Prenatal identification of fetal growth restriction and risk of stillbirth

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article;
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The aim of the work is to determine the frequency and impact of prenatal identification of fetal growth restriction (FGR) on obstetric and perinatal outcomes based on a retrospective analysis.

Materials and methods. In total, 618 birth histories in singleton normal pregnancies complicated by FGR in the city of Zaporizhzhia were analyzed. Of these, in 546 cases of FGR, women gave birth to live infants (group I), and in 72 such cases, pregnancies ended up in a stillbirth (group II). The mean age of pregnant women in the studied groups was 28.7 ± 3.1 and 31.7 ± 3.1 years and it was significantly greater in group II ($p < 0.0001$). In all the cases, the gestational age was ≥22 weeks, and the fetal weight was less than the 10th percentile for the relevant gestational age according to the current Order of the Ministry of Health of Ukraine No. 1718 dated 02.10.2023. Growth restriction in newborns was determined according to the criteria of the Consensus Definition (2018) including birth weight the <3rd percentile, or a combination of three of the following criteria: birth weight the <10th percentile; head circumference the <10th percentile; prenatal diagnosis of FGR; prenatal risk factors associated with FGR. A stillbirth was defined as death of a fetus after 22 weeks of gestation without any signs of life. Exclusion criteria from the study were: multiple pregnancy, the presence of a chromosomal abnormality in a fetus, an undetermined gestational age in the 1st trimester.

Results. A significant proportion of fetuses with FGR signs has been revealed in group II, which was 17 times more than that in group I. The study data have demonstrated a rather low level of prenatal FGR identification in both groups (35.6 %), while in group II, the diagnosis of FGR was made before delivery only in every fifth case ($p < 0.05$). Data analysis has shown a higher percentage of preterm births among pregnant women in group II ($p < 0.0001$) with the maximum number of births in this group at 28- and 36-weeks' gestation. The average weight percentile was significantly higher in group II, namely 4.12 compared to 3.77 ($p < 0.0001$), however, the number of fetuses with a weight the <1st percentile occurred significantly more often in group I ($p < 0.05$). The frequency of fetal distress in group I was greater among fetuses with the birth weight 10th percentile than among those with fetal weight less than the 3rd percentile.

Conclusions. The conducted study results have shown a large percentage of FGR fetuses in the structure of stillbirths with no downward trend. A low level of FGR prenatal identification has been found in both groups (35.6 %), while in the group of stillbirths, the indicator was significantly lower and amounted to 22.22 %. The presence of FGR has resulted in a significant increase in the relative risk of stillbirth – 28.4, 95 % CI [21.2; 38.3]. Besides, the additional risk was increased (11.0, 95 % CI [8.7; 13.8]) if FGR was not diagnosed during pregnancy. At the same time, the odds ratio was 32.1, 95 % CI [23.3; 44.1].

Пренатальна ідентифікація затримки росту плода та ризику мертвонародження

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Мета роботи – на підставі ретроспективного аналізу визначити частоту а також вплив допологової ідентифікації затримки росту плода (ЗРП) на акушерські та перинатальні наслідки.

Матеріали і методи. Проаналізували 618 історій пологів з одноплідними, не аномальними вагітностями, які були ускладнені ЗРП, в м. Запоріжжі. З них у 546 випадках ЗРП жінки народили живу дитину (I група), а в 72 випадках вагітність завершилася мертвонародженням (II група). Середній вік вагітних у групах дослідження становив 28,7 ± 3,1 та 31,7 ± 3,1 року відповідно; достовірно більший – у II групі ($p < 0,0001$). У всіх випадках термін вагітності становив ≥22 тижні, а маса плода – менша за 10 перцентиль для відповідного терміну гестації, згідно з чинним наказом МОЗ України від 29.12.2005 № 782. Затримку росту в новонароджених діагностували відповідно до критеріїв Консенсусного визначення (2018), що включає вагу дитини при народженні <3 процентиль або комбінацію трьох критеріїв: вага при народженні <10 процентиль; обвід голови <10 процентиль; допологовий діагноз ЗРП; пренатальні фактори ризику, пов'язані із ЗРП. Як мертвонароджену визначали дитину, яка народилася після 22 тижня вагітності та не мала ознак життя. Критерії виключення з дослідження – багатоплідна вагітність, наявність хромосомної аномалії плода, невизначений термін гестації в I триместрі.

Результати. У II групі визначили істотну частку плодів з ознаками ЗРП: у 17 разів більше щодо відповідного показника в I групі. Результати дослідження показали доволі низький рівень допологової ідентифікації ЗРП в обох групах (35,6 %). Зазначимо, що в II групі діагноз ЗРП до часу пологів встановлено лише в кожному п'ятому випадку ($p < 0,05$). Аналіз даних показав вищий відсоток передчасних пологів у вагітних II групи ($p < 0,0001$) з максимальною кількістю пологів у цій групі в термінах 28 і 36 тижнів гестації. Середній процентиль ваги достовірно більший у II групі – 4,12 проти 3,77 у I групі ($p < 0,0001$), але кількість плодів із масою <1 процентиль вірогідно більша в I групі ($p < 0,05$). Частота дистресу плодів у I групі більша в дітей із 10 процентилем ваги, ніж у плодів із вагою, що менша за 3 процентиль.

Висновки. Результати дослідження показали значну частку плодів із ЗРП у структурі мертвонароджених, що не має тенденції до зниження. Встановлено низький рівень допологової ідентифікації ЗРП в обох групах (35,6 %), у групі мертвонароджень цей показник становив 22,22 %. Статистичний аналіз свідчить, що наявність ЗРП призводить до значного підвищення відносного ризику (RR) мертвонародження – 28,4, 95 % ДІ [21,2; 38,3]. Крім того, якщо ЗРП не була діагностована під час вагітності, додатковий ризик зростає на 11,0, 95 % ДІ [8,7; 13,8]. Відношення шансів (OR) при цьому становить 32,1, 95 % ДІ [23,3; 44,1].

Improvement of perinatal outcomes is one of the main directions both in obstetrics and perinatology and the State as a whole. The most unacceptable complication of pregnancy is stillbirth. Although stillbirth rates have declined in many countries, these declines have been less pronounced than infant mortality rates [1,2]. At the same time, antepartum fetal death occurs in more than 80% [3].

A number of recent studies have focused on the impact of stillbirth on women's health and social consequences [4,5,6]. The main cause of stillbirth, neonatal mortality, short-term and long-term neonatal morbidity is fetal growth restriction (FGR), which refers to a common complication of pregnancy worldwide [7,8,9] and is defined as a fetus failing to realize its growth potential due to a pathological factor, most often placental dysfunction [10,11,12].

Recent studies have shown that the global prevalence of FGR in the world is about 20.5 % [12]. This points to the importance of timely diagnosis and management of FGR cases, which has a key role to play in reducing infant mortality and morbidity. However, in practice, more than 50 % of FGR cases remain undiagnosed even in high-income countries [13], and more than 70 % of infant death cases associated with FGR were not diagnosed before birth [14]. Such a low percentage of fetal growth abnormality detection significantly increases the risk of adverse perinatal outcomes and stillbirths, and therefore many cases of stillbirths, which can be prevented, are related precisely to undetected antenatally FGR [12,14].

The prevalence of FGR varies in different countries and rises with increasing gestational age [15,16,17]. In high-income countries such as the United States and Australia, the incidence of FGR was approximately 11 %, but in low- and middle-income countries, approximately 32.5 million infants were born with FGR, and the majority of these infants (53 % – 16.8 million) were born in South Asia [17,18]. The FGR level is currently the highest in the world for the past 20 years and it is likely to continue rising [19].

According to the Human Capital Index 2020, Ukraine was among the worst rates for quality-of-life scores in Europe [20,21]. It has not changed significantly over the past eight years, on the contrary, there has been an increase in the frequency of perinatal losses. The negative trend of the past ten years has been the annual decrease in the number of births in Ukraine [30]. Based on the State Statistics of Ukraine, the number of births decreased almost twice, from 565,900 to 258,813, in 2021 compared to 2014.

At the same time, the level of perinatal losses during this time period increased from 8.72 ‰ to 9.21 ‰, respectively. In Ukraine, the number of births decreased in absolute terms by 307,087 people in 2021 compared to 2014 [22]. Attention is drawn to an increased frequency of low birth weight and preterm birth, which are characterized by a high risk of neonatal morbidity and mortality. In addition, an increase in the perinatal mortality rate amid a declined birth rate is causing concern. In the Zaporizhzhia region, during that period, the same dynamics of changes in the structure of the decreased birth rates has been observed (by an average of 1,100 births per year), while the rates of perinatal losses were increased even more significantly (from 8.58 ‰ in 2014 to 10.46 ‰ in 2021). Thus, prenatal care, aimed at identifying fetuses with impaired growth rates, could become an effective strategy for preventing stillbirth [1], allowing a pregnant woman at a high risk of fetal death to give birth timely and thus to improve perinatal outcomes.

Aim

The purpose of the study is to determine the frequency and impact of prenatal identification of FGR on obstetric and perinatal outcomes based on a retrospective analysis.

Materials and methods

According to the purpose, 618 birth histories of singleton normal pregnancies, complicated by FGR, were analyzed in the city of Zaporizhzhia. Of these, in 546 cases, women gave birth to live infants (group I), and in 72 such cases, pregnancies ended up in a stillbirth (group II). In all the cases, the gestational age was ≥22 weeks, and the fetal weight was less than the 10th percentile for the relevant gestational age according to the current Order of the Ministry of Health of Ukraine No. 1718 dated 02.10.2023. The mean age of the pregnant women was 28.7 ± 6.8 years and 31.1 ± 7.4 years, ranged from 18 to 36 years, being significantly higher in the group II women ($p < 0.0001$).

Growth restriction in newborns was determined according to the criteria of the Consensus Definition (2018) including birth weight the $<3^{rd}$ percentile, or a combination of three of the following criteria:
1. birth weight the $<10^{th}$ percentile;
2. head circumference the $<10^{th}$ percentile;
3. prenatal diagnosis of FGR;
4. prenatal risk factors associated with FGR [23].

Stillbirth was defined as intrauterine fetal death after 22 weeks of gestation without any signs of life [24]. Stillborn gestational age was adjusted by subtracting two days from the gestational age at birth to correct an assumed average delay of 48 hours between intrauterine death and delivery [25].

Exclusion criteria from the study were: multiple pregnancy, the presence of a chromosomal abnormality in a fetus, an undetermined gestational age in the 1st trimester. Data on maternal and obstetric history, childbirth course, short-term neonatal outcomes, and detailed information about hospitalization of newborns were retrieved. The study was carried out in accordance with the current requirements of moral and ethical principles outlined in the Declaration of Helsinki (1964), the Conference of the Council of Europe on Human Rights and Biomedicine, as well as in the provisions of legislative acts of Ukraine.

The chosen study trend is related to the plan of research work of the Department of Obstetrics and Gynecology of Zaporizhzhia State Medical and Pharmaceutical University. Statistical processing of the results was carried out using licensed standard packages of multivariate statistical analysis application programs Statistica for Windows 13 (StatSoft Inc., No. JPZ804I382130ARCN10-J). Data were presented as M ± SD (mean ± standard deviation) or n/%. The Student's test was used in the testing of hypothesis for comparison of means between the groups. Differences were considered statistically significant at a level of $p < 0.05$.
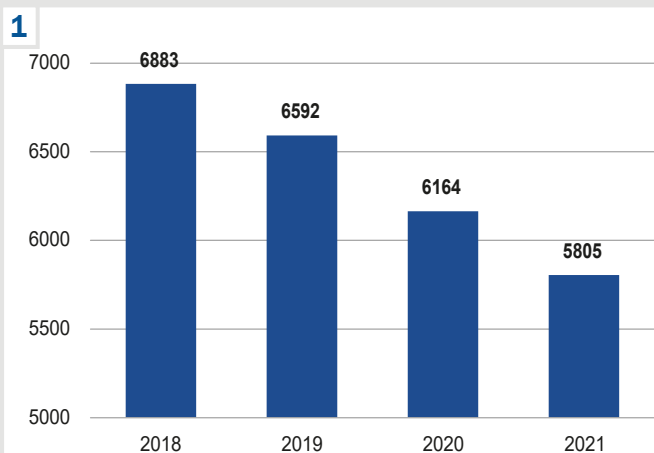
Fig. 1. The number of births in the city of Zaporizhzhia in 2018–2021.

Table 1. The analysis of the course of pregnancy and childbirth, n, (%)

Parameter	Group I (n = 546)	Group II (n = 72)	p
Gestational age at detection (weeks)	31.1 ± 2.1	30.2 ± 2.5	<0.0001
Cardio-vascular disorder	83 (15.2)	23 (31.94)	<0.0001
Chronic hypertension	6 (1.10)	10 (13.89)	<0.0001
Gestational hypertension	17 (3.1)	0 (0.0)	>0.05
Preeclampsia	31 (5.68)	4 (5.56)	>0.05
Severe preeclampsia	14 (2.56)	2 (2.78)	>0.05
Placental abruption	7 (1.28)	5 (6.94)	<0.001
Preterm birth	83 (15.2)	55 (76.4)	<0.0001
FGR detected	204 (37.36)	16 (22.22)	<0.01

Table 2. Neonatal outcomes in women of the studied groups, absolute percentage (%)

Parameter	Group I (n = 546)	Group II (n = 72)	p
Gestational age at birth (weeks)	35.5 ± 3.1	31.4 ± 2.8	<0.0001
Female sex	233 (42.7)	41 (56.9)	<0.05
Birth weight (g)	2360 (2180; 2630)	1130 (700; 1980)	<0.0001
Birth weight < 1000,0 g	7 (1.3)	16 (22.2)	<0.0001
Birth weight (percentile)	3.77 ± 0.21	4.12 ± 0.38	<0.0001
<1st percentile	209 (38.3)	19 (26.4)	<0.05
Birth weight (10th percentile)			
In all	82 (15.8)	17 (23.6)	<0.0001
<32 weeks	1 (1.2)	12 (16.7)	<0.0001
>32 weeks	81 (98.8)	5 (6.9)	<0.0001
Fetal distress*			
<3rd percentile	166/437 (38.0 %)	–	–
3–10th percentile	35/80 (43.8 %)	–	–

*: among group I fetuses.

Results

In the period from 2018 to 2021, there were 25,394 births at gestational ages of more than 22 weeks in the city of Zaporizhzhia. Of these, 71 cases were multiple births, 29 cases were detected with developmental anomalies, and 4 instances of an undetermined gestational age in the 1st trimester. The number of births in dynamics during the relevant period, both in Ukraine and the Zaporizhzhia region, has demonstrated a downward trend over four years *(Fig. 1)*.

Of the 25,290 studied births in the city of Zaporizhzhia from 2018 to 2021, 546 live-birth newborns (group I) showed signs of FGR, which was 2.38 % of total births. 196 (0.77 %) stillbirths were recorded over this period, including 176 (0.7 %) singleton pregnancies without fetal structural anomalies. The number of fetuses with FGR signs among stillborn (II group) was 72 (40.91 %) cases, which was 16 times more than those in group I.

The relative risk (RR) of stillbirth in the FGR presence was 28.4, 95 % CI [21.2; 38.3]. Additional risk was 11.0, 95 % CI [8.7; 13.8]. The odds ratio (OR) was 32.1, 95 % CI [23.3; 44.1].

The analysis of the stillbirth number throughout the period reviewed has shown an overall downward trend from 7.69 in 2018 to 6.84 in 2021 per 1,000 births, meanwhile, there was a rise in the percentage of fetuses with FGR signs in the structure of stillbirths, from 35.1 % to 50.0 %, respectively, over this period.

The analysis of the clinical and anamnestic characteristics *(Fig. 2)* has shown that the mothers of both studied groups were more often housewives with no statistically significant differences in the level of education, profession, and marital status (p > 0.05).

Every third woman in both groups smoked during pregnancy. The group I women gave the first birth more often – 307 (56.2 %) as compared to those in group II – 32 (43.4 %) (p < 0.001). Somatic pathology occurred in every fourth case in group II – 18 (25.0 %), which was statistically higher compared to the group I women – 89 (16.3 %) (p < 0.0001). Hypertensive disorders prevailed among somatic pathologies in group II – in 10 (13.9 %) women versus 6 (1.1 %) women in group I, in which kidney disease, anemia, obesity, and thyroid disease were more common *(Fig. 3)*.

In addition, traditional risk factors for FGR (chronic arterial hypertension, kidney disease, autoimmune diseases, stillbirth in anamnesis) were also more often detected in the group II women – 19 (26.4 %) versus 13 (2.4 %) in group I (p < 0.0001).

The analysis of the course of pregnancy and childbirth, presented in *Table 1*, has demonstrated that the mean gestational period at the time of diagnosis was between 31.7 ± 2 weeks in group I and 30.2 ± 2 weeks in group II (p < 0.001).

In the group II women, cardiovascular diseases (chronic arterial hypertension, varicose disease, somatomorphic disorders) were almost twice higher, but the incidence of preeclampsia was higher in the group I women. It is worth noting that preterm birth occurred in 22.33 % in both groups. Meanwhile, it was 5 times higher in group II (76.4 %) compared to group I (15.2 %) (p < 0.0001). A fairly low level of FGR antenatal diagnosis has to be noticed in both groups (35.6 %) with FGR diagnosis only in every fifth case by the time of birth (p < 0.05) in group II.

The mean gestational age at birth was statistically greater in the group I women – 35.5 weeks versus 31.4 weeks in group II (p < 0.0001). The analysis of the number of newborns depending on the gestational age has shown that the majority of births occurred at 38–40 weeks' gestation in group I. At the same time, two peaks of the maximum birth number were observed in group II, namely, at 28–36 weeks' gestation *(Fig. 4)*. The majority of stillbirth cases were diagnosed at these particular
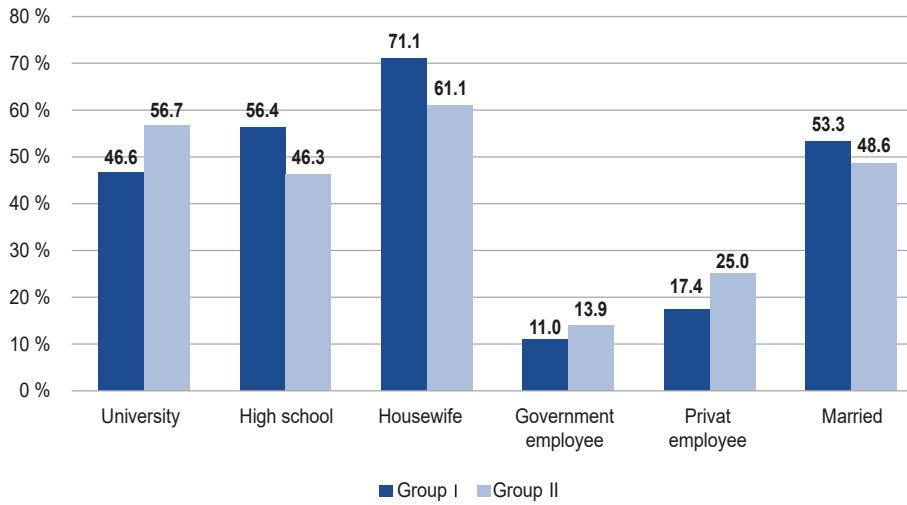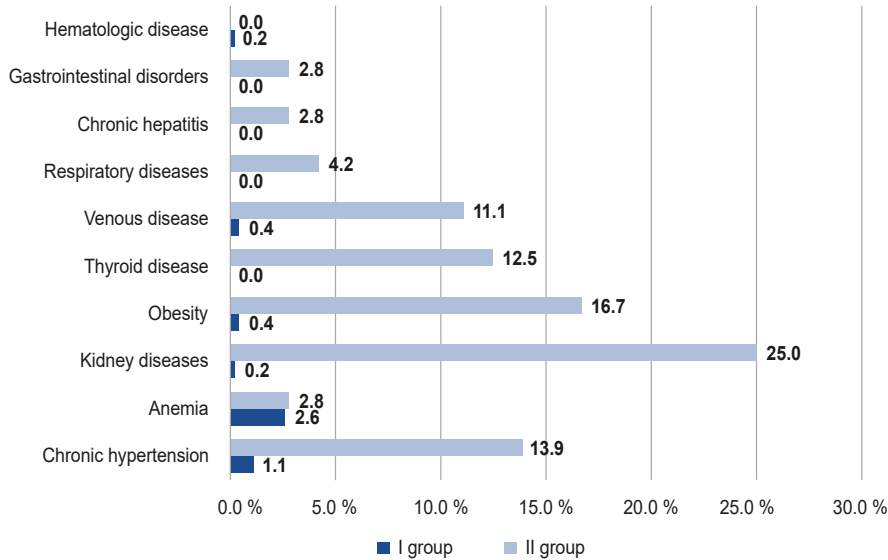
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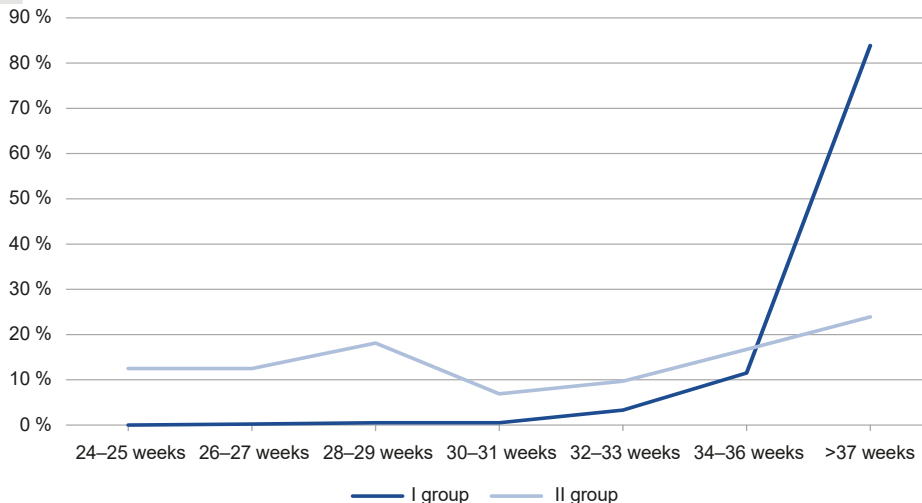
gestational periods, in which FGR was not identified before the moment of birth.

Notably, the number of infants born before 28 weeks of gestation was 4 times higher in group II and amounted to 25 %.

From the data presented in *Table 2*, it can be seen that there were significantly more female fetuses in group I, 57.23 % versus 43.77 % in group II (p < 0.001).

The mean weight of newborns in group I was 2360 [2180; 2630] g and 1130 [700; 1980] – in group II (p < 0.0001). Although fetuses with a birth weight of less than 1000 g predominated in group II due to the higher number of preterm births therein, the mean weight percentile was significantly greater in group II, namely 4.12 compared to 3.77 (p < 0.0001). However, the number of fetuses with a birth weight <1st percentile was significantly more in group I (p < 0.05). Distribution analysis of fetuses with the 10th percentile of birth weight in group II has revealed gestational age before 32 weeks in 16.7 % of cases and after 32 weeks – only in 6.9 % of cases, in contrast, group I fetuses with the 10th percentile of birth weight after 32 weeks' gestation accounted for 98.8 % (p < 0.0001). Regarding the frequency of fetal distress among group I fetuses, it was detected in 43.8 % (35/80) of fetuses with the 10th percentile of birth weight, and, accordingly, in 38.0 % (166/437) of fetuses with a birth weight of less than the 3rd percentile.

Discussion

The study results have found the prevalence of fetuses with FGR signs in the structure of stillbirths (40.9 %) over recent years. This indicator is higher compared to our earlier study of 2014–2018, where it was 38 % [26], as well as to the data of recently conducted studies in France and Japan (24.9 % and 34.4 %, respectively) [1,2]. Noteworthy is also the rate of FGR prenatal identification in these fetuses, which was only 22 %, being significantly lower than in European countries, where this rate varies from 31.0 % to 53.3 % [1], and in our earlier study, when this indicator amounted to 32.6 % [26]. The findings have indicated an increase in severe placental lesions in the structure of fetuses with growth restriction, resulting in early pathological process manifestations and progressive deterioration of the fetal condition, as evidenced by the lower mean gestational age in group II at the time of diagnosis, as well as the mean gestational age at the time of childbirth diagnosis (p < 0.0001). Meanwhile, with regard to live births, the indicators of prenatal diagnosis were almost the same when compared with the results of other studies [1], as the rate was 37.36 % in our study and 36.20 % in the French.

The majority of infants were full-term in group I, while two peaks of the maximum number of births were observed at 28- and 36-weeks' gestation in group II. Most cases of stillbirth occurred at these gestational periods, when FGR was not diagnosed prior to death. The mean body weight percentile was significantly higher in group II. The higher percentage of fetuses with the 10th percentile of body weight in group II, especially in terms of gestation before 32 weeks, has also been pointed out. The significantly greater number of fetuses with a body weight <1st percentile was also found in group I, which is consistent with the data of other studies [1,2,27,28,29,30].

It is worth giving a mention to the fact that the frequency of fetal distress in group I fetuses with the 10th percentile of body weight was significantly higher than in those with a body weight <1st percentile. The data presented indicate that FGR prenatal diagnosis based only on ultrasound assessment of fetal weight is better if the latter is more than 1000 g (28 weeks), but it is not adequate at gestational ages close to full-term pregnancy.

Conclusions

1. The conducted study results have shown a large percentage of FGR fetuses in the structure of stillbirths (40.9 %) with no downward trend.

2. Cardiovascular diseases take an important place in the structure of somatic pathology among women who experienced a stillbirth.

3. The childbirth results have indicated a significant predominance of preterm births among women of the stillbirth group compared to the group of women with a live birth.

4. A low level of FGR prenatal identification has been found in both groups (35.6 %), while in the group of stillbirths, the indicator was significantly lower and amounted to 22.22 %.

5. Statistical analysis has revealed that the presence of FGR resulted in a significant increase in the relative risk of stillbirth – 28.4, 95 % CI [21.2; 38.3]. Besides, the additional risk was increased (11.0, 95 % CI [8.7; 13.8]) if FGR was not diagnosed during pregnancy. At the same time, the odds ratio was 32.1, 95 % CI [23.3; 44.1].

Conflicts of interest: authors have no conflict of interest to declare.
Конфлікт інтересів: відсутній.

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