Research Article ISSN 2835-6276

American Journal of Medical and Clinical Research & Reviews

Fetal oxygenation

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Received: 05 Oct 2023; Accepted: 07 Oct 2023; Published: 10 Oct 2023

Citation: Felis S. Fetal oxygenation. AJMCRR 2023; 2(10): 1-15.

ABSTRACT

This review focuses on the role of oxygen and the changes in oxygen levels in pregnancy in the human placenta. In the first trimester, the physiological conversion of the spiral arteries restricts maternal blood flow into the intervillous space creating a low oxygen environment for the trophoblast and the embryo. In the second trimester, progressive conversion of the spiral arteries allows unhindered entrance of maternal blood into the intervillous space. In early pregnancy, pathology of spiral artery conversion may promote premature flow of maternal blood resulting in miscarriage. In more advanced pregnancy, incomplete conversion of spiral arteries impairs maternal blood flow to the placenta, causing chronic hypoxia and growth restriction of the fetus. Chronically reduced maternal supply of oxygen to the placental-fetal unit may be partially balanced by metabolic reprogramming of the placenta. Acute impairment of oxygenation in the perinatal period and its effect on the placental-fetal unit will also be discussed. Uterine contractions in labor result in a 60% reduction in uteroplacental perfusion, causing transient fetal and placental hypoxia. A healthy term fetus with a normally developed placenta is able to accommodate this transient hypoxia by activation of the peripheral chemoreflex, resulting in a reduction in oxygen consumption and a centralization of oxygenated blood to critical organs, namely the heart, brain, and adrenals. Providing there is adequate time for placental and fetal reperfusion between contractions, these fetuses will be able to withstand prolonged periods of intermittent hypoxia and avoid severe hypoxic injury. However, there exists a cohort of fetuses in whom abnormal placental development in the first half of pregnancy results in failure of endovascular invasion of the spiral arteries by the cytotrophoblastic cells and inadequate placental angiogenesis. This produces a high-resistance, low-flow circulation predisposing to hypoperfusion, hypoxia, reperfusion injury, and oxidative stress within the placenta. Furthermore, this renders the placenta susceptible to fluctuations and reduction in uteroplacental perfusion in response to external compression and stimuli (as occurs in labor), further reducing fetal capillary perfusion, placing the fetus at risk of inadequate gas/nutrient exchange. This placental dysfunction predisposes the fetus to intrapartum fetal compromise. In the absence of a rare cata-

strophic event, intrapartum fetal compromise occurs as a gradual process when there is an inability of the fetal heart to respond to the peripheral chemoreflex to maintain cardiac output. This may arise because of placental dysfunction reducing pre-labor myocardial glycogen stores necessary for anaerobic metabolism or due to an inadequate placental perfusion between contractions to restore fetal oxygen and nutrient exchange. If the hypoxic insult is severe enough and long enough, profound multiorgan injury and even death may occur. This review provides a detailed synopsis of the events that can result in placental dysfunction, how this may predispose to intrapartum fetal hypoxia, and what protective mechanisms are in place to avoid hypoxic injury.

Keywords: fetal hypoxia; hypoxic ischemic encephalopathy; inadequate placentation; intrapartum fetal compromise; peripheral chemoreflex; physiology; placental development.

Physiology of fetal oxygenation.

All human cells require oxygen and glucose for their survival and function. Glucose can be stored in intracellular reserves and subsequently mobilized when needed, while oxygen requires a constant and continuous supply to ensure aerobic metabolism. Fetal cells have the same oxygen and glucose requirements as adult human cells for maintaining aerobic metabolism and energy production. The fetal peculiarity lies in the mode of supply: in fact, the intrauterine life of the child is not autonomous, and the supply of gas and nutrients depends on several factors such as maternal respiration and circulation, perfusion and placental function and fetal umbilical and systemic circulation.

Maternal-fetal gas exchange

Oxygen accounts for about 21% of the air breathed. In inspiration, oxygen tension (or oxygen partial pressure, pO_2) is about 21% of the total atmospheric pressure and, in the arterial blood of an adult, corresponds to about 95-100 mmHg. The oxygen tension in the fetus in utero, however, is different from that of the adult population: as oxygen is transferred through the various maternal compartments (from the lung to the systemic circulation and finally to the uterus), the oxygen tension progressively decreases and that which reaches the fetus is decidedly lower than the initial maternal one. The characteristics of the intrauterine fetal pO_2 can be summarized with the metaphor "monte Everest in utero", with an oxygen tension inside the umbilical vein equal to about 30 mmHg; this does not mean that the fetus spends 9 months in oxygen deficiency. In fact, fetal physiology is characterized by several suitable mechanisms that allow the fetus to be adequately oxygenated despite the relatively low oxygenation environment. These adaptive mechanisms facilitate the transfer of gas between maternal and fetal circulation.

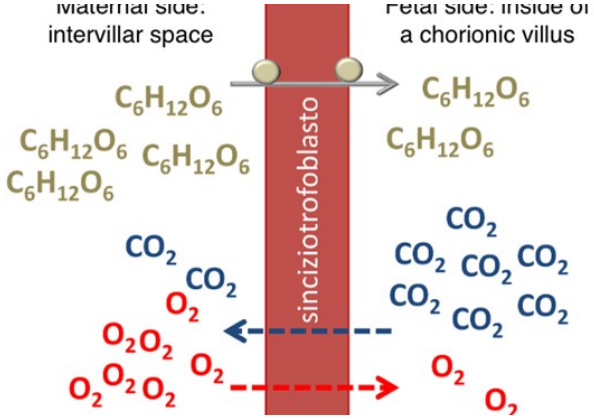
Remembering that oxygen diffusion depends on pO_2, hemoglobin (Hb) concentration, Hb type, oxygen saturation and blood flow, the typical mechanisms of intrauterine life will now be briefly described:

1. The concentration of hemoglobin in the fetus is 40% higher than the concentration of hemoglobin present in the adult. Fetal hemoglobin (HbF) is also widely present which, with the same pO_2, has a greater affinity for oxygen than adult hemoglobin.
2. PO_2 is higher in maternal circulation than in fetal circulation; the difference between the two compartments facilitates maternal-fetal oxygen transfer through transplacental diffusion (figure

1). The physiological maternal hyperventilation that occurs during pregnancy also reduces maternal pCO_2 and maintains a negative gradient across the placenta, such as to facilitate the transfer of CO_2 from the fetus to the mother [1].

3. The fetal heart rate is higher than the adult heart rate, and cardiac output (that is, per kilogram of body weight) is about four times higher in the fetus than in the adult; This makes it possible to compensate in quantity a "quality defect": thanks to a relative overflow of blood, the relatively low oxygenation is compensated.

Figure 1. Transplacental passage of gas and glucose. Gases such as oxygen (O 2) and carbon dioxide (CO_2) cross the placenta by simple diffusion (dashed arrow). Simple diffusion is a passive movement of substances that pass from one compartment at a higher concentration to another at a lower concentration, according to gradient and without energy consumption. The placental trophoblast is highly permeable to respiratory gases. Oxygen passes rapidly by simple diffusion from the maternal blood (higher concentration compartment) to the fetal one (lower concentration compartment) while carbon dioxide takes the opposite path. The difference in the partial pressure of oxygen between the maternal blood present in the intervillar space and the fetal blood present in the capillaries of the placental villi represents the regulating factor of the transfer between the two compartments.



Glucose (C 6 $H_{12}O_6$) is the major carbohydrate transported through the placenta from mother to fetus and is the main source of carbon and energy. It crosses the placenta by means of an easier diffusion mechanism (continuous arrow). Facilitated diffusion is the process by which a substance is transported according to gradient, from one compartment to another, through the use of a membrane transporter protein. The transport of glucose occurs through transport proteins (circles above the continuous arrow) called GLUT. Maternal blood glucose is higher than fetal blood by about 20mg / dl, so there is a maternal-fetal gradient and transport takes place according to gradient from the area with greater concentration (mother) to that with lower concentration (fetus). During pregnancy there is a significant increase in the transplacental gradient of glucose, with an increase in transport through the placenta. This system is faster than a simple diffusion and does not involve energy consumption but is a stereo-specific and saturable mechanism.

The mechanisms described above contribute to allow adequate fetal oxygenation to support the development, growth and vital functions of the child in a physiological environment with relatively low oxygen concentration. Alterations in maternal respiration and circulation and/or perfusion and placental function and/or fetal umbilical and systemic circulation may instead lead to alterations in fetal oxygenation. The types of alterations capable of causing fetal oxygenation deficiency are summarized in Table 1.

Table 1: Conditions that can reduce oxygen supply to the fetus.

Category	Main alterations
Maternal oxygenation	Impaired breathing (e.g., asthma, pneumonia, atelectasia, respiratory depression due to medications). Impaired circulation (severe anaemia, haemoglobinopathies). Alteration of cardiac function (e.g. alterations of contractility as can happen for cardiomyopathies, diabetes, heart failure, myocardial ischemia; alterations of frequency-arrhythmias; increase in vascular resistance as in case of arterial hypertension; reduction of blood supply-hypovolemia; episodes of transient hypotension as can happen by compression of the vena cava from the supine position or hypotension due to peridural analgesia; abnormalities congenital structural of the heart or large vessels).
Placental function	Alteration of placental vascular supply (decidual arterial disease such as failure to modify spiral vessels, thrombosis of spiral vessels, acute atherosis). Alteration of the possibility of maternal-fetal exchanges due to loss of functioning tissue (placental infarctions, areas of abruption). Alteration of placental function due to inflammation (acute chorioamnionitis with fetal inflammatory response – chorionitis and/or funisitis). Alteration of the possibility of maternal-fetal exchanges by obliteration of the intervillar space (massive deposits of perivillar fibrinoid). Obstruction of the fetal vascular network (due to thrombotic cause – fetal thrombotic vasculopathy or from inflammatory cause-chronic villitis).
Fetal circulation	Obstructive situations (cord compression as in case of severe oligohydramnios or funicular prolapse). Cardio-circulatory situations (alterations in cardiac function related to anatomical abnormalities, congenital cardiomyopathies or acquired cardiomyopathies such as diabetes hypertrophy; alterations in the heartbeat related to arrhythmia; alterations in blood oxygen transport linked to the amount of circulating hemoglobin as in case of anemia or linked to the quality of hemoglobin as in cases of hemoglobinopathies).

Alterations in maternal respiration can lead to a reduction in the transfer of oxygen from the pulmonary alveoli to the pulmonary capillaries and then to the systemic circulation, finally resulting in a reduced supply of oxygen to the uterus and then to the fetus.

Alterations in maternal circulation can reduce oxygen transport. About 98% of oxygen binds to hemoglobin and is transported in the maternal blood, in case of severe anemia the hemoglobin available for oxygen transport is scarce. In case of hemoglobinopathies, the possibility of oxygen binding to hemoglobin may be lower. Both of these conditions, as well as alterations in maternal heart function, can result in reduced oxygen supply to the fetus.

Alterations in placental function, both on the maternal and fetal side, reduce the oxygen supply to the baby as well as alterations in fetal circulation, both in quantitative and qualitative terms.

Placental function

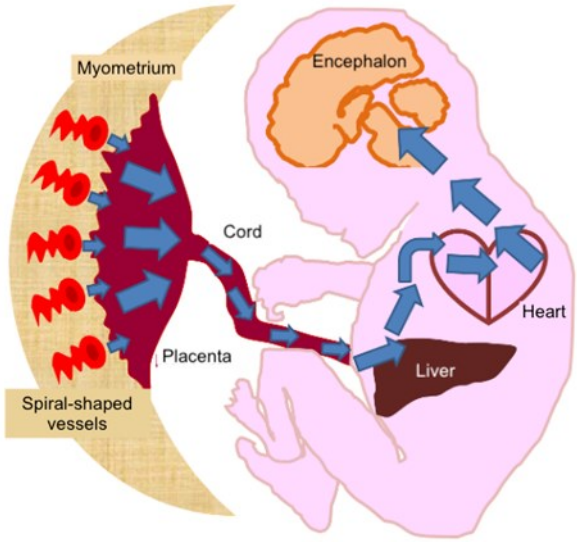
The placenta is a fundamental organ for the fetal supply of substances suitable for cellular functioning and an action that can be defined as "multi-organ": it acts as a lung, kidney and gastrointestinal tract, allowing the exchange of gases, the elimination of waste and the absorption of nutrients that reach the placenta through the maternal blood supply. In the placental intervillar space, in fact, oxygenated and nutrient-rich blood comes from the maternal spiral arteries and flows inside the placen-

tal chorionic villi. Chorionic villi contain fetal capillaries derived from branches of umbilical cord vessels. The branches of the two umbilical arteries deepen into the placenta vascularizing the chorionic villi. The two fetal umbilical arteries carry blood and deoxygenated waste produced by the baby from the fetus to the placenta. The fetal capillaries contained in the chorionic villi, immersed in the maternal blood of the intervillar space, then give the waste products of the fetus arrived at the placenta to the maternal blood. Thanks to the maternal blood, the capillaries contained in the chorionic villi are then reoxygenated and "nourished" and return to the fetus, bringing oxygen and nutrients through branches of vessels that flow into the umbilical vein.

The fetal cardiovascular system is designed in such a way that the most oxygenated blood reaches easily and directly to the myocardium and brain (figure 2), through preferential shunts. Blood from the placenta passes into the umbilical vein and, almost unhindered, arrives at the brain passing through the venous duct, right atrium, foramen ovale, left atrium, left ventricle, aortic arch, neck vessels, and then the brain. The heart is equipped with baroreceptors and volume receptors that sense changes in blood pressure and volume (figure 3). The aortic arch and carotids contain chemoreceptors that are well positioned to detect any alteration in the oxygen content of blood coming from the placenta. Thanks to the exploitation of these "sensors", the fetus is therefore able to adapt its cardiovascular response to the state of placental functioning and environmental oxygenation.

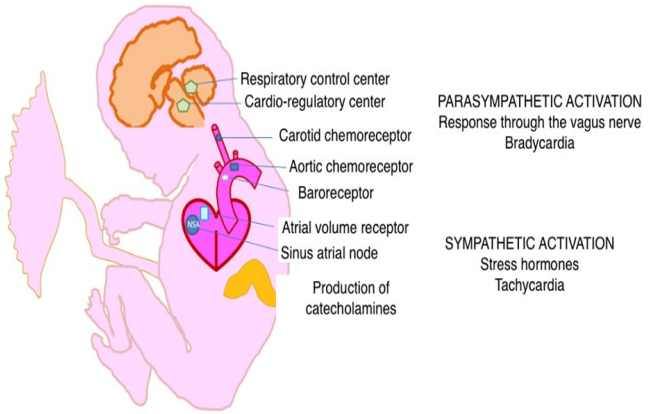
Figure 2. Preferential targeting of oxygenated blood from the placenta to the fetal brain.

The umbilical vein carries oxygenated blood from the placenta to the fetus. In the blood distribution of blood from the umbilical vein, most of the flow avoids the liver by passing through the ductus venous (first shunt). The blood then enters the inferior vein and then into the right atrium. At this point, since the fetal lungs do not yet have their respiratory function, two other shunts distribute the blood almost completely avoiding the pulmonary passage: a part of the blood entering the right atrium is directly diverted into the left atrium through the foramen ovale (second shunt); The blood that instead enters the right ventricle is pumped into the pulmonary trunk where, through the ductus arteriosus (third shunt) it is diverted from the pulmonary trunk to the aorta. Through the supra-aortic trunks, oxygenated blood then reaches the brain.



The aorta carries blood to the tissues of the fetus' body and finally back to the placenta through the two umbilical arteries. The umbilical arteries then transport blood containing CO_2 and waste products from the fetus to the placenta.

Figure 3. Localization of fetal oxygen level "sensors"



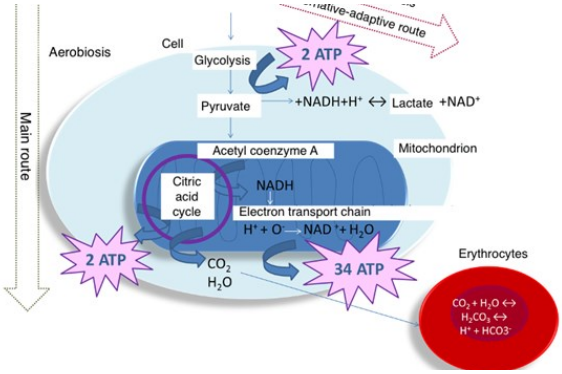
Energy supply and fetal metabolism

The fetal oxygen requirement is determined by the size of the fetus, its state of activity and essential metabolism processes. If supply and demand are in balance, the fetus has enough oxygen to aerobolize glucose aerobically and thus to produce the energy necessary for the function of its cells and organs. It therefore has enough energy for its own growth and to make active movements.

During metabolism, the body produces carbonic acid and other organic acids. Carbonic acid (H 2 CO $_3$) is formed by the hydration of carbon dioxide (CO_2, also called carbon dioxide) during oxidative metabolism. Carbon dioxide diffuses through the placenta very quickly and is therefore rapidly eliminated. The share of this elimination is directly related to the share of blood flow on both sides of the placenta.

Let's now go into a little more detail about metabolic reactions. The fetal energy supply is shown in Figure 4. As exemplified in the figure, fetal energy derives mainly from aerobic metabolism and is mainly produced by glycolysis, a process that begins with the conversion of glucose to pyruvate and ends with the formation of adenosine triphosphate (ATP). In aerobic conditions, pyruvate is usually converted into acetyl coenzyme A and, in the presence of oxaloacetate, enters the citric acid cycle (also called Krebs cycle). It is then subjected to mitochondrial oxidation, obtaining CO_2 and water. Crossing the electron transport chain finally ATP is obtained.

Figure 4. Cellular metabolism in aerobiosis and anaerobiosis. In the presence of oxygen (aerobiosis) a molecule of glucose produces 36 molecules of ATP. In the absence of oxygen (anaerobiosis), one molecule of glucose produces 2 molecules of ATP and 2 molecules of lactic acid. In anaerobiosis, therefore, in order to obtain the same



energy level, the fetus needs to accelerate glycolysis, resulting in the formation of a greater quantity of lactic acid, pyruvic acid and hydroxybutyric acid; these products cannot be degraded to H 2 O and CO_2 through use the citric acid cycle because the lack of oxygen prevents mitochondrial conversion of hydrogen into water. During anaerobiosis, all the NAD present in the cell cytoplasm is transformed into NADH, increasing the share of non-volatile fixed acids.

The CO 2 produced by the cells diffuses into the surrounding blood through the cell membrane and enters erythrocytes where it is rapidly converted into carbonic acid (H_2CO 3) and bicarbonate ion (HCO_3^-) by the enzyme carbonic anhydrase. Any excess CO_2 is rapidly removed from the bicarbonate system, which imposes large increases in acidity that hydrogen ions (H^+) could cause:

$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO3^-$

This reaction occurs bidirectionally until the blood reaches the placenta, where CO_2 is eliminated. The rate at which CO_2 crosses the placenta depends on blood flow [3,4]. Under physiological conditions, the total production of cellular CO_2 is equal to the elimination of transplacental CO_2 and therefore no changes in the oxygenation and acidity of fetal blood occur.

However, the margin of safety for fetal elimination of CO_2 is limited. If necessary, the way the fetus can increase the elimination of CO_2 is to increase its heart rate, which in turn will result in increased placental perfusion [2].

In addition to 6 molecules of CO_2, the final product of the citric acid cycle consists of 36 molecules of ATP (which provide energy to the fetus) and NADH, which is formed by combining NAD+ and H^+.

Hydrogen ion concentrations are expressed as pH values and are calculated as a negative logarithm of the hydrogen ion concentration [H^+]; the pH then decreases as [H^+] increases. As in adults, even in the fetus, the neutralization of H^+ production occurs by buffer systems. A buffer system is therefore intended to allow the body to maintain pH at relatively constant physiological levels, despite the continuous production of acids physiologically resulting from cellular metabolism.

In the fetus, plasma bicarbonates and haemoglobin are the two most important buffer systems and together account for about 70% of the total of all buffer systems in the blood. Other minority buffer systems include erythrocyte bicarbonates (18%), plasma proteins (7%) and inorganic phosphates (5%) [3].

The bicarbonate system or bicarbonate buffer, mentioned above, is the main plasma buffer system and alone represents 35% of fetal buffering blood capacity [1,2]. However, it is a system that takes time. Bicarbonate and fixed acids cross the placenta much slower than CO_2; balancing them takes hours.

The other important swab is hemoglobin (Hb) which accounts for about another 35% of fetal blood buffer capacity [1]:

$HbH \leftrightarrow Hb^- + H^+$

$HbO_2H \leftrightarrow HbO_2^- + H^+$

The hemoglobin buffer system, like the bicarbonate system, also takes time to function.

Fetal oxygenation in labor

Labor is a potential period of increased risk of impaired fetal oxygenation. In fact, uterine contractions produce a physiological transient decrease in blood supply to the placenta (figure 5), which can in turn lead to brief and temporary interruptions in transplacental gas exchange. Changes in the level of fetal oxygenation, pO_2, CO_2 and bicarbonates are therefore physiological during labor, with moderate levels of physiological hypoxemia and acidemia.

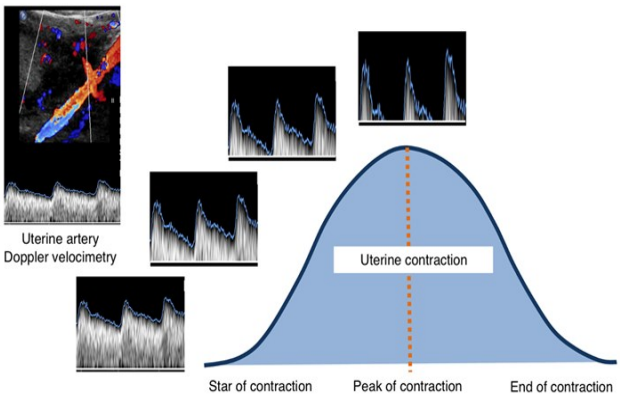


Figure 5. Blood supply during uterine contraction. As a result of the contracting of muscle fibers, the spiral vessels that supply or the placenta are compressed. Vascular compression leads to progressive loss of the diastolic blood component, reaching the minimum perfusion at the apex of contraction. As the contraction subsides, normal vascularization is recovered. Labor is therefore an event of physiological, short, rhythmic but persistent reduction of blood supply to the placenta and therefore to the fetus.

Table 2 lists the values of acid-base balance in the healthy full-term fetus assessed before, during and after labor and compared with the values of the adult human being.

Table 2: Acid-fetal balance before, during and after labour and compared with adult subjects.

	Umbilical vein before labor	Fetal scalp, initial 1st stage*	Fetal scalp, 1st advanced stage*	Fetal scalp, 2nd stage*	Umbilical artery at birth*	Umbilical vein at birth*	Artery subject adult[#]
pH	>7.38	7.33±0.03	7.32±0.02	7.29±0.04	7.27±0.069	7.34±0.063	7.36-7.44
pCO2 (mmHg)	<42	42±4.5	44±5.1	46.3±4.2	50.3±11.1	40.7±7.9	35.2-18.7
pO2 (mmHg)	>21.9	21.8±2.6	21.3±2.1	16.5±1.4	15.7 (5.2-30.7) [§]	26.2 (12.7-36.7) [§]	75-105
BD (mmol/l)	<3	3.9±1.9	4.1±2.5	6.4±1.8	2.7±2.8	2.4±2	-3.0 - 3.0

*Expressed as mean ± standard deviation

[#] Expressed as a 95% reference range

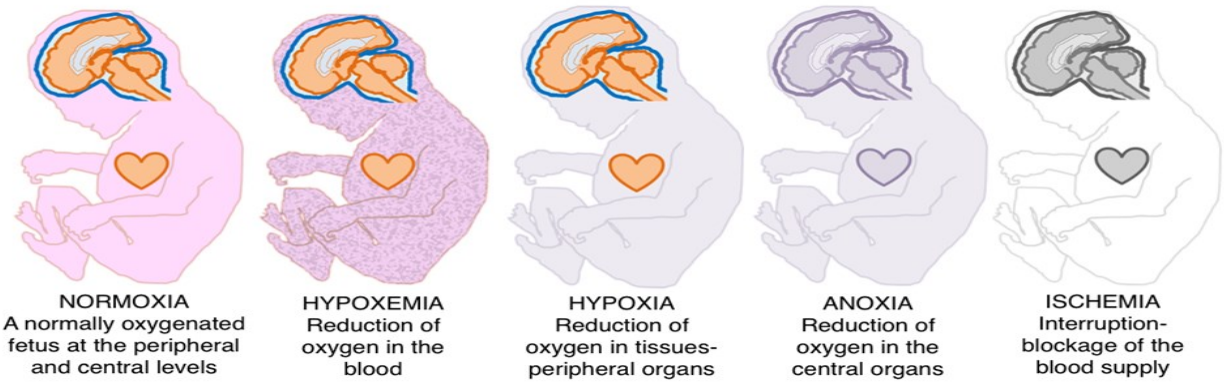
[§]Mediana (2.5 - 97.5 percentile).

Fetal responses to hypoxia

During labor, as at any other time of intrauterine life, oxygenation and fetal acid-base balance may be compromised due to events that involve the reduction of blood supply on the maternal side (resulting in insufficient placental circulation) and / or on the fetal side (with umbilical cord obstruction and therefore insufficient fetal circulation).

During these events, the oxygen content of fetal blood may decrease, leading to a condition called hypoxemia. The levels of modification of the fetal oxygen content are schematized in Figure 6, showing the various degrees of severity of oxygenation reduction.

Figure 6. Degrees of fetal response to oxygen deficiency



CO_2 can increase by producing hypercapnia. For some time, excess CO 2 can be removed with increased fetal heart rate and the use of buffer systems, but as the insult persists, it can reach such high levels of pCO_2 that it exhausts the capabilities of the buffer systems and has a significant decrease in blood pH, with a fetal state defined as acidosis [5,6]. (Figure 7).

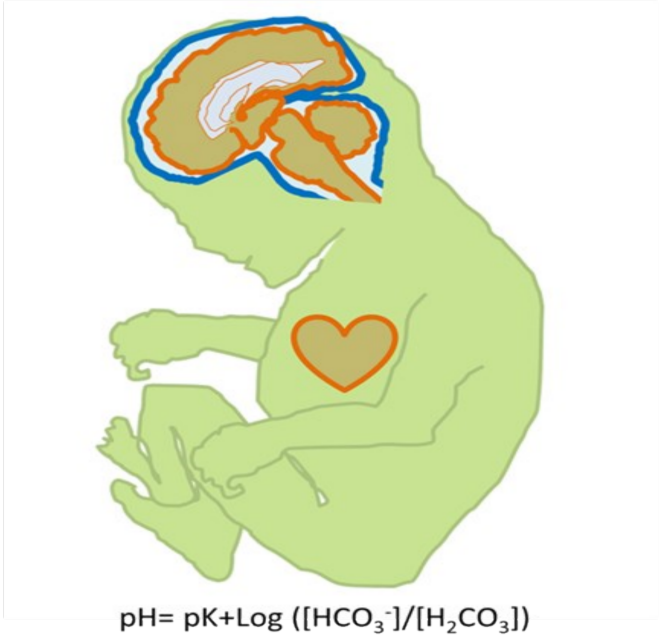


Figure 7. Fetal acidosis. Acidosis reflects the degree of anaerobic metabolism implemented during a period of hypoxia. It is evaluated by measuring the pH (logarithm of the inverse of the concentration of hydrogen ions) and the base defect. The pH of a solution depends on the ratio between the concentrations of bases and acids; therefore, it depends on the concentrations of HCO3- and H2CO3 where HCO3- represents the metabolic component and is expressed in mEq/l while the concentration of H2CO3 expresses the respiratory component and is reported in mmHg of pCO2. Metabolic acidosis results in excess acid production and a decrease in basic buffers, resulting in base deficiency.

Under hypoxic conditions, the first outcome is therefore fetal accumulation of CO_2. The increase in pCO_2 leads by hydrolysis to the dissociation of carbonic acid (H_2CO_3) and to a drop in ph. For values of pO_2 <12 mmHg in the fetus, anaerobic glycolysis is activated and lactate production increases. Lactic acid (C 3 H_6O_3) is buffered in the fetus by sodium bicarbonate leading to an increase in CO_2 and a decrease in buffer bases. Acidosis also greatly reduces the affinity of hemoglobin to oxygen (Bohr effect), favoring its release. The released hemoglobin thus acts as an additional acid-base buffer, picks up hydrogen ions and slows down the pH drop.

However, the process of counteracting the acidosis just exposed cannot last long and, when the buffer systems are saturated, the pH begins to fall. The displacement of the buffers leads to an increase in pCO_2 and a decrease in bicarbonate, adding a metabolic component to respiratory acidosis.

In summary, therefore, the fetus can undergo both respiratory and metabolic acidosis: respiratory acidosis arises due to the accumulation of CO 2 which is responsible for the production of H+ ions due to a rightward movement of the equation CO 2 + H_2 O ↔ H^+ + HCO_3^-; the diagnosis of respiratory acidosis is based on an elevation of pCO_2 in the blood of the umbilical artery (>75 mmHg). Metabolic acidosis, on the other hand, is related to the transition to the anaerobic pathway (which will be explained in detail in the next paragraph) during a state of prolonged hypoxia. Anaerobic glycolysis converts glucose to pyruvate, and then to lactate and H^+ ions; hydrogen ions decrease pH; the diagnosis of metabolic acidosis is based on the finding in the blood of the umbilical artery of consumption of buffer systems (base deficiency >12 mmol/l) and high levels of lactate (>10 mmol/l). Clinically, acute conditions that disrupt normal blood flow between the fetus and placenta (e. g. compression

of the Maternal aorta, placental abruption, umbilical cord occlusion) could cause a rapid increase in CO_2 and consequent respiratory acidosis; persistent conditions of reduced Fetal blood perfusion (e.g. placental insufficiency in fetuses with intrauterine growth retardation) may lead to chronic hypoxia and metabolic acidosis.

Anaerobic fetal metabolism

When a tissue is exposed toa reduced oxygen supply, it loses the efficiency of its oxidative phosphorylation capacity; the transition from aerobic to anaerobic metabolism then occurs in the cells. Under anaerobic conditions, pyruvate is reduced to lactate, through lactate dehydrogenase in the presence of nicotinamide adenine dinucleotide (NADH). This leads to a state of energy inefficiency with depletion of ATP reserves, accumulation of lactic acid and H^+ and impaired cellular functioning [4].

As previously explained, the final product of the citric acid cycle consists of 36 molecules of ATP and NADH, which is formed by combining NAD+ and H^+. Under aerobic conditions, the reaction

NADH+H+ Lactate +NAD^+ ↔ reverses and the lactate is oxidized back to pyruvate. The lactate can then be converted back into glucose and glycogen through gluconeogenesis. Under physiological conditions, the ratio of lactate to pyruvate is normally 10-16: 1 [2]. In anaerobic conditions, on the other hand, the accumulated NADH promotes the regeneration of NAD^+ by increasing the reduction of pyruvate to lactate (figure 4). Anaerobic metabolism then leads to the accumulation of lactate and subsequently to the decrease in ph. An increase in the lactate: pyruvate ratio is therefore a sign of hypoxia, and the accumulation of lactate determines metabolic acidosis.

Anaerobic metabolism is a strategy of compensating the fetus to maintain its myocardial function and thus to survive. The efficiency and efficacy of this compensation strategy depend on the myocardial glycogen content pre-existing in the hypoxic state [7]. Glycogen stores are consumed rapidly during anaerobic metabolism, since one molecule of glucose provides only two ATP molecules, compared to aerobic metabolism that produces 36 (figure 4). The pre-existing myocardial glycogen content therefore makes a difference on the effectiveness and duration of this compensation system.

Changes in fetal pH

If the fetal oxygen deficiency is prolonged over time and fetal metabolism becomes anaerobic, there is an increase in the concentrations of free hydrogen ions (H^+; [H^+]). As explained above, hydrogen ion concentrations are expressed as pH values. Anaerobic fetal metabolism therefore leads to a decrease in ph.

The rate of pH reduction depends on the severity of the oxygen reduction: when the oxygen supply is totally interrupted, the pH drops by 0.5 units in 3-4 minutes; When the oxygen intake is reduced by 10%, the pH drops by 0.5 units in 30 minutes; when the oxygen intake is reduced by 4%, the pH drops by 0.5 units in 60 to 80 minutes [8].

We have already presented how anaerobic metabolism leads to an accumulation of lactate, which results in a consumption of buffer systems and an increase in base deficiency (BD). According to international consensus, metabolic acidosis at birth is defined as the condition of pH <7.00 and BD≥ 12.0 mmol / l [9].

It is important to remember, on the basis of the characteristics of the fetal circulation described above, that the state of neonatal acidosis can be evaluated through the value obtained in the blood taken from the umbilical arteries, while the sampling obtained from the umbilical vein reflects the maternal acid-base state and placental function.

The persistence of lactic acid accumulation, depletion of buffer systems, reduction of pH and increase in BD, causes the sodium potassium ATPase pump to fail and disrupts the exchange of ions across the cell membrane, initiating a cascade of reactions leading to increasingly serious cell lesions, with brain damage and impaired fetus neonatal conditions up to death. The alterations of the cerebral picture, visible by histological analysis, are summarized in Table 3 and an example of brain injury is represented in Figure 8. Before dying, however, the fetus reacts and tries to protect its survival by implementing behavioral adaptations to reduce energy expenditure and waste.

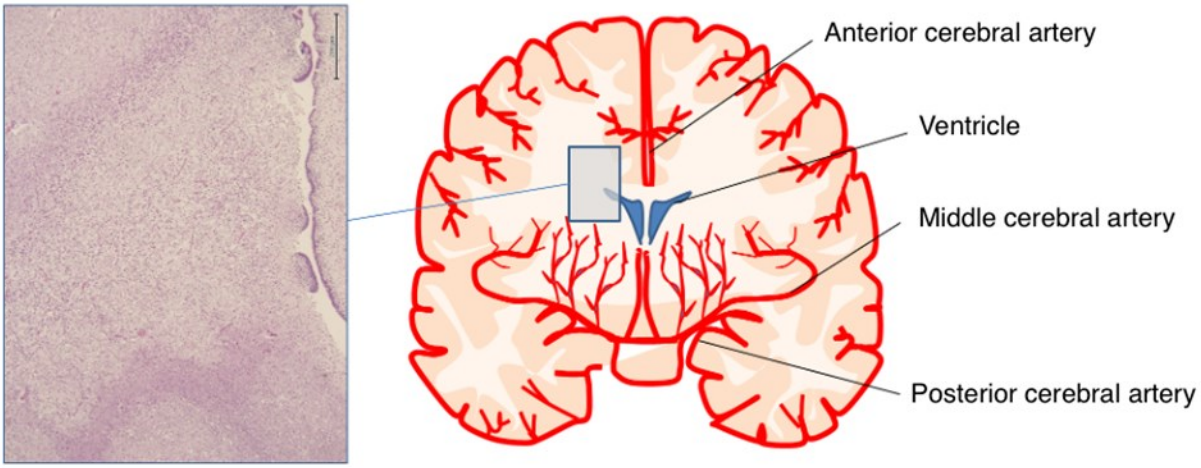


Figure 8: Brain damage from hypoxia.

An area of cerebral infarction in the initial phase of organization is observed in the periventricular area: the necrotic tissue appears infiltrated by cells in macrophage activity. Histological image courtesy of prof. G. Bulfamante, San Paolo Hospital, Milan.

Table 3: histological changes of the fetal brain according to the time elapsed since the insult.

Histological lesion	**Tempo**
Edema	Hours
Coagulatory necrosis	3 hours
Swellings neuronal	
Visible with immunohistochemistry techniques (βAPP marker)	1, 1/2 hours
Visible with hematoxylin and Eosin stains	15-24 hours
Cell death	
Cell necrosis	5-6 hours
Apoptosi	12-48 hours
Endothelial reaction	
Swelling of endothelial cells	1-3 days
Capillary proliferation	5-8 days
Microglia reaction	1-3 days
Macrophages containing intracytoplasmic material	≥3 days
Cyst formation	8-10 days
Gliosis	
Astrocyte reaction	1-3 days
Fibrillar gliosis	≥6 days

The "time elapsed since the insult" represents the minimum time necessary between the time of damage and the death of the child for the injury to be histologically visible. The time indicated is purely indicative and may also vary according to the resuscitation techniques and the care given to the child. Data from Squier W et al. Seminars in Neonatology. 2004; 9:331-345.

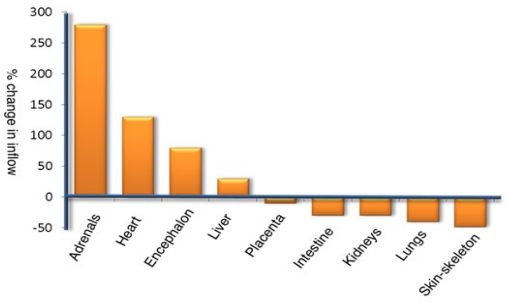


Figure 9. Changes in **fetal blood supply to organs in conditions of reduced oxygenation**. The fetus implements a process of centralization of the circulation aimed at maximizing the circulation of the brain, myocardium and adrenal glands to the detriment of the circulation of the liver, intestines, kidneys, lungs, muscles and skin.

Fetal behavioral changes

In case of hypoxia, the fetus manifests adaptive behavioral, metabolic, and cardiovascular responses, which work through neuroendocrine compensation mechanisms designed to maintain the integrity of the acid-base balance.

Compensation mechanisms include:

- reduction of oxygen consumption
- metabolic changes
- changes in heart rate

The reduction of oxygen consumption is achieved by the cessation of non-essential fetal functions such as active body movements, reduction of body temperature and, if the condition of oxygen reduction persists, redistribution of cardiac output with centralization of the circulation. The continuation of the reduced oxygen supply to the fetus, for many minutes or hours, involves the redirection of the fetal blood stream, in order to maximize the flow to the brain, myocardium and adrenals. Blood flow to the intestine, kidneys, liver, skeleton, muscles and skin is reduced (Figure 9); at the same time, blood flow is also redirected within the brain, resulting in a shift of blood flow from the cerebral cortex to the central and basal encephalic portions [10,11].]. This brainstem sparing model, called brainstem spearing, protects the respiratory and vasomotor centers.

Metabolic adjustments are intended to maintain sufficient oxygenation of vital organs through the transition to anaerobic cellular metabolism, initially only in the peripheral organs and subsequently, also in the central organs [12,13,14]. Metabolic adjustments are, in fact, intended to reduce the energy demand of the tissues. The metabolic rate of the fetal brain is actually already particularly low compared to adult tissues: it is partly due to the lower permeability of cell membranes (which results in delayed depolarization), and partly due to a reduced release of excitatory amino acids from nerve endings and a lower density of the synaptic network compared to the cervix fully developed [15]. The reduction of peripheral metabolism contributes to improving the efficiency of cerebral oxygenation by improving fetal gas exchanges and oxygen diffusion in tissues [15,16].

The fetal heart rate is regulated by the cardiorespiratory center located in the medulla oblongata, which in turn is influenced by the activity of the cerebral cortex and hypothalamus. The fetal heart

rate is therefore regulated by the sympathetic autonomic (catecholamines-mediated) and parasympathetic nervous system. In the fetus, unlike what happens during adult life, circulating catecholamines are produced by the adrenal medulla that predominates over sympathetic nervous effects. Aortic and carotid chemoreceptors feel changes in pO_2 in circulating blood, while chemoreceptors present in the medulla oblongata or perceive blood changes in pCO_2 and $[H^+]$. Any change in blood pressure is detected by baroreceptors present in many of the large arteries of the chest and neck, and particularly at the level of the aortic arch and carotid artery. Together with the bone marrow receptors and cardiorespiratory centers, these receptors provide the autonomic nervous system with information about the circulatory and respiratory state of the body, helping the fetus adjust its heart rate according to its own needs [20]. Initially, the heart is stimulated by catecholamines to increase its frequency, as a compensation mechanism. Alpha-adrenergic receptors regulate the degree of peripheral vascular constriction, while beta receptors affect cardiac function and metabolic reactions such as glycolysis and lactate formation [17]. The parasympathetic nervous system acts instead on the sinoatrial and atrioventricular nodes through the vagus nerve. The action of the vagus nerve and the release of the neurotransmitter acetylcholine decrease the fetal heart rate [18,19], leading to bradycardia, a sign of exhaustion of fetal compensatory capacities. The mechanisms of fetal heart rate regulation are schematized in Figure 10.

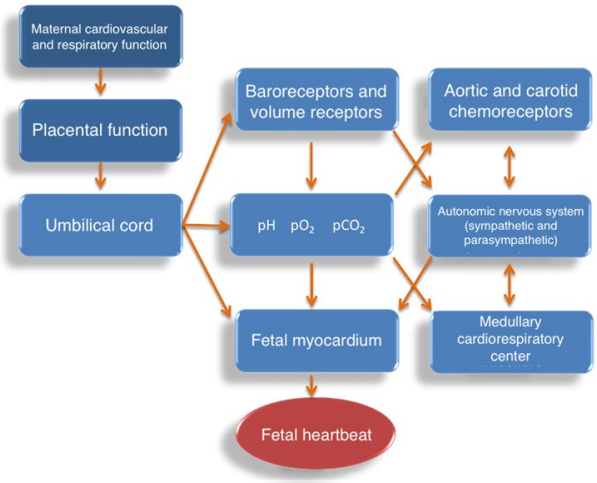


Figure 10. Fetal heart rate regulation systems.

Unlike the brain, the heart does not reduce its oxygen needs during hypoxia and is forced to work harder due to an increase in catecholamines. The fetal heart is therefore often the last organ to fail during hypoxia. The results of severe myocardial hypoxia are bradycardia, hypotension, and cardiovascular collapse.

The degree of effectiveness of the above mechanisms in preventing irreversible fetal damage depends on the previous general health condition of the fetus, the functional capacities of the placenta, as well as the duration, frequency and intensity of hypoxemic events [21]. A fetus in previous good health will be better able to tolerate and overcome hypoxic insults without results while a fetus with suboptimal starting conditions, associated with placental insufficiency, will have less tolerance. A typical example of reduced tolerance to hypoxia is that of the fetus with intrauterine growth retardation: the fetus with reduced growth has fewer placental functional reserves and fewer personal adaptive reserves, therefore less tolerance to insult. The fetus with growth retardation is therefore more rapidly predisposed to hypoxic damage, with long-term outcomes.

If hypoxia progresses over time, the fetus loses the ability to protect its vital organs. There is a reduction in blood pressure due to a decrease in cardiac output, therefore a decrease in cerebral blood supply. The combination of severe hypoxia (systemic and central) and ischemia due to hypotension and hypoperfusion may result in hypoxic brain damage, multiple organ failure, and eventually mortal and fetal impairment [22].

Fetal responses to aggravation of oxygen deficiency are summarized in Figure 11.

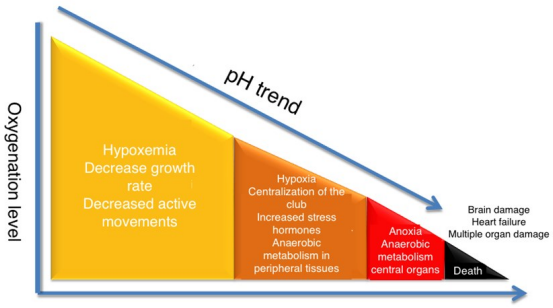


Figure 11. Fetal adaptations and impairments to varying levels of oxygen deficiency.

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