Review

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Trends in the use of preconditioning to hypoxia for early prevention of future life diseases

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Summary **Environmental factors during fetal life program the health outcomes regarding many diseases in future life. This idea has been supported by worldwide epidemiological studies, but the underlying mechanisms are still poorly understood. Three questions should be answered. (*i*) Does a common underlying cause of ordinary pathological fetal development exist? (*ii*) If such a cause exists, which mechanism might develop disease in later life? (*iii*) Is it possible to prevent this underlying cause and therefore the associated obstetric complications to primarily prevent future life diseases? The objective of this review is to attempt to answer these three questions by using PubMed (extending to October 2012) and other sources. Three data-based answers corresponding to these questions were found: (*i*) hypoxia, (*ii*) excessive stimulation of neurogenesis, and (*iii*) preconditioning/adaptation to hypoxia. The method for such preconditioning/adaptation is intermittent hypoxic training (IHT), in which air with low oxygen concentration is breathed through a mask to protect against subsequent strong adverse influences. Data are cited for IHT applications for the prevention/treatment of diseases in different fields, particularly in obstetrics. Data suggested that all common fetal origins of adult diseases are likely predetermined by changes in the fetal brain; therefore, early detection of these changes must be very important. The use of IHT may be a real means to primarily prevent obstetric complications and therefore, prevent future life diseases.**

Keywords: Fetus, pregnancy, neurogenesis, primary prevention

1. Introduction

Environmental factors during fetal life program the health outcomes in future life. This David Barker's hypothesis (*1*) has been supported by worldwide studies, including large scale epidemiological studies (*2-5*). These studies confirmed that abnormalities of early growth, including preterm birth, intrauterine growth restriction/retardation, and low weight/height at birth, are tightly associated with future life diseases: cardiovascular and cardiopulmonary diseases, diabetes and obesity, neuropsychiatric, and others. Majority of authors believe that the most important causative factor here is undernutrition. However, Morley considers that "human studies in general provide limited and unconvincing evidence that differences in maternal macronutrient intake are important. Nevertheless there is a need to understand the underlying causal pathways" (*6*). All of this shows that profound underlying causes of these abnormalities are still poorly understood.

The aim of this review paper is to attempt to clarify these causes by answering the following questions: Does a common underlying cause of ordinary pathological fetal development exist? If such a common cause exists, which mechanism might develop disease in later life? Is it possible to prevent the underlying cause and therefore the associated obstetric complications to prevent future life diseases?

A literature review was conducted using the PubMed database and other sources, with a time frame extending to October 2012. The review was conducted from the viewpoint of hypoxia, an important factor in any pathological process.

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2. Causes of abnormalities during pregnancy: Relationship to hypoxia

2.1. *Obstetric complications: Relationship to hypoxia*

The main obstetric complications are considered to be as follows: hypoxic hypoxia, asphyxia at birth, hypoxia/ischemia, hypoxic/ischemic encephalopathy, preeclampsia, infection/inflammation, and maternal psychological stress. We will not consider here the effects of undernutrition, fetal nicotine, cocaine, alcohol, and glucocorticoids exposure.

Hypoxic hypoxia results from insufficient oxygen reaching the blood, as might occur by breathing air with low oxygen content, for example, in the mountains.

Asphyxia at birth and hypoxia/ischemia (with its consequence in a form of hypoxic/ischemic encephalopathy) are related to stagnant (circulatory) hypoxia. These types of hypoxia are associated with the failure to transport sufficient oxygen because of inadequate blood flow.

Preeclampsia is a multisystem disorder affecting about 5-10% of all pregnancies. It is a major cause of maternal, fetal and neonatal mortality and morbidity. Despite intensive research, the aetiology of this disease remains unknown. Preeclampsia originates in the placenta, starting with inadequate cytotrophoblast invasion and ending with widespread maternal endothelial dysfunction. Production of placental anti-angiogenic factors has been shown to be up-regulated in preeclampsia. These factors are released into the maternal circulation where their actions disrupt the maternal endothelium and result in hypertension, proteinuria, and the other systemic manifestations of preeclampsia. The molecular basis for placental dysregulation of these pathogenic factors remains unknown, although hypoxia is likely an important regulator (*7*).

An important role of the systemic inflammatory response syndrome in preeclampsia, which is tightly connected with tissue hypoxia, is suggested in previous studies (*8,9*). Tissue (histotoxic, cytotoxic, cytopathic) hypoxia appears when tissues are unable to use oxygen despite normal oxygen delivery.

Infection/inflammation is a pathological process which is widely recognized as the inflammatory response syndrome (*8-10*) based on tissue hypoxia. The cells under tissue hypoxia behave as if there is too little oxygen because of an inflammation-induced alteration in cellular function, not because there is too little oxygen for cellular function (*11*).

Maternal psychological stress produces fetal asphyxia (*12*), this was revealed in animal experiments. Stress experienced during pregnancy not only leads to pregnancy complications like miscarriage, preeclampsia, preterm parturition, low birth weight or major congenital malformations, stress also increases the risk of the child to develop diseases in the subsequent periods of life (*13*). Note that any obstetric complication or adverse event/process may be accompanied by maternal psychological stress, and it may be difficult to distinguish their effects.

This data show that all considered obstetric complications are tightly related to some types of hypoxia.

2.2. *Abnormalities of early growth: Relationship to hypoxia*

The role of different types of hypoxia in abnormalities of early growth (preterm birth, intrauterine growth restriction/retardation, low weight/height at birth) was clarified in many studies. Preterm birth may be caused by hypoxic hypoxia (*14*), infection/inflammation (*15,16*), preeclampsia (*17*), or maternal psychological stress (*18*). Intrauterine growth restriction/retardation may be caused by hypoxic hypoxia (*19*), preeclampsia (*20*), or maternal psychological stress (*21*). Low weight/height at birth may be caused by hypoxic hypoxia (*22*) or preeclampsia (*20*). Therefore, all considered abnormalities of early growth are tightly related to some types of hypoxia.

2.3. *Abnormalities during pregnancy: Consequences for future offspring's life*

Consequences for future offspring's life due to abnormalities during pregnancy, including obstetric complications and abnormalities of early growth, have been known for a long time. However, the list of these consequences increased sufficiently during the last 20-30 years because of the works of David Barker and his followers. Many of these works are the epidemiologic studies with great numbers of participants, so the results of the studies are reliable. It was found that abnormalities during pregnancy might give many pathologic consequences for future offspring's life, for example: cardiovascular and cardiopulmonary diseases, including high blood pressure and risk of stroke (*1-5,23-25*); behavioral, neurological and mental diseases, including cerebral palsy, depression, schizophrenia, epilepsy (*24,26-30*); metabolic diseases, including overweight, type 2 diabetes (*2-5,31-33*); bronchopulmonary diseases, including asthma (*34,35*); hearing loss (*36*). This data show that abnormalities during pregnancy, including obstetric complications and abnormalities of early growth, are associated with or caused by some types of hypoxia.

3. The role of hypoxia in the neurogenesis stimulation

The abnormalities during pregnancy are tightly connected with hypoxia, and involvement of neurogenesis should be considered.

The role of hypoxia in neural stem cells (NSC) development and functioning is discussed (*37*). The

authors noted that scant information on intermittent hypoxia effects on stem cells that was obtained generally in cell culture models, reveals that intermittent hypoxia at certain duration and intensity is a more potent trigger of transcription activation than constant hypoxia. In future, a method of intermittent hypoxia training/treatment could be effectively used for correction of physiological changes and disorders.

NSCs exist within a "physiological hypoxic" environment of 1 to 5% O_2 in both embryonic and adult brains (*38*). The studies showed that hypoxia could promote the growth of NSCs and maintain its survival *in vitro*. *In vivo* studies also showed that ischemia/hypoxia increased the number of endogenous NSCs in the subventricular zone and dentate gyrus. In addition, hypoxia could influence the differentiation of NSCs. More neurons, especially more doparminergic neurons, were produced under hypoxic condition.

Contrary to the long-held dogma, neurogenesis occurs in discrete areas of the adult brain, the hippocampus and the subventricular zone, and NSCs reside in the adult central nervous system. Proliferation of NSCs was observed in experiments involving adult rats treated in a hypobaric chamber (*39*). Researchers reported activation of protein synthesis and an increase of RNA concentration in the brain.

Recent studies have shown that neurogenesis is increased in the diseased brains, after strokes and traumatic brain injuries, and that new neuronal cells are generated at the sites of injury, where they replace some of the degenerated nerve cells. Thus, the central nervous system has the capacity to regenerate after injury (*40*). Endogenous neurogenesis in the hippocampus of developing rat after intrauterine infection was observed in the study (*41*). That is, in essence, the influence of tissue hypoxia, tightly connected with infection/inflammation.

Hypoxic hypoxia was used in animal experiments to develop pathologic neurogenesis to mimic diseases including schizophrenia (*42*) and bronchopulmonary dysplasia (*43*) in the offspring's future life.

Thereby hypoxia of any type stimulates neurogenesis, especially during gestational age.

Considering that the brain is the organ most vulnerable to hypoxic influence, excessive hypoxia produces the damage in the brain, for example, white matter damage (*44*). This programs future life diseases. David Barker (*1*) points to the importance of long-term programming in early life and parallel findings in clinical and animal research. Above cited data show that "programmer" of the future life diseases is most likely the brain, so the way to avoid future life diseases is to early detect and correct pathological brain changes (the "program") instead of treating the disease as it appears. The most difficult task here is probably to find these early changes related to nonmental diseases. Currently, the brain changes have been found in newborns with congenital heart disease (*45,46*). For other diseases, changes have been found in adult brain for type 2 diabetes (*47-50*), asthma (*51,52*), and chronic obstructive pulmonary disease (*53-55*). Improvements in diagnostic methods will make it possible to establish changes during early life. This trend is in its beginning just now, and more favourable trends will be considered in the text sections.

4. Trends in the studies and in the routine use of hypoxic hypoxia for prevention and treatment

Some preventive or treatment methods have been proposed for obstetric complications: maternal nutrition, physical activity, vaccination, the use of vitamins, magnesium sulphate; hypothermia (which improves oxygen supply by reducing oxygen demand). No method was found to be effective and safe. Particularly, for preeclampsia the only successful treatment is delivery; no definitive preventive strategies have been identified (*7*). Therefore, it may be important to examine the possibility of the use of hypoxia as a preventive or therapeutic means.

4.1. *Hypoxic hypoxia as a general protective means: Animal studies*

Many animal studies have been performed with the use of hypoxic hypoxia as a protective means. Generally, these studies describe hypoxia-induced tolerance to hypoxia, or preconditioning/adaptation to hypoxia.

The first fundamental study on the protective features of hypoxic hypoxia (*56*) contained the results of numerous animal experiments (rats, mice, and rabbits). Hypoxic hypoxia (10% O_2) was administered once for 30 min before a harmful pharmaceutical agent was injected or was administered during 10-15 days for 30 min daily before applying physical force or introducing an infection. The following data were obtained (control *vs.* experiment):

- Asphyxia: heartbeat stopped in pregnant rabbits, min: 34.5 ± 4.8 *vs.* 66.2 ± 5.4; heartbeat stopped in the rabbit fetus after the mother's asphyxia, min: 93.0 ± 8.2 *vs.* 136.0 ± 6.4.
- Acute hypoxia with hypercapnia: lifetime of the rats, min: 18.1 ± 0.36 *vs.* 25.5 ± 0.5.
- Haemorrhagic shock: breathing stopped in rats, min: 9.9 ± 0.3 *vs.* 18.5 ± 0.6; heartbeat stopped in rats, min: 18.3 ± 0.4 *vs.* 30.5 ± 0.4; breathing stopped in rabbits, min: 23.8 ± 0.3 *vs.* 41.7 ± 0.4.
- Physical load: duration of swimming of rats, min: 4.6 ± 0.3 *vs.* 8.0 ± 0.3; heartbeat stopped after submersion on the bottom: 5.8 ± 0.2 *vs.* 9.4 ± 0.4.
- Survival rate of mice after tick-borne encephalitis virus infection (%): 33.3 ± 5.1 *vs.* 51.7 ± 5.4.

Sufficient data were also presented in (*56*) on the survival rate in mice after injection of pharmacological

agents (eight types).

Useful review on hypoxic preconditioning is done by Lin (*57*).

Hypoxic preconditioning also protects against brain injury or attenuates its consequences. For example, it attenuates global cerebral ischemic injury following asphyxial cardiac arrest through the regulation of the delta opioid receptor system (*58*), protects against cerebral and cardiac ischemia (*59*), protects the right ventricle from ischemia and reperfusion (*60*), protects the brain and likely other organs of neonatal and adult rats (*61*).

Protective effects of hypoxic preconditioning on the development of depressive states in rat models were studied. Three episodes of intermittent preconditioning using hypobaric hypoxia (360 mmHg, 2 h) prevented the onset of depressive behavioral reactions, hyperfunction of the hypophyseal-adrenal system and impairments in its suppression in the dexamethasone test in rats following unavoidable aversive stress in a model of endogenous depression (*62*). The authors consider that the data received indicate the possible use of hypoxic preconditioning for the prophylaxis of post-stress depressive episodes.

Prenatal hypoxia preconditioning improves the hypoxic ventilatory response and reduces mortality in neonatal rats (*63*).

Preventive influence of hypoxic hypoxia on cerebral circulation was studies in a model of acoustic stress in the KM line rats genetically predisposed to audiogenic seizures (*64*). The 2 h influence of an 'altitude' of 5000 m reduces the death rate and the extent of neurological changes (the frequency and severity of motion disorders and the development of intracranial haemorrhages) under conditions of acoustic stress.

After 2 weeks of adaptation to simulated altitude in adult rats (*65*), cardiac output was increased by 22% and total peripheral resistance was decreased by the same value. Angiogenesis seems to increase the stability of oxygen transport in microcirculation.

Adaptation to periodic hypoxic hypoxia effectively prevented oxidative and nitrosative stress, protecting against neurodegenerative changes, and protecting cognitive functions in experimental Alzheimer's disease (*66*).

An important role of hypoxia-inducible factor in hypoxic preconditioning is discussed in several reviews (*59,61,67*). Oxygen-independent activation of this factor is a promising therapeutic strategy for the prevention of organ injury and failure (*67*).

Mechanism of hypoxic influence has been the subject of many studies. Over the course of evolution, aerobic organisms have developed sophisticated systems for responding to alterations in oxygen concentration, as oxygen acts as a final electron acceptor in oxidative phosphorylation for energy production. Hypoxia-inducible factor (HIF) plays a central role in the adaptive regulation of energy metabolism, by triggering a switch from mitochondrial oxidative phosphorylation to anaerobic glycolysis in hypoxic conditions. HIF also reduces oxygen consumption in mitochondria by inhibiting conversion of pyruvate to acetyl coenzyme A, suppressing mitochondrial biogenesis and activating autophagy of mitochondria concomitantly with reduction in reactive oxygen species production (*68*).

Studies carried out by Sharp *et al.* (*59*) show that animals exposed to brief periods of moderate hypoxia (8% to 10% oxygen for 3 h) are protected against cerebral and cardiac ischemia between 1 and 2 days later. Hypoxia preconditioning requires new RNA and protein synthesis. The mechanism of this hypoxia-induced tolerance correlates with the induction of HIF, a transcription factor heterodimeric complex composed of inducible HIF-1α and constitutive HIF-1β proteins that bind to the hypoxia response elements in a number of HIF target genes. Studies show that HIF-1α correlates with hypoxia induced tolerance in neonatal rat brain. HIF target genes, also induced following hypoxia-induced tolerance, include vascular endothelial growth factor, erythropoietin, glucose transporters, glycolytic enzymes, and many other genes. Particularly, the role of erythropoietin was studied previously (*69*). The authors concluded that, in mice, IHT reduces bodyweight and serum glucose by increasing EPO synthesis which secondarily increases leptin and insulin production in liver.

A bioenergetic mechanism for development of urgent and long-term adaptation to hypoxia was considered also in a paper (*70*). Hypoxia induces reprogramming of respiratory chain function and switching from oxidation of NAD-related substrates to succinate oxidation. Succinate therfore is a signaling molecule, which effects are realized at three levels in hypoxia, intramitochondrial, intracellular and intercellular.

4.2. *IHT and its clinical applications*

IHT, also known as intermittent hypoxic treatment, intermittent hypoxic therapy, normobaric intermittent hypoxic therapy, normobaric hypoxytherapy, or hypoxytherapy, is a method for treatment or prevention of diseases by hypoxic preconditioning or adaptation to hypoxic hypoxia. Such an adaptation is produced by breathing air with low oxygen content, usually 10-12% through a mask, at normobaric conditions, *e.g.* in a room at sea level. This method was developed in the former USSR beginning in the 1970s, by Professor Rostislav Strelkov and colleagues, originally as a radioprotective method for military and oncological (hypoxiradiotherapy) applications. Methodical recommendations prepared by Strelkov and colleagues and issued by the Russian Health Ministry (*71*) (also see subsequent editions) recommend the use of IHT (10-

12% O_2, 5 min breathing, 5 min rest, 1 h per session, 1-4 weeks per course) for the treatment of various diseases. This drug-free method, which is almost without contraindications, has been routinely used by about 2 million patients in the last 30 years. The method is also applied to increase physical working capacity and endurance, especially in sports (*56,72*).

Much literature and practical pictures may be found on the websites *www.go2altitude.com* (mostly sport), particularly *http://www.go2altitude.com/iht.html* – some IHT centers worldwide; and *www.bionova.ru* (mostly medicine), particularly *http://www.bionova.ru/?page=4* and *http://www.bionova.ru/?page=6#pol* – the use of the IHT in the different fields of medicine in Russia.

The effects of high altitude stay on the incidence of common disorders in men were described (*73*). The study involved 130,700 men stationed on the plains between 760 m and sea level, and 20,000 men stationed at altitudes between 3,692 and 5,538 m from 1965 to 1972 (during the Indo-Chinese conflict). A significantly lower number of cases of most disorders were found among the men at high altitude than among those at sea level. In particular, the difference in morbidity rates per thousand was 0.16/1.25 (diabetes mellitus), 0.22/0.96 (ischemic heart diseases), 0.37/2.15 (asthma), and 1.07/2.82 (neuroses).

Some trials were performed by means of sojourns in the high mountains, by the use of hypobaric chamber and by the use of normobaric hypoxia (*74*). The results were negligible or insufficiently strong (for schizophrenia) or moderate (for depression). One of these trials carried out in the USA in 1930s have used acute hypoxic hypoxia and gave encouraging results initially, but unfortunately was not completed.

The IHT was also used as a method to enhance nonspecific resistance in epilepsy treatment (*75,76*). The optimizing effect of hypoxic hypoxia on physiological functions of the patients with epilepsy consisted in increased level of hemoglobin and erythrocytes in the blood, less frequent systole, systolic and diastolic pressure reduction and prolongation of breath holding during Stange's test). As a result of these changes, the frequency of epileptic attacks decreased and normalization of behavioural responses was observed.

The use of IHT together with standard drug treatment in patients with migraine without aura (*77*) resulted in a decrease of the rate and severity of migraine attacks, an improvement in the state of the autonomic nervous system, and a decreased level of personal anxiety and degree of manifestation of depression to a markedly greater extent than in control patients.

Beneficial results of the application of IHT were obtained for bronchial asthma and chronic obstructive pulmonary disease (*78*). Bronchial obstruction decreased by 10-15%, exercise tolerance, general condition, ventilation, and haemodynamic and immunological parameters improved, and the frequency of bronchopulmonary infection exacerbations decreased 2-fold.

Hypoxytherapy was also applied for treatment of hypertension (*79*). It was concluded that hypoxytherapy exerted a robust, persistent therapeutic effect and can be considered as an alternative, nonpharmacological treatment for patients with stage 1 arterial hypertension. The antihypertensive action of IHC is associated with normalization of nitric oxide production.

IHT has also been used for preparation to surgery to increase patient's nonspecific resistance: general (*80*); in patients with ischemic cardiomiopathie preparing to coronary bypass with artificial circulation (*81*) (see an official Instruction of the Belarus Health Ministry (*82*)); before cesarean section (*83,84*); before and after gynecological surgery (*85*).

Combined hypoxic-hyperoxic training was used in the treatment of the metabolic syndrome (*86*). The use of hypo-hyperoxic exercise (alone or in combination with systemic hyperthermia and hardware vibratory) leads to a significant reduction in body weight. It was achieved mainly by reducing fat mass accompanied by a reduction of total cholesterol, LDL (low-density lipoprotein), FPG (fasting plasma glucose), optimization of blood pressure, increased hypoxic stability, physical endurance, improved mental status.

IHT was used to increase nonspecific systemic resistance in 107 patients with chronic salpingo-oophoritis for treatment or rehabilitation purposes (*87*). IHT promoted the recovery of compromised oxygen metabolism in all patients, resulting in activation of oxygen transport mechanisms and the normalization of tissue respiration. Recovery was recorded in 67.3% of patients, and the frequency of aggravations of the chronic condition was reduced in the rest.

4.3. *IHT as a possible method for the primary prevention of fetal origins of future life diseases*

IHT could prevent adverse hypoxic influences and is routinely used in general clinics. The use of IHT, as a drug-free method, is especially important in obstetrics, where it has also been recommended (*71,88*).

In one study (*89*) researchers reported the discovery of hypoxic cycles with a 2-fold difference in PO_2 levels of oxygen content in the uterine tissue of pregnant (3-5 days) rats as compared with non-pregnant rats. The frequency of the PO_2 pulsation was much lower in the uterine tissue of non-pregnant rats. The hypoxic cycles were assessed as a mechanism of rhythmic periodic stimulation of metabolic reactions directed towards not only the increased resistance to hypoxia, but also towards the nonspecific resistance of uterine fetal tissues and the female body in and out of pregnancy. This discovery suggests that IHT acts as a natural biorhythmic process. Impulse biorhythm change of

cyclic pO_2 in the uterus tissues and intrauterine fetus of rats, guinea pigs and dogs is regarded as evolution-fixed physiological mechanism aimed to increase nonspecific resistance of the fetus (*90*).

Research was conducted on the development of children born to mothers with preeclampsia who were treated with normobaric hypoxia (*91*). One hundred women cured by IHT and fifty control women (given conventional treatment) were under care. IHT was carried out at 16-35 weeks of pregnancy and consisted of 8-30 sessions. Each session included 5 min of breathing a hypoxic gas mixture (10% O_2) through a mask, interrupted by 5 min of breathing atmospheric air, with a total of six cycles in 1 h. All children were under care at birth and monthly during the first year of life. The following parameters were measured: percentage of premature births, Apgar scores, characteristics of physical and neuropsychic development, breastfeeding duration, percentage of children with allergic diathesis, haemoglobin content in child's peripheral blood, and prevalence of acute respiratory disorders. All measured parameters were significantly better in children whose mothers had been treated by IHT.

In another study, researchers examined the efficiency of preventive usage of IHT in 44 pregnant females at high risk for preeclampsia in the presence of essential hypertension, stages I-II, and neurocirculatory asthenia of the hypertensive type. The authors paid attention to a decrease in the incidence of preeclampsia, in particular its severity patterns, and perinatal mortality (*92*).

Pregnant females at high risk of preeclampsia who underwent IHT in the second and third trimester, compared with controls, showed (*93*) more successful delivery; less frequent occurrence of nephropathy, fetal hypoxia, and premature labour; and better physical condition of newborns.

In the paper (*94*) oxygen metabolism kinetics was investigated in 90 pregnant females at high risk for preeclampsia and associated vascular disorders. Patients were treated with IHT. The study revealed that initial disorders of tissue respiration featured compensatory stimulation of tissue oxygen consumption. In early signs of preeclampsia, the consumption intensity was found to be diminished. During treatment, there was evidence of normalization in oxygen metabolism. This treatment proved to be an efficient drug-free method of preeclampsia prevention. Energy metabolism of maternal and fetal tissues during preconditioning/ adaptation to intermittent experimental normobaric hypoxia was also considered in (*95*).

Experimental studies have also been conducted on increasing the nonspecific body resistance of mother, fetus and newborn to extreme factors by hypoxic training (*96*). Strelkov *et al.* (*97*) conclude "the use of

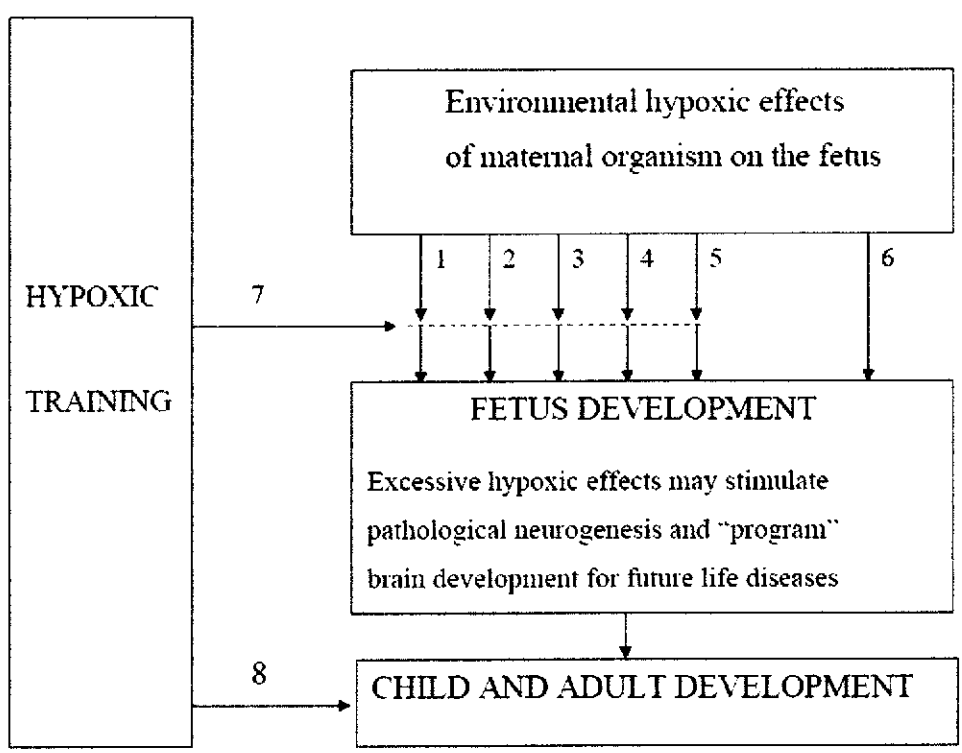

Figure 1. Simplified scheme of hypoxic influences on development. 1-6, environmental effects of maternal organism on the fetus, including harmful and useful (**1-5**) effects (**6**). 1, preeclampsia; **2**, hypoxia/ischemia; **3**, asphyxia at birth; **4**, infection/ inflammation; **5**, maternal psychological stress; **6**, natural hypoxic training of the fetus by maternal organism: increased pO_2 levels of pulsation of oxygen content in the uterine tissue of pregnant rats as compared with non-pregnant rats. **7** and **8**, preventive/ therapeutic effects of hypoxic training. All of those effects are tightly connected with hypoxia.

IHT with 10% O_2 is not only absolutely harmless for the fetus with no unfavourable effects on the course of the pregnancy or its outcome, but was also accompanied by a significant increase in the mass of the placenta by 26.9-33.2% and the mass of the fetus by 8.5-12.2%". Many other clinical data in support the harmlessness of IHT have been provided.

Data from the literature (*71,88,91-94*) related to the IHT procedure, suggest, particularly in preventive obstetrical applications, one course of IHT before pregnancy and one or two courses during pregnancy after the 16th week. All authors consider this procedure as effective and safe, but improved doubling study is needed.

The given data of this article are illustrated by the simplified scheme of hypoxic influences on development (Figure 1).

5. Conclusion

Data cited show the following trends in the studies: (*i*) hypoxia of different types plays a key role in almost all ordinary abnormalities and complications of pregnancy; (*ii*) hypoxia stimulates neurogenesis and is necessary for normal neurodevelopment, but excessive hypoxia leads to brain injuries and pathological development of different organs; and (*iii*) preconditioning/adaptation to hypoxic hypoxia primarily prevents obstetric complications and therefore future life diseases. It is a clear trend to use IHT for such adaptation, but improved doubling research is needed before wide using this method for primary prevention of obstetric complications.

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