Review

Low Fetal Resistance to Hypoxia as a Cause of Stillbirth and Neonatal Encephalopathy

Petr Shabanov[1] , Aleksandr Samorodov[2],* , Natalya Urakova[3,4] , Evgeny Fisher[4],
Albina Shchemeleva[4]

[1]Department of Psychopharmacology, Institute of Experimental Medicine, 197376 Saint Petersburg, Russia
[2]Department of Pharmacology with a Course of Clinical Pharmacology, Bashkir State Medical University, 450008 Ufa, Bashkortostan, Russia
[3]Department of Obstetrics and Gynecology, Izhevsk State Medical Academy, 426034 Izhevsk, Udmurt Republic, Russia
[4]Department of Experimental and Clinical Research and Inventive, Institute of Thermology, 426054 Izhevsk, Udmurt Republic, Russia
*Correspondence: avsamorodov@gmail.com (Aleksandr Samorodov)
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Abstract

Objective: Low fetal resistance to hypoxia is a factor in stillbirth and neonatal encephalopathy. This review examines fetal movement patterns in response to hypoxia as a predictor of the likelihood of stillbirth. Monitoring the dynamics of fetal movements during maternal apnea could allow the assessment of fetal resistance to hypoxia. The goal of this study is to describe the practical application of this method by doctors and pregnant women. **Mechanism**: We searched relevant keywords in the international scientific literature databases Scopus and Web of Science, as well as databases for patents granted in China, India, USA, Japan, Germany, Russia and other countries. Devices, drugs and medical technologies that provide diagnosis, modeling, prevention and treatment of intrauterine fetal hypoxia, stillbirth and neonatal encephalopathy were considered. **Findings in Brief**: During apnea by a pregnant woman in the second half of normal pregnancy, if the maximum duration of fetal immobility exceeds 30 seconds from the onset of breath-holding, then the fetus is considered to show good resistance to hypoxia, thus preserving its health and life during vaginal delivery. On the other hand, excessive fetal movements <10 seconds after the onset of apnea in a pregnant woman indicates low fetal resistance to hypoxia. When fetal resistance to hypoxia is low, there is no alternative to immediate cesarean section for the preservation of fetal life and health. **Conclusions**: The monitoring of fetal movements during apnea in pregnant women allows real-time assessment of fetal resistance to intrauterine hypoxia. Obtaining timely information on fetal resistance to hypoxia is critical for determining the optimal timing and type of delivery in order to prevent encephalopathy and stillbirth.

Keywords: fetal movement; hypoxia; resistance; reserves; stillbirth

1. Introduction

Despite the involvement of various specialties in research, stillbirth remains an unresolved health problem worldwide [1–7]. Even in high-income countries, stillbirth rates have remained virtually unchanged in recent decades [8,9]. The lack of progress in preventing stillbirth is due to the fact that almost half of all cases remain unexplained [10–13]. The known causes of stillbirth have been attributed mainly to placental dysfunction and/or umbilical cord pathology [14–18]. However, these do not provide a complete account of the pathogenesis of fetal death during pregnancy and vaginal delivery [9,19]. Against this background, it is important to note that fetal demise occurs predominantly during the last weeks of pregnancy, with a maximum at 38–40 weeks of gestation [19,20]. Moreover, the rate of stillbirth in economically developed countries has been reduced through the widespread use of cardiotocography and cesarean section [21,22].

These observations imply that the interaction between the fetus and its mother at 38–40 weeks of gestation and during vaginal delivery is a very important factor in stillbirth

that deserves further attention. Hence, the characteristics of the fetal/maternal interaction during these periods should be carefully studied. This will address the fundamental issue of how prenatal care at the end of pregnancy, and obstetric care during labor, could be modified to prevent stillbirths [19,23–25].

According to expert opinion, new ideas regarding the mechanisms of fetal death during pregnancy and childbirth may help in the prevention of stillbirths [9]. Therefore, it may be useful to return to long-established facts regarding the death process in humans and warm-blooded animals of all ages and for various diseases and injuries, and not just during their intrauterine development. One such well-established fact is that the process of biological death is inseparable from hypoxia and brain temperature [9,24–30]. The cause of biological death in all humans and warm-blooded animals is hypoxic damage of brain cells, of which the rate of onset depends on the temperature in accordance with the Arrhenius law [31–41]. The damage occurs not so much because of the lack of oxygen, but due to the oxygen demand by the cells exceeding the rate at which it can

be delivered to them. The terms "low resistance of a biological object to hypoxia", and "exhaustion of the object's adaptation reserves to hypoxia", are most often used to describe this phenomenon [32,34–42]. These terms were first applied for the assessment of fetal resistance to intrauterine hypoxia more than 10 years ago (RU Patent No. 2432118, 27.10.2011) [43,44]. Unfortunately, they were mostly ignored by specialists in the field, and therefore fetal resistance to hypoxia is still an understudied factor in stillbirth.

2. Materials and Methods

We analyzed the data available in the literature on the relationships between fetal movement, stillbirths and neonatal encephalopathy with intrauterine hypoxia and fetal body temperature. In addition, we analyzed the dynamics of movement of fish and their live preservation in water under conditions of acute hypoxia at different water temperatures. Fish were chosen as the biological model for comparison, since they have a similar temperature homeostasis to human fetuses, i.e., the body temperature of fish and fetuses depends on the temperature of the water in which they swim. It is well-known that the body of fish and fetuses does not resist artificial cooling in the physiological temperature range. The screening of literature was performed while paying special attention to the possible similarities between fetal and fish conditions under potentially dangerous hypoxia. No time limits were selected for the research, and all types of articles in the English language were included. A comprehensive search was conducted in PubMed (MEDLINE), EMBASE, SCOPUS, Web of Science, Google Scholar, Questel-Orbit, Science Direct, Yandex, and E-library databases. In addition, relevant articles from the "References" section of the selected scientific articles were also analyzed. The information contained in inventions was searched using the following databases: Google Patents, EAPATIS, RUPTO, USPTO, Espacenet, PATENTSCOPE, PatSearch, DWPI and FIIP (RF). Analogs and prototypes of selected inventions were also studied.

The following keywords were used in the search: "fetus", "newborn", "health status", "vaginal delivery", "Cesarean section", "development", "evaluation", "criterion", "indication", "fish", "hypoxia", "apnea", "fish conservation", "transplantation", "movement", "stillbirth", "oxygen", "oxygen exchange", "oxygenation", "saturation", "air", "encephalopathy", "resistance", "temperature", "life", "adaptation", "time", "hypotermia", "asphixia", "detection", "diagnostics", "brain", "cell", "damage", "treatment", "method", "ultrasound", "sonography", "tactile sensation", "obstetrics", "gynecology", "diagnostic test", "Apgar scale", "placental insufficiency", "doppler", "Stange test", "hypoxic-ischemic brain damage", "metabolism", "intensity", "antihypoxant" and "death". This systematic review was conducted according to the quality standards described in the AMSTAR measurement tool and in the PRISMA 2009 check-list [45,46].

The search strategy was based on the PICO (impact of patient, intervention, comparison, outcome) model [47,48]. The co-authors selected, evaluated, and extracted data independently of each other. Inconsistencies in the reviews were resolved by consensus. The block diagram for article selection was a spiral in which each turn of the spiral was an iteration [49,50]. The information included in the review was limited to physical factors and medical technologies used in obstetrics and gynecology, and to the preservation of live fish during storage and transportation relating to the effects of aerobic metabolism. The following criteria was used to exclude information from the review: unsuitable for use by pregnant women, and for inventions the lack of global novelty and/or patent. The risk of bias from individual judgments was reduced by relying on the essence of inventions, since this is the generally accepted criterion of novelty. The analysis included 114 inventions, of which the essence of 8 inventions was included in the conclusion of the review.

Any disagreements between co-authors regarding specific articles were resolved through discussion with a third (external) collaborator.

3. Results

It was reported almost 50 years ago that at the beginning of pregnancy, the fetus inside the uterus develops mainly by anaerobic processes. During the second half of pregnancy, fetal development increasingly starts to depend on aerobic metabolism. As the gestational age increases, the fetus consumes more and more oxygen [51]. Researchers have long sought a link between fetal oxygen deficiency (hypoxia) and stillbirth in the second half of pregnancy. Although this research is still incomplete, the results obtained thus far confirm that fetal hypoxia and stillbirth may be linked. In particular, it has been shown that the fetus adapts to acute hypoxia by urgently increasing oxygen delivery to the brain and heart via arterial blood [52,53]. In addition, it was found that the fetus inside the uterus normally receives excess oxygen. The supply of oxygen in the fetal body has been assumed to play an adaptive role. It appears likely that the oxygen supply allows stillbirth to be avoided in conditions of probable intrauterine hypoxia. Together with the suppression of energy-consuming processes and motor activity by the fetus, the excess oxygen determines the preservation of brain viability under hypoxic conditions. In other words, the size of the oxygen reserve and the absence of motor activity provide the fetus with a "safety margin" for occasional short-term hypoxia [54,55]. The fetus was also found to have a limited "safety oxygen reserve" inside the uterus, and is unable to completely stop intensive oxidative phosphorylation from occurring in the mitochondria of brain cells. Therefore, the oxygen reserve is completely consumed during excessively prolonged hypoxia, and hypoxic damage in the mitochondria of fetal brain cells is initially reversible but then be-

comes irreversible [34,35,51–56]. It has been shown that aerobic metabolism is most intense in fetal brain cells, and more specifically in mitochondria [56–59]. Brain cells are the most oxygen-dependent cells in the human body and are the first to use up all oxygen reserves during prolonged hypoxia. Therefore, under conditions of prolonged intrauterine hypoxia, fetal brain cells are the first to become damaged and/or die [56–60]. Fetal brain cells therefore have the least resistance to hypoxia, and hypoxic damage to these cells is a major factor in encephalopathy and stillbirth. On the flip side, supplemental oxygen and/or additional oxygen conserving mechanisms, such as complete absence of fetal motor activity and reduced body temperature, are mechanisms that can be used for adaptation to hypoxia.

3.1 Fetal Resistance to Intrauterine Hypoxia as a Factor in Stillbirth and Neonatal Encephalopathy

Stillbirth is characteristic of the second half of pregnancy, with the number of stillbirths reaching a maximum by 38–40 weeks of gestation [19,20,61]. The cause of the biological death of fetuses is hypoxic damage to brain cells due to their low resistance to hypoxia [56–58,61]. Moreover, intrauterine hypoxia causes not only biological fetal death, but also postpartum encephalopathy [25–51,62–69]. The pathogenic role of hypoxic-ischemic fetal brain damage in stillbirth and encephalopathy has been demonstrated by the high therapeutic efficacy of timely hypothermia of the fetus and newborn [56–58,70–76]. The fact is that the body temperature of a pregnant woman and fetus during pregnancy and labor plays a very important role in the regulation of the intensity of aerobic processes in the cells of the fetal cerebral cortex due to the high dependence of the functional activity of their mitochondria on temperature. Therefore, under conditions of intrauterine hypoxia, brain cells can be saved from hypoxic damage not only by increasing oxygen delivery to the brain but also by immediate cooling of the fetal brain [58]. In particular, mild neonatal hypothermia applied to neonates after perinatal hypoxia-ischemia reduces mortality and neurologic sequelae without side-effects [77]. In other words, the evidence suggests that reducing the temperature of newborns improves their recovery from a hypoxic event.

It is important to note that from the beginning of the second trimester of pregnancy, the size and volume of the fetal head greatly increase, and hence the size and volume of the brain begin to predominate in the fetal body. The head and brain reach their maximum size by the 40th week of gestation [78]. In parallel, from the beginning of the second trimester of pregnancy the importance of oxygen for fetal brain development increases with gestational age [79]. Moreover, fetal resistance to hypoxia decreases [80], whereas oxygen plays only a minor role in early intrauterine development [51]. The placenta is the main intermediary between the mother and fetus and not only provides the fetus with oxygen, but also exchanges gas [81]. There-

fore, most researchers believe that placental pathology is the main reason for hypoxia and stillbirth [10,82]. However, real time studies of the placental condition during intrauterine hypoxia indicate that it is not identical to the dynamics of the fetal condition. In other words, the placenta does not accurately reflect the condition of the fetus with hypoxia.

Cesarean section has been reported to reduce the risk of hypoxic fetal brain injury and stillbirth [83], whereas vaginal delivery increases the risk of hypoxic fetal brain injury [84]. Since vaginal delivery occurs by uterine contraction, the uterus may squeeze the blood vessels and cause placental ischemia and fetal hypoxia [35,62]. Although elective cesarean section does not cause fetal hypoxia, it does have some disadvantages [85]. However, these have less impact on the health and life of the fetus and mother compared to vaginal delivery.

The normal fetus has a certain oxygen reserve and adaptation reserve to cope with natural periods of short-term hypoxia during pregnancy and vaginal delivery. Therefore, fetuses can normally withstand the challenge of natural, short-term periods of hypoxia without harm to their health [35,62,86]. However, in some cases the fetus may not have a sufficient oxygen supply or a large reserve of adaptation to hypoxia. In such cases, even short-term hypoxia may cause some hypoxic damage to fetal brain cells, giving rise to postpartum encephalopathy and even fetal death [35,86,87]. An adaptive change in the blood circulation known as the "brain-saving effect" occurs in the normal fetus under conditions of natural hypoxia [88,89]. This change can be detected by ultrasonography using the Doppler cerebral/umbilical ratio. However, this method does not provide an assessment of the fetal adaptation reserves to hypoxia, or of fetal resistance to hypoxia [88–91].

3.2 Dynamics of Fetal Motor Activity as an Indicator of Its Resistance to Hypoxia

Changes in fetal motor activity in pregnant women during the second half of pregnancy have long attracted the attention not only of pregnant women but also of researchers [92–99]. Mothers commonly perceive a decrease or lack of movement of their fetuses in the days leading up to death of the fetus. For this reason, caregivers often advise mothers to monitor fetal movements to assess the well-being of the baby. Changes in the dynamics of fetal movement intensity and tremor were considered to be a reason for pregnant women to urgently consult with an obstetrician-gynecologist, as this could indicate intrauterine hypoxia [100]. In particular, increased/excessive fetal movements have been suggested to predict unfavorable neonatal outcomes, such as large gestational age [101]. An association between episodes of vigorous fetal motor activity and stillbirth has also been suggested [102–107]. Therefore, the idea of studying clinical tests for fetal motor excitation has been put forward by several authors [105,106].

Such ideas regarding a possible diagnostic role for fetal motor activity in predicting pregnancy outcomes and preventing stillbirth were supported by results obtained from studies with artificial acute hypoxia caused by apnea in pregnant woman. Other supporting data were derived from studies on the cessation of oxygen supply to aquarium water in which fish were swimming. Similarities were found between the behavioral response of fetuses inside the uterus during voluntary apnea by their mother, and aquarium fish of the blue neon and guppy breeds after sudden cessation of the water oxygen supply. Both the fetuses and fish initially adopted a motionless state and remained in this state until the hypoxia was eliminated and/or their adaptation reserves were exhausted [107–109]. Such minimization of motor activity by the fetus and fish under hypoxia has long been regarded as a protective (adaptation) mechanism that allows them to use the available "oxygen reserve" more economically. This permits longer preservation of viability under conditions of oxygen deficiency [54,55]. The longer the maximum duration of immobility in fetuses and fish under hypoxia, the greater their reserves of adaptation to hypoxia. In other words, the greater the hypoxia adaptation reserve in fetuses and fish, the longer they remained immobile from the onset of acute hypoxia [35,49,50]. However, prolongation of the hypoxic period to the complete exhaustion of adaptation reserves caused similar rapid motor activity in fish and fetuses [49,110].

Visual monitoring of fish revealed a regularity in the dynamics of their motor activity at the time of exhaustion of their adaptation reserves to acute hypoxia. The fish were observed to have active movements of gill fins, respiratory movements of gill arches, mouth open wide, and swallowing of water with the mouth wide open. At the same time, the color of the fins changed. If at this point the "right" dose of oxygen and/or hydrogen peroxide was added to the water, the motor activity reduced and the fish remained alive and healthy. If hypoxia persisted further, the fish died after a few minutes [111].

Ultrasound monitoring of fetal locomotor activity during the second half of pregnancy revealed the following changes during voluntary apnea by the mother. Without exception, all living fetuses immediately assumed a motionless state at the moment when their mother started apnea. Normally, the duration of the immobile state of the fetus during apnea by the mother was >30 seconds [35,43,44,62,110]. However, fetuses with fetoplacental insufficiency were reported to be immobile for <30 seconds during maternal apnea. Fetuses showing evidence of severe fetoplacental insufficiency were reported to be immobile for <10 seconds after the onset of maternal apnea. In addition, at the start of the exhaustion of the fetuses' adaptation reserves to hypoxia, the ultrasound echogenicity of the pads of their fingers and toes began to change. Respiratory movements of the thorax suddenly began, and at the

same time sharp movements of the arms and legs occurred. Moreover, the fingers of the hands, which had previously been in a compressed state, straightened.

The above dynamics of the fetuses' behavioral response during maternal apnea, detected by ultrasound, formed the basis of several invented methods for assessing fetal resistance to intrauterine hypoxia (RU Patent No. 2432118, 27.10.2011; RU Patent No. 2511084, 10.04.2014; RU Patent No. 2529377, 27.09.2014). These inventions proposed novel assessments of fetal resistance to intrauterine hypoxia based on the maximum duration of fetal immobility during voluntary apnea by its mother. For the first time it was shown that in the second half of pregnancy, fetuses normally have good resistance to hypoxia and can remain immobile for >30 seconds during their mothers' apnea. It was also shown for the first time that fetal respiratory chest movements <10 seconds after the onset of apnea indicated poor fetal resistance to hypoxia. Based on these observations, it was proposed that good fetal resistance to hypoxia should be considered as an indication for vaginal delivery, whereas poor fetal resistance to hypoxia should be considered as a contraindication. In addition, it was suggested that poor fetal resistance to hypoxia should be considered an indication for cesarean delivery.

A method of delivery based on monitoring the dynamics of ultrasound echogenicity of the fetal fingertips was invented in parallel (RU Patent No. 2441592, 10.02.2012). Ultrasonic echogenicity of fetal and adult human fingertips reflects the oxyhemoglobin content of blood, and can therefore be used to diagnose hypoxia. The description of this invention describes how uterine contractions during vaginal delivery can compress the uterine vessels and cause placental ischemia and fetal hypoxia. This in turn can manifest as decreased echogenicity of the subcutaneous fatty tissue in the fetal fingertips. Echogenicity in the normal fetal fingertip is restored between periods of myometrial contractions. However, the echogenicity of the fetal fingertips does not normalize between periods of uterine contractions during natural labor in some cases with signs of fetoplacental insufficiency. This is a serious situation because it indicates the reserves for fetal adaptation to hypoxia have been exhausted. In such cases it is therefore recommended to immediately increase the mother's blood oxygen saturation to toxic values and/or immediately perform a cesarean section to preserve fetal brain cells [107–109].

Several inventions have recently been created for the practical implementation of these proposals. In particular, a method for choosing the type of delivery was invented (RU patent No. 2749637, 06.16.2021). This involves performing a functional test in which the pregnant woman holds her breath after a deep breath for as long as possible, while measuring the duration of fetal immobility during apnea. To perform the test, the woman chooses a date and time during the day when the fetus is immobile for an extended period of time and she tactilely monitors fetal movement with the

fingers of her working hand. She first identifies the head and upper part of the fetus and presses them firmly against her spine with her fingers and holds the fetus in this position until it is immobile. Next, she holds her breath, records the time, and continues tactile monitoring of the fetus until its arms and chest are mobile. She then records the time of onset of this moment, immediately hyperventilates her lungs until a feeling of dizziness appears. After the normalization of breathing, she determines the duration of immobility by the fetus starting from the onset of apnea. When the duration of this period is >60 seconds, delivery through the vaginal birth canal is recommended. When the duration is 30–60 seconds, the choice of type of delivery may be postponed. When the duration of the specified period is <30 seconds, a cesarean section is recommended.

Other related inventions include a diagnostic bandage for pregnant women (RU patent No. 2780137, 19.09.2022), and a tag with sensors and sticky tape for measuring the duration of the immobile state of the fetus during diagnostic apnea (RU patent No. 2780274, 21.09.2022). Both are medical diagnostic devices for personal use that allow a pregnant woman to assess fetal resistance to intrauterine hypoxia and to choose the type of delivery according to the result. Both devices have special fetal motion sensors and an electronic device for transmitting information to a smartphone, with a stopwatch function to automatically measure the duration of the fetal immobility period during diagnostic apnea. The advantages of these devices are in their simplicity and convenience for measuring the duration of fetal immobility during diagnostic apnea in domestic conditions and during the second half of pregnancy. Other advantages relate to the recording of obtained values, the diagnosis of the state of health of the fetus, and its readiness for vaginal delivery. However, there is a need for additional examination of the pregnant woman and her fetus, regardless of the participation of a medical worker and the presence of an exchange card of the pregnant woman.

4. Discussion

Obstetricians first reported a relationship between fetal motor dynamics and stillbirth in 1973 [92]. Sudden changes in fetal motor activity are somehow associated with unfavorable fetal outcomes, especially in the last weeks and days of pregnancy [92,112]. Subsequently, there have been reports that fetal hypokinesis may be part of the fetal adaptation to placental ischemia [113,114]. Extremely vigorous fetal movements occur late in pregnancy and have been shown to increase the risk of stillbirth three-fold, or to increase the incidence of postpartum encephalopathy in cases of live birth. However, this type of excessively vigorous fetal motor activity has usually been reported in retrospective studies and is therefore difficult to explain [115–117].

Cardiotocography, ultrasound and magnetic resonance imaging (MRI) have been used to quantify fetal movements. However, these techniques have proven to be insufficiently effective or reliable [104]. The idea of assessing the dynamics of fetal movement based on maternal sensation was first proposed more than 50 years ago [118]. However, maternal analysis of fetal movement dynamics is highly subjective. This justified the mathematical processing of motor activity of the fetal lower limbs and the conclusion surrounding the peculiarities of the biomechanics involved [104]. Nevertheless, the significance of these findings and the conclusion regarding the biomechanics remains to be clarified.

The incidence of stillbirths is known to increase with increasing gestational age and fetal brain size. Analysis of this pattern has established that increased fetal brain mass and volume with increasing gestational age naturally increases the total oxygen demand of the brain and fetus. This becomes an important factor during any rapid depletion of fetal oxygen reserves under hypoxic conditions. In other words, the increase in mass and volume of fetal brain tissue beginning in the second trimester and reaching a maximum at the end of pregnancy may be a major factor in decreased fetal resistance to hypoxia, all other things being equal. Under conditions of excessively prolonged hypoxia in the fetus, brain cells are the first to be damaged and/or killed [56–60]. Brain cells have the lowest resistance to hypoxia in the fetal organism. Even in cases of live birth, 30–60% of neonatal encephalopathy is the clinical manifestation of neonatal brain dysfunction resulting from hypoxic-ischemic damage [119]. Therapeutic hypothermia is the standard of care for neonates with encephalopathy. Despite this however, the risk of death or disability in clinical trials is about 50% [120].

Obstetricians have noted that periods of excessive fetal motor activity resemble epilepsy and are one of the intrapartum pathology symptoms that precede stillbirth and/or live birth with encephalopathy. It has also been reported that hypoxic-ischemic encephalopathy is often a cause of neonatal seizures in the newborn [121,122]. However, until recently it was not known how to predict stillbirth and/or neonatal encephalopathy based on excessive intrauterine fetal motor activity. In 2011 it was shown for the first time that stillbirth and encephalopathy in the newborn can be predicted by assessing fetal resistance to hypoxia according to the dynamics of fetal motor activity [43]. This was the first time that attention had been drawn to the possibility of using the Stange test for this purpose.

It is well known that the risk of hypoxic fetal brain damage is increased by vaginal delivery due to the compression of uterine blood vessels at the peak of contractions, thereby causing a period of placental ischemia and fetal hypoxia [35,62,84]. Normal fetuses have an oxygen reserve that allows them to withstand without harm these natural periods of hypoxia lasting up to 30 seconds and that occur during pregnancy and vaginal delivery [35,62,86]. However, in some cases, the fetus may not have the "right" supply of oxygen. In such cases even short-term hypoxia can

cause reversible and/or irreversible hypoxic damage to fetal brain cells, postpartum encephalopathy, and even fetal death [35,87].

Before using voluntary apnea in pregnant women as a means of assessing fetal resistance to intrauterine hypoxia through the dynamics of fetal movement, the motor activity in aquarium fish under similar conditions of acute hypoxia was first studied. This work assumed there were appropriate behavioral analogies between fish and fetuses. The experiments with fish revealed the following dynamics of motor activity under conditions of acute hypoxia. At the start of the hypoxic condition, the fish assumed a motionless state until the exhaustion of oxygen reserves. At this point the fish showed excessively rapid motor activity combined with respiratory movements of gill arches, active movements of gill fins, wide opening of the mouth, and swallowing of water [110,111,123,124]. Based on these results, the dynamic behavioral response of fetuses was evaluated during voluntary apnea by their mother while visiting the antenatal clinic in the second half of pregnancy. Ultrasound revealed that during acute hypoxia, fetuses behave like fish and immediately adopt a motionless state until the hypoxic condition is stopped and/or their adaptation reserves are exhausted, after which they show excessively vigorous motor activity [35,43,44,62,110].

In normal fetuses, the duration of fetal immobility during maternal apnea exceeded 30 seconds. In fetuses with fetoplacental insufficiency, the duration of immobility was <30 seconds. Fetuses with severe fetoplacental insufficiency were found to be immobile for <10 seconds after the onset of maternal apnea. Based on these results, it was suggested that good fetal resistance to hypoxia should be considered as an indication for vaginal delivery, while poor fetal resistance to hypoxia is an indication for cesarean section. For the practical implementation of these suggestions, pregnant women can rely on their own subjective feelings by using a modified Stange test [125]. For this purpose, a stopwatch and the ability to record the maximum period of fetal immobility during voluntary apnea is sufficient for the mother to obtain diagnostic information. In addition, special portable maternal devices could in future be used to monitor fetal motor activity. Maternal wearable devices were reported to compare favorably with expensive laboratory equipment such as ultrasound devices [126]. Moreover, they can detect fetal movement over a long period of time instead of the short period of clinical measurement.

5. Conclusions

Careful long-term studies of the relationship between fetal motor dynamics and stillbirth (or neonatal encephalopathy in the case of live birth) has led to the identification of several risk factors. Unfortunately, most of the factors cannot be prevented or predicted [127]. Nevertheless, novel ideas have recently emerged about the diagnostic role of low fetal resistance to hypoxia. During apnea by a pregnant woman in the second half of a normal pregnancy, the duration for the absence of fetal movement from the onset of breath-holding exceeds 30 seconds. In this case, the fetus has good resistance to hypoxia, thus preserving its health and life during vaginal delivery. On the other hand, excessive fetal movement <10 seconds after the onset of apnea by the mother indicates low fetal resistance to hypoxia. In such cases, immediate cesarean section may be necessary to preserve fetal life and health.

Finally, recent medical technologies allow fetal resistance to hypoxia to be independently determined by the mother in any conditions. This technology is based on a modified Stange test and provides women with additional information about stillbirth and encephalopathy that may help with prevention [128].

Author Contributions

PS, NU and ASam conceived and designed the review; PS, ASam, NU, EF and AShc collected the data and references; NU and EF wrote the paper; PS, ASam, NU, EF and AShc revised the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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