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; E – critical revision of the article; F – final approval of the article

Keywords: antenatal diagnosis, fetal growth restriction, stillbirth, perinatal consequences.

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, 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 in 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 <10th 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 22.2 %. 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. Проаналізовано 618 історій пологів з однолітніми, не аномальними вагітностями, які були ускладнені ЗРП, в м. Запоріжжя. З них у 546 випадках ЗРП жінки народили живу дитину (І група), а в 72 випадках вагітність завершилася мертвонародженням (ІІ група). Середній вагітніх у групах дослідження становив 28.7 ± 3.1 та 31.7 ± 3.1 року відповідно; достовірно більший – у ІІ групі (p < 0.0001). У всіх випадках термін вагітності становив 22 тижні, а маса плода – менша за 10 процентиль 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 <10 процентиль; обвід голови <10 процентиль; ширина обвідшу голови при народженні <10 процентиль. Результати дослідження показали, що частота акушерських та перинатальних наслідків у групах значно варіювалися.

Результати. У ІІ групі визначено істотну частку плодів з ознаками ЗРП: у 17 разів більше щодо відповідного показника в І групі. Результати дослідження показали досить низький рівень допологової ідентифікації ЗРП в обох групах (35.6 %). Зазначимо, що в ІІ 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 ІІ групи (p < 0.0001) з максимальною кількістю пологів у цій групі в термінах 28 і 36 тижнів гестації. Середній вагітніх у групах дослідження становив 28.7 ± 3.1 та 31.7 ± 3.1 року відповідно; достовірно більший – у ІІ групі (p < 0.0001). У всіх випадках термін вагітності становив 22 тижні, а маса плода – менша за 10 процентиль 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 <10 процентиль; обвід голови <10 процентиль; ширина обвідшу голови при народженні <10 процентиль. Результати дослідження показали значну частку плодів з ознаками ЗРП у структурі мертвонароджених, що не має тенденції до зниження. Встановлено низький рівень допологової ідентифікації ЗРП в обох групах (35.6 %), у групі мертвонародження цей показник становив 22.2 %. Статистичний аналіз свідчить, що нівелю ЗРП призводить до значного підвищення вагітності, різниця щодо вагітності, додатковий ризик зростає на 11.0, 95 % ДІ [8.7; 13.8]. Відношення шансів (ОР) 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 increase 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, perinatal 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 <3rd percentile, or a combination of three of the following criteria:
1. birth weight the <10th percentile;
2. head circumference the <10th 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. JZ804382130ARCHN10-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.
Table 1. The analysis of the course of pregnancy and childbirth, n, (%)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group І (n = 546)</th>
<th>Group ІІ (n = 72)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at detection (weeks)</td>
<td>31.1 ± 2.1</td>
<td>30.2 ± 2.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardio-vascular disorder</td>
<td>83 (15.2)</td>
<td>23 (31.34)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>6 (1.10)</td>
<td>10 (1.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>17 (3.1)</td>
<td>0 (0.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>31 (5.68)</td>
<td>4 (5.6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Severe preeclampsia</td>
<td>14 (2.56)</td>
<td>2 (2.78)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>7 (1.28)</td>
<td>5 (6.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>83 (15.2)</td>
<td>55 (74.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FGR detected</td>
<td>204 (37.36)</td>
<td>18 (22.22)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group І (n = 546)</th>
<th>Group ІІ (n = 72)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at birth (weeks)</td>
<td>35.5 ± 3.1</td>
<td>31.4 ± 2.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex</td>
<td>233 (42.7)</td>
<td>41 (56.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2360 (2180-2630)</td>
<td>1100 (700-1980)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Birth weight &lt; 1000,0 g</td>
<td>7 (1.3)</td>
<td>16 (22.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Birth weight (percentile)</td>
<td>3.77 ± 0.21</td>
<td>4.12 ± 0.38</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;1 percentile</td>
<td>209 (38.3)</td>
<td>19 (26.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Birth weight (10 percentile)</td>
<td>82 (15.8)</td>
<td>17 (23.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>In all</td>
<td>1 (1.2)</td>
<td>12 (16.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;32 weeks</td>
<td>81 (98.6)</td>
<td>5 (6.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;32 weeks</td>
<td>168/437 (38.0 %)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fetal distress*</td>
<td>35/80 (43.8 %)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*: among group І 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 І) 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 (ІІ group) was 72 (40.91 %) cases, which was 16 times more than those in group І.

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 І women gave the first birth more often – 307 (56.2 %) as compared to those in group ІІ – 32 (43.4 %) (p < 0.001). Somatic pathology occurred in every fourth case in group ІІ – 18 (25.0 %), which was statistically higher compared to the group І women – 89 (16.3 %) (p < 0.0001). Hypertensive disorders prevailed among somatic pathologies in group ІІ – in 10 (13.9 %) women versus 6 (1.1 %) women in group І, 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 anamnysis) were also more often detected in the group ІІ women – 19 (26.4 %) versus 13 (2.4 %) in group І (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 І and 30.2 ± 2 weeks in group ІІ (p < 0.001).

In the group І women, cardiovascular diseases (chronic arterial hypertension, varicose disease, somatomorphic disorders) were almost twice higher, but the incidence of preeclampsia was higher in the group І women. It is worth noting that preterm birth occurred in 22.33 % in both groups. Meanwhile, it was 5 times higher in group ІІ (76.4 %) compared to group І (15.2 %) (p < 0.001). 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 ІІ.

The mean gestational age at birth was statistically greater in the group І women – 35.5 weeks versus 31.4 weeks in group ІІ (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 ІІ. At the same time, two peaks of the maximum birth number were observed in group ІІ, namely, at 28–36 weeks’ gestation (Fig. 4). The majority of stillbirth cases were diagnosed at these particular...
Fig. 2. Clinical and anamnestic characteristics of the studied groups.

Fig. 3. Somatic pathology in the studied groups (%).

Fig. 4. Percentage of newborns by weeks of gestation in the studied groups (%).
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 <1 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, the mean weight percentile was significantly higher than in those with a body weight <1% 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 22.2%.

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].

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Conflicts of interest: authors have no conflict of interest to declare.

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