

OBSERVATIONAL CASE-CONTROL STUDY ON THE RISK FACTORS OF FETAL MACROSOMIA AND FETAL-MATERNAL ASSOCIATED PATHOLOGY

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Abstract

Background and aims: The purpose of this study was to evaluate the frequency of demographic and clinical risk factors for fetal macrosomia, maternal pregestational, gestational and intra partum pathology associated with macrosomia, and to investigate the dynamic of these parameters in a decade. **Material and method:** We conducted two studies, a case-control study of 261 mothers who delivered macrosomic babies and 241 mothers who delivered normal weight babies in 2016, and then we compared the parameters obtained from the study group of 261 women who delivered in 2016 macrosomic babies with those of a study group of 220 women who delivered macrosomic babies in 2006 at Gynecology I County Hospital of Cluj-Napoca. The data was stored and analyzed using Microsoft Excel. **Results and conclusions:** Overweight before pregnancy, the excessive weight gain during pregnancy, and the delivery of a macrosomic baby increase the risk to deliver in the future a macrosomic baby. Mothers who delivered macrosomic babies had a higher incidence of thyroid gland pathology (hypofunction) and gestational diabetes than those who delivered normal weight babies.

key words: macrosomia, large for gestational age, gestational diabetes

Background and aims

Macrosomia is defined as the weight at birth of 4000g or more [1,2], regardless of the gestational age; the large for gestational age (LGA) newborn's weight exceed the 90th percentile or has more than 2 standard deviations for the gestational age, and ethnicity [3,4]. Globally, every year 10% of the newborns weigh

4000g or more, 1,5% of them weigh 4500g or more [3]. According with the increasing rate of obesity and diabetes among women at childbearing age, the incidence of macrosomia is expected to raise [5]. The prevalence of obesity has tripled from 1975 (WHO, World Health Organization), and in 2016, among children, nearly 10% were considered overweight or obese [6].

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The most important risk factors in fetal macrosomia are: the overweight of the mother before pregnancy, the BMI (body mass index) ≥ 25 [7-9] and the excessive weight gain during pregnancy [1-3,10-12], especially in the first trimester of pregnancy [13]. Obesity is often associated with thyroid gland dysfunction, women with subclinical hypothyroidism have increased risk to deliver LGA babies [14]. The effect of the maternal overweight and the altered glucidic metabolism on the fetus is obvious even when the mother is not diabetic (Knight 2007, Ong 2008), and her glycemic values are normal (Claussen 2005). According to the IOM (Institute of Medicine) recommendations from 2009 the recommended weight gain in pregnancy is: 28-40 lbs, for BMI <18.5 ; 25-35 lbs for BMI 18.5-24.9; 15-25 lbs for BMI 25.0-29.9, and 11-20 lbs for BMI ≥ 30.0 [7]. Women who gave birth to newborns weighing 4000g or more, have a bigger chance to deliver macrosomic babies in the future [4]. The baby boy newborns weigh more than the girls [10], and this is shown by the proportion of male/female macrosomic newborns [1,4].

Multiparity is another important risk factor [1,9,10,15], with each newborn the weight increase with 100-150g [3] it is supposed that with each pregnancy the uterine vascularization modifies (Camilleri and Cremona, 1970, Hafner and co 2000). Among newborns at term, the macrosomic babies are 1%, and among those delivered over 42 weeks, 3-10% from all deliveries [7]; the fetus grows around 150-200g/week before term. Age of the mother under 17 years [1,7], or over 40 years [1,9,16] increase the risk to deliver a macrosomic baby. Diabetes with onset before pregnancy (not more than 10 years; after 10 years the angiopathy causes fetal growth restriction) and gestational diabetes are associated with macrosomia [4,8,10,13]. Gestational diabetes causes a bigger incidence of

fetal growth than the diabetes with onset before pregnancy (Lupea, 2000). Some studies suggested that thyroid dysfunction could be a risk factor for gestational diabetes [17]. Other studies found that mothers with subclinical hypothyroidism had higher odds to deliver LGA babies, and the levels of fT4 in early pregnancy were inverse correlated with the birth weight, especially in male newborns [18]. Macrosomia is associated with a higher rate of cesarean deliveries, and in the case of spontaneous delivery, postpartum hemorrhage, perineal laceration and neonatal trauma, like humeral dystocia, clavicle fracture, humeral fracture and brachial palsy together with neonatal hypoxia, respiratory distress syndrome, and cerebral ischemia. The need for intensive care is higher when the baby weighs more than 4500g, and the rate of stillbirth is almost doubled [7]. These children are later in life exposed to obesity, cardio-vascular diseases and metabolic syndrome [19]. Although many risk factors can lead to macrosomia, many women gave birth to normal weight babies.

We conducted two studies in order to analyze the frequency of demographic and clinical risk factors for fetal macrosomia, and the maternal pregestational, gestational and intra partum pathology associated with macrosomia, in a case-control study which included the mothers who delivered macrosomic babies, compared with a group of mothers who delivered normal weight babies in 2016, and then we compared the study group from 2016 with a study group of mothers who delivered macrosomic babies in 2006, in order to investigate the dynamic of these parameters.

Material and method

We have studied the documents of all newborns from 2016 and of their mothers, from the Gynecology I County Hospital of Cluj-

Napoca, which were 2238. We have made a study group which included the mothers who delivered newborns weighing 4000 g or more, together with their newborns, and a control group, selected through stratified random sampling by age, including 241 pregnant women who delivered newborns at term weighing between 2700g and 3999g, together with their children.

In the second part of the study we analyzed the newborns and their mother's documents from 2006, which were 2158. We have made a study group which included the mothers who delivered newborns weighing 4000 g or more, they were 220, together with their children. We compared the two groups of mothers who delivered macrosomic babies in 2016 together with their children, with the group of 220 mothers who delivered in 2006 macrosomic babies, together with their children.

Anthropometric and clinical data collection

We collected the anthropometric and clinical data from the birth registry of the Gynecology I County Hospital of Cluj-Napoca hospital with

the agreement of the Ethics Committee of the County Clinical Emergency Hospital of Cluj-Napoca. It was not nominal and didn't include any identification data, so written consent was not needed.

Statistical analysis

The data was stored and analyzed using Microsoft Excel, the average, the standard deviation, the p (chi-square test, significant if $p < 0,05$), and the risk ratio (RR) was calculated.

Results

From the 2238 of the newborns from 2016, 11,66% weighed 4000g or more.

The average birth weight in the study group was $4184g \pm 222,4(M+2d)$, and $3298,05 \pm 258g$ in the control group. The average length at birth was 57 ± 2 cm ($M+2d$) in the study group, and $52,6 \pm 2,33$ cm in the control group. The average cranial perimeter was $36 \pm 1,2$ cm in the study group, and $34 \pm 1,3$ cm in the control group. The gender ratio masculine/feminine, M/F in the study group was 163/98, and in the control group was 124/117.

Table 1. The anthropometric characteristics of the newborns.

The characteristic	Macrosomia (n=261)	Control (n=241)	OR
Weight (g)	$4184 \pm 222,4$	$3298,05 \pm 258$	-
Length (cm)	57 ± 2	$52,6 \pm 2,33$	
Cranial perimeter (cm)	$36 \pm 1,2$	$34 \pm 1,3$	
Gender ratio (M/F)	163/98	124/117	1,57

Table 2. Demographic characteristics of the mothers.

Characteristic	Macrosomia (n=261)	Control (n=241)	OR
Age over 40 years	3% (n=8)	1% (n=3)	2,5
Parity more than 1	45% (n=117)	57% (n=137)	
Parity more than 2	12% (n=32)	25% (n=59)	
Urban residence	53% (n=140)	61% (n=147)	
College studies	51% (n=134)	52% (n=126)	

Mothers age over 35 years was in percentage of 19,1 % in the study group, and over 40 years in 3%. In the control group 19,5 % were over 35 years old, and 1,2% were over 40 years old (OR=2,5; CI 95%).

In the study group 53,6 % of the mothers had urban residence, and in the control group, 60,99%.

College studies had 51,3 % of the mothers from the study group, and 52,28% from the control group.

Data regarding weight before pregnancy were available in 238 of the mothers who delivered in 2016 children weighing 4000g or more, and at 67 mothers who delivered in 2016 normal weight children. The BMI ≥ 25 before pregnancy, was present in 38,65% (n=92) of the mothers who delivered macrosomic babies, (p=0,1; RR=1,2), and the BMI < 25 was present in 61,34% (n=146) of the cases. The average birth weight of the children delivered by mothers having a BMI ≥ 25 was $4193,478 \pm 250,737$ g, compared with the average birth weight of the children delivered by women with BMI < 25 was $4171,027 \pm 204,422$ g. In the control group, the

BMI ≥ 25 before pregnancy was present in 19,4% (n=13) of the cases, and the BMI < 25 was present in 80,59% (n=54) of the cases; the average birth weight delivered by the control group mothers with BMI ≥ 25 was $3323,077 \pm 207,7813$ g, compared with the average birth weight: $3299,074 \pm 233,410$ g, of the children delivered by the mothers from the control group with the BMI < 25 .

The average weight gain during pregnancy from the study group (n=238) was $16,632 \pm 5,720$ kg, and the average birth weight of their children was $4180,464 \pm 223,383$ g. In the control group (n=71) the average weight gain during pregnancy was $13,943 \pm 4,544$ kg, and the average birth weight of their children was $3278,169 \pm 237,055$ g.

Table 3. Clinical and anthropometric characteristics of mothers and babies.

	Macrosomia (n=238)	Control (n=67)	p	RR
BMI ≥ 25	38,65% (n=92)	19,4% (n=13)	0,01	1,2
BMI < 25	61,34% (n=146)	80,59% (n=54)	0,08	
Average birth weight of the babies delivered by the mothers with BMI ≥ 25 (g)	4193,478 \pm 250,737	3323,077 \pm 207,7813		
Average birth weight of the babies delivered by the mothers with BMI < 25 (g)	4171,027 \pm 204,422	3299,074 \pm 233,410		
Average weight gain during pregnancy (kg)	16,632 \pm 5,720	13,943 \pm 4,544		
Exceeded IOM recommended weight gain during pregnancy	56% (n=147)	9% (n=25)	0,01	1,28
Exceeded IOM recommended weight gain	30,74% (n=91)	66,19% (n=47)		
Average birth weight of the babies delivered by the mothers who exceed the IOM recommended weight gain (g)	4181,589-195,503	3231,25 \pm 274,975		
Average birth weight of the babies delivered by the mothers who didn't exceed the IOM recommended weight gain(g)	4176,437 \pm 265,763	3308,51 \pm 214,759		

Table 4. Pathology of the mothers.

	Macrosomia (n=261)	Control (n=241)	P	RR
Gestational diabetes mellitus	6% (n=15)	1% (n=3)	0,01	1,64
Hypothyroidism	5% (n=14)	2% (n=5)	0,06	1,44

NS= non-significant

In the study group, the IOM recommended weight gain during pregnancy was exceeded in 63,44% (n=151) of the cases (p=0,01; RR=1,28), and the average birth weight of their babies was 4181,589-195,503g. 30,74% (n=87) of the mothers didn't exceed the recommended weight gain during pregnancy, and the average birth weight of their children was 4176,437±265,763g. In the control group, 33,8% (n=24) of the mothers exceeded the IOM recommended weight gain during pregnancy, and the average birth weight of their babies was 3231,25±274,975g. 66,19% (n=47) of the mothers didn't exceed the recommended weight gain during pregnancy, and the average birth weight of their babies was 3308,511±214,759g.

Pathology during pregnancy:

- in the study group, *gestational diabetes* was diagnosed in 5,74% (n=15) of the cases. Nine of them exceeded the recommended IOM weight gain during pregnancy. Most of them were balanced through hypocaloric diet, in only one case insulin therapy was needed. In the control group, gestational diabetes was diagnosed in 1,24% (n=3) of the cases, (p= 0,001; RR= 1,64);

Pathology before pregnancy:

- in the study group, *diabetes before pregnancy* was present in 1,5% (n=4), of the cases: the *type I diabetes* was present in 2 of the cases, and 2 were diagnosed with *diabetes mellitus type II* (these ones were both overweight and had severe preeclampsia). In the control group, none of the mothers were diagnosed with diabetes mellitus;
- the *thyroid gland pathology* was present in 5,3% (n=14) of the cases in the study group, (5 Hashimoto thyroiditis, 6 hypothyroidism, 1 Basedow, 1 nodular goiter, 1 thyroid cyst)

and 2% (n= 5) in the cases from the control group (2 Hashimoto thyroiditis, and 3 hypothyroidism), (p=0,06; RR=1,44).

Obstetrical history:

- 8% (n=21) of the mothers from the study group gave birth to *macrosomic* children (p=0,01), compared with the control group, where only 0,41% (n=1) delivered macrosomic babies in the past.

Table 5. Obstetrical history.

Obstetrical history	Macrosomia (n=261)	Control (n=241)	P	RR
Macrosomic baby deliveries	8% (n=21)	0% (n=1)	0,001	1,9

Excess of subcutaneous tissue was mentioned at 6 new born babies (2,27%) in the study group and in none of the babies from the control group.

Neonatal birth injuries in the study group occurred in 3% of the cases: clavicle fracture (n=7) and brachial palsy (n=1); in the control group, occurred in 1,24% of the cases clavicle fracture (n=3).

Table 6. Birth injuries.

	Macrosomia (n=261)	Control (n=241)	P
Neonatal-clavicle fracture	3% (n=7)	1% (n=3)	0,2

Comparative study between the group of mothers who delivered in 2006 macrosomic babies and the group of mothers who delivered in 2016 macrosomic babies:

The total number of the newborns in 2006 was 2158, from which 10,19% (n=220) were weighing 4000g or more, and in 2016 from the total of 2238 newborn babies, 11,66% (n=261) weighed 4000g or more. 1,39 (n=30) from the 2006 newborns weighed 4500g or more, and 2 weighed ≥5000g; 1,02 (n=23) of the newborns from 2016, weighed 4500g or more, and 3 weighed ≥5000g.

Table 7. Macrosomic newborns in 2006 and 2016.

	2006 (n=2158)	2016 (n=2238)
Nr of newborns weighing $\geq 4000\text{g}$	10,19% (n=220)	11,66% (n=261)
Nr of newborns weighing $\geq 4500\text{g}$	1,39% (n=30)	1,02% (n=23)
Nr of newborns weighing $\geq 5000\text{g}$	2	3

In 2006, the average weight of the macrosomic newborns was $4193,55 \pm 225,4\text{g}$, over 2 standard deviations (M+2 d) and of $4184 \pm 222,4\text{g}$ (M+2 d) in 2016. The average length of the macrosomic newborns in 2016 was $57 \pm 1,2\text{ cm}$ (M+2 d), compared with $57 \pm 2\text{ cm}$ (M+2d) in 2016. In 2006 the average cranial perimeter was $36 \pm 1,5\text{ cm}$ in the study group, compared to $36 \pm 1,2\text{ cm}$ in 2016. The gender rate masculine/feminine of the macrosomic newborns from 2006, was M/F:149/71, and in 2016, was M/F:163/98.

Table 8. Anthropometric characteristics of the macrosomic newborns from 2006 and 2016.

	2006	2016
Average birth weight(g)	$4193,55 \pm 225,4$	$4184 \pm 222,4$
Average birth length (cm)	$57 \pm 1,9$	57 ± 2
Average cranial perimeter (cm)	$36 \pm 1,5$	$36 \pm 1,2$
Gender ratio M/F	149/71	163/98

In 2006, 11,81% (n=26) of the mothers were more than 35 years of age, and in 0,45% (n=1) of the cases were over 40 years; in 2016, 19% (n=50) of the mothers were over 35 years, and 3% (n=8) were over 40 years.

In 2006, 44,54% (n=98) of the mothers were multiparous, and 2,72% (n=6) of them gave birth to more than 4 children. In 2016, 44,8% (n=117) of the mothers were multiparous and 1,9% (n=5) of them gave birth to more than 4 children.

Urban residence had 75,36% of the mothers (n=168) in 2006, and in 2016, 62,4% of the mothers (n=163).

College studies had 21,36% (n=47) of the mothers who delivered in 2006, and 51,13% (n=134) of the mothers who delivered in 2016.

Table 9. Socio-economic characteristics of the mothers.

	2006	2016
Age >35 years	11,81% (n=26)	19% (n=50)
Age >40 years	0,45% (n=1)	3% (n=8)
Parity >1	44,54% (n=98)	44,8% (n=117)
Parity >4	2,72% (n=6)	1,9% (n=5)
Urban residence	75,36% (n=168)	62,4% (n=163)
College studies	21,36% (n=47)	51,13% (n=134)

Data related to weight gain during pregnancy was available in the case of 93 pregnant women who delivered macrosomic babies in 2006 and in the case of 238 mothers who delivered in 2016.

The average of the weight gain during pregnancy in 2006 was $20,075 \pm 6,292\text{g}$, and the average birth weight of their babies was $4272,151 \pm 266,58\text{ g}$. IOM weight gain recommendations during pregnancy was exceeded by 63,44% (n=59) of the mothers, the average exceeded weight gain during pregnancy was $7,474 \pm 4,7356\text{g}$, and the average birth weight of their babies was $4293,39 \pm 264,1682\text{g}$. The IOM recommended weight gain during pregnancy was not exceeded in the case of 36,56% (n=34) of the mothers, and the average birth weight of their babies was $4235,294 \pm 270,6696\text{g}$.

The average weight gain during pregnancy in 2016 was $16,632 \pm 5,720\text{g}$, and the average of the birth weight of their children was $4180,464 \pm 223,3835\text{g}$. The weight gain over the IOM recommendations was exceeded by 63,44% (n=151) of the mothers, the average exceeded weight gain from the IOM recommendations was $6,251 \pm 4,832\text{g}$, and the average birth weight of their babies was $4181,589 - 195,503\text{g}$. 36,56% (n=87) of the mothers didn't exceed the IOM recommended weight gain during pregnancy, and the average birth weight of their babies was $4176,437 \pm 265,763\text{g}$.

BMI ≥ 25 before pregnancy was present in 24,44% (n=11) of the 45 mothers who delivered in 2006, and the average birth weight of their babies was 4305,455 \pm 385,651g. 75,56% (n=34) of the mothers had BMI <25 before pregnancy, and the average birth weight of their babies was 4179,412 \pm 198,142g. In 2016 the BMI ≥ 25 before pregnancy was present in 38,65% (n=92)

of the 238 mothers, and the average birth weight of their babies was 4193,478 \pm 250,737g. The percentage of mothers with BMI < 25 before pregnancy who delivered in 2016 macrosomic babies was 61,35% (n=146), and the average of their babies birth weight was 4171,027 \pm 204,422g.

Table 10. Comparative nutritional indicators between 2006 and 2016.

	2006	2016	Percentage ratio
Mother s BMI ≥ 25	24,44%(n=11)	38,65% (n=92)	38,65:24,44=1,58
Average birth weight (g) of the babies of the mothers with BMI ≥ 25	4305,455 \pm 385,651	4193,478 \pm 250,737	1,02
Mother s BMI <25	38,66% (n=34)	61,35% (n=146)	61,35:38,66=1,58
Average birth weight (g) of the babies of the mothers with BMI <25	4179,412 \pm 198,142	4171,027 \pm 204,4226	1,00
Average weight gain during pregnancy(kg)	20,075 \pm 6,292 (n=93)	16,632 \pm 5,720 (n=237)	
Average birth weight (g)	4272,151 \pm 266,58	4180,464 \pm 223,383	
Weight gain exceeding IOM recommendations (kg)	7,474 \pm 4,7356 (63,44%; n=59)	6,251 \pm 4,832 (63,44%; n=151)	
Average birth weight of the babies from the mothers that exceeded the IOM recommended weight gain (g)	4293,39 \pm 264,1682	4181,589- 195,503	
Average birth weight of the babies from the mothers who didn't exceed the recommended IOM weight gain (g)	4235,294 \pm 270,6696	4176,437 \pm 265,763	

Pathology during pregnancy:

- in 2006, 1,52% (n=3) of the mothers were diagnosed with *gestational diabetes*. In 2016, 5,74% (n=15) of the mothers were diagnosed with gestational diabetes.

Pathology before pregnancy:

- in 2006, none of the mothers were diagnosed with *diabetes before pregnancy*; in 2016, type I diabetes mellitus was present in 2 cases, and type II diabetes mellitus was present in two of the cases;
- *thyroid pathology*, was present in one case in 2006 (thyroid node), and in 2016 at 5,36% (n=14) of the mothers, (5 Hashimoto

thyroiditis, 6 hypothyroidism, 1 Basedow, 1 nodular goiter, 1 thyroid cyst), (two of them were overweight, and two of them were obese);

Table 11. Pathology in pregnancy.

	2006	2016	Percentage ratio
Gestational diabetes mellitus	1,52% (n=3)	5,74% (n=15)	5,74:1,52= 3,77
Diabetes before pregnancy	0	1,53% (n=4)	
Thyroid pathology	0,4% (n=1)	5,36% (n=14)	5,36:0,4=13,4

Obstetrical history:

In 2006, 7,69% (n=17) of the mothers gave birth in the past to macrosomic babies, and in 2016, 8,04% (n=21);

Table 12. Obstetrical history of mothers who delivered macrosomic babies.

Obstetrical history	2006	2016
Macrosomic babies delivery	7,69%(n=17)	8%(n=21)

In 2006, a single clavicle fracture was mentioned in the study group (0,5%), and in 2016, in the case of 7 newborns (2,65%); brachial palsy occurred in a single case in 2016.

Discussion and conclusions

In the first study, the age of the mothers, residence and socio-economic status was similar between the two groups, there were no significant differences.

Regarding the BMI before pregnancy ≥ 25 , the p correlation was $p=0,01$, (RR=1,2). In the case of weight gain during pregnancy exceeding the IOM recommendations, the p correlation was $p=0,006$ (RR=1,28), which indicates that overweight before pregnancy and the excessive weight gain during pregnancy are significant risk factors in fetal macrosomia.

Gestational diabetes has a significant importance in the pathophysiology of fetal macrosomia, $p=0,01$, (RR=1,64), together with the thyroid gland pathology (hypofunction), $p=0,06$, (RR=1,44).

The delivery of a macrosomic baby increase the risk to deliver in the future a macrosomic baby, $p=0,001$, (RR=1,9).

In the comparative study between 2006 and 2016, the incidence of macrosomia increased from 2006 to 2016 with 1,47% (11,66-10,19=1,47).

The ratio between overweight mothers (BMI ≥ 25) from 2016 and 2006 is 1,58 (38,65/24,44), and the ratio between mothers with normal weight (BMI < 25) from 2016 and 2006 is 1,58 (61,35/38,66), as well, which shows that the contributing factors for the nutritional status of the mothers didn't change, it was a relatively stable period. As well, the percentage of mothers from 2006 and 2016 who gained weight over the IOM recommended limit was identical, 63,44%, it indicates that the influence of the factors which conducted to exceed the IOM recommended limits in 2006 didn't change till 2016. The overweight of mothers and the exceeding of the IOM recommendations were not the main factors that contributed to the increase of the incidence of fetal macrosomia.

Regarding maternal pathology, the frequency of gestational diabetes increased 3,77 folds, and the thyroid gland pathology, especially hypothyroidism, increased 13,4 folds.

As a conclusion, before conceiving a baby is recommended to adjust the weight in case the BMI is more than 25, and to pay attention on the weight gain during pregnancy, according to the IOM recommendations. Before pregnancy, and in early pregnancy as well, is indicated to monitor the thyroid gland function, glycemia, and if indicated, to make a screening for gestational diabetes, in order to avoid the excessive fetal growth, and the exposure for later in life, both for the mother and baby, at obesity, diabetes and metabolic syndrome.

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