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PERINATAL DETERMINANTS OF CARDIOVASCULAR PATHOLOGY IN CHILDREN WITH MINOR ANOMALIES OF CARDIAC DEVELOPMENT: A CLINICAL AND STATISTICAL STUDY

REFORMA DA LEI DE PROCESSO PENAL: CONTRA A DECISÃO PRÉ-JULGAMENTO DA INDONÉSIA

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Abstract
Objective: to assess the impact of perinatal factors and comorbid conditions on the development of cardiovascular pathology in children with minor anomalies of cardiac development (MACD). Materials and methods: a clinical and statistical examination of children with MACD and varying degrees of connective tissue dysplasia (CTD) was conducted using relative and attributable risk indicators. Results: maternal anemia, gestosis, infections, complicated delivery, and hereditary burden showed the strongest association with cardiovascular pathology. Conclusions: perinatal factors and comorbid diseases significantly increase the risk of cardiovascular pathology in children with MACD.

Keywords: Minor Anomalies of Cardiac Development. Connective Tissue Dysplasia. Perinatal Factors. Cardiovascular Pathology. Children.

Resumo
Objetivo: avaliar o impacto dos fatores perinatais e das comorbidades no desenvolvimento de patologias cardiovasculares em crianças com anomalias menores do desenvolvimento cardíaco (MACD). Materiais e métodos: foi realizado um exame clínico e estatístico de crianças com MACD e vários graus de displasia do tecido conjuntivo (CTD) utilizando indicadores de risco relativo e atribuível. Resultados: anemia materna, gestose, infecções, parto complicado e carga hereditária mostraram a associação mais forte com patologia cardiovascular. Conclusões: fatores perinatais e doenças comórbidas aumentam significativamente o risco de patologia cardiovascular em crianças com MACD.

Palavras-chave: *Anomalias Menores do Desenvolvimento Cardíaco. Displasia do Tecido Conjuntivo. Fatores Perinatais. Patologia Cardiovascular. Crianças.*

1 INTRODUCTION

Cardiovascular pathology in children with minor anomalies of cardiac development (MACD) remains a significant problem in modern pediatrics and

cardiology. Although MACD are not always accompanied by pronounced hemodynamic disorders. they are often associated with connective tissue dysplasia (CTD). which may aggravate the course of cardiovascular diseases and increase the risk of adverse outcomes in childhood [1].

Perinatal factors. including infectious processes during pregnancy. placental insufficiency. and genetic predisposition. influence the development of MACD and cardiovascular pathology in children [5]. Echocardiographic detection of MACD in children with CTD is important for early identification of structural anomalies and optimization of diagnostic and preventive strategies [3].

Studies by foreign authors demonstrate the significant role of perinatal factors and biomarkers in the development of cardiovascular disorders: the influence of perinatal conditions on vascular biophysical parameters in children is associated with a long-term risk of cardiovascular diseases [4]. This confirms the importance of investigating not only structural factors but also early perinatal risk markers.

Moreover. studies of functional and rhythm disturbances of the heart in the context of CTD reveal a complex morphological and mechanical basis of cardiac complications in patients with connective tissue dysplasia. highlighting the multisystem nature of the disorder and the need for in-depth clinical and statistical analysis [2. 6].

Despite the available studies. a comprehensive investigation of perinatal factors. obstetric history. and comorbidities in children with MACD against the background of CTD remains insufficiently explored. particularly with regard to the quantitative assessment of their association with cardiovascular pathology [3. 7]. This underscores the relevance and practical significance of the present study for clinical practice and further scientific research.

2 OBJECTIVE

To assess the impact of obstetric history. the course of pregnancy and delivery. and previous and concomitant diseases on the formation of cardiovascular pathology in children with minor anomalies of cardiac development.

3 MATERIALS AND METHODS

A clinical and statistical examination was conducted involving children divided into three groups depending on the presence and severity of connective tissue dysplasia and MACD. Data on maternal obstetric history. pregnancy and delivery course. perinatal development. and comorbid and previous diseases in children were analyzed.

Relative risk (RR) and attributable risk (AR) indicators were used to quantify the association between risk factors and cardiovascular pathology. Statistical analysis was performed using standard methods of variation statistics; differences were considered significant at $p<0.01$.

4 RESULTS AND DISCUSSION

As a risk factor for the development of various diseases in children. maternal obstetric history and the characteristics of pregnancy and delivery play a major role. The comparative characteristics of obstetric history in mothers of the three examined groups are presented in Table 1.

Table 1

Comparative characteristics of obstetric history of mothers in the examined groups of children (n=115)

Parameter	Group I (n=55)	Group II (n=40)	Group III (n=20)
Stillbirths (n=16)	14.5% (n=8)*	17.5% (n=7)**	5% (n=1)
Miscarriages (n=26)	29.1% (n=16)*	20% (n=8)**	10% (n=2)
Medical abortions (n=16)	12.7% (n=7)	17.5% (n=7)**	10% (n=2)
Intergenetic interval observed (n=71)	70.9% (n=39)*	57.5% (n=23)	45% (n=9)
Intergenetic interval not observed (n=44)	29.1% (n=16)	42.5% (n=17)	55% (n=11)
Gestational age. weeks	37.7±0.18	38.6±0.12	39.35±1.1
Mean maternal age. years	33.5±1.6	32.8±3.79	30.95±6.77

Note: * significant difference ($p<0.01$) between Group I and comparison group; ** significant difference between Group II and comparison group

An unfavorable obstetric history inevitably affected the course of pregnancy and delivery (Table 2).

Table 2

Comparative characteristics of the course of pregnancy and delivery depending on the severity of CTD in Group I (n=55)

Pathology of pregnancy and delivery	Grade I (n=26)	Grade II (n=24)	Grade III (n=5)
Diseases during pregnancy (n=20)	26.9% (n=7)*	41.6% (n=10)**	60% (n=3)
Medication use (n=37)	53.8% (n=14)*	79.1% (n=19)	80% (n=4)
Allergic manifestations (n=27)	46.1% (n=12)	50% (n=12)	60% (n=3)
Exacerbation of chronic pathology (n=21)	30.7% (n=8)*	41.6% (n=10)**	60% (n=3)
Threatened miscarriage (n=11)	15.4% (n=4)*	20.8% (n=5)**	40% (n=2)
Nephropathy of pregnancy (n=7)	7.7% (n=2)*	16.6% (n=4)**	20% (n=1)
Gestosis of pregnancy (n=20)	34.6% (n=9)	37.5% (n=9)	40% (n=2)
Anemia (n=41)	69.2% (n=18)*	79.1% (n=19)	80% (n=4)
Intrauterine hypoxia and birth asphyxia (n=9)	11.5% (n=3)*	16.6% (n=4)**	40% (n=2)
Birth trauma (n=5)	7.7% (n=2)*	8.3% (n=2)**	20% (n=1)
Rapid labor (n=7)	11.5% (n=3)*	12.5% (n=3)**	20% (n=1)

Note: * significant difference ($p<0.05$) between Grade I and Grade III CTD; ** significant difference between Grade II and Grade III CTD

Detailed analysis of anamnesis revealed that pregnancy in mothers of children in Group I was more often complicated by anemia. and the severity of anemia increased with the severity of CTD (69.2%–79.1%–80%). Acute infectious diseases were noted in 26.9%. 41.6%. and 60% of cases. respectively. Medication use depending on CTD severity was identified in 53.8%. 79.1%. and 80% of cases. while allergic manifestations were observed in 46.1%. 50%. and 60%. respectively. Complicated pregnancy was most frequently observed during the first trimester in the form of gestosis (34.6%–37.5%–40%). threatened miscarriage (15.4%–20.8%–40%). nephropathy (7.7%–16.6%–20%). and exacerbation of chronic diseases (30.7%–41.6%–60%).

It is precisely during this critical period of intrauterine development that intensive tissue differentiation and organ formation occur. including the mitral valve. The course

of labor was complicated by birth asphyxia in 11.5%–16.6%–40% of children depending on CTD severity. rapid labor in 11.5%–12.5%–20%. and birth trauma in 7.7%–8.3%–20%. A relationship was observed between the burden of pregnancy and delivery complications and the severity of CTD in both Groups I and II (Table 3).

Table 3

Comparative characteristics of the course of pregnancy and delivery depending on the severity of CTD in Group II (n=40)

Pathology of pregnancy and delivery	Grade I (n=14)	Grade II (n=19)	Grade III (n=7)
Acute infectious diseases during pregnancy (n=12)	21.4% (n=3)*	31.6% (n=6)**	42.8% (n=3)
Medication use (n=24)	42.8% (n=6)*	57.9% (n=11)	71.4% (n=5)
Allergic manifestations (n=15)	35.7% (n=5)	36.8% (n=7)	42.8% (n=3)
Exacerbation of chronic pathology (n=14)	28.6% (n=4)*	31.6% (n=6)*	57.1% (n=4)
Threatened miscarriage (n=9)	21.4% (n=3)*	21.1% (n=4)	28.6% (n=2)
Nephropathy of pregnancy (n=3)	0% (n=0)	5.3% (n=1)*	28.6% (n=2)
Gestosis of pregnancy (n=19)	42.8% (n=6)*	47.4% (n=9)	57.1% (n=4)
Anemia (n=28)	78.6% (n=11)*	68.4% (n=13)	57.1% (n=4)
Intrauterine hypoxia and birth asphyxia (n=7)	14.3% (n=2)	21.1% (n=4)	14.3% (n=1)
Birth trauma (n=3)	0% (n=0)	5.3% (n=1)**	28.6% (n=2)
Rapid labor (n=6)	7.1% (n=1)*	21.1% (n=4)	14.3% (n=1)

Note: * significant difference ($p<0.01$) between Grade I and Grade III CTD; ** significant difference ($p<0.05$) between Grade II and Grade III CTD

The burden of pregnancy and delivery in mothers of children in Group II and its association with the severity of connective tissue dysplasia (CTD) was similar to that observed in mothers of children in Group I; however. the proportion of pregnancy and delivery pathology in mothers of children in Group II was lower. A comparative characterization of the course of pregnancy and delivery in mothers across the three examined groups of children is presented in Table 4.

Table 4

Comparative characteristics of the course of pregnancy and delivery in the three examined groups of children (n=115)

Pathology of pregnancy and delivery	Group I (n=55)	Group II (n=40)	Group III (n=20)
Acute infectious diseases during pregnancy	36.3% (n=20)*	30% (n=12)**	10% (n=2)
Medication use	67.3% (n=37)*	60% (n=24)**	20% (n=4)
Allergic manifestations	49.1% (n=27)*	35% (n=14)	25% (n=5)
Exacerbation of chronic pathology	38.2% (n=21)	37.5% (n=15)	25% (n=5)
Threatened miscarriage	20% (n=11)*	22.5% (n=9)**	10% (n=2)
Nephropathy of pregnancy	12.7% (n=7)*	7.5% (n=3)**	0% (n=0)
Gestosis of pregnancy	36.4% (n=20)*	47.5% (n=19)**	30% (n=6)
Anemia	74.5% (n=41)*	70% (n=28)**	45% (n=9)
Intrauterine hypoxia and birth asphyxia	16.4% (n=9)*	17.5% (n=7)**	5% (n=1)
Birth trauma	9.1% (n=5)*	7.5% (n=3)**	5% (n=1)
Rapid labor	12.7% (n=7)*	15% (n=6)**	10% (n=2)

Note: * significant difference ($p<0.01$) between Group I and comparison group; ** significant difference between Group II and comparison group.

When comparing the course of pregnancy and delivery in the three examined groups. a significantly greater burden ($p < 0.01$) was observed in the group of patients with CTD and minor anomalies of cardiac development (MACD) compared with the control group. Exposure to damaging factors at any stage of pregnancy may lead to various developmental disorders. i.e.. connective tissue dysplasia of the heart. The emergence of a specific adaptive response in the fetus and newborn represents a “mirror” response to maternal reactions under the influence of various factors. forming a characteristic phenotypic stereotype in ontogenesis.

In order to determine the significance of risk factors for the development of MACD and cardiovascular pathology. we performed a quantitative assessment of the association between risk factors and the formation of CTD and cardiovascular pathology.

Attributable risk (AR) represents the proportion of disease risk that is associated with a given risk factor. explained by it. and potentially preventable if the factor is eliminated. It is expressed as a percentage or a relative value.

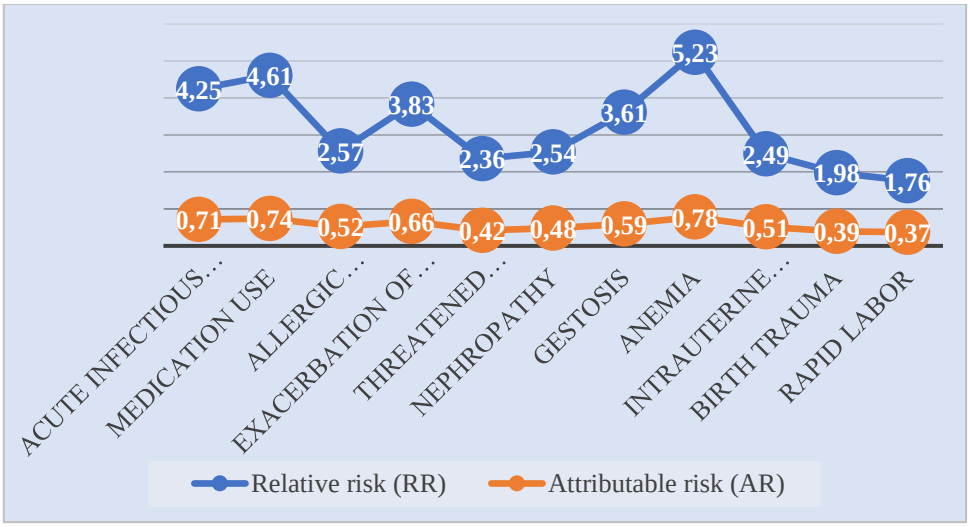
Relative risk (RR) is the ratio of the frequency of the observed outcome among exposed and unexposed individuals. RR reflects the strength of the association between exposure and disease. When $RR > 1$. the probability of an adverse outcome in the exposed

group is higher than when RR < 1. Analysis of the obtained data shows that the strength of the association between risk factors and cardiovascular pathology in children with MACD is particularly high for maternal anemia (RR = 5.23). medication use (RR = 4.61). acute infectious diseases during pregnancy (RR = 4.25). exacerbation of chronic pathology (RR = 3.83). and gestosis of pregnancy (RR = 3.61). A high probability of cardiovascular pathology formation was also observed in complicated deliveries: birth asphyxia (RR = 2.49). birth trauma (RR = 1.98). and rapid labor (RR = 1.76).

The quantitative assessment of the association between perinatal development characteristics and the formation of cardiovascular pathology in children with MACD is presented in Figure 1.

Figure 1

Quantitative assessment of the association between perinatal development characteristics and cardiovascular pathology formation in children with MACD



The influence of comorbid and previous diseases on the frequency of cardiovascular pathology development in children with MACD was determined using quantitative assessment (Table 5).

Table 5

Quantitative assessment of the association between previous and comorbid diseases and the formation of cardiovascular pathology in children with MACD

Risk factor	Attributable risk (AR)	Relative risk (RR)
Anemia	0.45	3.89
Frequent ARVI	0.52	4.71
Recurrent pneumonia	0.56	5.36
ENT pathology	0.43	3.85
Food and drug allergy	0.46	3.97
Family history of cardiovascular disease	0.81	7.59

As can be seen from the presented data. a close association was identified between comorbid conditions and the risk of developing cardiovascular pathology in children with MACD. In addition. we assessed the risk of cardiovascular pathology formation in children with MACD depending on hereditary background as well as past and concomitant diseases. The highest risk estimates were observed for a positive family history of cardiovascular diseases (RR = 7.59). recurrent pneumonia (RR = 5.36). food and drug allergies (RR = 3.97). anemia (RR = 3.89). pathology of ENT organs (RR = 3.85). and frequent ARVI (RR = 4.71).

Thus. the conducted study of risk factors for the development of cardiovascular pathology in children with MACD demonstrated that the most significant factors include a positive family history of cardiovascular disease. severe gestosis. nephropathy. anemia. and acute respiratory viral infections during pregnancy. Other important risk factors include complicated labor. birth asphyxia. and the presence of diseases in the child such as anemia. allergies. recurrent pneumonia. frequent ARVI. and ENT pathology.

5 CONCLUSIONS

Mothers of children with MACD and CTD significantly more often exhibit unfavorable obstetric history. as well as complicated pregnancy and delivery. The most significant perinatal risk factors for the development of cardiovascular pathology include maternal anemia. gestosis. nephropathy. ARVI and exacerbation of chronic diseases during pregnancy.

A substantial role in the development of cardiovascular pathology in children with MACD is played by complicated labor. birth asphyxia. and birth trauma. A high risk of cardiovascular pathology formation is also associated with a positive family history of cardiovascular disease. anemia. allergic disorders. recurrent pneumonia. frequent ARVI and ENT pathology in children.

The obtained data substantiate the need for early identification of high-risk groups and the implementation of preventive measures beginning from the perinatal period.

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Authors' Contribution

All authors contributed equally to the development of this article.

Data availability

All datasets relevant to this study's findings are fully available within the article.

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