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Analysing risk factors for foetal growth outcomes – the influence of maternal conditions and congenital cytomegalovirus infection

Analýza rizikových faktorov rastu plodu – vplyv maternálnych faktorov a kongenitálnej cytomegalovírusovej infekcie

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Summary: **Objective:** This study aimed to analyse the risk factors differentiating small for gestational age (SGA) and appropriate for gestational age (AGA) neonates. **Materials and methods:** A retrospective-prospective cohort study was conducted from 2019 to 2024 at the 2nd Department of Obstetrics and Gynaecology, University Hospital Bratislava. The study involved 174 term neonates from singleton pregnancies, including 125 SGA and 49 AGA infants. Various maternal, foetal, and placental risk factors were analysed, with a particular focus on congenital cytomegalovirus infection (cCMV). **Results:** Neonates' birth weights ranged from 1,480 to 4,470 grams. Of the risk factors assessed, only maternal COVID-19 infection during pregnancy was significantly associated with AGA outcomes (P = 0.009). No significant associations were found between common risk factors (e. g. hypertension, diabetes mellitus) and foetal growth restriction. Congenital CMV infection was not significantly associated with SGA. Logistic regression analysis confirmed the association of COVID-19 infection with foetal weight, while no significant effect was observed for CMV. **Conclusion:** Maternal COVID-19 infection was associated with AGA outcomes, potentially due to enhanced medical surveillance and immune responses. However, the study's small sample size limits the interpretation of these findings, and further research is required to fully understand the impacts of COVID-19 on pregnancy. No significant association between congenital CMV infection and foetal growth restriction was found in this cohort, which was most likely due to the low prevalence of cCMV. Moreover, documented risk factors for foetal growth restriction, including hypertension and diabetes mellitus, were not statistically significant in our study population.

Key words: foetal growth restriction – small for gestational age – risk factors – clinical characteristics – appropriate for gestational age – congenital cytomegalovirus infection – perinatal outcomes in COVID-19 pregnancies

Súhrn: **Cieľ:** Cieľom tejto štúdie bolo analyzovať rizikové faktory, ktoré sa odlišujú u novorodencov s nízkou pôrodnou hmotnosťou vzhľadom na gestačný vek (SGA – small for gestational age) a novorodencov s primeranou pôrodnou hmotnosťou vzhľadom na gestačný vek (AGA – appropriate for gestational age). **Materiály a metódy:** Retrospektívno-prospektívna kohortová štúdia bola realizovaná v rokoch 2019–2024 na II. gynekologicko-pôrodníckej klinike Univerzitnej nemocnice Bratislava. Do štúdie bolo zahrnutých 174 donosených novorodencov z jednoplodových tehotenstiev, z toho 125 novorodencov s nízkou pôrodnou hmotnosťou (SGA) a 49 novorodencov s primeranou pôrodnou hmotnosťou (AGA). Analyzované boli rôzne materské, fetálne a placentárne rizikové faktory, s osobitným zameraním na kongenitálnu cytomegalovírusovú infekciu (cCMV). **Výsledky:** Pôrodná hmotnosť novorodencov sa pohybovala v rozmedzí od 1 480 do 4 470 gramov. Z hodnotených rizikových faktorov bola významne asociovaná s AGA materská infekcia covidom-19 počas tehotenstva (p = 0,009). Nebola zistená štatisticky významná súvislosť medzi bežnými rizikovými faktormi (napr. hypertenzia, diabetes mellitus) a rastovou reštrikciou plodu. Kongenitálna CMV infekcia nebola významne spojená s SGA. Analýza pomocou logistickej regresie potvrdila asociáciu infekcie covidom-19 s pôrodnou hmotnosťou, zatiaľ čo pri CMV nebol pozorovaný žiadny významný vplyv. **Záver:** Materská infekcia covidom-19 bola asociovaná s primeranou pôrodnou hmotnosťou vzhľadom na gestačný vek, pravdepodobne v dôsledku zvýšeného lekárskeho dohľadu a imunitnej odpovede. Interpretácia týchto výsledkov je však obmedzená malou veľkosťou súboru, a preto je potrebný ďalší výskum na pochopenie vplyvu covidu-19 na tehotenstvo. V tejto kohorte nebola zistená významná súvislosť medzi kongenitálnou CMV infekciou a rastovou reštrikciou plodu, pravdepodobne v dôsledku nízkej prevalencie cCMV. Dokumentované rizikové faktory intrauterinná rastove reštrikcie, vrátane hypertenzie a diabetes mellitus, neboli v študovanej populácii štatisticky významné.

Kľúčové slová: intrauterinná rastová reštrikcia – nízka pôrodná hmotnosť vzhľadom na gestačný vek – rizikové faktory – klinické charakteristiky – primeraná pôrodná hmotnosť vzhľadom na gestačný vek – kongenitálna cytomegalovírusová infekcia – perinatálne výsledky tehotenstiev s covidom-19

Introduction

Foetal growth restriction (FGR) is defined as the inability of the foetus to reach its growth potential due to certain pathological factors, most often due to placental dysfunction. FGR is considered a leading cause of stillbirth, neonatal mortality, and morbidity [1]. Growth restriction during pregnancy poses a risk for the development of neurodevelopmental, cardiovascular, and metabolic disorders, as well as endocrine changes later in life. It is also associated with an increased risk of obesity and metabolic syndrome [2]. The overall incidence of FGR is estimated between three and nine percent of pregnancies in the developed world, and up to 25% of pregnancies in low- and middle-income countries [3,4].

Various maternal, foetal, and placental factors or conditions can impact growth regulation, potentially resulting in foetal growth restriction. In many instances, a clear cause of growth restriction may remain unidentified. Likewise, the presence of a risk factor does not necessarily indicate a direct causal relationship with growth limitation. Despite the varying pathophysiological mechanisms underlying these risk factors, they often converge on a common result: insufficient placental perfusion and inadequate foetal nutrition [5].

Maternal conditions such as hypertension, preeclampsia, diabetes mellitus, systemic lupus erythematosus, chronic renal failure, and antiphospholipid syndrome affect microcirculation and reduce foetal perfusion, leading to hypoxia and subsequently to FGR [6]. Moreover, the young and advanced maternal age, low socioeconomic status, and risk behaviour (smoking, alcohol consumption, and drug abuse) during pregnancy increase the risk of FGR. Placental insufficiency is a major contributor to FGR, affecting over 30% of all pregnancies. This condition is associated with a reduction in both the mass and functional capacity of the placenta. Neonates with FGR are found to have placentas that are slightly lighter and approximately 24% smaller in volume compared to those of healthy foetuses [7]. Furthermore, growth is influenced by foetal factors, such as chromosomal or structural anomalies, metabolic disorders, or foetal infections [8]. Cytomegalovirus infection (CMV) is the most common congenital infection, which is often asymptomatic [9]. Foetal growth can be impacted by placental damage, where viral infection disrupts its function, reducing the transfer of nutrients and oxygen to the foetus. Additionally, the direct effects of the virus on foetal tissues may cause inflammation and organ damage, impeding normal growth [10]. Neonates with congenital CMV infection are at risk not only of growth restriction and perinatal complications, but also of later outcomes such as hearing loss, vision impairment, and cognitive delays [11].

The aim of this study is to analyse the risk factors differentiating small for gestational age (SGA) and appropriate for gestational age (AGA) neonates. Knowledge of potential risk factors of FGR, as well as preventive strategies, maternal education, appropriate prenatal care, and early intervention can reduce the adverse outcomes associated with foetal growth restriction.

Materials and methods

Study design and patients

The retrospective-prospective cohort study was conducted at the 2nd Department of Obstetrics and Gynaecology, University Hospital in Bratislava between 2019 and 2024. Newborns from singleton pregnancies with a birth weight below the 10th percentile for their gestational age (SGA) were selected for the study. Fenton growth charts, stratified by sex, were used to assess percentiles [12]. Based on the calculated percentiles, newborns were classified as either SGA or AGA. In total, 125 cases of term SGA neonates were delivered, comprising of 65 males and 60 females. It should be noted that our study may also include constitutionally small foetuses that did not experience foetal growth restriction. A total of 49 healthy AGA patients born at the same time with the same gestational age were randomly included as the control group, comprising of 29 males and 20 females. Inclusion criteria for the study subjects included term neonates from singleton pregnancies, with a gestational age ranging from 37 to 42 weeks.

Data collection

Detailed medical history collection

A comprehensive medical history was obtained, focusing on risk factors that could influence foetal growth. We documented maternal internal and infectious diseases (such as anaemia, asthma, hypertension, preeclampsia, hypothyroidism, diabetes mellitus, overcoming COVID-19 infection during pregnancy), substance abuse (smoking, drug use), socioeconomic status, maternal age, and the use of assisted reproduction techniques.

Testing neonates for congenital cytomegalovirus (cCMV) infection

Neonates underwent a non-invasive saliva test within the first few days after birth to detect possible congenital CMV infection. PCR testing offers a rapid and effective method to identify asymptomatic newborns at risk.

Statistical analysis

Comparisons between groups were performed using the Chi-square test (χ^2). A multiple regression logistic model was realized to validate the independent association of confounding factors on SGA. Variables associated with SGA in the literature were included in the model. The following covariates were considered as possible confounders: hypertension including preeclampsia, asthma, anaemia, hypothyroidism, diabetes mellitus, overcoming COVID-19 infection during pregnancy, smoking, drug use, and the use of

Tab. 1. Clinical characteristics of the study group.
Tab. 1. Klinické charakteristiky študijnej skupiny.

Parameter	N = 174	Mean	Standard deviation	Min.	Max.
Birth weight (grams)	174	2,795	556	1,480	4,470
Gestational age	174	39.4	1.3	37.0	42.0
Weight to gestational age (percentile)	174	16.5	25.5	0.0	92.0
Birth length (cm)	174	47.8	2.6	40.0	54.0

N – number/počet

assisted reproduction techniques. These variables were included, and χ^2 for the odds ratios for each exposure level compared with the first exposure level was calculated.

Results

The study included 174 observations, demonstrating considerable variability in neonatal birth weights, which ranged from 1,480 grams to 4,470 grams. These values corresponded to the 0th to 92nd percentile of weight based on gestational age of the neonates in the reference population. Clinical characteristics of the patient cohort included in the study are detailed in Tab. 1.

In the initial step of our analysis, we assessed whether the distribution of individual risk factors between the SGA and AGA groups was random by applying the χ^2 statistical method (Tab. 2). The first three mentioned risk factors (drug use, smoking, anaemia) were present exclusively in the SGA group, making it statistically inappropriate to assess the presence of these risk factors using the χ^2 method. Of the remaining risk factors, only a history of COVID-19 infection during pregnancy was found to be statistically significant (P-value = 0.009) in the AGA group.

No statistically significant differences were found in the occurrence of other risk factors between the AGA and SGA groups.

One of the main objectives of the study was to investigate the presence of congenital CMV infection (cCMV). We hypothesized that some neonates within the SGA group might have low birth weight primarily due to an infectious cause. In the present study, we observed four positive CMV PCR results within our sample, with three instances occurring in the SGA group and one in the AGA group. In one CMV-positive case from the SGA group, the foetus was monitored for growth restriction prenatally. Prenatal ultrasound abnormalities of the central nervous system were also detected, including dilation of the right cerebral ventricle with septation and a mildly enlarged cisterna magna. However, the presence of congenital CMV was not confirmed to be a statistically significant risk factor for low birth weight. The distribution of cCMV within the observed sample was randomly allocated between the SGA and AGA groups (Tab. 3).

Tab. 2. Prevalence of risk factors in the respective groups.
Tab. 2. Prevalencia rizikových faktorov v príslušných skupinách.

Risk factor	SGA group N (%)	AGA group N (%)	P-value
Drug use	1 (0.8)	0	
Smoking	8 (6.4)	0	
Anemia	3 (2.4)	0	
Hypothyroidism	16 (12.8)	5 (10.2)	0.636
Hypertension and preeclampsia	16 (12.8)	3 (6.12)	0.204
Diabetes mellitus	13 (10.4)	9 (18.4)	0.155
Asthma	6 (4.8)	1 (2.0)	0.405
COVID-19	2 (1.6)	5 (10.2)	0.009
In vitro fertilization	6 (4.8)	3 (6.12)	0.723

AGA – appropriate for gestational age/primeraná pôrodná hmotnosť vzhľadom na gestačný vek, N – number/počet, SGA – small for gestational age/nízka pôrodná hmotnosť vzhľadom na gestačný vek

Tab. 3. Incidence of cCMV infection in SGA and AGA neonates.
Tab. 3. Výskyt cCMV infekcie u novorodencov SGA a AGA.

Risk factor	SGA group N (%)	AGA group N (%)	N
CMV nagative	122 (97.6)	48 (98)	170
CMV positive	3 (2.4)	1 (2)	4
Total	**125**	**49**	**174**

$\chi^2 = 0.0202$; P = 0.887
AGA – appropriate for gestational age/primeraná pôrodná hmotnosť vzhľadom na gestačný vek, cCMV – congenital cytomegalovirus/vrodenej cytomegalovírus, N – number/počet, SGA – small for gestational age/nízka pôrodná hmotnosť vzhľadom na gestačný vek

Tab. 4. Results of the logistic regression analysis.
Tab. 4. Výsledky logistickej regresnej analýzy.

Risk factor	Odds ratio	Std. err.	Z	P > |Z|	95% CI	
CMV	0.541	0.763	–0.44	0.663	0.034	8.581
Hypothyroidism	0.648	0.368	–0.76	0.446	0.213	1.975
Hypertension and preeclampsia	0.437	0.293	–1.23	0.218	0.117	1.630
Diabetes mellitus	1.970	0.967	1.38	0.167	0.753	5.158
Asthma	0.704	0.807	–0.31	0.759	0.074	6.653
COVID-19	6.642	5.947	2.11	0.034	1.149	38.405
Other infections	1.000	(omitted)				
Smoking	1.000	(omitted)				
Drug use	1.000	(omitted)				
Anemia	1.000	(omitted)				
Cons	0.442	0.097	–3.7	0	0.287	0.681

CMV – cytomegalovirus/cytomegalovírus, P – value/hodnota, Z – value/hodnota

Logistic regression analysis was used for the risk factor analysis. To evaluate the combined or cumulative impact of multiple factors (compounded effect), the odds ratio (OR) was calculated. OR was used to quantify the strength of the association between two variables. Results of the Chi-square test were confirmed. Only the occurrence of a COVID-19 infection during pregnancy showed a statistically significant effect on birth weight (Tab. 4).

Discussion

The unexpected association between maternal COVID-19 infection during pregnancy and AGA outcomes warrants further investigation. Previous studies have primarily highlighted the adverse effects of COVID-19, including an increased incidence of pregnancy-related complications and foetal growth restriction, which was often attributed to severe maternal inflammation or placental insufficiency [13,14]. However, our findings suggest a possible protective mechanism. It is possible that the experience of COVID-19 during pregnancy was associated with enhanced medical surveillance and healthcare, leading to early detection of potential complications. Moreover, the pandemic may have provided pregnant women with more opportunities for rest and reduced physical activity, potentially benefiting foetal development. Some studies indicate that mild or asymptomatic infections may not negatively affect foetal growth or birth weight [15], and could even trigger beneficial immune adaptations, such as increased immune cell frequency, offering protective effects. Furthermore, while infection triggers immune responses, there is evidence that these responses could positively influence placental function [16]. However, it is important to note that these potential benefits likely depend on the severity and timing of the infection.

Nevertheless, these findings are based on a small sample size, and our study did not account for the severity of COVID-19 infections among participants. Future studies with larger sample sizes, more detailed data on infection severity, and long-term follow-up are needed to better understand the potential impacts of COVID-19 on pregnancy outcomes.

In our study, no statistically significant association was found between common risk factors such as hypertension, preeclampsia, and diabetes mellitus, which are frequently linked to foetal growth restriction in the literature [17,18]. This lack of association may be due to several factors, including small sample size, which limits the statistical power needed to detect these associations. Additionally, the severity of conditions such as hypertension or diabetes was not controlled for, which could have influenced the outcomes. Anaemia and lifestyle factors, including smoking and drug use, were observed exclusively in the SGA group. This finding supports previous studies [19,20], which report similar associations.

Regarding CMV infection, our study did not find a statistically significant association with foetal growth restriction. CMV infection is, however, known to be associated with FGR in other studies [21]. The lack of association in our cohort may be due to the low incidence of CMV in our sample, as only four positive cases were identified.

A primary limitation of this study is its small sample size, which limits the strength of the conclusions. To gain a more comprehensive understanding of the relationship between maternal risk factors and foetal growth, larger and more diverse cohorts are essential. Future research should also explore maternal immune responses during infection and their potential effects on placental function, as this could offer valuable insights into developing strategies for the prevention and management of foetal growth restriction.

Conclusions

This study found that maternal COVID-19 infection was associated with AGA outcomes, which might be attributed to enhanced medical surveillance and immune responses. However, the small sample size and lack of data on the severity of infection limit the conclusions. Further studies are needed to fully clarify the effects of maternal COVID-19 infection on pregnancy outcomes. Additionally, no significant link was found between congenital CMV infection and foetal growth restriction, most likely due to the low prevalence of cCMV in our cohort. Furthermore, common risk factors for FGR, such as hypertension and diabetes mellitus, were not found to be statistically significant in our sample, possibly due to the small number of observations. Knowledge of potential risk factors of FGR, as well as preventive strategies, maternal education, appropriate prenatal care, and early intervention can reduce the adverse outcomes associated with foetal growth restriction.

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