Physiology of the Placenta—
Gas Exchange

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ABSTRACT

The placenta serves as the fetus' organ of gas exchange throughout intrauterine life. While the dependence of fetal well-being on an intact maternal-placental unit has been recognized for centuries, it is only in the last several decades that research with fetal animals has begun to unravel the mechanisms by which it regulates blood supply and oxygen, as well as its role in the maternal-to-fetal transfer of carbohydrates, proteins, fats, water, and inorganic salts. The anatomy and physiology of the placenta are presented here as they relate specifically to gas exchange. In addition, compensatory adaptations of the fetus and placenta to acute asphyxial events will be discussed.

Introduction

"... it may be objected, That the Foetus in the Womb lives, its Heart pulses and its Blood circulates; and yet it draws in no Air, neither hath the Air any access to it. To which I answer, That it doth receive Air, so much as is sufficient for it in its present state, from the maternal Blood by the Placenta. ... I say then, That the chief use of the Circulation of the Blood. . . . thro' the Placenta . . . . in an Human Foetus, seems to be the Impregnation of the Blood with Air, for the feeding of the Vital Flame."—J. Ray 1701

The importance of the placenta to fetomaternal gas exchange—its role for the duration of pregnancy as the "fetal lung"—has been suspected for centuries. Only in the last several decades, however, have the physiological mechanisms by which this is accomplished begun to be unraveled. As with many advances in physiology, the understanding of placental function has depended on research with animal models, especially the intact, non-exteriorized fetal lamb. This animal model system and the introduction of radioactive microspheres for the study of regional blood flow have been key developments advancing the understanding of placental physiology. Motivation to pursue this area of research has increased with the growing appreciation of the placenta's pivotal role as arbiter of both acute and chronic asphyxial assaults to the feto-maternal unit.

Historically, the consequences of perinatal asphyxia on subsequent human
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Development were first described in 1862 by Dr. W. J. Little, in a presentation to the Obstetrical Society of London. In this now classic paper, he differentiates birth injury resulting from birth asphyxia, that is "interruption of the proper placental relation of the foetus to the mother," from that related to actual delivery, "from direct mechanical injury to the brain and spinal cord." This new and, at the time, controversial distinction required another hundred years and experimental verification in fetal animals before its gradual acceptance. Today, perinatal asphyxia remains a significant neonatal problem, accounting for 90 percent of cerebral palsy, with the remaining 10 percent being attributed to postnatal factors.

Anatomy and Physiology

The placenta physically attaches the fetus to the uterine wall and is composed of both a maternal (decidual) and fetal portion (chorionic plate and villi). Maternal arterial blood reaches the placental cotyledons through spiral, terminal branches of the uterine arteries which evert blood through arteriolar orifices in the decidual plate into the intervillous space. This arterIALIZED lake of blood then bathes the chorionic villi projecting into it, which contain the fetal capillaries. Carbon dioxide and other waste products of fetal metabolism, arriving by way of the umbilical arteries, are exchanged across this intervillous space by simple, passive diffusion as oxygen and nutrients pass into the fetal circulation through the umbilical vein from the maternal side. Blood in the intervillous space drains intermittently back through the decidual plate, returning to the maternal circulation via the uterine vein. Anatomically, the human placenta is classified as hemochorial in type, gas being exchanged from maternal red blood cells free in the intervillous lakes, across the chorionic membrane and fetal endothelial cell wall to the fetal red blood cells.

Under normal conditions, the arterialized blood flow exiting the placenta through the umbilical vein divides as it traverses the liver, approximately half perfusing the liver parenchyma and entering the inferior vena cava from the hepatic vein. The other 50 percent of umbilical venous blood passes directly through the ductus venosus from which it enters the inferior vena cava and selectively streams into the right atrium and across the foramen ovale into the left heart, providing blood with the highest oxygen saturation to the fetal brain and myocardium.

Oxygen delivery to the fetus is a function of two variables: umbilical venous blood oxygen concentration and umbilical blood flow. Since umbilical venous blood oxygen concentration is a reflection of uterine blood flow, factors affecting it are primarily maternal, such as hypotension, hypertension, uterine contractions, and obstruction of the maternal inferior vena cava. Factors adversely affecting umbilical blood flow include umbilical cord compression, hemorrhage (placenta previa, abruptio placenta), polycythemia (excessive placental transfusion), and catecholamine release. Thus, the oxygen delivered to the fetus is first dependent on maternal uterine blood supply, modified by placental diffusion of oxygen, and finally the product of umbilical venous blood flow and oxygen content. The normal oxygen pressure values in maternal and umbilical blood vessels in humans are uterine artery, 80 to 100 PO₂ mmHg; uterine vein, 40 to 45; umbilical vein, 25 to 35; and umbilical artery, 20 PO₂ mmHg.

Two striking aspects of this oxygen transport cascade are the inefficiency of sequential oxygen transfer and the low PO₂ environment that results for the fetus. Measurements in the unstressed pregnant ewe show umbilical venous
PO$_2$ to range from 25 to 35 mmHg in the fetal lamb, rarely exceeding 40 mmHg. Fetal adaptations to this relative hypoxemia include the oxyhemoglobin dissociation curve of fetal blood, to be discussed later, and fetal cardiac output, which is high relative to the adult.

Much controversy and experimental investigation have focused on the physiology of placental gas exchange, the majority of experimental work, by necessity, being done with fetal animals, particularly the fetal lamb. Of particular interest have been efforts to account for the decrease in oxygen tension that occurs across the placental interface. Experimental manipulations of uterine, and hence fetal, oxygen supply in fetal sheep have shown that umbilical venous blood oxygen tension equilibrates with, but is never equal to or higher than its donor stream, the uterine venous blood. As seen in figure 1, maternal hyperoxia in sheep results in incremental elevations of uterine venous and umbilical venous oxygen tensions with an approximately 15 to 20 mmHg difference between the two. Over a wide range of low uterine venous blood oxygen tensions, this relationship to umbilical venous PO$_2$ is preserved as well. Physiologically, then, the ovine placenta behaves most like a concurrent exchanger (figure 2) in which the maternal to fetal blood streams run in the same direction, such that the venous blood of the recipient stream equilibrates with that of the donor stream.

A similar relationship has been reported for the human placenta. The 10 to 20 mmHg oxygen mismatch between uterine and umbilical venous circuits has been attributed to a combination of placental oxygen consumption and nonhomogeneous placental perfusion. The latter relates to the uneven and haphazard ejection of blood from the uterine arteries into the intervillous space surrounding the chorionic villi, as well as the direct arteriovenous anastomoses in both the maternal and fetal circuits of the placenta, allowing blood to bypass areas of gas exchange. The diffusion of oxygen across the placental membrane may also account for some reduction in umbilical venous PO$_2$ compared to uterine venous PO$_2$. In contrast to the lung, in which the diffusion distance between alveolus and pulmonary capillary is 0.1 u, the distance from intervillous space to fetal capillary across the placenta is approximately 3.5 u. The placenta, however, is highly permeable to oxygen and, in general, efficiency of gas transfer is felt to be more dependent on flow-related factors than on diffusion.
MODELS OF PLACENTAL PERFUSION

A COUNTER CURRENT

P\textsubscript{O}\textsubscript{2}

\begin{array}{c}
\text{MATERNAL BLOOD FLOW} \\
90 \rightarrow \text{PLACENTA} \\
90 \rightarrow \text{FETAL BLOOD FLOW}
\end{array}

B CONCURRENT

P\textsubscript{O}\textsubscript{2}

\begin{array}{c}
\text{MATERNAL BLOOD FLOW} \\
90 \rightarrow \text{PLACENTA} \\
25 \rightarrow \text{FETAL BLOOD FLOW}
\end{array}

A: Expected maximum P\textsubscript{O}\textsubscript{2} in the fetal blood leaving the placenta when flows are concurrent across a highly permeable membrane.

B: Expected P\textsubscript{O}\textsubscript{2} in the presence of concurrent blood flow.

Figure 2. Models of placental perfusion.

Role of Fetal Hemoglobin in Placental Gas Exchange

Among the factors important for oxygen transfer from maternal-to-fetal blood are the relative positions of the oxygen dissociation curve (ODC) of both mother and fetus. Prior to the discovery of the role of 2,3-diphosphoglycerate (2,3-DPG) in regulating Hb-O\textsubscript{2} affinity, many investigators had noted differences between "adult blood" and "fetal blood," including the position of the ODC, resistance to alkaline denaturation, sedimentation constants, electrophoretic mobility, absorption spectra, crystal form, and amino acid composition.\textsuperscript{1,2,3,11,22} Physiologically, the most important and fascinating of these differences is the observation that in-vivo fetal blood has higher oxygen affinity than adult blood, allowing greater oxygenation of fetal hemoglobin at lower PO\textsubscript{2} (figure 3).

The high affinity of fetal blood is well suited to the intrauterine environment, since the highest PO\textsubscript{2} in umbilical vein blood is about 40 mmHg. As seen in figure 4, as the oxygen tension of adult blood drops from an alveolar level of 100 mmHg to a tissue level of 40 mmHg, Hb A will unload 4.7 ml O\textsubscript{2} per 100 ml blood, whereas Hb F can only unload 3.0 ml O\textsubscript{2} per 100 ml blood during the same traverse.\textsuperscript{29} In the fetus in-utero, however, Hb F will unload 10.3 ml O\textsubscript{2} per 100 ml blood and Hb A will unload only 8.8 ml O\textsubscript{2} per 100 ml blood in passing from a placental PO\textsubscript{2} of 35 mmHg to a fetal tissue PO\textsubscript{2} of 15 mmHg. These facts are functions purely of the relative slopes of the respective dissociation curves; the adult ODC has the greater slope (and oxygen unloading advantage) at high levels of oxygenation, whereas the loading-unloading advantage lies with the fetal ODC at lower oxygen tensions. These changes in slope, in turn, are functions

\[ P_{O_2} \text{ mmHg (pH 7.40)} \]

Figure 3. Oxyhemoglobin dissociation curve. Curve A represents the fetal-neonatal curve, P50 = 19 mmHg. The curve is left-shifted. Curve B represents the normal adult curve, P50 = 27 mmHg. Sigmoid shape is attributable to heme-heme interaction. Curves can be shifted right or left by changes in temperature, PCO\textsubscript{2}, pH, 2,3-DPG level, and by differing percentages of Hb F and Hb A.
of lateral displacements of the ODC, whether produced by pH, PCO₂, temperature, ionic surroundings of hemoglobin, or its degree of interaction with 2,3-DPG. The latter factor is one of the most important regulators of the position of the ODC in maternal blood; the concentration of 2,3-DPG is usually elevated in pregnancy.

Despite the advantages to the fetus of having Hb F, substitution of "adult" erythrocytes in the fetus by intrauterine transfusion (as for Rh-isocom immunization), shifts the fetal ODC to the right. This procedure, however, does not as a rule result in undergrown, stillborn, or otherwise impaired neonates, showing that the fetal ODC is not essential for fetal well being.

![Figure 4](image-url)  
**Figure 4.** Oxygen loading and unloading capacities of adult and fetal blood at various oxygen tensions. See text for further explanation. (From Nelson, N. M. in Smith, C. A. and Nelson, N. M., Physiology of the Newborn Infant, 1976.)

When fetal growth is severely compromised by placental insufficiency, increased Hb F synthesis results. Premature infants have higher Hb-O₂ affinity, secondary to lower 2,3-DPG and increased percentage of Hb F. The fetus responds to maternal cigarette smoking by decreasing its P50 in relationship to the increase in maternal carboxyhemoglobin. This change in P50 is due to statistically significant increase in Hb F synthesis, which is, however, biologically incapable of compensating for changes in oxygen transport secondary to maternal smoking.

The transition in-utero from predominantly (90 to 95 percent) Hb F synthesis to Hb A synthesis occurs at 30 wks, and is not altered by the birth process. Prematurely born infants follow the in-utero transition. Hemoglobin F synthesis declines rapidly in term infants postnatally until it is negligible at 16 to 20 wks of age.
Fetal Response to Acute Asphyxia Events

Asphyxia occurs when tissue metabolism continues in the absence of adequate oxygen supply. Intrauterine asphyxia, specifically the failure of the placenta to provide adequate gas exchange for the fetus, is expressed clinically as fetal hypoxia, hypercarbia, and acidosis associated with late decelerations of the fetal heart rate and/or passage of meconium. Given the anatomical and physiological arrangement of the fetal-placental unit described in the previous section, what capacity does the system have to adjust to alterations in oxygen supply. This section will discuss compensatory mechanisms invoked during acute asphyxial events. Again, as with experiments determining the normal state, the data presented are primarily from studies of fetal animals, especially the fetal lamb.

The most extensive studies of acute deprivation of fetal oxygen supply have involved reduced maternal arterial $O_2$ content. Fetal hypoxemia induced by maternal breathing of reduced oxygen concentrations resulted in increased fetal arterial pressure, decreased fetal heart rate, and only a minimal decrease in fetal cardiac output. There was also a significant redistribution of fetal cardiac output, with an increase in blood flow to the fetal heart, brain, and adrenals, accompanied by a reduction in flow to the gut, kidneys, spleen, carcass, and lungs. When fetal lambs were acemic as well as hypoxic, these circulatory responses were even more dramatic, with greater increases in fetal brain, cardiac, and adrenal flow while flow to the rest of the body decreased. In addition, fetal cardiac output was diminished in the hypoxic-acemic lambs and the percent distribution of cardiac output to the placenta increased.

Severe partial asphyxia secondary to umbilical cord compression, to a pH of 7.04 and an $O_2$ saturation of 19 percent from 50 percent in fetal lambs, produced the expected increase in cerebral blood flow to all regions of the brain, with largest increases to the brain stem and deep cerebral structures. Fetal arterial blood pressure rose during asphyxia and correlated closely with regional cerebral blood flow increases, suggesting that it may be a critical factor in determining cerebral blood flow. The redistribution of blood flow to the fetal brain during asphyxia is a potentially reversible phenomenon. Fetal lambs subjected to a 90 minute period of hypoxia ($PO_2$ 12 to 15 mmHg) were studied 4, 24, and 48 hours after hypoxia. Regional cerebral blood flows, which rose an average of 95.9 percent compared to control during the hypoxia, had returned to pre-hypoxia levels by four hours and remained stable at 24 and 48 hours post-hypoxia, showing no evidence of post-ischemic hypoperfusion syndrome. Other organ blood flows also returned to near baseline levels by four hours post-hypoxia.

Fetal oxygen supply is a function of umbilical blood flow as well as umbilical venous oxygen content, but, as discussed earlier, feto-maternal gas exchange is particularly vulnerable to alterations in flow. Cineangiographic studies of the Rhesus monkey placenta, which is hemochorial and therefore structurally similar to the human placenta, have demonstrated reduced flow through endometrial spiral arterials into the intervillous spaces during uterine contractions. Later studies using radioactive microspheres, also in pregnant Rhesus monkeys near term, have more quantitatively documented the effects of labor on uterine and, especially, placental blood flow. Compared to baseline levels prior to labor, the placenta received markedly different flow during contractions (−64 percent) than during the
relaxation phase between contractions (+60 percent). These alternating periods of placental ischemia and reactive hyperemia may balance each other when contractions are regular and well spaced. However, when contractions become more frequent and vigorous, as happens in later states of human labor, or when tetanic contractions occur as a result of excessive oxytocin infusion, this balance may be altered, resulting in fetal hypoxemia and/or acidemia as evidenced by decelerations of fetal heart rate.

Umbilical blood flow has been shown to remain constant despite acute changes in fetal blood oxygen concentrations over a wide range of values.\textsuperscript{15,17,33} Furthermore, alterations in maternal systemic or uterine circulations (increased venous pressure or decreased arterial pressure) have no direct effect on umbilical blood flow.\textsuperscript{10,38} A variable and delayed fall in umbilical blood flow is observed once fetal hypoxemia and bradycardia occur, but this response was abolished when atropine was given to prevent the bradycardia of fetal hypoxemia. Elevations of umbilical venous pressure or reduction of umbilical arterial pressure, however, do effect umbilical blood flow instantaneously and reproducibly. This resultant fall in umbilical flow could not be abolished by atropine, suggesting that fetal bradycardia—prevented by atropine—was not responsible for the umbilical flow decrease.

Another important element in the fetal response to asphyxial stress is decreased heart rate, especially with the expanded role of fetal heart rate monitoring currently in clinical obstetrics. The primary trigger of fetal bradycardia is hypoxemia. Studies with fetal sheep\textsuperscript{19,28,32} have demonstrated a chemoreceptor response to hypoxemia that stimulates the vagus nerve, which in turn mediates the decrease in fetal heart rate. The response can be abolished by B-adrenergic block-

ade with atropine. The degree of fetal bradycardia appears to be a function of fetal PaO\textsubscript{2}, but first requires PaO\textsubscript{2} to fall below a critical threshold level.

In the fetal lamb, this critical PaO\textsubscript{2} has been identified as approximately 16 mmHg,\textsuperscript{19} while in the human fetus it is 19 mmHg.\textsuperscript{13} Fetal heart rate, then, does not fall in response to hypoxemia until the critical PaO\textsubscript{2} level has been reached. These same studies have shown that tissue hypoxia is not necessarily present when fetal bradycardia occurs, implying that tissue O\textsubscript{2} demands can still be met in the presence of significant fetal hypoxemia. Clinically, this would explain why fetal heart rate reductions in human fetuses, so-called late decelerations, are not necessarily associated with evidence of hypoxia at birth,\textsuperscript{14,23} as reflected by acidemia or low Apgar scores (an assessment scale based on heart rate, color, tone, respiratory effort, and reflex, used in the delivery room to evaluate a newborn at one and five minutes). Fetal lamb studies\textsuperscript{39} demonstrate the capacity of the fetus to withstand a 40 to 50 percent reduction in O\textsubscript{2} delivery during decreased uterine blood flow, without affecting fetal O\textsubscript{2} consumption. One factor in this remarkable adaptability is the relatively high percentage of total fetal oxygen requirement designated for growth under steady-state conditions, which can be eliminated during times of stress. Another potential compensatory mechanism for reduced O\textsubscript{2} delivery is an increase in fetal O\textsubscript{2} extraction at the tissue level.

The mechanisms by which fetal responses to hypoxic stress are regulated are only beginning to be understood. Arginine vasopressin is one chemical mediator that appears to have a role. Infused intravenously in fetal sheep\textsuperscript{20} to achieve serum levels actually seen with fetal hypoxia, arginine vasopressin resulted in characteristic redistribution
of fetal blood flow with increases to myocardial, cerebral, and umbilical-placental circuits. There was also a decrease in fetal heart rate and increase in blood pressure with little change in combined ventricular output. While these findings suggest that vasopressin may contribute to the fetal response to acute hypoxemia, other associated circulatory changes, such as decreased adrenal, renal, and pulmonary blood flow, did not occur in response to vasopressin alone, favoring a multi-factor triggering response mechanism. Catecholamines and prostaglan-
dins may prove important in this regard, and certainly fetal baroreceptors and chemoreceptors also participate in the fetal response to acute asphyxia.

Summary

The placenta is a highly specialized organ that forms the critical link between maternal and fetal circulations throughout gestation. While gas exchange is but one of its functions, it is uniquely adapted for this role in many ways. Maternal and fetal vasculature intersect in such a way (concurrent exchanger) that umbilical venous blood, the “arterialized” fetal stream, equilibrates with uterine venous blood, providing a stable although relatively hypoxemic environment for the fetus. The fetus, in turn, has adapted to this oxygen transfer scheme with its unique oxygen dissociation curve and high cardiac output. In addition, the fetus is capable of responding to both acute and chronic deprivations of oxygen supply from the placenta. Acutely, fetal hypoxia results reversibly in decreased heart rate and redistribution of fetal blood flow to favor cerebral, myocardial, and adrenal flow. Less severe but more steady-state hypoxemia, as seen with maternal cigarette smoking, or placental insufficiency, compromises fetal growth capacity and increases Hb F production. The current challenge to placent al physiologists is further delineation of both the chemical and structural mediators of maternal-fetal interaction.

References


