Placenta in the Critically Ill Mother

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ABSTRACT

The placenta is a temporary, multifunctional organ composed of both maternal and fetal components. It maintains homeostasis to ensure the growth of the fetus and well-being of the mother. Abnormalities in placental development have been known to be responsible for several disorders of pregnancy. Conditions coincident with pregnancy can upset the homeostasis and result in critical illness, which can greatly impact placental function and in turn affect the fetus. Decreased blood flow, acidemia, hypercarbia, and hypoxia seen in critically ill pregnant mothers can result in fetal death. Understanding the physiological changes and functioning of the maternal–fetal–placental unit will aid in better management of critically ill mothers.

Keywords: Critical care, Obstetric critical illness, Placenta, Pregnancy.

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INTRODUCTION

The placenta is the earliest organ to form during the course of embryonic development, and it is the key organ that has resulted in the success of viviparity among mammals. It has been referred to as “chimeric” as it comprises both maternal and fetal components.1 One of the earliest papers on comparative placentation described the mammalian placenta as “an apposition or fusion of the fetal membranes to the uterine mucosa for physiological exchange.”2 Recent studies have demonstrated that the placenta has many roles. It essentially performs the functions of all the diverse organ systems that are hitherto undeveloped in the fetus and is instrumental in fetal maturation. These include the bidirectional transfer of both nutrients and wastes, metabolic functions (like the liver), gas transfer (such as the lungs), barrier function to protect against some viruses, immune barrier against maternal immunological responses, regulation of early development of the embryo, and endocrine function.3,4 The placental endocrine function has a wide-ranging impact on maternal health by secretion of placental progesterone, lactogen, and estrogen. Recent research has revealed that it is also a source of serotonin that plays a role in the development of the fetal forebrain. Disturbances such as those seen in preterm neonates have been linked with childhood attention and anxiety disorders, as well as autism.3,4 The physiological changes occurring in pregnancy create a balance to ensure both maternal and fetal well-being.

The critically ill pregnant patient can develop hypoxia, hypotension, acidosis, and other physiological disturbances.5 The placenta plays a central role in a group of diseases that have been described as the “great obstetrical syndromes.”6 The fetoplacental unit is greatly affected by nonobstetric illnesses as well.

Normal Placental Anatomy and Hemodynamics

The human placenta has been described as hemochorial, i.e., vessels lined by endothelial cells containing the fetal blood, whereas the maternal blood is in spaces that are lined by subtypes of specialized trophoblastic cells.4,7 The placenta is formed from the differentiation of the trophectoderm into the trophoblastic cells, which give rise to syncytiotrophoblasts and cytotrophoblasts. These interact with the maternal tissues to form the placenta. The fetal end is known as the chorionic plate which gives rise to the villi. The villous space is divided into cotyledons and the villi are surrounded by maternal blood. Transport of nutrients and waste takes place across this interface either by active transport or passive diffusion.1,4,7 The cytotrophoblastic cells invade the maternal spiral arteries by a process known as “endothelial mimicry”3 and line them. There is extensive remodeling of the spiral arteries which occurs, including vascular smooth muscle loss and replacement of extracellular matrix of the vessel with fibrinoid substance. This prevents constriction and reduces arterial tone resulting in decreased peripheral vascular resistance.8 This results in the high-flow and low-resistance circulation characteristic of the uteroplacental unit.9 A recent study used magnetic resonance imaging (MRI) of placental flows to demonstrate that the velocity of blood reduces as it passes from the wall of the uterus to the placenta. This supports the theory that trophoblastic invasion into the spiral artery results in a reduction in the velocity of blood flow to the placenta.10 Uterine natural killer cells have been found to play an important role in mediating spiral artery transformation by secretion of chemokines and cytokines and also promoting trophoblastic invasion and arterial remodeling.11

CRITICAL ILLNESS IN PREGNANCY

During pregnancy, the body of the mother goes through many physiological changes. Critical illness results in derangements that can impact uteroplacental blood flow and transfer of oxygen and nutrients.
Critical illness in pregnancy can be related to the pregnancy itself (obstetric causes) or due to nonobstetric causes (Table 1). Defective placentation is one of the most common causes of obstetric critical illnesses. It results in preeclampsia, eclampsia, abruptio placentae, and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome.

Certain preexisting conditions such as congenital heart disease, connective tissue diseases, diabetes, liver diseases like cirrhosis, and neurological diseases like epilepsy may worsen during the pregnancy. Such illnesses disturb the physiological balance and adversely affect the mother and fetus.

**Placental Role in the “Great Obstetric Syndromes”**

The role of spiral arterial remodeling is one of the theories to explain the pathophysiology of preeclampsia. Abnormal remodeling of the spiral artery was first associated with the development of preeclampsia in 1964. It has since been implicated to cause preterm labor, intrauterine growth restriction, preterm premature rupture of membranes, abruptio placentae, and late spontaneous abortion—collectively known as the “great obstetric syndromes.”

Defective placentation occurs in the paracentral part where features like thrombosis of the spiral arteries and placental infarcts have been identified, whereas normal physiological changes are present in the center of the placental bed. These physiological changes usually extend deep into the myometrium, involving the radial arteries. In preeclampsia, the myometrial segment fails to undergo physiological changes.

It is also characterized by acute atherosis within the vessels and is similar to pathological changes seen secondary to hypertension. This has been corroborated by MRI evaluation of placental flows in preeclampsia, which showed greater velocity of flow through the intervillous space and increased resistance to flow, unlike what is seen in normal pregnancy. This defective remodeling results in intrauterine hypoxia secondary to vasospasm and reduced placental flows. It results in increased oxidative stress and abnormal systemic inflammatory response in the mother. This can result in fetal hypoxia, fetal acidosis, and growth retardation. It forms the basis of the “two-stage theory of preeclampsia.” The first stage is the abnormal placentation and the second stage is immune activation.

Maternal endothelial dysfunction has been attributed to be the reason behind the clinical features of preeclampsia. It has been proposed that this is due to the production of free radicals which result in increased circulating inflammatory mediators, like soluble vascular endothelial growth factor (VEGF) receptor (sFLT1), and soluble E-selectin (cause endothelial cell activation) and leukocyte activation with increased Th1 cytokine; all of which result in features like hypertension, kidney injury, and proteinuria and liver injury.

While this theory has been challenged by some, it has been largely accepted as the underlying reason for preeclampsia. Large number of studies have validated the theory that angiogenic factor imbalance results in pathophysiological changes in preeclamptic patients. This led to the use of antioxidants (vitamin C and vitamin E) and low-dose aspirin as a means of

**Table 1: List of causes of critical illness in pregnancy**

| Conditions directly related to pregnancy | Preexisting conditions aggravated by pregnancy | Conditions with more susceptibility during pregnancy |
|-----------------------------------------|-----------------------------------------------|---------------------------------------------------|
| Abnormal placentation                   | Cardiovascular diseases                        | Infections                                        |
| Preeclampsia                            | Congenital heart disease                       | Falciparum malaria                                |
| Eclampsia                               | Pulmonary hypertension                         | Hepatitis E                                       |
| Placental abruption                     | Valvular heart diseases                        | Varicella pneumonia                               |
| HELLP syndrome                          | Coarctation of aorta                           | Listeriosis                                       |
| Placenta prævia                         | Systemic hypertension                          | Urinary tract infection                           |
| Infectious                              | Respiratory                                    | Hematologic                                       |
| Chorioamnionitis                        | Cystic fibrosis                                | Deep vein thrombosis                              |
| Septic abortion                         | Obstructive sleep apnea                        | DIC                                               |
| Puerperal sepsis                        | Bronchial asthma                               | HUS/TTP                                           |
| Postpartum                              | Renal                                          | Respiratory                                       |
| Postpartum hemorrhage                   | Chronic kidney disease                         | Pulmonary thromboembolism                         |
| Retained products of conception         | Glomerulonephritis                             | Aspiration                                        |
| Cardiac                                 | Endocrine                                      | Endocrine                                         |
| Peripartum cardiomyopathy               | Prolactinomas                                  | Sheehan syndrome                                  |
| Hepatic                                 | Hepatic                                        |                                                   |
| Acute fatty liver of pregnancy          | Cirrhosis                                      |                                                   |
|                                          | Budd–Chiari syndrome                           |                                                   |
| Endocrine                               | Connective tissue diseases                     |                                                   |
| Gestational diabetes mellitus           | Scleroderma                                    |                                                   |
|                                          | Systemic lupus erythematosus                   |                                                   |
| Miscellaneous                           | Neurologic                                     |                                                   |
| Amniotic fluid embolism                 | Epilepsy                                       |                                                   |
|                                          | Intracranial tumors                            |                                                   |
|                                          | Hematological                                  |                                                   |
|                                          | Sickle cell disease                            |                                                   |

HELLP syndrome, hemolysis, elevated liver enzymes, and low platelets; DIC, disseminated intravascular coagulation; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura
reducing oxidative stress in the placental unit. However, larger trials have uncovered uncertainties around benefits of aspirin or vitamin C especially in the later stages of gestation.

**Placental Role in Acute Fatty Liver of Pregnancy**

Acute fatty liver of pregnancy has been attributed to an increase in circulating fatty acids in the mother and oxidative stress. One of the prevailing theories is that this occurs due to a fetal deficiency of mitochondrial long-chain acyl-coenzyme A dehydrogenase (LCHAD). However, it has been observed that in a majority of cases of acute fatty liver of pregnancy, fatty acid oxidation disorders could not be demonstrated in the fetus.

It has been proposed that defective mitochondrial function in the placenta could lead to oxidative stress and free radical formation. This could further result in fatty acid deposition in the placenta and subsequent rise in serum fatty acids leading to acute fatty liver of pregnancy.

**Placenta: Immunity and Infections**

Pregnancy was initially considered to be an immunosuppressed state. In 1953, Medawar proposed the immunological paradox where he compared the fetus to a semi-allogeneic graft that could survive for 9 months without immunosuppression. He proposed that this was because of three main reasons: (i) placental barrier between mother and fetus, (ii) immature fetal antigens that failed to elicit an immune response in the mother, and (iii) pregnancy induced a state of immunological inertness. Most of these theories have been disproved.

Subsequent investigators proposed that throughout pregnancy, there is a balance between Th1 and Th2 responses mediated by estrogen and progesterone level fluctuations. It was widely believed that it resulted in a predominantly anti-inflammatory or Th2 cytokine state. Any insults such as infections that affect this were thought to be the perpetrators of disease states in the pregnant mother as well as fetal development.

Another proposition has been that pregnancy consists of three separate immunological phases. The first trimester is a predominantly proinflammatory phase resulting in symptoms such as nausea. The second trimester is an anti-inflammatory state and allows for optimal growth of the fetus. The third trimester has been described as a proinflammatory phase which finally culminates in expulsion of the products of conception.

**Placenta and Infections**

The placenta is believed to be capable of interacting with various pathogens as it displays tropism to some. It has also been described as an active immunological site capable of generating immune responses to infections. In early stages, placental vascular development is dependent on a balance between various proangiogenic as well as antiangiogenic factors. Infections like malaria and human immunodeficiency virus (HIV) can cause inflammation and immunological responses, which throw these factors off balance. This can translate to inadequate placental vascular development and adverse fetal outcomes. Viremia is essential for the virus to reach the fetoplacental unit. A number of developmental abnormalities in the fetus have been associated with congenital infections such as Toxoplasmosis, Other—syphilis, varicella zoster, parvovirus B19, Rubella, Cytomegalovirus, and Herpes simplex (TORCH). However, even in the absence of placental transfer, maternal infections can impact fetal well-being. Activation of maternal immune responses by certain viral infections can result in developmental abnormalities in the fetal heart, brain, and lung. This may also produce an inflammatory response in the placental unit, which may have long-lasting effects on fetal immunity including the ability to respond to vaccines and the development of allergic tendencies. It can also trigger abortion or preterm labor.

Placental infections have been disproved. However, larger trials have uncovered uncertainties around benefits of aspirin or vitamin C especially in the later stages of gestation.

**What Happens to the Placenta in Critical Illness?**

In critical illness, both obstetric and nonobstetric, the mother and fetus are subjected to stressors such as immunological activation, hypoxia, acidosis, organ hypoperfusion, and systemic inflammation. In subsequent sections, we will discuss the impact of each of these on the utero-feto placental unit.

**Placenta in Shock States in the Critically Ill**

In shock states, there is decreased organ perfusion that results in decreased blood flow to the placenta. Compensatory maternal responses are not protective to the fetus as they focus on maintenance on perfusion to vital organs of the mother. Alpha-adrenergic receptors present in the placental vascular bed respond to sympathetic stimulation which results in constriction and further reduction in flows.

Various types of shock result in tissue hypoperfusion, resulting in increased anaerobic metabolism and rising lactate levels. The placenta serves as a lactate buffer and shields the fetus against increased maternal lactate levels. The placenta plays an active role by ensuring that lactate flux to the maternal circulation is higher than lactate flux to the fetus. On the contrary, it is hypothesized that it can enhance its own metabolic activity to supply lactate to the fetus when levels are low. In the absence of this buffer, or if it gets overwhelmed, there can be progressive fetal acidosis and can lead to fetal demise.

**Placenta, Acidosis, and Hypoxia**

In the first trimester of gestation, the spiral arteries are plugged with the invading trophoblastic cells and there is no maternal blood in the villous spaces. This ensures that the placental and fetal development occurs in an environment with low oxygen tension. Placental nutrition is provided by increased endometrial vascular development and adverse fetal outcomes. Viremia is essential for the virus to reach the fetoplacental unit. A number of developmental abnormalities in the fetus have been associated with congenital infections such as Toxoplasmosis, Other—syphilis, varicella zoster, parvovirus B19, Rubella, Cytomegalovirus, and Herpes simplex (TORCH). However, even in the absence of placental transfer, maternal infections can impact fetal well-being. Activation
Anemia and Placental Oxygen Transfer

Anemia has been demonstrated to have a large impact on oxygen transfer across the placenta. It has been demonstrated that uterine oxygen delivery is predominantly impacted by blood flow, oxygen saturation, and hemoglobin concentration. As physiological anemia of pregnancy already reduces the hematocrit, a further drop in hemoglobin may significantly affect fetal oxygen levels.

Effect of Vasoactive Drugs on Uteroplacental Flow

Cardiogenic shock has been observed in critically ill pregnant women. Some of the commonly used agents in treatment include dopamine, dobutamine, and milrinone. The impact of vasopressors and inotropes on uteroplacental flows has been evaluated largely by conducting animal studies. Dopamine at higher doses results in reduction in uterine blood flows and leading to a progressive decrease in fetal arterial pH and rise in fetal arterial pCO₂. Milrinone was found to produce an increase in uterine blood flow. Dobutamine was found to result in a relatively unchanged mean arterial pressure (MAP) but reduced uterine blood flow. The effect, however, was less than that of dopamine. It was observed in another study that the fall occurred...
after 60 minutes, probably due to effects of 3-O methyldobutamine (a metabolite of dobutamine). This reduction, however, did not result in decreased fetal oxygen concentration. In fact, fetal oxygenation improved with dobutamine. This was explained by the increase in maternal hemoglobin as a result of splenic contraction caused by dobutamine.48

Vasopressor agents used in septic shock also reduce blood flow to the uterus by causing vasoconstriction. Uterine blood flow is reduced in response to use of epinephrine, norepinephrine as well as dopamine.49 Phenylephrine and ephedrine have been found to preserve placental blood flow compared to the rest of the vasopressors, especially during spinal anesthesia. Among the two, studies showed that ephedrine caused more fetal acidosis by resulting in increased fetal oxygen consumption, increased fetal CO₂ production, and increased lactate.50

Effect of Extracorporeal Circulation on Placenta
Extracorporeal circulation membrane oxygenation and cardiopulmonary bypass result in significant variations in uterine blood flow and oxygen delivery. Extracorporeal circulation results in hemodilution, systemic inflammation, leukocyte activation, alteration in coagulation, hypotension, and hypothermia.51 All of these factors can affect oxygen delivery to the fetus, especially hemodilution (as explained above). Uterine contractions occurring during extracorporeal circulation have been associated with fetal death.52

Placental Transfer of Drugs
The placenta acts like a selective barrier and there is transfer of drugs which can occur to the fetus. While due attention must be given to this, essential treatment still must be given to the pregnant mother irrespective of teratogenic concerns after advising them about risks involved. Teratogenic effects of commonly used drugs like antibiotics are highest in the first trimester.54 A Cochrane review recently concluded that antibiotic use in the second and third trimesters did not significantly increase risk of congenital abnormalities. However, they concluded that they had insufficient evidence to do a comprehensive evaluation of effects on the fetus.55

Pregnancy results in a number of hemodynamic changes such as hemodilution, increase in circulating blood volume, decreased gastric motility, and increase in glomerular filtration rate. This can impact usual drug pharmacokinetics and must be kept in mind while deciding dosage. Therapeutic drug level monitoring can be employed when possible.55

Conclusion
The placenta is one of the most unique organs that has developed during the course of evolution. Its diversity of function is what results in successful viviparity. The placenta has an unquestionable role in both maternal and fetal health and can cause serious effects on both. We are still trying to understand the complexity of its workings. Critical illness poses an additional challenge. Due consideration to the anatomical and physiological nature of the materno-fetoplacental relationship will result in better outcomes for both the mother and fetus.

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