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Hyperglycemia in pregnancy — prevalence and perinatal outcomes. A retrospective multicenter cohort study in Poland

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ABSTRACT

Objectives: Hyperglycemia in pregnancy (HIP) is one of the most common complications of pregnancy. Recently adopted new criteria for the diagnosis of HIP as well as the greater prevalence of risk factors could have a significant impact on HIP prevalence. The objective of the study was to assess the rates of HIP and the associated complications.

Material and methods: This was a retrospective analysis of clinical records from pregnant women who delivered in eight tertiary hospitals in Poland in 2016.

Results: The number of pregnant women with hyperglycemia totaled 1280 (7.25%), including gestational diabetes mellitus (GDM) in 1169 (6.62%) women and pregestational diabetes mellitus (PGDM) in 111 (0.63%). In addition to dietary modifications, 477 (41% of the GDM group) women received medical treatment (GDMG2). In women with PGDM multiple daily insulin injections (MDI) were used in 53 (47.7%) cases, continuous subcutaneous insulin infusions (CSII) in 57 (51.3%) cases and one woman was treated with metformin. The rate of cesarean sections was 69.4% and 62.9% for PGDM and GDM, respectively. Large-for-gestational-age (LGA) infants accounted for 38% and 21% of births in the PGDM and GDM groups, respectively. Of note are high rates of hyperbilirubinemia in infants born to mothers treated with insulin (13.5% for PGDM and 14.4% for GDMG2) vs infants born to mothers with diet (GDMG1) (3.4%).

Conclusions: In Poland, the prevalence of HIP has nearly doubled in the past twenty years. Even with appropriate management, HIP is a significant risk factor for a cesarean section delivery, bearing an LGA infant and adverse neonatal outcomes.

Key words: hyperglycemia in pregnancy; HIP; gestational diabetes mellitus; GDM; pregnancy; cesarean section; large for gestational age; LGA

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INTRODUCTION

Hyperglycemia is currently one of the most common complications of pregnancy, with the prevalence ranging from 2% to 25%, depending on the population. These differences in estimates may be accounted for by, among other things, different screening modalities and criteria for the diagnosis of hyperglycemia in pregnancy (HIP). The results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study performed in a cohort of over 23 000 pregnant women demonstrated that even a subtle oral glucose tolerance test (OGTT) abnormality may be associated with adverse perinatal outcomes [1]. Epidemiologic studies also indicate a higher risk of the polymetabolic syndrome developing in later in life in the offspring of mothers with diabetes in pregnancy [2]. The new criteria for the diagnosis of HIP proposed in 2010 by the International Association of Diabetes and Pregnancy Study Group (IADPSG) consensus panel and based on the HAPO study results were widely debated as these new recommendations with lower OGTT thresholds to define HIP resulted in a considerable increase in the rate of HIP (17.8% of the HAPO study population) and the cost of HIP-related antenatal care [3]. In 2013, the World Health Organization changed the criteria for the diagnosis of HIP and adopted the IADPSG recommendations [4]. In recent years, with the support of the International Federation of Gynecology and Obstetrics (FIGO), a number of international and national associations of gynecologists and obstetricians have recommended universal screening for hyperglycemia in pregnancy according to the IADPSG and WHO criteria, in view of the recognized impact of HIP on fetal development and on long-term health outcomes in the mothers and offspring [5]. In 2014, the Polish Gynecological Society (PTG) adopted these new WHO recommendations regarding screening for HIP [6].

In the early 2000s, when 2-step screening for gestational diabetes mellitus (GDM) was applied comprising a glucose challenge test (GCT) and an oral glucose tolerance test (OGTT), the prevalence of GDM was 3.5% as shown by an epidemiologic survey conducted in two regions of Poland [7]. Since the introduction of a 1-step screening using OGTT and the IADPSG and WHO criteria for the diagnosis of GDM there have been no new data on the rates of GDM in Poland. Apart from the new criteria, other factors may be responsible for increased GDM rates such as maternal obesity and age ≥ 35 years. The aim of the present study was to assess the prevalence of HIP and of the associated complications.

MATERIAL AND METHODS

Initially, a retrospective analysis of clinical records of women with HIP who delivered in 2016 was planned in 10 hospitals in nine provincial capital cities in Poland. Ultimately, data were obtained from eight hospitals in eight provinces with a total of 17 654 deliveries, *i.e.*, 4.65% of all deliveries in Poland in 2016. The study population included women with pregestational diabetes mellitus (PGDM) and gestational diabetes mellitus (GDM). The diagnosis of GDM was based on the 75 g OGTT with the following criteria for gestational diabetes: fasting 92 mg% (5,1 mmol/L), 1-hour 180 mg% (10 mmol/L) and 2-hour 153 mg% (8.5 mmol/L). The following were considered in the analysis: subject demographics, obstetric history, including complications and details of previous deliveries vs diabetes type and management.

Statistical analysis

Statistical significance was determined for the differences in the parameters describing the study groups of pregnant women. Included in the analysis were the differences between the PGDM and GDM groups and within the GDM group between the diet treated (GDMG1) and drug therapy (GDMG2) subgroups. The nonparametric Wilcoxon Rank Sum test was used to determine if the differences in quantitative traits [height, BMI (Body Mass Index)] between groups were statistically significant. The p-value was reported (the probability of a difference as large or larger assuming the two groups have the same distribution with the same means for a given trait). A logistic regression model was used for each qualitative trait [BMI > 25, diabetes mellitus in first-degree relative(s)] to determine if the differences in qualitative traits between groups were statistically significant; the trait was a dependent variable and the study group to which a pregnant women belonged was an independent variable. The differences between the PGDM and GDM groups and within the GDM group between the GDMG1 and GDMG2 subgroups were determined as for the quantitative traits. A Z-test was performed for the parameter which determined the difference between groups and the p-value was reported.

To assess the risk for high birth weight a logistic regression model was developed. High birth weight was assumed when it was above the 90th percentile for infants born in a given week. The absolute value of the correlation coefficients between independent variables did not exceed 0.5. The Variance Inflation Factor (VIF) was not greater than 2.5. The correlations between the variables had no significant effect on the results. Z-test was performed to assess significance of factors. These factors for which p-values were lower than 0.05 were considered as significant. The following independent variables were used in the analysis: BMI, maternal age, multiparity, insulin-treated gestational diabetes mellitus, prior macrosomic birth (> 4000 g), diabetes mellitus in previous pregnancy, gestational hypertension, gestational week at delivery, diabetes mellitus diagnosed before 20 weeks of gestation.

Table 1. Characteristics of the study group

Diabetes type Parameter	PGDM (n = 111)	GDM (n = 1169)	GDMG1 (n = 673)	GDMG2 (n = 477)
Maternal age, years (mean ± SD)	31.69 ± 5.30*	33.01 ± 5.03*	32.86 ± 5.10	33.29 ± 4.96
BMI (mean ± SD) 25–30 > 30	26.78 ± 5.80 42 (38%) 22 (20%)	26.26 ± 5.64 409 (35%) 198 (17%)	25.18 ± 5.23*** 195 (29%)*** 81 (12%)***	27.56 ± 5.74*** 200 (42%)*** 110 (23%)***
Multiparity	50 (45%)	607 (52%)	343 (51%)	258 (54%)
GDM in a previous pregnancy	—	117 (10%)	67 (10%)	50 (10.5%)
A history of high birth weight delivery (> 4000 g)	10 (9%)	58 (5%)	34 (5%)	24 (5%)
Diabetes mellitus in first-degree relative(s)	35 (32%)**	235 (20%)**	121 (18%)*	110 (23%)*
Infertility treatment	5 (4.5%)	105 (9%)	67 (10%)	33 (7%)
Gestational hypertension	25 (22.5%)*	165 (14.1%)*	83 (12.3%)*	81 (16.9%)*
Intrahepatic cholestasis of pregnancy	4 (3.6%)	49 (4.2%)	27 (4.1%)	22 (4.6%)
Polyhydramnios	7 (6.3%)	37 (3.2%)	24 (3.6%)	13 (2.7%)
Gestational week at delivery (mean ± SD) < 34 < 37 > 40	37.6 ± 1.9** 4 (3.6%) 25 (22.5%) 1 (0.9%)	38 ± 2.1** 44 (3.8%) 184 (15.7%) 62 (5.3%)	38.1 ± 2.1* 30 (4.5%) 106 (15.8%) 38 (5.7%)	37.9 ± 2* 14 (3%) 78 (16.5%) 22 (4.7%)
Induction of labor	20 (18%)	208 (17.8%)	126 (18.7%)	74 (15.6%)
Vaginal delivery Forceps Vacuum extraction	34 (30.6%) 1 (0.9%) 0	433 (37%) 5 (0.4%) 7 (0.6%)	275 (40.9%)* 3 (0.4%) 6 (0.9%)	150 (31.5%)* 2 (0.4%) 1 (0.2%)
Cesarean section Elective Emergency	77 (69.4%) 60 (54%) 17 (15.3%)	736 (62.9%) 574 (49.1%) 162 (13.8%)	398(59.1%)** 310 (46%)** 88 (13.1%)	327 (68.5%)** 257 (53.9%)** 70 (14.6%)
Shoulder dystocia	1 (0.9%)	3 (0.25%)	0	3 (0.6%)
Obstetric hemorrhage	0	16 (1.4%)	9 (1.3%)	5 (1%)

Statistically significant differences for PGDM vs GDM and GDMG1 vs GDMG2: *p < 0.05; **p < 0.01; ***p < 0.001

RESULTS

In 2016, 1280 women with diabetes in pregnancy delivered in the study centers, which accounted for 7.25% of the survey population. There were 61 twin births and one triplet birth. In 1169 (91.3%) women hyperglycemia was diagnosed in pregnancy and 111 (8.7%) had PGDM. In the prepregnancy period, most PGDM women were treated with insulin (87%), 7% took metformin and 6% were managed with modified diet alone. During pregnancy, all PGDM women, but one who continued metformin, received insulin therapy (multiple daily insulin injections [MDI] — insulin pens in 53 women [47.7%], continuous subcutaneous insulin infusions [CSII] — short-acting insulin analogue in 57 women [51.3%]).

GDM was diagnosed in 6.62% of the survey population based on abnormal results of a 75 g OGTT, mostly between 24 and 28 gestational weeks. In 16% of the GDM group, hyperglycemia was detected during the first half of pregnancy. In 98% of cases appropriate management was instituted at the time of diagnosis while 19 women with the abnormal OGTT results remained without therapy. In 477 (41%) women drug therapy was used in addition to dietary modifications (GDMG2 group). Three women were treated with metformin and in the remaining cases insulin was prescribed, usually as MDI (insulin pens) and in 12 (2.5%) women as CSII (insulin pump). A higher rate of insulin therapy (44%) was reported in women with GDM diagnosed earlier than 20 gestational weeks.

Table 1 presents the characteristics of women stratified by the type of diabetes. Women with GDM were significantly older than PGDM women. The mean BMI value was higher in women with gestational diabetes receiving insulin therapy (GDMG2) than in women requiring dietary modification alone (GDMG1). The BMI > 25 considered

a risk factor for hypertension in pregnancy was significantly more frequent in both PGDM (22%) and GDMG2 (17%) vs GDMG1 (12%).

The gestational age at delivery in both PGDM and GDMG2 women was lower than that in the GDMG1 women, at less than 37 weeks in 16%, including nearly every fourth delivery (23%) at less than 34 weeks. A high rate of premature deliveries was noted in women with PGDM (23%), and it was significantly higher than that for all women who delivered in the hospitals included in the analysis (14%).

Induction of labor was used in 18% of women with diabetes and elective cesarean section was performed in every second woman. The rate of elective cesarean sections was statistically significantly higher in women with GDMG2 and PGDM (54%) than in women with GDMG1 (46%) ($p = 0.009$). Over a third of cesarean sections (35%) were performed in women with a prior cesarean birth and 96% received a repeat cesarean section while only nine had vaginal delivery after cesarean (VBAC). The total rate of cesarean sections in all women with diabetes was 63.5% vs 55% in non-diabetic women who delivered in the same hospitals.

Only a third of all women with diabetes had a vaginal delivery. There were 13 operative vaginal deliveries, including six forceps deliveries (0.4%) and seven vacuum extractions (0.5%). Shoulder dystocia occurred in four cases, three in women with GDMG2 and one in a woman with PGDM and accounted for 0.8% of vaginal deliveries. Obstetric hemorrhage occurred in 16 (1.2%) women.

Table 2 presents adverse infant outcomes which were seen in 21% of neonates. Although the gestational age at delivery was statistically significantly lower in PGDM and GDMG2, the mean birth weight was higher vs infants born to mothers with GDMG1. The highest proportion (above the 90th percentile) of large-for-gestational-age (LGA) infants were born to mothers with PGDM (39%). Also, every fourth infant (26%) in the GDMG2 group had a birth weight above the 90th percentile, a higher rate compared to the GDMG1 group where LGA infants accounted for 18% of all births. Of all infants, 109 (8.5%) had birth weight above 4000 g, including 15 with a birth weight above 4500 g (1.2%). Small-for-gestational-age (SGA) infants with a birth weight below the 10th percentile accounted for only 6.4% of all births.

Logistic regression analysis found that in GDM women a history of high birth weight delivery and a higher prepregnancy BMI value were two risk factors for giving birth to an LGA infant, but such associations were not established for PGDM.

Congenital anomalies were diagnosed in 50 (3.9%) neonates, including heart defects in 50%. Genetic conditions were diagnosed in seven infants, including six cases of trisomy 21. Hypoglycemia was found in every tenth infant born to a mother with PGDM, nearly three times as often as in infants of GDM mothers (3.4%). The rates of hyperbilirubinemia were similar in infants born to insulin-treated mothers with PGDM and GDMG2, 13.5% and 14.4%, respectively, but higher than in the GDMG1 group (8.2%). Respiratory disorders occurred in 13% of the infants and 85 infants (6.6%) were admitted to a neonatal intensive care unit (NICU). Neonatal infection was diagnosed in 71 (5.5%) of cases.

Logistic regression analysis found that in GDM the need for insulin therapy and early gestational age at delivery were two risk factors for adverse neonatal outcomes (hypoglycemia, hyperbilirubinemia, infection, respiratory disorders) while in PGDM these were early gestational age at delivery and the use of CSII.

Table 2. Birth weight and adverse infant outcomes

Diabetes type Parameter	PGDM (n = 111)	GDM (n = 1169)	GDMG1 (n = 673)	GDMG2 (n = 477)
Birth weight, g (mean ± SD) > 4000 g > 4500 g LGA SGA	3335.7* ± 699.9 22 (19.8%)*** 2 (1.8%) 43 (38.7%)*** 8 (7.2%)	3159.6* ± 671.3 87 (7.4%)*** 13 (1.1%) 252 (21.6%)*** 74 (6.3%)	3114.9** ± 678.9 50 (7.4%) 9 (1.3%) 121 (18%)%*** 45 (6.7%)	3195.7** ± 657.4 33 (6.9%) 4 (1%) 127 (26.6%)*** 29 (6.1%)
Hypoglycemia	11 (9.9%)**	40 (3.4%)**	19 (2.8%)	21 (4.4%)
Hyperbilirubinemia	15 (13.5%)	124 (10.6%)	55 (8.2%)***	69 (14.4%)***
Infection	6 (5.4%)	65 (5.6%)	30 (4.4%)*	35 (7.3%)*
Respiratory disorders	16 (14.4%)	146 (12.5%)	88 (13.1%)	58 (12.1%)
NICU admission	10 (9%)	75 (6.4%)	43 (6.4%)	32 (6.7%)
Congenital anomalies	5 (4.5)%	45 (3.8%)	25 (3.7%)	20 (4.2%)

Statistically significant differences for PGDM vs GDM and GDMG1 vs GDMG2: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

DISCUSSION

This is the first report on the prevalence of hyperglycemia in pregnancy in Poland estimated after adoption in 2014 of a 1-step screening approach and the new IADPSG criteria for the diagnosis of gestational diabetes. We found an increase by 46% in the rate of GDM, now at 6.5% vs 3.5% when a 2-step screening for hyperglycemia in pregnancy was used [7]. The 2-step approach was based on a 1-hour 50 g glucose challenge test (GCT) and a 75 g OGTT according to the 1997 WHO criteria (fasting glycemia and values at 2 hours) performed in pregnant women with the GCT result above 139 mg%.

A similar trend, though higher GDM rates, was found in studies comparing 1-step and 2-step approaches conducted in other countries. A retrospective cohort study from Switzerland reported a considerable increase in the prevalence of GDM with the adoption of the IADPSG criteria, from 3.3% observed with a 2-step approach to 11.8% with a 1-step screening [8]. In the hospitals in Tuscany, Italy an increase in the prevalence of GDM to 10.9% was reported when a 1-step approach with new cut-off values was applied, i.e., the prevalence 25% greater than that determined 10 years earlier with a 2-step approach [9]. A study in a cohort of women who delivered during a 12-month period in hospitals in one district in New Zealand showed that adoption of the IADPSG criteria would increase the rate of GDM from 6% to 10% [10]. A retrospective study of pregnant women who delivered in a tertiary medical center in Canada attributed the increase in the GDM rate to the use of a single abnormal value to define GDM (the Canadian Diabetes Association, CDA, requires the presence of at least two abnormal values) (5.3% increase) rather than the use of lower threshold values (1.8% increase) [11]. A prospective study conducted by Duran et al. [12] in the university hospital in Madrid demonstrated that the change in the criteria for GDM resulted in a 3-fold increase in the population which required treatment for GDM as well as the improvement in pregnancy outcomes with a decrease in the rates of macrosomia and cesarean section. Similar findings were reported for a cohort of pregnant women in Taiwan [13].

Of note for the cohort assessed in this study is a large proportion of women treated with insulin (41%) which in earlier Polish studies in GDM ranged from 23% to 37% [14–16]. This may have been the result of promoting stringent glycemic control, especially in cases of fasting glycemia < 90 mg%. However, even with frequent institution of insulin therapy, the proportion of large-for-gestational-age infants remained high at 20% and was twice as high as when GDM was diagnosed under previous criteria [14–16]. Also, other studies find a higher proportion of macrosomia and insulin treatment in women with GDM diagnosed under the IADPSG criteria [11, 17]. In the present study, a higher maternal BMI was identified by logistic regression analysis as a significant risk factor for LGA. Nearly half of women with GDM had excess body weight, 35% were overweight and 17% obese. Which is more harmful for fetal growth, maternal obesity or maternal hyperglycemia, has been for years a matter of debate among clinicians.

The study also shows the impact of new treatment options for PGDM. In nearly half of the women CSII was used. Of note is a low rate of congenital defects, likely to result from a growing use of intensive insulin therapy in women of reproductive age. Meta-analyses demonstrate in the first trimester a better control of type 1 diabetes in women treated with CSII vs MDI [18]. However, the percentage of LGA infants born to women with type 1 pregestational diabetes remains high at nearly 40% and is similar to the findings in other recent epidemiologic studies [19–21].

As shown by studies conducted in other countries, e.g., Canada, France or Sweden, cesarean section is performed more frequently in women with diabetes compared to the general population [11, 22, 23]. In the present cohort it was performed in nearly 70% of women with GDMG2 and 60% of women with GDMG1, 20–30% increase compared to previously assessed Polish GDM cohorts [15, 16] and reports from other countries. However, in Poland the rate of cesarean sections has been growing rapidly in recent years also in the general population [24]. On the other hand, the proportion of operative vaginal deliveries was very small at less than 1%, a ten-fold lower rate than those reported from cohort studies in other countries [11].

In the study group, adverse neonatal outcomes (hypoglycemia, hyperbilirubinemia, infection, respiratory disorders) were mostly associated with an earlier gestational age at delivery. A considerably greater proportion of adverse outcomes was observed in infants born to insulin-treated mothers, both with PGDM and with GDMG2, which is in agreement with reports from other countries [11, 14, 20]. Interestingly, an association was observed between the use of CSII and a higher rate of adverse neonatal outcomes, but the analyzed groups were relatively small. This is different from the findings from a tertiary center in Poland which demonstrated a lower incidence of neonatal complications in 122 infants born to mothers with type 1 diabetes treated with CSII compared to 175 infants born to mothers treated with MDI [25]. However, recent meta-analyses show a higher rate of LGA infants with CSII and no significant differences regarding the rate of neonatal complications [18, 26].

Limitations of the study

The study used clinical records from tertiary medical centers delivering high-quality perinatal care and there-

fore the reported rates of hyperglycemia in pregnancy may not fully reflect the actual prevalence of HIP in the general population. However, the available epidemiologic surveys used as a point of reference were conducted nearly two decades earlier and in two provinces of Poland only. This is a retrospective study based on the clinical records related to deliveries and does not include data related to pregnancies that ended in miscarriage or were terminated because of severe fetal anomalies. The rate of congenital anomalies in infants born to mothers with diabetes may therefore be underestimated. The data were obtained from hospitals in eight provinces of Poland and in spite of the above limitations are an important source of information, especially as in Poland there is no national registry of pregnancy complications.

CONCLUSIONS

In Poland, the prevalence of hyperglycemia in pregnancy has nearly doubled in the past twenty years. Even with appropriate management, hyperglycemia in pregnancy is a significant risk factor for a cesarean section delivery, bearing an LGA infant and adverse neonatal outcomes.

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Conflict of interest

All authors declare no conflict of interest.

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