Predictive role of altered leptin, adiponectin and 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid secretion in gestational diabetes mellitus

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Abstract. Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy, leading to considerable maternal and fetal risks. The main aim of this study was to determine the predictive value of the levels of adiponectin (AN), leptin (L) and CMPF (3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid) in the development of GDM. We conducted a prospective longitudinal study on 68 pregnant women that were not at risk of developing GDM, in whom we determined AN, L, CMPF levels at 11-13 weeks +6 days of pregnancy during the first trimester screening. Twenty-one of all the patients included in the study developed GDM during pregnancy. Oral glucose tolerance test (OGTT)/75 g was performed at 24-28 weeks of gestation. L levels were significantly higher in patients who developed GDM than in those who did not develop diabetes (P<0.001). The AN/L ratio was significantly lower in patients with GDM (P=0.03). AN and CMPF levels were not associated with GDM. The probability of developing gestational diabetes was higher in patients with L levels above the L cut-off value of 16 ng/ml [area under the curve (AUC), 0.775; 95% confidence interval (CI) 0.658-0.867], sensitivity 100% (95% CI 83.9-100), specificity 48.9% (95% CI 34.1-63.9) (P<0.001). Advanced maternal age and higher L levels were found to be predictive factors [odds ratio (OR)=1.16 and OR=1.06, respectively] independently associated with gestational diabetes. In as far as general factors are concerned, the patient BMI (body mass index) at the beginning of the pregnancy and smoking were found to be the main risk factors for the onset of GDM. This study showed that elevated L levels are a strong predictor of GDM, while AN and CMPF levels are not, as they failed to show a significant association.

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Abbreviations: CMPF,3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid; GDM, gestational diabetes mellitus; AKs, adipokines; AN/L, adiponectin/leptin ratio; OGTT, oral glucose tolerance test; BMI, body mass index; WG, weeks of gestation; PROM, premature rupture of membranes

Key words: leptin, adiponectin, CMPF, adiponectin/leptin ratio, gestational diabetes mellitus, adipokines

Introduction

Gestational diabetes mellitus (GDM), defined as glucose intolerance that develops or is diagnosed during pregnancy, is one of the most common complications of pregnancy, leading to considerable maternal-fetal risks (1). There has been an increase in the prevalence of GDM worldwide, as a consequence of the increase in the frequency of type 2 diabetes mellitus (T2DM) and maternal obesity. Patients with GDM are 2-3 times more likely to develop T2DM throughout their lifetime, a pathology that is the seventh leading cause of death worldwide, and whose treatment requires numerous resources (2).

The International Association of Diabetes and Pregnancy Study Groups (IADPSG) report an average worldwide incidence rate of 17.8% for GDM (between 9.3-25.5%) (3).

GDM is known to negatively influence pregnancy as early as the first trimester; the frequency of malformations being higher in patients with GDM than in the general population. The most frequent anomalies are cardiovascular and neural tube defects (4). Therefore, an early diagnosis of GDM would help improve maternal-fetal prognosis (5).

Current trends in therapeutic management aim at the discovery of biomarkers for the early detection of GDM or a better selection of the patients at risk. Adipokines (AKs) have also been studied in this regard, and adiponectin (AN) and leptin (L) have been reported to play an important part in the early detection of GDM. AKs are proteins secreted by adipocytes that interfere with the glycoregulatory processes and are involved in numerous other endocrine and metabolic processes such as insulin secretion, insulin resistance

regulation, as well as a number of inflammatory processes, and body weight regulation (6). Studies have shown abnormal regulation of AKs at the placental level in patients with GDM, due to a low expression of AN (7).

Metabolomics, that can identify metabolites resulting from biochemical reactions, is yet another promising direction of research attempting to explain the pathophysiology of GDM. These metabolites cause subtle metabolic changes in human fluids and tissues and may be involved in the development of GDM. 3-Carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) is a furan-fatty acid whose level appears to be elevated in the blood of patients with T2DM and GDM compared to patients without diabetes. Furan-fatty acids are incorporated by phospholipids or cholesterol esters and are metabolized into dibasic urofuranic acids that also include CMPF, which are excreted in the urine (8,9).

In mice, elevated CMPF levels cause glucose intolerance, inadequate insulin secretion, and decreased peripheral glucose utilization (10). Some of the mechanisms of action of CMPF are improper mitochondrial function in pancreatic β-cells, low ATP glucose storage, increased oxidative stress, dysfunction of cellular transcription mechanisms and, finally, decreased insulin secretion. As antioxidant treatments counteract the negative effects of CMPF on pancreatic β-cells, we could envisage future treatment of GDM (10).

Starting from the assumption that the onset of GDM occurs early in the very first weeks of pregnancy, the present study aimed to verify whether the biological markers tested (AN, L, AN/L and CMPF) can be associated with the diagnosis of GDM.

The main objective of this study was to propose a method for the early, first trimester diagnosis of GDM, which would include a panel of biomarkers associated with certain clinical and demographic parameters in the Caucasian population, considered to be at low risk of developing GDM. The secondary endpoint was to analyze the maternal-fetal complications associated with GDM.

Patients and methods

Study population. We conducted a prospective longitudinal study at the Obstetrics and Gynecology Clinic I, County Clinical Emergency Hospital of Cluj-Napoca, Romania, in the period between January 2018 and March 2019. The study included a total of 111 first trimester pregnant women.

The inclusion criteria were: Pregnant women aged 18-40 years, gestational age of 11-13 weeks +6 days singleton pregnancy, performance of an oral glucose tolerance test (OGTT) at 24-28 weeks of gestation (WG), compliance with the follow-up conditions, and delivery at the Obstetrics and Gynecology Clinic I of Cluj-Napoca.

All the procedures performed were in accordance with the ethical standards of the Institutional and National Research Ethics Committee and with the Declaration of Helsinki (1964) and its later amendments. Our report is based on the STROBE Statement (Strengthening the Reporting of Observational studies in Epidemiology) (11).

The exclusion criteria were: Patients known to be suffering from type 1 and 2 diabetes, with acute or chronic infectious pathology, multiple or intrauterine fetal death, pregnancies with chromosomal abnormalities or fatal fetal malformations, patients who did not comply with the follow-up conditions and those who refused to participate in the study.

The control group included 47 singleton pregnancy patients with physiological pregnancies who accepted to provide a blood sample at 11-13 weeks+6 days in order to determine L, AN and CMPF levels, with a normal OGTT result, and who gave birth at the Obstetrics and Gynecology Clinic I of Cluj-Napoca.

Structured questionnaires and hospital medical records provided information regarding maternal age, ethnicity, height, pre-pregnancy weight, smoking before pregnancy, reproductive, obstetrical and medical history during pregnancy and after delivery, and the APGAR score.

Blood collection and biochemical assays. Maternal blood samples were collected between 11 and 13 +6 weeks of gestation (WG) at the time of the combined first-trimester screening for aneuploidy, according to standardized surgical procedures. Venous blood samples were collected from peripheral vessels into commercially available Vacutainer CAT 6-ml PET tubes with clot activator to determine L, AN, and CMPF levels. The blood samples were centrifuged at 4,000 x g for 5 min after allowing the blood to clot for 30 min at room temperature, while maintained in a vertical position. Serum and plasma samples were stored at -80˚C until analysis. The diagnosis of gestational diabetes was set between 24-28 WG based on OGTTs and in compliance with the international recommendations of the International Association of the Diabetes and Pregnancy Study Groups criteria (IADPSG) (12). The OGTT was performed with 75 mg of glucose intake (after 8 h of fasting). Gestational diabetes was diagnosed when one of the 3 values determined was altered: Fasting blood glucose >92 mg/dl (5.1 mmol/l), 1-h glycemia >180 mg/dl (10 mmol/l), 2-h glycemia >153 mg/dl (8.5 mmol/l).

Serum CMPF, AN and L levels were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits. The concentrations of CMPF and of AN and L were determined according to the manufacturers' instructions included in the commercially available kits (MyBioSource, Inc. and Invitrogen/ThermoFisher Scientific, Inc., respectively).

Statistical analysis. Statistical analysis was performed using MedCalc Statistical Software version 19.1.5 (MedCalc Software by, Ostend, Belgium; https://www.medcalc.org; 2020). The continuous variable data were tested for normal distribution (Shapiro Wilk test) and were described by median and 25-75 percentiles. All quantitative variables had a non-normal distribution. The nominal data were characterized by frequency and percentage. Comparisons between groups were performed using the Man-Whitney or Chi-square test, whenever appropriate. Correlations between quantitative variables were verified using the Spearman's rank correlation coefficient. The cut-off value for L was calculated in order to differentiate between GDM and normal patients, using a receiver operating characteristic (ROC) curve. The independent association between variables and the presence of GDM were assessed by multivariate logistic regression. The model included the variables that achieved a P-value <0.05

Table I. Demographic characteristics of the study groups.

Variables	GDM group (N=21)	Control group (N=47)	P-value
Maternal age, years [mean (range)]	32 (30-35.5)	30 (27-33)	**0.030**
Smoking, n (%)	7 (33.3%)	5 (10.6%)	**0.030**
BMI (kg/m^2)	24.3 (21.3; 28.4)	20.9 (19.8; 24.1)	**0.003**
Family history of diabetes, n (%)	8 (38.1%)	8 (17%)	**0.007**
Parity, n (%)			
Nulliparous	8 (38.8%)	31 (66%)	0.060
Multiparous			0.070
Previous GDM	3 (14.28%)	-	
Non-previous GDM	10 (47.61%)	16 (34%)	
Previous macrosomia, %	7 (53.84%)	3 (18.7%)	NS

BMI, body mass index; GDM, gestational diabetes mellitus. NS, not significant. Significant P-values are noted in bold print.

Table II. Comparison of biochemical markers according to GDM status.

Biochemical markers	GDM groupmedian (25; 75 percentiles)	Control group median (25; 75 percentiles)	P-value
Adiponectin (AN)	26.8 (17.6; 70.1)	28.4 (18.2; 50.79)	0.800
Leptin (L)	32.7 (25; 48.1)	16.8 (9.5; 32)	**<0.001**
AN/L	0.88 (0.58; 2.9)	1.42 (0.89; 7.4)	**0.030**
CMPF	180.6 (154.4; 201.9)	179.2 (153.1; 213.1)	0.900

GDM, gestational diabetes mellitus; AN/L, adiponectin/leptin ratio; CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid. Significant P-values are noted in bold print.

in the univariate analysis. A P-value <0.05 was considered statistically significant.

Results

Out of the selected 111 patients, 68 patients underwent OGTT and were able to be monitored until delivery. The rest of the patients included in the study did not meet the follow-up criteria (43 were excluded from the study: 25 patients gave birth in others hospitals and 18 patients were lost during follow-up). Twenty-one patients were diagnosed with GDM based on the test results and 47 patients were non-GDM and were selected as a control group. The prevalence of GDM in the study group was 18.91% (21 patients confirmed with GDM/111 cases). The demographic data of the groups are summarized in Table I. The age of the patients with GDM was significantly more advanced than that of the patients who did not develop diabetes, and they also had a higher pre-pregnancy BMI (P=0.030 and P=0.003, respectively). Smokers were more likely to develop GDM (P=0.030). The group of patients with GDM included more multiparous women (61.9% compared to 34% in the control group), especially women who had previously developed GDM in a previous pregnancy. This group also included a higher percentage of patients with fetus macrosomia in previous pregnancies (53.8% in GDM group vs. 18.7% in control group) (Table I).

Patients who developed GDM had significantly higher levels of L compared with those who did not develop diabetes (P<0.001). AN levels did not differ significantly between the patient groups. The AN/L ratio was significantly lower in the patients with GDM (P=0.030). We did not find significant values of CMPF in patients with GDM compared to those in the control group (Table II).

The L cut-off value we calculated was 16 ng/ml. The probability of developing GDM was higher in the case of patients with levels above this cut-off value [area under the curve (AUC)=0.775, 95% confidence interval (CI), 0.658-0.867], sensitivity 100% (95% CI, 83.9-100), specificity 48.9% (95% CI, 34.1-63.9) (P<0.001) (Fig. 1).

In order to ascertain which variables independently predict the onset of GDM, we constructed a model using logistic multivariate regression. We introduced the statistically significant variables that were associated with GDM in the univariate analysis. Patients of advanced maternal age and higher L levels had a 1.16 and 1.06 time higher risk, respectively, of developing GDM (Table III).

There was a weak negative correlation between AN values and newborn weight and a weak positive correlation with the initial weight of the mother. AN/L coefficient was moderately correlated with newborn weight (Table IV).

In patients diagnosed with GDM, the rate of obstetric complications, such as preterm birth, premature rupture of

Table III. Multivariate logistic regression for the presence of GDM.

	B	P-value	OR	95% CI for OR Min	95% CI for OR Max
Maternal age	0.15	0.050	1.16	1.00	1.36
Pre-pregnancy BMI	0.05	**0.500**	1.05	0.88	1.26
Smoking	0.39	0.600	1.48	0.31	7.07
Leptin	0.06	**0.020**	1.06	1.00	1.11

BMI, body mass index; GDM, gestational diabetes mellitus; OR, odds ratio; CI, confidence interval. Significant P-values are noted in bold print.

Table IV. Correlations for newborn weight and APGAR score.

	Newborn weight R	Newborn weight P-value	APGAR score R	APGAR score P-value
Maternal age	0.024	0.800	0.088	0.400
Pre-pregnancy BMI	0.280	**0.020**	0.030	0.800
Adiponectin	-0.289	**0.020**	-0.014	0.900
Leptin	0.175	0.100	-0.048	0.600
AN/L	-0.332	**0.007**	-0.049	0.700
CMPF	0.102	0.400	-0.215	0.070

BMI, body mass index; AN/L, adiponectin/leptin ratio; CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid. Significant P-values are noted in bold print.

membranes (PROM), hydramnios, dystocia of the shoulders, cervical or perineal lacerations, was higher compared to the control group, but only polyhydramnios presented with a significant difference. In addition, the rate of Cesarean section (P<0.001), the number of cases of fetal macrosomia (P=0.01) and the frequency of hypoglycemia in newborns (P=0.030) was higher in the GDM group compared to the control group. Newborns born to mothers in the GDM group, who required neonatal intensive care unit (NICU) admission were more numerous than those of the non-diabetic mothers (P=0.040) (Table V).

Discussion

The present study demonstrated that L levels and AN/L ratio can predict GDM development as early as the first trimester of pregnancy, alone or in combination with demographic parameters such as age, smoking, or pre-pregnancy body mass index (BMI), while AN and 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) levels do not. Elevated L levels proved to be a good predictor of GDM. In addition, the AN/L ratio was found to be significantly correlated with the

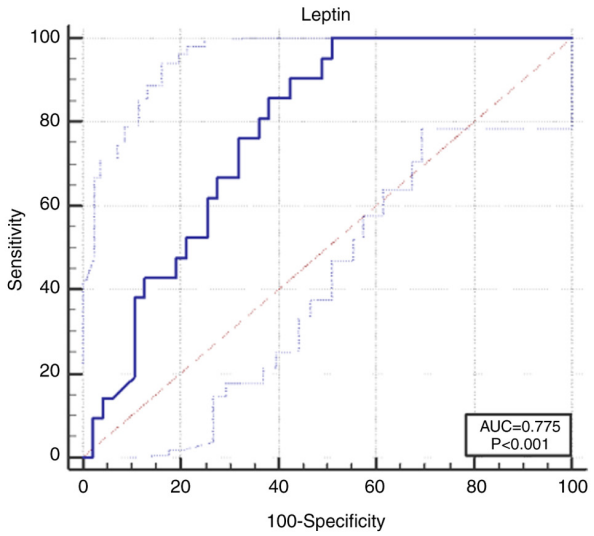

Figure 1. ROC curve for leptin. ROC, receiver operating characteristic; AUC, area under the ROC curve.

development of GDM. However, in our research, AN and CMPF levels were not associated with GDM. The results were independent of age, BMI and smoking habits. Elevated L levels were found in all patients with GDM, regardless of age. The more advanced the age of the patients, the higher the frequency of GDM when several risk factors were accumulated. Nonetheless, the changes in L levels and the AN/L ratio occurred independently of age. The logistic regression (Table III) showed that the independent nature of the variables that were introduced in the model, was preserved.

In our study, L levels were elevated as early as the first trimester in pregnant women who developed GDM, independently of age, pre-pregnancy BMI and smoking habits (OR=1.16). Moreover, there was a direct correlation between elevated L levels and the risk of developing GDM [AUC 0.775 (95% CI, 0.658-0.867), sensitivity 100% (95% CI, 83.9-100), specificity 48.9% (95 % CI 34.1-63.9), P<0.001].

The strong point of this study consists in the way in which the patients were selected. OGTT was performed in all patients included in the study, unlike in other studies, in which OGTT was performed only in patients with risk factors. Thus, we avoided overdiagnosis in the monitored groups and implicitly the highlighting of some biased AN, L, AN/L and CMPF values (13).

It is also important to note that this study was conducted on a Caucasian population, with a very low rate of diabetes compared to the black population (14,15). These results are consistent with those of a meta-analysis published by Bao *et al* which concluded that L levels in the first trimester or in the early second trimester were 7.25 ng/ml higher (95% CI 3.27-11.22), among women who later developed GDM than women who did not (16).

The results obtained in the present study are confirmed by other studies. In a study performed on 47 pregnant women Qiu *et al* obtained a GDM frequency rate of 5.7% (18.9% in our study). The increase in L levels in the first trimester were found to be highly significant for the development of GDM (P<0.001). An increase in L levels above 31.0 ng/ml resulted in a 4.7 times

Table V. Peripartum parameters in the GDM and control groups.

	GDM group (N=21) (%)	Control group (N=47) (%)	P-value
Maternal complications, n (%)			
PROM	2 (9.52)	2 (4.25)	
Preterm labor	2 (9.52)	1 (2.12)	
Polyhydramnios	7 (33.3)	-	**<0.001**
Postterm pregnancy	-	2 (4.25)	
Shoulder dystocia	2 (9.52)		NS
Lacerations	2 (9.52)	1 (2.12)	NS
Fetal dystocia	4 (19.1)	5 (10.63)	NS
Fetal complications, n (%)			
IUGR	1 (4.76)	-	NS
Perinatal asphyxia	1 (4.76)	1 (2.12)	NS
Mode of delivery, n (%)			
Vaginal birth	7 (33.3)	32 (68)	**<0.001**
Cesarean section	14 (66.6)	15 (32)	
Newborn gender, n (%)			
Male	10 (47.6)	22 (46.8)	NS
Female	11 (52.3)	23 (53.2)	
Birth weight (g)			
≥2,500	2 (9.52)	1 (2.12)	**0.040**
2,500-3,900	11 (52.38)	41 (87.23)	**0.010**
≤3,900	8 (38.1)	5 (10.6)	
APGAR score, n (%)			
≥7	1 (4.76)	1 (2.12)	NS
<7	20 (95.23)	46 (97.87)	
Neonatal morbidity, n (%)			
Monitoring in NICU	7 (33.3)	6 (12.76)	**0.040**
Hypoglycemia	6 (28.57)	1 (2.12)	**0.030**

GDM, gestational diabetes mellitus; PROM, premature rupture of membranes; IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit. NS, not significant. Significant P-values are noted in bold print.

increase in the risk of developing GDM (95% CI, 1.2-18.0). At the same time, other authors found a close linear increased association between L levels and the risk of developing GDM. Thus, a 10 ng/m increase in leptin levels was followed by a 20% increase in the risk of developing GDM (17). In our study, L values that were double compared to those in the control group were associated with a 16% increased risk in GDM.

While conducting a study in which only pregnant women at risk for GDM underwent OGTT, Thagaard *et al* reported an increase in L levels only in obese patients with GDM and not in normal weight patients (13). In the present research, the low AN/L ratio showed a statistically significant correlation with the development of GDM and fetal macrosomia. Thagaard *et al* also reported that alterations of this ratio in the first trimester of pregnancy have a good predictive value for GDM in patients with normal weight or moderate obesity (BMI <35 kg/m^2) (13). Skvarca *et al* showed that the AN/L ratio is the best marker for assessing insulin resistance in normal weight pregnant women, being correlated with the HOMA-IR index (6).

Various studies have reported maternal obesity as the leading cause of increased L levels in pregnant women with GDM. In this case, elevated L levels would be the result of changes due to obesity combined with pregnancy-related physiological changes, and not the result of independent changes due to GDM. In normal-weight pregnant women GDM is caused by inadequate insulin synthesis, while in overweight/obese pregnant women, GDM is the result of inadequate insulin synthesis and increased peripheral insulin resistance (15-22).

Therefore, increased L levels are the result of the above mentioned changes and obese patients may develop peripheral resistance to L, similar to insulin resistance. However, the mechanisms involved in the correlation between L levels, peripheral insulin resistance, insulin levels and obesity during pregnancy, are still incompletely elucidated and represent a current study issue of international interest on family health (23).

Our study did not show statistically significant associations between AN levels and GDM development; the values being

similar between the GDM and the non-GDM group (26.8 vs. 28.4 g/ml). Therefore, AN does not predict GDM development. Instead, our research showed an inversely proportional association between AN levels and the weight of newborns at birth (P=0.020). This result was also confirmed by Nanda *et al*, who showed the role of hypoadiponectinemia in predicting fetal macrosomia (24).

Studies on the connection between the decrease in AN levels in pregnancy and the development of GDM are controversial. Many of these studies could not find a correlation between changes in AN levels in the first trimester and the development of GDM, similarly to our findings (6,25-27).

Another study reported a positive correlation between AN levels and fetal weight at birth, as well as a negative correlation between AN levels and head circumference (28). Paradisi *et al* reported a 5% physiological decrease in AN levels during pregnancy in the second trimester of pregnancy compared to the first trimester, as well as a 20% decrease in AN levels in the third trimester, compared to the first trimester, which was not due to GDM. However, given that AN level variations in the first trimester in pregnant women with GDM were not significantly altered compared to non-GDM patients, this biomarker did not prove to be effective as a predictive factor for GDM (29).

On the other hand, some studies have shown that AN levels are decreased in GDM, highlighting that this decrease in AN levels is independent of maternal adiposity and could be predictive of GDM development (17,30,31).

Another biomarker of interest when trying to explain the changes leading to the development of GDM is CMPF, a metabolite of furan whose level is elevated in the plasma of patients with T2DM and in pregnant women with GDM. Our research did not reveal significant differences between the two groups (GDM and non-GDM group) in as far as this metabolite is concerned [mean (25; 75 percentiles): 180.6 (154.4; 201.9) vs. 179.2 (153.1; 213.1)]. Lankinen *et al* showed that elevated CMPF levels may be the result of a diet rich in fish, and that elevated levels are not associated with the development of GDM (32). However, further studies on a large number of cases are needed to demonstrate the relationship between the increase in CMPF levels and the development of GDM.

The limitations of this study consist, first of all, in the small number of patients, the short time allotted to the selection of cases, and the number of samples collected during pregnancy.

The markers (L, AN and CMPF) were determined at the same time with the genetic screening, and there may be variations depending on various factors (fasting prior to sample collection or not). Multiple harvests during pregnancy would be needed in order to clarify how these markers change with the evolution of the pregnancy.

A second issue includes the determination of the way in which BMI can influence L and AN levels or, in other words, to what extent L and AN levels are altered by the presence of GDM and/or by obesity in patients with a high BMI.

Continuing this research on large groups of patients could help physicians select patients at risk to develop GDM, open new horizons in as far as the therapeutic conduct in the case of these patients is concerned, and provide a better understanding of the pathophysiological mechanisms of this disease.

The use of biomarkers for the early diagnosis of GDM can have a beneficial impact on maternal health decreasing the mortality rate and maternal-fetal morbidity by changing lifestyle, diet, and early treatment.

In conclusion, our results concerning L values are encouraging and predictive of the development of GDM as early as the first trimester of pregnancy. Most importantly, this parameter is independent of the patient BMI, contrary to what many other studies report. A low AN/L ratio value is predictive of GDM development and is associated with fetal macrosomia. Research on far larger study groups is needed to demonstrate the predictive role of CMPF and AN.

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Availability of data and materials

The datasets used and/or analyzed in the present study are available from the corresponding author on reasonable request.

Authors' contributions

ARF was the main coordinator of the project and was responsible for the study design. GC and ARF drafted the manuscript of the present paper. RMP was involved in the supervising of the data collection and stratification. AS contributed to data assembly and analysis. SF and MD contributed to the study design and manuscript revision. All authors contributed intellectually to this manuscript and have approved this final version.

Ethics approval and consent to participate

The study was approved by the Bioethics Commission of the 'Iuliu Hatieganu' University of Medicine and Pharmacy in Cluj-Napoca, Romania (Nr.247/08.06.2017). Patients who participated in this research had complete clinical data. Signed informed consents were obtained from the patients or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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