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# FREQUENCY AND ASSOCIATION OF THE FACTORS INFLUENCING FETAL GROWTH RESTRICTION IN THE REPUBLIC OF KAZAKHSTAN

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**Summary**

**Introduction:** A fetus with fetal growth restriction (FGR), characterized by not reaching its intrauterine growth potential as a result of multiple risk factors, is prone to high morbidity and mortality compared to healthy infants.

**The aim** of the present study was to evaluate the influence of risk factors hypothesized to negatively affect FGR.

**Materials and Methods:** The design of this study was a retrospective study, occurring between 1 January 2016 and 31 December 2021. The Inclusion criteria: the presence of ultrasound screening of the first trimester of pregnancy at 10-14 weeks, single pregnancy, pregnancy between 22 and 42 weeks gestation. The exclusion criteria included multiple pregnancies, pregnancies complicated by neonatal chromosomal or structural anomalies of the fetus.

*Statistical analysis.* All variables were examined to determine whether they were normally distributed. Descriptive statistics included median (Q1 – Q3) for the continuous non-normally distributed variables. Results were compared between newborns with FGR and without FGR. The Mann-Whitney test was used between two groups to compare the means of non-normally variables. The $\chi 2$ test was performed for comparing differences in categorical variables between groups. All confidence intervals (CI) were 95%. Statistical significance was defined as $p<0.05$ for a single test.

**Results:** In this study, 3211 girls and 3336 boys were born, out of which 85 girls and 75 boys had FGR. 6355 newborns were born alive and 192 newborns were stillborn, of which 136 newborns with FGR were born alive and 24 newborns with FGR were stillborn ($p = 0.001$). Pregnancies with pre-eclampsia had significantly higher odds of developing FGR than pregnancies without pre-eclampsia ($p < 0.001$). Placental abruption of normally located placenta; Disorder of maternal-placental blood flow according to Doppler results; fetal distress and oligohydramnios were more common in newborns with FGR than newborns without FGR ($p < 0.001$). Umbilical cord anomaly in this pregnancy, newborns with FGR occurred more frequently compared to newborns without umbilical cord anomaly ($p = 0.029$). Low-lying placenta and complete placenta previa according to the ultrasound scan were more common in newborns with FGR compared to newborns without FGR ($p = 0.006$) and ($p = 0.001$), respectively.

**Conclusions:** In our study, FGR was more common in pregnant women with AH, cardiac rhythm disturbance, pulmonary and bronchial diseases and syphilis than in pregnant women without these diseases. FGR was associated with pre-eclampsia, presence of uterine scar, HELLP, placental abruption of a normally located placenta, disorder of maternal-placental blood flow according to Doppler results, oligohydramnios, fetal distress, umbilical cord anomalies, Low-lying placenta and complete placenta previa according to the ultrasound scan.

***Keywords:*** *Fetal growth restriction, maternal and perinatal risk factors, perinatal outcomes, low fetal weight.*

**Резюме**

# ЧАСТОТА И АССОЦИАЦИЯ ФАКТОРОВ, ВЛИЯЮЩИХ НА ЗАДЕРЖКУ РОСТА ПЛОДА В РЕСПУБЛИКЕ КАЗАХСТАН

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**Введение:** Плод с задержкой роста плода (ЗВУР), характеризуется тем, что не достиг потенциала своего внутриутробного роста в результате влияния множества факторов риска, подвержен высокой заболеваемости и смертности по сравнению со здоровыми младенцами.

**Цель:** Целью настоящего исследования было оценить влияние факторов риска, которые, согласно гипотезе, могут негативно влиять на ЗВУР.

**Материалы и методы:** Ретроспективное исследование, проведенное в период с 1 января 2016 года по 31 декабря 2021 года. *Критерии включения:* наличие ультразвукового скрининга первого триместра беременности на сроке 10-14 недель, одноплодная беременность, беременность в сроке от 22 до 42 недель гестации. Критерии исключения: многоплодная беременность, беременность, осложненная хромосомными или структурными аномалиями плода. *Статистический анализ.* Все переменные были исследованы на предмет их нормального распределения. Описательная статистика включала медиану (Q1 - Q3) для непрерывных ненормально распределенных переменных. Результаты сравнивали между новорожденными с ЗВУР и без ЗВУР. Для сравнения средних ненормально распределенных переменных между двумя группами использовался тест Манна-Уитни. Для сравнения различий категориальных переменных между группами использовался тест $\chi 2$. Все доверительные интервалы (ДИ) составляли 95%. Статистическая значимость определялась как $p<0,05$ для одного теста.

**Результаты:** В этом исследовании родилось 3211 девочек и 3336 мальчиков, из которых 85 девочек и 75 мальчиков имели ЗВУР. 6355 новорожденных родились живыми и 192 - мертворожденными, из них 136 новорожденных с ЗВУР родились живыми и 24 новорожденных со ЗВУР - мертворожденными ($p = 0,001$). У беременных с преэклампсией вероятность развития ЗВУР была значительно выше, чем у беременных без преэклампсии ($p <0,001$). Преждевременная отслойка нормально расположенной плаценты, нарушение маточно-плацентарного кровотока по данным допплерографии; дистресс плода и маловодие чаще встречались у новорожденных с ЗВУР, чем у новорожденных без ЗВУР ($p <0,001$). Патология пуповины при данной беременности у новорожденных со ЗВУР встречалась чаще по сравнению с новорожденными без аномалии ($p = 0,029$). Аномалии прикрепления плаценты, по данным УЗИ, чаще встречались у новорожденных со ЗВУР по сравнению с новорожденными без ЗВУР ($p = 0,006$) и ($p = 0,001$), соответственно.

**Выводы:** В нашем исследовании ЗВУР чаще встречалась у беременных с АГ, нарушениями сердечного ритма, заболеваниями легких и бронхов, сифилисом, чем у беременных без этих заболеваний. Также определена ассоциация с преэклампсией, наличием рубца на матке, HELLP, преждевременно отслойкой нормально расположенной плаценты, нарушением маточно-плацентарного кровотока по данным допплерографии, маловодием, дистрессом плода, аномалиями пуповины, низко расположенной плацентой и полным предлежанием плаценты по данным УЗИ.

***Ключевые слова:*** *нарушения роста плода, материнские и перинатальные факторы риска, перинатальные исходы, низкая масса плода.*

**Түйіндеме**

# ҚАЗАҚСТАН РЕСПУБЛИКАСЫНДА ҰРЫҚТЫҢ ДАМУЫНЫҢ ТЕЖЕЛУІНЕ ӘСЕР ЕТЕТІН ФАКТОРЛАРДЫҢ ЖИІЛІГІ МЕН АССОЦИАЦИЯСЫ

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**Кіріспе:** Ұрық дамуының тежелуі (ҰДТ) көптеген қауіп факторлар әсерінің нәтижесінде өзінің құрсақішілік потенциалына жетпеуімен, сау нәрестелермен салыстырғанда аурушаңдық пен өлімге аса бейімділігімен сипатталады.

**Мақсаты:** Біздің зерттеудің мақсаты – гипотезаға сәйкес ҰДТ негативті әсер ететін қауіп факторлардың әсерін бағалау.

**Материалдар мен тәсілдер**: Осы зерттеудің дизайны – 2016 жылдың 1 қаңтарынан 2021 жылдың 31 желтоқсанына дейін өткен ретроспективті зерттеу. Зерттеуге қосу критерийлері: жүктіліктің алғашқы үш айында 10-14 апта мерзімдегі УДЗ скрининг болуы, жүктіліктің асқынбаған ағымы, бір ұрықты жүктілік. Зерттеуге қоспау критерийлері: көп ұрықты жүктілік, ұрықтың жамбаспен орналасуы, ұрықтың дұрыс емес жағдайда орналасуы (көлденең, қиғаш), ұрықтың салмағы 2500 грамм дейін немесе 4000 граммнан жоғары, уақытынан ерте босану, гипертензиялық жағдайлар, ұрықтың антенаталды өлуі, ұрықтың жатырішілік ақаулары, қағанақ суының көптігі, қағанақ суының аздығы, экстрагениталды патология.

*Статистикалық анализ.* Барлық айналмалар олардың қалыпты таралуына тексерілді. Суреттейтін статистика үздіксіз қалыпты емес таралған айналмалар үшін медианаңы (Q1 - Q3) қосты. Нәтижелерді ҰДТ бар және ҰДТ жоқ нәрестелер арасында салыстырылды. Қалыпты емес таралған айналмаларда орташа мәндерін салыстыру үшін екі топтың арасында Манна-Уитни тесті қолданылды. Топтар арасында категориялық айналмалар айырмашылықтарын салыстыру үшін χ2 қолданылды. Барлық сенімділік интервалдары (СИ) 95% құрады. Бір тест үшін статистикалық маңыздылық p<0,05 ретінде алынды.

**Нәтижелер:** Осы зерттеуге 3211 қыз бен 3336 ұл туды, оның ішінде 85 қыз бен 75 ұлдарда ҰДТ болған. 6355 нәресте тірі туған және 192 – өлі туған, оның ішінде ҰДТ бар 136 нәресте тірі туған, ал ҰДТ бар 24 нәресте – өлі туған (p = 0,001). Преэклампсиясы бар жүкті әйелдерде ҰДТ даму мүмкіндігі преэклампсиясы жоқ жүкті әйелдермен салыстырғанда анағұрлым жоғары болды (p<0,001). Қалыпты орналасқан планцентаның жыртылуы; допплерография мәліметтері бойынша ана-планценталық қанайналымның бұзылуы; ұрықтың дистрессі және олигогидрамниоз ҰДТ бар нәрестелерде ҰДТ жоқ нәрестелермен салыстырғанда жиі кездесті (p <0,001). Осы жүктілік кезіндегі кіндіктің аномалиясы бар нәрестелерде ҰДТ кіндіктің аномалисы жоқ нәрестелерге қарағанда жиі кездесті (p = 0,029). УДЗ бойынша төмен орналасқан плацента және плацентаның толық төмен орналасуы ҰДТ бар нәрестелерде ҰДТ жоқ нәрестелермен салыстырғанда жиі кездесті, сәйкесінше (p = 0,006) және (p = 0,001).

**Қорытынды:** Біздің зерттеуде ҰДТ АГ, жүрек ырғағының бұзылуы, өкпе мен бронх аурулары, мерез бар жүкті әйелдерде осы аурулары жоқ әйелдермен салыстырғанда жиі кездесті. ҰДТ преэклампсиямен, жатырдағы тыртықтың болуымен, HELLP-пен, қалыпты орналасқан планцентаның жыртылуымен, ана-планценталық қанайналымның бұзылуымен, олигогидрамниозбен, ұрықтың дистрессімен, кіндік аномалиясымен, УДЗ бойынша төмен орналасқан плацентамен және плацентаның толық төмен орналасуымен байланысты болды.

***Түйінді сөздер:*** *ұрық дамуының бұзылуы, жекеленген графиктер, аналық пен перинаталды қауіп факторалары, перинаталды нәтижелер, ұрықтың төмен салмағы.*

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**Introduction**

A fetus with fetal growth restriction (FGR), characterized by not reaching its intrauterine growth potential as a result of multiple risk factors, is prone to high morbidity and mortality compared to healthy infants [1]. Defining FGR as a fetal weight that is less than the 10th percentile for gestational age does not provide a way to account for the individual growth potential of each fetus [7]. Because it may not be detected in a timely manner in fetuses that have a weight greater than the 10th percentile, but it has also not realized its growth potential and conversely leads to over diagnosis of FGR in constitutionally small, healthy fetuses. Conversely, misdiagnosis of FGR for some constitutionally small fetuses may result [1]. The overall incidence of FGR ranges from 3% to 9% of pregnancies in the developed world and up to 25% of pregnancies in low- and middle-income countries [12]. The causes of FGR can be divided

into maternal (gestational diabetes mellitus (DM), renal failure, autoimmune disease, erythematous disease, cyanotic heart defects, pregnancy-related arterial hypertension (AH) (hypertension, gestational hypertension (GH) or pre-eclampsia), antiphospholipid syndrome, substance use and abuse, multiple pregnancies, exposure to teratogens, infectious diseases), fetal (genetic and structural disorders of the fetus) and placental factors (placental disorders and umbilical cord anomalies) [1].

The development of FGR in a healthy fetus is the result of the pathophysiological mechanism of placental insufficiency, where the fetus is unable to fulfill its internal growth potential due to impaired placental function [25, 34]. Placental insufficiency occurs most commonly due to poor remodelling of the uterine spiral arteries in early pregnancy, leading to hypoperfusion of maternal vessels, but there are many other types of causative placental damage as well [10]. High flow resistance in the fetoplacental circulation, reduced villous surface area (hypoplasia), secondary shear stress injury and placental infarcts reduce oxygen and nutrient delivery in maternal vascular malperfusion [34]. This all leads to impaired fetal development throughout pregnancy. During birth, the combination of uterine contractions and placental dysfunction leads to hypoxic shock and birth asphyxia of the fetus [12].

FGR is a major contributor to morbidity and mortality of perinatal age and increases the risk of long-term neurological and neurodevelopmental complications in the future [9, 17, 45]. Also, newborns with FGR have an increased risk of developing cardiovascular disease in adulthood [5, 28]. Fetal growth retardation is assessed by ultrasonography, which can deviate from birth weight by 20% in 95% of cases and in the remaining 5% of cases the deviation is even more than 20% [11, 15, 42]. When fetal ultrasound weight is below the 10th percentile of gestational age, evaluation of amniotic fluid and Doppler examination of umbilical artery blood flow are recommended [41]. Since the incidence of structural and genetic anomalies is high in fetuses with FGR, ultrasound examination of the fetal anatomy should be performed if it has not already been done [2]. Therefore, the aim of this study is to evaluate the influence of risk factors hypothesized to negatively affect FGR R.

**Materials and methods**

*Study population*

The retrospective data collection includes 6547 materials of the study were individual cards f No. 077/y, No. 111/y, birth histories f No. 096/y, 001/y, which were selected from women's consultations and maternity hospitals in Semey city and nearby settlements Zyryanovsk city, Astana city, Aksu city, Almaty city, Atyrau city, Republic of Kazakhstan occurring between 1 January 2016 and 31 December 2021. The consultations and maternity hospitals serve a population of similar ethnic and social background and have similar clinical management standards for pregnant women.

The Inclusion criteria: the presence of ultrasound screening of the first trimester of pregnancy at 10-14 weeks, single pregnancy, pregnancy between 22 and 42 weeks gestation. The exclusion criteria included multiple pregnancies, pregnancies complicated by neonatal chromosomal or structural anomalies of the fetus. The gestation period was calculated from the first day of the last menstrual period and was corrected the index of the coccygeal-parietal size at the first screening ultrasound according to the Clinical Protocol of the Ministry of Health of the Republic of Kazakhstan "Management of physiological pregnancy" dated September 19, 2013. The present study complied with the principles outlined in the Helsinki Declaration of the World Medical Organization. This study was approved by the Ethics Committee of the Semey Medical University approved the research protocol (Protocol # 2 of from 10/25/2018).

*Data collection*

Clinical data were obtained from individual cards f No. 077/y, No. 111/y, birth histories f No. 096/y, 001/y. Relevant demographic and clinical characteristics were included maternal age, height, weight, pre-pregnancy body mass index (BMI), parity, obstetrical history, life history, known diseases (anemia, hypertension, other cardiovascular diseases, pulmonary and bronchial diseases, diabetes mellitus, thyroid diseases, viral hepatitis, epilepsy, syphilis, myoma of the uterus, uterine anomalies), smoking status, neonatal characteristics. Body mass index (BMI) was calculated by the formula: weight (kg)/ height ($m^2$). The group of pulmonary and bronchial diseases included pregnancies with chronic obstructive pulmonary disease, bronchial asthma, bronchitis, pneumonia. In this study, preterm birth was defined as birth at more than 22 full gestation weeks to 37 full gestation weeks. Newborns with FGR include both live born and still born newborns whose birth weight was below 2500 grams and who were >22 completed gestation weeks. In our study, 10 pregnant women had early or latent form of syphilis. Fetal distress was defined as a compromised condition of the fetus, discovered during birth or intrapartum period, characterized by a markedly abnormal heart rate or rhythm.

**Statistical analysis**

All statistical analyses were performed using the Stat Tech v. 3.0.9 program (developed by Stattech LLC, Russia). Cases without complete maternal and neonatal parameters were excluded. All variables were examined to determine whether they were normally distributed. Descriptive statistics included median (Q1 – Q3) for the continuous non-normally distributed variables. Results were compared between newborns with FGR and without FGR. The Mann-Whitney test was used between two groups to compare the means of non-normally variables. The $\chi 2$ test was performed for comparing differences in categorical variables between groups. All confidence intervals (CI) were 95%. Statistical significance was defined as $p<0.05$ for a single test.

**Results**

***Comparisons of the subjects, general information***

The study population included 6547 pregnancies aged at onset from 18 to 47 years, which fulfilled the inclusion criteria and qualified for data analysis (age: Me ($Q_1$,-$Q_3$) = 28 years (24-32)). Table 1 shows neonatal characteristics of the study participants comparing fetal growth groups. In terms of birth, weight significantly statistical differences between fetal growth groups. In our study, 3211 girls and 3336 boys were born, out of which 85 girls and 75 boys had FGR (Tab. 1). FGR occurred irrespective of fetal sex

(p=0.296). According to our result, 6355 newborns were born alive and 192 newborns were stillborn, of which 136 newborns with FGR were born alive and 24 newborns with FGR were stillborn (p=0.001) (Tab. 1). The odds of being stillborn increased OR = 6.53 (95% CI: 4.12 - 10.35) in the presence of FGR (p=0.001). 604 newborns were premature born, of which 73 newborns with FGR were premature born (p=0.001) (Tab. 1). The odds of premature born increased OR = 9.25 (95% CI: 6.7 - 12.79) in the presence of FGR (p=0.001). The mean fetal weight of newborns without FGR was Me = 3420 grams ($Q_1$,-$Q_3$ = 3080 grams - 3750 grams) and the mean weight of newborns with FGR was Me = 2200 grams ($Q_1$,-$Q_3$ = 1413 grams - 2420 grams) (p=0.001) (Tab. 1).

*Table 1.*

**Neonatal characteristics between fetal growth groups (n=6547).**

| | | Normal fetal growth; n=6387 | Fetal Growth Restriction; n=160 | p-value* |
|---|---|---|---|---|
| | | n (%) | n (%) | |
| Gender; n (%) | Males (n=3336) | 3261 (49.81) | 75 (1.14) | 0.296 |
| | Females (n=3211) | 3126 (47.75) | 85 (1.3) | |
| Birth; n (%) | Live (n=6355) | 6219 (94.99) | 136 (2.08) | 0.001 |
| | Still (n=192) | 168 (2.57) | 24 (0.36) | |
| Premature birth; n (%) | No | 5856 (89.45) | 87 (1.33) | 0.001 |
| | Yes | 531 (8.11) | 73 (1.11) | |
| Weight; (grams) Me (Q1 – Q3) | | 3420 (3080 – 3750) | 2200 (1413 – 2420) | 0.001** |
| *Note:* Median (Q1-Q3) for weight. Those p-values less than 0.05 were considered statistically significant. * - $\chi 2$ test. ** - Mann - Whitney test. | | | | |

Statistically significant differences were found when studying the presence of FGR depending on maternal parity (p<0.001) (Tab. 2). The odds of developing FGR after 1st delivery and 2nd delivery were lower compared to pregnancies who had their first birth (OR = 0.49 (95% CI: 0.33-0.73) (p=0.002) and OR =0.43 (95% CI: 2.67-0.7) (p=0.002), respectively). The pregnancies who have had three or more deliveries lower OR =0.92 (95% CI: 0.58-1.47) (p=0.039). The social status of the mother in marriage did not influence the FGR (p=0.184) (Tab. 2). In our study, only 87 pregnancies said they smoked, of which only 3 pregnancies gave birth to a newborn with FGR (Tab. 2). Out of 6460 non-smoking pregnancies, only 157 pregnancies gave birth to newborns with FGR. Maternal smoking had no effect on the newborn's FGR (p=0.541). 26 pregnancies used in vitro fertilisation and they did not have newborns with FGR (p=0.419) (Tab. 2).

*Table 2.*

**Maternal socio-demographic characteristics between fetal growth groups (n=6547).**

| | | Normal fetal growth; n=6387 | Fetal Growth Restriction; n=160 | p-value* |
|---|---|---|---|---|
| | | Me (Q1 – Q3) | Me (Q1 – Q3) | |
| Age; (years) | | 28 (20 - 36) | 27 (18 - 36) | 0.28 |
| BMI; (kg/m2) | | 23 (20 – 26) | 22 (20 – 26) | 0.340 |
| Marriage; n (%) | Registered | 5805 (88.67) | 139 (2.12) | 0.184 |
| | Not registered | 467 (7.13) | 16 (0.24) | |
| | Single | 115 (1.76) | 5 (0.08) | |
| Parity; n (%) | 0 birth | 2076 (31.71) | 75 (1.14) | 0.001** |
| | 1 birth | 2180 (33.3) | 39 (0.59) | |
| | 2 births | 1409 (21.52) | 22 (0.34) | |
| | 3 or more | 722 (11.03) | 24 (0.37) | |
| Smoking; n (%) | No | 6303 (96.27) | 157 (2.41) | 0.541** |
| | Yes | 84 (1.28) | 3 (0.04) | |
| Extracorporeal insemination; n (%) | No | 6361 (97.16) | 160 (2.44) | 0.419** |
| | Yes | 26 (0.4) | 0 (0) | |
| Note: Median (Q1-Q3) for age, BMI. Those p-values less than 0.05 were considered statistically significant. * - Mann - Whitney test. ** - $\chi 2$ test. | | | | |

As shown in Table 3, if the pregnancy was complicated by pre-eclampsia, the newborn had a higher incidence of FGR compared to pregnancies without pre-eclampsia (p=0.001). Pregnancies with pre-eclampsia had significantly higher odds of developing FGR than pregnancies without pre-eclampsia, adjusted OR = 6.33 (95% CI: 4.41 - 9.07) (p=0.001) (Tab. 3). Depending on the severity of pre-eclampsia, moderate degree of pre-eclampsia and severe degree of pre-eclampsia compared to pregnancies without pre-eclampsia had a higher incidence of FGR by OR = 2.49 (1.08 - 5.77) (p=0.027) and OR = 8.29 (5.64 - 12.18) (p=0.001), respectively (Tab. 3). In our study 4 pregnancies had a complication of HELLP, in both cases newborns were born with FGR (p=0.003) (Tab. 3).

*Table 3.*

**The frequency of complication of this pregnancy in the groups fetal growth groups (n=6547).**

| | | Normal fetal growth | Fetal Growth Restriction | OR (95% CI) | p-value* |
|---|---|---|---|---|---|
| | | n=6387 | n=160 | | |
| Pre-eclampsia; n (%) | No | 6015 (91.87) | 115 (1.76) | 1.0 | 0.001 |
| | Yes | 372 (5.68) | 45 (0.69) | 6.33 (4.41 – 9.07) | |
| Pre-eclampsia; n (%) | No | 6015 (91.87) | 115 (1.76) | 1.0 | |
| | Moderate | 126 (1.92) | 6 (0.09) | 2.49 (1.08-5.77) | 0.027 |
| | Severe | 246 (3.76) | 39 (0.6) | 8.29 (5.64 – 12.18) | 0.001 |
| HELLP; n (%) | No | 6385 (97.53) | 158 (2.41) | 1.0 | 0.003 |
| | Yes | 2 (0.03) | 2 (0.03) | 40.41 (5.65-288.72) | |
| Placental abruption of a normally located placenta; n (%) | No | 6269 (95.75) | 147 (2.25) | 1.0 | 0.001 |
| | Yes | 118 (1.8) | 13 (0.2) | 4,7 (2,59 – 8,52) | |
| Disorder of maternal-placental blood flow according to Doppler results; n (%) | No | 6289 (96.06) | 113 (1.72) | 1.0 | 0.001 |
| | Yes | 98 (1.5) | 47 (0.72) | 26.69 (17.99 – 39.6) | |
| Polyhydramnios; n (%) | No | 6280 (95.92) | 156 (2.38) | - | 0.425 |
| | Yes | 107 (1.63) | 4 (0.06) | - | |
| Oligohydramnios; n (%) | No | 6271 (95.78) | 113 (1.72) | 1.0 | 0.001 |
| | Yes | 116 (1.77) | 47 (0.72) | 22.48 (15.28 – 33.1) | |
| Fetal distress; n (%) | No | 6214 (94.91) | 140 (2.14) | 1.0 | 0.001 |
| | Yes | 173 (2.64) | 20 (0.3) | 5.13 (3.14 – 8.39) | |
| Umbilical cord anomalies; n (%) | No | 6352 (97.02) | 157 (2.4) | | 0.029 |
| | Yes | 35 (0.53) | 3 (0.04) | 3.47 (1.05 – 11.39) | |
| Chorioamnionitis; n (%) | No | 6338 (96.81) | 160 (2.44) | - | 0.266 |
| | Yes | 49 (0.75) | 0 (0) | - | |
| Meconium leaking into the amniotic fluid; n (%) | No | 6137 (93.74) | 151 (2.31) | - | 0.273 |
| | Yes | 250 (3.82) | 9 (0.14) | - | |
| Placenta accreta; n (%) | No | 6382 (97.48) | 160 (2.44) | - | 1.0 |
| | Yes | 5 (0.08) | 0 (0) | - | |
| Low-lying placenta according to the ultrasound scan; n (%) | No | 6327 (96.64) | 155 (2.37) | 1.0 | 0.006 |
| | Yes | 60 (0.92) | 5 (0.08) | 3.4 (1.35 – 8.59) | |
| Battledore placenta previa according to the ultrasound scan; n (%) | No | 6376 (97.39) | 159 (2.43) | - | 0.186 |
| | Yes | 11 (0.17) | 1 (0.01) | - | |
| Complete placenta previa according to the ultrasound scan; n (%) | No | 6377 (97.4) | 158 (2.41) | | 0.001 |
| | Yes | 10 (0.15) | 2 (0.03) | 8.07 (1.75 – 37.14) | |

* - χ2 test OR (95% CI) - Odds ratio (95% confidence interval)

Placental abruption of normally located placenta was more common in pregnancies with FGR than newborns without FGR, adjusted OR = 4.7 (95% CI: 2.59 - 8.52) (p=0.001) (Tab. 3). Placental insufficiency was more common in pregnancies with FGR OR = 26.69 (95% CI: 17.99 - 39.6) compared to pregnancies without FGR (p=0.001) (Tab. 3). The presence of oligohydramnios in a present pregnancy increased the odds of FGR compared to pregnancies without oligohydramnios, adjusted OR = 22.48 (95% CI: 15.28 - 33.1) (p=0.001) (Tab. 3). Fetal distress occurred more frequently in pregnancies with FGR compared to pregnancies without FGR, adjusted OR = 5.13 (95% CI: 3.14 - 8.39) (p=0.001) (Tab. 3). And for umbilical cord anomaly in this pregnancy, newborns with FGR occurred more frequently compared to newborns without umbilical cord anomaly, adjusted OR = 3.47 (95% CI: 1.05 - 11.39) (p=0.029) (Tab. 3). The development of FGR in present pregnancy was not influenced by polyhydramnios (p=0.425), placenta accrete (p = 1.000), chorioamnionitis (p=0.266), and meconium discharge into amniotic fluid (p=0.273) (Tab. 3).

Low-lying placenta according to the ultrasound scan was more common in newborns with FGR compared to newborns without FGR, adjusted OR = 3.4 (95% CI: 1.35 - 8.59) (p=0.006) (Tab. 3). Complete placenta previa according to the ultrasound scan was more common in newborns with FGR compared to newborns without FGR, adjusted OR = 8.07 (95% CI: 1.75 - 37.14) (p=0.001) (Tab. 3). Battledore placenta previa according to the ultrasound scan had no effect on the development of FGR (p=0.186) (Tab. 3).

Women with anemia (Iron deficiency anemia and B12 vitamin deficiency anemia) before pregnancy were less likely to have newborns with FGR compared to women without anemia (p=0.001) (Tab. 4). Women with anemia had lower odds of developing FGR compared to women without anemia, adjusted (OR = 0.56; 95% CI: 0.41 to 0.77) (p=0.001). Women with previous pulmonary and bronchial

diseases had higher odds of developing FGR compared to women without previous pulmonary and bronchial diseases, adjusted (OR = 6.21; 95% CI: 2.39 to 16.12) (p=0.001). The development of FGR was not influenced by the presence of gestational DM (p = 0.327), gestational AH (p=0.608), prediabetes (p=0.526), type 1 and type 2 DM (p=0.808) and congenital and acquired heart defects of the mother (p=0.392) (Tab. 4). Women who had a heart rhythm abnormality before pregnancy were more likely to give birth to newborns with a FGR compared to women with a heart rhythm normality (p=0.001) (Tab. 4). There was a higher odds of developing FGR compared to women without a heart rhythm disorder, adjusted OR = 4.79 (95% CI: 1.68 - 13.67) (p=0.001). Whereas, women who had a history of AH before pregnancy were more likely to have newborns with FGR compared to women without AH (p=0.049) (Tab. 4). Women with AH had higher odds of developing FGR compared to women without AH, adjusted OR = 2.05 (95% CI: 0.99-4.24) (p=0.049).

Women with syphilis were more likely to have a newborns with FGR (p=0.023) (Tab. 4). Women with syphilis had a higher chance of developing FGR compared to women without syphilis, adjusted OR = 10.09 (95% CI: 2.13 - 47.91). The presence of maternal epilepsy (p=0.513), thyroid disease (p = 0.977), uterine myoma (p = 0.460), uterine anomaly (p = 1.0), pregnancy cholestasis (p = 0.447), viral hepatitis (p = 0.823) did not affect the development of FGR of newborn (Tab. 4).

*Table 4.*

**Frequency of maternal extracorporeal disease in fetal growth groups (n=6547).**

| | | Normal fetal growth | Fetal Growth Restriction | OR (95% CI) | p-value* |
|---|---|---|---|---|---|
| | | n=6387 | n=160 | | |
| Anaemia; n (%) | No | 2570 (39.25) | 87 (1.3) | 1.0 | 0.001 |
| | Yes | 3817 (58.3) | 73 (1.1) | 0.56 (0.41 – 0.7) | |
| Hypertension; n (%) | No | 6227 (95.11) | 152 (2.32) | 1.0 | 0.049 |
| | Yes | 160 (2.44) | 8 (0.12) | 2.05 (0.99 – 4.24) | |
| Heart rhythm disturbance; n (%) | No | 6353 (97.04) | 156 (2.38) | 1.0 | 0.001 |
| | Yes | 17 (0.26) | 1 (5.6) | 4.79 ( 1.68 – 13.67) | |
| Congenital and acquired heart defects; n (%) | No | 6370 (97.3) | 159 (2.43) | - | 0.392 |
| | Yes | 17 (0.26) | 1 (0.01) | - | |
| Pulmonary and bronchial diseases; n (%) | No | 6354 (97.05) | 155 (2.37) | 1.0 | 0.001 |
| | Yes | 33 (0.5) | 5 (0.08) | 6.21 (2.39 – 16.12) | |
| Prediabetes; n (%) | No | 6371 (97.31) | 160 (2.44) | - | 0.526 |
| | Yes | 16 (0.25) | 0 (0) | - | |
| Diabetes mellitus; n (%) | No | 6370 (97.3) | 160 (2.44) | - | 0.808 |
| | 1 type | 12 (0.18) | 0 (0) | - | |
| | 2 type | 5 (0.08) | 0 (0) | - | |
| Thyroid diseases; n (%) | No | 6370 (97.3) | 160 (2.44) | - | 0.977 |
| | Yes | 17 (0.26) | 0 (0) | - | |
| Viral hepatitis; n (%) | No | 6337 (96.79) | 159 (2.43) | - | 0.823 |
| | Yes | 50 (0.77) | 1 (0.01) | - | |
| Pregnancy cholestasis | No | 6364 (97.2) | 160 (2.44) | - | 0.447 |
| | Yes | 23 (0.36) | 0 (0) | - | |
| Epilepsy; n (%) | No | 6257 (95.57) | 155 (2.37) | - | 0.37 |
| | Yes | 130 (1.98) | 5 (0.08) | - | |
| Syphilis; n (%) | No | 6379 (97.43) | 158 (2.82) | 1.0 | 0.023 |
| | Yes | 8 (0.12) | 2 (0.03) | 10.09 (2.13 – 47.91) | |
| Myoma of the uterus; n (%) | No | 6309 (96.36) | 157 (2.4) | - | 0.460 |
| | Yes | 78 (1.19) | 3 (0.04) | - | |
| Uterine anomalies; n (%) | No | 6379 (97.43) | 160 (2.44) | - | 1.0 |
| | Yes | 8 (0.12) | 0 (0) | - | |
| * - $\chi 2$ test OR (95% CI) - Odds ratio (95% confidence interval) | | | | | |

The presence of a uterine scar influenced the chance of FGR (p=0.003) (Tab. 5). Pregnancies with uterine scar had a higher chance of FGR compared to pregnancies without uterine scar, adjusted OR = 1.92 (95% CI: 1.23 to 2.99) (p=0.003). Depending on the number of uterine scars, the odds of developing FGR increased each time (p=0.007) (Tab. 5). Pregnancies with one uterine scar and pregnancies with two uterine scars had higher chance of FGR development compared to pregnancies without uterine scar, adjusted OR = 1.65 (95% CI: 0.99 - 2.75) and OR = 3.22 (95% CI: 1.38 - 7.52), respectively. And pregnancies with three or more uterine scars had a higher chance of fetal FGR compared to pregnancies without uterine scar, adjusted OR = 3.07 (95% CI: 0.4-23.53).

A history of abortion had no effect on the development of FGR (p=0.76) (Tab. 5). Pregnancies that had pre-eclampsia in the previous birth were more likely to have a newborn with FGR at the next birth (p = 0.001). Pregnancies with previous pre-eclampsia had increased odds of developing FGR compared to women

without previous pre-eclampsia, adjusted OR = 5.14 (95% CI: 2.93 - 9.0) (p=0.001) (Tab. 5). Preterm birth in previous births, previous birth of a baby with congenital malformations and birth of newborn weighing less than 2500 grams influenced the development of FGR in the maternal next pregnancy (p=0.001) (Tab. 5). Previous maternal preterm birth increased the odds of developing FGR in the next pregnancy by compared to pregnancies without previous preterm birth, adjusted OR = 4.35 (95% CI: 2.87 - 6.61) (p=0.001) (Tab. 5). Having a newborn weighing less than 2500 grams in the previous birth increased the odds of developing FGR in the next pregnancy by compared to pregnancies who had a previous newborn weighing more than 2500 grams, adjusted OR = 3.63 (95% CI: 2.47 - 5.35). Having a newborn with congenital malformations in previous births increased the odds of developing newborns with FGR by compared to women who had previous healthy newborns, adjusted OR = 2.8 (95% CI: 1.0 - 7.8) (p=0.04) (Tab. 5).

*Table 5.*

**Frequency of complications of previous pregnancies in maternal history by fetal growth (n=6547).**

| | | Normal fetal growth n=6387 | Fetal Growth Restriction n=160 | OR (95% CI) | p-value* |
|---|---|---|---|---|---|
| Abortion; n (%) | No | 5047 (77.09) | 128 (1.95) | - | 0.76 |
| | Yes | 1304 (19.92) | 32 (0.49) | - | |
| A scar on the uterus; n (%) | No | 5849 (89.34) | 136 (2.08) | 1.0 | 0.003 |
| | Yes | 538 (8.22) | 24 (0.37) | 1.92 (1.23 - 2.99) | |
| A scar on the uterus; n (%) | No | 5849 (89.34) | 136 (2.08) | 1.0 | 0.007 |
| | 1 scar | 444 (6.78) | 17 (0.26) | 1.65 (0.99 – 2.75) | |
| | 2 scars | 80 (1.22) | 6 (0.09) | 3.22 (1.38 – 7.52) | |
| | 3 or more scars | 14 (0.21) | 1 (0.01) | 3.07 (0.4-23.53) | |
| Pre-eclampsia; n (%) | No | 6261 (95.63) | 145 (2.21) | 1.0 | 0.001 |
| | Yes | 126 (1.93) | 15 (0.23) | 5.14 (2.93 – 9.0) | |
| Pre-eclampsia; n (%) | No | 6261 (95.63) | 145 (2.21) | 1.0 | |
| | Moderate | 117 (1.79) | 12 (0.19) | 4.43 (2.39 - 8.2) | 0.001 |
| | Severe | 9 (0.14) | 3 (0.04) | 14.39 (3.86–53.72) | 0.001 |
| Premature birth; n (%) | No | 6078 (92.84) | 131 (2.0) | 1.0 | 0.001 |
| | Yes | 309 (4.72) | 29 (0.44) | 4.35 (2.87 – 6.61) | |
| Gestational diabetes mellitus; n(%) | No | 6230 (95.16) | 158 (2.41) | - | 0.327 |
| | Yes | 157 (2.4) | 2 (0.03) | - | |
| Births of newborns weighing up to 2500 grams; n (%) | No | 5930 (90.57) | 125 (1.92) | 1.0 | 0.001 |
| | Yes | 457 (6.98) | 35 (0.53) | 3.63 (2.47 – 5.35) | |
| Birth of newborns with congenital malformations; n (%) | No | 6329 (96.67) | 156 (2.38) | 1.0 | 0.04 |
| | Yes | 58 (0.89) | 4 (0.06) | 2.8 (1.0 – 7.8) | |
| * - $\chi 2$ test OR (95% CI) - Odds ratio (95% confidence interval) | | | | | |

***Logistic regression between risk of FGR and maternal and perinatal risk factors***

Logistic regression analysis revealed that the risk of developing FGR was lower in pregnancies with 1st delivery and 2nd delivery than in those without delivery (adjusted OR = 0.49; 95% CI: 0.33 – 0.73; p=0.001 and OR = 0.43; 95% CI: 0.27 – 0.7; p=0.001, respectively) (Table 6). By contrast, anemia was protective and was associated with a reduced risk of FGR (OR = 0.56; 95% CI: 0.41 – 0.77; p=0.001) in this sample. As shown in Table 6, hypertension and heart rhythm disturbance were associated with an increased risk of developing FGR in the study sample (adjusted OR = 2.05; 95% CI: 0.99 – 4.24; p =0.05 and OR = 4.79; 95% CI: 1.68 – 13.67; p=0.003, respectively). Pulmonary and bronchial diseases and Syphilis increased the risk of FGR in the study sample (adjusted OR = 6.21; 95% CI: 2.39 – 16.12; p=0.001 and OR = 10.09; 95% CI: 2.12 – 47.89; p=0.004, respectively) (Table 6).

Logistic regression analysis showed that risk of FGR were significantly higher in pregnancies with pre-eclampsia and with HELLP than in pregnancies without pre-eclampsia and without HELLP, (adjusted OR = 6.33; 95% CI: 4.41 – 9.07; p=0.001 and OR = 40.41; 95% CI: 5.66 – 288.59; p=0.001, respectively) (Table 6). Moderate degree and severe degree of pre-eclampsia were more frequent the pregnancies with FGR compared with those without FGR, (adjusted OR = 2.49; 95% CI: 1.08 – 5.77; p=0.03 and OR = 8.29; 95% CI: 5.64 – 12.18; p=0.001, respectively). Placental abruption of a normally located placenta and Disorder of maternal-placental blood flow according to Doppler results were associated with increased risk of FGR in this sample, (adjusted OR = 4.7; 95% CI: 2.59 – 8.52; p=0.001 and OR = 26.69; 95% CI: 17.99 – 39.61; p=0.001, respectively) (Table 6).

Table 6 displays oligohydramnios and Fetal distress were associated with an increased risk of developing FGR in the study sample (adjusted OR = 22.49; 95% CI: 15.27 – 33.08; p=0.001 and OR = 5.13; 95% CI: 3.14 – 8.4; p=0.001, respectively). Umbilical cord anomalies were associated with a high risk of FGR (adjusted OR = 3.47; 95% CI: 1.05 – 11.39; p=0.04). Table 6 gives Low-lying placenta and complete placenta previa according to the ultrasound scan were associated with an increased risk of developing FGR (adjusted OR = 3.4; 95% CI: 1.35 – 8.58;

p=0.01 and OR = 8.07; 95% CI: 1.75 – 37.15; p=0.007, respectively).

Table 6 showed that risk of FGR were significantly higher in pregnancies with scar on the uterus than in pregnancies without scar on the uterus, (adjusted OR = 1.92; 95% CI: 1.23 – 2.99; p=0.004). The 2 scars on the uterus were more frequent the pregnancies with FGR compared with those without FGR and who had 1 scar or 3 and more scars on the uterus, (adjusted OR = 3.23; 95% CI: 1.38 – 7.52; p=0.007). By contrast, previous pre-eclampsia and previous premature birth were associated with an increased risk of developing FGR in the study sample (adjusted OR = 5.14; 95% CI: 2.94 – 9.0; p=0.001 and OR = 4.35; 95% CI: 2.87 – 6.61; p=0.001, respectively) (Table 6).

Table 6 displays that risk of FGR were significantly higher in pregnancies with previous births of newborns weighing up to 2500 grams and with previous birth of newborns with congenital malformations than in pregnancies without previous births of newborns weighing up to 2500 grams and without previous birth of newborns with congenital malformations, (adjusted OR = 3.63; 95% CI: 2.47 – 5.35; p=0.001 and OR = 2.8; 95% CI: 1.0 – 7.8; p=0.049, respectively) (Table 6).

*Table 6.*

**Maternal and perinatal risk factors for fetal growth restriction, OR derived from logistic regression analysis (n=6547).**

| | | AOR | 95% CI | p-value |
|---|---|---|---|---|
| Parity | | 0.88 | 0.76 – 1.02 | 0.1 |
| Parity | 0 birth | 1.0 | | |
| | 1 birth | 0.49 | 0.33 – 0.73 | 0.001 |
| | 2 births | 0.43 | 0.27 – 0.7 | 0.001 |
| | 3 or more | 0.92 | 0.58 – 1.47 | 0.72 |
| Anaemia | | 0.56 | 0.41 – 0.77 | 0.001 |
| Hypertension | | 2.05 | 0.99 – 4.24 | 0.05 |
| Heart rhythm disturbance | | 4.79 | 1.68 – 13.67 | 0.003 |
| Pulmonary and bronchial diseases | | 6.21 | 2.39 – 16.12 | 0.001 |
| Syphilis | | 10.09 | 2.12 – 47.89 | 0.004 |
| Pre-eclampsia | | 6.33 | 4.41 – 9.07 | 0.001 |
| Pre-eclampsia | No | 1.0 | | |
| | Moderate | 2.49 | 1.08 – 5.77 | 0.03 |
| | Severe | 8.29 | 5.64 – 12.18 | 0.001 |
| HELLP | | 40.41 | 5.66 – 288.59 | 0.001 |
| Placental abruption of a normally located placenta | | 4.7 | 2.59 – 8.52 | 0.001 |
| Disorder of maternal-placental blood flow according to Doppler results | | 26.69 | 17.99 – 39.61 | 0.001 |
| Oligohydramnios; n (%) | | 22.49 | 15.27 – 33.08 | 0.001 |
| Fetal distress | | 5.13 | 3.14 – 8.4 | 0.001 |
| Umbilical cord anomalies | | 3.47 | 1.05 – 11.39 | 0.04 |
| Low-lying placenta according to the ultrasound scan | | 3.4 | 1.35 – 8.58 | 0.01 |
| Complete placenta previa according to the ultrasound scan | | 8.07 | 1.75 – 37.15 | 0.007 |
| A scar on the uterus | | 1.92 | 1.23 – 2.99 | 0.004 |
| A scar on the uterus | No | 1.0 | | |
| | 1 scar | 1.65 | 0.98 – 2.75 | 0.057 |
| | 2 scars | 3.23 | 1.38 – 7.52 | 0.007 |
| | 3 or more scars | 3.07 | 0.4 – 23.52 | 0.28 |
| Previous pre-eclampsia | | 5.14 | 2.94 – 9.0 | 0.001 |
| Previous pre-eclampsia | No | 1.0 | | |
| | Moderate | 4.43 | 2.39 – 8.21 | 0.001 |
| | Severe | 14.39 | 3.86 – 53.73 | 0.001 |
| Previous premature birth | | 4.35 | 2.87 – 6.61 | 0.001 |
| Previous births of newborns weighing up to 2500 grams | | 3.63 | 2.47 – 5.35 | 0.001 |
| Previous birth of newborns with congenital malformations | | 2.8 | 1.0 – 7.8 | 0.049 |
| AOR – adjusted Odds ratio; 95% CI - 95% confidence interval | | | | |

**Discussion**

In our study, 6547 data were analyzed out of which 160 cases were with newborns with FGR. The results of our data analysis showed that first-time mothers are a significant risk factor for the development of FGR. Our results are in agreement with the results of other researchers. The authors of another study reported that first-time mothers often had newborns with FGR [17]. According to some studies, the fetus loses 10% to 30% of its body weight between the time of intrauterine death and subsequent postnatal assessment, if we consider the fact those two-thirds of dead fetuses had a body weight greater than the 10th percentile at birth. This suggests that the majority of stillbirths may have been of normal weight before death and FGR appeared after birth. Alternatively, stillbirths with FGR who were born with normal birth weight

may be missed [38].

In our study, only 87 women said they smoked. But it is possible that not all pregnant women answered honestly about their smoking status. In this study, smoking was not a significant risk factor for FGR. A similar lack of association between smoking and FGR was found in a study conducted in Australia [24], smoking status was not a significant risk factor for FGR[18]. But other studies have shown smoking as a risk factor for FGR [33, 37].

Placental ischemic manifestations in FGR and in pre-eclampsia are identical, as they share a common pathophysiological pathway involving impaired uteroplacental hypoperfusion [34]. In our study, when pregnancy was complicated by pre-eclampsia, neonates with FGR were more common in such cases compared to pregnant women without pre-eclampsia. Also, when the severity of pre-eclampsia was severe, there was high frequency of neonates with FGR compared to moderate pre-eclampsia and without pre-eclampsia. Some researchers have reported an association between the incidence of placental lesions as a consequence of maternal hypoperfusion and gestational age in pre-eclampsia [36]. They argued that maternal hypoperfusion disorders were more frequent in pregnant women with pre-eclampsia compared with those without pre-eclampsia and that pre-eclampsia in early pregnancy increased the frequency of placental lesions corresponding to maternal hypoperfusion. In another study, the authors revealed that pregnant women with pre-eclampsia in early pregnancy showed vascular lesions and placental hypoplasia, while in contrast, pregnant women with pre-eclampsia diagnosed at the end of the third trimester showed placental hyperplasia [35]. The Chinese-American Collaborative Project on Prevention of Neural Tube Defects, a large population-based cohort study investigated the association of GH and pre-eclampsia on FGR, where the authors revealed that early onset of GH and pre-eclampsia proved to be relatively more unfavourable to the fetus, and increased the risk of developing FGR [23]. Elevated blood pressure during pregnancy causes endothelial dysfunction and decreased placental perfusion, resulting in reduced fetal growth and lower birth weight [16].

In a retrospective cohort study, the authors revealed that newborns born to pregnancies with placental abruption increased the risk of low birth weight, perinatal death, and stillbirth [31]. In a prospective longitudinal study, they obtained clinical evidence suggesting that placental insufficiency may occur in preterm fetuses with FGR who have growth retardation late in gestation [4]. Previous studies have reported that FGR is associated with an increased risk of adverse perinatal outcomes and has been associated with emergency delivery for fetal distress, hospitalization of newborns in the intensive care department [22, 32, 40]. In a study comparing placental abnormalities in preterm and preterm fetuses associated with fetal growth restriction (FGR), the authors found that the placentas of preterm infants with FGR had multiple abnormalities reflecting uteroplacental insufficiency and impaired blood supply [3]. Previous preterm birth increased the chance of developing FGR in the next maternal pregnancy in this study. Our results were similar to other studies [20, 24]. Placental abruption of a normally located placenta; Disorder of maternal-placental blood flow according to Doppler results; Oligohydramnios; Fetal distress; Umbilical cord anomalies; Low-lying placenta and complete placenta previa according to the ultrasound scan were associated with the chances of developing FGR in this study.

In this study, maternal anemia had a protective effect on fetal FGR. In another study examining risk factors for preterm birth, low birth weight, and low birth weight for gestational age of infants among Aboriginal women living in remote areas of Australia, the authors revealed that anemia had a protective effect [24]. Higher hemoglobin concentrations and lower hemoglobin decline may indicate poor plasma volume expansion, hemoconcentration [26] or high blood viscosity [43, 44]. High blood viscosity impairs placental blood flow, thereby reducing the supply of oxygen and nutrition to the fetus, causing FGR [19, 23, 44]. In some cases, hemodilution occurs, that is, a physiological adaptation that can facilitate uteroplacental circulation and reduce the risk of FGR [27]. Previous studies have shown that low hemoglobin levels in late pregnancy may reflect normal hemodynamic adaptation and plasma volume changes rather than poor maternal nutrition [13, 18, 47]. These may explain the protective effect of maternal anemia on the risk of developing FGR.

In our study, AH and heart rhythm disturbance were associated with the development of fetal FGR. In one study, the authors stated that a fetus with FGR is more common in women with coronary heart disease, AH and with insulin resistance [6]. A recent retrospective cohort study examined the impact of cardiac arrhythmias on perinatal outcomes, with the authors stating that pregnant women with cardiac arrhythmias had an increased risk of intrauterine fetal death [21]. In this study, we found that cardiac rhythm disturbance increased the chance of developing FGR. In a cohort study that assessed the risk of adverse perinatal outcomes in gestational DM, the authors state that gestational DM was associated with an increased risk of preterm birth, increased risk of stillborn fetus and pre-eclampsia, macrosomia [8]. In a recent study, pregnancies with DM and gestational DM were often observed to have macrosomic newborns, as even moderate maternal hyperglycemia increases the rate of accelerated fetal growth [14]. In our study, DM and gestational DM were not associated with FGR.

Pregnancies with syphilis had higher chance of developing FGR compared to pregnancies without syphilis in this study. A recent study compared differences in long-term growth and health between children exposed to syphilis but not infected with syphilis and a group of children not exposed to syphilis, where the authors found that syphilis infection did not have a significant negative effect on the growth and health of children from birth to 18 months of age [30]. In another study, women with syphilis, especially untreated syphilis and with higher titres (greater than 1:8), were at increased risk of FGR [39, 46, 48].

In conclusion, although knowledge and understanding of these pathological conditions has improved in recent years, there is still no uniform standard for identifying a fetus with FGR. Better identification of newborns that at risk of FGR, regardless of size, is necessary to prevent potentially harmful interventions in healthy newborns, but small newborns who were born as if of normal weight but have growth retardation. This will enable doctors to

recognise in a timely and appropriate manner newborns with seemingly normal size but with developmental growth retardation. Therefore, versatile future studies are needed to investigate the problem of FGR in the fetus.

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***Authorship contributions***

***Sharipova M.G., Tanysheva G.A. and Sharipova H.K.*** *- were major contributors to the study and made substantial contributions to the conception and design of the study.*

***Sharipova M.G., Khamidullina Z.G., Sharipova H.K., Zhaksylykova Z.K., Lozhkina E.Yu., Kozhakhmetova D.K., Akimzhanov K.D. -*** *participated in the collection of study materials.*

***Sharipova M.G., Shakhanova A.T. -*** *and performed data collection and statistical analyses of the data. Participated in writing the manuscript. Authenticate all original data.*

***Tanysheva G.A., Kozhakhmetova D.K., Sharipova H.K., and Kozhakhmetova D.K. -*** *gave final approval of the version to be published. All authors have read and approved the final version of the manuscript.*

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