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FETAL MACROSOMIA IN THE DIABETIC WOMAN

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Abstract

Diabetes mellitus complicates up to 10% of pregnancies, while in Romania the incidence is this under 5%. In most of the cases we are talking about gestational diabetes, while only in 0.1 - 0.3% of the cases, the diabetes was pregestational (mainly Type 1 diabetes and rarely Type 2 diabetes or Mody). The study we conducted concerned the incidence of macrosomia in the general population; in the study we investigated 3,000 pregnant patients who gave birth in the Unit of Obstetrics & Gynecology of 'Dr Cantacuzino' Hospital from 13th January 2007 to 30th March 2010. The 7.1% of incidence of diabetes mellitus highlighted by the study which aimed to trace gestational diabetes conducted in 2007-2010 period with the assistance of the 'Dr Cantacuzino' Hospital, represents just the tip of the iceberg. The positive diagnosis of gestational diabetes identified not only women who had diabetes mellitus pre-existing the pregnancy, without their being aware of it, but also women with a pathology of carbohydrate metabolism who will in the future run a higher risk of developing type 2 diabetes mellitus.

key words: *fetal macrosomia, gestational diabetes, prenatal risk factors*

Introduction

Certain factors have been empirically associated with fetal macrosomia, for instance history of macrosomia, multiparity, excessive maternal weight or height (women with more than 25% excess weight or with the ratio prenatal weight/height ratio >2.4), ethnicity (Pima Indians), excessive maternal weight during pregnancy (above 16 Kg or 35 pounds), delayed birth (more than 294 days), and a difficult or prolonged travail [1]. The frequency of macrosomic newborns in gestations with gestational ages between 40 and 41 weeks is 20% and reaches 43% for pregnancies between 24 and 44 weeks of gestation [2, 3].

Normal fetal growth is influenced by intricate genetic and hormonal factors which send signals to the growing fetus. The growth of the fetus is nevertheless limited, especially during the third term. Maternal and/or fetal diseases as well as environmental factors may lead to accelerated or retarded models of fetal growth.

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The most frequent maternal pathology associated with an abnormal fetal growth during pregnancy is diabetes mellitus. The most frequent consequence of maternal diabetes is fetal macrosomia, which is directly related to traumatisms (shoulder dystocia and paralysis of the brachial plexus) and marked by metabolic and respiratory complications [4].

Objective of the Study

The study we conducted concerned the incidence of macrosomia in the general population; during the study we investigated 3,000 pregnant patients who gave birth in the Unit of Obstetrics & Gynecology of 'Dr Cantacuzino' Hospital from 13th January 2007 to 30th March 2010.

The data was collected before delivery and afterwards completed with the real birth weight – more precisely with the classification in the group of macrosomia or LGA (long for gestational age).

We included maternal age in the pregnancy risk because this parameter becomes a risk factor for macrosomia during a pregnancy, not in its absence. It is obvious that preconception counseling should include risk data related to maternal age, among which macrosomia is not the most important for an age above 35. There are numerous studies and articles about the impact of maternal age on pregnancy and about its results in a society where the planning or delaying of having a baby has become ever more frequent. As expected, advanced maternal age was associated with an increased risk of spontaneous abortions and chromosome abnormalities.

In this study we analyzed the prevalence of macrosomia and LGA in the general population, as well as aspects of macrosomia related to the complications of pregnancies with gestational diabetes mellitus and of pregnancies for pregnant women with diabetes mellitus pre-existing the pregnancy.

Material and Method

In this study we have examined maternal characteristics, using anamnestic data relative to the antecedents of macrosomia, multiparity, the mother's maternal height, ethnicity, prenatal weight of the mother, maternal weight excess during pregnancy, delayed birth (>294 days), as well as prolonged or overdue travail and the newborn's sex at birth.

For the diagnosis of fetal macrosomia we used methods of clinical and paraclinical diagnosis.

The clinical diagnosis was pronounced on the basis of the height of the uterus on the due date over 40cm and on the increased abdominal circumference.

The clinical capacity of evaluating fetal weight remains low, with only 25 to 60% of macrosomic fetuses being identified due to excessively increased values of the uterus' fundal height.

Paraclinical diagnosis

Ultrasound diagnosis of macrosomia

The ultrasound scan may highlight an increased risk of fetal macrosomia, without specifying exactly the existence of macrosomia [5, 6, 7]. In the course of time, several parameters of fetal bio-anthropometry have been suggested for tracing fetal macrosomia:

- Transverse thoracic diameter (TTD);
- Biparietal diameter (BPD);
- Abdominal circumference (AC);
- Femur length (FL);
- Humeral subcutaneous tissue.

Originally macrosomia was assessed by ultrasound scans through serial determinations of the biparietal diameter and of the abdominal circumference [29]. Values exceeding the standard average by two standard mean deviations at 28-32 weeks of gestation allow the diagnosing of macrosomic fetuses.

Results

In the study we conducted at 'Dr Cantacuzino' Hospital in the Clinic of Obstetrics-Gynecology in the period 13th January-30th March 2010, when we analyzed 3,000 patients who gave birth in this time interval, the prevalence of macrosomia was 7.1% and of LGA, 16.2%, as seen in Table 1.

Table 1. Incidence of macrosomia according to the two definitions.

YEAR	4 Kg macrosomic		LGA		Births
	No	%	No	%	
2007	47	5.7	119	14.1	841
2008	61	7.4	128	15.3	834
2009	73	8.1	160	17.8	902
2010	32	7.5	78	18.4	423
TOTAL	213	7.1	485	16.2	3000

Table 2. Analysis of prenatal risk factors.

Risk factors	4 Kg macrosomic		LGA	
	No -213	P	No /485	P
>30 years	64	<0.001	123	0.007
>35 years	25	<0.001	44	NS
Gestations(>3)	72	NS	157	NS
Parity(>1)	97	0.001	164	0.004
Parity(>2)	27	NS	55	NS
DM I	4	<0.001	8	<0.001
DM II	1	NS	1	NS
Obesity	8	<0.001	13	<0.001
Hypothyroid	2	NS	2	NS
Urban environment	48	0.031	350	NS

The use of tests of concordance led to the conclusion that the definition with weight in excess of 4Kg allowed us to identify 89.43% of the macrosomias defined according to groups of weight on gestational ages, with the rest of 10.67% being undiagnosed. The majority of these unidentified cases belong to children with an accelerated growth who, due to various reasons, are not delivered on the expected date and are born weighing less than 4,000g, but who if they had kept their growth rhythm and would have been delivered on the expected date would probably reach that weight [8].

Table 2 above includes the analysis of the risk factors of macrosomia of the case-study group according to the Pearson χ^2 test. The statistically significant risk factors were maternal age in excess of 30 years, parity above 1, type 1 diabetes mellitus pre-existing pregnancy, obesity, while the specifics for macrosomia were the urban provenance environment and a maternal age exceeding 35.

During their reproductive life women tend to give birth to children at gestational ages and with weights which belong to the same weight category, although fetal weight has a slightly ascending trend from one pregnancy to the next, up to a parity of 5. Thus, a woman who gave birth to a '*child who is big for its gestational age*' or '*small for its gestational age*' will very likely give birth to other children who belong to the same weight groups [9]. This reproductive pattern seems to belong to the maternal lineage, suggesting a stronger genetic linkage than the paternal one. A group of researchers have studied several generations of a family of Rhesus monkeys (Macaca mulatta) who benefited from an adequate nutritive intake and optimal health care in laboratory conditions [10]. A marked increase of birth weight was reported for some females with certain maternal characteristics. This may constitute the proof that there exists an intrauterine mechanism transmitted to the offspring which regulates fetal development [11].

The recurrence of gestational diabetes in future pregnancies is between 20 and 50%, which may serve to explain the recurrence of macrosomia in some families, afterwards followed by the onset of maternal diabetes in 50% of the women after approximately 10 years from the onset of gestational diabetes and from the birth of a child, and in 70% of the women who have gestational diabetes and two children [12, 13].

Table 3. Analysis of risk factors associated with pregnancy.

Risk factors	4 Kg macrosomic		LGA	
	No's-213	P	No's/485	P
Gestational diabetes	2	0.012	4	0.001
Weight excess	16	<0.001	22	<0.001
Pregnancy induced HBP	8	0.026	14	NS
Masculine sex of fetus	143	<0.001	295	<0.001
Post-maturity	3	<0.001	2	<0.001
Not investigated	13	<0.001	45	<0.001

Women who gave birth to macrosomic children had the following statistically significant variables compared to the control group: a higher age, obesity (defined as a weight in excess of 90 Kg), diabetes (gestational or pre-existing) and post-maturity (more than 42 weeks of gestation). The sex of the macrosomic infants was predominantly masculine, they presented birth traumatisms and shoulder distocia much more frequently and had much higher rates of mortality and a lower APGAR score (Table 3).

Metabolic asymmetric macrosomia is associated with accelerated fetal growth. It generally occurs in pregnant diabetics with a poor metabolic control [3, 14]. This type of macrosomia is characterized by visceromegaly and must be considered as a pathological entity. In order to analyze the risk factors associated with pregnancy and their influence more thoroughly, they were grouped in risk factors for macrosomia other than the dysfunctions of carbohydrate metabolism, and these included the age of the mother exceeding 30, parity, obesity (Body mass index- BMI > 25), weight excess (above 16 Kg), hypothyroid, pregnancy-induced HBP, and masculine sex (Table 4). The manner of

presentation and rank of gestation were not included, while the carbohydrate metabolism dysfunctions that comprised type I and II diabetes pre-existing the pregnancy and gestational diabetes [15, 16] were grouped separately.

Table 4. Analysis of cumulated risk factors.

Risk factors	4 Kg macrosomic		LGA	
	No's-213	P	No's/485	P
Cumulated prenatal factors	31	<0.001*	58	<0.001*
Pathology of carbohydrate metabolism	6	<0.001*	13	<0.001*

*P<0,001 highly significant statistically; **NS statistically non-significant

As expected, the existence of pathology associated with the carbohydrate metabolism – regardless of the type – or with dysfunctions of maternal weight yielded highly significant statistical results. The cumulated analysis of the factors does not lend statistical significance to each and every factor and neither does it contradict or correct the previously obtained data, but it confirms the validity of associating these factors as cumulated risk factors for macrosomia [17].

The value of HBP proved more difficult to assess, since it, by itself, as pathology, should be associated with a restriction of growth. There exist studies which situate it alongside smoking and high altitude as a 'protective' factor against macrosomia, due to the negative influence it exerts on the curve of growth, and also on the risk of birth before the expected date [18, 19]. But in our case-study group, the separate analysis of subjects with HBP in fact led to a predominant presence of associating HBP, obesity, and diabetes mellitus [28]. The incidence of obesity was actually 24 times as high, that of weight excess 17.5 times as high and that of diabetes mellitus 7 times as frequent in the women with pregnancy-induced HBP.

The newborns' average weight in the case of mothers who had diabetes mellitus pre-existing the pregnancy was 3,429.8 g (+/–846g), significantly higher than the average of 3,192.5g (+/–568g) (p<0.001), while the prevalence of macrosomia was 26.2%. Although the number of pregnancies complicated by maternal diabetes mellitus pre-existing the pregnancy was only 0.5%, and of those cumulated with type 2 diabetes and gestational diabetes reached 0.8% of the analyzed births, the majority of the maternal and fetal complications associated with birth occurred associated with this pathology and posed problems of obstetrical care of the pregnant woman to diabetologists and neonatologists.

In the case-study group of births from 'Dr I. Cantacuzino' Hospital, the incidence of obesity was 1.2% (BMI > 25), despite the fact that the uniformity of the data gathered during the 3 years allowed us not only to assess an increase of obesity, but also to ascertain that the latter is constantly underreported.

Analyzing the births by women with obesity, the incidence of macrosomia was 34%, compared to the 16% for the group of pregnant women with normal weight.

Excessive weight defined as an increase of maternal weight of more than 16 Kg on examination (a maximum of 10 days before birth) proved to be an independent risk factor

for macrosomia, with an OR of 1.7 (p=0.001, CI 95%:1,2-2.3) identical for a maternal age of more than 30 and 35 respectively.

Analyzing births for women with excessive weight during pregnancy, the incidence of macrosomia was 28%, compared to the 16% we ascertained in the group of pregnant women with normal weight.

The analysis of the data concerning women who presented obesity led to the conclusion that maternal obesity was positively correlated to the weight at birth (p<0.001), which means that the weight average of children of obese mothers is significantly higher than that in the case-study group, namely 3,500g (+/– 586g) and 3,192g (568,5g) respectively. While this has no statistical significance, women with obesity were in the moment of birth older than the average value for the entire group, which was 28.8 years of age (+/– 5.3 years) compared to 26.5 years (+/ –5.4 years). Women with obesity gave birth predominantly to masculine sex fetuses (p=0.041). Maternal obesity was positively correlated to the rank of gestation and to parity, for both of which there exists a high statistical significance (p<0.0001), just like type I maternal diabetes mellitus (p<0.0001).

Paradoxically, although a very clear clinical explanation does exist, neither type II-diabetes mellitus nor gestational diabetes represented significant associations, due to the reduced number of diagnosed cases in both instances. Type II-diabetes mellitus is quite infrequent for the reproductive age, although its reported incidence also tends to be on the rise due to the association with the increased prevalence of obesity [18]. Gestational diabetes is a rare diagnosis because no screening is done in the second term [24, 25], and obesity does not represent a reason for family physicians to routinely indicate TTGO [19, 20].

The risk of HBP induced by pregnancy and eclampsia was higher for women with obesity (p+0.018).

It is also because of the characteristics of the population analyzed in the study that the maternal environment of provenance did not represent a risk for macrosomia in the case-study group with BMI > 25.

Maternal age represented a risk factor in the pregnancies investigated at 'Dr Cantacuzino" Hospital – 22.5% of the women were older than 30, 7.9%, older than 35, and only 0.6% were aged over 40.

Conclusions

Fetal weight at birth is an important parameter owing to the message it carries. The correct interpretation may result in a preventive and curative clinical attitude for the fetus and the mother, not only immediately during pregnancy and delivery, but also afterwards [21, 25].

Fetal growth is the result of the interaction between the genetic factors of growth and the limitations imposed by intake (amino acids, free fatty acids, and especially glucose) [26, 27].

The analysis of birth weight by the method proposed by Wilcox and the statistical analysis of the groups of macrosomia in the 3,000 births in the period 13th January 2007-30th March 2010 in the unit of Obstetrics-Gynecology of the 'Dr Cantacuzino' Clinical Hospital in Bucharest resulted in the identification of the value of 4,000g as the limit which permits the most accurate reflection of the characteristics of the studied population, compared to other values proposed

by the national guidelines in other countries, namely 4,500g or 5,000g.

Gestational diabetes mellitus is one public health problem that has constantly been sub-diagnosed in our country. The incidence of 7.1% highlighted by the study made in the period 2007-2010 with the assistance of the 'Dr Cantacuzino' Hospital, which aimed to trace gestational diabetes, represents just the tip of the iceberg. The positive diagnosis of gestational diabetes identified not only women who had diabetes mellitus pre-existing the pregnancy, without their being aware of it, but also women with a pathology of carbohydrate metabolism who will in the future run a higher risk of developing type II-diabetes mellitus. The macrosomic fetus secondary to gestational diabetes is a fetus with great fragility that is different from a fetus with constitutional sturdiness. This data is also confirmed by recent materials published in literature, subsequent to our embarking on the study.

REFERENCES

1. **Alexandru Carmina, Nicolau A. Ceausu I, Guja C, Ionescu Targoviste C**. Trends in the Outcome of Dibetic Pregnancies in Bucharest. *Acta Diabetologica* 28 (2002)

2. **Metzger BE, Coustan DR**. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus: the organizing committee. *Diabetes Care* 21 (Suppl.2): B161-B167, 1998.

3. **O'Sullivan JB, Maham CM**. Criteria for oral glucose tolerance test in pregnancy. *Diabetes* 13: 278-285, 1964.

4. **Cutchie WA, Cheung NW, Simmons D.** Comparison of international and New Zealand guidelines for the care of pregnant women with diabetes. *Diabet Med* 23: 460-468, 2006.

5. **Metzger BE, Buchanan TA, Coustan DR, De Leiva A, Dunger DB, Hadden DR, Hod DR, Hod M, Kitzmiller JL, Kjos SL, Oats JN, Pettitt DJ, Sacks DA, Zoupas C.** Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care* (Suppl. 2): S251-S260, 2007.

6. **World Health Organization:** WHO Expert Committee on Diabetes Mellitus: Second Report. Geneva, World Health Org., (Tech. Rep. Ser., no. 646) 1980.

7. **Jarret RJ.** Reflections on Gestational diabetes. *Lancet* 28: 1220-1221, 1981.

8. **Hunter DJS, Keirse MJNC.** Gestational diabetes in effective care. In Pregnancy and Chil;dbirth I, Enkin M, Kierse M, Eds New York, *Oxforn University Press* p. 403-410, 1989.

9. **Spellacy WN, Miller S, Winegar A, Peterson PQ.** Macrosomia: maternal characteristics and infant complications. *Obstet Gynecol* 66: 158-161, 1985.

10. **Coustan DR.** Management of gestational diabetes. *JAMA* 275: 1199-1200, 1996.

11. **Jensen DM, Damm P, Sorensen B, Molsted-Pedersen L, Westergaard JG, Klebe J, Beck-Nielsen H.** Clinical impact of mild carbohydrate intolerance in pregnancy: a study of 2904 nondiabetic Danish women with risk factors for gestational diabetes. *Am J Obstet Gynecol* 185: 413-419, 2001.

12. **Yang X, Hsu-Hage B, Zhang C, Zhang Y.** Women with impaired glucose tolerance during pregnancy have significantly poor pregnancy outcomes. *Diabetes Care* 25:1619-1624, 2002.

13. **Vambergue A, Nuttens MC, Verier-Mine O, Dognin C, Cappoen JP, Fontaine P.** Is mild gestational hyperglycaemia associated with maternal and neonatal complications? The Diagest Study. *Diabet Med* 17: 203-208, 2000.

14. **Langer O, Brustman L, Anyaegbunam A, Mazze R**. The significance of abnormal glucose tolerance value on adverse outcome in pregnancy. *Am J Obste Gynecol* 157: 758-763, 1987.

15. Sacks DA, Abu-Fadil S, Greenspoon JS, Fotheringham N. Do the current standards for glucose tolerance testing in pregnancy represent a valid conversion of O'Sullivan's original criteria*? Am J Obstet Gynecol* 161: 638-641, 1989.

16. Ferrara A, Weiss NS, Hedderson MM, Quesenberry CP Jr, Selby JV, Ergas IJ, Peng T, Escobar GJ, Pettitt DJ, Sacks DA. Pregnancy plasma glucose levels exceeding the American Diabetes Association thresholds, but below the National Diabetes Data Group thresholds for gestational diabetes mellitus, are related to the risk of neonatal macrosomia, hypoglycemia and hyperbilirubinaemia. *Diabetologia* 50: 298-306, 2007.

17. U.S. Preventive Services Task Force. Screening for gestational diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 148: 759-765, 2008.

18. Scott DA, Loveman E, McIntyre L, Waugh N. Screening for gestational diabetes: a systematic review and economic evaluation. *Health Technol Assess* 6:1-161, 2002.

19. Canadian Task Force on the Periodic Health Examination. The Canadian guide to clinical preventive health care. *Health Canada* 15-23, 1994.

20. National Collaborating Centre for Women's and Children's Health. Diabetes in pregnancy: management of Diabetes and its Complications from Preconception to the postnatal period. London, U.K., *RCOG Press*, 2008.

21. Ogden CL, Carroll MD, Curtin LR, Mc-Dowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA* 295: 1549-1555, 2006.

22. Narayan KM, Boyle JP, Thompson TJ, Gregg EW, Williamson DF. Effect of BMI on lifetime risk for diabetes in the U.S. *Diabetes Care* 30: 1562-1566, 2007.

23. Dunstan DW, Zimmet PZ, Welborn TA, De Courten MP, Cameron AJ, Sicree RA, Dwyer T, Colagiuri S, Jolley D, Knuiman M, Atkins R, Shaw JE. The rising prevalence of diabetes and impaired glucose tolerance: the Australian *Diabetes Care* 25: 829-834, 2002.

24. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: *Intl J Gynecol Obstet* 78: 69-77, 2002.

25. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Coustan DR, Hadden DR, McCance DR, Hod Mm, Persson B, Rogers MS, Sacks DA. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 358: 1991-2002, 2008.

26. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. *Diabetes* 58:453-459, 2009.

27. Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index. *Bjog* 117: 575-84, 2010.

28. C. Ionescu-Tirgoviste, F. Despa. Biophysical alteration of the secretory track in β-cells due to molecular overcrowding: the relevance for diabetes. *Integr. Biol* vol. 2: 1039/C0IB00029A, 2011.

29. Carmen Mihaela Mihu, Dan Mihu, Tudor Drugan, Sorin Dudea, Răzvan Ciortea, Mihaela Oancea. Study of Intraplacental Vascularization by 3D Power Doppler Ultrasound in Pregnancies with Normal Evolution. *Gineco.ro* vol 6: 210-216, 2010.