Maternal risk factors in newborns with plurimal formative syndromes

Raluca Marian[1], Marta Simon[2], Anca Sin[1], Manuela Cucerea[2]

1. Departament of Cellular and Molecular Biology, University of Medicine and Pharmacy Tg. Mureș (Romania)
2. Departament of Neonatology, University of Medicine and Pharmacy Tg.Mureș (Romania)

Correspondence:
Dr. Manuela Cucerea
e-mail: manuelacucerea@yahoo.com

Abstract

Objective. *The purpose of our study was to valuate the maternal risk factors for neonatal plurimalformative syndromes.* ***Methods.*** *About 92 newborns with plurimalformative syndromes and 92 healthy neonates were included in a survey conducted in Târgu-Mureș (Romania) neonatal tertiary unit between January 2007 and December 2010. A complete maternal history was taken. Statistical analysis was performed with using SPSS 17.* ***Results.*** *The incidence of plurimalformative syndromes was 0.94%. We did not found any association between malformative risk and mother's age (p=0.544), only with mother's residence (p=0.02), with an increased risk for newborns of mothers from rural areas (RR=1.39). There was a statistically association between plurimalformative syndromes and history of previous malformed children (p=0.042), maternal pathology (p=0.034) and maternal smoking (p=0.003), excepting the maternal alcohol consumption (p=0.649).* ***Conclusion.*** *Multicenter study with higher number of cases is needed to confirm these findings and initiate a national registry for congenital malformations.*

Keywords: *maternal risk factors, neonates, plurimalformative syndromes*

Introduction

Congenital malformations/anomalies or birth defects are structural abnormalities of the body that develop during embryogenesis and the fetal period and are a major cause of stillbirth and neonatal death. Major malformations, compared with minor malformations, require medical or surgical intervention or are of substantial cosmetic importance. Plurimalformative syndromes represent a combination of three or more birth defects, and they are the expression of morphogenesis errors[1,2,3,4]. Multiple anomalies may occur together in a statistically associated basis, or may occur together merely by chance[5]. It is estimated that 2.5% of newborns have detectable malformations at birth and about 50% of cases display multiple malformations[6]. Plurimalformative syndromes represent about 4.2% of all congenital anomalies. In 50% of cases the underlying causes remain obscure, unexplained. Genetic defects cause 15% of major structural anomalies, teratogenic agents cause 5-10% of major anomalies, while 25% are multifactorial induced during the vulnerable embryogenesis period due a genetic predisposition[6,7,8]. Several maternal, fetal and environmental risk factors are described[1]. The aim of the study was to evaluate the role of maternal risk factors in neonatal plurimalformative syndromes.

Methods

In this prospective study conducted in the regional neonatal tertiary unit Târgu-Mureș during 1st January 2007 to 31 December 2010, 92 newborns with plurimalformative syndromes (study group, n=92) were included, born or transferred in our unit over this period. This number represent all consecutive cases of plurimalformative syndromes in the mentioned period. The presence of congenital malformations was identified from medical records of antenatal and delivery care, clinical exam of the newborns, neonatal and ultrasounds examination, in the absence of a functional National Register of congenital malformations. Stillbirths and induced abortions for congenital anomalies were not included due to lack of complete data, and neither the cases presenting less than three anomalies. Diagnosis involved a multidisciplinary team consisting of obstetricians, neonatologists, pediatric cardiologists, pediatric surgeons, neurosurgeons, geneticists. For comparative analysis a control group of 92 healthy neonates (control group, n=92) born at the same gestational ages and in the same days with the newborns from study group was established. A complete maternal history was taken including family history of congenital anomalies, consanguinity, maternal age, parity, residence, antenatal care, imminent abortion, previous history of delivery of malformed newborn, oligohydramnios, polyhydramnios, maternal diseases (i.e. diabetes mellitus, hypertension, rubella, cytomegalovirus infection, toxoplasmosis, syphilis) drug intake and also exposure to alcohol and smoking during antenatal period. Data were included in a personal datasheet for each case. Statistical analysis was performed with SPSS v. 17 for Windows (Statistical Package for the Social Sciences, Chicago, Illinois). Existence of statistically significant differences between different subgroups was tested using parametric or non-parametric tests. Student t test was used, Pearson-$\chi 2$, Fisher's exact test, ANOVA test and logistic regression.

Results

The survey included 9748 newborns admitted in regional neonatal tertiary unit Târgu-Mureș during the study period, of which 607 (6.22%) were identified as

Received: *September 01, 2012*
Revised: *November 12, 2013*
Accepted: *February 23, 2013*

Table 1 Plurimalformative syndromes detected in neonatal period

year	Plurimalformative syndromes detected in neonatal period		
	Total infants admitted	No. of cases	%
2007	2629	30	1.14%
2008	2543	24	0.94%
2009	2462	18	0.73%
2010	2114	20	0.95%
Total	**9748**	**92**	

Table 2 Type of malformation in plurimalformative syndromes

Type of malformation	N	%
Teratoma	2	2.17%
Cardiovascular system	61	66.30%
Central nervous system	51	55.43%
Genitourinary	14	15.21%
Gastrointestinal tract	11	11.95%
Limb	33	35.86%
Ocular	17	18.47%
Respiratory tract	11	11.95%
Facial dysmorphism	59	64.13%
Total	**92**	

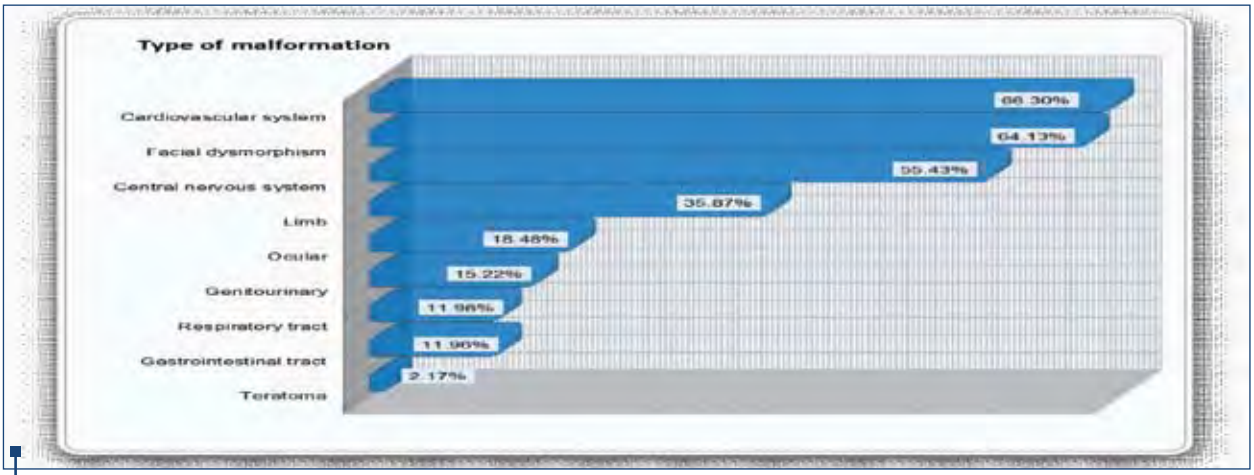

Figure 1. Type of malformation in plurimalformative syndromes

having major birth defects. Among them 92 (0.94%) had plurimalformative syndromes, respectively 15,15% from all major detected defects (Table 1).

Tabel 2 summarizes the type of malformations founded in study group (Table 2, Figure 1). Genetic tests were performed in 50 cases (54.35%) of study group showing a higher frequency of trisomy 21 (18.84%). Less common were cases of trisomy 18 (7.61%) and trisomy 13 (6.52%), and rarely met were cases of trisomy 9 (1.09%) and 4p syndrome (1.09%). Normal

Table 3 Genetic Tests in study group

Genetic Test	No	%
Not done	42	45.65%
Done	50	54.35%
Normal karyotype	18	19.57%
trisomy 18	7	7.61%
trisomy 13	6	6.52%
trisomy 9	1	1.09%
4p syndrome	1	1.09%
trisomy 21	17	18.48%
Total	**92**	

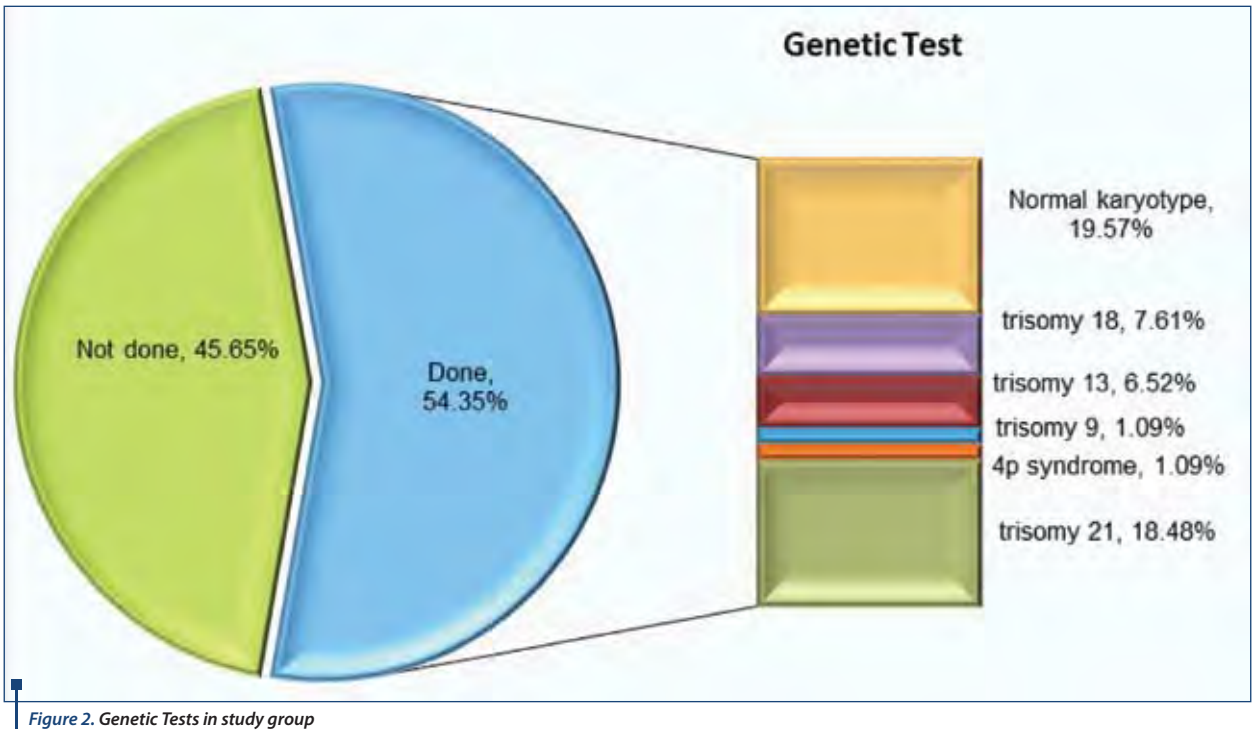

Figure 2. Genetic Tests in study group

Table 4 Distribution of study and control groups by mother's age

Group	16-20 yrs	21-25 yrs	26-30 yrs	30-35 yrs	over 35 yrs	Total
Study	15	22	22	32	1	92
	16.30%	23.91%	23.91%	34.78%	1.09%	
Control	16	25	25	26	0	92
	17.39%	27.17%	27.17%	28.26%	0.00%	
All Groups	31	47	47	58	1	184

Figure 3. Distribution of study and control groups by mother's age

karyotype was detected in 19.57% of cases (Table 3 and Figure 2).

Study and control groups distribution by mother's age is represented in Table 4 and Figure 3. Mean maternal age in study group was 27.5±6.78 years not significantly different (p=0.544) from mean maternal age of the control group wich was 27±6.34 years. It was found no association between the occurrence of congenital anomalies and the age of the mother (p=0.72). Table 5 summarize the distribution of both study and control groups by residence of mothers.

It was found an association between neonatal plurimalformative syndromes and rural residence of mothers (p=0.02). The increased value of risk ratio (RR=1.39, 95% CI=1.03-1.88) indicates an increased risk for plurimalformative syndromes in neonates of mothers from rural areas.

In our study group 51 cases (55.4%) were born of mothers without prenatal care. Regarding antenatal care, we found no significant association between the plurimalformative syndromes and pregnancy follow-up with lack of prenatal screening (p=0.55).

In 21 cases (22.80%) plurimalformative syndromes were diagnosed antenatally, while in 71 cases (76.19%), the diagnose was postnatally established.

Table 5 Distribution of study and control groups by residence of the mother

	group		Total
	Study	control	
Rural	55	40	95
	59.78%	43.48%	
Urban	37	52	89
	40.22%	56.52%	
Total	**92**	**92**	**184**

Table 6 Distribution of study and control groups by maternal pathology

	Maternal pathology		Total
	No	Yes	
Study group	65	27	92
	70.65%	29.35%	
Control group	77	15	92
	83.70%	16.30%	
Total	**142**	**42**	**184**

Amniocentesis was performed in 3 cases (3.3%), being positive for trisomies. Maternal pathology was detected in 27 cases of plurimalformative syndromes (29.35%): in 6 cases (6,52%) imminent abortion, in 4 cases (4,34%) pregnancy associated hypertension, polyhydramnios, toxoplasmosis, cytomegalovirus infection, 3 cases each (3.26%), diabetes mellitus in 2 cases (2.17%), oligohydramnios, epilepsy, chickenpox, syphilis, 1 case each (1.09%). In 67 cases (72.82%) was not detected during pregnancy any maternal pathology (Table 6).

Analysis of maternal pathology in the study group showed significant association with the presence of the plurimalformative syndromes in newborns (p=0.034). The newborns from the study group, born of mothers with pathology had a significantly higher incidence of plurimalformative syndromes when compared with those born from mothers without pathology. The risk for babies born of mothers with pathology to develop plurimalformative syndrome as 1.8 times higher (RR=1.80, 95% CI=1.03-3.15).

Statistical analysis of the data showed the absence of significant correlations between maternal hypertension and plurimalformative syndromes of the newborns (p=0.717). In the presence of maternal diabetes it has not been identified a significant association between its presence and plurimalformative syndromes in newborns (p=0.613).

Consanguinity was present in the study group only in 4.4% of cases. This explains the moderate correlation between consanguinity and occurrence of multiple malformations in newborns (p=0.042). The incidence of history of malformed children was significantly higher in the study group (7.61%) compared with controls (1.09%). There was demonstrated a significant correlation between the history of malformed child and plurimalformative syndromes (p=0.03). The risk of a newborn whose mother presented a history of malformed child to have multiple birth defects is 1.81-2.45 times higher (RR = 1.81, 95% CI=1.34-2.45).

In the study group maternal smoking had a higher incidence (39.13%), with correlation between smoking and plurimalformative syndromes in newborns (p=0.003). Risk is 2.64 times higher in babies of smoking mothers

(RR=1.55, 95% CI=1.18-2.03). Ocasional alcohol consumption during pregnancy did not influence the occurence of plurimalformative syndromes in neonates (p=0.649).

Antenatal drug exposure showed a low incidence in both study and control groups. The small number of cases had influenced the nonparametric correlation test, so there is not a conclusive analysis.

Discussion

The incidence of congenital anomalies in the present study was 6.22%. Some authors considered that congenital malformations occur in 2-3% of live births(9), others raport an incidence of 6.9%(10). EUROCAT records a total incidence rate of major congenital anomalies of 19.9 per 1000 live-births[11] which is nearly three times smaller than in our study. A plausible explanation would be that in regional neonatal tertiary unit Târgu-Mureş (Romania) are transferred mostly of the high-risk pregnancies from Mureş region and mostly of newborns with complex congenital heart malformations from entire Romania. According to our study, 15.15% from all cases with major birth defects had plurimalformative syndromes. Other study reports an incidence of 7-10.5%[12].

Mean maternal age of study group was not significantly different (p=0.544) from mean maternal age of the control group. In this study there was found no association between the occurrence of congenital anomalies and the age of the mother. Some studies report a higher incidence of malformations in the babies born to mothers aged over 35 years. Older maternal age is a distinct risk factor for chromosomal anomalies such as Down syndrome[13,14,15].

In the present study, the increased value of risk ratio (RR=1.39) indicates an increased risk for plurimalformative syndromes in neonates of mothers from rural areas, probably related to a lower socioeconomic status including a lack of antenatal care, maternal nutrition, occupational exposures, cultural factors.

Statistical analysis of the data from this study showed the absence of significant correlations between maternal diabetes, hypertension and plurimalformative syndromes of the newborns. It's a well known fact that some women are at a higher risk of delivering infants with congenital anomaly due to these chronic diseases[16,17].

Our results indicate that plurimalformative syndrome risk is 2.64 times higher in babies of smoking mothers, but risk we found of ocasional alcohol consumption for neonatal multiple anomalies is insignificant. Tobacco and alcohol teratogenic effects in humans are still debated. Some studies have shown an elevated risk of oral clefts with tobacco smoking during pregnancy[18,19], whereas other studies have not[20]. For alcohol consumption and smoking during the first trimester, in several case-control studies has been reported as a risk factor for oral cleft[21,22].

Conclusions

The incidence of congenital anomalies in the present study was higher than reported in literature reviews. Prenatal screening and antenatal diagnosis of congenital malformations should be of serious concern among perinatologists in Romania. Few studies are available regarding congenital anomalies risk factors. Multicenter study with a higher number of cases is needed to confirm these findings. It is required to initiate a national registry for congenital malformations, and collaboration with similar networks in Europe. The challenge for obstetricians and neonatologists is to achieve effective primary prevention and early antenatal diagnosis of congenital malformations for improving the outcome of malformed infant. ■

References

1. Sadler TW. Birth defects and prenatal diagnosis. In: Langmans's Medical Embriology, 10th edition, Lippincott Wiliams&Wilkins 2006; 8:111-22.
2. Gorduza EV. Medical and human genetics compendium, Ed. Tehnopress Iasi Ed.; 2007: 330-50.
3. Gorduza EV, Bivoleanu A, Iliev G, Grămescu M. Clinic and cytogenetics correlations in malformation neonatal pathology, The 13th National Congress of Neonatology Tg. Mures 23-26 September 2009, University Press Tg. Mures Ed.; 2009: 96-103.
4. Wynshaw-Boris A, Biesecker LG. Dysmorphology. In: Kliegman RM, Behrman RE. Editors. Nelson text book of Pediatrics.18th Edition Saunders Philadelphia; 2007:786–7.
5. Sulagna C, Elaine H. Zackai. Evaluation of the Dysmorphic Infant. In: Christine A. Gleason and Sherin U. Devaskar eds. Avery's Diseases of the Newborn. 9th Edition, Saunders Philadelphia 2012; 19:186-96.
6. Gillani S, Hussain N, Kazmi S. Frequencies of congenital anomalies among newborns admitted in nursery of Ayub teaching hospital Abbottabad Pakistan, J Ayub Med Coll Abbottabad 2011; 23:1
7. Lee K, Khoshnood B, Chen L, Wall S, Cromie W, Mittendorf R. Infant Mortality from Congenital Malformations in the United States 1990–97.Am J Obstet Gynaecol 2000; 98:620-7.
8. Congenital Anomalies in Canada. A Perinatal Health Report, 2002.
9. Memo L.The newborn infant with a suspected malformation syndrome. Minerva Pediatr 2010; 62 (3 Suppl 1):197-8.
10. Queisser-Luft A, Stolz G, Wiesel A, Schlaefer K, Spranger J. Malformations in newborn: results based on 30,940 infants and fetuses from the Mainz congenital birth defect monitoring system (1990-1998). Arch Gynecol Obstet. 2002 Jul; 266(3):163-7.
11. EUROCAT Working Group. EUROCAT Report 8: Surveillance of Congenital Anomalies in Europe 1980-1999. University of Ulster, 2002.
12. Garne E, Dolk H, Loane M, Wellesley D, Barisic I, Calzolari E, Densem J. EUROCAT Working Group: Paper 5. Surveillance of multiple congenital anomalies: implementation of a computer algorithm in European registers for classification of cases, Birth Defects Res A Clin Mol Teratol 2011; 91 Suppl 1:S44-50.
13. Luke B, Brown MB. Elevated risks of pregnancy complications and adverse outcomes with increasing maternal age. Hum Reprod 2007; 22(5):1264-72.
14. Reddy UM, Ko CW, Willinger M. Maternal age and the risk of stillbirth throughout pregnancy in the United States. Am J Obstet Gynecol 2006; 195(3):764-70.
15. Luke B, Brown MB. Contemporary risks of maternal morbidity and adverse outcomes with increasing maternal age and plurality. Fertil Steril 2007; 88(2):283-93.
16. Garne E, Loane M, Dolk H. Spectrum of congenital anomalies in pregnancies with pregestational diabetes. Birth Defects Res A Clin Mol Teratol 2012; 94(3):134-40.
17. Fleming KM, Bailey JA et al. Perinatal mortality and congenital anomalies in babies of women with Type 1 or Type 2 diabetes in England, Wales, and Northern Ireland: population-based study. BMJ 2006; July 22. (2006) 333, 7560: 177.
18. Christensen K, Olsen J, Norgaar-Pedersen B et al. Oral clefts, transforming growth factor alpha gene variants, and maternal smoking: a population-based case-control study in Denmark, 1991–1994. Am J Epidemiol 1999; 149: 248-55.
19. Wyszynski DF, Duffy DL, Beaty TH. Maternal cigarette smoking and oral clefts: a metaanalysis. Cleft Palate Craniofac J 1997;34: 206-10.
20. Castles A, Adams EK, Melvin CL, Kelsch C, Boulton ML. Effects of smoking during pregnancy. Five meta-analyses. Am J Prev Med. 1999; 16(3): 208-15.
21. Munger RG, Romitti PA, Daack-Hirsh S, Burns T, Murray JC, Hanson J. Maternal alcohol use and risk of orofacial cleft birth defects. Teratology 1996; 54: 27–33.
22. Mattson SN, Schoenfeld AM, Riley EP: Teratogenic effects of alcohol on brain and behavior. Alcohol Res Health 2001; 25(3):185-91.