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Karyogram in neonatology: Necessity or past?

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ABSTRACT

Objective: This research was conducted at the Clinic for Children's Diseases of the University Clinical Hospital (SKB) Mostar. The aim of this study is to assess the frequency and reasons for performing karyotyping in neonatology practice over the past 15 years in the Herzegovina region.
Material and methods: A retrospective epidemiological study was conducted covering a 15-year period from January 1, 2009, to December 31, 2023. The study included 150 newborns who underwent karyotype testing at the Intensive Care and Neonatology Department of the Clinic for Children's Diseases at University Clinical Hospital (SKB) Mostar.
Results: Over the 15-year period, 48 % (73/150) of the karyotypes were classified as normal, while 51 % (77/150) were identified as pathological. The most common chromosomal abnormality was trisomy 21, which accounted for 70.13 % (54/77) of the pathological cases. The results indicated that a majority of the fathers were older than 35 years (62.33 %, or 48/77), whereas the age of the mothers was not statistically significant in this study. Additionally, 57 % of multiparous women gave birth to children with chromosomal abnormalities. Premature newborns were more likely to have positive karyotype results.
Conclusion: This research found no significant difference in the occurrence rates of pathological versus physiological karyotypes. Just over 50 % of the children had confirmed karyotype deviations from normal variations. However, this suggests that healthcare resources may be misallocated in performing karyotyping, as the significance of the results may not always justify the testing.

Introduction

A karyotype represents the complete set of chromosomes of a species, detailing both the number and appearance of prometaphase or metaphase chromosomes. The term "human karyotype" refers to the chromosomal complement of an individual [1]. Congenital

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malformations encompass a diverse group of morphological, functional, or biochemical defects that can manifest in utero, at birth, or during the postnatal period, with a wide range of etiopathogenesis, clinical profiles, and treatment principles. The signs and symptoms associated with these malformations can vary from mild to moderate, severe, or even fatal [2]. Mortality can occur antenatally, at the time of birth, during the neonatal period, in childhood, or later in life. The personal, familial, social, medical, and financial impacts can be minimal or overwhelming, depending on the specific diagnosis and its classification [2]. Risk factors associated with human aneuploidy primarily include maternal age, alterations in the recombination patterns between homologous chromosomes, as well as various genetic and environmental influences. The most common aneuploidies in the human population include trisomies of chromosomes 21, 13, and 18 [3]. Down syndrome (DS), or trisomy 21, typically occurs as the standard form of the condition, where each cell in the body has three copies of chromosome 21 instead of the usual two. This form of DS is the most prevalent in the human population and arises from improper separation of chromosomes during oogenesis, and less frequently during spermatogenesis. DS can also present as a chromosomal mosaic, where one cell line exhibits trisomy 21 while another has a normal chromosomal count. A smaller percentage, approximately 4 % of patients, may have the translocation type, which involves a Robertsonian translocation that can either be inherited from parents or result from a new mutation [3]. The characteristic phenotype is often evident at the neonatal stage, with the most significant features including intellectual disability, facial dysmorphism, and a reduced resistance to infections. The disease also impacts internal organs, with malformations being a major cause of shortened lifespan. As maternal age increases, so does the risk of having a child with DS [4].

The aim of this research at the Clinic for Children's Diseases is to assess the frequency and reasons for performing karyotyping in neonatology practice over the past 15 years in the Herzegovina region.

Material and methods

This study is a fifteen-year retrospective analysis conducted at the Clinic for Children's Diseases, SKB Mostar, specifically within the Department of Neonatology and Intensive Care. The research utilized discharge letters and newborn records. It included all newborns who underwent blood sampling for karyotyping, encompassing premature infants, those with low birth weight, and cases of chromosomal abnormalities. The study accounted for all newborns meeting these criteria from January 1, 2009, to December 31, 2023. The parameters evaluated for the newborns included sex, gestational age, Apgar score, birth weight, birth length, and the reasons for obtaining a karyotype. These reasons included minor anomalies (such as slanted eye slits, nuchal fold, and crossed fingers) and major anomalies (such as heart defects and cleft palate), along with the karyotype results. For the mothers, the parameters considered were maternal age, number of pregnancies, births, and abortions, method of conception, pregnancy course, any pathological conditions during pregnancy, delivery method, medications taken during pregnancy, and other relevant medical record data, including the father's age. All children were clinically assessed through laboratory tests and ultrasonography at SKB Mostar. From 2009 to 2015, karyotype samples were sent to the Cytogenetic Laboratories in Split and Tuzla, as SKB Mostar did not have its own cytogenetic facility during that time, resulting in less frequent karyotyping. However, since 2015, SKB Mostar has established its own Cytogenetics laboratory, allowing for more frequent karyotyping, even for individuals with only minor anomalies.

Statistics

The software system R (RStudio Team (2021). RStudio: Integrated Development Environment for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/) and Microsoft Excel for Microsoft 365 MSO (Version 2111. Microsoft Corporation, Redmond, WA, USA) were used for statistical analysis and graphical display of data. The frequency of occurrence was stated for the nominal variables in the research and the differences between the frequencies were tested with the Chi-squared test. And for variables that are not normally distributed, differences were tested with the Mann Whitney test.

Results

We analyzed 150 blood samples for chromosome analysis (karyotyping) in the Intensive Care and Neonatology Department at SKB Mostar between January 1, 2009, and December 31, 2023. In the earlier years, we did not have an on-site cytogenetic laboratory, so samples were sent to distant locations. Fortunately, a cytogenetic lab is now available at the medical school, which has allowed us to perform karyotypes more frequently. Of the 150 karyotypes, 77 (51.33 %) were found to be pathological, while 73 (48.67 %) were physiological, indicating no significant difference between the two groups. This can be attributed to the increased frequency of karyotyping in recent years, even for individuals with minor anomalies (Fig. 1). Notably, during the first half of the study (2009–2015), we observed a higher number of pathological karyotypes compared to physiological ones. However, this discrepancy was not evident in the period from 2015 to 2023 (Fig. 1). Mothers were divided into two age groups: under 35 and over 35. No statistically significant differences were found in the frequency of karyotype findings between these maternal age groups. In contrast, for fathers over 35, we observed significant differences at the 10 % level of significance in the frequency of karyotype findings (Table 1). In this older paternal age group, pathological karyotype findings were present in 62.34 % (48/77) of cases, compared to physiological findings (Table 1). The most common pathological condition observed in mothers was infection, affecting 18.67 % (28/150) of cases. Multiparous women accounted for 57.00 % of births with chromosomal abnormalities. As gestational age was not normally distributed ($W = 0.92503$, $p < 0.01$), differences were assessed using the Mann-Whitney test, revealing statistically significant differences; specifically, children with pathological karyotypes were born earlier compared to those with physiological karyotypes (Table 2). Birth weight and length were also not normally distributed (S-W: 0.97023, $p < 0.01$), and similar statistical

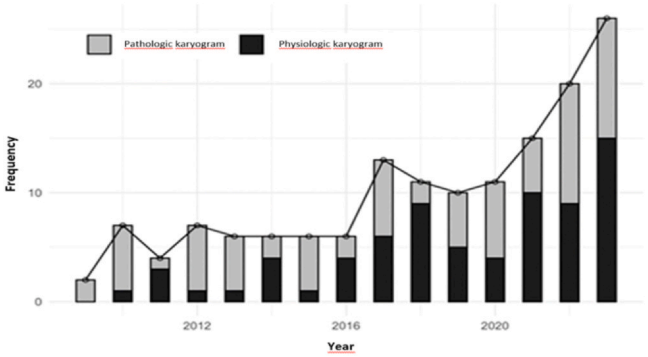

Fig. 1. Distribution of blood sampling for karyogram in the period from 2009 to 2023 in SKB Mostar (annual frequency).

Table 1
Distribution of characteristics of pregnant women, father's age on the result of pathologic or physiologic karyogram.

Number (%)					
	Karyogram				
	Total	p	Pathologic	Physiologic	p
Father's age		0.414			0.035
Up to 35 years	70 (46.67 %)		29 (37.66 %)	41 (56.16 %)	
Over 35 years	80 (53.33 %)		48 (62.34 %)	32 (43.84 %)	
Mother's age		0.034			0.375
Up to 35 years	88 (58.67 %)		42 (54.55 %)	46 (63.01 %)	
Over 35 years	62 (41.33 %)		35 (45.45 %)	27 (36.99 %)	
Number of pregnancies		0.012			0.073
1	50 (33.33 %)		20 (27.4 %)	30 (38.96 %)	
2	45 (30 %)		28 (38.36 %)	17 (22.08 %)	
3	27 (18 %)		17 (23.29 %)	10 (12.99 %)	
4 +	28 (18.67 %)		12 (16.44 %)	16 (20.78 %)	
Method of insemination		<0.001			0.235[B]
Natural insemination	148 (98.67 %)		77 (100 %)	71 (97.26 %)	
Artificial insemination	2 (1.33 %)		0 (0 %)	2 (2.74 %)	
Pathology		<0.001			0.210[B]
No pathologic conditions	90 (60 %)		53 (68.83 %)	37 (48.05 %)	
Gestational diabetes	9 (6 %)		4 (5.19 %)	5 (6.49 %)	
Hypertension in pregnancy	8 (5.33 %)		2 (2.6 %)	6 (7.79 %)	
Hypothyreosis	14 (9.33 %)		5 (6.49 %)	9 (11.69 %)	
Infections	28 (18.67 %)		12 (15.58 %)	16 (20.78 %)	
Preeclampsia	1 (0.67 %)		0 (0 %)	1 (1.3 %)	
Others	17 (11.33 %)		7 (9.09 %)	10 (12.99 %)	
Complications in pregnancy		<0.001			0.898[B]
No complications	113 (75.33 %)		59 (76.62 %)	54 (70.13 %)	
Cervical cerclage	2 (1.33 %)		2 (2.6 %)	0 (0 %)	
Amniotic fluid leakage	14 (9.33 %)		6 (7.79 %)	8 (10.39 %)	
Bleeding	6 (4 %)		3 (3.9 %)	3 (3.9 %)	
Oligohydramnios	6 (4 %)		3 (3.9 %)	3 (3.9 %)	
Polyhydramnios	10 (6.67 %)		5 (6.49 %)	5 (6.49 %)	
Premature uterine contractions	3 (2 %)		1 (1.3 %)	2 (2.6 %)	

B Fisher's test.

tests indicated no significant difference between newborns with pathological versus physiological karyotype results. Most newborns exhibited good vitality scores (Table 2). Down syndrome was the most frequently diagnosed condition, occurring in 54 newborns, representing 70.13 % (54/77) of pathological findings. The second most common reason for karyotyping was heart defects, identified in 64 newborns, with pathological karyotypes present in 40 of these cases, accounting for 51.95 % (Table 3). There were no significant statistical differences among other diagnoses confirmed by karyotype (Table 3). The prevalence of pathological and physiological karyotype results was similar across both male and female newborns.

Discussion

Prenatal medicine emerged in the 1960s to address the screening for genetic anomalies in fetuses. Congenital anomalies affect 3–5 % of all newborns and constitute a significant percentage of morbidity and mortality during the prenatal period and infancy [5]. Although patients with multiple congenital anomalies pose diagnostic challenges for pediatricians and clinical geneticists, it is crucial

Table 2
Distribution of newborn characteristics in relation to pathologic or physiologic karyogram.

Number (%)					
	Karyogram				
	Total	p	Pathologic	Physiologic	p
Sex		1			0.191
Male	75 (50 %)		43 (55.84 %)	32 (41.56 %)	
Female	75 (50 %)		34 (44.16 %)	41 (53.25 %)	
Weight (g)		< 0.001			0.100[B]
1000 - 1499	2 (1.33 %)		1 (1.3 %)	1 (1.3 %)	
1500 - 2499	33 (22 %)		18 (23.38 %)	15 (19.48 %)	
2500 - 3499	87 (58 %)		45 (58.44 %)	42 (54.55 %)	
3500 - 3999	19 (12.67 %)		12 (15.58 %)	7 (9.09 %)	
> 4000	9 (6 %)		1 (1.3 %)	8 (10.39 %)	
Length (cm)		< 0.001			0.084[B]
< 48	29 (19.33 %)		14 (18.18 %)	15 (19.48 %)	
49 - 52	64 (42.67 %)		39 (50.65 %)	25 (32.47 %)	
53 - 56	47 (31.33 %)		22 (28.57 %)	25 (32.47 %)	
57 - 60	10 (6.67 %)		2 (2.6 %)	8 (10.39 %)	
Gestational age		< 0.001			0.318[B]
$< 25^{+6/7}$	0 (0 %)		(0 %)	(0 %)	
$26^{+0/7}$ - $33^{+6/7}$	3 (2 %)		1 (1.3 %)	2 (2.6 %)	
$34^{+0/7}$ - $36^{+6/7}$	21 (14 %)		14 (18.18 %)	7 (9.09 %)	
$37^{+0/7}$ - $42^{+6/7}$	126 (84 %)		62 (80.52 %)	64 (83.12 %)	
APGAR		< 0.001			0.709[B]
0 - 3	3 (2 %)		1 (1.3 %)	2 (2.6 %)	
4 - 7	9 (6 %)		4 (5.19 %)	5 (6.49 %)	
8 - 10	138 (92 %)		72 (93.51 %)	66 (85.71 %)	

B Fisher's test.

Table 3
Reason for taking a karyograma.

Number (%)					
	Karyogram				
	Total	p	Pathologic	Physiologic	p
Reason for karyogram		< 0.001			< 0.001
Antimongoloid set eye slits, stigmata sy.Down	73 (48.67 %)		58 (75.32 %)	15 (19.48 %)	
Kidney disease	21 (14 %)		7 (9.09 %)	14 (18.18 %)	
Intestinal malformations	18 (12 %)		12 (15.58 %)	6 (7.79 %)	
Skeletal system	1 (0.67 %)		0 (0 %)	1 (1.3 %)	
Short and edematous limbs	27 (18 %)		13 (16.88 %)	14 (18.18 %)	
Malformations of the ear	12 (8 %)		5 (6.49 %)	7 (9.09 %)	
Nuchal fold	53 (35.33 %)		43 (55.84 %)	10 (12.99 %)	
Cleft palate	13 (8.67 %)		4 (5.19 %)	9 (11.69 %)	
Heart failure	64 (42.67 %)		40 (51.95 %)	24 (31.17 %)	
Dark scrotum, mobile testicles	22 (14.67 %)		7 (9.09 %)	15 (19.48 %)	
Thrombocytopenia	2 (1.33 %)		1 (1.3 %)	1 (1.3 %)	
Fingers crossed position	54 (36 %)		46 (59.74 %)	8 (10.39 %)	
Nervous system (small VF, accentuated sutures, convulsions)	39 (26 %)		16 (20.78 %)	23 (29.87 %)	

B Fisher's test.

to identify specific combinations of clinical signs, symptoms, or behavioral patterns indicative of genetic disorders. Clinical genetics involves the skillful visual recognition and comparison of features that aid in establishing an appropriate differential diagnosis. A congenital anomaly is defined as a structural, functional, or metabolic deviation from the normal developmental process that is present at birth [5]. Numerous genetic disorders contribute to neonatal morbidity and mortality during the neonatal period. Genomic medicine, which utilizes genomic information in clinical care, has the potential to significantly reduce morbidity and mortality in neonates and improve outcomes for this vulnerable population. Diagnostic genomic testing, particularly rapid testing in symptomatic newborns, has shown feasibility and clinical benefits, especially in the short term, as suggested by D'Gamma AM et al. [6]. Early diagnosis can facilitate timely prognostic counseling for families and enable precise care, ultimately improving outcomes, according to Carroll J et al. [7]. While technologies such as comparative genomic array hybridization (a-CGH) and next-generation sequencing (NGS or exome) have gained rapid adoption in the medical field, karyotyping has gradually lost its prominence among genetic tests [8]. The clinical presentation of genetic diseases can vary widely. Various malformations and congenital anomalies present either in utero or postpartum may raise suspicion for a genetic disorder. Thus, the clinical examination of the child is essential for diagnostics.

Signs of genetic disorders can often be indicated by various forms of facial dysmorphia. Although modern whole-exome analysis technologies may struggle to identify chromosomal translocations or inversions that sometimes affect the same gene, karyotyping remains a valuable tool in such cases, according to Pasquier L [8]. Throughout our 15-year study, we primarily conducted blood sampling for karyotyping due to indicators of Down syndrome, which accounted for 48.67 % (73/150) of the cases, with Down syndrome confirmed in 58 children. Down syndrome (DS) is the most common autosomal aneuploidy and the leading cause of intellectual disability of genetic origin worldwide, with a global prevalence ranging from 1 in 700 live births [9]. Research has consistently shown that the primary established risk factor associated with DS is maternal age over 35 years [9], a finding also supported by the Atlanta DS project [10]. However, in our study, maternal age did not yield statistically significant results. The relationship between DS and parental age has been the focus of extensive research globally, with epidemiological studies confirming this association [11–13]. While prenatal diagnosis for DS is accessible in our community, it appears that many mothers do not utilize these services due to cultural and religious considerations. Even when informed about carrying a child with DS, mothers in our community often choose to continue with the pregnancy. Additionally, improved medical care over the past two decades has positively influenced the outcomes for newborns with severe cardiac and other anomalies, leading to a greater acceptance of the choice to give birth despite potential health challenges. This reflects a strong religious perspective regarding unborn life, as noted by Šumanović-Glamuzina [14]. It is also worth mentioning that in recent years, there has been an increased registration of DS cases among younger mothers, possibly due to the selective nature of prenatal diagnostics, which often leads to the termination of affected pregnancies in older women. This trend is particularly evident in countries with higher economic standards. Although prenatal diagnostics (such as ultrasound, biochemical screening, fetal amniocentesis, and NIFTY—Non-Invasive Prenatal Testing) are available at SKB Mostar and in the surrounding region, cultural and religious frameworks often hinder their utilization [14]. The second most common reason for conducting blood samples for karyotyping was heart defects, which accounted for 42.67 % (64/150) of cases, with pathological karyotypes found in 51.95 % of these instances. A study conducted in Brazil by Trevison P et al. confirmed that chromosomal abnormalities are present in approximately one in ten patients with congenital heart defects [15]. These patients frequently exhibit associated extracardiac malformations, increasing the risk of morbidity and mortality, thereby complicating cardiac surgery. Despite significant advancements in cytogenetics over recent decades, karyotyping remains a crucial tool for evaluating patients with congenital heart disease. Comprehensive dysmorphological assessments are essential to determine the necessity for a karyotype [15]. Neonatologists and pediatric cardiologists must understand the implications of performing karyotyping for diagnosis, treatment, prognosis, and genetic counseling for patients and their families [16]. Parental age plays a significant role in reproductive outcomes, and this age has been steadily increasing for various reasons. In our study, maternal age was not statistically significant, while paternal age over 35 years showed significant differences at the 10 % significance level in karyotype findings. In this older paternal age group, pathological karyotype findings were 62.34 % more frequent than physiological findings. Generally, older parents have a considerable impact on the genetics and health of their offspring. Specifically, advanced parental age is associated with an increased risk of adverse neurodevelopmental outcomes in children, as noted by Chu B et al. [17]. The average age of fathers has risen significantly over the past decade, influenced by factors such as longer life expectancy, better access to contraception, and later marriage. Advanced paternal age has been linked to various conditions, including autism, schizophrenia, bipolar disorder, and pediatric leukemia [18]. Therefore, it is essential to inform infertile couples about the concerning correlations between older fathers and the increased risk of diseases in their children. Timely detection of latent genetic diseases and malformations, beyond those presenting as acutely endangered conditions, can facilitate the development of treatment principles and prevent the progression and irreversibility of certain conditions. Patients and their families should be allowed to make informed choices regarding genetic testing results to ensure holistic well-being—physically, mentally, and socially [19]. Through timely genetic diagnostics, we can potentially connect the pathogenetic mechanisms of various conditions arising from the same genetic alteration, thereby alerting families to possible future challenges in the life of their child and later as adults. There are ethical considerations and questions surrounding genetic counseling that warrant attention, alongside the overarching need for improved healthcare practices.

Conclusion

The increasing reproductive age of parents is a global trend observed in modern society over the past few decades. This shift impacts healthcare costs and underscores the necessity for further research, particularly due to the growing challenges associated with older parents and the potential implications for their offspring. In the conclusion of this fifteen-year study, we found that pathological karyotypes were present in slightly over 50 % of cases, and cytogenetic diagnostics confirmed clinical suspicions of Down syndrome that could often be identified through physical examination alone. This raises important questions about whether we have placed an unnecessary burden on the healthcare system for diagnosing conditions that are clinically evident. Geneticists play a crucial role in improving treatment outcomes through timely diagnosis and effective genetic counseling, as well as in implementing preventive measures for the development of genetic disorders. A collaborative approach involving healthcare professionals from various specialties is essential to address individual cases effectively. This interdisciplinary cooperation can offer support to families when they need it most, ensuring comprehensive care that encompasses not only medical needs but also emotional and social considerations. Overall, our findings emphasize the importance of karyotyping in the detection of genetic disorders and the need for continued investment in prenatal diagnostics and genetic counseling. As the landscape of reproductive medicine evolves, it is imperative that we remain attentive to the implications of parental age and the associated risks, while fostering an environment that supports informed decision-making for families. By enhancing our understanding of genetic conditions and their presentations, we can improve outcomes for both children and their families, ultimately contributing to better healthcare practices in our community.

Ethical approval and consent to participate

This retrospective study was conducted according to all the ethical principles of the University Clinical Hospital Mostar. Ethical Approval was obtained from the Ethics Committee of the Clinical Hospital Center Mostar (reference number 1384/23, dated 06/07/2023).

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Declaration of Competing Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and composition of the paper.

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Author contributions

Svjetlana Grubeša Raguž and all authors designed the research study. All authors read and approved the final manuscript.

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