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Factors associated with fetal growth restriction and small for gestational age newborns

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ABSTRACT

Objectives: To identify risk factors that contribute to the occurrence of fetal growth restriction (FGR) and small for gestational age (SGA) and quantify the strength of their impact.

Material and methods: This study was designed as a retrospective-prospective observational cohort study conducted on pregnant women at the Clinic for Gynecology and Obstetrics at the University Clinical Centre Kragujevac, Serbia. We measured the intrauterine degree of fetal development through the estimated fetal weight (EFW) on ultrasound examination, which was calculated using Hadlock's formula 3. Fetuses whose EFW was below the 10th percentile on the World Health Organization (WHO) fetal growth charts adjusted for gender and gestational age were classified as FGR fetuses, while newborns weighing less than the 10th percentile were considered SGA.

Results: The study included 320 pregnant women with an average age of 30.3 ± 5.5 years who gave birth to 332 newborns. The results of univariate and multivariate stepwise backward conditional binary logistic regression showed that the occurrence of FGR during the second trimester was more likely in pregnant women with lower body height and proteinuria. The risk factors for the occurrence of FGR during the third trimester were lower body height and proteinuria, while iron supplementation had a protective effect. SGA newborns were more common in pregnant women who were shorter, had proteinuria, used corticosteroids, or smoked during pregnancy.

Conclusions: Clinicians should pay special attention to pregnant women with lower body height, proteinuria, who smoke and use corticosteroids in order to prevent FGR and SGA.

Key words: fetal growth restriction; small for gestational age; estimated fetal weight; risk factors

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INTRODUCTION

Fetal growth restriction (FGR) refers to the slowing of the growth of a fetus whose growth potential exceeds its achieved growth [1]. FGR can occur at any time during pregnancy and is most commonly defined as a condition in which the estimated intrauterine fetal body weight is below the 10th percentile on the curve of predicted fetal body weight adjusted for gestational age and gender [2]. Newborns whose birth weight is less than the 10th percentile for gestational age and gender are marked as small for gestational age (SGA) [2]. FGR is an important clinical problem associated with many complications. FGR fetuses have a higher rate of neonatal mortality and morbidity compared to normally developing fetuses, as well as a higher risk of later metabolic, cardiovascular, cognitive, social, and behavioral problems [3].

Despite the development of ultrasound diagnostic methods that can be used for early detection of FGR, the results of previous studies indicate that in as many as 75% of cases, intrauterine FGR remains unrecognized until birth [4]. The FGR detection rate is even lower in low-risk pregnancies and is only 15% [5]. Therefore, risk factor assessment is a particularly important element of FGR screening. Several epidemiological and clinical studies that have detected a number

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of factors predisposing to FGR have been conducted so far. However, there are numerous controversies when it comes to the impact of certain risk factors on the occurrence of FGR, especially regarding the impact that chronic diseases of pregnant women and the use of medications for their treatment have on fetal development. The results of some authors have shown that chronic hypertension in pregnant women does not increase the risk of the occurrence of FGR [6]. Furthermore, calcium channel blockers have been identified as predictors of SGA in some studies [7], whereas no statistically significant association has been found between calcium channel blocker use during pregnancy and low birth weight infants in another study [8]. In light of these unknowns and the great clinical significance of the problem of FGR and SGA newborns, the aim of our study was to identify risk factors that contribute to the occurrence of FGR and SGA and quantify the strength of their impact.

MATERIAL AND METHODS

This study was designed as a retrospective-prospective observational cohort study. The study population consisted of pregnant women whose pregnancy was monitored at the Clinic for Gynecology and Obstetrics at the University Clinical Centre Kragujevac, Serbia. Pregnant women were included in the study based on voluntary consent by signing the form of informed consent. The Ethics Committee of the Clinical Centre Kragujevac had approved the study prior to its initiation.

Pregnant women were consecutively recruited during their visits to the Clinic for Gynecology and Obstetrics for pregnancy control and monitoring between September 29, 2020, and October 13, 2021. All pregnant women with pregnancies confirmed by a gynecology specialist (by biochemical and/or ultrasound examination) were taken into account, except pregnant women under the age of 18, functionally illiterate pregnant women, and those with a confirmed high risk of genetic abnormalities of the fetus (Down syndrome, Edwards syndrome, and other chromosomal aberrations of the fetus) by a combination of ultrasound and biochemical examination (double test) during the 12^{th} week of pregnancy. Also, pregnant women who gave birth to stillborn children were subsequently excluded.

The following data were collected from the medical files of pregnant women: age, place of living (urban or rural area), educational level, height, lifestyle habits during pregnancy (smoking, consumption of alcohol and psychoactive substances), presence of chronic and/or active diseases during pregnancy (anxiety, depression, varicose veins, myoma, diabetes mellitus, hyperinsulinemia, epilepsy, thrombophilia, thrombocytopenia, hypertension, proteinuria, tachycardia, anaemia, cystitis, colpitis, other infections, hypothyroidism, Hashimoto's thyroiditis, preeclampsia, asthma, chronic obstructive pulmonary disease, kidney disease, systemic lupus erythematosus, antiphospholipid syndrome), data on medications used by pregnant women during pregnancy (number of drugs including vitamins and minerals, number of drugs excluding vitamins and minerals, number of drugs from Food and Drug Administration (FDA) pregnancy categories A, B, C and D [9], the use of progesterone, insulins, oral antidiabetic agents, antiepileptic drugs, sedatives, antibiotic drugs, antifungal drugs, probiotics, calcium channel blockers, methyldopa, anticoagulant drugs, levothyroxine, corticosteroids, acetaminophen, aspirin, proton pump inhibitors, folic acid, vitamin B6, vitamin C, vitamin D, vitamin E, vitamin K, iron, magnesium, calcium, alpha lipoic acid), number of previous births, number of previous miscarriages, number of fetuses (singleton or multiple pregnancy), way of conception (natural conception or in vitro fertilization), presence of uterine or placental abnormalities. To assess the quality and diversity of pregnant women's nutrition, we used the Balkan Food Quality and Diversity in Pregnancy Questionnaire-18 (BFQDPQ-18) that pregnant women completed once during the second or third trimester of pregnancy [10].

Medical documentation was used to collect the following newborn data: gender, weight (g), length (cm), head circumference (cm), Apgar score at the first minute and time of delivery [11]. When it comes to the time of delivery, newborns were classified into one of five groups according to the American College of Obstetricians and Gynecologists recommendation [12]: premature newborns (born until 36 6/7 weeks of gestation), early term newborns (born from 37 0/7 weeks of gestation through 38 6/7 weeks of gestation), full term newborns (born from 39 0/7 weeks of gestation through 40 6/7 weeks of gestation), late term newborns (born from 41 0/7 weeks of gestation through 41 6/7 weeks of gestation) and postterm newborns (born from 42 0/7 weeks of gestation and beyond).

We used three dependent variables in our study. The first was the intrauterine degree of fetal development during the second trimester of pregnancy (14–26 weeks), the second was the intrauterine degree of fetal development during the third trimester of pregnancy (27–40 weeks), and the third was the degree of fetal development at birth. We measured the intrauterine degree of fetal development through the estimated fetal weight (EFW) on ultrasound examination. EFW was calculated after ultrasonic determination of values for AC, HC, FL and BPD using Hadlock's formula 3 [13]: EFW (g) = 10^(1.335 – 0.0034 × AC × FL + 0.0316 × BPD + 0.0457 × × AC + 0.1623 × FL). EFW and individual anatomical parameters of fetal development (AC, HC, BPD, and FL) were analyzed according to the World Health Organization (WHO) fetal growth charts adjusted to gestational age and fetal gender [14]. We also used percentile growth charts for multiple pregnancies in order to estimate the degree of fetal

development of the twins. Normal EFW, AC, HC, BPD, and FL values were considered between the 10th and 90th percentiles on the WHO fetal growth charts adjusted to gestational age and gender [2, 14]. Fetuses whose EFW was below the 10th percentile on the WHO fetal growth charts adjusted to gestational age in at least one point of observation during the second or third trimester were classified as FGR fetuses [2]. Newborns with a birth weight between the 10th and 90th percentiles on the WHO fetal growth charts adjusted to gestational age and gender were classified as normal, while newborns weighing less than the 10th percentile were considered SGA [2].

The baseline characteristics of the pregnant women and newborns were summarized by descriptive statistics. Means ± standard deviations were used for presenting continuous data and frequencies (percentages) for presenting categorical variables. The influence of independent variables on the dichotomous outcomes was tested using univariate and stepwise backwards conditional multivariate logistic regression analysis. The influence of potential risk factors on the outcome was assessed by their B coefficients in the regression equation, including 95% confidence intervals (CIs). Statistical significance was defined as a p value of 0.05. The results were shown as crude and adjusted odds ratios (ORs) with corresponding 95% CI.

RESULTS

Characteristics of pregnant women and newborns

The study included 320 pregnant women, whose characteristics are shown in Table 1. All pregnant women included in this study used folic acid supplements. The average number of drugs, including vitamins and minerals, taken by pregnant women in our study was 4.5 ± 3.3. On the other hand, pregnant women included in this study used an average of 2.2 ± 2.2 drugs excluding vitamins and minerals. When it comes to the safety of used medicines, at least 1 drug from the FDA categories A, B, C and D was used by 83 (25.9%), 220 (68.8%), 120 (37.5%) and 28 (8.8%) of our participants, respectively.

A total of 332 newborns (12 pairs of twins) were included in this study. Characteristics of newborns are shown in Table 2.

Risk factors for the occurrence of FGR in the second trimester of pregnancy

During the second trimester of pregnancy, EFW below the 10th percentile for the appropriate gestational age was detected at least at one point in 81 fetuses (24.4%), while 251 fetuses (75.6%) had EFW above the 10th percentile during this period of pregnancy. The results of both univariate and multivariate stepwise backward conditional binary logistic regression from the last step with satisfactory goodness of fit (Cox & Snell R square 0.057, Nagelkerke R2 0.085) with adjustment for potential confounders are shown in Table 3. After adjustment for potential confounders and other independent variables, it was shown that the occurrence of FGR during the second trimester was more likely in pregnant women with lower body height and proteinuria.

Risk factors for the occurrence of FGR in the third trimester of pregnancy

During the third trimester of pregnancy, EFW below the 10th percentile for the appropriate gestational age was detected at least at one point in 70 fetuses (21.1%), while 262 fetuses (78.9%) had EFW above the 10th percentile during the second trimester of pregnancy. The results of both univariate and multivariate stepwise backward conditional binary logistic regression from the last step with satisfactory goodness of fit (Cox & Snell R square 0.054, Nagelkerke R2 0.085) with adjustment for potential confounders are shown in Table 3. After adjustment for potential confounders and other independent variables, it was shown that the occurrence of FGR during the third trimester was more likely in pregnant women with lower body height and proteinuria, while iron supplementation was a protective factor for the occurrence of FGR in this period of pregnancy.

Risk factors for the occurrence of SGA

Two hundred and seventy-nine (84.0%) newborns in our study had normal weight at birth versus 53 newborns (16.0%) who were classified as SGA based on birth weight. The results of both univariate and multivariate stepwise backward conditional binary logistic regression from the last step with satisfactory goodness of fit (Cox & Snell R square 0.125, Nagelkerke R2 0.213) with adjustment for potential confounders are shown in Table 3. After adjustment for potential confounders and other independent variables, it was shown that the occurrence of SGA was more likely in pregnant women with lower body height, proteinuria, and those who use corticosteroids and smoke during pregnancy.

DISCUSSION

In our study, 24.4% and 21.1% of fetuses had FGR in the second and third trimesters, respectively, while 16.0% of newborns were classified as SGA. Significant risk factors associated with FGR or SGA in our study were lower body height (FGR during the second and third trimesters and SGA), smoking during pregnancy (SGA), proteinuria (FGR during the second and third trimesters and SGA), and use of corticosteroids (SGA), while iron supplementation was a protective factor for the occurrence of FGR during the third trimester.

Table 1. Demographic and clinical characteristics of pregnant women

Variable	Mean ± standard deviation (range) or number (%)
Age [years]	30.3 ± 5.5 (18–46)
Place of living	
Urban areas	227 (70.9%)
Rural areas	90 (28.1%)
Missing data	3 (0.9%)
Educational level	
Primary school	17 (5.3%)
Secondary school	160 (50.0%)
Higher educational level	139 (43.5%)
Missing data	4 (1.3%)
Body height [cm]	168.1 ± 6.9
Any smoking during pregnancy	64 (20.0%)
Consumption of alcohol during pregnancy	2 (0.6%)
In vitro fertilization	16 (5.0%)
Number of fetuses	
Singleton pregnancy	308 (92.8%)
Twin pregnancy	12 (7.2%)
History of births	
Primigravida	191 (59.7%)
1 previous birth	82 (25.6%)
2 previous births	32 (10.0%)
≥ 3 previous births	15 (4.7%)
History of miscarriages	
Without previous miscarriages	248 (77.5%)
1 previous miscarriage	54 (16.9%)
≥ 2 previous miscarriages	18 (5.7%)
Threatened premature labor	21 (6.5%)
Preterm premature rupture of the membranes	3 (0.9%)
Uterine or placental abnormalities	14 (4.4%)
Amniotic fluid problems	
Oligohydramnios	10 (3.1%)
Polyhydramnios	8 (2.5%)

Table 1. cont. Demographic and clinical characteristics of pregnant women

Variable	Mean ± standard deviation (range) or number (%)
Presence of acute or chronic non-gynecological disease during pregnancy	
Yes	241 (75.3%)
No	79 (24.7%)
Obesity	46 (14.3%)
Varicose veins	14 (4.4%)
Diabetes mellitus	36 (11.3%)
Hyperinsulinemia	7 (2.2%)
Epilepsy	5 (1.6%)
Thrombophilia	71 (22.2%)
Thrombocytopenia	5 (1.6%)
Hypertension	59 (18.4%)
Proteinuria	34 (10.6%)
Tachycardia	18 (5.6%)
Anaemia	39 (12.2%)
Cystitis	18 (5.6%)
Colpitis	61 (19.1%)
Other infections	46 (14.4%)
Hypothyroidism	31 (9.7%)
Hashimoto's thyroiditis	4 (1.3%)
Preeclampsia	4 (1.3%)
The most commonly used drugs	
Antibiotic drugs	111 (34.7%)
Progesterone	90 (28.1%)
Anticoagulant drugs	77 (24.1%)
Calcium channel blockers	56 (17.5%)
Antifungal drugs	53 (16.6%)
Methyldopa	51 (15.9%)
Corticosteroids	38 (11.9%)
The most commonly used vitamins and minerals	
Folic acid	320 (100%)
Vitamin C	73 (22.8%)
Iron	112 (35.0%)
Magnesium	67 (20.9%)

It is estimated that from 3% to 9% of pregnancies in the developed world and up to 25% of pregnancies in low- and middle-income countries are affected by FGR [15]. These percentages are similar to those identified in our study. However, it should be noted that the overall incidence of FGR and SGA depends on the definition used as well as on the population being evaluated [15].

Shorter maternal height was associated with an increased risk of FGR in the second and third trimesters and SGA, which is consistent with the findings of previous studies [14, 16]. This association is likely a consequence of a combination of increased risk of cephalo-pelvic disproportion and a possible indicator of poor supply of nutrients to the fetus due to chronic maternal malnutrition [16, 17].

Maternal smoking during pregnancy significantly increased the odds of SGA, which is consistent with the conclusions of the meta-analysis by Philips et al. [18] who found that children of mothers who continued smoking during pregnancy had a higher risk of SGA. They also found that a reduction in the number of cigarettes from the first to third trimester

Table 2. Characteristics of newborns

Variable	Frequency (%) or mean ± standard deviation (range)
Gender	
Male	181 (54.5%)
Female	151 (45.5%)
Time of delivery [12]	
Premature (until 36 6/7 weeks of gestation)	60 (18.1%)
Early term (from 37 0/7 weeks of gestation through 38 6/7 weeks of gestation	88 (26.5%)
Full term (from 39 0/7 weeks of gestation through 40 6/7 weeks of gestation)	151 (45.5%)
Late term (from 41 0/7 weeks of gestation through 41 6/7 weeks of gestation)	30 (9.0%)
Postterm (from 42 0/7 weeks of gestation and beyond)	3 (0.9%)
Apgar score	
10	39 (11.7%)
9	219 (65.8%)
8	52 (15.7%)
≤ 7	22 (6.6%)
Weight of newborns at birth [g]	
Normal birth weight group (n = 279)	3386.9 ± 581.1 (990–4790)
SGA group (n = 53)	2335.8 ± 470.5 (1180–3140)
Length of newborns at birth [cm]	
Normal birth weight group (n = 279)	49.4 ± 2.9 (35–59)
SGA group (n = 53)	44.8 ± 3.3 (35–50)
Head circumference at birth [cm]	
Normal birth weight group (n = 279)	34.6 ± 1.9 (25–39)
SGA group (n = 53)	32.5 ± 1.8 (25–36)

SGA — small for gestational age

lowered the risk of SGA, but that risk was still elevated compared with children born to nonsmoking mothers [18]. Tobacco smoke consists of several thousand chemicals, including numerous toxic substances that exacerbate oxidative stress and inflammation, which can harm placental development and/or be passed through the placenta to the fetus [19]. In addition, there is growing evidence that supports a gene–environment interaction where women having polymorphisms in genes encoding proteins involved in toxin metabolism are at increased risk for having infants with SGA [20].

We have found that proteinuria increased the risk of FGR during the second and third trimesters and SGA. Previous studies have also found that proteinuria noted in early pregnancy independently elevates the risk of fetal growth compromise [21] as well as that women with random proteinuria have a significantly higher incidence of intrauterine growth restriction [22]. Also, women with gestational hypertension with proteinuria are more likely to have infants with SGA [23]. Women with proteinuria also tend to have lower serum albumin values, lower estimated glomerular filtration rates, and a higher incidence of hematuria, which could explain poor fetal outcomes [22].

The use of corticosteroids, which are well-known to inhibit cell growth and DNA replication [24], was associated with SGA in our study. Other studies have also observed that infants who were exposed to antenatal corticosteroids were more likely to be SGA [25], while a randomized trial of single versus serial courses of antenatal corticosteroids found a reduction in birth weight and an increase in the number of infants who were SGA, especially after four courses of corticosteroids [26]. In addition, the summary of product characteristics of corticosteroids also warns that they may increase the risk of intra-uterine growth retardation when administered for prolonged periods or repeatedly during pregnancy, as well as that they should only be prescribed when the benefits to the mother and child outweigh the risks [27].

The only protective factor for the occurrence of FGR during the third trimester in our study was iron supplementation. Iron is an important micronutrient in pregnancy because of its role in the growth, haematopoiesis, and development of the fetus [28]. Previous studies have also confirmed that iron supplements have a protective effect against SGA, even in women without anemia [28, 29]. However, there are

Table 3. Crude and adjusted odds ratios (OR) of the risk factors for fetal growth restriction (FGR) and small for gestational age (SGA)

	FGR in the second trimester		FGR in the third trimester		SGA	
Risk factors	**Univariate model Crude OR with 95% CI p**	**Multivariate model Adjusted[#] OR with 95% CI p**	**Univariate model Crude OR with 95% CI p**	**Multivariate model Adjusted[##] OR with 95% CI p**	**Univariate model Crude OR with 95% CI p**	**Multivariate model Adjusted[###] OR with 95% CI p**
Age	0.943 (0.900–0.989) p = 0.014*	0.954 (0.909–1.002) p = 0.061	0.969 (0.924–1.017) p = 0.203	–	0.983 (0.932–1.036) p = 0.520	–
Height	0.935 (0.898–0.973) p = 0.001*	0.934 (0.897–0.972) p = 0.001*	0.936 (0.898–0.976) p = 0.002*	0.932 (0.893–0.972) p = 0.001*	0.942 (0.899–0.986) p = 0.010*	0.904 (0.856–0.954) p = 0.000*
Threatened premature labor	0.715 (0.233–2.190) p = 0.557	–	1.544 (0.576–4.137) p = 0.388	–	0.537 (0.121–2.375) p = 0.412	0.247 (0.047–1.297) p = 0.098
Smoking	0.810 (0.429–1.529) p = 0.515	–	1.398 (0.755–2.588) p = 0.286	–	2.245 (1.180–4.272) p = 0.014*	2.361 (1.104–5.048) p = 0.027*
Hypertension	1.041 (0.554–1.957) p = 0.901	–	1.186 (0.619–2.271) p = 0.608	–	2.331 (1.209–4.494) p = 0.012*	–
Proteinuria	1.728 (0.839–3.561) p = 0.138	2.132 (1.006–4.522) p = 0.048*	1.878 (0.894–3.944) p = 0.096	2.271 (1.044–4.937) p = 0.039*	3.302 (1.562–6.980) p = 0.002*	3.688 (1.576–8.632) p = 0.003*
Diabetes mellitus	/	/	/	/	0.609 (0.206–1.796) p = 0.368	–
Thrombophilia	/	/	/	/	1.441 (0.743–2.794) p = 0.280	–
Anaemia	/	/	/	/	1.134 (0.473–2.719) p = 0.777	–
Cystitis	/	/	/	/	1.545 (0.488–4.891) p = 0.459	–
Colpitis	/	/	/	/	0.833 (0.384–1.809) p = 0.644	–
Other infections	/	/	/	/	1.967 (0.946–4.092) p = 0.070	–
Number of drugs without vitamins and minerals	1.009 (0.902–1.130) p = 0.873	–	0.950 (0.839–1.075) p = 0.417	–	1.140 (1.108–1.290) p = 0.037*	–
Number of drugs from FDA B category	/	/	/	/	1.264 (1.014–1.576) p = 0.037*	–
Number of drugs from FDA C category	/	/	/	/	1.494 (1.091–2.046) p = 0.012*	–
Number of drugs from FDA D category	/	/	/	/	2.464 (1.150–5.279) p = 0.020*	–

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Table 3. cont. Crude and adjusted odds ratios (OR) of the risk factors for fetal growth restriction (FGR) and small for gestational age (SGA)

	FGR in the second trimester		FGR in the third trimester		SGA	
Risk factors	**Univariate model Crude OR with 95% CI p**	**Multivariate model Adjusted[#] OR with 95% CI p**	**Univariate model Crude OR with 95% CI p**	**Multivariate model Adjusted[##] OR with 95% CI p**	**Univariate model Crude OR with 95% CI p**	**Multivariate model Adjusted[###] OR with 95% CI p**
Progesterone	0.880 (0.506–1.528) p = 0.649	–	0.818 (0.454–1.472) p = 0.503	–	1.797 (0.981–3.291) p = 0.058	–
Calcium channel blockers	1.308 (0.707–2.420) p = 0.392	–	1.355 (0.714–2.573) p = 0.352	–	2.135 (1.098–4.151) p = 0.025*	–
Methyldopa	0.979(0.496–1.935) p = 0.952	–	1.229 (0.618–2.447) p = 0.557	–	2.145 (1.069–4.304) p = 0.032*	–
Antibiotic drugs	/	/	/	/	1.682 (0.927–3.052) p = 0.087	–
Corticosteroids	/	/	/	/	3.350 (1.617–6.941) p = 0.001*	2.626 (1.025–6.728) p = 0.044*
Number of previous births	1.080 (0.825–1.414) p = 0.574	–	0.951 (0.706–1.281) p = 0.741	–	0.898 (0.637–1.265) p = 0.538	–
Number of previous miscarriages	0.993 (0.663–1.490) p = 0.975	–	1.101 (0.731–1.660) p = 0.645	–	1.070 (0.676–1.694) p = 0.773	–
Twin pregnancy	1.610 (0.662–3.913) p = 0.294	–	0.984 (0.354–2.735) p = 0.975	–	2.345 (0.921–5.970) p = 0.074	-
In vitro fertilization	0.817 (0.263–2.537) p = 0.727	–	1.263 (0.440–3.629) p = 0.665	–	1.972 (0.679–5.728) p = 0.212	–
Iron supplementation	0.945 (0.559–1.599) p = 0.833	–	0.561 (0.311–1.013) p = 0.055	0.540 (0.291–0.994) p = 0.049*	0.604 (0.313–1.165) p = 0.133	–
Uterine or placental abnormalities	0.228 (0.029–1.770) p = 0.157	–	1.018 (0.276–3.752) p = 0.979	–	3.113 (1.000–9.692) p = 0.050	–
Quality and diversity of nutrition	1.012 (0.987–1.036) p = 0.350	–	1.006 (0.982–1.031) p = 0.620	–	0.994 (0.969–1.020) p = 0.650	–
Preterm delivery	/	/	/	/	3.339 (2.737–6.419) p = 0.000*	–

* — statistically significant; # — adjusted for age, threatened premature labor, smoking, number of previous births, number of previous miscarriages, in vitro fertilization, iron supplementation, uterine or placental abnormalities, twin pregnancies and quality and diversity of nutrition; ## — adjusted for age, threatened premature labor, smoking, hypertension, number of previous births, number of previous miscarriages, in vitro fertilization, twin pregnancy, uterine or placental abnormalities and quality and diversity of nutrition; ### — adjusted for age, threatened premature labor, number of drugs without vitamins and minerals, number of previous births, number of previous miscarriages, uterine or placental abnormalities, quality and diversity of nutrition and iron supplementation; (/) — slashes indicate variables that were not entered into a model; (–) — dashes indicate variables that were not entered into the final multivariate models; CI — confidence interval; p — statistical significance

also studies that didn't find any association between iron supplementation and SGA [30, 31].

Given that FGR can cause severe neonatal and postnatal complications, the Polish Society of Gynecologists and Obstetricians (PSOGO) advises assessing the risk factors for FGR at the beginning of pregnancy as well as at each visit to the gynecologist [32]. According to the PSOGO, we need to distinguish between early-onset FGR (before 32 weeks of gestation) and late-onset FGR (after 32 weeks of gestation) [32]. Early-onset FGR is characterized by more frequent absence of end-diastolic flow in the umbilical cord, which, in addition to the suspicious CTG recording, reduction of fetal movements, oligohydroamnion, vaginal bleeding, and abnormal biophysical profile, is an indication for hospitalization of pregnant women [32]. In pregnant women with FGR and an indication for termination of pregnancy after the 37th week of gestation, PSOGO advises a vaginal delivery with cardiotocographic monitoring, while a caesarean section is indicated for the breech position of the fetus [32].

Our study has some limitations that need to be considered. First, the study was unicentric, which may limit the generalizability of the findings. Second, we were unable to collect data for some potentially important variables, such as information about testing for TORCH infections (toxoplasmosis; other — parvovirus B19, varicella-zoster virus, syphilis, *hepatitis B*; rubella virus; cytomegalovirus; *herpes simplex virus*) and maternal serum markers (e.g., pregnancy associated plasma protein A, placental growth factor). Another significant limitation of our study is related to the fact that we used only the definition of the American College of Obstetricians and Gynecologists' Committee for FGR and SGA [2]. We did not consider other definitions of FGR and SGA, such as the definitions proposed by Beune et al. [33], so it is not excluded that some other risk factors for the occurrence of FGR and SGA would be detected if these definitions were applied. Finally, for technical reasons, we did not examine the influence of biochemical parameters of preeclampsia as potential risk factors for FGR and SGA that have been routinely used in clinical practice in recent years [34].

CONCLUSIONS

Clinicians should pay special attention to pregnant women with lower body height, and proteinuria, who smoke and use corticosteroids in order to prevent FGR and SGA. Identified risk factors can be implemented in clinical practice as an important additional element of screening for impaired fetal growth. These predictors can contribute to timely recognition of pregnancies accompanied by inadequate fetal growth, adequate care of such pregnant women, and prevention of somatic complications and intellectual and cognitive impairment occurring in infants with low body weight and anthropometric measures at birth. In line with the current guidelines, it is recommended to assess risk factors for growth restriction in every woman at the beginning of pregnancy and at each subsequent visit [32].

Article information and declarations

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Conflict of interest

The authors declare no conflict of interest.

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