Maternal lipids associated with large-for-gestational-age birth weight in women with type 1 diabetes: results from a prospective single-center study

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Abstract

Introduction: Despite improvement in diabetes care over the years, the incidence of macrosomia in type 1 diabetic mothers is still very high and even shows an increasing tendency. It is suggested that other factors that maternal hyperglycemia might be associated with excessive fetal growth in diabetic mothers. The aim of this study was to determine whether maternal lipids might contribute to high rates of large-for-gestational-age (LGA) newborns in women with type 1 diabetes (T1DM).
Material and methods: This prospective, single-center study was performed in a population of women with T1DM admitted to the perinatal center for women with diabetes. Data were collected in the first trimester (< 12th week), in mid-pregnancy (20th–24th weeks), and before delivery (34th–39th weeks).
Results: Among 114 women included in the analysis, 30 (26.3%) delivered LGA newborns. The remaining 84 (73.7%) newborns were appropriate for gestational age (AGA). Lower high-density lipoprotein (HDL) HDL concentration in the first trimester was significantly associated with LGA (p = 0.01). Similar associations were observed for the HDL concentrations in mid-pregnancy (p = 0.04) and before delivery (p = 0.03). Higher triglyceride concentrations in the first trimester (p = 0.02) and before delivery (p = 0.008) were associated with LGA. Higher glycated haemoglobin (HbA_{1c}) levels in mid-pregnancy and before delivery were associated with LGA. The associations between maternal lipids and LGA were independent of maternal body mass index at onset of the study, gestational weight gain and HbA_{1c} concentrations.
Conclusions: Decreased HDL and increased triglycerides during pregnancy might contribute to the development of LGA in women with type 1 diabetes.

Key words: type 1 diabetes, pregnancy, fetal weight, lipids, large-for-gestational-age.

Introduction

Excessive fetal weight, which is defined as large for gestational age (LGA), is one of the most significant complications of pregnancy in women with type 1 diabetes. Despite improvement in diabetes care over the years, the incidence of LGA in type 1 diabetic mothers is still very high and even shows an increasing tendency [1–3]. This is worrying as LGA is associated with a high risk of maternal and fetal complications [4, 5]. The importance of prevention of LGA is not only an issue in perinatal medicine as LGA infants are at increased future risk of developing obesity,

diabetes, and cardiovascular disease due to fetal programming [6–11].

The association between maternal hyperglycemia and LGA has been confirmed in a number of studies [12–14]. Therefore, preventive strategies against excessive fetal growth have been focused on achieving and maintaining near normal glycemic levels throughout pregnancy. However, such an approach was proved to be not fully effective in many women with type 1 diabetes whose fetuses develop LGA despite good glycemic control [15].

Some other factors have been previously linked with LGA, including maternal overweight/obesity, excessive gestational weight gain, and lipids. The first two factors have also been studied in women with type 1 diabetes, but the association between lipids and LGA in this population has not been extensively investigated [16–18]. There is one study in the literature showing that increased levels of triglycerides and decreased levels of high-density lipoprotein (HDL) in the third trimester might be linked to LGA in patients with pregestational diabetes. However, the results of this study cannot be directly extrapolated to women with type 1 diabetes as the analyzed group consisted of both type 1 and type 2 diabetics [19]. Much more data on lipids and LGA come from normal pregnancies and pregnancies complicated by gestational diabetes mellitus (GDM). In non-diabetic patients LGA was related to increased triglycerides, increased free fatty acids, and decreased HDL during early pregnancy [20]. In women with GDM similar findings were reported in mid-pregnancy and near delivery, except that a relationship with HDL was not demonstrated [21–23].

Moreover, recent data suggest that maternal lipid profile in early gestation is an independent factor related to childhood adiposity at the age of 5 to 6 years in non-diabetics [24].

The aim of our study was to determine whether changes in maternal lipids analyzed at three different time points during pregnancy (in the first trimester, in mid-pregnancy, and before delivery) are associated with LGA in women with type 1 diabetes.

Material and methods

Study setting

This study was conducted in the Department of Obstetrics and Women's Diseases, Gynecologic and Obstetrical University Hospital in Poznan, Poland. The department with its outpatient clinic is the biggest perinatal center for pregnant women with diabetes in Poland, providing care for patients from the Greater Poland province (population of approximately 3.4 million). According to Polish Diabetes Association recommendations and our internal standards, every patient with preexisting diabetes from Greater Poland is immediately referred to our department once pregnancy is confirmed. The process of care delivered to diabetic women without complications is based on at least 3 planned, short-stay hospital admissions during pregnancy: in the first trimester, in mid-pregnancy (20^{th}–24^{th} weeks of gestation), and near delivery (34^{th}–35^{th} weeks of gestation). Patients who require more vigilant surveillance are admitted more frequently. In between hospital admissions patients are referred biweekly for regular check-ups in the hospital-based outpatient clinic.

Study design and patients

This prospective study was conducted between June 2012 and December 2014. The study group represents a population of pregnant women with type 1 diabetes admitted to the Department of Obstetrics and Women's Diseases in the first trimester and followed up to delivery.

Patients were all Caucasian and received standard pregnancy care for diabetes as recommended by the Polish Diabetes Association and Polish Gynecological Society, targeting a fasting glucose level of 3.3–5.5 mmol/l, 1-hour postprandial glucose below 6.7 mmol/l, and glycated haemoglobin (HbA_{1c}) below 6.1% (43 mmol/mol) [25].

All women were on intensive insulin therapy using either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII).

Exclusion criteria were multiple pregnancy, miscarriage, preeclampsia, delivery before completed 34^{th} week of gestation, delivery in another hospital, or loss to follow-up.

Anthropometric, clinical, and laboratory data were collected during 3 planned hospitalizations: in the first trimester (< 12^{th} week of gestation), in mid-pregnancy (20^{th}–24^{th} weeks of gestation), and before delivery (34^{th}–39^{th} weeks of gestation).

Blood samples were taken after overnight fasting and immediately transported to the central laboratory of the Gynecologic Obstetrical University Hospital in Poznan for analysis. HbA_{1c} level in whole blood was determined using the turbidimetric inhibition immunoassay (TINIA), Tina-quant Hemoglobin A_{1c} II test in a Cobas c311 analyzer (Roche Diagnostics, Basel, Switzerland). The normal range for this test is 4.8–6.0% (29–42 mmol/mol) for a non-pregnant population.

The total serum cholesterol, HDL cholesterol and triglyceride (TG) levels were determined with Roche Diagnostics reagents (Cholesterol CHOD-PAP, HDL-C plus, and Triglycerides GPO-PAP, respectively) on a Cobas c501 analyzer. The following formula was used to calculate the level of low-density lipoprotein (LDL) cholesterol: LDL cholesterol = total cholesterol – HDL cholesterol – (TG/5).

Anthropometric measurements (height, weight, and waist/hip circumference) and blood pressure measurements were performed at the onset of the study.

Large for gestational age was defined as birth weight greater than the 90th percentile using age- and sex-specific regional growth charts [26].

The Institutional Ethical Committee of Poznan University of Medical Sciences (no. 673/12, June 12, 2012) approved the study protocol. Informed, written consent was obtained from every patient before inclusion in the study.

Statistical analysis

Statistical analyses were performed using MedCalc for Windows, version 12.1.3.0 (MedCalc Software, Mariakerke, Belgium). Testing for normality of data distribution was performed using the D'Agostino-Pearson test. Student's *t*-test was used to measure the significance of the difference between two continuous variables when data fitted a normal distribution, with results expressed as mean ± standard deviation (SD). In the case of non-normally distributed data, comparisons were made using the Mann-Whitney test, with results expressed as the median and interquartile range (IQR). The χ^2 and Fisher exact tests were used for the comparison of categorical variables. Spearman's rank correlation coefficient was used to test the relationship between two variables when data did not follow a normal distribution.

Simple logistic regression was used to search for lipid fractions associated with LGA. Those parameters found to be independently associated with LGA were included in multivariate logistic regression (stepwise) models built separately for each follow-up hospitalization.

Based on clinical judgment, we included the following confounders in the stepwise models: maternal age, duration of diabetes, body mass index (BMI) at onset of the study, gestational weight gain, parity (multipara vs. primipara), mode of insulin therapy (CSII vs. MDI), and HbA_{1c} [27].

According to the stepwise method, variables were entered into the model if their associated *P*-values were less than 0.05 and then sequentially removed if their associated *p*-values became greater than 0.2. Testing for the goodness of fit of a logistic regression model was performed with the Hosmer-Lemeshow test.

Statistical significance was defined as $p < 0.05$ (two-sided).

Results

Of the 171 women with type 1 diabetes admitted to our department in the first trimester, 114 (64%) were eligible for the final analysis. Two patients chose not to participate in the study. One patient was excluded from the study group due to twin pregnancy. There were 12 spontaneous abortions and 1 intrauterine fetal death in the third trimester. One woman delivered preterm in the 28th week of gestation. Eleven women were excluded from the analysis due to preeclampsia. Twenty-nine patients were lost to follow-up or delivered in other hospitals.

Among 114 women included in the analysis 30 (26.3%) delivered LGA newborns. The remaining 84 (73.7%) newborns were appropriate for gestational age (AGA). There were no small-for-gestational-age (SGA) newborns in the analyzed group.

Clinical and laboratory characteristics of the AGA and LGA groups are compared in Tables I and II.

In the first trimester, mothers of LGA newborns had lower HDL (1.64 vs. 1.99, $p = 0.0012$), higher triglycerides (0.75 vs. 0.62, $p = 0.04$), and comparable HbA_{1c} (6.9 vs. 6.2, $p = 0.1$).

In mid-pregnancy, lower HDL persisted in the LGA group (2.17 vs. 2.32, $p = 0.05$), but there was no significant difference in maternal triglycerides between the groups. Metabolic control of diabetes improved between the first and the second hospital admission in both groups. However, women who delivered LGA newborns had significantly higher HbA_{1c} in mid-pregnancy (5.8 vs. 5.4, $p = 0.0002$).

Before delivery, lower HDL was still observed in the LGA group (1.85 vs. 2.08, $p = 0.03$) as well as higher triglycerides (2.61 vs. 2.32, $p = 0.04$), and HbA_{1c} (6.3 vs. 5.7, $p = 0.0015$).

We did not find any differences in total cholesterol and LDL during all follow-up hospitalizations. There was no difference in triglycerides in mid-pregnancy between the groups.

Triglycerides were inversely correlated with HDL in the first trimester (rho = –0.303, $p = 0.001$), in mid-pregnancy (rho = –0.255, $p = 0.01$), and before delivery (rho = –0.325, $p = 0.001$).

Prediction of LGA with maternal lipids and HbA_{1c}

In the multivariate logistic regression analysis lower HDL concentration in the first trimester was significantly associated with LGA (Table III).

A similar association was observed for the HDL concentrations in mid-pregnancy and before delivery.

Higher TG concentration in the first trimester and before delivery was associated with increased risk of LGA. There was no association between second trimester TG and LGA.

Both total cholesterol and LDL in the first trimester, in mid-pregnancy, and before delivery were not associated with LGA.

Higher HbA_{1c} was positively associated with LGA in mid-pregnancy and before delivery, with no association in the first trimester.

Table I. Comparison of clinical characteristics between study groups

Variable	AGA *N* = 84	LGA *N* = 30	*P*-value
Maternal characteristics:			
Gestational age at onset of study, mean ± SD [weeks]	8 ±2	9 ±2	0.24
Maternal age at onset of study, median (IQR) [years]	29 ±4	28 ±5	0.23
Primipara, *n* (%)	49/84 (58.3)	13/30 (43.3)	0.23
Preconception care, *n* (%)	38/84 (45.2)	13/30 (43.3)	0.97
Duration of diabetes mean ± SD [weeks]	11 ±7	13 ±7	0.11
BMI at onset of study, median (IQR) [kg/m²]	22.6 (20.7–24.8)	23.4 (21.6–26.7)	0.08
Waist-to-hip ratio at onset of study, mean ± SD	0.79 ±0.06	0.79 ±0.06	0.65
Gestational weight gain, mean ± SD [kg]	11.5 ±4.7	12.3 ±3.8	0.4
Mode of insulin therapy during pregnancy, *n* [MDI/CSII]	20/64	7/23	0.84
Systolic blood pressure at onset of the study, mean ± SD [mm Hg]	115 ±10	114 ±10	0.57
Diastolic blood pressure at onset of the study, mean ± SD [mm Hg]	71 ±7	72 ±8	0.52
Infant characteristics :			
Gestational age, median (IQR) [weeks]	38 (37–39)	38 (37–38)	0.67
Birth weight, median (IQR) [g]	3390 (3040–3630)	4035 (3900–4260)	< 0.0001

Table II. Comparison of laboratory characteristics between study groups

Variable	AGA *N* = 84	LGA *N* = 30	*P*-value
HbA_{1c} I, %; median (IQR) [mmol/l]	6.2 (5.8–7.2); 44 (40–55)	6.9 (6.1–7.6); 52 (43–60)	0.1
HbA_{1c} II, %; median (IQR) [mmol/l]	5.4 (5.1–5.7); 36 (32–39)	5.8 (5.6–6.1); 40 (38–43)	0.0002
HbA_{1c} III, %; median (IQR) [mmol/l]	5.7 (5.5–6.2); 39 (37–44)	6.2 (5.9–6.6); 44 (41–49)	0.0015
Serum total cholesterol I, mean ± SD [mmol/l]	4.39 ±0.63	4.23 ±0.62	0.23
Serum total cholesterol II, mean ± SD [mmol/l]	5.88 ±1.01	5.89 ±0.86	0.97
Serum total cholesterol III, mean ± SD [mmol/l]	6.93 ±1.37	6.50 ±1.49	0.22
Serum HDL cholesterol I, median (IQR) [mmol/l]	1.99 (1.70–2.21)	1.64 (1.54–1.87)	0.0012
Serum HDL cholesterol II, median (IQR) [mmol/l]	2.32 (2.06–2.66)	2.17 (1.79–2.50)	0.05
Serum HDL cholesterol III, median (IQR) [mmol/l]	2.08 (1.78–2.45)	1.85 (1.46–2.23)	0.03
Serum LDL cholesterol I, median (IQR) [mmol/l]	2.03 (1.72– 2.45)	2.12 (1.70–2.41)	0.86
Serum LDL cholesterol II, median (IQR) [mmol/l]	2.99 (2.49–3.42)	3.14 (2.56–3.52)	0.38
Serum LDL cholesterol III, median (IQR) [mmol/l]	3.74 (3.00–4.39)	3.18 (2.88–3.95)	0.22
Serum triglycerides I, median (IQR) [mmol/l]	0.62 (0.51–0.77)	0.75 (0.56–0.96)	0.04
Serum triglycerides II, median (IQR) [mmol/l]	1.40 (1.12–1.74)	1.58 (1.11–1.96)	0.27
Serum triglycerides III, median (IQR) [mmol/l]	2.32 (1.97–2.93)	2.61 (2.31–3.55)	0.04

Table III. Prediction of LGA with maternal lipids (mmol/l) and HbA_{1c} (%) using multivariate logistic regression models*

Variable	Odds ratio (95% CI)	Coefficient	*P*-value
Serum HDL cholesterol I	0.225 (0.069–0.74)	–1.49	0.01
Serum HDL cholesterol II	0.329 (0.112–0.967)	–1.11	0.04
Serum HDL cholesterol III	0.304 (0.101–0.918)	–0.19	0.03
Serum triglycerides I	5.522 (1.279–23.843)	1.71	0.02
Serum triglycerides III	2.14 (1.128–3.765)	0.76	0.008
HbA_{1c} II	2.279 (1.143–4.541)	0.824	0.01
HbA_{1c} III	1.962 (1.096–3.513)	0.674	0.02

**Data shown as adjusted odds ratios (OR) and associated 95% confidence intervals (95% CI). Models adjusted for maternal age, duration of diabetes, BMI at onset of the study, gestational weight gain, parity (multipara = 1 vs. primipara = 0), mode of insulin therapy (CSII = 1 vs. MDI = 0). Models assessing lipids were additionally adjusted for HbA_{1c} from the same follow-up hospitalization.*

Discussion

This study is among the first to evaluate the influence of maternal lipid profile on the risk of fetal excessive growth in women with type 1 diabetes.

We demonstrated that lower HDL in all trimesters and higher triglycerides in the first and third trimesters were associated with LGA in this population.

Such an association has been shown previously, but only in the third trimester, by Göbl *et al.* in women with pregestational diabetes. The authors did not find any association between either total cholesterol or LDL and LGA, which is in line with our findings [19]. Additionally, their study is not fully representative of solely the population of women with type 1 diabetes, because their study group also included women with type 2 diabetes.

As fetal nutrition depends mainly on glucose, maternal hyperglycemia has been suggested to be the major determinant of abnormal fetal growth in diabetic mothers. However, it has been shown by Evers *et al.* that many women with type 1 diabetes deliver LGA infants despite relatively good glycemic control. The authors demonstrated that third trimester HbA_{1c} was the most powerful predictor of macrosomia, but its predictive capacity was weak [15].

In our patients the association between HbA_{1c} and the risk of LGA was the strongest in the second trimester, followed by the third trimester. Nonetheless, it should be emphasized that despite statistically higher levels of HbA_{1c}, mothers of LGA infants were relatively well controlled in the second part of pregnancy. This further suggests that not only maternal hyperglycemia might be responsible for abnormal fetal growth in women with type 1 diabetes, which has been shown in our study.

We found that prediction of LGA might be possible early in pregnancy based on the maternal lipid profile, but cannot be based on HbA_{1c}. In our study, many patients who were uncontrolled on enrollment in the study achieved satisfactory glycemic control in the second part of pregnancy due to intensification of treatment. This might explain the lack of capacity of first trimester HbA_{1c} for the prediction of LGA. However, we found that lower levels of HDL and higher levels of triglycerides in the first trimester were both associated with LGA. Importantly, these effects were sustained during the whole pregnancy for HDL and before delivery for triglycerides. The association between decreased HDL and macrosomia in the first half of pregnancy (17–19 weeks) has been demonstrated previously by Clausen *et al.* in a large cohort of non-diabetic women. However, high triglyceride level was not a risk factor for macrosomia in that study [28]. In our study, we did not find an association between triglycerides and LGA between 20 and 24 weeks of gestation. However, an association was present in the first trimester and before delivery, and requires further study. Unlike Clausen *et al.*, who used non-fasting samples, our women were fasting at the time of blood collection. It eliminated the influence of prandial status on serum triglycerides. However, we cannot exclude the possibility that maternal triglyceride level in mid-pregnancy was altered by rapid improvement of glycemic control related to intensification of treatment that took place between the first and second hospitalizations.

The mechanism by which low HDL might be linked to abnormal fetal growth has not yet been studied. The fundamental function of HDL is to transport cholesterol and other lipids from peripheral tissues to the liver for further processing and excretion [29]. The inverse correlation between HDL and triglycerides has been well documented [30]. In our study, such a correlation was observed throughout the whole pregnancy. Because triglycerides are the main source of non-esterified

fatty acids (NEFA) for placental transfer, it can be hypothesized that higher levels of maternal HDL might prevent the fetus from the excessive load of NEFA [31].

Emerging data suggest that many perinatal morbidities are rooted in early pregnancy [32, 33]. Therefore, early prediction of pregnancy complications has become a challenge in obstetrics. It has been shown by Poon *et al.* that macrosomia can be predicted in the first trimester by a combination of maternal characteristics and laboratory parameters such as PAPP-A and β-hCG used in screening for aneuploidy [34]. However, predictive capacity of this test was weak. Searching for new determinants of LGA, especially in high-risk populations, may help to improve screening performance and, therefore, implement new preventive strategies.

Despite the relatively small sample size, which is the main limitation of our study, the results might be considered population based. This is due to the fact that our department is the only perinatal center for diabetic women in the region and all of them are referred there once pregnancy is confirmed. Nonetheless, we excluded some women due to preeclampsia and some of them were lost to follow-up, mainly due to delivery in another hospital. Thus the incidence of LGA in our study group might not fully reflect its true values in this population. Our decision to exclude women with preeclampsia from the analyzed group was based on the fact that this disease is known to be associated with dyslipidemia [35, 36]. In addition, as shown in other studies, preeclampsia significantly restricts fetal growth potential [37]. Therefore inclusion of those patients could potentially lead to bias in the analysis of the association between maternal lipids and macrosomia.

The strength of the current study is that all women were treated in one center according to the same protocols. Furthermore, all laboratory measurements were performed in the same certified laboratory, thus limiting the possibility of non-random errors resulting from procedural differences.

In conclusion, our study confirms the important role of maternal HDL and triglycerides in promoting excessive fetal growth in women with type 1 diabetes. However, large epidemiological studies are needed to establish outcome-based reference thresholds for lipids in pregnancy. Data derived from such studies would provide the basis for interventional trials aimed at modification of lipids during pregnancy, especially in high-risk patients.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Jensen DM, Damm P, Moelsted-Pedersen L, et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. Diabetes Care 2004; 27: 2819-23.
2. Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: a large, population-based study. Diabetes Care 2009; 32: 2005-9.
3. Pilacinski S, Zozulinska-Ziolkiewicz DA. Influence of lifestyle on the course of type 1 diabetes mellitus. Arch Med Sci 2014; 10: 124-34.
4. Berk MA, Mimouni F, Miodovnik M, Hertzberg V, Valuck J. Macrosomia in infants of insulin-dependent diabetic mothers. Pediatrics 1989; 83: 1029-34.
5. Ballard JL, Rosenn B, Khoury JC, Miodovnik M. Diabetic fetal macrosomia: significance of disproportionate growth. J Pediatr 1993; 122: 115-9.
6. Rijpert M, Evers IM, de Vroede MA, de Valk HW, Heijnen CJ, Visser GH. Risk factors for childhood overweight in offspring of type 1 diabetic women with adequate glycemic control during pregnancy: nationwide follow-up study in the Netherlands. Diabetes Care 2009; 32: 2099-104.
7. Buinauskiene J, Baliutaviciene D, Zalinkevicius R. Glucose tolerance of 2- to 5-yr-old offspring of diabetic mothers. Pediatr Diabetes 2004; 5: 143-6.
8. Manderson JG, Mullan B, Patterson CC, Hadden DR, Traub AI, McCance DR. Cardiovascular and metabolic abnormalities in the offspring of diabetic pregnancy. Diabetologia 2002; 45: 991-6.
9. Cardwell CR, Stene LC, Joner G, et al. Birthweight and the risk of childhood-onset type 1 diabetes: a meta-analysis of observational studies using individual patient data. Diabetologia 2010; 53: 641-51.
10. Januszek-Trzciakowska A, Malecka-Tendera E, Klimek K, Matusik P. Obesity risk factors in a representative group of Polish prepubertal children. Arch Med Sci 2014; 10: 880-5.
11. Rahmanian M, Kelishadi R, Qorbani M, et al. Dual burden of body weight among Iranian children and adolescents in 2003 and 2010: the CASPIAN-III study. Arch Med Sci 2014; 10: 96-103.
12. Glinianaia SV, Tennant PW, Bilous RW, Rankin J, Bell R. HbA(1c) and birthweight in women with pre-conception type 1 and type 2 diabetes: a population-based cohort study. Diabetologia 2012; 55: 3193-203.
13. Nowak N, Skupien J, Cyganek K, Matejko B, Malecki MT. 1,5-Anhydroglucitol as a marker of maternal glycaemic control and predictor of neonatal birthweight in pregnancies complicated by type 1 diabetes mellitus. Diabetologia 2013; 56: 709-13.
14. Wender-Ozegowska E, Gutaj P, Szczepanek U, Ozegowska K, Zawiejska A, Brazert J. Influence of pregnancy planning on obstetrical results in women with pregestational diabetes mellitus. Ginekol Pol 2010; 81: 762-7.
15. Evers IM, de Valk HW, Mol BW, ter Braak EW, Visser GH. Macrosomia despite good glycaemic control in type I di-

abetic pregnancy: results of a nationwide study in the Netherlands. Diabetologia 2002; 45: 1484-9.
16. Scifres CM, Feghali MN, Althouse AD, Caritis SN, Catov JM. Effect of excess gestational weight gain on pregnancy outcomes in women with type 1 diabetes. Obstet Gynecol 2014; 123: 1295-302.
17. Secher AL, Parellada CB, Ringholm L, Asbjornsdottir B, Damm P, Mathiesen ER. Higher gestational weight gain is associated with increasing offspring birth weight independent of maternal glycemic control in women with type 1 diabetes. Diabetes Care 2014; 37: 2677-84.
18. Barrett HL, Dekker Nitert M, McIntyre HD, Callaway LK. Normalizing metabolism in diabetic pregnancy: is it time to target lipids? Diabetes Care 2014; 37: 1484-93.
19. Göbl CS, Handisurya A, Klein K, et al. Changes in serum lipid levels during pregnancy in type 1 and type 2 diabetic subjects. Diabetes Care 2010; 33: 2071-3.
20. Vrijkotte TG, Krukziener N, Hutten BA, Vollebregt KC, van Eijsden M, Twickler MB. Maternal lipid profile during early pregnancy and pregnancy complications and outcomes: the ABCD study. J Clin Endocrinol Metab 2012; 97: 3917-25.
21. Schaefer-Graf UM, Graf K, Kulbacka I, et al. Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. Diabetes Care 2008; 31: 1858-63.
22. Di Cianni G, Miccoli R, Volpe L, et al. Maternal triglyceride levels and newborn weight in pregnant women with normal glucose tolerance. Diabet Med 2005; 22: 21-5.
23. Son GH, Kwon JY, Kim YH, Park YW. Maternal serum triglycerides as predictive factors for large-for-gestational age newborns in women with gestational diabetes mellitus. Acta Obstet Gynecol Scand 2010; 89: 700-4.
24. Gademan MG, Vermeulen M, Oostvogels AJ, et al. Maternal prepregancy BMI and lipid profile during early pregnancy are independently associated with offspring's body composition at age 5-6 years: the ABCD study. PLoS One 2014; 9: e94594.
25. Wender-Ozegowska E, Bomba-Opon D, Brazert J, et al. Polish Gynecological Society standards of medical care in management of women with diabetes. Ginekol Pol 2011; 82: 474-9.
26. Gadzinowski J, Kaliszewska-Drozdowska MD, Kosinska M, Mazela J, Stoinska B. Birth weight and gestational age of newborns from Wielkopolski and Lubuski regions. Ginekol Pol 2003; 74: 186-92.
27. Gutaj P, Zawiejska A, Brazert J, Wender-Ozegowska E. Preconceptional treatment with insulin pumps is associated with improved metabolic status in early pregnancy in women with type 1 diabetes. Pol Arch Med Wewn 2015; 125: 329-36.
28. Clausen T, Burski TK, Oyen N, Godang K, Bollerslev J, Henriksen T. Maternal anthropometric and metabolic factors in the first half of pregnancy and risk of neonatal macrosomia in term pregnancies. A prospective study. Eur J Endocrinol 2005; 153: 887-94.
29. Brown WV. High-density lipoprotein and transport of cholesterol and triglyceride in blood. J Clin Lipidol 2007; 1: 7-19.
30. Patsch W, Sharrett AR, Sorlie PD, Davis CE, Brown SA. The relation of high density lipoprotein cholesterol and its subfractions to apolipoprotein A-l and fasting triglycerides: the role of environmental factors: the Atherosclerosis risk in Communities (ARIC) Study. Am J Epidemiol 1992; 136: 546-57.
31. Herrera E, Amusquivar E, López-Soldado I, Ortega H. Maternal lipid metabolism and placental lipid transfer. Horm Res 2006; 65 (Suppl. 3): 59-64.
32. Nicolaides KH. Turning the pyramid of prenatal care. Fetal Diagn Ther 2011; 29: 183-96.
33. Gutaj P, Wender-Ozegowska E, Iciek R, Zawiejska A, Pietryga M, Brazert J. Maternal serum placental growth factor and fetal SGA in pregnancy complicated by type 1 diabetes mellitus. J Perinat Med 2014; 42: 629-33.
34. Poon LC, Karagiannis G, Stratieva V, Syngelaki A, Nicolaides KH. First-trimester prediction of macrosomia. Fetal Diagn Ther 2011; 29: 139-47.
35. Basu A, Alaupovic P, Wu M, et al. Plasma lipoproteins and preeclampsia in women with type 1 diabetes: a prospective study. J Clin Endocrinol Metabol 2012; 97: 1752-62.
36. Spracklen CN, Smith CJ, Saftlas AF, Robinson JG, Ryckman KK. Maternal hyperlipidemia and the risk of preeclampsia: a meta-analysis. Am J Epidemiol 2014; 180: 346-58.
37. Xiao R, Sorensen TK, Williams MA, Luthy DA. Influence of pre-eclampsia on fetal growth. J Matern Fetal Neonatal Med 2003; 13: 157-62.