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Современный взгляд на причины антенатальной гибели плода

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АННОТАЦИЯ

Ежегодно регистрируют около 2 млн случаев антенательной гибели плода, то есть каждые 16 с рождается мертвый ребенок. Однако даже столь внушительные данные не отображают весь масштаб проблемы. Данные Всемирной организации здравоохранения не включают показатели мертворождаемости на сроках 22–28 нед., что по оценкам ряда исследований, ведет к увеличению показателя примерно на 40 %. Различия по мертворождаемости в развитых и развивающихся странах указывает на уровень медицинского обслуживания и, как следствие, качества медицинской системы страны. По данным Федеральной службы государственной статистики, показатель мертворождаемости на территории Российской Федерации составляет большую долю перинатальных потерь (79 %) без тенденции к снижению. Кроме того, в настоящее время отсутствует единая классификация причин антенатальной гибели плода, что затрудняет анализ случаев мертворождаемости и возможных резервов ее снижения. Важно отметить, что доля случаев с неустановленной причиной перинатальной смертности растет: в 2019 г. она составила 3,1 %, в 2020 г. — 4,7 %. Несмотря на то что показатель необъяснимых причин антенатальной гибели плода в Российской Федерации почти в 3 раза ниже по сравнению с зарубежными, большая доля причин, связанных с асфиксией плода, лишает эти данные конкретики. На фоне демографического кризиса в Российской Федерации (коэффициент рождаемости в 2022 г. составил 1,4) выявление факторов риска антенатальной гибели плода стоит особенно остро, поскольку лежит в основе создания профилактических мер с целью снижения риска неблагоприятных акушерских исходов.

Ключевые слова: антенатальная гибель плода; мертворождение; факторы риска; беременность.

Как цитировать

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Modern view of the causes of antenatal fetal death

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ABSTRACT

About two million cases of prenatal fetal death are recorded annually, that is, a stillborn baby is born every 16 seconds. However, even such impressive data does not reflect the full scale of the problem. The WHO data does not include stillbirth rates at 22–28 weeks, which some studies estimate would increase the rate by about 40%. The difference in stillbirth rates in developed and developing countries indicates the quality of medical care and, as a result, the country's medical system. According to the Federal State Statistics Service, the stillbirth rate in the Russian Federation accounts for a large share of perinatal loss (79%) and does not have a downward trend. Besides, there is currently no unified classification of the causes of prenatal fetal death, which complicates the analysis of stillbirth cases and possible reserves for their reduction. It is noteworthy that the proportion of cases with an unknown cause of perinatal mortality is growing (3.1% in 2019 and 4.7% in 2020). Despite the fact that the rate of unexplained causes of antenatal fetal death in the Russian Federation is almost three times lower than abroad, the large proportion of causes associated with fetal asphyxia deprives these data of specificity. Against the backdrop of the demographic crisis in the Russian Federation (the birth rate for 2022 was 1.4), identifying risk factors for antenatal fetal death is especially acute, since this underlies the creation of preventive measures to reduce the risk of adverse obstetric outcomes.

Keywords: antenatal fetal death; stillbirth; risk factors; pregnancy.

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Antenatal fetal death (AFD) is defined as the cessation of fetal cardiac contractions after 22 completed weeks of gestation and before labor begins [1]. The global prevalence of stillbirth is estimated at 1.9 million every year, including cases occurring between 22 and 28 weeks of gestation. The incidence of stillbirth ranges from 1 to 31 per 1,000 births in different countries [2]. In developing countries, stillbirth rates are higher (up to 97%) than in developed countries due to the level and availability of medical care [2, 3]. Stillbirth rates in high-income countries declined dramatically from about 1940, but this decline has slowed or stalled over recent times [4]. Some cases remain unexplained due to the multifactorial nature of AFD [5]. Early identification of risk factors and adequate prenatal care can reduce the number of potentially preventable stillbirths and improve pregnancy outcomes.

Some authors report maternal age as a risk factor for AFD [6–9]. The average age at birth continues to rise worldwide every year, more than doubling the risk of adverse perinatal outcomes [6, 7]. For example, Saccone et al. showed a direct correlation between the increased risk of AFD and maternal age of 40 years or older [6]. Some authors obtained similar results, but in a population older than 35 years [8, 9].

Gestational obesity is associated with the high risk of gestational diabetes mellitus and gestational hypertension, both of which can be complicated by AFD [10]. There are conflicting data on whether obesity is an independent risk factor for stillbirth [11–14]. Shinohara et al. and Pritchard et al. showed that the risk of AFD was positively associated with an increase in the body mass index (BMI) above 25 kg/m^2 [11, 12]. Ikedionwu et al. showed that women with morbid obesity (BMI of 40 kg/m^2 or more) had a 9-fold higher risk of AFD than those with normal weight [13]. Mahomed et al. reported a controversial position because they found no statistically significant association between the incidence of stillbirth and an increase in BMI [14]. However, the authors reported that AFD in obese women is associated with pre-existing extragenital conditions or current obstetric complications [14].

Both active and passive smoking during pregnancy increase the risk of AFD [15, 16]. Qu et al. found a more than 2-fold increase in the risk of stillbirth with active maternal smoking and a 1.7-fold increase in the risk with passive smoking (compared with non-smoking women) [16]. Pathogenetically, components of tobacco smoke cause a decrease in the expression of oxidative protective enzymes and an increase in DNA susceptibility to oxidative damage in the placenta [17].

Alcohol abuse has also been evaluated in the context of the AFD risk. Ethanol is the most commonly abused substance during pregnancy and a recognized public health issue [18]. Worldwide, approximately 10% of women in the general population consume alcohol in pregnancy [18]. Odendaal et al. showed that the risk of stillbirth in pregnant women who consume alcohol is 2 times higher than in abstinent women [15]. In addition, combined smoking and ethanol consumption tripled the risk of AFD compared with controls [15].

Sleep disturbances are considered to be another risk factor for AFD. A meta-analysis by Lu et al. evaluated studies on the association between maternal sleep during pregnancy and adverse fetal outcomes [19]. Four maternal sleep parameters were assessed, including respiratory disorders, sleep duration, sleep quality, and sleep position [19]. Women who had less than 6 hours or more than 8 hours of sleep per night during the third trimester were more than three times more likely to have a stillbirth than women who had 6–8 hours of sleep per night [19]. Falling asleep in the supine position increased the risk of AFD compared to sleeping on the left side. Studies reported rates ranging from 4% to 37% [19, 20]. One hypothesis explained the association between sleep disturbances and AFD as effects of maternal sleep position on fetal cardiac output and oxygen saturation [19, 20]. The enlarged uterus compresses the vena cava and aorta in the supine or right lateral position, resulting in decreased uterine blood flow and subsequent fetal hypoxia [19, 20].

Stillbirth prevention includes careful prenatal monitoring of pregnant women in an outpatient setting. The World Health Organization currently recommends a minimum of four antenatal visits for uncomplicated pregnancies [21]. Prenatal care allows healthcare providers to monitor pregnancy and inform women about their health status and the condition of the fetus [22–24]. Mukherjee et al. conducted a study to assess the role of antenatal care in preventing stillbirths [22]. The authors concluded that gestational age at the time of the prenatal care visit was not associated with an increased risk of AFD [22]. However, women who attended less than 50% of the recommended visits were three times more likely to have a stillbirth than women who attended all visits [22]. A statistically significant association was also found between decreased number of visits and increased risk of stillbirth [22]. Kumar et al. found that the incidence of AFD was almost 10 times higher in pregnant women with small-for-gestational-age fetuses [23]. Therefore, identification of small-for-gestational-age fetuses may reduce the risk of stillbirth, highlighting the important role of regular voluntary antenatal care [22, 23].

With increasing gestational age, the risk of AFD associated with cord anomalies (such as true knots in cord and marginal and velamentous insertion of the cord) increases ranging from 19% to 56.6% of stillbirths, with an incidence of 5.7 per 1,000 births [25].

The stillbirth rate in pregnancies complicated by maternal extragenital disease is 6–7 per 1,000 births, or about 10% of AFD cases [10]. Among these conditions, hypertension and diabetes mellitus are the most prevalent [26–28].

Hypertension complicates pregnancy in 7%–10% of cases [10, 26]. Approximately 5.6%–9.4% of pregnancies complicated by chronic hypertension and pre-eclampsia result in AFD [26]. The stillbirth rate is 5–52/1000 births, depending on the severity of complications from hypertension [26]. Prevention of progression to pre-eclampsia and subsequent complications such as placental abruption (also a possible cause of AFD) remains the primary goal of care for women with high-risk pregnancies [27]. For example, in pregnancies complicated by pre-eclampsia, the risk of stillbirth is 1.5 to 1.9 times greater than in normotensive pregnancies [26]. The causes and extent of placental abruption are positively correlated with the severity of placental blood flow disturbance and fetal asphyxia [10]. Placental abruption complicates 1.00%–3.75% of pregnancies and is present in 9.0%–15.2% of stillbirths [10]. The incidence of AFD due to placental abruption is approximately 0.5 per 1,000 births [10]. Although the etiology of most cases of placental abruption is unknown, there are several predisposing factors, both traumatic and non-traumatic [29, 30]. Traumatic factors are associated with accidents, whereas non-traumatic factors are usually associated with a history of caesarean section, hypertensive disorders, parity, maternal age, and smoking [29, 30]. Therefore, the number of preventable stillbirths due to placental abruption can be reduced by monitoring pregnancy and preventing predisposing factors.

Approximately 3% of stillbirths are caused by diabetes mellitus. The incidence of AFD in pregnancies complicated by diabetes mellitus is 5–35 per 1,000 births [10]. Meta-analysis by Malaza et al. showed that diabetes increased the risk of stillbirth by 2–5 times [27]. Pregestational type 1 or type 2 diabetes mellitus increases the risk of AFD by 3 times compared to gestational diabetes mellitus [27], which is also a risk factor for stillbirth [27]. There are also controversial data. Lemieux et al. found no significant association between gestational diabetes mellitus and AFD [31]. In addition, with appropriate management of gestational diabetes, pregnancy outcomes are similar to those in the general population [31].

Hypothyroidism is a risk factor for pre-eclampsia, fetal growth restriction, and AFD [32]. Hypothyroidism accounts for about 0.83% of the total number of stillbirths [10]. Delayed treatment of thyroid dysfunction increases the risk of stillbirth [32]. With adequate treatment of hypothyroidism, the risk of fetal death is no greater than that with normal thyroid function [32].

Systemic lupus erythematosus (SLE) is an autoimmune disease in young women of reproductive age [33]. The overall stillbirth rate is 3.6%–7.1% for pregnancy complicated by SLE [33]. The incidence of AFD of 40–150 per 1,000 births was observed in women with SLE diagnosed prior to pregnancy [32, 33].

Antiphospholipid syndrome is an autoimmune blood coagulation disorder that manifests as habitual miscarriage and vascular thrombosis [33]. However, in patients with antiphospholipid syndrome, pregnancy may be complicated by both early reproductive loss and AFD [32]. Antiphospholipid antibodies were found in 9.5% of women with a history of stillbirth [32].

About 10%–20% of stillbirths are attributed to intrinsic fetal anomalies, giving a stillbirth rate of 0.5–0.9 per 1000 births [33, 34]. In fetuses with birth defects, the risk of AFD was found to be 20 times higher than in normal fetuses [33]. Anencephaly was the most common cause of stillbirth in fetal birth defects [33]. Fetal chromosomal abnormalities are present in 6%–13% of stillbirths [34]. Monosomy X and trisomy 21 are the most common chromosomal abnormalities in stillbirths, followed by Edwards' syndrome and Patau's syndrome [34].

Premature rupture of membranes (PROM) has a multifactorial nature and the prognosis depends on the gestational age [35]. ROM accounts for 0.8% of total stillbirths, a stillbirth rate of 0.03/1000 births [36]. However, with chorioamnionitis (a common complication of PROM), the incidence of AFD increases to 22.6%–36.9% of stillbirths [37, 38]. After 28 weeks of gestation, PROM and chorioamnionitis represented nearly 6% of stillbirths, whereas before this gestational age, the rate increased to 15% [37, 38].

The role of the infectious component in stillbirth should not be underestimated. Cytomegalovirus (CMV) is a common intrauterine infection, as 50%–95% of pregnant women have anti-CMV antibodies [35]. Currently, the association of AFD with CMV is mainly based on isolated case reports [35]. However, Page et al. showed that 8% of infection-related stillbirths were associated with CMV [39].

Hepatitis virus infection causes more than 3,000 stillbirths annually [39]. Velavan et al. showed that, unlike hepatitis E, hepatitis B and C are not associated with an increased risk of stillbirth, but are associated with other adverse pregnancy outcomes, including spontaneous abortion [40].

Globally, approximately 38.6 million people are infected with HIV, with 2 million new cases annually [41]. According to the World Health Organization, half of all infections occur in women of reproductive age [41]. HIV infection, especially with high viral load, can increase AFD risk 1.67-fold compared with healthy women [42]. In addition, the risk doubled in women not receiving antiretroviral therapy and in those with co-infections, including CMV, hepatitis C, and active tuberculosis [42].

Some studies show an association between adverse pregnancy outcomes and novel influenza strains [43, 44]. Fell et al. showed that the risk of AFD in pregnant women with H1N1 influenza was 2.35 times higher than the risk in healthy patients [44].

Group B streptococcus is known to infect a fetus in both the second and third trimesters and can lead to stillbirth

[45–47]. Some data estimate that there were approximately 57,000 (range: 12,000 to 104,000) group B streptococcus-associated stillbirths worldwide in 2015 [48]. Stephens et al. used molecular analysis and showed that colonization with group B streptococcus increased the risk of stillbirth by 7.6 times [47].

In many cases, AFD remains an unpredictable pregnancy outcome. Despite multiple studies, the rate of unexplained stillbirths has not decreased. Identification of pathogenetic mechanisms of AFD is crucial for primary prevention of stillbirth. Further research is required to understand the causes of AFD and improve its prevention.

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