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Changes in the clinical characteristics of women with gestational diabetes mellitus — a retrospective decade-long single center analysis

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Abstract: Aims: Gestational diabetes mellitus (GDM) is an emerging worldwide problem. Changes in clinical characteristics of women affected by GDM in a long-term perspective are still not properly investigated. We aimed to examine such changes over a decade in a retrospective single-center analysis.
Methods: The medical documentation from Department of Metabolic Diseases, Krakow, Poland was analyzed. We included 633 women consecutively diagnosed with GDM in one of three time intervals: 2007–2008 (N = 157), 2012–2013 (N = 272), 2016–2017 (N = 234). Statistical analyses were performed.
Results: Comparison of the three groups identified differences in the mean age of women at the GDM diagnosis (30.7 ± 5.0 years vs. 31.2 ± 4.7 vs. 32.5 ± 4.7, respectively, starting from the earliest 2007–2008 group), pregnancy week at GDM diagnosis (28.0 ± 5.3 wks. vs. 25.9 ± 4.9 vs. 23.4 ± 6.8), the proportion of women diagnosed before the 24th week of pregnancy (12.8% vs. 16.5% vs. 31.3%), and gestational weight gain (12.4 ± 5.0 kg vs. 10.4 ± 5.2 vs. 10.0 ± 5.7); (p = 0.001 or less for all comparisons). We also found differences for glucose values on fasting and at 2 hours with the highest (0 min) and lowest level (120 min) in the 2016–2017, respectively. Finally, a borderline difference for the weight, but not for BMI, was found (64.1 ± 14.1 kg vs. 66.2 ± 13.1 vs. 67.8 ± 15.6; p = 0.04). Differences were also identified in the post hoc analysis between cohorts.
Conclusion: This retrospective analysis illustrates changes in characteristics of women with GDM occurring over the period of decade in Poland. They likely result from both epidemiological trends and modifications of the WHO criteria for the GDM diagnosis.

Keywords: diabetes, diabetes mellitus, gestational diabetes mellitus, GDM, hyperglycemia.

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Introduction

Gestational diabetes (GDM) is an emerging health problem and one of the most common medical complications of pregnancy [1]. It constitutes a challenge for professionals from the field of gynecology and obstetrics, diabetology, internal medicine, pediatrics and midwifery. Numerous scientific studies showed that hyperglycemia in pregnancy might adversely influence pregnancy and perinatal period affecting newborns' and mothers' health [reviewed in 1, 2]. GDM frequency increases worldwide; for example, over the last 15 years, the frequency of its diagnosis has almost doubled in some European countries resulting in much higher cost of health care [1, 3, 4]. This rise seems to be associated with several reasons. One of them is a modification of GDM diagnostic criteria [5]. Another group of factors is related to the objective epidemiological trends involving women in a reproductive age. First, there is the obesity epidemic caused by sedentary lifestyle and unhealthy diet, which is one of the main risk factors for GDM [6]. Additionally, women currently plan their motherhood later, what creates an additional risk of developing disorders of glucose metabolism during pregnancy [7].

There is ongoing debate concerning the criteria and algorithm of GDM diagnosis in the community of diabetologists and gynecologists worldwide. Of note, there are various diagnostic algorithms for GDM in different regions of the world. In some countries screening is limited only to women from the risk groups of GDM (obesity, age above 35 years, a history of GDM in a previous pregnancy, birth of macrosomic baby, miscarriages), while in the other ones universal testing is a long-term standard [1, 8, 9]. For example, in Poland, pregnancy screening for GDM has been universal since 1994 [9]. Additionally, over the last 25 years, the diagnostic criteria of GDM have been changed several times in many countries what have had an impact on the prevalence of this form of diabetes mellitus [9, 10]. The most substantial changes were made after the publication of the HAPO (Hyperglycemia and Adverse Pregnancy Outcome) study results on pregnant women with mild hypoglycemia [11]. As a result of this publication, the GDM WHO diagnostic criteria were substantially toughened in 2013 [12]. In Poland, the criteria for GDM diagnosis were modified in 2014 following these changes introduced by WHO [13].

Specific data on changes in clinical characteristics of GDM patients from different populations in a long-term perspective, that seem inevitable in the light of the objective epidemiological trends and modifications of diagnostic criteria and algorithms, is scare. We aimed to examine changes in the clinical characteristics of women with GDM over the last decade in a retrospective single-center analysis from Poland.

Materials and Methods

This is a retrospective observational analysis based on medical documentation (years: 2007–2008, 2012–2013, 2016–2017) collected at the Outpatient Clinic in Department of Metabolic Diseases, University Hospital in Krakow, a tertiary reference center for pregnant women with diabetes in the Lesser Poland region. Medical data of all consecutive patients were collected from 3 time intervals depending on the years in which they were diagnosed and treated in our center (group I — 2007–2008, group — II 2012 and 2013, group III — 2016–2017). This retrospective study was accepted by the local Bioethical Committee and the authorities of the University Hospital in Krakow.

We gathered the following information from the medical records of women with GDM — age at GDM diagnosis, gestational week of diagnosis, anthropometric measurements (weight and BMI before pregnancy), weight before delivery, gestational weight gain (GWG), glycemic data (fasting glucose level and oral glucose tolerance test at the GDM screening) (Table 1), treatment (diet or insulin) and family history of diabetes. GWG was calculated as a difference between the last measured pregestational body weight and the last weight recorded during outpatient pregnancy care. Additionally, we collected the information for the medical history (past miscarriages, delivery of baby over 4000 g, GDM in previous pregnancies) and existing comorbidities (arterial hypertension, polycystic ovary syndrome, lipid abnormalities, asthma) with the exception of the earliest period 2007–2008 for which they were not available.

Women included in the analysis met the diagnostic criteria of GDM applicable in Poland for the year of diagnosis (Table 1).

Table 1. Diagnostic GDM criteria in Poland over the study period.

Venous plasma glucos (at least one criterion must be met)	Group 2016–2017	Group 2012–2013 and 2007–2008
Fasting glucose level	92–125 mg/dl (5.1–6.9 mmol/l)	100–125 mg/dl (5.6–6.9 mmol/l)
OGTT 75g 60'	≥180 mg/dl (≥10 mmol/l)	—
OGTT 75g 120'	153–199 mg/dl (8.5–11 mmol/l)	≥140 mg/dl (≥7.8 mmol/l)
one hour oral glucose challenge test (GCT) 3rd trimester	—	≥200 mg/dl (≥11.2 mmol/l) 141–199 mg/d (7.8–11.1 mmol/l)–>OGTT 75 g

Pregnancy screening in Poland is universal since 1994. It is recommended to perform the initial examination, usually fasting plasma glucose, at the pregnancy booking. Women with high risk of GDM are immediately referred to OGTT. The OGTT test is obligatory in the third trimester. Until 2014 GCT (glucose challenge test 50 g) was also acceptable as the first step test.

Patients were also divided into two groups: with a GDM diagnosis below 24th week of pregnancy and at or after 24th week of pregnancy. We used this a proxy for a GDM diagnosis made at either the initial or 24th week of pregnancy screening as the Polish Diabetes Association clinical recommendations suggests that the second screening is done at the 24th week of pregnancy or in subsequent weeks. The following variables were compared in this sub-analysis: age at GDM diagnosis, BMI as well as fasting and 2-hour glucose level.

The statistical analysis was performed in *R ver 3.6.1*. Shapiro–Wilk test was used to test the normality of the data. Chi Square test was used to test relationships between categorical variables. To compare three independent time intervals ANOVA or Kruskal–Wallis test was used. To calculate pairwise comparisons between group levels with corrections for multiple testing pairwaise (Bonferoni) pairwise.wilcox.test was used. Based on the statistical data, a trend line model with a coefficient of determination (R^2) was determined for individual variables.

Results

Overall, we analyzed 633 women with GDM who were consecutively diagnosed within three time intervals — 2007–2008 (N = 157), 2012–2013 (N = 272) and 2016–2017 (N = 234). The clinical characteristics of the defined groups of patients are described in Table 2.

Table 2. Population characteristics.

Characteristics	Group I (2007–2008) (N = 157)	Group II (2012–2013 (N = 272)	Group III (2016–2017) (N = 234)	P value*	Group I vs. III p value	Group II vs. III p value	Group I vs. II p value
Age at GDM diagnosis mean ± SD [years]	30.7 ± 5.0	31.1 ± 4.7	32.6 ± 4.7	**<0.0001**	**0.0008**	**0.0014**	**<0.0001**
Body weight before pregnancy mean ± SD [kg]	64.1 ± 14.1	66.2 ± 13.2	67.8 ± 15.6	**0.04**	0.07	1.0	0.1
Prepregnancy BMI mean ± SD [kg/m^2]	23.7 ± 4.7	24.3 ± 4.5	24.9 ± 5.5	0.2			
GWG mean ± SD [kg]	12.4 ± 5.0	10.4 ± 5.1	10 ± 5.7	**<0.0001**	**<0.0001**	0.7	**0.0004**
Week of pregnancy at the last pre-delivery visit mean ± SD [weeks]	34.1 ± 3.5	34.4 ± 3.3	33.9 ± 4.0	0.2			
Week of pregnancy at GDM diagnosis mean ± SD [weeks]	28 ± 5.3	25.9 ± 4.9	23.4 ± 6.9	**<0.0001**	**<0.0001**	**0.0004**	**<0.0001**

GDM diagnosis before 24 weeks of pregnancy [N, %]	20 (12.8%)	45 (16.5%)	73 (31.3%)	**<0.0001**	**<0.0001**	0.3	**<0.0001**
GDM diagnosis at or after 24 weeks of pregnancy [N, (%)]	137 (87.2%)	227 (83.5%)	161 (68.7%)	**<0.0001**	**<0.0001**	**<0.0001**	0.3
Insulin treatment [N, (%)]	77 (49.0%)	108 (39.7%)	112 (47.9%)	0.1			
Glucose level in OGTT 0 min mean ± SD [mmol/l]	4.7 ± 0.7	4.7 ± 0.7	5.0 ± 0.6	**<0.0001**	**0.0003**	**<0.0001**	1.0
Glucose level in OGTT 120 min mean ± SD [mmol/l]	8.9 ± 1.3	8.9 ± 1.4	8.3 ± 1.6	**<0.0001**	**0.0004**	**<0.0001**	1.0
Diabetes family history [N, (%)]	83 (58.9%)	153 (56.3%)	141 (60.8%)	0.7			
GDM in a previous pregnancy [N, (%)]	No data	48 (17.7%)	43 (18.4%)	1.0	—	—	—
Past miscarriages [N, (%)]	No data	57 (20%)	46 (19.7%)	0.7	—	—	—
History of delivery of baby over 4000 g [N, (%)]	No data	19 (7%)	25 (10.7%)	0.1	—	—	—
Hypertension [N, (%)]	No data	26 (9.6%)	13 (5.6%)	0.2	—	—	—
Lipid disorders [N, (%)]	No data	2 (0.7%)	3 (1.3%)	0.8	—	—	—
Asthma [N, (%)]	No data	6 (2.2%)	4 (1.7%)	0.7	—	—	—
Polycystic ovary syndrome [N, (%)]	No data	3 (1.1%)	8 (3.4%)	0.2	—	—	—

Data are presented as mean and standard deviation (SD). For categorical variable numbers and percentage were used. *P-value derived from one-way analysis of variance (ANOVA) or Kruskal–Wallis test to detect a significant difference in the variable levels among study groups.

A comparative analysis of the three groups identified differences in the mean age of women at the GDM diagnosis (30.7 ± 5.0 years vs. 31.2 ± 4.7 vs. 32.5 ± 4.7, respectively, starting from the earliest group), pregnancy week at GDM diagnosis (28.0 ± 5.3 wks. vs. 25.9 ± 4.9 vs. 23.4 ± 6.8), the proportion of women diagnosed before the 24th week of pregnancy (12.8% vs. 16.5% vs. 31.3%), and GWG (12.4 ± 5.0 kg vs. 10.4 ± 5.2 vs. 10.0 ± 5.7); ($p = 0.001$ or less for all comparisons). Additionally, we also found differences for glucose values on fasting and at 2 hours with the highest (0 min) and lowest (120 min) level in the 2016–2017 group, respectively. Finally, a borderline difference for the weight, but not for BMI, was found (64.1 ±

14.1 kg vs. 66.2 ± 13.1 vs. 67.8 ± 15.6; p <0.04). Interestingly, there was no significant difference for the insulin treatment between the analysed groups. Similarly, comparing the data on the patient's medical history, no differences were noted in diabetes family history, history of miscarriages, childbirth above 4000 g, GDM in previous pregnancy and comorbidities.

Plural differences were also identified between the cohorts in the post hoc analysis, that was performed for variables with significant discrepancies in the Anova analysis. First, we compared the 2007–2008 and 2012–2013 groups. Of note, for these two groups the same diagnostic criteria for GDM and algorithm were used (Table 1). In spite of this, we observed differences in age at diagnosis, gestational age at the GDM diagnosis, proportion of diagnosis before the 24th week of pregnancy and GWG.

In the second set of post-hoc analysis, the group treated in 2016–2017 as compared to the earliest 2007–2008 cohort was older at the time of GDM diagnosis, had a higher pre-gestational body weight and earlier GDM diagnosis during pregnancy as well as a higher proportion of GDM diagnosis made before 24 weeks of pregnancy and lower GWG. The groups also differed in terms of both analyzed glucose values as the fasting glucose level was lower and 2-hour higher in the earlier cohort.

Finally, the group treated in 2016–2017 in comparison to the 2012–2013 cohort was characterized by an older age at GDM diagnosis, earlier diagnosis of GDM during gestation with a higher proportion of diagnosis made before the 24th week of gestation and by a lower GWG. This very recent group was also characterized by a higher fasting and lower 2-hour glucose level.

We also compared the subgroups of women from the examined cohorts diagnosed before 24th week of pregnancy and at the 24th week or later as shown in Table 3. In the group of patients with GDM below 24 weeks of pregnancy differences were observed between the cohorts for BMI before pregnancy and 2-hours glucose level.

Table 3. Selected clinical features of examined women from three cohorts as divided according to week (<24 and >24) of GDM diagnosis.

	2007–2008 N = 157	2012–2013 N = 272	2016–2017 N = 234	P value
Women diagnosed before week 24 [N]	20	45	73	
Age at GDM diagnosis mean ± SD [years]	31.5 ± 5.0	30.6 ± 5.2	32.5 ± 4.9	0.2
Prepregnancy BMI mean ± SD [kg/m^2]	25.2 ± 6.4	24.6 ± 4.2	26.8 ± 6.8	0.0002
Fasting glucose mean ± SD [mmol/l]	5.0 ± 1.1	5.0 ± 0.7	5.2 ± 0.6	0.1
2 h glucose mean ± SD [mmol/l]	8.7 ± 1.1	7.9 ± 1.4	7.8 ± 1.8	0.004
Proportion of GDM with pathological: — fasting glucose mean ± SD [N, (%)] — 1 h glucose mean ± SD [N, (%)] — 2 h glucose mean ± SD [N, (%)]	 6/17 (35.3%) No data 9/17 (52.9%)	 12/38 (31.6%) No data 26/41 (63.4%)	 41/68 (60.3%) 23/64 (35.9%) 26/66 (39.4%)	

Women diagnosed after week 24	N = 137	N = 227	N = 161	
Age at GDM diagnosis mean ± SD [years]	30.6 ± 5.0	31.3 ± 4.6	32.6 ± 4.5	0.001
Prepregnancy BMI mean ± SD [kg/m^2]	23.6 ± 4.5	24.3 ± 4.6	24.0 ± 4.5	0.4
Fasting glucose mean ± SD [mmol/l]	4.6 ± 0.6	4.7 ± 0.7	5.0 ± 0.6	0.0001
2 h glucose mean ± SD [mmol/l]	8.9 ± 1.3	8.8 ± 1.4	8.5 ± 1.5	0.3
Proportion of GDM with pathological: — fasting glucose mean ± SD [N, (%)] — 1 h glucose mean ± SD [N, (%)] — 2 h glucose mean ± SD [N, (%)]	 20/126 (15.9%) No data 72/137 (52.6%)	 46/224 (20.5%) No data 118/224 (52.8%)	 52/157 (33.1%) 71/148 (48.0%) 94/156 (60.3%)	

Data are presented as mean and standard deviation (SD). For categorical variable numbers and percentage were used. *P-value derived from one-way analysis of variance (ANOVA) to detect a significant difference in the variable levels among study groups.
For some number of women from the examined cohorts, the original glucose results used for GDM diagnosis were missing in the medical documentation.

In the analysis for the sub-groups of women diagnosed with GDM at or after 24th week of pregnancy differences in age at the diagnosis and fasting glucose level in those groups were also observed.

Discussion

In this study, a retrospective analysis was conducted comparing the clinical characteristics of patients with GDM diagnosed in three different time periods (2008–2009, 2012–2013, 2016–2017). We report differences in several variables between the cohorts and discuss the possible reasons for these observations.

The age at GDM diagnosis was one of the variables with a significant difference between the groups with step-wise increase over the period of the analysis, i.e. 2007–2017. This probably reflects a more general trend of post-pone pregnancy planning that is observed in Poland and the other European countries [14, 15]. The situation is similar in many populations worldwide, for example, in the United States over the last 50 years the proportion of pregnant women aged over 35 years has increased almost eight times [16]. Women report several different reasons for delaying childbearing, such as family situation, economic status, professional career being the priority, unawareness of the age impact on fertility [17]. Very similar results to ours showing a trend of increasing age in women diagnosed with GDM were also reported from the Asian population [18].

Another characteristic showing a difference between the three groups is time of GDM diagnosis during gestation which was getting earlier during the observation. This seems to be closely related to a significantly rising proportion of women with early diagnosis of GDM, defined in our study as <24th week of pregnancy. Of note, the proportion of women with early GDM diagnosis in our cohort increased 2.5 times

over the study period. In Poland, the initial screening for GDM by the evaluation of fasting venous blood glucose level is advised at the first visit to the obstetricians during pregnancy. The oral glucose tolerance test is recommended at that time only for women at risk of GDM [13]. There are several possible reasons for the phenomenon observed by us in this study. One of them may be a growing patients' and physicians' awareness of the necessity of early screening. There is no formal assessment of such awareness in Poland among the medical staff available; however, the annual publication of the clinical recommendations by both the Polish Diabetes Association and the Polish Society of Gynecologists and Obstetricians as well as the full agreement reached by these organizations in terms of GDM criteria and diagnostic algorithm seem to be favorable factors for such increasing consciousness [13, 19]. This may result in a more frequent referral of patients to the OGTT test as an effect of more common classifying women as at-risk individuals. Finally, this growing proportion of early GDM diagnosis may be related to a rising number of women with pregestational diabetes, type 1 or type 2, being misdiagnosed as gestational form of disease [20].

Another variable showing a significant difference between the three groups was GWG, interestingly presented as a gradual fall in the pregnancy weight gain over the study period. While this trend should be considered a desirable phenomenon, as the excessive GWG is a considerable risk factor of many pregnancy outcomes, such as large for gestational age (LGA) birth weight, macrosomia, and gestational hypertension [21], its reason in our study is unclear. Of note, larger values of pregestational BMI were found to be associated with a greater difficulty in maintaining adequate GWG [22]. A trend observed in our cohorts seems to go in an opposite direction as pregestational weight and BMI tended to go slightly up. The possible explanation may be a sooner dietary intervention related to the earlier GDM diagnosis in consecutive cohorts introduced in the tertiary center. The impact of growing awareness and efficacy of this dietary intervention cannot be also excluded.

Changes in pre-pregnancy weight and BMI were both borderline, although a tendency of rise for both variables were observed. Of note, none of the cohorts reached the formal cut-off for overweight. Our data and observed trend are very similar to some other populations, for example, in Australia and New Zealand between 1997 and 2016 the mean pregnancy booking-in BMI climbed from 24.9 to 25.3 in 2012 before rising to 25.6 in 2016 [23]. The almost doubling of the incidence of GDM in the United States between 1978 and 2010 is mainly being explained by the increase in BMI in this population [24]. The observed worldwide increase in BMI among patients with diagnosed GDM is related to the population trend of growing obesity, but also parallel phenomenon of older age of getting pregnant [25].

Finally, we identified differences in glucose levels, both fasting and 2-hour, between the three cohorts. In the post hoc analysis, the latest 2016–2017 cohort showed differences as compared to both earlier groups, that were similar to each other in

terms of glucose. While this is an expected observation taking into account the change in GDM diagnostic criteria and algorithm that occurred in Poland in 2014, the direction of these differences is surprising. The modification of GDM glycemic criteria resulting from the HAPO study decreased the fasting cut-off point from 100 mg/dL to 92 mg/dL and increased the 2-hour glucose level from 140 mg/dL to 153 mg/dL [12, 13]. Thus, one should expect a fall of fasting glucose level and a rise in post-challenge one. Both changes in our study unexpectedly showed an opposite direction. One can speculate that this is a secondary phenomenon related to significant differences in age, pregnancy weeks of GDM diagnosis as well as borderline discrepancies in body mass.

The limitation of this study is its observational, retrospective character, relatively small size of the investigated groups and difficulty in extrapolating the results of the study outside of the Polish population, because the algorithm and criteria for GDM diagnosis are not universal worldwide. However, it is worth pointing out that there are very few studies on the time change in characteristics of the GDM pregnant women. The differences described above are very likely to be a global phenomenon. Finally, we should acknowledge, that we were not able to include in this study delivery and neonatal outcomes, such as macrosomia, congenital defects, perinatal injuries and many others.

In conclusion, this retrospective analysis revealed significant changes in characteristics of women with GDM occurring over the period of decade in Poland. They probably result from both epidemiological trends, for example related to social factors such as later age of pregnancy and increase in obesity in society, as well as modifications of the local recommendations for the GDM diagnosis.

Disclosure

The authors declare have nothing to declare.

Conflict of interest

None declared.

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