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Risk factors associated with congenital anomalies in children

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ABSTRACT
The practical approach to effective prevention and diagnosis of congenital anomalies involving them early (prenatal or neonatal), correctly and completely. Both actions require but etiopathogenic knowledge, clinical skills and appropriate means of exploration. Epidemiological studies can contribute in a meaningful way to identify and assess risk factors involved in the etiopathogenesis of congenital anomalies. This research is part of a large study (retrospective and prospective), which aims to identify factors involved in congenital anomalies determinism towards a diagnostic algorithm for an early and optimal case management.

Keywords: congenital anomaly, risk factors, prevention

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Introduction

Congenital anomalies (CA) are a current problem in human pathology as a result of frequency and etiopathogenic aspects of medical and social implications, which requires the undertaking of essential steps in organizing services for children with malformations. The knowledge of disease prevalence and etiopathogenic factors generating abnormal development is necessary for a real image about birth defects, the image that will serve as a basis for strategies and measures to be taken in this area. Many international statistics, national and regional considers that the overall incidence of malformations, visible at birth and detectable by clinical examination in infants living and dead, ranges on average between 3-5% [1]. According to data published by the WHO in January 2014 [2], a newborn of 33 defects resulting from birth and approximately 3.2 million cases annually associate defects, which are the cause of 20 percent of premature deaths.

Malformation pathology etiology is largely unknown [3, 4], but it is estimated that many of the anomalies are caused by mutations in genes that are involved in controlling development processes. Remarkable complexity and fragility of embryogenesis mechanisms make them vulnerable in the context of risk factors, causing numerous developmental anomalies or malformations. At present, the study of congenital anomalies is a major concern for population health although in this area, there are many unknown aspects [5], due to the large number of factors teratogens (malformative) and that they can interact with each other [6].

Identifying the causes of congenital anomalies is an important target for prevention and genetic counseling but their determination is difficult because a congenital anomaly may have different causes [7]. Risk factors increase the risk of malformation pathology. There are predisposing factors related to the environment, heredity, stress, etc. When speaking of risk factors for congenital anomalies are considered pre-conception risk factors, family history of both mother and father, origin, social and cultural environment and risk factors after conception [8]. According to national and international statistics [9-11], the main risk factors in the determinism of congenital anomalies are:

- Maternal age over 35 years (chromosomal syndromes risk increases with age of the mother at conception)
- Healthy carriers' genitors of balanced chromosomal anomalies
- Family history of chromosomal anomalies (eg. DS)
- Congenital genetic disease husband (Duchenne muscular dystrophy, hemophilia, diseases linked to chromosome X)
- Reproductive history (fetus with chromosomal abnormalities, birth defects, miscarriages early newborn deaths)
- Women exposed to radiation, consuming potentially teratogenic drugs, carriers of metabolic disease (diabetes)
- Multitude of risk factors, unfortunately unidentified.

A general conclusion of the studies to date is that action should be intensified early detection neonatal congenital defects [12], in order to prevent complications and achieve adequate medical recovery measures. However, due to the variety of clinical and etiopathogenic complex, doctors from various specialties will face malformative pathology and therefore they must know the major phenotypic markers "can signal" this type of pathology.

Materials and methods

The aim of the research was to assess risk factors in a group of patients' malformative pediatric age with congenital anomalies diagnosed and treated in the Emergency County Hospital "St. Andrew "Constanta.

Research has as its starting point a large retrospective study, based on a casuistry investigated over a period of 7 years (2008-2014) and based observations and conclusions that support the importance and pathogenic mechanism as early diagnosis of congenital anomalies, preferably in the utero period.

In retrospective epidemiological study we used a thorough analysis of medical documents (spreadsheets observation, medical records, and statistical bulletins) from which we obtained valuable data related to age, sex, origin, family history, whether the pregnancy was monitored and if upon antenatal diagnosis, type of birth, gestational age, birth weight and Apgar score, associated malformations, therapeutic management.

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Statistical analysis was performed using Microsoft Office applications Excel 2010 (Microsoft Corporation, Redmond, WA) and SPSS® v.16.0 (SPSS Inc., Chicago, IL).

Results

During the period studied, reported 2019 cases with different clinical forms of congenital anomalies (Code ICD 10 AM: Q00 - Q99) investigated the SCJU "St. Andrew Constance ". Regarding the type of congenital anomalies in the present study were identified 202 entities, as shown in Table. I.

Table I. Distribution of congenital anomalies depending on the type of fault, the County Emergency Hospital "St. Andrew" Constanta in 2008-2014

Clinical and genetic variants (entities)	Solitary		Associated		Total
	Nr	%	Nr	%	
Malformations (38 entities)	*232*	28.93	593	48.78	825
Disruptions (9 entities)	*43*	5.36	52	4.27	95
Deformations (6 entities)	*116*	14.46	69	5.67	185
Dysplasia (21 entities)	*108*	13.46	178	14.63	286
Other CA unclassified (26 entities)	*92*	11.47	142	11.67	234
Specified multiple CA (102 entities)	*211*	26.31	183	15.04	394
TOTAL (202 entities)	**802**	**100**	**1217**	**100**	**2019**

Prevalence etiopathogenic factors is illustrated in figures in the Table. II. Note that 43.21% of cases of congenital anomalies investigated etiopathogenical had no known cause.

Table II. Distribution of congenital anomalies according to etiopathogenic factor in County Emergency Hospital "St. Andrew" Constanta in 2008-2013

Etiopathogenic factors		Number of cases with AC	% of all cases with AC	
Genetic factors 1124 cases	***Chromosomes***	78	3.85	55,67 %
	Monogenic	234	11.61	
	Multi-factorial polygenic	812	40.21	
Teratogen factors		23	1.12	
Unknown factors		872	43.21	
TOTAL		2019	100	

Based on data from the literature and analyzing the results in the retrospective study, we presented in Table III malformative main risk factors identified in the study.

Table III. Malformative main risk factors for congenital anomalies

Cases of maternal and neonatal factors	CA (= 2019) documented		
	No. cases		% cases
Maternal age at conception > 35 years	521		25.80
Parity (multiparous)	1134		56.16
History of abortions or still born	949		47.00
Antenatal medical examinations	755		37.42
Consumption of multivitamins and folic acid during pregnancy	698		34.58
Diabetes	97		4.82
Fever	369		18.26
Pre-eclampsia	574		28.43
Polihidramnios	226		11.20
Oligohidramnios	190		9.42
Infectious contact	529		26.19
Maternal smoking active or passive	1159		57.42
Drugs (medicines)	782		38.74
Contact with pollutants	871		43.12
Twins	57		2.80
Gestational age	**< 37 weeks**	**37 – 40 weeks**	**> 40 weeks**
	672 (33.28%)	1283 (63.54%)	64 (3.16%)
Presentation	**Cranial**		**Pelvic**
	1923 (95.17%)		65 (3.2%)
Type of birth	**Natural**		**Cesarean**
	1609 (79.69%)		410 (20.31%)
Birth weight	**< 2700 g**		**> 2700 g**
	483(23.93%)		1536 (76.07%)
Paternal factors			
Paternal age > 45 years old	72		3.56
CA spouse or AHC positive	170		8.43
CA – congenital anomalies; AHC – medical family history			

Discussion

Congenital anomalies by phenotypic changes they produce, high morbidity and mortality, are a real public health problem, justifying the intensification and diversification strategies currently used to identify as early as possible malformative risk factors.

In the present study, it can be noted that high-risk female population is aged over 35 years (1/3 of the cases, without significant difference compared with data from the literature). It is well known that maternal age is the most important risk factor, perhaps the most documented non-genetic risk factor for the

occurrence of chromosomal abnormalities in the fetus [13, 14]. On the other hand, it is estimated that low maternal age is a risk factor for neural tube defects [15].

Multiparity seems to be another risk factor associated with congenital anomalies, as evidenced in 56.16% of cases. Since 1990, Sipila P et al. [16] mentioned in an article, a higher frequency of congenital anomalies multiparous mothers, especially those who had more than 3 births. In another study, however, Perveen and Tyyab [17] found a higher incidence of congenital malformations in infants of. primiparous mothers.

Although the literature mentions that minor and major congenital abnormalities are more common in twin pregnancies, and more frequently in monozygotic [18, 19], in the present study gemelarity cannot be considered a risk factor malformation, while the only 2.8% of cases with AC come from twin pregnancy.

As shown in the table above, only 37.42% of the mothers of children with congenital anomalies included in the study received antenatal care and medical examinations and made repeated medical examinations during pregnancy. This aspect emphasize the importance of promoting health and disease prevention of population illness paying special attention to prenatal period, which influence neonatal indicators and would prevent congenital malformations.

Regarding periconceptional folic acid and vitamin supplementation of data analyzed show that it was made only 34.58% of cases. It is now recommended that all women during periconceptional period (one month before conception and at least three months after conception) to consume folic acid 400 mg daily to reduce the risk of neural tube defects [20]. It has also been reported in a study by L. Beil (2008) on 38,000 women, that folic acid supplementation before conception 1 year significantly decreases the risk of premature birth [21].

Drinking alcohol in early pregnancy increases the risk of birth of children with various deformities [22], and smoking increase the risk of ectopic pregnancy, miscarriage, premature birth, fetal death.

Both behaviors were identified in the present study in 50% of cases with congenital anomalies investigated.

The association between maternal smoking and the risk of malformation is especially important for mothers who do not take folic acid periconceptional [23].

Anomalies occur due to the effects of carbon monoxide which reduces tissue oxygenation and nicotine and stimulates the release of hormones that cause vasoconstriction in the uterus and placenta, so it carries less oxygen and fewer nutrients to the fetus.

In this study we tried to identify the cases of maternal diabetes associate CA. Thus, 4.82% of mother's cases were diagnosed with hyperglycemia or diabetes. The association between glycemic level and congenital anomalies is well documented, so hyperglycemia, hypoglycemia and hiperketonemia in the first trimester were associated with increased risk of major anomalies [24].

Apeland et al. established in a study that major abnormalities occurring in 6.4% of cases of diabetic mothers and Hod et al. [26] revealed that in 19.4% - 20.5% of cases are associated minor anomalies. It is estimated that the most common congenital anomalies existing in children from diabetic mothers are those involving the cardiovascular, skeletal, central nervous system, gastrointestinal and genitourinary, although Schafer-Graf UM et al. [27] showed in a study that increased hyperglycemia during pregnancy is associated with an increased risk of congenital abnormalities, generally with multiple organ involvement, with a predilection for a specific organ / system. Also congenital anomalies detected in fetuses of women with gestational diabetes type 2 are similar and affect the same organ described in pregnancies complicated by type 1 diabetes (Schafer-Graf UM, et al., 2000).

Maternal obesity, which although not mentioned in this study, but which is frequently associated with maternal diabetes, it seems that adversely affect organogenesis and favors the occurrence of birth defects such as spina bifida, heart defects, limb abnormalities, anorectal atresia, omphalocele, diaphragmatic hernia, hypospadias. On the other hand, underweight mothers seem to have a higher risk for orofacial cleft to have fetuses with (DK Waller et al., 2007) [28].

History of miscarriages and stillborn in the study group was achieved in 47% of cases, probably due to some severe malformations incompatible with life as mentioned in other studies [29]. Oligohydramnios and polyhydramnios were detected in over 20% of the cases included in this study. Stoll et al. reported that 55% of cases showed polyhydramnios associate more than a congenital anomaly, 13.4% of them were due to chromosomal abnormalities and 32% associate multiple malformation syndrome not. Also the same study reported that the incidence of congenital anomalies in pregnancies complicated by oligohydramnios was 1.88% and among the most common anomalies detected are those of the urinary system (15.9%), genital (5.9%), states (5.7 %) and 5.9% were detected chromosomal anomalies [30]. The frequency of cases with CA which had a breech was 3.2%, which is harmless, although it is known that fetuses with breech frequently associated with congenital anomalies compared to those in cranial presentation [31].

Another risk factor examined was the presence of fever during pregnancy, and this was noted in 18.26% of cases. Fever or hypothermia is estimated that in the first trimester of pregnancy are risk factors for the occurrence of congenital anomalies, particularly anencephaly, spina bifida, hydrocephalus, congenital undescended testicle cleft lip and [32]. Also, in 28.43% of the cases of CA, a pre-eclampsia was noted. It is believed that this constitutes a risk factor for tasks commonly associated fetuses with chromosomal abnormalities [33].

An important factor is the normal embryo-fetal development and maternal health. It is well known that maternal pathologies (chronic, hereditary dismetabolii mother) can induce malformations in children [34].

More commonly incriminated maternal infections: rubella (which increase the risk for cataracts, glaucoma, cardiac malformations, deafness, dental abnormalities); Cytomegalovirus (risk: microcephaly, mental retardation, fetal death); herpes simplex virus (microphthalmia, microcephaly, retinal dysplasia); varicella virus (limb hypoplasia, mental retardation, muscular atrophy); toxoplasmosis (hydrocephalus, cerebral calcification, microphthalmia); syphilis (mental retardation, deafness). Also, diabetes (increased risk of malformations diverse, the most common being cardiac and neural tube defects) and obesity (cardiac malformation, omphalocele) are maternal diseases more common in cases with congenital anomalies.

Paternal factors are included in the category of risk factors also. Although paternal age effect is not understood, Zhu et al. have shown that the prevalence of congenital malformations of the extremities, plurimalformative syndrome and Down syndrome increases with paternal age (≥ 40 years) [35].

It is estimated also that advanced paternal and maternal age is associated with an increased risk of congenital heart defects (Maternal-Kiryluk A et al., 2009). It is also a positive association between advanced paternal age and hypospadias and velo-palatal defect [19]. In the present study we did not find a significant correlation between paternal age and the presence of congenital anomalies (t-test, p = 0.12), the average age for the group CA paternal chromosomal abnormalities without being 34.04 (dev.std. = 4 14), unlike the average age of the group AC paternal chromosomal abnormalities who was 38 (dev. std. = 1.73) between the two variables there is no statistically significant difference.

Conclusions

Significance alarming etiology teratogenic - higher than the literature data - reflects a failure of prevention of congenital malformations by avoiding teratogens during pregnancy. Therefore, reducing the prevalence at birth and infant mortality and morbidity attributable to congenital anomalies may be attainable through screening programs aimed at identifying risk factors malformation and an optimal management and prevention measures in place as early as possible.

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