient manifestation of longstanding metabolic impairment with predisposition to relapse in the future [37]. Aside from the risk of developing type 2 DM, GDM is also associated with polycystic ovary syndrome with possible reproductive dysfunction in the future[41, 42]. Diagnosing GDM in the third trimester may provide a chance for lifestyle modification, not only during pregnancy but also postpartum.

In summary, the performance of OGTT in women with risk factors during the third trimester should be considered following further prospective trials.

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Declarations

Conflict interests The authors have no relevant financial or non-financial interests to disclose.

Ethics approval This study was conducted according to the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Galilee Medical Center (0115–20-NHR).

Informed Consent Informed consent was unnecessary due to the retrospective nature of the study.

References

1. Kautzky-Willer A, Harreiter J, Winhofer-Stöckl Y, Bancher-Todesca D, Berger A, Repa A, Lechleitner M, Weitgasser R (2019) Gestationsdiabetes (GDM) (Update 2019) [Gestational diabetes mellitus (Update 2019)]. Wien Klin Wochenschr 131(Suppl 1):91–102. https://doi.org/10.1007/s00508-018-1419-8
2. Metzger B, Coustan D (1998) Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus: the organising committee. Diabetes Care 21(Suppl 2):B161–B167
3. Deputy NP, Kim SY, Conrey EJ, Bullard KM (2018) Prevalence and changes in preexisting diabetes and gestational diabetes among women who had a live birth - United States, 2012–2016. MMWR Morb Mortal Wkly Rep 67:1201
4. Lee KW, Ching SM, Ramachandran V, Yee A, Hoo FK, Chia YC, Wan Sulaiman WA, Suppiah S, Mohamed MH, Veettil SK (2018) Prevalence and risk factors of gestational diabetes mellitus in Asia: a systematic review and meta-analysis. BMC Pregnancy Childbirth 18:494. https://doi.org/10.1186/s12884-018-2131-4
5. ACOG Practice Bulletin No. 190 (2018) Gestational Diabetes Mellitus. Obstet Gynecol 131:e49
6. Fuller KP, Borgida AF (2014) Gestational diabetes mellitus screening using the one-step versus two-step method in a high-risk practice. Clin Diabetes 32(4):148–150. https://doi.org/10.2337/diaclin.32.4.148
7. Yoles I, Sheiner E, Wainstock T (2021) First pregnancy risk factors and future gestational diabetes mellitus. Arch Gynecol Obstet 30(4):929–934. https://doi.org/10.1007/s00404-021-06024-8
8. Stewart A, Malhotra A (2015) Gestational diabetes and the neonate: challenges and solutions. Res Rep Neonatol 5:31–39. https://doi.org/10.2147/RRN.S30971
9. Sheiner E, Kapur A, Retnakaran R, Hadar E, Poon LC, McIntyre HD, Divakar H, Staff AC, Narula J, Kihara AB, Hod M (2019) FIGO (International Federation of Gynecology and Obstetrics) Postpregnancy Initiative: Long-term maternal implications of pregnancy complications-follow-up considerations. Int J Gynaecol Obstet 147(Suppl 1):1–31. https://doi.org/10.1002/ijgo.12926
10. Abokaf H, Shoham-Vardi I, Sergienko R, Landau D, Sheiner E (2018) In utero exposure to gestational diabetes mellitus and long term endocrine morbidity of the offspring. Diabetes Res Clin Pract 144:231–235. https://doi.org/10.1016/j.diabres.2018.09.003
11. Huang Y, Zhang W, Go K, Tsuchiya KJ, Hu J, Skupski DW, Sie SY, Nomura Y (2020) Altered growth trajectory in children born to mothers with gestational diabetes mellitus and preeclampsia. Arch Gynecol Obstet 301(1):151–159. https://doi.org/10.1007/s00404-020-05436-2
12. Leybovitz-Haleluya N, Wainstock T, Landau D, Sheiner E (2018) Maternal gestational diabetes mellitus and the risk of subsequent pediatric cardiovascular diseases of the offspring: a population-based cohort study with up to 18 years of follow up. Acta Diabetol 55(10):1037–1042. https://doi.org/10.1007/s00592-018-1176-1
13. American Diabetes Association (2021) 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2021. Diabetes Care 44:S15
14. Hillier TA, Pedula KL, Ogasawara KK, Vesco KK, Oshiro CES, Lubarsky SL, Van Marter J (2021) A pragmatic, randomized clinical trial of gestational diabetes screening. N Engl J Med 384:895
15. Zilberberg E, Mazaki S, Zilberman N, Mazkereth R, Weisz B, Sivan E, Schiff E, Yinon Y (2012) Should late third trimester oral glucose tolerance test be offered for patients with suspected macrosomia or polyhydramnios? Evidence in support of the clinical importance of this policy. Am J Obstet Gynecol 206(1):S122. https://doi.org/10.1016/j.ajog.2011.10.267
16. Lao TT, Tam KF (2001) Gestational diabetes diagnosed in third trimester pregnancy and pregnancy outcome. Acta Obstet Gynecol Scand 80(11):1003–1008. https://doi.org/10.1034/j.1600-0412.2001.801106.x
17. Mohr Sasson A, Shats M, Goichberg Z, Mazaki-Tovi S, Morag I, Hendler I (2019) Oral glucose tolerance test for suspected late onset gestational diabetes. J Matern Fetal Neonatal Med 18:1–5. https://doi.org/10.1080/14767058.2019.1702945
18. Arbib N, Gabbay-Benziv R, Aviram A, Sneh-Arbib O, Wiznitzer A, Hod M, Chen R, Hadar E (2017) Third trimester abnormal oral glucose tolerance test and adverse perinatal outcome. J Matern Fetal Neonatal Med 30(8):917–921. https://doi.org/10.1080/14767058.2016.1190825
19. Carpenter MW, Coustan DR (1982) Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol 144:768–773
20. Harrison RK, Cruz M, Wong A, Davitt C, Palatnik A (2020) The timing of initiation of pharmacotherapy for women with gestational diabetes mellitus. BMC Pregnancy Childbirth 20:773
21. Hadlock FP, Shah YP, Kanon DJ, Lindsey JV (1992) Fetal crown-rump length: reevaluation of relation to menstrual age (5–18 weeks) with high-resolution real-time US. Radiology 182(2):501–505. https://doi.org/10.1148/radiology.182.2.1732970
22. Villar J, Cheikh Ismail L, Victora CG et al (2014) International standards for newborn weight, length, and head circumference by gestational age and sex: The Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet 384(9946):857–868. https://doi.org/10.1016/S0140-6736(14)60932-6
23. de Wit L, Bos DM, van Rossum AP, van Rijn BB, Boers KE (2019) Repeated oral glucose tolerance tests in women at risk for gestational diabetes mellitus. Eur J Obstet Gynecol Reprod Biol 24:79–85. https://doi.org/10.1016/j.ejogrb.2019.09.022
24. Israel Association of Obstetric and Gynecology Guidelines- gestational diabetes, No. 16, May, 2017. https://gynecology.mednet.co.il/%D7%A0%D7%99%D7%99%D7%A8%D7%95%D7%AA-%D7%A2%D7%9E%D7%93%D7%94-%D7%AA%D7%A7%D7%A4%D7%99%D7%9D/
25. Kurtbas H, Keskin HL, Avsar AF (2011) Effectiveness of screening for gestational diabetes during the late gestational period among pregnant Turkish women. J Obstet Gynaecol Res 37(6):520–526. https://doi.org/10.1111/j.1447-0756.2010.01395.x
26. Griffin ME, Coffey M, Johnson H, Scanlon P, Foley M, Stronge J, O'Meara NM, Firth RG (2000) Universal vs. risk factor-based screening for gestational diabetes mellitus: detection rates, gestation at diagnosis and outcome. Diabet Med 17(1):26–32. https://doi.org/10.1046/j.1464-5491.2000.00214.x
27. Wang YY, Liu Y, Li C, Lin J, Liu XM, Sheng JZ, Huang HF (2019) Frequency and risk factors for recurrent gestational diabetes mellitus in primiparous women: a case control study. BMC Endocr Disord 19:22. https://doi.org/10.1186/s12902-019-0349-4

28. Getahun D, Fassett MJ, Jacobsen SJ (2010) Gestational diabetes: risk of recurrence in subsequent pregnancies. Am J Obstet Gynecol 203(5):467.e1-467.e4676. https://doi.org/10.1016/j.ajog.2010.05.032
29. Gambioli R, Forte G, Buzzaccarini G, Unfer V, Laganà AS (2021) Myo-inositol as a key supporter of fertility and physiological gestation. Pharmaceuticals (Basel) 14(6):504. https://doi.org/10.3390/ph14060504
30. Dinicola S, Unfer V, Facchinetti F, Soulage CO, Greene ND, Bizzarri M, Laganà AS, Chan SY, Bevilacqua A, Pkhaladze L, Benvenga S, Stringaro A, Barbaro D, Appetecchia M, Aragona C, Bezerra Espinola MS, Cantelmi T, Cavalli P, Chiu TT, Copp AJ, D'Anna R, Dewailly D, Di Lorenzo C, Diamanti-Kandarakis E, Hernández Marín I, Hod M, Kamenov Z, Kandaraki E, Monastra G, Montanino Oliva M, Nestler JE, Nordio M, Ozay AC, Papalou O, Porcaro G, Prapas N, Roseff S, Vazquez-Levin M, Vucenik I, Wdowiak A (2021) Inositols: From established knowledge to novel approaches. Int J Mol Sci 22(19):10575. https://doi.org/10.3390/ijms221910575
31. Chan KY, Wong MMH, Pang SSH, Lo KKH (2021) Dietary supplementation for gestational diabetes prevention and management: a meta-analysis of randomized controlled trials. Arch Gynecol Obstet 303(6):1381–1391. https://doi.org/10.1007/s00404-021-06023-9
32. Shindo R, Aoki S, Nakanishi S, Misumi T, Miyagi E (2021) Impact of gestational diabetes mellitus diagnosed during the third trimester on pregnancy outcomes: a case-control study. BMC Pregnancy Childbirth 21:246. https://doi.org/10.1186/s12884-021-03730-8
33. Macrosomia: ACOG Practice Bulletin, Number 216 (2020) Obstet Gynecol 135(1):e18–e35 doi: https://doi.org/10.1097/AOG.0000000000003606
34. Kc K, Shakya S, Zhang H (2015) Gestational diabetes mellitus and macrosomia: a literature review. Ann Nutr Metab 66(suppl 2):14–20. https://doi.org/10.1159/000371628
35. Simsek D, Akselim B, Altekin Y (2021) Do patients with a single abnormal OGTT value need a globally admitted definition such as "borderline GDM"? Pregnancy outcomes of these women and the evaluation of new inflammatory markers. J Matern Fetal Neonatal Med 34(22):3782–3789. https://doi.org/10.1080/14767058.2021.1946779
36. Langer O, Brustman L, Anyaegbunam A, Mazze R (1987) The significance of one abnormal glucose tolerance test value on adverse outcome in pregnancy. Am J Obstet Gynecol 157(3):758–763. https://doi.org/10.1016/s0002-9378(87)80045-5
37. Corrado F, D'Anna R, Laganà AS, Di Benedetto A (2014) Abnormal glucose tolerance later in life in women affected by glucose intolerance during pregnancy. J Obstet Gynaecol 34(2):123–126. https://doi.org/10.3109/01443615.2013.841658
38. Noctor E, Dunne FP (2015) Type 2 diabetes after gestational diabetes: The influence of changing diagnostic criteria. World J Diabetes 6(2):234–244. https://doi.org/10.4239/wjd.v6.i2.234
39. Aagaard KA, Al-Far HM, Piscator U, Krogh RA, Lauszus FF (2020) Manifest diabetes after gestational diabetes: a double-cohort, long-term follow-up in a Danish population. Arch Gynecol Obstet 302(5):1271–1278. https://doi.org/10.1007/s00404-020-05669-1
40. Yefet E, Schwartz N, Sliman B, Nachum Z (2021) One elevated oral glucose tolerance test value in pregnancy increases the risk for future diabetes mellitus type 2. Arch Gynecol Obstet 303(4):933–941. https://doi.org/10.1007/s00404-020-05827-5
41. D'Alterio MN, Sigilli M, Succu AG, Ghisu V, Laganà AS, Sorrentino F, Nappi L, Tinelli R, Angioni S (2022) Pregnancy outcomes in women with polycystic ovarian syndrome. Minerva Obstet Gynecol 74(1):45–59. https://doi.org/10.23736/S2724-606X.21.04758-4
42. Thong EP, Codner E, Laven JSE, Teede H (2020) Diabetes: a metabolic and reproductive disorder in women. Lancet Diabetes Endocrinol 8(2):134–149. https://doi.org/10.1016/S2213-8587(19)30345-6