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Risk factors, predictive markers and prevention strategies for intrauterine fetal death. An integrative review

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ABSTRACT

According to World Health Organization (WHO), fetal death is defined as the death of the fetus prior to its complete expulsion, independent of the duration of pregnancy, thus only ascribing the term stillbirth to fetal deaths in the case of pregnancies after 28 weeks of gestation. The great progress of perinatology care is reflected in a significant reduction in the rate of stillbirths, especially in well-developed countries, with approximately 98% of stillbirth cases now occurring in poor and developing countries. Stillbirth powerfully impacts both the patient and the practitioner. Because nearly half of stillbirth cases result from apparently uncomplicated pregnancies, we considered it critical to review the known predictive markers for intrauterine fetal death. In both preterm and term infants, perinatal mortality is increased in fetuses small for their gestational age, and this risk grows proportionally with the severity of the fetal growth restriction. A protracted first stage of labor has not been associated with an increased risk of perinatal mortality and morbidity, but a prolonged second stage of labor has been associated with mortality and neonatal morbidity characterized by sepsis, seizures, and hypoxic-ischemic encephalopathy. Ultrasound examination of the placenta and the umbilical cord is essential for appropriate pregnancy monitoring. Various findings from ultrasound examination have been related to variable adverse perinatal outcomes, including intrauterine fetal death. After reviewing the evidence for predictors of intrauterine fetal death, we offer a general strategy for reducing the likelihood of stillbirths.

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Introduction

The preferred term for intrauterine fetal death, describing the in-utero death of a fetus after 24 weeks of gestation, or at least 500 grams, is stillbirth. According to the World Health Organization (WHO), fetal death is defined as the death of the fetus prior to its complete expulsion, independent of the duration of pregnancy, ascribing the term stillbirth only to fetal deaths in case of pregnancies after 28 weeks of gestation [1]. The limit between miscarriage and stillbirth varies from country to country, ranging between 16 and 28 weeks of gestation [2-4]. Conversely, stillbirth can be "early" if it occurs between 20 and 27 weeks of gestation and "late" if it complicates pregnancies with a gestational age higher than 28 weeks. If the gestational age is unknown, the second criterion that differentiates a miscarriage from a stillbirth is the weight and the length if the first two mentioned are unavailable (cut-off 25 cm).

The great progress of perinatology is reflected in the significant reduction in the rate of stillbirths, especially in developed countries, with approximately 98% of stillbirth cases occurring in underdeveloped and developing countries [5]. A number of fetal, maternal, and placental factors correlate with the still birth rate, including black race, extreme maternal age, marital status, multiple gestations, and fetal sex [6,7]. According to McClure et al, the main factors responsible

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are prolonged labor, preeclampsia, and infectious factors in developing countries, and congenital and various karyotype anomalies in developed countries [8].

Stillbirth strongly impacts both the patient and the practitioner, especially since nearly half of stillbirths result from apparently uncomplicated pregnancies. Stillbirth that occurs in early term is more likely to have an obvious cause than one that occurs in late term [9-11]. Stillbirth that cannot be explained by an obvious maternal, fetal, placental or obstetric factor has an impressive incidence of 25 to 60%, with two thirds of these cases occurring after 35 weeks of gestation. Given its relatively high rate of unpredictability, we considered it important to review the known predictive markers for intrauterine fetal death.

Discussions

Fetal growth restriction and intrauterine fetal death

A fetus diagnosed with fetal growth restriction, meaning an estimated fetal weight below the 10th percentile for its gestational age, implies a differential diagnosis that distinguishes between a constitutionally small fetus versus growth restriction from placental, fetal, or maternal pathologies [12-15]. This differentiation is important due to the associated adverse perinatal outcomes, including preterm delivery, impaired thermoregulation, impaired immune function, perinatal asphyxia, hypoglycemia, diabetes, and mortality. According to Zeitlin et al. [9], in both preterm and term infants, perinatal mortality is increased in fetuses small for their gestational age. This risk grows proportionally with the severity of the fetal growth restriction and shows a steep rise when fetal weight is below the 6th percentile. In one recent study, researchers examined more than 1.5 million singletons' births and found a significant difference in neonatal mortality between term infants without fetal growth restriction (0.6/1,000) and term infants with fetal growth restriction (2.8/1,000), and a larger difference between preterm infants with normal weight (22.9/1,000) and preterm infants with fetal growth restriction (60.0/1,000) [16]. The authors concluded that methods that can detect and prevent fetal growth restriction represent important tools in decreasing fetal mortality.

In our unit, the Department of Obstetrics and Gynecology, University Emergency Hospital Bucharest, we conducted a retrospective study over a period of 5 years, January 2014 – October 2018, on 1405 preterm infants and term infants with fetal growth restriction [17-20]. The overall results agree with previously cited results [10,21,22]. Table 1 lists the short-term complications encountered in the studied population, with the study group divided as follows: Group 1 consists of preterm newborns small for their gestational age; Group 2 consists of preterm newborns appropriate for their gestational age; and Group 3 consists of term newborns small for their gestational age.

Table 1. The incidence of newborns in preterm and term newborns with intrauterine fetal growth restriction [9].

Characteristic	Group 1		Group 2		Group 3		Total		P value
	No.	%	No.	%	No.	%	No.	%	
Total subjects	78	6%	1,121	80%	206	15%	1,405	100%	
Males	37	3%	573	41%	85	6%	695	49%	0.032
Demise	14	18%	51	5%	2	1%	67	5%	<0.001

The shaded row of the table highlights the differences in perinatal mortality among the three groups, with the highest percentage corresponding to the preterm infants with growth restriction. No difference was found between term infants with fetal growth restriction and preterm infants with a weight appropriate for their gestational age.

We developed a management protocol for complicated cases with fetal growth restriction that includesd: (1) serial ultrasound evaluation, biophysical profile, and Doppler velocimetry (from one to seven times per week) for guiding the subsequent pregnancy management; (2) administering antenatal corticosteroids for pregnancies from 24 to 34 weeks of gestation; and (3) executing immediate delivery of fetuses with abnormal ductus venosus Doppler flow rates prior to 32 weeks gestation, reversed diastolic flow of the umbilical artery at a gestational age greater than 32 weeks, or absent diastolic flow of the umbilical artery at the gestational age over 34 weeks. In order to prolong the duration of pregnancy over 32 weeks gestation, daily biophysical profiles were recommended, and delivery was

imposed only by reversed diastolic flow of the umbilical artery associated with an abnormal biophysical profile.

Prolonged labor and fetal death

Conventionally, labor abnormalities are described as protraction disorders or arrest disorders. An abnormally long active phase is called protracted, and an abnormally long latent phase is described as prolonged [23]. Regarding effects on the mother, these disorders are associated with an increased risk of postpartum hemorrhage, operative vaginal delivery, caesarean delivery, third or fourth degree perineal lacerations, and chorioamniotitis [24, 25]. As for the neonate, a protracted first stage of labor has not been associated with an increased risk of perinatal mortality and morbidity, whereas a prolonged second stage of labor has been associated with mortality and neonatal morbidity that can includes sepsis, seizures, and hypoxic-ischemic encephalopathy [26,27]. Usually, a prolonged second phase of labor is associated with fetal macrosomia or persistent malposition, thus increasing the risk of perinatal mortality and morbidity. The duration of the second phase is considered prolonged if a nulliparous woman has pushed for three hours or a multiparous woman has pushed for two hours, in the absence of epidural anesthesia, with a minimum or absent progression [28].

Augmentation with oxytocin is indicated after 60-90 minutes of pushing if birth progression is minimal or absent, and the uterine contractions have a frequency of less than 1 to 3 minutes, considering the fact that the main causes of prolonged second phase are macrosomia, a small maternal pelvis, and malposition or malpresentation, but not hypocontractility specifically during the first phase of labor. Extending these intervals is allowed only if a safe vaginal delivery is achievable from an obstetrical point of view, assessed by careful weighing of the risks and benefits that take into account obstetrical history, clinical pelvimetry, maternal height and weight, fetal position, surgical history, estimated fetal weight, fetal heart rate, and the patient's consent after understanding the risks of prolonging labor [29-32].

Interventions have been aimed at preventing the prolongation of labor, such as delayed pushing, changed maternal position, and pelvic floor muscle exercises. None of these interventions appears to affect the length of the second phase [18, 33].

Pathology and intrauterine fetal death

Ultrasonic examination of the placenta and the umbilical cord is essential for appropriate pregnancy monitoring. Multiple findings on sonographic examination can be related to adverse perinatal outcomes, including intrauterine fetal death. Here we discuss the particular ultrasound aspects of the umbilical cord and the placenta, along with their association with poor perinatal prognosis.

1. *Single umbilical artery* - This diagnosis is based on the visualization of a single vessel around the fetal bladder, occurring in about 0.5% of pregnancies. This characteristic has been associated with maternal diabetes, smoking, and seizure disorders [34, 35]. The outcome of such cases is influenced by the associated conditions. Single umbilical artery without other anomalies does not demonstrate a statistically significant increase in fetal, neonatal, and infant death [20], but results in an increased risk when associated with anatomical and chromosomal anomalies. Recommended antepartum fetal monitoring, in the absence of other associated conditions, involves following fetal growth every 4-6 weeks, as there is a significant association between single umbilical artery and intrauterine growth restriction. A postnatal renal screening of infants should also be considered if the kidneys were poorly visualized on prenatal ultrasound [36, 37].

2. *Hypoplasia* of one umbilical artery may occasionally be diagnosed during ultrasound screening. There is no standard definition for the disparity between the sizes of the umbilical arteries. This condition has a higher prevalence in the high-risk population, and thus screening for other fetal anomalies should be performed.

3. *Aneurysm and varix* of the umbilical cord have a low incidence, but they are also highly associated with fetal demise through rupture, intra-amniotic hemorrhage, and fetal exsanguination [21, 38]. If this abnormality is diagnosed prenatally, frequent fetal monitoring with non-stress testing, ultrasound, and delivery after lung maturation are indicated [22, 23].

4. *Velamentous cord insertion* has a prevalence of 1% in singleton pregnancies, and it can be diagnosed through prenatal ultrasound examination by observing the umbilical cord insertion several centimeters from the placenta at the point where the umbilical vessels divide [39]. Fetal death can occur when fetal membranes rupture, which can lead to the rupture of the umbilical vessels, especially in the case of vasa previa [25, 40]. Considering these complications, if the ultrasound examination suggests velamentous cord insertion, a detailed ultrasound screening is required for the evaluation of coexisting vasa previa. Moreover, serial assessment of fetal growth, weekly non-stress testing after 36 weeks of gestation, and delivery at 40 weeks of gestation are also recommended. Specifically, these cases require continuous intrapartum fetal heart monitoring [41-43].

5. *True knot in* the cord is associated with a high risk of fetal demise if the knot is tight or multiple [44, 45]. These pregnancies require close monitoring particularly in the last trimester, with serial ultrasound examinations that include Doppler evaluation, assessment of fetal growth, determining amniotic fluid index, biophysical profile scoring, and non-stress testing.

6. *Abruptio placentae* affects about 1% of pregnancies, with the sensitivity of a prenatal ultrasound for this condition at only 25-60% [27, 46]. Chronic abruption is associated with a high risk for fetal growth restriction and all the consequences of this pathology, whereas acute abruption has a perinatal mortality of 3 to 12%, with more that 50% of these cases ending in stillbirth [47]. The diagnosis is mainly clinical, and the details of management include continuous fetal monitoring, secure intravenous access, monitoring the maternal hemodynamic status, and evaluating for coagulopathy [48, 49]. Subsequent medical decisions will depend on fetal and maternal status. Immediate delivery is recommended if the fetal heart rate pattern is non-reassuring or ominous. If the mother and the fetus are stable, but an abruption placenta is suspected, delivery is suggested for pregnancies after 34 weeks of gestation, as the benefits of delivery at this time surpass the risks. Because the risk of recurrence of this pathology (3-15%) is common, a subsequent pregnancy for the patient should be considered a high-risk pregnancy.

7. *Placenta previa* is associated with a 3-5 times increased risk of preterm birth [50, 51]; thus perinatal and neonatal morbidity and mortality are directly related to prematurity complications. In order to reduce neonatal morbidity and mortality rates, the administration of antenatal corticosteroids before 34 weeks of gestation is recommended for all placenta previa cases, and planned late preterm cesarean delivery should be considered. Several characteristics appear predictive of antepartum bleeding, including a cervical length less than 3 centimeters, and a decrease in cervical length in the last trimester, as well as a thick placental edge with echo free space over the internal os [52].

Post-term pregnancy

A post-term pregnancy may be associated with continued fetal growth with a subsequent birth of a large fetus, or a poorly functional placenta, resulting in fetal growth restriction and a small malnourished fetus for the gestational age [53]. A recent study [54] regarding the incidence of stillbirths in post-term pregnancies has indicated a twofold increase compared to term pregnancies. Factors that increase perinatal mortality incidence are feto-placental insufficiency, asphyxia, intrauterine infection, primigravidity, and older maternal age [55]. For singleton, cephalic, uncomplicated pregnancies, the induction of labor at 41 weeks gestation, irrespective of the cervical status, is recommended in the context of a well predefined gestational age and a reassuring fetal assessment. This approach offers a 70% reduction in perinatal mortality and stillbirth [56]. Each decision must be adapted to the individual case, with the maternal perception of decreased fetal movement considered a marker for increased risk of fetal death [57].

Gestational diabetes

Pregnancies involving gestational diabetes require monitoring and treatment of the conditions associated with glucose impairment. The risk of stillbirth associated with gestational diabetes is higher than in the general population, and it is primarily related to poor glycemic control [58]. The presence of polyhydramnios appears to be an important marker for an increased stillbirth risk in all non-anomalous pregnancies with or without gestational diabetes [59]. Good glycemic control is the essential point in the management of these cases. Antenatal fetal testing includes non-stress testing twice a week and ultrasound examination of the amniotic fluid beginning at 32 weeks of gestation for all women with a poor glycemic control or treatment with insulin or oral anti-hyperglycemic drugs. Optimal timing of delivery for pregnancies with gestational diabetes may help avoid possible complications, including stillbirth. After discussing the risks and benefits with the patient, a recommended approach is to induce labor for euglycemic women after 39 weeks gestation, and for women with medically controlled gestational diabetes at 39 weeks gestation. For women with poor glycemic control, delivery at 37+0 - 38+6 weeks gestation is considered reasonable [38, 60].

Infections

Infection is responsible for one half of stillbirths in developing countries and 10 to 25% in developed countries [61, 62]. The effect is mediated through severe systemic maternal illness, placental infection, and placental dysfunction, or through fetal systemic illness. Most cases cause premature birth due to preterm premature rupture of membranes. Trans-placental infection is caused mostly by viral pathogens and less frequently by bacteria, fungi, spirochetes, and protozoa. Fetal death due to infection is not common, even though almost all systemic infections that occur during pregnancy can cause placental infection. In endemic areas, malaria is a common cause of stillbirth. Well-known maternal infections that can lead to fetal

demise include cytomegalovirus, parvovirus, toxoplasmosis, listeria, and herpes simplex virus [63, 64]. Asymptomatic maternal vaginal infections are highly frequent, therefore, successive screening for urinary and genital infection during pregnancy is mandatory.

It is important to mention infection with Group B streptococcus, which is a frequent cause of asymptomatic bacteriuria, as well as urinary tract infection and upper genital tract infection. Data from Centers for Disease Control and Prevention (USA) indicate a 0.12 per 1000 live births rate of infection with Group B streptococcus, which can lead to adverse outcomes such as neonatal infections, fetal death, neonatal death, and pregnancy loss for 50% of cases [52, 65].

Conclusions

Based on this review, we formulated a prevention strategy for stillbirth that involves 10 basic interventions:

1. Periconceptional supplementation with folic acid
2. Prevention of malaria in endemic areas
3. Screening for and treatment of syphilis
4. Detection, prevention, and treatment of hypertensive disorders of pregnancy
5. Detection and appropriate management of gestational diabetes
6. Screening, monitoring, and management of pregnancies complicated with intrauterine growth restriction
7. Identification and induction of post-term pregnancies
8. Delivery in a specialized unit assisted by a skilled birth attendant
9. Capacity for possible basic emergency obstetric care
10. Capacity for possible comprehensive emergency obstetric care.

Although no research trials have demonstrated an effective method for reducing stillbirth rates in the general population, the above strategies are generally applicable and important. By identifying conditions that increase the risk of stillbirth, its occurrence can be reduced through an appropriate obstetrical approach, as management with suboptimal care is responsible for 10 to 60% of perinatal deaths. Interventions to lower modifiable risk factors, the prevention of obesity or encouragement of weight reduction, the avoidance of pregnancies at extreme maternal age, smoking cessation, and alcohol and recreational drug abstinence could reduce the number of stillbirths. Antenatal fetal monitoring that identifies fetuses with intrauterine growth restriction or fetuses with non-reassuring status are key strategies for stillbirth reduction, as they lead to increased monitoring and care. As an example, an audit from Northern Ireland reported that the most common error leading to intrauterine fetal death was failure in diagnosing and appropriately managing cases with intrauterine growth restriction.

On a final note, as a practitioner, it may be difficult to choose an appropriate way to react to and communicate with the parents after the birth of a stillborn child. Several key points described in this article may offer grieving parents explanation of the situation, which may support them during their bereavement.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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