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Uteroplacental Circulation and Fetal Vascular Function and Development

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Abstract

Although blood flow in the placental vasculature is governed by the same physiological forces of shear, pressure and resistance as in other organs, it is also uniquely specialized on the maternal and fetal sides. At the materno-fetal interface, the independent uteroplacental and umbilicoplacental circulations must coordinate sufficiently to supply the fetus with the nutrients and substrates it needs to grow and develop. Uterine arterial flow must increase dramatically to accommodate the growing fetus. Recent evidence delineates the hormonal and endothelial mechanisms by which maternal vessels dilate and remodel during pregnancy. The umbilical circulation is established de novo during embryonic development but blood does not flow through the placenta until late in the first trimester. The umbilical circulation operates in the interest of maintaining fetal oxygenation over the course of pregnancy, and is affected differently by mechanical and chemical regulators of vascular tone compared to other organs. The processes that match placental vascular growth and fetal tissue growth are not understood, but studies of compromised pregnancies provide clues. The subtle changes that cause the failure of the normally regulated vascular processes during pregnancy have not been thoroughly identified. Likewise, practical and effective therapeutic strategies to reverse detrimental placental perfusion patterns have yet to be investigated.

Keywords

Blood flow regulation; vasculature; placental insufficiency; compromise; pregnancy

INTRODUCTION

By the time a baby is born, it will have transformed from a 1 cell diploid zygote to a trillion-cell individual capable of existence outside the womb. This enormous feat requires the de novo formation and expansion of a cardiovascular system that circulates blood in the embryo and the fetus. The nutrient flow for the growing fetal body is delivered to the placenta via a newly remodeled maternal cardiovascular system. The growth, development and function of

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

the nascent vascular system in the embryo/fetus is a fascinating field of study that has become specialized by anatomical region. However, there are a few basic physiological principles that are foundational to all vascular beds.

The physical principles that regulate blood flow through an organ are simple enough in their basic form and are explained in any basic physiology text or website [1]. The difference between arterial (P_a) and venous (P_v) pressures drives blood through an organ. The magnitude of the resulting flow (Q_o) depends on the energy required to overcome the vascular resistance within the organ (R_o) and can be expressed in a form analogous to Ohm's Law:

$$Q_o = (P_a - P_v)/R_o$$

This convective flow equation holds true under the following conditions: 1) steady flow and 2) Newtonian fluid. While these two requirements that are not technically met for blood in the mammalian circulatory system, the equation, nevertheless, reasonably approximates most normal blood flow conditions. The resistance to the flow of blood is determined by well described physical principles (Poiseuille's law) where the resistance R_o is defined as

$$R_o = (8\eta L)/\pi r^4$$

where η is viscosity, L is length and r is radius. When a more sophisticated understanding of flow in an organ is needed, there are well conceived mathematical equations that describe pulsatile pressure-flow relationships with corrections for changing viscosity with vessel diameter and equations that estimate organ impedance have been derived. Most all considerations of pulsatile hemodynamics are derived from McDonald's original treatise [2] on the topic.

It has become increasingly clear that shear and wall forces provide remodeling signals that regulate vessel endothelial function as well as the structural integrity of the vessel wall. These forces are especially important in pregnancy. In a vessel, the frictional shear force that is sensed by the endothelium lining the vessel wall can also be expressed in the form of the Poiseuille's relationship,

$$\tau_s = (4\eta Q)/\left(\pi r^3\right)$$

Thus the shear stress, τ_s, is related to the ratio of viscous flow and shear rate, where η is the viscosity and Q the flow, to vessel radius to the 3rd power [3, 4].

A successful pregnancy requires adaptations of the maternal cardiovascular system, the establishment of a placenta with its two sided vasculature and a well constructed fetal vascular tree. While in most organs the resistance to flow is found at the level of the arteriole which is innervated, the placenta is not innervated. The vascular smooth muscle tone, however, is sensitive to local transmural pressure conditions (myogenic tone) and to vasoactive substances. The local substances that regulate arteriolar function include those

that are carried to the organ in the blood (e.g. angiotensin II, arginine vasopressin, atrial natriuretic peptide), those released from nerve endings (e.g. norepinephrine, acetylcholine), those derived from endothelium (e.g. nitric oxide, NO, prostaglandins), those released from endocrine tissue (e.g. steroid hormones such as estrogens, progestins and glucocorticoids) and those released from various cells in the vessel milieu. The maternal hormonal environment changes dramatically over the course of pregnancy and many maternal vascular structures are sensitive to these changes. For example, human chorionic gonadotropin peaks early in pregnancy and plateaus at about 24 weeks [5, 6] and estrogens and progestins rise over the course of pregnancy [5, 6].

MATERNAL ADAPTATIONS TO PREGNANCY

In mammals, the normal adaptation to pregnancy requires enormous changes in the structure and function of the maternal circulatory system [7, 8], largely under the influence of sex steroid hormones [9]. Uterine blood flow increases by 2 to 3 times over the last half of pregnancy in women and ewes (Reviewed by [10]). During pregnancy, maternal oxygen consumption increases about 33%, body weight normally increases by 20% [11] while blood volume increases by 40%. Red cell mass increases by only 30%; thus, the concentration of red blood cells is reduced in the maternal circulation. The structure of the maternal heart also is remodeled. The term “cardiac remodeling” often refers to a pathological process that leads to cardiac restructuring and consequent dysfunction. In the case of pregnancy, non-pathological cardiac structural changes lead to an increase in end diastolic volume over the first half of pregnancy so that stroke volume is augmented about 30%. This increase in end diastolic volume is profound because the chambers of the ventricles actually enlarge- the whole heart gets bigger [11]. Because ejection fraction is maintained during pregnancy, the larger heart ejects a larger volume each beat. This is accomplished without an undue load on the myocardial wall because vascular impedance is simultaneously decreased through the remodeling of the arterial tree, making it possible to eject a stroke volume without large increases in wall stress. Aortic diameter and aortic compliance are increased as are venous capacitance and venous blood volume.

There are racial differences in uterine arterial adaptation to pregnancy. In comparing uterine arterial Doppler flow in Andean and European residents of La Paz, Bolivia (3600 m) at weeks 20, 30, 36 of pregnancy, Andean women had greater uterine cross sectional areas and blood flows by 36 weeks and 1.6 times greater uteroplacental oxygen delivery [12]. With adjustments for gestational age, maternal height, and parity, Andean babies were consistently heavier than European babies. While there are undoubtedly genetic underpinnings explaining these differences, it is becoming increasingly clear that there are transgenerational influences of maternal diet, fetal nutrition and structural features of reproductive organs that are passed on via epigenetic and nonepigenetic mechanisms. Which of these is most important across races in the adaptation to altitude is not known.

Recent studies in non-human primates show that maternal diet affects uteroplacental blood flow. In this model, pregnant macaques are fed a high fat diet – some become obese (high fat diet sensitive) whereas a subset does not become obese (high fat diet resistant). Using Doppler ultrasonography in early third trimester pregnancies (gestational day 120), Frias *et*

al. [13] showed that calculated volume flow in the uterine artery, normalized to maternal weight, was decreased significantly even in maternal animals that were resistant to gaining weight on the high fat diet and in monkeys that were sensitive and gained weight (Fig. 1). Uterine arterial flow was reduced by an average of 38% in the former group and 56% in the latter compared to controls. Both of the experimental groups had a significant increase in the pulsatility index of the uterine artery (Fig. 1). In contrast, umbilical vein flow was decreased by 32% but only in the high fat diet sensitive group (Fig. 1). The pulsatility index in the umbilical artery was not changed in either diet group. The role of diet in regulating utero-placental blood flow in the human has not been explored in depth and is ripe for mechanistic investigation.

As mentioned above, the rate at which oxygen is delivered to the uteroplacental bed depends upon the driving pressure across the uterine and umbilical beds, the resistance to flow in these beds, as well as the maternal hemoglobin concentration and oxyhemoglobin saturation. Failure of maternal adaptations can lead to maternal hypertension and subsequent stunting of fetal growth. The reasons that fetal well being suffers from this maternal condition are not entirely clear. However, it is clear that the increase in uterine arterial flow capacity must increase dramatically to accommodate the large increases in flow. There are really only two mechanisms by which vessel dimension could be increased enough to accommodate flow adequate to care for fetal growth needs- dilation and structural remodeling. If the vessel could dilate adequately, then simple dilation would be the only mechanism required. If, on the other hand, flow is needed beyond maximal vasodilatory capacity, then one must also postulate vessel structural remodeling. Thus, in a manner similar to the maternal heart, the structural capacity and material properties of the vessel are likely to be profoundly altered.

UTERINE BLOOD FLOW AND ITS REGULATION

The remodeling of the human cardiovascular system accommodates needed increases in blood flow to the breast, kidney and uterus such that breast flow increases by 2.5×, renal flow by 1.7× and uterine blood flow by 10× or greater (Fig. 2). Uterine blood flow has been measured during pregnancy in a number of experimental animals including guinea pig [14, 15], rat [16, 17], pig [18, 19], cow [20], sheep [21, 22] and rabbits [23]. Among these animals there is considerable variability in the degree of increase in uterine blood flow in pregnancy, ranging from 10- to 100-fold [24]. However, in no mammal thus far studied is the resting level of uterine blood delivery adequate to accommodate the increases in oxygen and nutrient flow required for a successful pregnancy. Thus, there must be profound local changes in the delivery system to accommodate the pregnancy in all mammals even though different species may use a variety of mechanisms to accomplish the adaptation.

Presumably the primary physiological changes that accompany pregnancy are under the control of changing hormone levels. The roles of hormones in regulating uterine blood flow have been recently reviewed [25]. While estradiol 17β (E2β) is believed to be the most potent and physiologically dominant in regulating maternal adaptations [26, 27], other important hormones include other estrogens, progesterone, human chorionic gonadotropin, cortisol, and androgens. Infused E2β leads to increased cardiac output and heart rate in ovariectomized nonpregnant ewes and decreases in their systemic vascular resistance [27].

E2β also causes an increase in uterine blood flow. It is becoming increasingly clear, however, that pharmacological levels of hormone may have different effects than those within the physiological range; thus experimental data need to be judged according to the concentration ranges used. The question remains: how does E2β increase uterine arterial flow? As described above, blood flow increases will necessarily be a result of a combination of increased driving pressure and decreased uterine vascular resistance through dilation and/or remodeling.

Estradiol ordinarily signals through its two primary soluble receptors, estrogen receptor alpha and beta (ERα & ERβ). These receptors are ligand-activated enhancer proteins that are members of the steroid/nuclear receptor superfamily. Once bound to ligand these receptors become transcription factors that bind with high affinity to estrogen response sequences found in the regulatory regions of specific genes and activate gene expression [28]. In addition, there are so called “non-genomic” often membrane associated signaling pathways that are stimulated by estrogens, one of which is a G-protein receptor mediated process via GPR30 [29]. ER associations with Gi proteins in the plasma membrane have been reported to mediate NO production [30] and cAMP inhibition [31]. The roles of these differing signaling pathways need to be investigated in the uterine circulation.

A role for endothelium derived nitric oxide (eNO) in regulating changes in muscular tone in the uterine artery has been appreciated for some time, and it has also been known that endothelial NO production is influenced by circulating estrogen levels [32]. E2β is a powerful regulator of uterine blood flow and its effect is reduced by some 70% if the catalytic enzyme, nitric oxide synthase (NOS) is inhibited [33]. E2β is known to activate endothelial NO synthase (eNOS) through the phosphoinositol-3 kinase cascade [34]. The rate of NO production by eNOS is determined by several features including the capacity of the cell (eNOS expression levels), the phosphorylation state of eNOS, and the intracellular $[Ca^{2+}]_i$ concentration [35]. While many scientists have assumed that pregnancy-associated changes in eNOS regulation are responsible for NO-induced increases in the uterine artery during pregnancy, evidence over the past decade suggests an adaptation of sustained $[Ca^{2+}]_i$ signaling responses may supersede in importance any changes in eNOS expression and phosphorylation. Thus, the regulation of local NO output in a vessel may occur at the level of the ‘capacitative entry’ $[Ca^{2+}]_i$ response which is in turn regulated by gap junction function [36]. Likewise NO output may be reduced by any inhibitor of gap junction function or capacitive entry of Ca^{2+} via transient receptor potential cation (TRPC) channels. Thus the degree to which estrogens affect these NO regulating processes is complex and not yet thoroughly clarified.

Many other endothelium specific mechanisms are likely to hold high importance in regulating vascular tone in the uterine artery [24, 37]. Some are important in the elevated resistance to vasoconstrictors during pregnancy [38], some are important for vessel remodeling [39], and others may participate as but one of a host of redundant mechanisms that underlie the changes in the chemical regulation of vasodilatory capacity. There is keen interest in the roles of large conductance Ca^{2+}-activated K^+ channels [40], release of vasodilator prostaglandins [41], endothelial hyperpolarizing factor [42], atrial natriuretic factor [43] among others. The coordinated roles of these factors have yet to be determined.

THE FETAL PLACENTA

The circulatory system in the fetus is characterized by four shunts, the ductus venosus, the foramen ovale, the ductus arteriosus and the placenta. During the transition from fetus to neonate, these shunts begin to close, and under normal conditions are anatomically sealed within weeks. Each of these shunts is physiologically unique in both its importance in the fetal circulation, but also in the regulation of its closure at birth [44–46]. Increasing evidence suggests that these shunts influence the fetal circulation and organ growth in ways that affect the long-term health of the offspring.

The umbilical circulation derives from the allantois in early embryonic development and is the obvious life line for delivering oxygen and nutrients for the developing fetus. Special features of the fetal placental circulation ensure an uninterrupted blood flow of oxygen during fetal life and a secure cessation of flow after birth to prevent post-partum hemorrhage. Umbilical blood flow increases to keep pace with fetal growth [10]. There is a delicate balance between fetal growth rate and nutrient acquisition and in cases of placental insufficiency, whether natural or experimental, fetal growth is restricted. Roberts *et al.* [47] showed in Rhesus macaques that disruption of the growth of the placenta and the fetus was dependent upon the timing of experimental reduction in placental exchange area following the ligation of the vessels that bridge the two placental lobes. The growth of the fetus was more depressed when placental tissue loss occurred at 0.7 gestation (110d GA) compared to 0.5 gestation (80d GA) because the earlier placenta as able to gain more mass and thickness than those placentas ligated at a later gestational age. Following the 80 dGA ligation the primary placental lobe increased by 2.2 g/day, a 30% increase above normal, whereas growth at the later gestational age decreased to 0.8 g/day, about half normal. These findings suggest that primate placentas are highly plastic, but have a diminished capacity for adaptive growth as gestation proceeds.

While the umbilical artery has gained notoriety among placentologists for being inert to the usual mechanical and chemical forces that regulate systemic arterial vasomotor activity, this pristine reputation is not wholly deserved. In sheep, umbilical blood flow is generally determined by its driving pressure, estimated by the difference between mean pressures in the umbilical artery and umbilical vein without an intervening surrounding pressure as found in the lung [48]. Placental vascular resistance is increased in response to chronic increases in fetal arterial pressure [49] an indication of autoregulatory capability. However this capacity is limited because placental vascular resistance is not decreased in response to hypotension [50, 51]. The lack of a relaxation response when driving pressure is decreased suggests that the placental resistance bed is normally in a state of maximal relaxation, at least from an autoregulatory point of view. This explanation is reasonable, but further experiments could test whether further relaxation under chemical control would be possible.

The development of the placental circulation is too complex to present in detail here. However, it is nevertheless important to note that the complexities of the inner workings of the vascular tree within the mature placenta proper are the result of early chemical interactions between maternal and fetoplacental tissues. The subject was summarized by Burton *et al.* [52]. The development of a proper vascular tree in the early placenta is

important not only because of the need for optimal placental transport function but because the vascular elements of the placenta offer a continuous loading resistance to the developing heart. In the embryo, pressure loading leads to heart defects [53, 54] while in the fetus it leads to abnormal cardiomyocyte development [55, 56]. Hemangioblastic cords arise from mesenchymal cells deep within the extracellular matrix of the primitive villous cores of the nascent placenta. Under the guidance of vascular endothelial growth factors (VEGFA in particular) primitive vascular elements connect the larger placental stem vessels forming up- and down-stream [57, 58]. VEGF signals through its FLT-1 and KDR receptors, but does not act alone. Placental growth factor, which also signals via the FLT-1 receptor, is a key player in the development of the placental vascular system. Angiopoietin-1 and −2 are both ligands for the tyrosine kinase receptor, TIE2. Activation of TIE2 promotes endothelial cell survival and stabilization of newly formed capillaries while ANG2 may inhibit ANG1 rendering the developing capillaries to be more sensitive to the angiogenic stimulus of other growth factors [52, 59].

The maternal chemical environment is part of the chemical “conversation” with the developing placenta. The trophoblast releases a number of soluble receptors into the maternal circulation [52]. These molecules bind maternal growth factors and affect their availability to act locally in the placenta. In addition, there are a host of molecules including cytokines and chemokines that can interfere with proper placental vasculogenesis and result in abnormal placental function. These molecules may be the basis for diseases ranging from preeclampsia to obesity-related placental inflammation [60, 61]. Maternal estrogen is also a regulator of placental growth in the early period and is thus important in degree of implantation and the establishment of the placental vascular tree. For example, in the baboon exogenous estrogen given at 6 weeks gestation inhibits spiral artery invasion [62].

In addition to the factors mentioned above, oxygen is a powerful regulator of vascular growth and development. The once controversial idea that the placenta develops in a very low oxygen environment during most of the first trimester is now mainstream thinking among placentologists. The relative hypoxia is the result of a lack of maternal blood flow through blocked spiral arteries during early pregnancy. Current evidence suggests that this hypoxic environment is crucial to the proper development of the placenta through the appropriate expression of VEGF, PlGF, ANG1, ANG2 and their receptors each of which is adversely affected by higher levels of oxygen [63]. Eventually, the spiral arteries open up beginning at the periphery and moving in a central direction [64]. Consequently, higher oxygen concentrations and increased levels of oxidative stress are found in the periphery compared to the central areas, as shown in villi sampled from these sites [64].

Several substances are known to affect placental vascular resistance and/or the contractile properties of umbilical vessels. Table 1 shows chemicals that are known or suspected to alter placental vascular resistance in sheep and in humans. The take home message is clear: the placental vascular bed is not inert but interestingly affected by several chemical agents. However, some agents that would alter the resistance of other fetal organs have little effect on the placenta at least in most experimental settings. The powerful vasodilator, adenosine, is an example.

MODELS OF COMPROMISED PREGNANCY

A number of models of compromised pregnancy have been developed in several species. These models have been an enormous benefit to the current understanding of the biology of pregnancy and the mechanisms that regulate fetal growth. The effects on uterine and umbilical flow have been nicely reviewed by Reynolds *et al.* [10] for many of these models in the sheep. In addition to those reviewed, there are studies of the umbilical circulation in fetuses with inadequate placental gas exchange. These include carunclectomy [65–67] and umbilicoplacental embolization [68–70]. The latter model has been used widely and has brought new insight to the adaptations of specific organs that respond to low oxygen and nutrient transport.

In sheep, placental embolization allows the study of changes in placental blood flow that can occur in late gestation placental insufficiency. Repeated injections of insoluble microspheres (15–50 μm diameter) into the umbilicoplacental circulation increases placental vascular resistance and decreases umbilical flow [68–70], and in severe cases can acutely modify the umbilical artery flow velocity waveform to demonstrate zero or reversed diastolic flow (Fig. 3) [71]. These changes are characteristic of placental insufficiency and intrauterine growth restriction in human fetuses [72]. In humans, the increase in blood flow resistance is correlated more closely with loss of small arteries (<90μm) in the placenta rather than other complications of pregnancy such as maternal hypertension [73]. This is supported by studies in sheep that demonstrate that in non-embolizing models of fetal stress, there are no changes in placental resistance despite decreased placental weight and size, fetal hypoxia, acidemia, blood hyperviscosity, or maternal hypertension [65, 74, 75].

Thus it is possible to isolate experimentally the effects of placental insufficiency stemming from umbilicoplacental embolization where uterine artery or uteroplacental flows are not altered [68]. In contrast, a subset of small-for-gestational age cases in humans include a maternal component in which uterine artery blood flow is impaired [76]. Similarly, utero-placental embolization in sheep can be used to limit nutrient availability to the fetus by injecting microspheres into the maternal uterine artery. Resistance in the uterine vascular bed is increased [77], but in contrast to umbilicoplacental embolization, fetal placental vascular resistance as estimated by umbilical artery pulsatility index is not altered, even under conditions of severe fetal distress [78].

Additionally, umbilicoplacental embolization (UPE) in sheep has been used to study the effects of placental insufficiency on growth and development, and mimics many clinical signs of intrauterine growth retardation (IUGR) including fetal hypoxemia, hypoglycemia and hypercortisolemia. The severity of the embolization is controllable and thus can be used to study different degrees of stress on fetoplacental physiological parameters, as well as the effects on specific tissues. In its most severe form, frequent injections of microspheres in a relatively brief period of time will induce severe fetal hypoxemia and acidemia, hypertension (+15mmHg), bradycardia, a 50% increase umbilical perfusion pressure, a 70% reduction in umbilical blood flow, a three- to five-fold increase in umbilical vascular resistance and umbilical artery pulsatility index, reversed umbilical artery diastolic flow and fetal demise within hours of embolization [71, 79].

More moderate and controlled UPE that allows for the study of fetoplacental adaptations to placental insufficiency can induce a 30–50% decrease in fetal oxygenation and blood glucose, as well as premature activation of the hypothalamic-pituitary-adrenal axis [69, 80, 81]. Consequent to the occlusion of the villous arteries [82] and increased placental resistance, fetal arterial pressure is transiently elevated [80, 83]. Given some placental vascular reserve, fetal oxygen levels can return to normal within a day of embolization, thus requiring daily microsphere administration. Prolonged embolization (days to weeks) diminishes this reserve, and the need for daily injections is reduced (Fig. 4) [69, 80, 83].

As the fetus adapts to this placental insufficiency, vascular and tissue remodeling occurs over days to weeks. These adaptations permit fetal survival in a reduced nutrient environment, but with consequences to the developing tissues. Although most organ sizes remain proportionate to the body, even those traditionally thought to be somewhat “protected” from prenatal hypoxic stress (brain, heart) show modifications to their cellular makeup [80, 84, 85]. Most notable is the consistent finding that maturation is delayed: the heart [80], lungs [81], kidney [86], retina [87] all show signs of structural immaturity. Cellular proliferation is also affected with fewer hematopoietic cell clusters in the liver [82] and fewer myocytes in the heart [80]. At least some of these fetal (mal)adaptations have been reported to persist into the postnatal period, notably in the brain and retina [85], adipose [88] and lungs [89], and have implications for long term health.

SUMMARY

Utero- and umbilico-placental bloods flow independently in separate circulatory units that interface at the placental membrane where they are separated by a few micrometers. The entire transplacental flow of nutrients and oxygen into the fetus over its life time is determined by a highly regulated chemical and mechanical regulation of matching vascular elements. Interestingly, the two circuits have enough autonomy and differences in chemical sensitivity that they grow under highly unique environments. What is not known is how the placenta is able to regulate its vascular growth and how tissue growth and vascular growth are matched. In some cases the placenta enlarges in response to apparent nutritional and oxygenation needs. In other cases it seems unable to mount a response and the normal development of the fetus is hindered. At present we do not know how to identify a poorly perfused placenta in its early stages nor do we know what therapeutic strategies might be helpful. These mysteries need to be solved because the lifelong health of the embryo and fetus is determined by the subtleties of the nutritional flow, about which we know little.

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ABBREVIATIONS

CTR	Control
dGA	Days gestational age
eNO	Endothelium derived nitric oxide
eNOS	Endothelial nitric oxide synthase
HFD	High fat diet
HFD-R	High fat diet resistant
HFD-S	High fat diet sensitive
IUGR	Intrauterine growth retardation
L	Length
NO	Nitric oxide
NOS	Nitric oxide synthase
P_a	Arterial pressure
P_v	Venous pressure
PI	Pulsatility index
Q	Blood flow
Q_o	Blood flow within an organ
R_o	Vascular resistance within an organ
r	Radius
TPRC	Transient receptor potential cation
UA	Umbilical artery
UPE	Umbilicoplacental embolization
Uta	Uterine artery
VEGF	Vascular endothelial growth factor
η	Viscosity
τ_s	Shear stress

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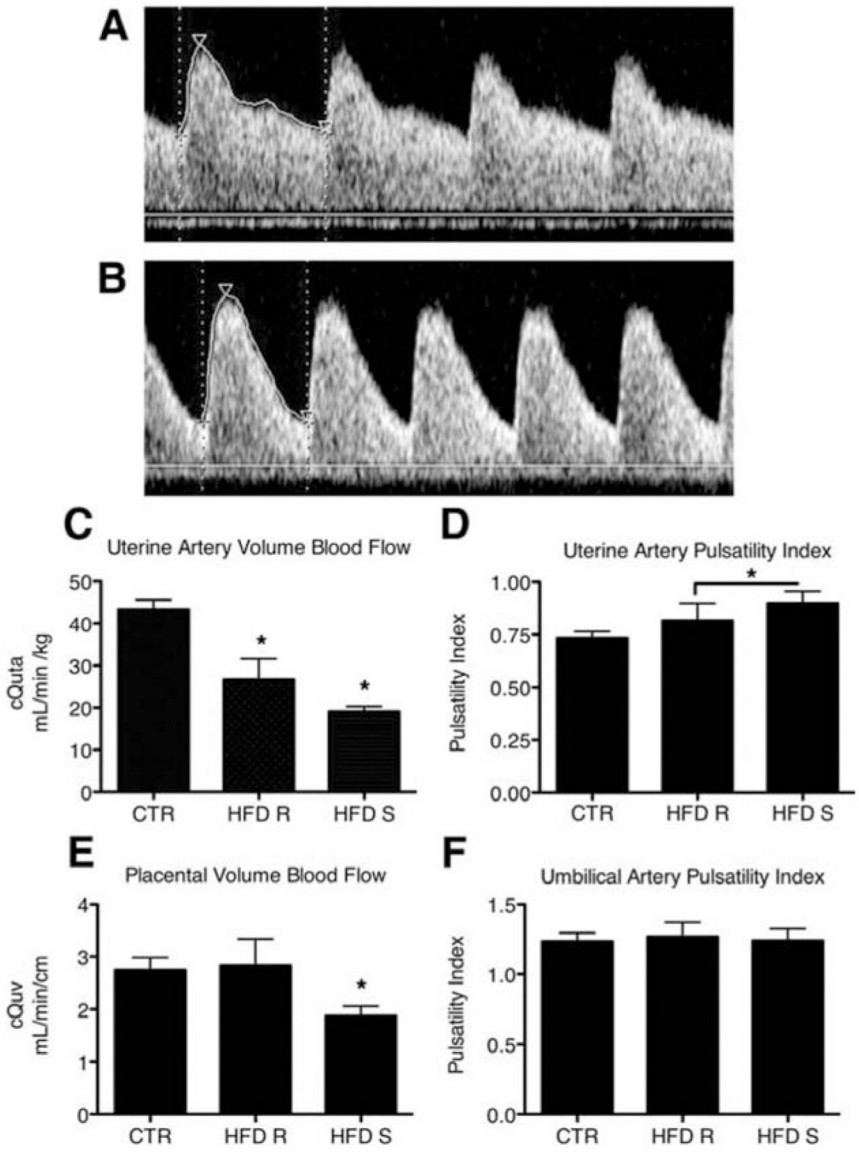

Fig. 1.

Decreased uteroplacental perfusion in Japanese macaques fed a high fat diet (HFD). Maternal HFD leads to increased uterine artery pulsitility index (PI). **A:** Uterine artery (Uta) PI is 0.74 in a representative control (CTR) animal. **B:** The Uta PI is 1.17 in a representative HFD-Sensitive (HFD-S) animal with a Doppler waveform that demonstrates decreased diastolic flow consistent with increased vascular impedance when compared with A. **C:** The cQUta normalized to maternal weight was significantly reduced in HFD-Resistant (HFD-R) and HFD-S animals when compared with CTR. **D:** Uta PI is increased in HFD-S animals when compared with CTR. As a group, HFD (HFD-R + HFD-S) had a significant increase in Uta PI when compared with CTR. **E:** The cQUV normalized to fetal abdominal circumference was reduced in HFD-S animals when compared with controls. There was no difference in HFD-R animals when compared with controls. **F:** The umbilical artery (UA) PI

was unaffected by diet group. * $P < 0.05$; CTR, n = 9; HFD-R, n = 6; HFD-S, n = 9. Reproduced, with permission [13].

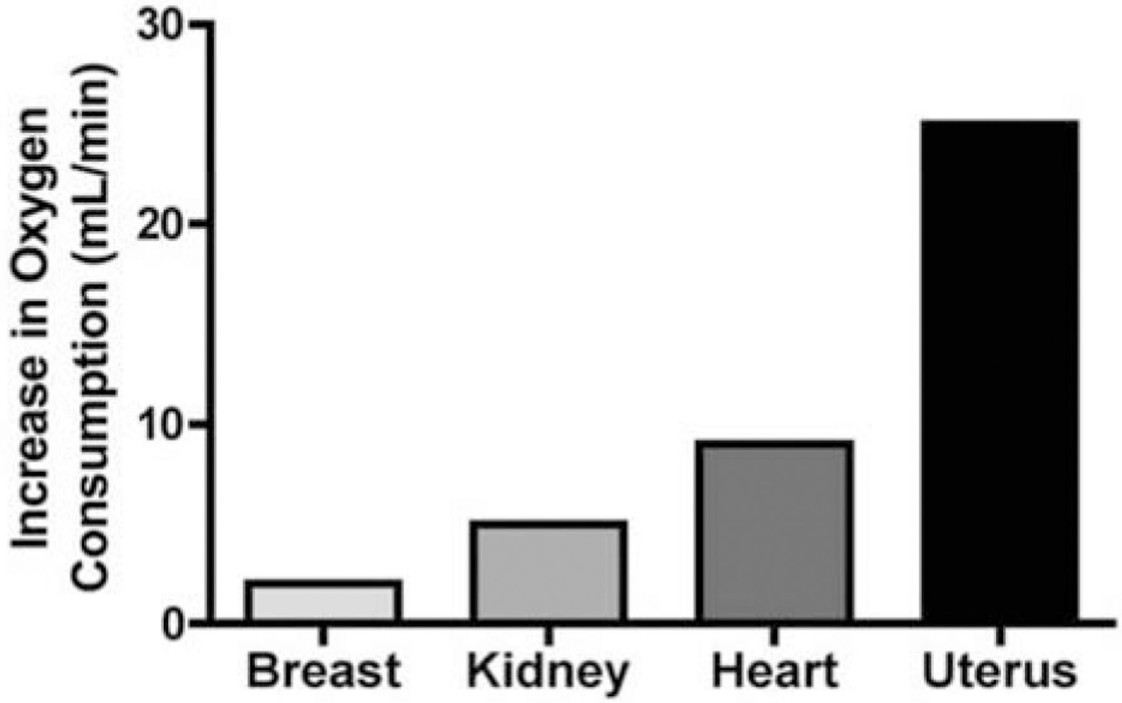

Fig. 2.

Increases in peak resting oxygen consumption in pregnancy compared to pre-pregnancy values. Data from Metcalfe *et al.* [11].

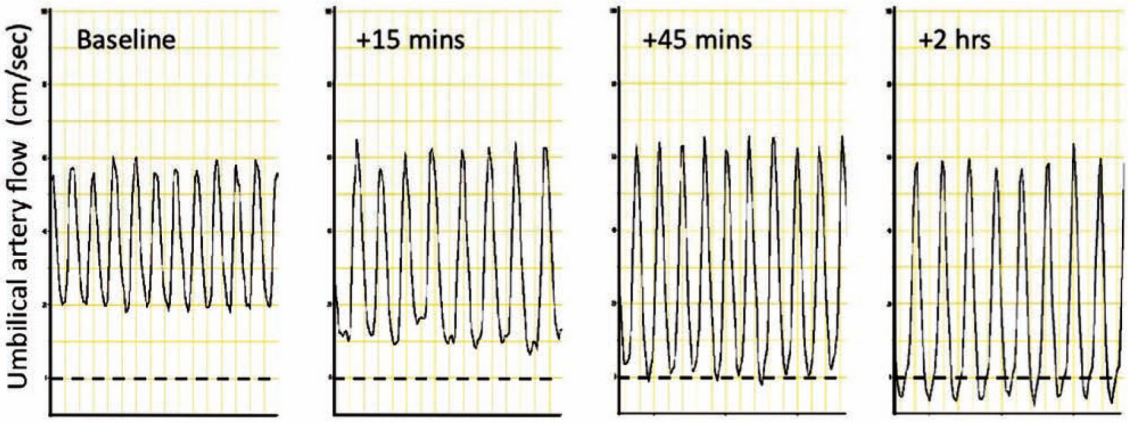

Fig. 3.

Umbilical artery flow (cm/sec) changes in response to severe umbilicoplacental embolization in sheep. Rapid, repeated injections of microspheres into the umbilicoplacental circulation will induce fetal distress and umbilical artery flow patterns that parallel those seen in human IUGR. In this experiment, diastolic flow became absent 45 minutes after embolization, and reversed flow was evident 2 hours after embolization. *Louey & Thornburg, unpublished data.*

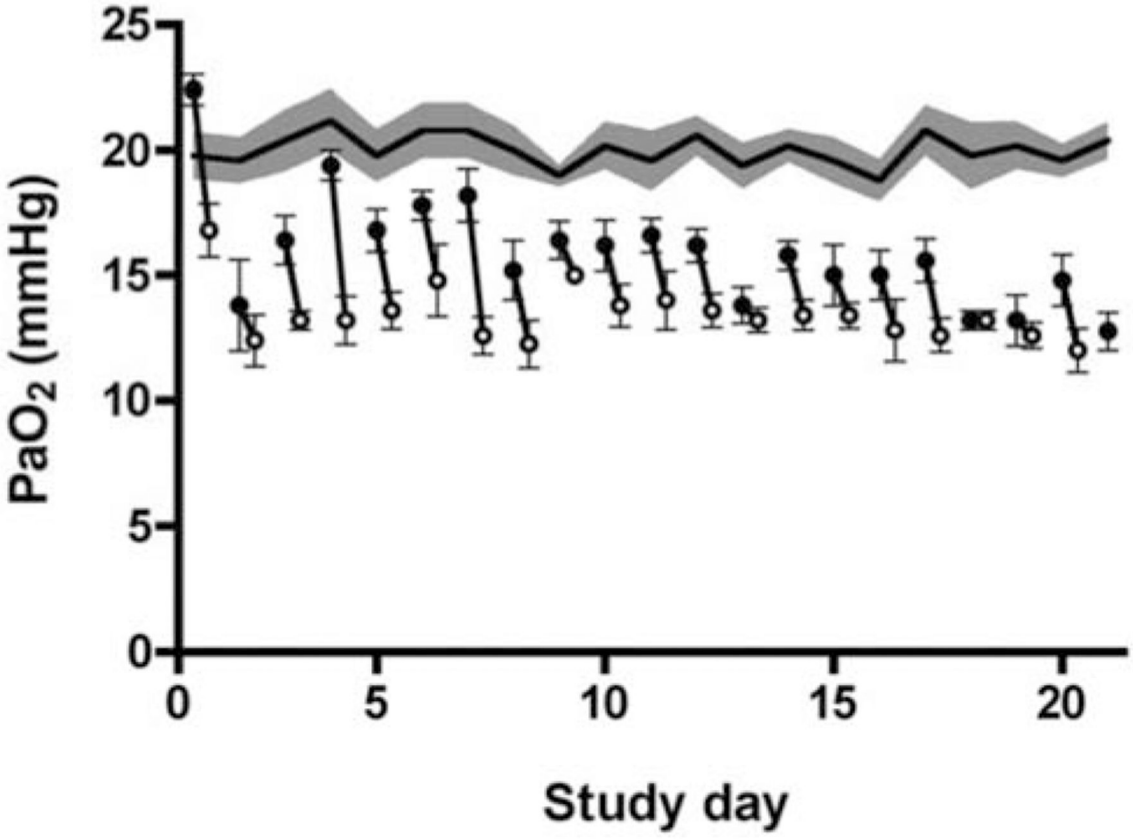

Fig. 4.

Fetal partial pressure of arterial oxygen during umbilicoplacental embolization (UPE) in sheep. Mean data for the control group (n=5) are shown by the continuous line ± SEM (shaded area). Mean ± SEM data for the UPE fetuses (n=5) are shown for the daily pre- (black circle, ●) and post-UPE periods (open circle, ○). Data modified from Louey *et al.* [80].

Table 1.

In vivo studies in sheep and *in vitro* studies of isolated human placental and umbilical blood vessels demonstrate the umbilical-placental circulation is responsive to a variety of vasoactive substances. However, it should be noted that some vasodilators (*) exert their effects *in vitro* only when vessels are pre-constricted with another substance. Compiled from several sources [90–100].

Substance	Umbilical artery and placental resistance (sheep)	Isolated placental or umbilical artery or vein (human)
Acetylcholine		constrict
Adenosine	↔	
Angiotensin II	↑	constrict
Bradykinin		constrict
Endothelin 1	↑	
Epinephrine	↑	constrict
Forskolin	↓	dilate
Histamine		constrict
Isoproteranol	↔	
Neurokinin B*		dilate
Nitrogycerin*	↔	dilate
Norepinephrine	↔	constrict
Oxytocin		constrict
Potassium		constrict
Prostacyclin*	↔	dilate
Prostaglandin A1		constrict
Prostaglandin $F_{2\alpha}$		constrict
Prostaglandin I_2	↔	
Serotonin		constrict
U-46619 (thromboxane mimetic)		constrict
Vasopressin	↑	constrict