UNIVERSITY "OVIDIUS" OF CONSTANȚA
DOCTORAL SCHOOL OF MEDICINE
DOCTORAL AREA - MEDICINE

SUMMARY OF THE DOCTORAL THESIS

DIAGNOSIS ALGORITHMS AND MANAGEMENT OF CONGENITAL ANOMALIES IN CHILDREN

Scientific coordinator,

Prof.univ. Constantin TICA, Ph.D.

Ph.D. student,

Dr. CAPĂȚINĂ Dănuț

CONSTANȚA, 2015

TABLE OF CONTENTS

PERSONAL CONTRIBUTION

Annexes

Annex 1. Clinical evaluation sheet of children with birth defects
Annex 2. National Registry of birth defects

KEY WORDS:

- ***birth defects***
- ***risk factors***
- ***diagnosis algorithm***
- ***prevention***
- ***management***

I. INTRODUCTORY ASPECTS

The thesis in itself presented on 261 pages, has attached a bibliography that includes 291 titles and two annexes (*Annex 1. Clinical evaluation sheet of children with birth defects; Annex 2. National Registry of birth defects*), being structured on two main parts:

1. GENERAL PART – extended on the 127 pages, is a bibliographic summary of the current state of knowledge in the field of research and is developed in four chapters:

Chapter I. Congenital anomalies – general data
Chapter II. Classification of congenital anomalies
Chapter III. Investigation and diagnosis of congenital anomalies
Chapter IV. Therapeutic approach and prevention of congenital anomalies

2. PERSONAL CONTRIBUTION – the 134 pages present, in detail, personal research, complying with the methodology related to the performance of scientific research; includes three chapters – materials and methods, results and discussions, followed by conclusion, proposals, bibliography and annexes.

The paper concludes with practical and theoretical conclusions regarding the etiopathogenesis and diagnosis algorithm of birth defects algorithm and the presentation of proposals aimed at addressing this pathology, the creation of a registry model to track the pattern of birth defects and achieve an effective prophylaxis.

The congenital anomalies (CA) are a current issue in human pathology as a result of frequency, ethiopatogenic aspects and social and medical implications, which require taking important steps in organizing the services for children with malformations. The knowledge of disease prevalence and ethio-pathogenetic factors which generate abnormal development is necessary to have a real image of birth defects, an image which will be considered the basis of strategies and measures required in this area[1].

This theme is a current subject, which is reflected in scientific research, taking place rapidly worldwide and whose results are capitalized in papers published regularly on the topic of congenital anomalies, approached from the perspective of identifying risk factors and ethiopatogenic mechanisms for diagnosis and prophylaxis as earliest and appropriate as possible.

[1]Centers for Disease Control andPrevention. Update on overall, prevalence of major birthdefects—Atlanta, Georgia, 1978–2005., MMWR Morb Mortal Wkly Rep. 2008;57(1):1–5.

Often, CA may bring difficulties in establishing the diagnosis, especially when talking about a plurimalformative syndrome; for parents key issues in caring and recovery of children affected and/or prevent/reduce the malformation risk of a new pregnancy. The aetiology of malformation pathology is largely unknown, but it is estimated that a good part of the anomalies are determined by mutations of genes that are involved on the control of development processes[2].

The studies conducted so far show that we still have many shortcomings in detecting and treating congenital anomalies, that the material and technical basis of medical-genetics institutions is insufficient to address the performance methods for cytogenetic and molecular diagnosis and the surgical departments do not have all the necessary equipment to intervene in all situations that require the correction of death defects. On the other hand, experts in various related fields require continuous training to improve the quality of medical services provided.

The steps to be taken for the prevention of birth defects must be associated with large and complex steps for the education for health addressed both to pregnant women and the population in general[3]. We must draw the attention on the factors of risk, of understanding the problem, of the importance of the prenatal diagnosis and the observance of the indications prescribed by the medic.

In this context, we need consistent, planned and continual activities, developed in a coordinated manner within the National Programme for prevention and reducing the mortality and morbidity of children by death defects and support, hereditary diseases, which can allow an improvement of the situation related this matter.

Therefore, this study was designed to provide the scientific benchmarks (records) to formulate the working hypotheses regarding the strategic approach to the problem caused by birth defects among the population of Constanta county, allowing both the identification of factors involved in the determinism of congenital abnormalities, the accomplishment of a diagnosis algorithm as early as possible and determining the optimal case management, and the assessment of the impact (psychological, social, economic etc.) that birth defects have on the health of the population.

---

[2]Amany M. A; Shadia Abd el Kader; Azza A. Abd El Hamid, Hassan M. Gaafar (2011), *Assessment of RiskFactors for Fetal Congenital Anomaliesamong Pregnant Women at CairoUniversity Hospitals.* Journal of American Science,;7(12) http://www.americanscience.org

[3]Siega-Riz AM et al (2009).*National BirthDefectsPreventionStudy. The jointeffects of maternal prepregnancy body mass index andage on therisk of gastroschisis.* PaediatrPerinatEpidemiol. 23(1):51-7

II. PERSONAL CONTRIBUTION

2.1. Methodology of research

The research started from a large ***retrospective study***, based on the cases investigated over a period of six years (2008 – 2013) in the County Emergency Hospital Constanța "Sf. Apostol Andrei" (Group I); it substantiates the observation and conclusions that support the importance of determining the etiopathogenic mechanism and of early diagnosis of congenital anomalies, preferably in the intrauterine period, and a correctly determination of the moment of starting the surgical treatment.

In the second stage of the research, I have conducted a horizontal ***prospective study***, in order to identify the clinical and progressive congenital anomalies variants in children diagnosed and treated in the Paediatric Surgery and Orthopaedics Hospital of SCJU Constanța within January 1 – December 31, 2014 (Group II), with the selection and introduction of the most important case studies.

The purpose of the research was to assess the causes, the diagnosis circumstances, modalities of treatment and after-surgery evolution, on a lot of very young patients with congenital anomalies, diagnosed and treated in the Paediatric Surgery and Orthopaedics Hospital of the County Emergency Hospital Constanța. The research was completed by drafting an early investigation and diagnosis protocol of the congenital anomalies in children and a registry template to monitor the congenital anomalies.

General objectives:

1. Identification of the etiopathogenic *factors involved in the determination of the congenital anomalies and the optimal investigation methods in order to ensure an early diagnosis there of.*

2. The assessment of the clinical and paraclinical particularities and improvement of treatment in patients with congenital anomalies, with the indication of the major indications to commence the surgical treatment.

Specific objectives:

1. Drafting a retrospective epidemiologic study and determination of the congenital anomalies prevalence, during the interval 2008 - 2013, reported at SCJU "Sf. Apostol Andrei Constanța":

2. Consideration of the clinical and progressive particularities in patients diagnosed with congenital anomalies that needed surgery.

3. Identification of cytogenetic changes that are associated with an unfavourable prognosis and which gives thus, the possibility of carrying out a proper prophylaxis and choice of appropriate treatment methods.

4. Identification of the optimal modalities for an early detection of congenital anomalies and improving the current screening in determining foetal anomalies.

5. Evaluation of therapeutic efficiency of different surgical methods used in the treatment of malformation syndromes in order to identify the optimal techniques.

6. Supporting the indications, moment and optimal amount of surgical intervention in the treatment of congenital defects.

7. Determining a curative and diagnosis algorithm in patients with congenital anomalies.

8. Identification of the role and place of congenital anomalies in public health and possibilities to mitigate their effect on family and society.

2.2. Results and discussions

The study included the cases diagnosed with congenital anomalies in children, starting with2008 until 2014; they were assessed in close relation with the gender, area of provenience (rural, urban), type of birth (natural, caesarean section), weight at birth (<2700 g, >2700 g), gestational age (<37 weeks, >37 weeks) andthe APGAR score (<7 and>7). At the same time, I noted the demographic data, age of parents and their social condition, their family history, information on the pregnancy (if the pregnancy was supervised and if the diagnosis was placed before giving birth), data about the birth (gestational age, type of birth, weight at birth and the APGAR score), type of malformations (unique / multiple / insulated / associated malformations), management right after giving birth, age of child and general health condition at admission, complications after surgery and distant complications, causes of deaths, period of hospitalization, evolution on short and medium term.

Data were collected by collaboration with the medical statistics services of the hospital and by studying the registry of children with congenital anomalies within the department of Neonatal / Paediatric Surgery. Histopathological and cytogenetic diagnosis was conducted at the Clinical Pathology Department of the Clinical Emergency Hospital Constanţa “Sf. Apostol Andrei”.

Data collected were processed and interpreted by epidemiologic, statistical and mathematical and computer based methods.

The final analysis of data obtained entailed also a comparison with data in the medical specialized literature existing up to current date, using statistic relevant methods in this regard, which allowed the identification of the optimal methods for early determination of congenital anomalies and improvement of current screening of foetal anomalies.

1. Retrospective epidemiological study - cases with congenital anomalies investigated, diagnosed and/or treated at SCJU "Sf. Apostol Andrei Constanța" within 2008 – 2013

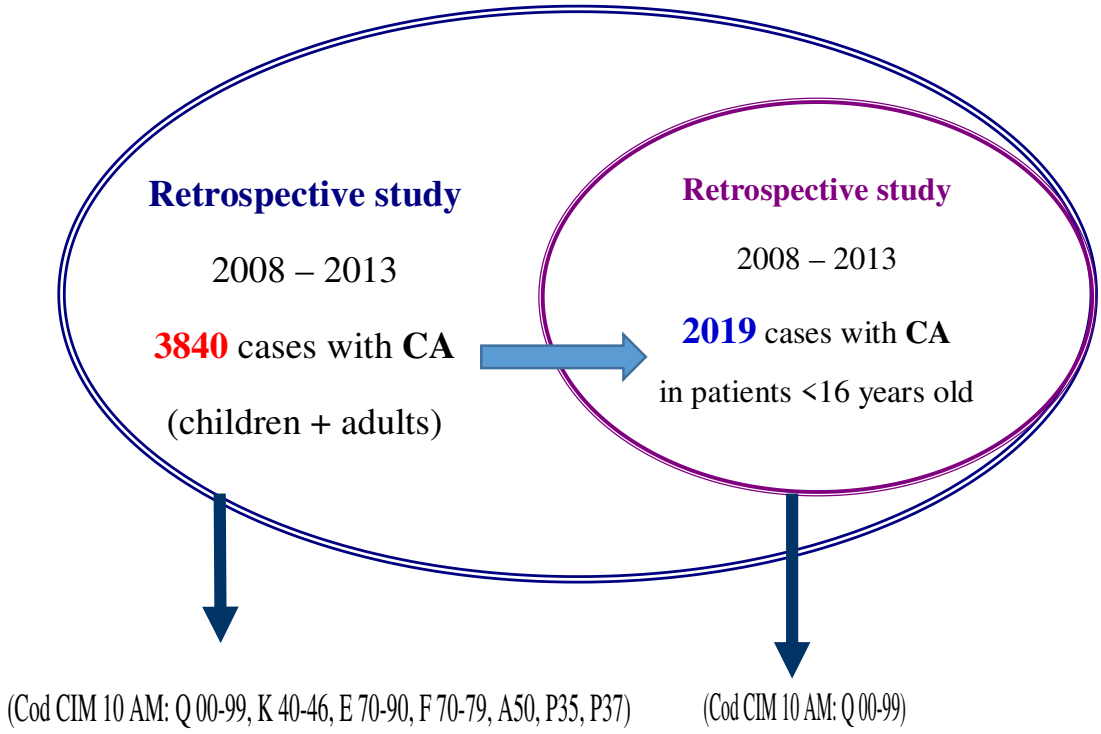


Figure 1. Characterization of Group I of subjects

- ***Prevalence of congenital anomalies during the interval 2008 - 2013, reported in the SCJU "Sf. Apostol Andrei" Constanța***

During the period under analysis, 3840 cases (children and adults) were reported (CIM code 10 AM: Q 00-99, K 40-46, E 70-90, F 70-79, A50, P35, P37) (Figure 1), with different clinical forms of congenital anomalies, having recorded a total prevalence of 1.74, and the highest prevalence amongst the anomalies were the bone and joints anomalies (4.16 in 100.000 new born children), followed by the anomalies of the circulatory system (Q20 – Q28), chromosomal disorders (Q90-Q99) and anomalies of the Central Nervous System (Q00-Q07).

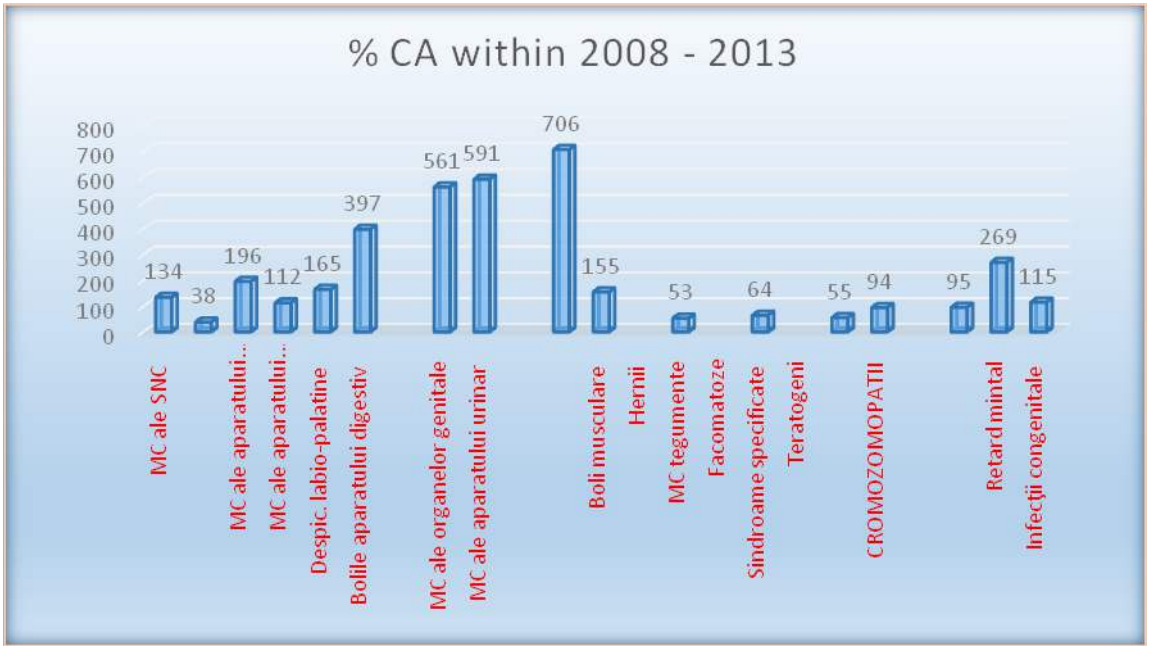


Figure 2. Distribution of congenital anomalies depending on the OMS group of congenital anomalies, SCJU "Sf. Apostol Andrei" Constanța (2008 – 2013)

Distribution on years of the congenital anomalies with CIM code 10 AM:Q00 – Q99 (Figure 3) investigated at SCJU "Sf. Apostol Andrei" Constanța (2008 – 2013) indicate a global decrease of this pathology in patients under 16, with a decrease by more than 57% of congenital anomalies incidence in 2013 as compared to 2008.

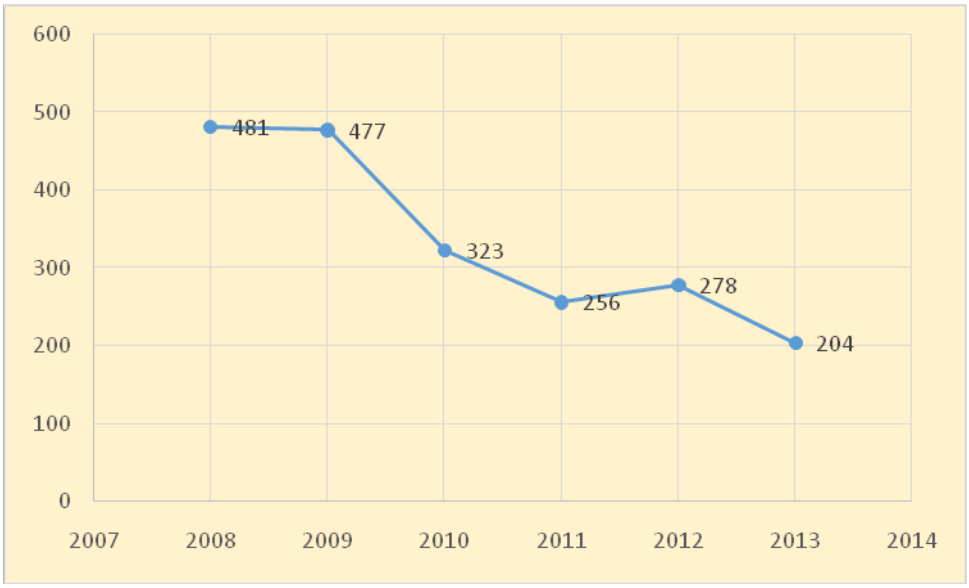


Figure 3. Distribution of congenital anomalies with CIM code 10 AM:Q00 – Q99 investigated atSCJU "Sf. Apostol Andrei" Constanța (2008 – 2013) for years included in the study.

➢ ***Distribution of congenital anomalies depending on the place of provenience*** indicate an occurrence of cases in the urban environment (69.73%), as compared with the rural environment (20.27%) (MU Report: MR = 2.3: 1).

➢ ***Distribution of congenital anomalies depending on the patient's gender*** indicate that 52.40% of the cases investigated and diagnosed with CA during 2008 – 2013,were male patients. Except for 2009, when a higher frequency in female patients with CA was recorded and a higher occurrence in those aged 6, the occurrence of CA in male patients was constantly over 50%.

➢ Another risk factor under investigation in this study was the ***age of parents of children with congenital anomalies*** (see Table 1).

Table 1. Distribution of congenital anomalies with CIM Code 10 AM: Q00 – Q99 investigated at SCJU"Sf. Apostol Andrei" Constanța (2008 – 2013) depending on the parents' age

Category of age		**Mother's age** Limits: 15 – 42 years Average: 27.68 years Dev.std.: 3.32		**Father's age** Limits: 19 – 47 years Average: 31.28 years Dev.std.: 3.43	
		Frequency	Percent	Frequency	Percent
Valid	10 - 20 years	164	9	118	6
	21 - 30 years	1132	55	1142	54
	31 - 40 years	639	32	673	36
	41 - 50 years	84	4	86	4
	Total*	1891	100,0	1879	100,0

** Total of cases where data concerning the parents' age were mentioned*

Mother's age varied between 15 and 42 years, with an average age of 27.68 years with a standard deviation of 3.32. As we can see from table 1, only 55% of the mothers of children diagnosed with congenital anomalies had an optimal reproductive age. *Father's age* varied between 19 and 47 years, with average paternal age being of 31.28 years, and the standard deviation was of 3.43.

➢ ***Analysis of the distribution of cases of congenital anomalies depending on the gestational age and weight at birth***.

During the period of the study, of the 2019 cases of CA recorded, 672 (33.28%) can from pregnancies that resulted in premature birth (before 37 weeks), 1283 (63.54%) were

delivered on due time (37 – 40 weeks of pregnancy), and the rest of 64 (3.16%) had a gestational age older than 40 weeks (Table 2).

Regarding the weight at birth, 483 (23.93%) children weighted less than 2700 grams and the rest of 1536 (76.07%) children weighted more than 2700 grams at birth.

Table2. Distribution of CA cases depending on the gestational age and weight at birth

Number of cases diagnosed with CA within 2008 – 2013 **CIM Code 10 AM: Q00 – Q99**				
Weight at birth		**Gestational age**		
< 2700 g	483(23.93%)	**< 37 weeks**	**37 – 40 weeks**	**> 40 weeks**
> 2700 g	1536 (76.07%)	672 (33.28%)	1283 (63.54%)	64 (3.16%)

The study on the weight registered at birth indicated for children born before the term and with low weight (G <2700 grams) the annual differences of occurrence (11% in 2008 and 32% in 2011) ($p \leq 0,05$), as compared with those with a normal weight (28% in 2010 and11% in 2013) ($p < 0,005$). During the other years, the differences had no special importance.

Table 3. Yearly distribution of cases of congenital anomalies, depending on the type of birth and APGAR score reported during the interval 2008 – 2013 at SCJU "Sf. Apostol Andrei" Constanța

Year	**No. of cases**	**Type of birth**				**APGAR Score**			
		Natural		**Cesarean section**		**< 7**		**> 7**	
		Nr.	**%**	**Nr.**	**%**	**Nr.**	**%**	**Nr.**	**%**
2008	481	398	82.81	83	17.19	101	21.01	380	78.91
2009	477	386	81.00	91	19.00	91	18.99	386	81.01
2010	323	262	81.14	61	18.86	83	25.59	240	74.41
2011	256	198	77.37	58	22.63	59	23.14	197	76.86
2012	278	212	76.17	66	23.83	74	26.41	204	76.17
2013	204	153	74.91	51	25.01	46	22.49	158	74.99
Total	2019	1609	79.19	410	10.81	454	22.71	1565	77.29

During the six years of study, it was found that the occurrence of natural births is decreasing, in case of children with CA and varies between 74.91% (in 2013) and 82.81% (in 2008), while the occurrence of caesarean births is increasing and varies between 17.19% (in 2008) and 25.01% (in 2013) (Table 3).

➢ ***Distribution of CA cases with reproductive antecedents and family history***

47% of the couples with children diagnosed with congenital anomalies had reproductive antecedents of miscarriages, varying between 1-5 miscarriages, the average number being of 0.97 and the standard deviation of 1.32 (see Figure 4). At the same time, 20% of the couples reported recurrent miscarriages during the first trimester of pregnancy.

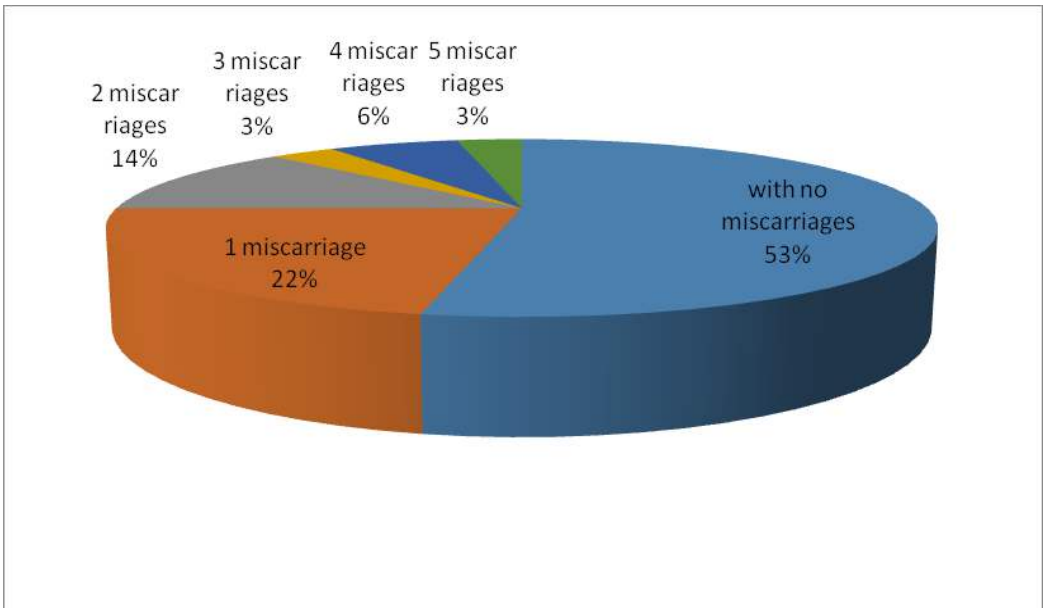


Figure 4. Classification of couples with children with CA depending on the occurrence of miscarriages

➢ ***Distribution of cases of CA depending on the frequency and type of chromosomal disorders in parents of children diagnosed with congenital anomalies***

Within 2008 – 2013, 74 couples genetically investigated were reported, in order to interpret certain chromosomal disorders identified in the conception products or children diagnosed with congenital anomalies. The cytogenetic analysis carried out on both members of the couple indicated the presence of certain balanced chromosomal disorders for 12.16% of the couples (9 couples). For couples with chromosomal disorders, they were present 66.64% for females and 33.36% in males. Beside the balanced chromosomal disorders, chromosomal polymorphisms (heteromorfism) were detected. The frequency of chromosomal polymorphism depending on the total number of cases of was 5.24%.

➢ ***Distribution of cases of CA depending on the insulated or multiple characteristics, of congenital anomalies occurrence.***

Within 2008 – 2013, among the 2019 cases of congenital anomalies, ***60.26%*** (1217 cases) were diagnosed with ***insulated anomalies***, and among these, the most frequent were the **skeletal** (24.95%) and **cardiac** ones (20.23%) (Table4).

Table 4. Distribution of insulated congenital anomalies, investigated at SCJU "Sf. Apostol Andrei" Constanța, during 2008-2013

Year	Insulated congenital anomalies						
	No. of cases	Cardiac		Skeletal		Others	
		Nr.	%	Nr.	%	Nr.	%
2008	253	54	21.34	72	28.46	127	50.19
2009	229	53	23.14	74	32.31	103	44.98
2010	208	43	20.67	54	25.96	111	53.36
2011	198	38	19.20	37	18.68	123	62.12
2012	173	32	18.50	35	20.23	106	61.27
2013	156	27	17.31	32	20.51	97	62.17
Total	1217	247	20.32	304	24.95	667	54.72

- ***Multiple congenital anomalies***.

The presence of association of different anomalies in the same case was recorded in a significant low number of cases ($p \leq 0,05$) as compared with the insulated ones. In the six years of study, 802 cases of multiple CA (39.74% of the total cases of CA) were seen.

Among these, the highest weight had the cases when two anomalies were associated (40.10%), followed by the cases when 4 anomalies were associated (30.27%) and cases when 3 anomalies were associated (24.24%).

Among the *plurimalformative syndromes,* the most frequent is the *Langdon Down syndrome*, determined by the trinomial 21 and which is characterized by an abnormal developmental specific phenotype.

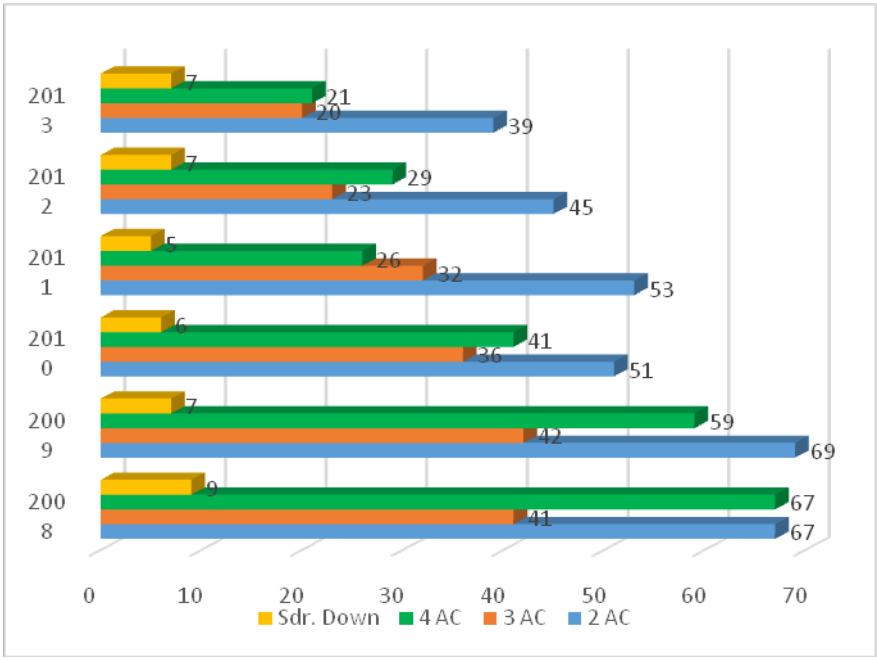


Figure 5. Occurrence of cases of congenital anomalies depending on the number of anomalies associated, reported at SCJU "Sf. Apostol Andrei" Constanța, during 2008-2013

➢ ***Type of congenital anomalies found depending on the occurrence mechanism***

Related to the type of congenital anomalies, this study identified 202 entities, mainly malformations, dysplasia and deformations (see Table5).

Table5. Distribution of congenital anomalies depending on the type of anomaly, la SCJU "Sf. Apostol Andrei" Constanța, during 2008-2013

Clinical and genetic variants (entities)	**Unique**		**Associated**		
	No.	**%**	**No.**	**%**	**Total**
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 unclassified CA (26 entities)	*92*	11.47	142	11.67	234
Multiple CA specified (102 entities)	*211*	26.31	183	15.04	394
TOTAL (202 entities)	**802**	**100**	**1217**	**100**	**2019**

About half of the congenital anomalies diagnosed are malformations (825 cases), of which 2/3 are cases with associated malformations, being followed by multiple CA specified (394 cases), dysplasia (286 cases) and unclassified CA (234 cases).

➢ ***Etiopathogenic factors involved in the occurrence of congenital anomalies***

The prevalence of etiopathogenic factors is indicated in figures in Table no.5. It is worth mentioning that **43.21%** of the cases with congenital anomalies investigated **did not** have a***known etiopathogenic cause***.

Table5. Distribution of congenital anomalies depending on the etiopathogenic factor, at the County Emergency Hospital "Sf. Apostol Andrei" Constanța, during 2008-2013

ETIOPATHOGENIC FACTOR		Number of cases with CA	% of total of cases with CA
Genetic factors 1124 cases	***Chromosomal***	78	3.85
	Monogenic	234	11.61
	Polygenic-multifactoral	812	40.21
Teratogen factors		23	1.12
Unknown factors		872	43.21
TOTAL		**2019**	100

55,67 %

➢ ***Type of treatment applied to children diagnosed with CA and age at surgery***

Among the patients of group I, 487 children, respectively 24.12% of the cases need surgery, and the rest were conservatively treated (see Figure 6), related to the age of children that went on surgery, the statistic values obtained indicate an average age of 58 months, with minimum of 1 month and a maximum of 198 months.

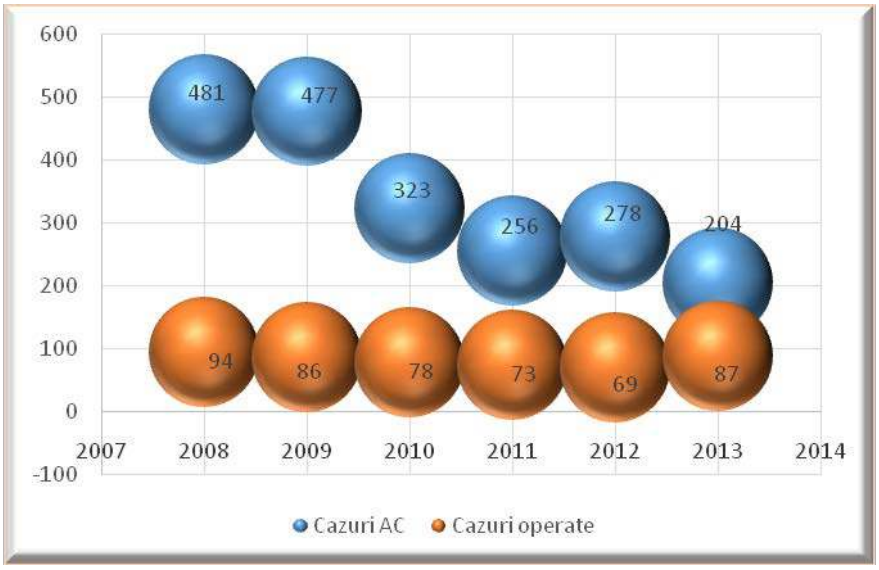


Figure 6. Distribution of cases with CA investigated and surgically treated between 2008 - 2013

➢ ***Duration of hospitalization and evolution after the surgery***

The duration of the hospitalization of patients that went under surgery was between 5 and 89 days, with an average of 21 days. In most of the cases (71%), children were hospitalized for maximum 20 days. In 8% of the cases, the patients had fever after the surgery, for 3 – 10 days, with an average of 7 days after the surgery. The preventive treatment with antibiotics was administrated in 86% of the cases that went under surgery and in 21% of those not treated by surgery.

2. Prospective epidemiologic study – cases with cases with congenital anomalies investigated, diagnosed and/or treated at SCJU "Sf. Apostol Andrei Constanța" within January 1, - December 31, 2014

According to statistic data reported for 2014 in SCJU "Sf. Apostol Andrei" Constanța, among the 384 cases with congenital anomalies investigated / treated in the hospital, 251 cases were diagnosed (CIM Code 10 AM: Q00 – Q99) at the category of age 0 – 16 years (see Table 6), representing 65% of the investigated cases.

As compared with the total number of cases investigated/treated for each category of age, the most frequent cases of congenital anomalies diagnosed was recorded in patients aged 6 – 16, respectively 2.61%, and the less significant occurrence was recorded for the category aged 17 – 85 (0.24%), as they benefited of medical services for another pathology than the malformations.

Table6.Distribution of congenital anomalieswith CIM Code 10 AM:Q00 – Q99, investigated atSCJU "Sf. Apostol Andrei Constanța"in 2014

Year	TOTAL CASES (Q02 - Q99) children	Male	Deceased	Rural	Less than 1 year old	1 - 4 years	6 - 16 years	17 – 85 years (≥ 85)	TOTAL CASES (Q02 - Q99)
2014	251	154	3	98	83	60	108	133	384
TOTAL DISCHARGED FROM HOSPITAL IN 2014	55,654	26,735	1,452	16,314	5,813	3,480	4,135	55,270	
Percent of cases (%) with CA of the total number of cases investigated/on categories of age					1.43	0.17	2.61	0.24	0.69

According to data obtained, we can see that during 2014, of the 251 cases with CA, the most frequent were with the involvement of the urogenital system (Q50-Q56 + Q60-Q64), respectively 1/3 of the cases, followed by the bone and joints MC (Q65- Q79), 15.11%, and diseases of the digestive system (Q38-Q45), with 6.25%. The rest of the type of congenital anomalies occurred with a frequency under 5%.

Depending on the gestational age and weight at birth, the cases with congenital malformations that went under surgery were most frequent among the children with normal weight at birth and delivered on due term (56.86%), followed by those with low weight at birth and children delivered before the due term (30.00%).

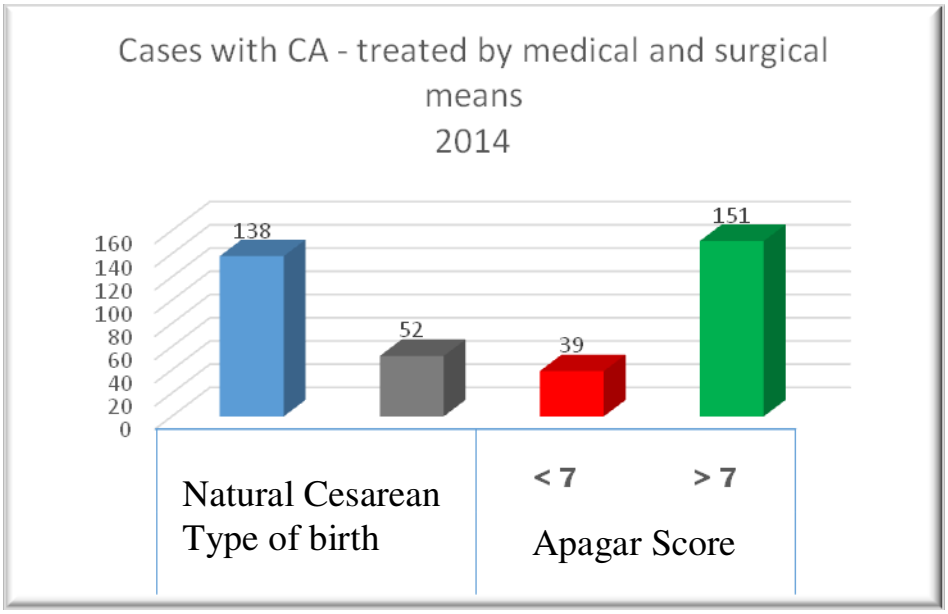


Figure 7. Distribution of congenital anomalies cases treated by medical and surgical means in 2014, depending on the type of delivery

The main diseases for which we needed a surgery within the Paediatric Surgery Department of SCJU "Sf. Apostol Andrei" Constanța, are the anomalies of the *urinary system, followed by the malformation of the genital system and of the digestive system.*

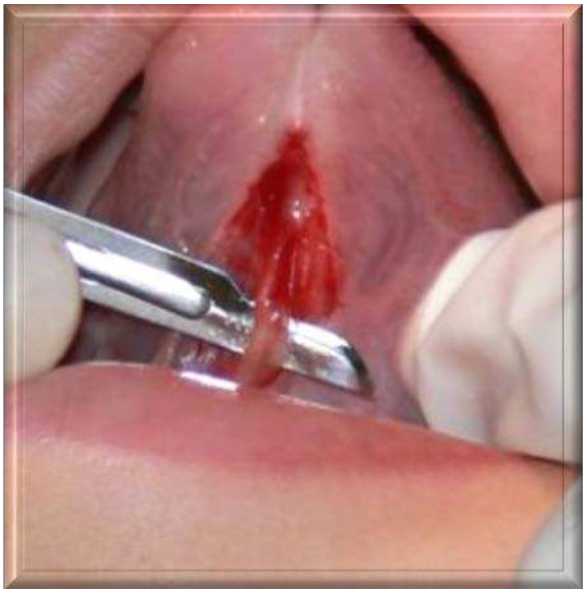


Figure 8. Ankyloglossia. Frenectomy

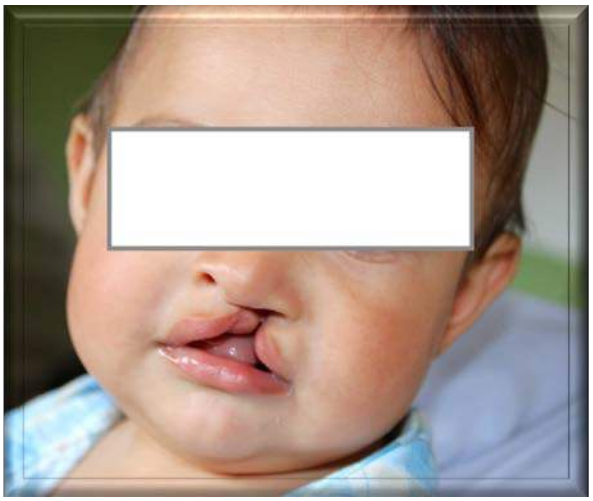


Figure 9. Cleft lip.

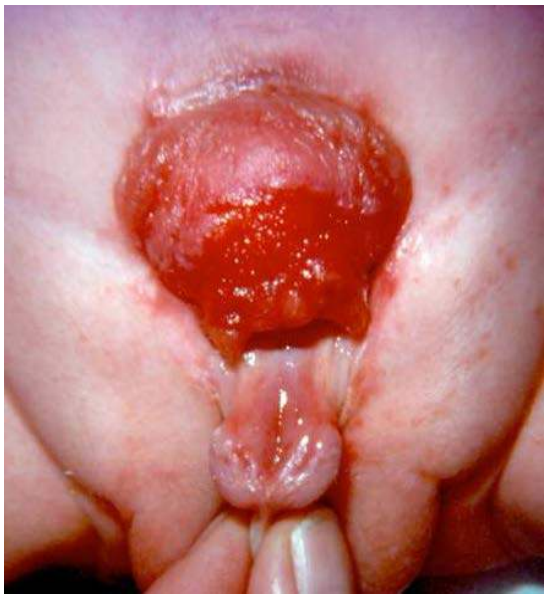


Figure 10. Hermaphroditism

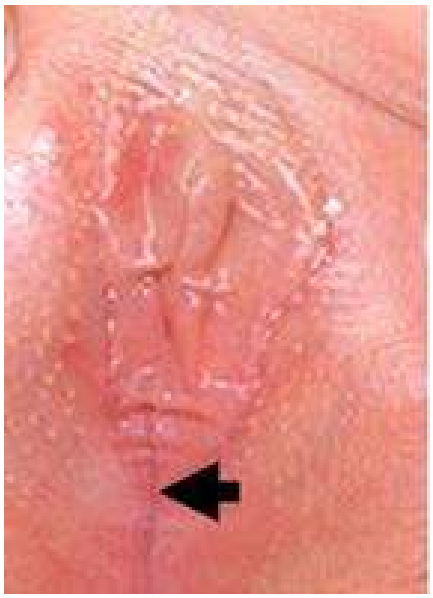


Figure 11. Labia united

The following analysis concerned the type of treatment administrated (etiologic, pathogenesis, of complications or adjuvant) for each group of diseases.

Starting from the fact that the aetiology and pathogenetic mechanism of structural variants of congenital anomalies is different, I tried to determine the place and role of the surgical treatment in the therapeutically strategy of clinical variants of congenital anomalies.

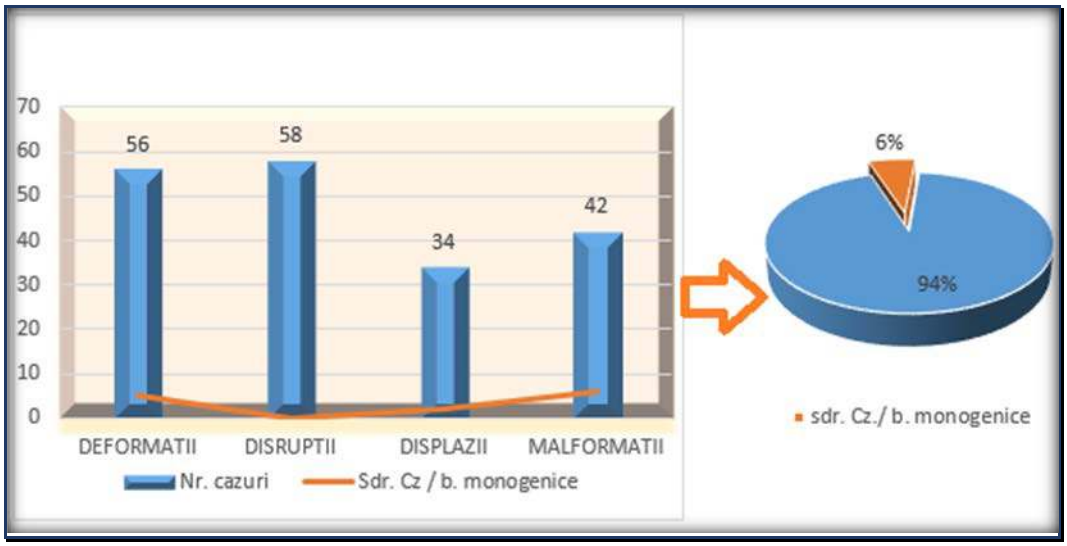


Figure 12. Distribution of cases depending on the pathogenic type

Thus, the weight of the surgical treatment (including orthopaedic) in different types of congenital anomalies spreads from 94% in plurimalformative syndromes, deformations and disruptions to 6% in the clinical and genetically variants (chromosomal syndromes, monogenic) (Figure 12).

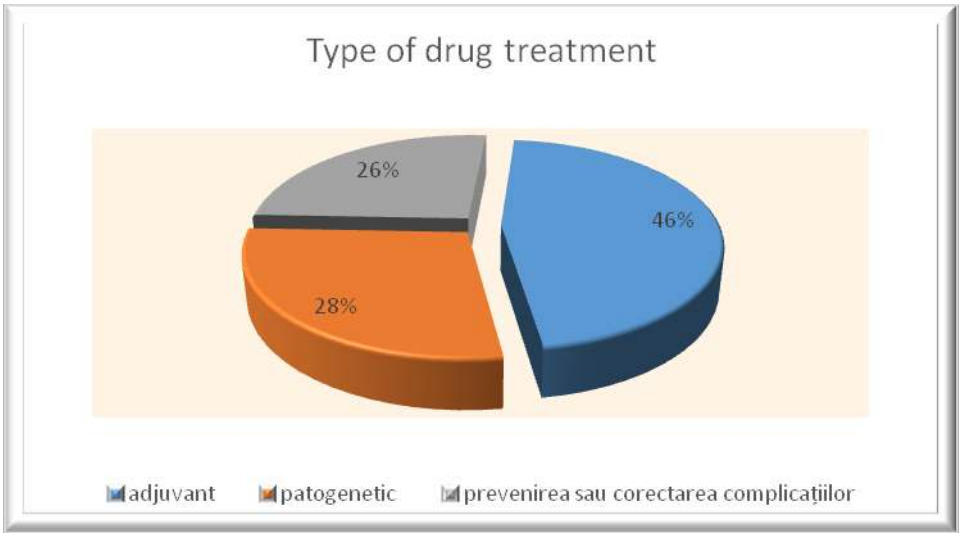


Figure 13. Distribution of cases depending on the type of drug treatment administrated.

Regarding the drug treatment, in most of the cases it was administrated as adjuvant in 46% of cases (pre-/post surgery), pathogenetic (28%), and in 26% of cases it concerned the prevention or correction of complications or as a substitute (Figure 13).

At the same time, we correlated the hospitalization period with certain factors that could have influenced the evolution and found out that the main factors which have a positive correlation and had a negative prognostic factor role, were (Table 7):

- precocity of diagnosis: the patients that were diagnosed before the delivery were hospitalized for lesser periods (p=0.054) compared with those without early diagnosis, respectively 6.07±4.23 days *versus* 7.16±5.62 days;
- type of delivery: new born children extracted by caesarean section were hospitalized for slightly longer periods of time compared to those delivered naturally (8.67±6.43 days *versus* 7.28±5.32 days) (p=0.756);
- weight at birth: cases with *low weight* at delivery (<2500 gr.) had a period of hospitalization significantly higher as compared with those with normal weight at birth, respectively 9.12±8.73 *versus* 6.24±6.27 days (p=0.526);
- gestational age: new born children before the delivery term had a period of hospitalization significantly higher as compared with those delivered on due time (11.06±7.11 days *versus* 7.37±6.47). p=0.468.
- type of congenital anomalies: simple malformations (generally deformation) had a period of hospitalization significantly lower as compared with the complex malformations (plurimalformative syndromes and severe malformations), respectively 2.46±2.11 days *versus* 17.87±9.34 (p=0.754).

Table 7. Table of correlations between the period of hospitalization and main factors that influence the evolution after the surgery

Variable	Duration of hospitalization *1 (average±DS)	Duration of hospitalization *2 (average±DS)	p-value
Precocity of diagnosis	6.07±4.23	7.16±5.62	0.054
Type of birth	8.67±6.43	7.28±5.32	0.756
Weight at birth	9.12±8.73	6.24-±6.27	0.526
Gestational age	11.06±7.11	7.37±6.47	0.46$
Type of congenital anomalies	2.46±2.11	17. 87±9.34	0.754

Duration of hospitalization *1	Duration of hospitalization *2
Diagnosis before birth	After the birth
Cesarean section	natural
<2500 gr	>2500 gr
<38 weeks	38-40 weeks
simple	Complex/severe

The investigations included in the work protocols were: ultrasound scan (trans-fontanelar, heart, and abdomen), radiography, scintigraphy, urography, retrograde cystography, CT, MRI, laparoscopic diagnosis. Surgeries were performed in the surgery room of the County Clinical Hospital "Sf. Apostol Andrei" Constanța.

The comprehensive approach of the treatment of congenital anomalies in children involved the presentation of four cases of CA diagnosed in the paediatric age: laparoschizis, duodenal atresia, plurimalformative syndrome, malformative uropathy. It was not a random choice; they were severe malformations of the most common birth defects that had the surgical treatment indication.

DISCUSSIONS

Many international, national and regional statistics consider that the overall rate of congenital malformations, that can be seen at delivery and detectable by clinical examination of new born children - born alive and still, ranges on average between 1.5 - 2% (COVIC M. et al., 2011). In the present study, the prevalence of cases with CA, investigated and treated at SCJU "Sf. Apostol Andrei" Constanța within 2008 – 2013, was 1.74, therefore being in line with the statistics reported in the national and global level.

In terms of the types of congenital malformations among children in the study group, they had a heterogeneous aspect, congenital defects concerning almost all apparatus and systems of the organism. The highest prevalence of the anomalies had the bones and joints ones (4.16 to 100.000 new born children), followed by anomalies of the circulatory system (Q20 – Q28) chromosomal disorders (Q90-Q99) and CNS anomalies (Q00-Q07).

The statistics presented differ from other studies in the literature, where the most common congenital anomalies reported are those involving the nervous system (anencephaly, spina bifida, hydrocephalus, etc.), congenital heart malformations (septal defects, ductus arteriosus persistent, aortic stenosis), followed by cleft lip with or without cleft palate, pyloric stenosis, congenital heart dislocation (Covic M. et al., 2011) and according to Oster et al. (2013), congenital heart malformations (MCC) are the most common type of congenital anomalies being the first cause of infant mortality due to CA.

Many studies have demonstrated the predominance of CA in male patients (Hollier LM et al., 2000; Lei Z., 1992), but in this study the child's gender does not influence the incidence of congenital anomalies (M : F = 1.2 : 1), an aspect that is consistent with the results of other studies showing that both genders are equally distributed (Akhavan Karbasi et al., 2009; Biri A. et al., 2005).

In the present study, it can be noted that high-risk female population is that over 35 years of age (1/3 of cases, without significant difference compared to data from the literature), with exposure to teratogens, physical or chemical factors, with history of recurrent spontaneous abortions (47%), with foetuses born with congenital anomalies.

Multiparity seems to be another risk factor associated with congenital anomalies, as evidenced in 56.16% of cases. Since 1990, Sipila P. et al. mentioned in an article, a higher frequency of congenital anomalies in mothers with multiple births, particularly those who had more than 3 children. Although the literature mentions that minor and major congenital anomalies are more common in twin pregnancies, and more frequent in monozygotic (Rabah M. Shawky, Doaa I. Sadik, 2011; Blickstein I, Keith L G, 2007), in the present study twin pregnancies cannot be considered a risk factor of malformations, given that only 2.8% of cases with CA come from twin pregnancy.

Regarding the prophylaxis before the conception with folic acid and vitamins from analyzed data it is clear that this was done only 34.58% of cases.

Alcohol consumption in early pregnancy increases the risk of giving birth to children with various malformations[4], and smoking increases the risk of ectopic pregnancy, miscarriage, premature birth, foetal death. Both behaviours have been identified in the present study in more than 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 during the pregnancy[5].

The 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 listed in other studies[6]. Also an important factor for embryo normal foetal development is the health condition of the mother. It is well known that maternal pathologies (chronic diseases, hereditary maternal diseases) can induce birth defects in children[7].

Maternal consumption of alcohol and drugs was associated with increased risk of congenital anomalies. These factors correlate a preterm birth/stillborn, birth by caesarean and repeated miscarriages (Table 8).

---

[4] Olimpia Oprea şi colab., (2013) Raport de cercetare privind frecvenţaşi cauzele malformaţiilor fetale înjudeţulTimiş, ISBN 978-606-8427-81-2, http://prenataldiagnosis.ro/wp-content/uploads//12/Raport-de-cercetare-.pdf

[5]Honein MA, Rasmussen SA, Reefhuis J, Romitti P, Lammer EJ, Sunl, et al. (2007), Maternal smoking, environmentaltobaccosmoke, andtherisk of oral clefts. Epidemiology;18(2):226–33.

[6]Devi R, Tilak P, Rajangam S. (2007) Multiple congenital anomalies – an aetiologicalevaluation. Bombay Hosp J.

[7]RizkFrancine , Salameh Pascale , Hamadé Aline, (2014), Congenital Anomalies: PrevalenceandRiskFactors, Universal Journal of Public Health 2(2): 58-63, , http://www.hrpub.org

The APGAR score positively correlates with parity and consumption of vitamins during pregnancy, while it is negatively correlated with maternal smoking during pregnancy.

Birth weight was negatively affected by maternal smoking during pregnancy and correlates inversely with caesarean delivery.

Head circumference is positively correlated with the presence of CA in other brothers and repeated abortions and negatively with smoking during pregnancy and prematurity. A relatively high incidence of CA in early stages was observed by Desai et al., while Anand et al. found no significant correlation between the degree of birth and congenital malformations.

Table 8. Multivariative analysis of cases of CA with different characteristics of the new born child

Dependant variable	**Independent variable**	**[95%CI]**	**p-value**	**R^2**
Congenital anomalies	Mother's consumption of alcohol Mother's consumption of drugs	1.92;54.71 2.24;12.44	0.007 <0.001	0.10
Delivery before the term/new born dead	Congenital anomalies Cesarean section Repeated abortion	2.57;20.67 0.78;3.22 1.12;2.55	<0.001 0.056 0.012	0.16
APGAR Score	Parity Mother's smoking Consumption of vitamins during the pregnancy	0.07;0.24 -0.76;-0.15 0.20;0.86	<0.001 0.004 0.002	0.04
Weight at birth	Mother's smoking Cesarean section	-313.91;-158.47 -134.62;-11.45	<0.001 <0.001	0.04
Head circumference	Brothers with CA Repeated abortion e Mother's smoking Prematurity	0.82;2.19 0.06;0.30 -0.62;-0.01 -0.51;-0.01	<0.001 0.001 0.019 0.042	0.05

The cases with CA included in the present study were more, most of the times, deliveries on due term. It is well known that an abnormal foetus is often delivered before the due time or aborted, taking into consideration that a significant percent of cases had a chromosomal abnormality. This is a phenomenon of "natural selection". Thus, the relationship between prematurity and congenital anomalies - is a ***cause*** or ***effect*** - it is difficult to comment.

Determining a correct clinical and genetic diagnosis is essential for guiding the type of investigations and recommended genetic analysis (karyotype, FISH, MLPA). Most cases with chromosomal anomalies ends with a miscarriage, so that their frequency at birth is approximately 0.6% (Connor and Ferguson-Smith, 1991).

Three to four percent of all births are associated with major birth defects, mental retardation or genetic diseases, the rate is doubled by the age of 7-8 years as a result of delayed manifestation of the genetic diseases or late detection detect (Rabah M. S, Doaa I. S, 2011; Rahele A, at al., 2014). Also in the case of this study, the frequency rate of 3.8% of cases with associated congenital malformations and chromosomal anomalies are consistent with reports of other studies.

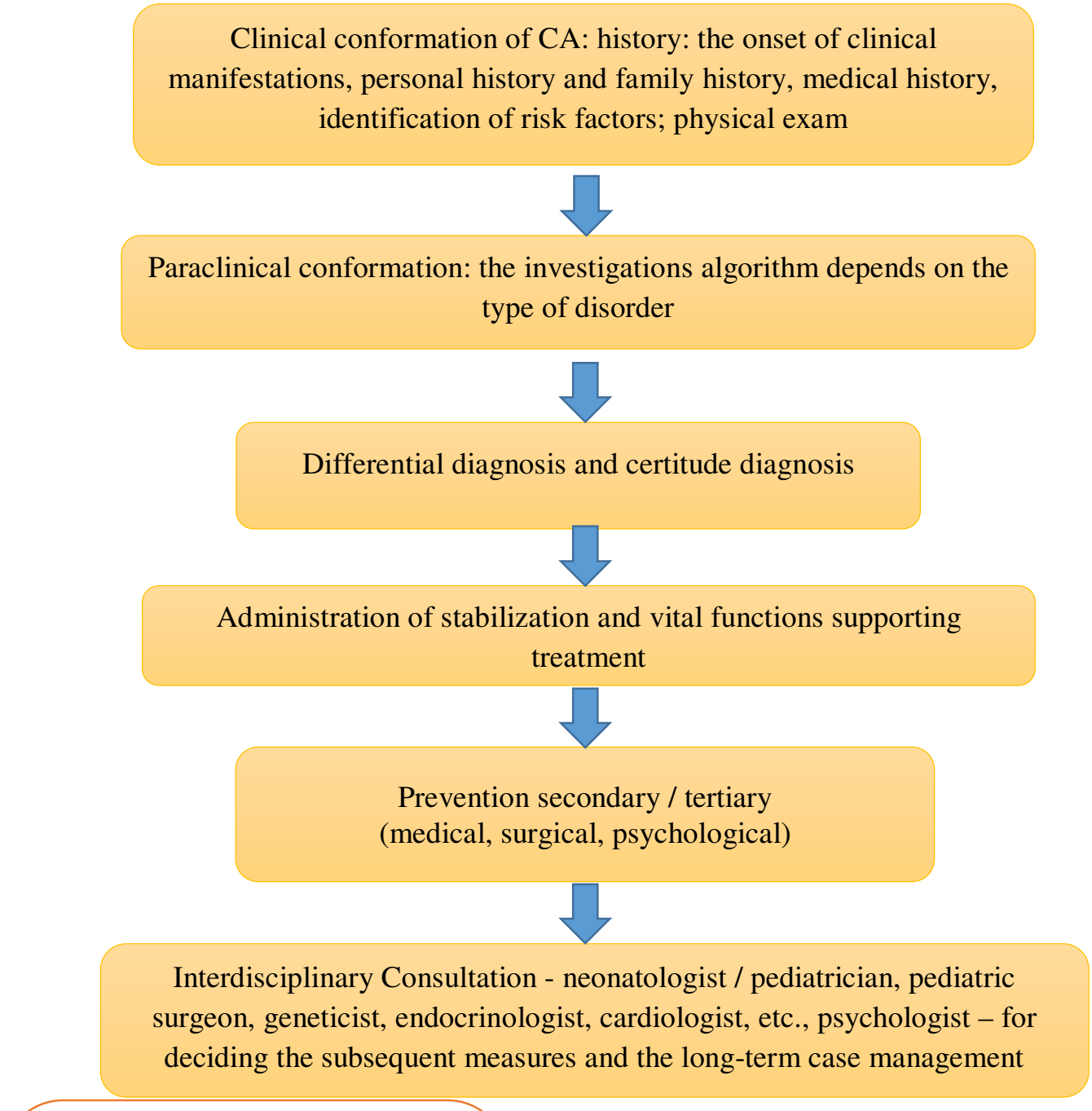
Among cases with chromosomal anomalies detected, trisomy 21 was the most frequent anomaly (52.56%), which is consistent with data from the literature (Navsaria et al. 1993; Kenu et al. 1995; Al Husain and Zaki 1999). 2 cases were detected, and 1 case respectively with that other aneuploidies, respectively trisomy 13 and 18, also a frequency that is consistent with the data presented in other studies. Among the gonosomal anomalies, Turner syndrome was the most common diagnosis in this study and the classic form of karyotype (45,X) was more frequent compared with somatic mosaicism (45,X/46,XX). Klinefelter syndrome was the second most common syndrome involving gender chromosomes, those cases presenting a classic phenotype.

As compared to the cases that associated chromosomal anomalies, 84.62% were numerical anomalies and the rest of them structural anomalies or metaphases that had extra chromosomal material of unknown origin.

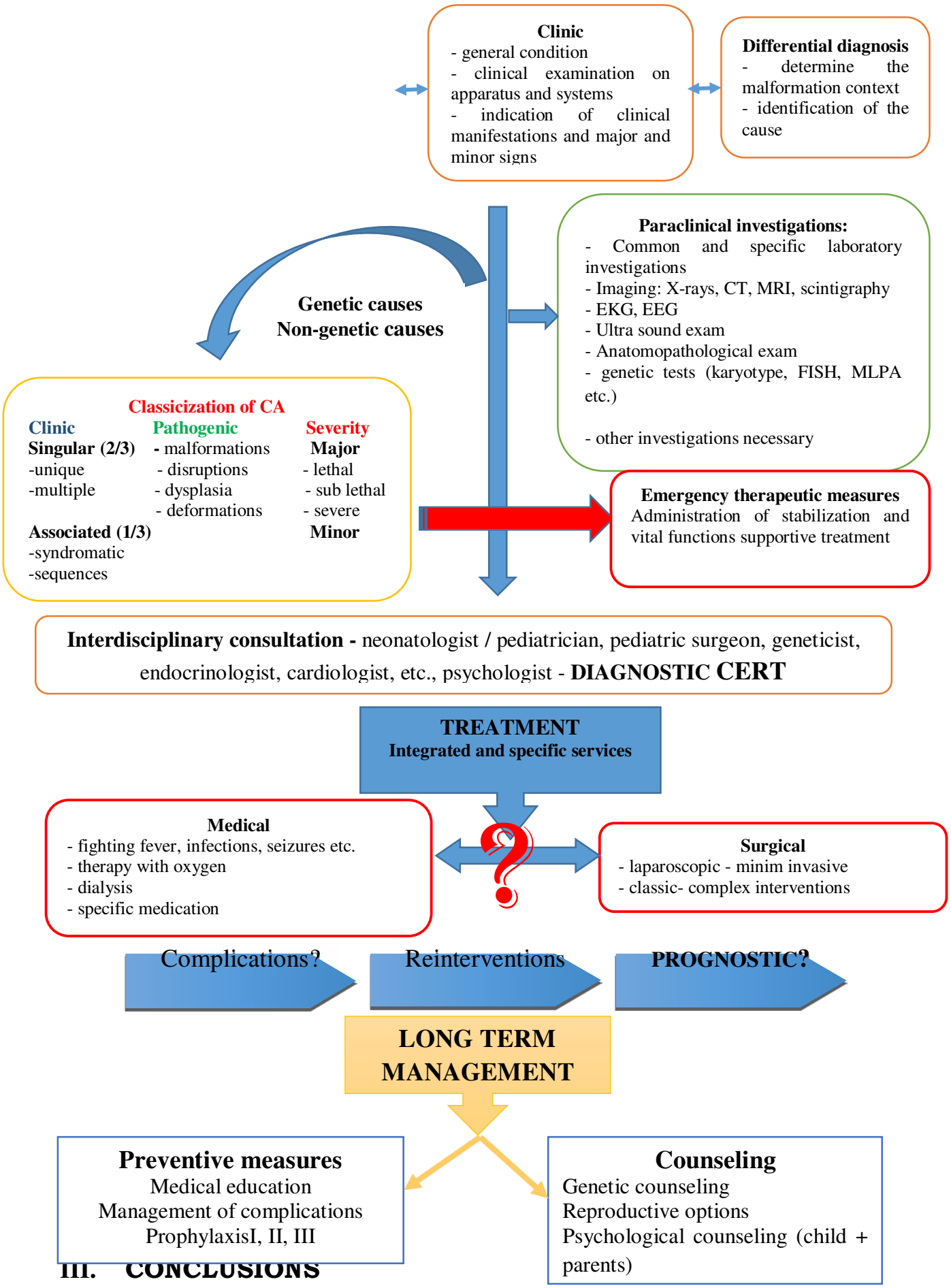
2.3. Protocol for diagnosis of the patient with congenital anomalies

Reducing the occurrence at birth and of infantile mortality due to congenital anomalies can be objectives that can be achieved by an optimal management and preventive measures implemented as early as possible (see the diagnosis algorithm).

GENERAL ALGORITHM OF BEHAVIOR IN CASE OF CONGENITAL ANOMALIES



Risk factors
- mother's age ≤ 16 years and ≥ 35 years
- father's age ≥ 45 years
- genitors carriers of balanced chromosomal anomalies
- AHC of CA, genetic diseases, metabolic diseases
- reproductive history



III. CONCLUSIONS

Beyond the medical concern of the pathology itself, the malformations issue faced by the current medical practice, it has become one of the priorities of medical scientific research, due to the frequency and severity of congenital anomalies. The possibility of detection and early diagnosis by means less invasive of congenital disorders is beneficial in determining the therapeutic behaviour and long-term evolution.

The estimation of the number of foetal malformations in Constanța County, during 2008 - 2014, shows relatively stable without experiencing an alarming increase according to global statistics.

As compared to the parents' age, the highest incidence of malformations was recorded in the age groups 20 – 40 years, groups with maximum fertile conditions, but especially after 35 years of age, an age is a recognized risk factor.

The insufficient educational level of pregnant women has contributed to the increase of number of foetal malformations; this category of pregnant women had no prenatal consultation.

Paradoxically, in the study I conducted, the percent of cases with congenital anomalies was not strictly influenced by the woman's area of origin, diet, blood group, Rh, gestational age, pregnancy associated diseases (diabetes, anaemia, hypertension, allergies). Also, there was no link with the use of antibiotics, anti-inflammatory medication, hormonal and anticoagulant therapy during the pregnancy. Alcohol consumption was not recognized by any pregnant woman, and smoking did not seem to have an influence on the health of the foetus in the group considered for this study. However, these risk factors should not be underestimated and should be taken into account that may not have been sufficiently emphasized in the medical documents.

The most common congenital anomalies concerned the musculoskeletal, cardiovascular, central nervous and digestive system, followed by genetic malformations and those with unspecified aetiology.

Concluding, congenital anomalies continue to be an important cause of morbidity and infant and paediatric mortality, especially in developed countries. At the individual level, the disease burden is more important in vulnerable categories, sometimes very high costs of care and specific treatment - when available - disproportionately affects those in the social and economic categories of disadvantaged people, especially children.

The screening of congenital anomalies should be done in each country and even in different geographic regions of the same countries in order to establish their prevalence, mode of occurrence, nature thereof, to identify the causes and associated risk factors and not least to prevent or reduce the incidence of malformation pathology.

It is really necessary to have a legislative framework to facilitate the access to early diagnosis and appropriate treatment (services that are sometimes highly specialized and

not available nationally) in specialized reference centres benefiting from the support of a wide range of practitioners in health, of integration of medical services with the social and educational services, and support from family.

SELECTIVE BIBLIOGRAPHY

1. Akhavan Karbasi S, Golestan M, Fallah R, Mirnaseri F, Barkhordari K, Sadr M. (2009), Prevalence of congenital malformations. Acta Med Iran,;47(2):149-153
2. Al Husain M, Zaki OK (1999), A survey of 1,000 cases referred for cytogenetic study to King Khalid University Hospital, Saudi Arabia. Hum Hered, 49: 208-214.
3. Amany M. A. at al, (2011), Assessment of Risk Factors for Fetal Congenital Anomalies among Pregnant Women at Cairo University Hospitals. Journal of American Science;7(12) http://www.americanscience.org
4. Biri A. et al., (2005) Birth prevalence and distribution of congenital anomalies in a university hospital. Perinatol Dergisi 2005;13:86-90
5. Blickstein I., Keith L.G., (2007), Prenatal Assessment of Multiple Pregnancy, CRC Press, ISBN 0203931661
6. Centers for Disease Control and Prevention. Update on overall, prevalence of major birth defects—Atlanta, Georgia, 1978–2005., MMWR Morb Mortal Wkly Rep. 2008;57(1):1–5.
7. Covic M, Ştefănescu D, Sandovici I (sub redacţia), (2011), Tratat de genetică medicală, Ediția II, Polirom, Iaşi
8. Devi R, Tilak P, Rajangam S. (2007), Multiple congenital anomalies – an aetiological evaluation. Bombay Hosp J [Review articles]. Avaible at: http://www.bhj.org/journal/2007.
9. Gagnon A, Wilson RD, Allen VM, et al. (2009), Evaluation of prenatally diagnosed structural congenital anomalies. J Obstet Gynaecol Can.;31(9):875-81.
10. Gorduza E. V., (2007), Compendiu de genetică umană şi medicală; Editura Tehnopress, Iaşi, 333-338.
11. Hollier LM et al. Cunningham FG. (2000), Maternal age and malformations in single ton births. Obstetrics and gynecology;96:701-6
12. Honein MA, Rasmussen SA, Reefhuis J, Romitti P, Lammer EJ, Sunl, et al. (2007) Maternal smoking, environmental tobacco smoke, and therisk of oral clefts. Epidemiology;18(2):226–33.
13. Kenue RK, Raj AK, Harris PF, el-Bualy MS (1995). Cytogenetic analysis of children suspected of chromosomal abnormalities. J Trop Pediatr, 41: 77-80

14. Lei Z. (1992), Epidemiology of birth defects among children in 8 provinces in China. Zhonghuayixue za zhi;72:412-5, 46-7.
15. Navsaria D, Mathews T, Conte RA, Verma RS (1993). Chromosomal anomalies in 1,000 children referred with suspected genetic disorders. Hum Hered, 43: 137-140.
16. Oprea O. și colab., (2013), Raport de cercetare privind frecvența şi cauzele malformațiilor fetale în județul Timiş, ISBN 978-606-8427-81-2, http://prenataldiagnosis.ro/wp-content/uploads/2013/12/Raport-de-cercetare
17. Oster ME, Lee KA, Honein MA, Colarusso T, Shin M, Correa A., (2013), Temporal Trends in Survival Among Infants with Critical Congenital Heart Defects, Pediatrics; 131:e1502–e1508.
18. Rabah M. S, Doaa I. S, (2011) Congenital malformations prevalent among Egyptian children and associate drisk factors, The Egyptian Journal of Medical Human Genetics 12, 69–78
19. Rahele A, Mehrdad M, Peimaneh A, Sadegh H., (2014), Associated RiskFactorsandPrevalence of Congenital Malformations in Ardabil, Iran, Iranian Journal of Neonatology, Article 7, Volume 5, Abstract, Autumn, Page 3-4
20. Rizk F., Salameh P., Hamadé A., (2014), Congenital Anomalies: Prevalence and Risk Factors, Universal Journal of Public Health 2(2): 58-63, , http://www.hrpub.org
21. Siega-Riz AM et al., (2009), National Birth Defects Prevention Study. The joint effects of maternal prepregnancy body mass index and age on the risk of gastroschisis. Paediatr Perinat Epidemiol. 23(1):51-7
22. Sipila P., Von Wendt L., Hartikainen-Sorri A.L., (1990), The grand multipara-still an obstetrical challenge? Arch Gynecol Obstet;247(4):187
23. Tinker Sarah C., Gilboa S, Reefhuis J, at all., (2015) Challenges in Studying Modifiable Risk Factors for Birth Defects, Curr Epidemiol Rep 2:23–30, DOI 10.1007/s40471-014-0028-y
24. European Surveillance of Congenital Anomalies (EUROCAT) - website http://www.eurocatnetwork.eu/
25. http://www.uptodate.com/contents/genetic-and-environmental-causes-of-birth-defects
26. https://www.nichd.nih.gov/news/resources/spotlight/Pages/062712-alcohol-drug-related-birth-defects.aspx
27. Orphanet – bază de date pentru boli genetice (http://orphanet.infobiogen.fr)
28. World Health Organization. Birth Defects. Report by the Secretariat. Sixty-Third World Health Assembly. Provisional agenda item 11.7 [Internet]. 2010 Apr [cited 2011 Nov]. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_10-en.pdf.