ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Glutathione S-transferase (*GSTM1*, *GSTT1*) gene polymorphisms, maternal gestational weight gain, bioimpedance factors and their relationship with birth weight: a cross-sectional study in Romanian mothers and their newborns

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Abstract

Introduction: The aim of this study was to assess the relationship between mother–child *GSTM1*, *GSTT1* gene polymorphisms, maternal weight gain, maternal bioimpedance parameters and newborn's weight, in order to identify the factors that influence birth weight. *Patients, Materials and Methods*: We performed a cross-sectional study on 405 mothers and their newborns, evaluated in an Obstetrics and Gynecology Tertiary Hospital from Romania. *Results*: Newborns whose mothers had the null genotype of *GSTT1* gene polymorphism were more likely to gain a birth weight of >3 kg, compared to newborns whose mothers had the *T1* genotype (odds ratio – OR: 2.14, 95% confidence interval – CI: [1.03; 4.44]). Also, the null genotype of *GSTM1* gene polymorphism in both mothers and newborns was associated with a higher birth weight. Gestational weight gain was positively associated with newborn's birth weight (p<0.001). The increased mother's fat mass (%) and basal metabolism rate were also independent factors for a birth weight of more than 3 kg (p=0.006 and p=0.037). The null genotype of *GSTT1* gene polymorphism in mothers and the null genotype of *GSTM1* in mothers and newborns had a positive effect on birth weight. Also, increased maternal fat mass and basal metabolism rate were associated with increased birth weight. *Conclusions*: We conclude that maternal *GSTM1*/*GSTT1* gene polymorphisms present an impact on birth weight, being involved in the neonatal nutritional status. The clinical relevance of our study is sustained by the importance of identifying the factors that influence birth weight, which can be triggers for childhood obesity.

Keywords: mothers, newborns, *GSTM1* and *GSTT1* gene polymorphisms.

Introduction

Birth weight and gestational weight gain in pregnant women are two of the most important predictor factors for the future weight of the child and also for its health and development [1]. The incidence of obesity increased in recent years, becoming a pandemic condition of the 21st century. Therefore, the *World Health Organization* (WHO) reported in 2014 over 41 million obese and overweight children less than five years of age and a doubling of the number of obese children in Africa [2]. Also, WHO reported over 1.9 billion overweight adults and over 600 million obese children [3]. Obesity is a multifactorial disorder determined by the interaction between genetic, behavioral and environmental factors [4]. Even though environmental and nutritional factors are very important, genetic ones play a considerable role, being responsible for an estimated 40–70% in body mass index (BMI) variation [5]. The etiology of childhood obesity originates even since intrauterine life. Maternal obesity and excessive gestational weight gain influence newborns' weight, being associated with poor birth outcomes and problems during labor [6]. Maternal obesity reached percentages of 35%, while 64% of pregnant women are overweight; in Great Britain, 20% of fertile women are obese [7]. The excessive gestational weight gain can be associated with preeclampsia/eclampsia, gestational diabetes, dystocic labor, macrosomia, etc. [6, 7]. Therefore, the *Institute of Medicine* (IOM) recommends a gestational weight gain for women according to their BMI at the onset of pregnancy [8, 9], for obese pregnant woman a weight gain of 5–9 kg, and for the overweight ones a weight gain between 6.8–11.3 kg [6, 8].

Birth weight is a very important predictor for both the perinatal health and the child's development, growth or even the adult's wellbeing, being influenced by maternal (mother's weight, gestational weight gain), obstetrical and gynecological, genetic, environmental but also socio-

economic factors [1, 10]. Both low weight and overweight carry a high risk of obstetrical and neonatal complications, and in addition can lead to metabolic and cardiovascular disorders later on in life [11, 12]. Obstetrical and maternal risks are strongly influenced by excessive BMI and gestational weight gain [13, 14]. Also, it was proven that excessive gestational weight gain is associated with both high birth weight and obesity risk further on in life [15]. Nevertheless, other important factors, such as genetic and environmental ones are involved in the multifactorial etiology of obesity (mother or infant obesity-related genes) [15]. Other studies that assessed different gene polymorphisms in obese children, such as of the leptin receptor – *LEPR 223*, *LEPR 492* and *LEPR 1019* genes, angiotensin converting enzyme – *ACE I/D*, and interleukin – *IL-6 572 C/G*, *IL-6 190 C/T* and *IL-6 174 G/C* gene polymorphisms [16–18]. The first study concluded that the most frequent combinations encountered in this group of children were AG/GG/GA, AG/GG/GG, and AA/GG/GA [16]. The same authors assessed also *ACE I/D* in obese children and found out that II genotype of this gene polymorpshism is a negative prognostic factor associated with severe obesity [17], while in the third study they evaluated *IL-6 572*, *IL-6 190* and *IL-6 174* gene polymorphisms in the same group of children with impaired nutritional status, and their conclusion was that the highest risk for developing obesity is owned by the carriers of *IL-6 572* and *IL-6 190 C* alleles [18].

Pregnant woman's nutritional habits are also important for providing an adequate development and growth during the intrauterine life, high-quality diets being recommended in order to fulfill this goal [19, 20].

Multiple studies showed the relationship between different gene polymorphisms, such as fat mass and obesity-associated genes – *FTO* rs9939609 and *LEPR* rs1137101 [21], interleukin – *IL-6 -572C>G*, *IL-6 -174G>C* [22] and BMI or birth weight, respectively.

The glutathione S-transferases (GSTs) are a family of enzymes that catalyze the conjugation reaction of different reactive intermediates with glutathione [23]. The null genotype of *M1* allele of *GST* gene (*GSTM1*) and *T1* allele of *GST* gene (*GSTT1*) polymorphisms underline the loss of function in the corresponding GSTs [24, 25]. Due to the fact that its major isomorphic forms (*GSTM1* and *GSTT1*) play a role in cellular protection against xenobiotic toxicants and oxidative stress [26, 27], they were incriminated in the etiology of preterm delivery [28, 29], younger gestational age at birth, and recurrent pregnancy loss [30]. The studies of Dusinská *et al.* [27], Suh *et al.* [28] and Mustafa *et al.* [29] identified correlations between the *GSTM1*/*GSTT1* polymorphisms and maternal smoking, heavy metals or influence on neonatal birth weight [31–33]. The study of Hur *et al.* [34] investigated the relationship between the presence of *GSTM1* and *GSTT1* and maternal iron intake during pregnancy, and neonatal weight, respectively, and noticed a positive association between dietary iron intake and neonatal birth weight in pregnant women with *GSTM1* or *GSTM1*/*GSTT1* genotype.

Increased oxidative stress is associated with obesity and consists in fat accumulation leading to adipocytokines dysfunctions and metabolic syndrome [35]. BMI is the best method for defining obesity in adults, but mid-upper arm circumference (MUAC) and tricipital skinfold thickness (TST) are used for defining obesity in children and adolescents [36, 37]. Assessing the mother's body mass composition is important because it can influence the newborn's weight. Through bioimpedance analysis, we can assess the mothers' body composition parameters (fat and fat-free mass) with an influence in the newborns' body composition. Recent studies reported that the gestational weight gain (GWG) in the second trimester is associated with fetal growth and birth weight [38, 39], while Farah *et al.* emphasized that gestational weight gain before the third trimester influences the birth weight in women with normal BMI and overweight, and the fat-free mass influence birth weight, respectively [11, 12, 40].

Aim

On the basis of the above-mentioned facts, the aim of our study was to investigate the relationship between the maternal–neonatal *GSTM1*, *GSTT1* gene polymorphisms, maternal gestational weight gain, bioimpedance factors and newborn's weight.

Patients, Materials and Methods

We performed a cross-sectional study on 405 mothers and their newborns, a consecutive representative population from an Obstetrics Gynecology Tertiary Hospital from Romania, between April 2016 and December 2016. We defined '*a posteriori*' the studied groups, cases and controls, during the analysis phase and not in the design phase. The explicative variables or outcome did not influence the selection of subjects, as it was performed independently. The inclusion criteria were represented by maternal age more than 18 years and singleton pregnancy, while the exclusion criteria were: mothers and newborns with chronic diseases, patients with a suspected infectious disease (clinical signs and C-reactive protein >5 mg/L); parity >5; newborns with intrauterine growth retardation due to congenital malformations, patients with incomplete clinical, anthropometrical, laboratory and genetic assessment, and the cases where we did not obtain the informed consent.

Exposure variables

Exposure variables of interest were *GSTT1* and *GSTM1* mothers–newborns gene polymorphisms, maternal gestational weight gain and maternal bioimpedance factors.

Outcome variable

In order to evaluate the potential effect of the studied factors on birth weight, we transformed the outcome variable (birth weight) into a nominal dichotomous variable considering an estimated mean (3 kg) as the cut-off value.

Covariates

We considered several potential covariates including maternal age, maternal smoking habits, educational level, parity, gestational age and newborn's gender.

According to the standards of IOM [8], the mothers and their newborns were divided into two groups: Group I, study group, comprising of 141 women who presented a weight gain above the superior recommended limits

(increased weight gain), and Group II, the control group, comprised 168 mothers presenting a weight gain within the recommended interval (normal weight gain).

The informed consent was signed by all mothers for them and their children, prior to inclusion in the study and research fulfilled the principles of the Helsinki Declaration, and was approved by the Ethics Committee of the University of Medicine and Pharmacy of Tîrgu Mureş, Romania (No. 32/March 16, 2015).

Measurement characteristics

Anthropometric characteristics

All measurements for both mothers and newborns were carried out by a single trained person. These parameters consisted in: weight (kg), height (cm), mid-upper arm circumference and tricipital skinfold thickness. Body weight was measured with a daily-calibrated scale, with ±10 g error. For height, we used a pedometer, calibrated daily, being evaluated by standard deviation – SD (0.1-cm error). Mid-upper arm circumference and tricipital skinfold thickness were measured with a tape measure calibrated in centimeters. Mid-upper arm circumference was measured at the midpoint between shoulder and elbow tips, and tricipital skinfold thickness at the level of posterior upper arm with the use of a thickness caliper. BMI was calculated by dividing weight (kg) by standing height squared (m^2).

The Tanita BC-420 MA body composition analyzer (Tanita Corporation, Tokyo, Japan) was the device used for the assessment of maternal body composition. The measurements by bioimpedance respected entirely the manufacturer's guidelines at a frequency of 50 kHz. Also, the mothers were asked to void their bladder prior to the measurement. The measurement procedure required the subject to stand barefooted on the analyzer. Height, gender and age were entered manually, while weight was provided automatically, after a 0.5 kg adjustment for the clothes weight. Bioimpedance analysis (BIA) assesses the difference in impedance due to the different electrical properties of fat and lean tissues. Among others, the device we used, Tanita Analyzer also estimates fat mass, fat-free mass, muscle mass and total body water.

Genotyping

Two milliliters of fresh blood samples collected on ethylenediaminetetraacetic acid (EDTA) vacutainers from the newborns and their mothers, which met the inclusion criteria, were used for deoxyribonucleic acid (DNA) isolation. The multiplex polymerase chain reaction, as described previously by Sharma *et al.*, was performed for the genotyping of *GSTM1* and *GSTT1* gene polymorphisms in the subjects included in the present study. The method used allowed us to identify the homozygous null genotype of the *GSTT1* and *GSTM1* gene polymorphisms, and to recognize the presence of at least one *GSTT1* or *GSTM1* allele but without distinguishing between the homozygous and the heterozygous genotype for the above-mentioned genes [41].

Statistical analysis

The characteristics of the studied sample were described by frequencies and mean (± SD) or median (interquartile interval). The choice of centrality indicators for quantitative variables was made according to the type of variable distribution (Gaussian or not). For the Gaussian distribution, we used mean (± SD), as the most representative descriptive measure, while for a violation from the normal probability distribution, median and interquartile interval (25^{th} percentile–75^{th} percentile) were used.

The possible relationship between the studied mother–newborn gene polymorphisms, maternal gestational weight gain, maternal bioimpedance factors and neonatal birth weight were modeled by logistic regression analysis. In order to quantify the intensity of association, we calculated both crude and adjusted odds ratios (OR), in order to demonstrate the newborn's probability of gaining a higher birth weight. The bioimpedance factors included in the multivariable model were fat mass (%) and basal metabolism rate due to the higher degree of multicolinearity between the bioimpedance factors. Adjusted OR from the multivariable model were estimated controlling for all independent variables (other exposure variables and covariates).

For all bilateral tests, a statistical significance was achieved if *p*-values were lower than the significance threshold (α=0.05).

The statistical analysis was performed with the advanced environment for statistical computing and graphics R (v.3.2.4, Vienna, Austria).

Results

Description of the studied sample

Among the total group of mothers included in our study (405), 96 (23.7%) had the age less than 25 years, 237 (58.52%) between 25–34 years, while 72 (17.72%) had 35 years or more. Therefore, the mothers' mean age ± SD was 28.42±6 years. Regarding the BMI before pregnancy, most of the mothers were included in the normal weight group (285 – 70.37%), while 42 (10.37%) were underweight, 61 (15.06%) were overweight, and 17 (4.2%) were obese (Table 1). Thus, the median BMI was 22.4±3.51. The median (interquartile range) of gestational age was 39 (38–40). From a maternal educational perspective, 143 (35.31%) completed up to 10 classes, 88 (21.73%) between 11–15 classes, and 174 (42.96%) owned an academic degree (Table 1). A number of 73 (8.02%) mothers presented smoking habits and 17 (4.2%) had arterial hypertension during pregnancy. Only three (0.74%) of the mothers included in our study presented diabetes mellitus during pregnancy. As for the gestational weight gain, 174 (42.96%) of the mothers presented excessive weight gain during pregnancy. The number of unipara and multipara mothers were similar, 200 (49.38%) and 205 (50.62%), respectively. Concerning the bioimpedance parameters, the median value of the mothers' fat mass was 20.37 kg, while the basal metabolism rate was 1459 kcal (Table 1). Among the studied neonates, 42 (10.37%) had a birth weight of less than 2500 g. Regarding the gender, 221 (54.6%) of the newborns were males, and 184 (45.4%) females.

In order to evaluate the potential effect of the studied exposure variables of interest (as gene polymorphisms) on birth weight, we transformed the outcome variable

(birth weight) into a nominal dichotomous variable considering an estimated mean (3 kg) as the cut-off value. Therefore, we encountered a number of 263 newborns with the birth weight above 3 kg.

Table 1 – ***Description of the sample regarding demographic, genetic and anthropometric measures***

	Variables		Total sample (*n*=405)	Birth weight >3 kg (*n*=263)
Mothers	*Age [years]*	<25	96 (23.7)[1]	56 (21.29)[1]
		25–34	237 (58.52)[1]	157 (59.7)[1]
		≥35	72 (17.78)[1]	50 (19.01)[1]
	BMI before pregnancy	Underweight (<18.5 kg/m^2)	42 (10.37)[1]	22 (8.37)[1]
		Normal weight (18.5–24.9 kg/m^2)	285 (70.37)[1]	184 (69.96)[1]
		Overweight (25–29.9 kg/m^2)	61 (15.06)[1]	45 (17.11)[1]
		Obese (≥30 kg/m^2)	17 (4.2)[1]	12 (4.56)[1]
	Smoking habits	Yes	73 (8.02)[1]	37 (14.07)[1]
		No	332 (81.98)[1]	226 (85.93)[1]
	Educational level [years]	0–10	143 (35.31)[1]	87(33.08)[1]
		11–15	88 (21.73)[1]	61 (23.19)[1]
		>15	174 (42.96)[1]	115 (43.73)[1]
	AHT_eclampsia	Yes	17 (4.2)[1]	8 (4.2)[1]
		No	388 (95.8)[1]	255 (95.8)[1]
	Diabetes	Yes	3 (0.74)[1]	2 (0.76)[1]
		No	402 (99.26)[1]	261 (99.24)[1]
	Gestational weight gain	Excessive weight gain*	174 (42.96)[1]	129 (49.05)[1]
		Non-excessive weight gain	231 (57.04)[1]	134 (50.95)[1]
	Parity	Unipara	200 (49.38)[1]	126 (47.91)[1]
		Multipara	205 (50.62)[1]	137 (52.09)[1]
	Gestational age [weeks]	<37	54 (13.33)[1]	7 (2.66)[1]
		37–42	351 (86.67)[1]	256 (97.34)[1]
	Gene polymorphisms genotypes	*GSTT1* null	58 (14.3)[1]	43 (16.3)[1]
		GSTT1	347 (85.7)[1]	220 (83.7)[1]
		GSTM1 null	24 (5.9)[1]	19 (7.2)[1]
		GSTM1	381 (94.1)[1]	244 (92.8)[1]
	MUAC [cm]		27.48 (3.62)[2]	27.84 (3.59)[2]
	TST [mm]		16.7 (7.03)[2]	17.2 (6.67)[2]
	Fat mass [kg]		20.37 (7.8)[2]	21.72 (7.64)[2]
	Fat [%]		28.64 (7.12)[2]	29.87 (6.82)[2]
	Muscle mass [kg]		45.3 (41.7–49.2)[3]	45.9 (42.7–49.75)[3]
	Bone mass [kg]		2.4 (2.2–2.6)[3]	2.5 (2.3–2.7)[3]
	TBW [kg]		33.9 (31–37.1)[3]	34.4 (31.9–37.35)[3]
	TBW [%]		50.2 (47.1–53.5)[3]	49.3 (46.45–52.45)[3]
	BMR [kcal]		1459 (1349–1587)[3]	1481 (1379.5–1602)[3]
Newborns	*Birth weight [kg]*		3.18 (0.58)[2]	
	Gender	Male	221 (54.6)[1]	146 (55.5)[1]
		Female	184 (45.4)[1]	117 (44.5)[1]
	Gene polymorphisms genotypes	*GSTT1* null	57 (14.1)[1]	37 (14.1)[1]
		GSTT1	348 (85.9)[1]	226 (85.9)[1]
		GSTM1 null	19 (4.7)[1]	16 (6.1)[1]
		GSTM1	386 (95.3)[1]	247 (93.9)[1]

*If gestational weight gain was above the Institute of Medicine (IOM) recommendations (>18 kg, >16 kg, >11.5 kg and >9 kg, respectively); [1]Data are expressed as number and percentage (%); [2]Data are expressed as the mean and standard deviation; [3]Data are expressed as the median and interquartile interval (Q1–Q3); AHT: Arterial hypertension; BMI: Body mass index; BMR: Basal metabolism rate; *GSTM1*: *M1* allele of *GST* gene; *GSTT1*: *T1* allele of *GST* gene; MUAC: Mid-upper arm circumference; TBW: Total body water; TST: Tricipital skinfold thickness.

The influence of gestational weight gain, bioimpedance measurements, mothers–newborns *GSTT1* and *GSTM1* gene polymorphisms

In the multivariate logistic regression model, the newborns whose mothers had the null genotype of *GSTT1* gene polymorphism were more likely to present a birth weight higher than 3 kg as compared to newborns whose mothers had the *GSTT1* genotype ($OR_{adjusted}$: 2.3, 95% CI: [1.12; 4.87]). On the other hand, the null genotype of *GSTM1* in newborns had a significant positive effect on birth weight (p=0.043) while mother's same gene polymorphisms had a positive effect on birth weight with a tendency towards statistical significance (p=0.072). The gestational weight gain as a univariate predictor was positively associated with birth weight (p<0.001). Nevertheless, if it was associated with other factors, as a part of a multivariate analysis, gestational weight gain did not influence significantly the newborns' birth weight (p=0.954). On the other hand, the mother's fat mass (%)

influenced significantly the newborn's birth weight as it resulted from both univariate and multivariate logistic regressions (p<0.001 and p=0.003, respectively). Similarly, the basal metabolism rate was positively associated with birth weight as a univariate predictor (p<0.001), but also when other factors were taken into account in the multivariate regression analysis (p=0.02) (Table 2).

Table 2 – ***The influence of the studied gene polymorphisms and bioimpedance factors on newborn's birth weight***

Independent variables	Univariate regression analysis		Multivariate regression analysis	
	*p-value**	OR_{crude} *(95% CI)*	*p-value**	$OR_{adjusted}$ *(95% IC)*
Gestational weight gain				
Excessive	**0.0008**	2.08 [1.36; 3.2]	0.954	1.02 [0.58; 1.78]
Non-excessive	Reference group			
Fat [%]				
>28.64[a]	**<0.001**	2.56 [1.69; 3.92]	**0.003**	2.21 [1.32; 3.72]
≤28.64	Reference group			
BMR [kcal]				
>1459[a]	**0.0003**	2.16 [1.43; 3.3]	**0.02**	1.91 [1.1; 3.34]
≤1459	Reference group			
GSTT1 mother				
Null	0.115	1.73 [1.4; 2.16]	**0.03**	2.3 [1.12; 4.87]
T1	Reference group			
GSTM1 mother				
Null	0.14	2.13 [0.84; 6.55]	0.072	3.14 [0.9; 10.88]
M1	Reference group			
GSTT1 newborn				
Null	0.996	0.99 [0.56; 1.82]	0.446	0.77 [0.39; 1.52]
T1	Reference group			
GSTM1 newborn				
Null	0.085	3 [0.98; 13.06]	**0.043**	5.46 [1.06; 28.14]
M1	Reference group			

*Obtained from Wald's test, [a]cut-off values represents estimated medians of the sample; OR from multivariable model were adjusted for independent variables (exposure variables of interest included in the model and maternal age as qualitative variable, educational level, multiparity, gestational ages qualitative variable and newborn's gender); BMR: Basal metabolism rate; CI: Confidence interval; *GSTM1*: *M1* allele of *GST* gene; *GSTT1*: *T1* allele of *GST* gene; OR: Odds ratio.

According to this logistic model, an overall percentage of 75.8% newborns were correctly classified, the goodness-of-fit indices showing a reasonable model fit to data [Hosmer–Lemeshow test, *chi*-square – $\chi^2(8)$=6.5, p=0.591, R^2 (Nagelkerke)=0.34, C-statistics=0.79, 95% CI: 0.73–0.83].

The relevance of the studied predictors was also graphically represented in the Figure 1. Therefore, the following factors assessed in our study had a significantly statistical contribution in newborns' obesity, such as: *GSTT1* gene polymorphism in mothers, *GSTM1* gene polymorphism in newborns, gestational age (GA), fat mass percentage (FAT), basal metabolism rate (BMR) were significant predictors for a birth weight >3 kg.

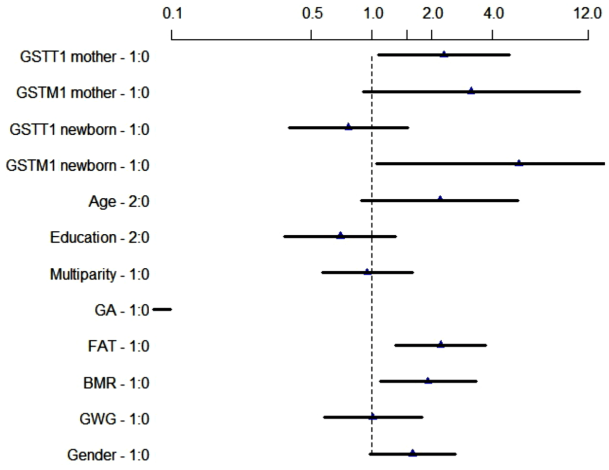

Figure 1 – ***OR and 95% CI for all factors included in the final model. The ruler contained a log-scale. Triangles indicate estimated OR and black bars indicate 95% CI for OR. Numbers (0, 1 and 2) next to the predictors name indicate the categories (target and reference) of the qualitative variables. For the studied gene polymorphisms: 1: null genotype, for age group 2: ≥35 years, 0: 18–25 years, for education: 2: academic degree and 0: ≤10 classes; OR: Odds ratio; CI: Confidence interval; GA: Gestational age; GWG: Gestational weight gain; FAT: Fat mass percentage with the categories 1: >28.64%; BMR: Basal metabolism rate with the categories 1: >1459 kcal and 0: ≤1459 kcal; GSTT1 in mothers; GSTM1 in newborns; GA, FAT, BMR were significant predictors for a birth weight >3 kg.***

Discussion

The determinism of birth weight

Multiple studies proved the fact that maternal body composition, especially maternal lean body mass, is positively correlated with birth weight [3]. Birth weight owns a great importance for the early and late complications of labor, such as: type of labor, *in utero* fetal attitude, neonatal hypoglycemia, obesity, and child's metabolic syndrome, respectively [42–44] for newborns with increased birth weight, but also neurological and cardiac disorders, metabolic syndrome, small height for newborns that present a small birth weight [45–49]. Similarly to other studies reported in the literature [50], our findings also underlined that approximately a fifth of the pregnant women were obese at the onset of pregnancy (19.26%). Birth weight was determined by multiple factors (maternal – mother's weight and gestational weight gain, obstetrical, genetic, environmental and socio-economical factors) and the interaction between them [1, 10].

The study of Wang *et al.* [31] proved that continuous maternal smoking during pregnancy was associated to a birth weight smaller with 377 g than without the exposure to this factor. In contrast, in our study, we noticed that a smaller number of newborns with increased or normal birth weight had smoker mothers (37/14.07%), but without obtaining any significant statistical correlations.

The percentage of women with preeclampsia/eclampsia was reduced, being at only 4.2% of cases, therefore we could not estimate its impact on newborn's birth weight, even though a smaller birth weight in newborns from

mothers with arterial hypertension [51] was reported in the literature. The following classification of the IOM [8] was used for gestational weight gain: underweight BMI <18.5 kg/m^2, recommended gestational weight gain 12.5–18 kg; normal weight BMI 18.5–24.9 kg/m^2, recommended gestational weight gain 11.5–16 kg; overweight BMI 25–29.9 kg/m^2, recommended gestational weight gain 7–11.5 kg; obese BMI>30 kg/m^2, recommended gestational weight gain 5–9 kg [8]. Our study also pointed out the correlation between excessive gestational weight gain, according to the IOM recommendations [8] and increased birth weight in 49.05%, similar data to those reported by other studies [6, 9]. Most of the women included in the study had medium and superior educational levels (64.69%).

Considerations according to the *GSTM1*/*GSTT1* gene polymorphisms and anthropometric parameters of mothers and newborns

GSTs represent an oxidative stress-related family of genes with an essential role in providing protection against the electrophiles and products of oxidative stress [52]. The human *GST* genes are divided into four subfamilies *GSTA*, *GSTM*, *GSTT*, and *GSTP* [53]. The deletion polymorphism of *GSTM1*/*GSTT1* genes leads to an increased oxidative stress and modulate the lipoprotein level [29, 54], being associated with an increased risk for obesity and its complications, such as: diabetes mellitus, arterial hypertension, metabolic syndrome, and their associated clinical outcomes [52, 55]. Strange & Fryer noticed that over 50% of the Asian population, 40% of the Africans and a quarter of the Caucasians do not express the *GSTT1* enzyme [56], the homozygotes that carry the deletion of this gene being called the null genotype [55]. The study of Wang *et al.* also showed that the *GST* gene defends the cells against oxidative stress and determine the development of type 2 diabetes mellitus associated to overweight or obesity [57]. The disequilibrium between oxygen reactive species and antioxidants increases insulin resistance [58]. Genetic changes consisting in the replacement of adenine with guanine in the DNA with a substitution of valine is associated with a reduction in enzyme activity. A decreased detoxification activity of the enzyme favors the development of obesity and its associated comorbidities [59, 60]. Almoshabek *et al.* showed on a group of 420 young Saudi obese patients *versus* 234 normal weight ones that *GSTM1*/*GSTT1* and *GSTM1*/*GSTT1* null genotypes were significantly associated with obesity and overweight risk. BMI and weight were more frequently encountered in the group with *GSTM1*/*GSTT1* genotypes, and low-density lipoproteins (LDL), diastolic blood pressure (DBP) and systolic blood pressure (SBP) were significantly higher in the group with null genotype [52].

GSTs are phase II xenobiotic metabolizing enzymes that catalyze the conjugation of electrophilic compounds with glutathione (GSH) [23]. Maternal *GSTM1* and *GSTT1* gene polymorphisms can modify the oxidative stress through exposure to cigarette smoke [26]. Between the *GSTM1*/*GSTT1* polymorphisms and newborn's weight, the existence of certain correlations was documented. Hur *et al.* [34] proved that an increased iron intake in pregnant women increased newborn's birth weight from mothers that carried the *GSTM1* polymorphism, but without a significant increase if they were from mothers with the *GSTM1* null genotype, reversely as in our study, in which we obtained a tendency towards statistical significance regarding a higher birth weight for newborns if both mother and newborn carried the null genotype of *GSTM1* (p=0.071). Also, Thompson *et al.* pointed out the fact that mothers carrying the *GSTM1* null genotype and the combination mothers–newborns with *GSTT1* null genotype were associated with a smaller birth weight [61].

The *GSTM1* null genotype in newborns is a predictor with a tendency toward statistical signification in the univariate analysis for the increased birth weight (p=0.085), while in the multivariable model it was an independent predictor for birth weight.

The same study of Hur *et al.* [34] did not establish any association between maternal iron intake and birth weight for the *GSTT1* polymorphism, while our findings revealed that applying the multivariate statistical regression model, the newborns whose mothers carried the *GSTT1* null genotype presented a higher birth weight (over 3 kg) compared to those whose mothers had the *T1* genotype ($OR_{adjusted}$: 2.14, 95% CI: [1.03; 4.44]). These results can be explained by the fact that we did not take into account the iron intake and we considered the model of multivariate regression in which we included the following parameters: mother–newborn gene polymorphisms, maternal gestational weight gain, maternal bioimpedance factors and neonatal birth weight.

The study of Wang *et al.* [31] pointed out that the presence of the *GSTT1* genotype was associated to a reduction of 285 g in weight, while the null genotype was associated to an increased birth weight, similar to our findings. Also, three other studies proved that the null genotype of the *GSTM1* and *GSTT1* polymorphisms had an influence on neonatal birth weight [31–33].

In our study, the *GSTM1* null genotype in newborns was an independent predictor for increased birth weight (p=0.042). Lau *et al.* proved that a gestational weight gain above the IOM [8] admitted limits increased the risk for overweight/obesity in the offspring [62]. Gestational weight gain and a severe increase in BMI before pregnancy carried important maternal and obstetrical risks [13, 14]. The excessive gestational weight gain increased birth weight and predicted a higher weight further on in life [15]. These factors correlated with the genetic and environmental ones carried a better prediction for the afterwards weight, increasing the obesity risk [15]. Newborns with a higher birth weight presented a risk for hypoglycemia and immediate obstetrical complications, but also obesity during childhood and adulthood [42–44], while those with a lower birth weight presented a risk for cardiac, neurological and metabolic impairment [45–49]. In our study, we identified gestational weight gain as a univariate predictor to be positively correlated with birth weight, but if included in the multivariate analysis together with other factors, it did not influence the newborn's weight.

Among the bioimpedance factors included in the multivariate model, we took into account fat mass (%) and basal metabolism rate due to the higher degree of multicolinearity between these bioimpedance factors. In one

previous study of our team, we found that fat mass, muscle mass, and metabolic rate were higher in mothers with excessive gestational weight gain [22, 63]. Also, in this study, we noticed that mother's fat mass (%) and basal metabolism rate were independent factors associated with higher birth weight (p=0.003 and p=0.02, respectively).

Limitations of the study

We have to underline some limitations of our study, such as: the fact that the patients were from a single geographic area, a not very big number of cases included in the study, the lack of longitudinal follow-up of the children with low and high birth weight as well as their impact on the future BMI and the potential risk for obesity when the implications of the studied gene polymorphisms presented an increased impact and the limitations associated to the design of the study, being a cross sectional study, and not involving any randomization of the sample. It would be useful to study the maternal nutritional habits, environmental factors, or their interactions with the genetic factors and to enlarge our study on a bigger number of cases, from an extended geographical area, in the future.

Strong points of the study

It is also important to underline the strong points of our study, like: the well-established work protocol, the accurate estimation of statistical parameters due to the fact that the selected sample was representative for the given population, and that the measurements were performed by a single trained, experimented person that provided the data after a well-established method. Both, mothers and newborns underwent all clinical and laboratory parameters, but also genotyping analysis. In addition, to our best knowledge there are no data in the literature that correlate the anthropometrical parameters in both mothers and newborns with *GSTM1* and *GSTM1* gene polymorphisms, this being a pilot study worth to be extended on larger population. Also, in our study we assessed a diversity of factors that may be involved in neonatal overweight determinism. Despite the fact that the previously mentioned strengths carry a great impact for our research, it is mandatory to continue our work, monitoring the newborns further on in life, in well-set developmental periods for a better understanding of the role of these parameters in the children's long-term nutritional status.

Conclusions

According to our findings, the null genotype of *GSTT1* gene polymorphism in mothers, and also the null genotype of *GSTM1* in both mothers and newborns present a positive effect on birth weight. Also, increased maternal fat mass and basal metabolism rate are independent factors associated with higher birth weight. We may consider that maternal *GSTT1*/*GSTM1* gene polymorphisms present an impact on birth weight, being involved in the newborns' nutritional status. This study also presents clinical relevance in the determinism of factors that influence birth weight, which can be trigger parameters for obesity, thus imposing further, larger studies and the elaboration of a protocol for predicting neonatal obesity risk.

Conflict of interests

None of the authors has any conflict of interests.

Author contribution

Claudiu Mărginean and Cristina Oana Mărginean equally contributed to this paper.

Acknowledgments

This research was partially supported by the Collective Research Grants of the University of Medicine and Pharmacy of Tîrgu Mureş, Romania ("The role of mother's genetic determinism in child's obesity correlated with bioimpedance and anthropometric parameters" No. 275/4/ 11.01.2017).

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Received: July 26, 2017

Accepted: January 14, 2018