Chapter 1 : Uteroplacental Blood Flow

The placenta is a unique vascular organ that receives blood supplies from both the maternal and the fetal systems and thus has two separate circulatory systems for blood: (1) the maternal-placental (uteroplacental) blood circulation, and (2) the fetal-placental (fetoplacental) blood circulation.

Graph showing average uterine blood flow and uterine fraction of cardiac output in pregnant, nonpregnant, and puerperal animals. Both rise markedly during pregnancy. Uterine and systemic hemodynamic interrelationships and their response to hypoxia. Am J Obstet Gynecol Some representative measurements of umbilical blood flow are listed in Table 2. This high flow rate is important in the transport of oxygen and nutrients from mother to fetus and is maintained by a number of anatomic differences in the fetal circulation. Because the fetal lungs do not have any respiratory function, a high vascular resistance is maintained in this organ by the mechanical effects of the unexpanded alveoli on the vessel walls and the vasoconstrictive effect of the low oxygen tension that prevails in the fetal blood. These two factors combine to shunt approximately two thirds of the right ventricular output away from the lungs toward the systemic circulation through the ductus arteriosus, which is maintained patent by the same low oxygen tension that keeps the pulmonary vessels constricted. With the large right-to-left shunt, a high cardiac output almost twice that of the mother is created, providing for a high flow rate across the placental exchange membranes. The controversy over the existence of shunts in the maternal and fetal placental circulations stems, at least in part, from the inconstant use of the word shunt. However, the actual maternal shunt may be greater than the nonplacental blood flow if there are additional shunts in the placental or preplacental vessels. A fetal shunt may be defined as the fraction of the umbilical blood flow that does not supply an area where exchange between fetal blood and maternal blood takes place. We cannot assume, however, that this value applies to other species, including primates, because of morphologic differences. As is true with the uterine circulation, the actual shunt in the umbilical circulation may be even greater if there are also shunts within the placenta. Regulation of Placental Blood Flows One must consider first whether the pressure in the surrounding tissue and the adjacent circulation plays a role in the regulation of either the maternal or the fetal placental blood flow. During labor, uterine contractions grossly impair maternal placental blood flow, presumably by distortion or occlusion of the preplacental vessels. Driving pressure under these conditions is the difference between arterial pressure and the surrounding pressure. Flow under these circumstances is called sluice flow. Sluice flow has been observed in the umbilical circulation only in artificially perfused placental preparations. Intact, unanesthetized fetal lambs have yielded no evidence that umbilical vascular resistance was affected by changes in uterine venous pressure. In species with hemochorial villous placentas in which the maternal blood flows in the intervillous space surrounding the fetal villi, sluice flow appears to be anatomically possible, but as yet there is no physiologic evidence for it. An important question is whether the uteroplacental circulation is able to autoregulate. Autoregulation is generally defined as the ability of an organ to adjust its vascular resistance by local control mechanisms in the face of changing perfusion pressure. From the standpoint of the fetus, autoregulation in the uteroplacental circulation would seem to be essential. Studies in pregnant sheep, however, indicate that uterine blood flow varies directly proportionally with mean arterial pressure and have failed to demonstrate a system of autoregulation. The presence of autoregulation mechanisms has been suggested by the maintenance of a constant flow rate over a wide range of pressures in pregnant rabbits and pregnant rhesus monkeys, but the evidence is not conclusive. Maternal regulation of uterine and placental blood flows does not appear to be strong. Both adrenergic and cholinergic sympathetic fibers are found in the uteri of most animals. Sacral nervous influences may be involved in the maintenance of a high uterine blood flow rate in those species that possess cholinergic innervation e. Adrenergic fibers are present in the uterus of all animals studied, but histologic examination reveals that pregnancy causes the complete disappearance of these fibers in the myometrium and a great reduction in their numbers around the uterine blood vessels. Nevertheless, electrical stimulation of the sympathetic chain in term pregnant sheep and dogs results in increased uterine vascular resistance and decreased uterine blood flow. There are a number of chemical factors

that are vasoactive in the uteroplacental circulation. The results of older studies in anesthetized pregnant sheep seemed to indicate that hypoxia could increase as well as decrease uterine blood flow, but experiments with conscious animals have failed to show any appreciable effect of maternal hypoxia or hyperoxia on uteroplacental blood flow. The uterine vasculature is also relatively insensitive to hypercapnia and hypocapnia, although hypocapnia has been reported to cause a reduction in placental, but not myometrial, blood flow in rabbits. The results of these studies may have been influenced by secondary factors such as catecholamine release, however. Thus, the available evidence strongly suggests that changes in maternal arterial blood gases are not of physiologic importance for short-term regulation of uteroplacental blood flow. Intravenous infusion of exogenous epinephrine and norepinephrine causes a strong dose-dependent decrease in uterine blood flow in both nonpregnant and pregnant sheep; in the latter, the response was observed in both the myometrial and the maternal placental blood flows. This seems to demonstrate the existence of an adrenergic vasoconstrictor mechanism in the uterine and maternal placental circulations. The real role of angiotensin II in the maintenance of the uteroplacental circulation is also unclear. Angiotensin II is a powerful vasoconstrictor, yet in various animals the response to angiotensin II infusion varies from an increase in vascular resistance to a decrease in vascular resistance in the maternal placental circulation. These conflicting reports probably reflect differences in dosage and the physiologic state of the animal preparation. This response is delayed, however, and the peak response is not attained until about 1. Similar but smaller responses have been observed during pregnancy, suggesting that the maintenance of a high rate of maternal placental blood flow may be, in part, due to the endocrine function estrogen production of the placenta. The actions of the prostaglandins in the maternal placental circulation are also unclear. These short-lived intermediates possess intrinsic biologic activity which can be inhibited by nonsteroidal anti-inflammatory agents NSAIDs. Thromboxane serves as a potent vasoconstrictor, stimulator of platelet aggregation, and stimulator of uterine contractility. PGE2 is also a vasodilator, but it causes uterine contractions and decreased placental blood flow when administered to pregnant sheep. When administered to the fetus, however, thus bypassing the myometrium, PGE2 causes vasodilation of the maternal placental circulation. Prostacyclin PGI2 , also derived from PGH2, is a vasodilator produced by the pregnant uterus that does not cause uterine contractions in the near-term sheep. PGI2 infusion results in a slight maternal placental vasoconstriction, but this response may be secondary to the maternal hypotension and release of circulating catecholamines. Blockage of prostaglandin synthesis with indomethacin in near-term pregnant sheep and rabbits causes vasoconstriction of the placental circulation but not of the myometrium. In addition to their direct role as vasoactive agents, prostaglandins also can modulate the response to other vasoactive agents. PGE2 infusion depresses the placental vasoconstriction response to norepinephrine; prostaglandin inhibition with indomethacin causes a potentiation of the vasoconstriction response of the placental vascular bed to epinephrine. This indicates that PGE2 suppresses the response of the placental vascular bed to circulating catecholamines and that there is an endogenous supply of PGE2 that, when eliminated, increases the sensitivity of the placental vascular bed to catecholamines. It has also been suggested that the estrogen-mediated increase in uterine blood flow is secondary to prostaglandin formation, based on the fact that indomethacin pretreatment depresses this response. There is no more conclusive evidence to support this hypothesis, however. The lipoxygenase enzymes catalyze the formation of hydroperoxyeicosatetraenoic acids HPETEs from arachidonic acid. Regulation of the fetal placental circulation is also poorly understood. Whereas histochemical methods have been unable to demonstrate either adrenergic or cholinergic fibers in the human placenta and umbilical cord, methylene-blue-staining fibers have been found in the umbilical arteries and the placenta of lower primates. Both adrenergic and cholinergic fibers are evident in the intrafetal umbilical vessels in the guinea pig. As with the maternal placental circulation, most of our understanding about the chemical control of the umbilical circulation comes from studies in pregnant sheep. Exogenously administered angiotensin and catecholamines both produce umbilical vasoconstriction, but their role in the normal physiologic state is still questionable. Estrogens have been shown to dilate the umbilical artery, and in most species, estrogen levels tend to increase near parturition, but it is not clear whether they play a role in regulation of the umbilical circulation. The influence of prostaglandins on the umbilical circulation is quite

different from that on the maternal placental circulation. The umbilical vascular bed is unresponsive to exogenous PGI2, but PGE2 produces a greater degree of vasoconstriction than the maximal response to angiotensin, norepinephrine, or any other chemical substance. However, indomethacin causes vasoconstriction in the fetal placental circulation, which argues against the existence of an endogenous prostaglandin vasoconstriction mechanism. There is no compelling evidence that any of these agents are involved in the regulation of the umbilical blood flow. Before leaving the discussion of uteroplacental blood flow regulation, one other possibility must be considered. If maternal placental blood flow is not controlled by the mother, could it be under fetal control? Such a similarity in blood flows and their distributions argues for the presence of a regulating mechanism. In such a system, a reduction of maternal flow would be accompanied by the synthesis of a fetal vasoconstrictor and maternal vasodilator, thereby maintaining the perfusion-perfusion ratio. PGE2 has been shown to cause vasodilation in the maternal placental vascular bed when given by way of the fetal circulation, and it also has a vasoconstricting effect on the umbilical circulation. Some evidence also suggests that fetal vessels synthesize PGE2. The existence of such a chemical link between mother and fetus is suggested by experiments in both sheep and rabbits in which occlusion of the umbilical blood flow causes a fall in uterine blood flow. The evidence for fetal control of the maternal placental circulation is by no means conclusive, but the lack of evidence for strong maternal control makes it an attractive possibility. Placental Transfer Throughout pregnancy, the placenta retains the primary role of all biologic membranes i. The ideal blood flow in a transport system such as that represented by the placenta is a countercurrent flow, in which the two bloodstreams flow in directions exactly opposite to each other Fig. With this flow, the widest possible gradient for exchange between the two bloodstreams exists over the entire length of the exchange membrane. This is important in the exchange of materials that cross the placenta by simple diffusion, because the only driving force is the concentration gradient. Concurrent flow, in which the two bloodstreams flow in the same direction i. In the human placenta, a compromise probably exists in that maternal blood flows randomly in all directions with respect to the fetal circulation. This is known as crosscurrent flow, or pool flow. The villi are bathed continually by a fountain of maternal blood with completely variable combinations of flow directions see Fig. Some transport efficiency is obviously lost by this distribution. Diagram of countercurrent and concurrent flow between maternal and fetal circulations. The two flows are randomly distributed in the human. Mental exercises in placental transfer. It is generally believed that the gases O2 and CO2 cross the placenta by simple diffusion, the driving force being the concentration difference on each side of the membrane. As nonpolar, lipid-soluble molecules, both O2 and CO2 are capable of diffusing rapidly through the lipid portion of cell membranes. Early attempts to determine the mean O2 gradient across the placental barrier used arterial and venous PO2 measurements Table 3. These studies indicated that the O2 diffusion capacity was rather low, suggesting that O2 delivery to the fetus was partially limited by diffusion resistance of the membrane. It is now known that these estimates are in error because O2 tensions in the uterine and umbilical veins are not necessarily representative of those in the end-capillary placental bloods, and the placenta and the uterus itself consumes a significant fraction of the O2 removed from the maternal blood. Using the diffusion characteristics of CO, the diffusion capacity for O2 has been estimated to be four times greater than that estimated from partial pressure gradients in the uterine and umbilical veins. Thus, it has been determined that O2 equilibrates completely in the maternal and fetal end-capillary bloods during a single pass of these bloods through the placental exchange vessels. The fetus compensates for low O2 levels with a higher blood concentration of hemoglobin see Table 3 , which has a greater affinity for O2. The fetal hemoglobin O2 dissociation curve is shifted to the left of that for maternal blood, which means that for any given O2 tension, fetal blood contains a greater amount of O2 than maternal blood. Furthermore, the release of fetal metabolites into the maternal blood results in a fall in the pH of maternal blood, which shifts the maternal O2 dissociation curve even further right, automatically increasing the mass transfer of O2 to the fetus i. There is some evidence that O2 may be transferred across the placenta by facilitated diffusion with cytochrome P as the carrier; however, this has not been confirmed. It could be argued that the O2-diffusing capacity of the placenta computed from the known CO-diffusing capacity fully accounts for the observed transplacental fluxes of O2; thus, postulation of a carrier is unnecessary.

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The feto-placental blood circulation within the placenta vasculature is responsible for producing a healthy baby by delivering the required oxygen and nutrients.

Multiple factors intervene to achieve appropriate uterine blood flow and the structuring of the placental vasculature during the early stages of pregnancy. Among these factors, oxygen concentrations, growth factors, cytokines, and steroid hormones are the most important. Sex steroids are present in extremely high concentrations in the maternal circulation and are important paracrine and autocrine regulators of a wide range of maternal and placental functions. In this regard, progesterone and estrogens act as modulators of uterine vessels and decrease the resistance of the spiral uterine arteries. On the other hand, androgens have the opposite effect, increasing the vascular resistance of the uterus. Moreover, progesterone and estrogens modulate the synthesis and release of angiogenic factors by placental cells, which regulates trophoblastic invasion and uterine artery remodeling. In this scenario, it is not surprising that women with pregnancy-related pathologies, such as early miscarriages, preterm delivery, preeclampsia, and fetal growth restriction, exhibit altered sex steroid concentrations. Introduction During pregnancy, the placenta has important nutritional, metabolic, and endocrine functions that constitute the link between the mother and the fetus. The transfer of oxygen and essentials nutrients from maternal blood to the fetal bloodstream requires an adequate uterine perfusion and a placental vascular network. Abnormalities in these processes are associated with an increased risk for miscarriage, preterm delivery, preeclampsia, and fetal growth restriction FGR Regnault et al. The formation of blood vessels involves two consecutive processes: Both processes are driven and regulated by multiple factors, including oxygen concentration, growth factors, cytokines, and steroid hormones. Sex steroids are essential to maintain a normal pregnancy, and they participate in the control of a wide range of maternal and placental functions as well as in the normal development of fetal organs such as the lungs and adrenal glands Seaborn et al. Moreover, variations in maternal serum concentrations of sex steroids have been described in conditions associated with abnormal placentation that impact placental perfusion, thus leading to pregnancy-related pathologies. Therefore, the aim of the present review is to summarize the current knowledge regarding the role of progesterone, androgens, and estrogens in the uterine-placental vasculature. Regulation of Uterine Vascular Tone During pregnancy, uterine blood flow increases dramatically mainly through a decrease in the uterine vascular resistance as a result of uterine arteries dilation and remodeling. Many of these effects are produced by changes in the muscular tone of uterine arteries that are mediated by the action of nitric oxide NO and prostanoids prostacyclins, prostaglandins, and thromboxane. Prostacyclin PGI2 also induces vasodilation. Other regulators of the uterine vascular tone during pregnancy include adrenomedullin Ross et al. Angiotensin 1â€”7 is released from syncytiotrophoblasts, which act as a potent vasodilator in contrast to angiotensin II, which induces vasoconstriction Valdes et al. Placental Vasculature The placenta originates from the differentiation of trophoblastic cells from the pre-implantation embryo into cytotrophoblasts and syncytiotrophoblasts Gerbaud and Pidoux, Two weeks after conception, the blastocyst cells acquire the ability to invade and migrate through the endometrial wall. The decidualization reaction of stromal endometrial cells subsequently results in an important increment in tissue permeability and vascular density. This reaction favors the migration of extravillous cytotrophoblasts EVT across the decidua to reach the endothelial cells of the terminal segments of the uterine arteries occluding their lumen Figure 1 , which restricts blood flow into the intervillous space and leads to a drop in oxygen concentration Figure 1. Between weeks 11â€”12 until weeks 18â€”20 of gestation, EVT remodel the uterine spiral arteries. The remodeling allows the uterine spiral arteries to acquire a large capacitance and low resistance, thus gradually increasing maternal blood flow and oxygen levels Rodesch et al. Placental angiogenesis during early pregnancy. The reaction of decidualization of stromal endometrial cells promotes the migration of extravillous cytotrophoblasts EVT across the decidua to reach the endothelial cells of the terminal segments of the uterine arteries occluding their lumen, which restricts the blood flow into the intervillous space and leads to reduced oxygen concentrations. Moreover, EVT remodel uterine spiral arterioles to increase maternal blood flow. On

the other hand, trophoblastic cells, Hofbaur cells Hc , and maternal decidual cells secrete VEGF, thus promoting angiogenesis. In addition, trophoblasts increase NOS activity, thus stimulating nitric oxide NO production and vasodilatation. The growth and development of the placental vascular network occurs through branching angiogenesis, which involves the formation of new vessels by the sprouting of preexisting vessels and a subsequent increase in the number of capillaries; it also occurs through non-branching angiogenesis, which involves the elongation of vessels and leads to the formation of capillary loops Charnock-Jones et al. The members of the vascular endothelial growth factor VEGF family are central in the regulation of placental vasculogenesis and angiogenesis Demir et al. VEGF family members are produced by trophoblastic cells, Hofbaur cells, and maternal decidual cells Figure 1 Clark et al. VEGF-A increases vascular permeability in endothelial cells, inducing placental vasculogenesis, and angiogenesis. In the human placenta, Flt-1 is located in syncytiotrophoblasts and endothelial cells of the placental villi Helske et al. On the other hand, KDR is almost exclusively expressed in endothelial cells, which mostly occurs during the first trimester of gestation in parallel to the high angiogenic activity at that time Yamazaki and Morita, The action of VEGF on angiogenesis is regulated by an impressive paracrine negative feedback system in which the soluble form of Flt-1 sFlt-1 acts as a potent inhibitor of angiogenesis that is regulated by VEGF. Other regulators of placental angiogenesis include angiopoietin Ang -1, Ang-2, and their receptor Tie These proteins are complementary to the VEGF system but participate in the later stages of angiogenesis. In early pregnancy, Ang-2 is more highly expressed than Ang However, Ang-2 decrease during the course of pregnancy Geva et al. Sex Steroids and Uterine Vascular Tone The role of progesterone and estrogen in the regulation of the uterine vascular tone has been recognized for a long time. However, the effects of testosterone have only been recently addressed. In the placenta, androgens are metabolized to estrogens by the P aromatase. Therefore, androgenic and estrogenic effects cannot be easily separated in this tissue. Progesterone Progesterone plays an important role in uterine vessel vasodilation before the 10th week of gestation Dickey and Hower, This feature, along with the decreased resistance of the placental bed, contributes to a reduction of systemic blood pressure until 28 weeks of gestation. Progesterone binds to its own receptors located in the nucleus and on the plasma membrane, mediating genomic, and non-genomic actions. Progesterone has been implicated in the rapid increase of eNOS activity and the production of NO in human endothelial cells Simoncini et al. In rats, the administration of androgen during pregnancy reduced uterine blood flow and elevated the maternal blood pressure due to an increased resistance of uterine vessels, which was due to the suppression of eNOS activity Chinnathambi et al. Moreover, testosterone contracted the uterine arteries and reduced vascular relaxation due to the decline of endothelial NO production and the expression of prostacyclin and small conductance calcium-activated channel-3 SK3. In contrast, hypoxia-responsive genes were increased, indicating poor uterine oxygenation induced by testosterone Chinnathambi et al. Estrogens Estrogens have an important function in the regulation of blood flow and microvascular volume because they control specific genes involved in vascular tone Pastore et al. Of interest, NO inhibition blunts the action of estradiol, suggesting that estrogen relaxation of myometrial arteries is mediated by both NO-dependent and -independent mechanisms Rosenfeld et al. However, its activation reduces vascular tone in the rat uterus during pregnancy Tropea et al. However, this effect is lower than that in the myometrial than placental vessels Corcoran et al. Sex Steroids and Placental Angiogenesis The role of sex steroids in placental angiogenesis has not been widely studied. Preliminary evidence suggests that sex steroids can regulate both endometrial and placental angiogenesis. Progesterone Progesterone has an important role in the activation of the decidual reaction in endometrial stromal cells, increasing the vascular permeability in the endometrial stroma through the activation of the nuclear receptor subfamily, group A, member 1 independently of VEGF action Figure 2A ; Goddard et al. Progesterone increases the number of uterine natural killer uNK cells Bulmer and Lash, , which most likely occurs indirectly through the decidualization reaction Figure 2A. Sex steroids regulate the uterine-placental vasculature. A During secretory phase of the endometrial cycle, progesterone, and estrogen induce endometrial stromal decidualization to increase vascular permeability, recruit uterine natural killer cells uNK , and increase endothelial cell proliferation. B During implantation, progesterone promotes remodeling of the arteries, most likely with the support of uNK. On the other hand, progesterone and estrogen regulate the

invasiveness of extravillous trophoblast EVT. C In early pregnancy, estrogen promotes the expression of vascular endothelial growth factor VEGF , thus stimulating early placental angiogenesis. On the other hand, androgens inhibit the angiogenesis process. In addition, estrogen regulates the invasion of the uterine spiral artery by placental EVT. During the entire process, estrogen and progesterone increase uterine blood flow. However, testosterone reduces blood flow. In early pregnancy, PR is expressed in the endothelial cells of decidual tissue, and the binding of progesterone stimulates endothelial cell proliferation. Moreover, progesterone regulates early trophoblast invasion because it reduces the invasive properties of EVT in vitro and the secretion of matrix metalloproteinase MMP - 2 and -9, which are primary mediators of vascular remodeling and angiogenesis in decidual tissue Goldman and Shalev, Figure 2B. However, progesterone promotes the migration of EVT by the upregulation of an insulin-like growth factor binding protein-1 and Dickkopf-related protein-1 Halasz and Szekeres-Bartho, Androgens Androgen receptor is present in the cells of the syncytiotrophoblast and in the decidua during the first trimester of gestation Horie et al. Rat models have shown that elevated androgen levels during pregnancy induce a reduction in placental weight and the activity of amino acid transporters Sathishkumar et al. Along with this antivasculogenic gene expression profile, the authors reported a reduction in radial and spiral artery diameters and branching angiogenesis Gopalakrishnan et al. Estrogens P aromatase is expressed in stromal uterine cells, indicating a local production of estrogen. In this regard, the estrogen signaling has also been involved in the regulation of trophoblast differentiation and its invasive capacity in the hypoxic environment of the first trimester primate placenta. For example, similar to progesterone, estrogens act as regulators of the extent of remodeling during early pregnancy because they inhibit the invasive capacity of EVT Figure 2B , reduce VEGF protein expression in the placenta anchoring villi and reduce the expression of integrins in cells from the anchoring villi and the cytotrophoblastic shell Bonagura et al. Moreover, estradiol can regulate placental angiogenesis by the degranulation of mast cells that secrete important amounts of VEGF, suggesting a role of inflammation in this process. In this regard, estradiol and progesterone attract mast cells to the uterus Corcoran et al. In many species, including humans, estradiol induces the expression of the VEGF protein in the cytotrophoblast and increases the percent of vascularized area and vessel density in placental tissue Albrecht et al. However, during the last two-thirds of pregnancy, the inhibition of P aromatase does not affect VEGF action in blood vessel development, suggesting that the cytotrophoblast loses its control by estrogen action during pregnancy Albrecht and Pepe, Clinical Implications An abnormal blood supply to the uterine-placental region leads to early miscarriage, preterm delivery, preeclampsia, and FGR. Women with unexplained recurrent pregnancy loss exhibit elevated uterine arterial impedance, which is negatively correlated with circulating progesterone levels. Of note, the administration of dydrogesterone, a synthetic progestin, reduced the resistance to blood flow in the uterine arteries, suggesting that insufficient progesterone action could be involved in a poor uterine blood supply and lead to miscarriage Habara et al. Moreover, the elevated expression of Dickkopf-related protein-1 and low expression of PR-A have been observed in women with unexplained recurrent spontaneous miscarriage Papamitsou et al. On the other hand, in growth-restricted pregnancies, PR expression in the placental tissue is positively correlated with IGF-1 expression and infant anthropometry, and it is independent of the presence of pregnancy pathologies Akram et al. A group of studies has demonstrated that preeclampsia is associated with increased levels of progesterone along with increased expression of CYP11A, which inhibits trophoblastic proliferation and potentially the production of prostacyclin; this association affects the development of placental vasculature Walsh and Coulter, ; He et al. Another group of studies demonstrated low circulating levels of progesterone and aldosterone in women with preeclampsia affected the secretion of endothelin-1, which is a potent vasoconstrictor. These results indicate that progesterone could be involved in the maintenance of normal blood pressure Kiprono et al. Therefore, normal development of placental vasculature is potentially dependent on physiological ranges of progesterone concentrations. Because estrogen is an important regulator of uterine blood flow and the production of angiogenic factors in placental tissue, it is possible to hypothesize that estrogens are involved in the pathophysiology of pregnancy-related pathologies. At the 27th gestational week, estriol is positively associated with birth weight, birth length, and placental weight Wuu et al. However, in rats, pharmacological doses of estradiol benzoate induce growth restriction, the

reduction of placental weight, and trophoblastic degeneration Matsuura et al. Elevated androgen levels are a recurrent finding in preeclamptic women Troisi et al. In women with polycystic ovary syndrome, which causes elevated androgen levels during pregnancy, the placenta presents an abnormal uterine blood flow as well as placentation with reduced endovascular trophoblast invasion Palomba et al. Therefore, abnormalities observed in PCOS women could be attributed to estrogen or androgen action. However, it is not clear whether these alterations are directly associated with elevated androgen levels, as PCOS mothers also exhibit elevated insulin levels and a pro-inflammatory pattern Sir-Petermann et al.

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See commentary " Are hematopoietic stem cells generated in the placenta? See other articles in PMC that cite the published article. These data suggest that in addition to providing a niche for a large pool of HSCs prior to liver colonization, the placenta is a true site of HSC generation. Of all stem cells, HSCs have had the greatest therapeutic impact on human disease, specifically in leukemia and aplastic anemia Bordignon, However, due to the shortage of matching donors for transplantation and the low yield of HSCs in more accessible sources such as cord blood, many patients are unable to benefit from this therapy Cairo and Wagner, Attempts to expand HSCs in vitro have failed due to loss of self-renewal ability and a propensity to differentiate in culture, highlighting the importance of the microenvironment in the maintenance of stem cell properties. Likewise, derivation of functional HSCs from human embryonic stem cells has not yet been achieved as the in vitro derived hematopoietic progenitors poorly self-renew in vivo McKinney-Freeman and Daley, To succeed in these endeavors, basic research on how fetal microenvironments support the development of self-renewing HSCs is essential. While defining the stem cell niche for adult HSCs has become an extensive area of research and both the cellular and molecular components of the niche are being unraveled, fetal HSC niches have proven highly complex and their unique molecular features remain relatively undefined Martinez-Agosto et al. HSCs in adult mice reside in the bone marrow, in the endosteal surface of trabecular bone and the vascular sinusoids Adams and Scadden, ; Kiel and Morrison, ; Suda et al. During embryogenesis HSCs migrate through a number of anatomical sites that likely impart unique cues to the cells as they transition through different developmental stages Mikkola and Orkin, Of note, newly formed HSCs are not equivalent to adult HSCs, as they require a maturation process before they can engraft into adult bone marrow and self-renew Mikkola and Orkin, ; Yoder et al. Thus, both the cell intrinsic regulatory mechanisms that govern developing HSCs and the microenvironmental niches where HSCs reside evolve during embryogenesis. To understand the impact of the microenvironment in establishing HSC properties, it is critical to define the cellular niches that support the emergence, maturation and expansion of HSCs. The first embryonic hematopoietic cells, the primitive erythroblasts, are generated after gastrulation in the yolk sac, as is a second wave of myelo-erythroid progenitors Lux et al. HSCs capable of engrafting newborn mice are found in the yolk sac and para-aortic splanchnopleure P-Sp within the embryo proper as early as E9. During subsequent days, definitive hematopoietic progenitors and HSCs colonize the fetal liver. Work by us and others subsequently showed that the mouse placenta harbors a large population of HSCs during midgestation Alvarez-Silva et al. These findings nominated the placenta as an important hematopoietic organ, unique in its capacity to sustain a large pool of HSCs while segregating them from signals that promote differentiation. However, these studies did not determine whether the placenta is capable of producing HSCs de novo or whether it functions solely as a niche for the maturation and expansion of HSCs originating from other sites. Defining the origin of HSCs in vivo has been complicated by circulation and the limitations of functional assays for developing HSCs. Once a heartbeat is initiated at E8. Although free distribution of progenitors is delayed until E Since developing HSCs are unable to engraft in lethally irradiated adult bone marrow before day E As transient embryonic progenitors with restricted myelo-erythroid potential develop prior to the emergence of HSCs, documentation of multilineage differentiation ability including lymphoid potential is essential to distinguish developing HSCs from transient embryonic hematopoietic progenitors. As all hematopoietic cells are derived from mesoderm, tracking the fate of the mesodermal tissues is critical when origin of hematopoietic cells is being explored. The placenta is comprised of trophectoderm and two mesodermal components; the chorionic mesoderm, which forms a continuum with the yolk sac, and the allantoic mesoderm, an appendage arising from the posterior primitive streak. The allantoic mesoderm migrates towards the ectoplacental cone, fuses with the chorion, and intertwines with the trophoblast to form the placental vascular labyrinth, which facilitates the exchange of nutrients, gas and minerals between mother and fetus Cross, ; Inman and Downs, Interestingly, earlier studies

on quail-chick chimeras showed that the avian allantois is a source of definitive hematopoietic cells Caprioli et al. Recently, the hematopoietic potential of the mouse chorionic and allantoic mesoderm was assessed Corbel et al. Strikingly, these studies documented myelo-erythroid hematopoietic potential in both the allantoic and chorionic mesoderm, supporting the hypothesis that HSCs may be generated in the placenta. Yet, these studies did not define lymphoid potential of the rudiments. Of note, one study in described B-lymphoid potential in the midgestation placenta, however, the origin of these cells was not defined Melchers, Our goal was to determine whether the mouse placenta is a true site of HSC generation, and identify the cellular niches in which placental HSCs reside. By using the Runx1-LacZ and Ncx1 knockout mouse models we demonstrate that definitive hematopoiesis is autonomously initiated in the placenta. The placental derived hematopoietic cells were capable of producing both myelo-erythroid and B- and T-lymphoid progeny, fulfilling the criterion of multipotentiality that is the defining feature of developing HSCs. The process of HSC emergence is always intimately associated with the large vessels in the placenta. Furthermore, the small vessels in the placental labyrinth may serve as a niche where HSCs convene for maturation and expansion prior to seeding the fetal liver. Runx1 is essential for the emergence of definitive HSCs and remains expressed in HSCs throughout fetal development and adult life North et al. As in other hematopoietic tissues, Runx1 expressing cells in the placenta co-expressed markers of developing HSCs. Although the kinetics of HSC development has been reported to be slightly altered due to Runx1 haploinsufficiency Cai et al. However, the activity of the Runx1 locus persists in the null embryos and drives the expression of the LacZ reporter, marking the sites where Runx1 dependent definitive hematopoiesis is initiated North et al. In contrast to the AGM, the liver does not generate HSCs de novo but functions as a site of expansion and differentiation for definitive hematopoietic cells seeded from other sources. The chorioallantoic mesenchyme harbored also cuboidal cells that stained for LacZ and cytokeratin Figure 1A; v. These cells are derived from ectoplacental endoderm and form structures called Crypts of Duval Duval, ; Ogura et al.

Chapter 4 : Placental blood circulation

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When tested, nonplacental vascular responses are similar to nonpregnant responses. The hemochorial structure of the human placenta adds a unique factor to those that normally control blood flow in other vascular beds. That is, blood traverses the spiral arteries to enter the swamplike intervillous space, perfuses the fetal villi, and then returns to the general circulation by many collecting veins in the basal plate. Effectively, blood leaves normal vascular channels to circulate in a new extravascular space grafted onto the uterus for the duration of pregnancy. Since the intervillous space lies within the uterine cavity and since the placenta is a flexible structure, pressure generated by the contracting myometrium will be transmitted equally to the amniotic cavity and the intervillous space. Thus, a factor extraneous to usual vascular control, myometrial activity, can change intervillous space pressure and influence PBF by its effects on perfusion pressure. A schematic representation of blood flow to the non-placental tissues and to a single cotyledon is shown in Figure 4, along with the formulas pertinent to the control of each. Nonplacental and placental circulations and the factors affecting each of the primate uterus. The relation between these factors and distributional blood flow is defined in the accompanying equation. From Greiss FC, Jr: The perfusion pressure delivering blood to nonplacental tissues is the difference between uterine arterial and venous blood pressures. However, the perfusion pressure delivering blood to the intervillous space is the difference between uterine arterial blood pressure and the intervillous space pressure. The latter is best approximated by amniotic fluid pressure IUP. In a muscular organ, resistance factors will include resistance from reactivity of vascular smooth muscle, or intrinsic resistance Ri , and the squeeze imparted to blood vessels as they traverse the contracting myometrium, or extrinsic resistance Re. It should be evident then that uterine contractions can affect PBF by two mechanisms: In clinical practice, three major characteristics of placental vascular control are important. These include the relationship between perfusion pressure and flow, the responses of the spiral arteries to vasoactive stimuli, and the effects of myometrial contractions. In addition, the unique effects of local anesthetic agents must be appreciated. Pressure-Flow Relationship When one observes changes in UBF secondary to reductions in perfusion pressure during myome-trial quiescence, a straight-line relationship with a slope of one can be developed Fig. This reflects the widely dilated nature of the placental vasculature and indicates that PBF will decrease almost in identical proportion to the decrease in perfusion pressure. Since uterine venous pressure is quite constant under most circumstances, changes in systemic blood pressure MBP may be used to approximate PBF changes. Such measurements should be made in the lateral decubitus position, however, since pressure of the gravid uterus on the aorta alone has been shown to decrease blood pressure in the pelvic area below that observed in the brachial artery. Pressure-flow regression line determined from pooled proportionate data in term pregnant ewes. Since the relation is linear, uterine blood flow will vary with and in proportion to any change in perfusion pressure. Am J Obstet Gynecol Responses to Vasoactive Stimuli Since the spiral arteries approach maximum dilatation in the resting state, vasodilator agents or stimuli have little or no effect even though receptors for such agents are present. However, the smooth muscles of these vessels are exquisitely sensitive to vasoconstrictor agents or stimuli, more so than most other peripheral vascular beds Fig. This means that although MPB may increase in response to stimulation by a peripherally acting vasopressor drug such as phenylephrine, the proportionate increase in placental vascular resistance Ri is SO much greater that the net effect is a marked decrease in PBF. Such differences in vasoconstrictor sensitivity must be considered whenever a vasopressor drug is indicated. Use of a more centrally acting drug such as ephedrine, although causing a small amount of placental vasoconstriction, will result in a proportionately greater improvement in MBP with an absolute increase in PBF. Original recordings showing effects of intravenous A levarterenol norepinephrine and B epinephrine on maternal blood pressure, cardiac output, and uterine blood flow at term ovine pregnancy. Proportionate changes from control levels of systemic and uterine

conductance the reciprocal of resistance have been inserted in parentheses. Note that the decrease in uterine conductance increase in resistance exceeds that of systemic conductance with oth agents. Myometrial Contractions Acting by the two mechanisms discussed above, increasing Re and decreasing perfusion pressure, myometrial contractions decrease PBF in direct proportion to the intensity and duration of each contraction. The relationship is so precise that a tracing of intrauterine pressure is almost an exact inverse image of PBF Fig. Increasing the frequency of contractions decreases PBF during a given unit of time by decreasing the duration of myometrial diastole, that time when PBF is at homeostatic levels. In addition, should intercontraction tonus be elevated, as in a placental abruption, intercontraction PBF will be proportionately reduced. Radioangiographic studies in subhuman primates and women show that during the acme of myometrial contractions of average intensity, PBF ceases. Relationship between uterine blood flow UBF and uterine contractions during spontaneous labor in a rhesus monkey. Note the inverse image relation, sharp decreases in UBF at the onset of contractions, and slower recovery of UBF of basal levels. Effect of increased frequency of contractions on UBF produced by oxytocin stimulation of the spontaneous labor shown in A. Note that the duration of the phases of normal tonus is decreased. UBF rate attained between contractions is dependent on the intensity of the preceding contraction and the duration of the phase of normal tonus. After contractions 7 and 12, flow recovery was incomplete because the succeeding contraction occurred without a normal tonus phase. Clin Obstet Gynecol Local Anesthetic Agents These drugs may exert effects on a vascular bed directly, as after inadvertent intravascular injection, and indirectly, as a result of paralysis of autonomic nerves that maintain normal vascular tonus. In most organs, intravascular injections have no significant effects on vascular resistance. However, the uterine and placental vasculatures respond to such stimuli with significant vasoconstriction. In addition, the myometrium is variably stimulated by such drugs Fig. Alone or together, these responses diminish PBF. Following paracervical block anesthesia administered during labor, a delayed fetal bradycardia may occur. The best hypothesis to explain the fetal response is that local anesthetic agents are injected close to the uterine arteries and that because of their excellent penetrance, they cross the arterial walls to cause their uterine effects decreasing PBF and causing fetal hypoxia. Dose-response relationships of local anesthetic agents administered directly into the uterine artery to uterine vascular conductance and intrauterine pressure during ovine gestation. Effective dose levels are within the ranges observed in fetuses during bradycardia following paracervical block anesthesia. From Fishburne JI, Jr et al: Responses of the gravid uterine vasculature to arterial levels of local anesthetic agents. Courtesy of The C. Therefore, to optimize the fetal environment, the clinical goal must be to prevent, minimize, or reverse these adverse effects. In addition, the effects of any dynamic stimulus must always be interpreted on the background of the adequacy of the homeostatic levels of PBF prior to the stimulus. A theoretical depiction of this background based primarily on oxygen delivery is shown in Figure 9 and will serve to illustrate the interplay of homeostatic and dynamic factors. Hypothetical relation between placental blood flow and the status of the fetus. Of the many factors determining fetal well-being, placental blood flow is the most variable and the most susceptible to pathologic change. The significance of detrimental influences on placental blood flow increases as the prestress level of flow decreases. The clear, stippled, and lined areas indicate levels of fetal reserve see Figure 3. Labor The effects of labor on PBF at three different levels of prelabor homeostasis are illustrated in Figure This shows mean PBF at four levels of uterine activity and assumes cessation of intervillous space flow for 30 seconds of a second contraction and 45 seconds of a second contraction. Whereas a fetus beginning labor at optimal maternal PBF levels is never jeopardized with respect to oxygen delivery even during a tumultuous labor, that fetus whose mother had suboptimal prelabor PBF could withstand average labor patterns but would have been depressed at birth or possibly stillborn had tumultuous labor occurred. It should be obvious in the third case that without any prelabor safety factor, even the mildest of uterine contractions would be sufficient to cause fetal compromise. This latter category probably describes the circumstances when a positive contraction stress test is evoked. Effect of uterine contractions on mean placental blood flow. As the duration and frequency of contractions increase, mean flow progressively decreases. If labor begins with optimal blood flow, placental perfusion is more than adequate even during very active contractions solid line. However, if placental perfusion is borderline before labor, as in preeclampsia,

even mild contractions may cause fetal distress or death short-dashed line. Regional Anesthesia Epidural or spinal anesthesia may cause maternal hypotension by paralysis of sympathetic nerves, peripheral vasodilatation, peripheral pooling, and reduced cardiac return of blood. Since the placental vasculature is normally widely dilated, sympathetic nerve paralysis would have no effect on these vessels. This response is illustrated in Figure 11, along with two methods of treating the hypotension: While each restores normotension, their effects on PBF are radically different. Predictably from the preceding discussion, the peripherally acting agent phenylephrine caused no sustained increase in UBF since the degree of induced placental vasoconstriction far exceeded the rise in MBP. Treatment of the underlying pathophysiology, a discrepancy between the capacity and the volume of the vascular system, with volume replacement simultaneously restored MBP and UBF to normal. Sometimes, however, volume replacement is ineffective and a vasopressor agent must be used. Figure 12 illustrates the more favorable PBF effects that can be obtained by the use of centrally acting agents and the critical difference this choice may make depending on the amount of pre-existing reserve PBF. Original recording illustrating changes induced by spinal anesthesia in a term pregnant ewe. Note the marked improvement in uterine blood flow from volume replacement as compared with vasopressor therapy. Effect of hypotension induced by spinal anesthesia on placental perfusion. Only those fetuses with initial suboptimal placental blood flow dashed lines will be affected by marked hypotension. If vasopressor therapy is required, appropriate selection of the drug according to its mode of action may be crucial to fetal survival. The placental vasculature will participate in this generalized vasoconstriction with a reduction in PBF. With further blood loss, the limits of compensation are exceeded and hypotension occurs, adding an additional factor to reduce PBF. These predictable responses are confirmed experimentally in Figure As with hypotension induced by a regional anesthetic block, therapy directed at the underlying problem, volume loss, will improve MBP and PBF simultaneously, and vasopressor agents should be used only as a last resort. Original recording illustrating systemic and uterine responses to hemorrhage in a term pregnant ewe. Note that uterine blood flow decreased before the blood pressure did and that the subsequent uterine blood flow reduction was proportionately greater than that of blood pressure. The central and peripheral effects of these agents cause varying degrees of maternal tachycardia, peripheral vasodilatation, and hypotension. Since the placental vessels are widely dilated normally, no further vasodilatation can occur and we have another clinical example of the pressure-flow experiment, PBF varying in direct proportion to changes in MBP. An example of the interplay of the myometrial and systemic effects of isoxsuprine on PBF in a patient in active labor is shown in Figure During isoxsuprine therapy, uterine contractions almost ceased and systemic blood pressure progressively decreased, causing a similar baseline reduction in PBF Fig. Prudently, isoxsuprine was stopped when MBP was halved although the fetal heart rate was still normal. The wrong decision for proper management was made at this point due to a failure to recognize that hypotension alone was not stressing the fetus. Rather it was the additional PBF decreases associated with uterine contractions.

Chapter 5 : Uterine and Placental Blood Flow | GLOWM

The placental circulation brings into close relationship two circulation systems: the maternal and the fetal. The supply of blood to the placenta is influenced by various factors, especially by the arterial blood pressure, uterine contractions, tobacco abuse, medications and hormones.

Abstract De formato foetu liber singularis by Adriaan van den Spiegel Sonographic analysis of the placenta and uterus and their associated blood flow are key diagnostic prenatal assessments in human development. This review will provide an overview of the basic biology of the placentation process and key events in the developmental timeline. This talk should be of value to those wanting a better understanding of the process of human haemochorial placentation. Placentation begins at the implantation site in the second week of development GA week 4 with conceptus trophoblast cells invading the maternal endometrial epithelium and stroma. From that time on the process of placentation involves complex interactions between maternal uterine and fetal tissues. While there are many animal models of this process, none currently exactly match that seen in humans. Maternally, these changes include modification of the maternal vascular, endocrine and immune response. Fetally, an entire organ is grown from extra-embryonic tissue that has many functions outside of acting as a simple exchange tissue. The main maternal vascular changes include increased vascularity and trophoblast modification of spiral arteries. The fetal vascular bed consists of large cord vessels and an exponentially growing capillary bed consisting of kilometres of villous capillaries. Identification of cord vessel number, size and blood flow, are important indices of normal fetal development. Furthermore extensive remodeled of the capillary bed occurs throughout development, with some villi morphologies influencing the efficiency of diffusional gas exchange. Clinically, abnormalities of placentation site, placental development, function and blood flow can have both maternal and fetal ramifications. This is such an interesting, and both clinically and diagnostically relevant topic in sonography. My talk will go through a time-course of development from earliest implantation through to the term placenta, specifically related to vascular development. Given that this process takes about 9 months, I will pick some key events in my 20 minute talk. I have designed this online resource for ongoing "self-directed" learning after the conference. As always, I welcome feedback and questions from my readers and encourage you to contact me with any potential educational materials that you would like to share. The beginning of the animation shows adplantation to the the uterus lining endometrium epithelium. The hatched blastocyst with a flat outer layer of trophoblast cells green , the inner cell mass which has formed into the bilaminar embryo epiblast and hypoblast and the large fluid-filled space blastocoel. The blastoceol cavity is converted into two separate spaces: The third space lies above the epiblast layer of the embryonic disc, the amniotic cavity.

Chapter 6 : Paper - Placental circulation - Embryology

Placental Vasculature and Circulation The foregoing information about placental vasculature and circulation is graphically summarized in the drawing by Ranice Crosby shown in Figure

Placentation The placenta begins to develop upon implantation of the blastocyst into the maternal endometrium. The outer layer of the blastocyst becomes the trophoblast , which forms the outer layer of the placenta. This outer layer is divided into two further layers: The syncytiotrophoblast is a multinucleated continuous cell layer that covers the surface of the placenta. It forms as a result of differentiation and fusion of the underlying cytotrophoblast cells, a process that continues throughout placental development. The syncytiotrophoblast otherwise known as syncytium , thereby contributes to the barrier function of the placenta. The placenta grows throughout pregnancy. Development of the maternal blood supply to the placenta is complete by the end of the first trimester of pregnancy week 14 DM. Placental circulation[edit] Maternal blood fills the intervillous space , nutrients, water, and gases are actively and passively exchanged, then deoxygenated blood is displaced by the next maternal pulse. Maternal placental circulation[edit] In preparation for implantation of the blastocyst, the uterine endometrium undergoes "decidualisation". Spiral arteries in decidua are remodeled so that they become less convoluted and their diameter is increased. The increased diameter and straighter flow path both act to increase maternal blood flow to the placenta. There is relatively high pressure as the maternal blood fills intervillous space through these spiral arteries bathes the fetal villi in blood, allowing an exchange of gases to take place. In humans and other hemochorial placentals, the maternal blood comes into direct contact with the fetal chorion , though no fluid is exchanged. As the pressure decreases between pulses , the deoxygenated blood flows back through the endometrial veins. This begins at day 5 - day 12 [11] Further information: Fetal circulation Deoxygenated fetal blood passes through umbilical arteries to the placenta. At the junction of umbilical cord and placenta, the umbilical arteries branch radially to form chorionic arteries. Chorionic arteries, in turn, branch into cotyledon arteries. In the villi, these vessels eventually branch to form an extensive arterio-capillary-venous system, bringing the fetal blood extremely close to the maternal blood; but no intermingling of fetal and maternal blood occurs "placental barrier". This may contribute to pre-eclampsia and other pregnancy complications. Placental expulsion Placental expulsion begins as a physiological separation from the wall of the uterus. The period from just after the child is born until just after the placenta is expelled is called the "third stage of labor". Placental expulsion can be managed actively, for example by giving oxytocin via intramuscular injection followed by cord traction to assist in delivering the placenta. Alternatively, it can be managed expectantly, allowing the placenta to be expelled without medical assistance. Blood loss and the risk of postpartum bleeding may be reduced in women offered active management of the third stage of labour, however there may be adverse effects and more research is necessary. Placental microbiome The placenta is traditionally thought to be sterile , but recent research suggests that a resident, non-pathogenic , and diverse population of microorganisms may be present in healthy tissue. However, whether these microbes exist or are clinically important is highly controversial and is the subject of active research. The placenta intermediates the transfer of nutrients between mother and fetus. The perfusion of the intervillous spaces of the placenta with maternal blood allows the transfer of nutrients and oxygen from the mother to the fetus and the transfer of waste products and carbon dioxide back from the fetus to the maternal blood. Nutrient transfer to the fetus can occur via both active and passive transport. Immunity[edit] IgG antibodies can pass through the human placenta, thereby providing protection to the fetus in utero. IgM , however, cannot cross the placenta, which is why some infections acquired during pregnancy can be hazardous for the fetus. Furthermore, the placenta functions as a selective maternal-fetal barrier against transmission of microbes. However, insufficiency in this function may still cause mother-to-child transmission of infectious diseases. Endocrine function[edit] The first hormone released by the placenta is called the human chorionic gonadotropin hormone. This is responsible for stopping the process at the end of menses when the Corpus luteum ceases activity and atrophies. If hCG did not interrupt this process, it would lead to spontaneous abortion of the fetus. The corpus luteum also produces and releases progesterone and estrogen ,

and hCG stimulates it to increase the amount that it releases. These tests will work when menses has not occurred or after implantation has happened on days seven to ten. Progesterone helps the embryo implant by assisting passage through the fallopian tubes. It also affects the fallopian tubes and the uterus by stimulating an increase in secretions necessary for fetal nutrition. Progesterone, like hCG, is necessary to prevent spontaneous abortion because it prevents contractions of the uterus, and is necessary for implantation. Estrogen is a crucial hormone in the process of proliferation. This involves the enlargement of the breasts and uterus, allowing for growth of the fetus and production of milk. Estrogen is also responsible for increased blood supply towards the end of pregnancy through vasodilation. The levels of estrogen during pregnancy can increase so that they are thirty times what a non-pregnant woman mid-cycles estrogen level would be. Human placental lactogen is a hormone used in pregnancy to develop fetal metabolism and general growth and development. Human placental lactogen works with Growth hormone to stimulate Insulin-like growth factor production and regulating intermediary metabolism. In the fetus, hPL acts on lactogenic receptors to modulate embryonic development, metabolism and stimulate production of IGF, insulin , surfactant and adrenocortical hormones. They are decreased with toxemia , choriocarcinoma , and Placental insufficiency. For this purpose, the placenta uses several mechanisms: This is the same mechanism used by parasitic nematodes to avoid detection by the immune system of their host. The characteristic large nucleus of a CMV-infected cell is seen off-centre at the bottom-right of the image. Numerous pathologies can affect the placenta. Placenta accreta , when the placenta implants too deeply, all the way to the actual muscle of uterine wall without penetrating it Placenta praevia , when the placement of the placenta is too close to or blocks the cervix.

Chapter 7 : ASA Meeting - Placenta - Embryology

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.

The uteroplacental circulation starts with the maternal blood flow into the intervillous space through decidual spiral arteries. Exchange of oxygen and nutrients take place as the maternal blood flows around terminal villi in the intervillous space. The in-flowing maternal arterial blood pushes deoxygenated blood into the endometrial and then uterine veins back to the maternal circulation. The fetal-placental circulation allows the umbilical arteries to carry deoxygenated and nutrient-depleted fetal blood from the fetus to the villous core fetal vessels. After the exchange of oxygen and nutrients, the umbilical vein carries fresh oxygenated and nutrient-rich blood circulating back to the fetal systemic circulation. It is estimated that the surface area of syncytiotrophoblasts is approximately 12m2 [1] and the length of fetal capillaries of a fully developed placenta is approximately kilometers at term [2 , 3]. The functional unit of maternal-fetal exchange of oxygen and nutrients occur in the terminal villi. No intermingling of maternal and fetal blood occurs in the placenta. The right panel shows the relationship of the uterus, placenta, and fetus during pregnancy. The left panel shows the directions of blood flow from mother to the placenta and more Maternal-placental blood circulation Uteroplacental circulation is not fully established until the end of the first trimester. Although the exact mechanism of how the uteroplacental circulation is established is not completely understood, two theories have been proposed. The first theory is that in the first trimester, endovascular trophoblasts migrate along the decidual spiral arteries, invade the vessel walls, and create a path for maternal blood to perfuse the placenta intervillous space. This theory is supported by the presence of endovascular trophoblasts in the decidual spiral arteries of the first trimester placenta [4 , 5]. The second theory proposes that trophoblasts invade decidual spiral arteries and form trophoblastic plugs. These trophoblastic plugs obstruct maternal blood flow into the intervillous space and prevent flow until the end of first trimester of pregnancy 10â€”12 weeks. The plugs then loosen and permit continuous maternal blood flow into the intervillous space. This theory is based on the observations of ex vivo histologic analysis of hysterectomy specimens of first-trimester placentas, in which plugs of trophoblasts were found either partially or fully obstructing or filling the vessel lumen of decidual spiral arteries [6]. Normal early placental development results in transformation of spiral arteries that extend from the decidua the layer of tissue lining the uterus to the muscle layer. Most textbooks provide the classic description of the placenta circulation based on studies of second-, or third-trimester placentas. As shown in Figure 2. It has been estimated that there are about spiral arterial entries into the intervillous space at term [7]. Maternal blood traverses through the placenta intervillous space and drains back through venous orifices in the basal plate, then returns the maternal systemic circulation via uterine veins. Maternal-placental blood flow is propelled by maternal arterial pressure because of the unique nature of low-resistance uteroplacental vessels, which accommodate the massive increase in uterine perfusion over the course of gestation [7]. During pregnancy, maternal blood volume increases progressively from 6â€”8 weeks of gestation and reaches a maximum approximately at 32â€”34 weeks and then keeps relatively constant until term. Remodeling of the uterine arteries is a key event in early pregnancy that begins after implantation. The trophoblast differentiates into villous trophoblasts and extravillous trophoblasts. These trophoblasts have distinct functions when in contact with maternal tissues. Villous trophoblasts give rise to the chorionic villi, the major structure of placental cotyledon. Chorionic villi primarily transport oxygen and nutrients between fetus and mother. Extravillous trophoblasts migrate into the decidua and myometrium and penetrate the maternal vasculature. The extravillous trophoblasts can be classified as interstitial trophoblasts and endovascular trophoblasts. Interstitial trophoblasts invade the decidua and surround spiral arteries. Endovascular trophoblasts invade spiral arteries. In the uterine spiral arteries, endovascular trophoblasts interdigitate between the endothelial cells, replacing the endothelial lining and most of the musculoelastic tissue in the vessel walls, thereby creating a high-flow, low-resistance placental circulation. In early pregnancy, two types of extravillous

trophoblasts are found outside the villous, endovascular and interstitial trophoblasts. Endovascular trophoblasts invade and transform spiral arteries more Placental blood flow is increased throughout pregnancy. Steep falls in the pressure occur in the transition from uterine arteries to intervillous spaces. The pressure is about 80â€" mmHg in uterine arteries, 70 mmHg in spiral arteries, and only 10 mmHg within intervillous space. The low-resistance of uteroplacental vessels and the gradient of blood pressure between uterine arteries and placental intervillous space allow the maternal blood to perfuse the intervillous space efficiently and effectively. The blood in the intervillous space is therefore completely exchanged two to three times per minute. In general, the spiral arteries are perpendicular to the uterine wall, while the veins are parallel to the uterine wall. This arrangement facilitates closure of the veins during uterine contractions and prevents squeezing of maternal blood from the intervillous space. Fetal-placental circulation Umbilical cord: The umbilical cord is the lifeline that attaches the placenta to the fetus. During prenatal development, the umbilical cord comes from the same zygote as the fetus. It extends from the fetal umbilicus to the fetal surface of the placenta or chorionic plates. The umbilical vein carries oxygenated, nutrient-rich blood from the placenta to the fetus, and the umbilical arteries carry deoxygenated, nutrient-depleted blood from the fetus to the placenta Figure 2. Any impairment in blood flow within the cord can be a catastrophic event for the fetus. Umbilical vessels are sensitive to various vasoactivators, such as serotonin, angiotensin II, and oxytocin. The contractility of smooth muscles in vessel walls is also influenced by substances produced by the neighboring endothelial cells in a paracrine manner [9]. Umbilical cord vessels produce several potent vasodilators. They found that placentas from women with abnormal umbilical artery flow velocity waveforms showed significantly lower mean NOS activity than did placentas from women with normal umbilical artery flow velocity wave-forms [12]. At the junction of umbilical cord and placenta, the umbilical arteries branch to form chorionic arteries and traverse the fetal surface of the placenta in the chorionic plate and branch further before they enter into the villi. The chorionic arteries are easily recognized because they always cross over the chorionic veins. These vessels are responsive to vasoactive substances as mentioned above. About two thirds of the chorionic arteries form networks supplying the cotyledons in a pattern of disperse-type branching. The rest of the chorionic arteries radiate to the edge of the placenta and down to a network. Please note the pattern of disperse-type branching of fetal vessels fetal surface in the chorionic plate. Used with permission more Each umbilical cord artery generally provides eight or more terminal chorionic plate arteries, which are referred to as stem arteries of the peripheral trunci chorii to the fetal villous cytyledons. The first order branches have an average length of 5â€"10 mm; the artery is an average of 1. These truncal vessels divide into four to eight horizontal cotyledonary vessels of the secondary order, with an average diameter of 1 mm. The horizontal distance varies with the size of the cotyledon, and as they curve toward the basal plate, they begin branching into the third-order villous branches. There are about 30â€"60 branches in each cotyledon, with calibers of 0. In the villi, the third-order villous branches form an extensive arteriocapillary venous system, villous capillaries, bringing the fetal blood extremely close to the maternal blood; but no intermingling between fetal and maternal blood occurs. There are about 15â€"28 cotyledons per placenta. The villous capillaries are branches of the umbilical vessels, and the capillary networks are the functional unit of maternal-fetal exchange. The blood pressure in the umbilical arteries averages about 50 mmHg, and the blood flows through smaller vessels that penetrate the chorionic plate to the capillaries in the villi where arterial blood pressure falls to 30 mmHg. In the umbilical vein the pressure is 20 mmHg. The pressure in the fetal vessels and their villous branches is always greater than that within the intervillous space. This protects the fetal vessels against collapse. Assessment of fetal blood flow: Ultrasound and Doppler flow measurements provide means to visualize the umbilical cord and to evaluate the fetal blood flow. By measuring the amount of forward blood flow through the umbilical artery during both fetal systole and diastole, an overall measure of fetal health can be obtained. In general, the more forward blood flow from the fetus to the placenta through the umbilical artery, the healthier the fetus. Therefore, an assessment of fetal blood flow through the umbilical cord by ultrasound color Doppler sonography has proven to be a valuable noninvasive procedure for assessing fetal well-being during pregnancy.

Chapter 8 : Placenta - Wikipedia

Ncx1 âˆ'/âˆ' Embryos Document the Emergence of Definitive Hematopoietic Cells in the Placental Vasculature in the Absence of Circulation To verify whether the HSCs found in the placenta are generated in situ or are merely imported via circulation we utilized the Ncx1 knockout mouse model.

Structure[edit] Blood from the placenta is carried to the fetus by the umbilical vein. In humans, less than a third of this enters the fetal ductus venosus and is carried to the inferior vena cava , [2] while the rest enters the liver proper from the inferior border of the liver. The branch of the umbilical vein that supplies the right lobe of the liver first joins with the portal vein. The blood then moves to the right atrium of the heart. In the fetus, there is an opening between the right and left atrium the foramen ovale , and most of the blood flows through this hole directly into the left atrium from the right atrium, thus bypassing pulmonary circulation. The continuation of this blood flow is into the left ventricle, and from there it is pumped through the aorta into the body. Some of the blood moves from the aorta through the internal iliac arteries to the umbilical arteries , and re-enters the placenta , where carbon dioxide and other waste products from the fetus are taken up and enter the maternal circulation. In the fetus, there is a special connection between the pulmonary artery and the aorta , called the ductus arteriosus , which directs most of this blood away from the lungs which are not being used for respiration at this point as the fetus is suspended in amniotic fluid. Placenta The circulatory system of the mother is not directly connected to that of the fetus, so the placenta functions as the respiratory center for the fetus as well as a site of filtration for plasma nutrients and wastes. Water, glucose, amino acids, vitamins, and inorganic salts freely diffuse across the placenta along with oxygen. The uterine arteries carry blood to the placenta, and the blood permeates the sponge-like material there. Oxygen then diffuses from the placenta to the chorionic villus, an alveolus -like structure, where it is then carried to the umbilical vein. Diagram of the human fetal circulatory system. The heart and blood vessels which form the circulatory system , form relatively early during embryonic development, but continue to grow and develop in complexity in the growing fetus. A functional circulatory system is a biological necessity, since mammalian tissues can not grow more than a few cell layers thick without an active blood supply. The prenatal circulation of blood is different than the postnatal circulation, mainly because the lungs are not in use. The fetus obtains oxygen and nutrients from the mother through the placenta and the umbilical cord. About half of this enters the fetal ductus venosus and is carried to the inferior vena cava , while the other half enters the liver proper from the inferior border of the liver. In the fetus, there is an opening between the right and left atrium the foramen ovale , and most of the blood flows from the right into the left atrium, thus bypassing pulmonary circulation. The majority of blood flow is into the left ventricle from where it is pumped through the aorta into the body. Adaptation to extrauterine life At birth, when the infant breathes for the first time, there is a decrease in the resistance in the pulmonary vasculature, which causes the pressure in the left atrium to increase relative to the pressure in the right atrium. This leads to the closure of the foramen ovale , which is then referred to as the fossa ovalis. Additionally, the increase in the concentration of oxygen in the blood leads to a decrease in prostaglandins , causing closure of the ductus arteriosus. The vessels or cross-connections remain open patent , leading to the following conditions:

Chapter 9 : Fertilization and Placenta

Patients with preeclampsia display evidence of the inflammation and endothelial dysfunction associated with oxidative stress in the circulation, vasculature, and placenta. We hypothesized that MPO levels in the circulation and placental extracts from women with preeclampsia would be greater than levels in women with normal pregnancies.

This means that while some scientific descriptions are still accurate, the terminology and interpretation of the developmental mechanisms reflect the understanding at the time of original publication and those of the preceding periods, these terms and interpretations may not reflect our current scientific understanding. No component of the endometrium illustrates this progression more strikingly than does the vasculature. Much of the story of uterine vascular pattern and circulatory mechanism is based upon studies in the rhesus monkey, employing in vivo techniques inapplicable to clinical patients. Following the menstrual slough the vasculature regenerates pari passu with the endometrial stroma and glands Fig. Initially a long capillary network forms between the stumps of spiral arteries in the basalis and the epithelial surface. Subsequently, muscular and elastic layers forming around the capillaries transform them into true arteries. Indeed, vascular growth during the lutein phase outstrips stromal growth, so that the increasing length of the arteries must be accomodated within the endometrium by ever increasing coiling Fig. Camera lucida drawings of the vascular bed at three stages of the menstrual cycle in the rhesus monkey. Reprinted with permission from Bartelmez. This meanwhile has itself been enlarged and transformed by the development of chorionic villi Fig. Reconstructions of representative uteroplacental arteries, both human and monkey, at comparable stages of gestation Fig. The coiling of the arteries continues and there is just a slight indication of a new process at the arterial tips where trophoblast is beginning to replace normal wall structure. Soon however a change does become manifest. Arterial elongation as determined by careful micromeasurements is continuing, but the thickness of the endometrium is being diminished as the result of trophoblastic erosion combined with pressure of the overlying conceptus. Thus, the previously vertical arterial stems are diverted toward the margins of the implantation site, an increasingly sharp angulation developing. A terminal dilatation of the artery develops proximal to its point of entry into the intervillous space. Photomicrograph of an early human implantation. Carnegie Collection , 7th day of pregnancy, section Reprinted with permission from Hertig and Rock. The coils are more fully smoothed away in the monkey than in man, probably because monkey endometrium undergoes the greater stretching. Photomicrograph of a portion of a monkey placenta in situ. Chorionic plate above; entrance of an endometrial spiral artery into the intervillous space at the left. Carnegie Collection C, 29th day of pregnancy, section 47b. The terminal dilatations of arteries communicating with the intervillous space appear to be the result of the weakening of the vessel wall brought about by replacement of muscle and elastic tissue by trophoblast. The invasion is earlier in the monkey and baboon than in the human, but it is deeper and more extensive in the latter. Human cytotrophoblast penetrates the endometrial stroma as well as entering the arterial lumen and invasion of the wall proceeds from without as well as from within Fig. The more drastic elimination of normal vascular wall resistance in man doubtless occasions the larger and more persistent terminal dilatations of human uteroplacental arteries. A further result of greater trophoblastic activity in the human is the erosion of arteries all the way to the midendometrium where branches arise from the main spiral stems. These branches then communicate with the intervillous space which explains why there is a proportionately greater number of arterial entries in humans than in monkeys. Upon occasion the trophoblastic action, in contrary fashion, may cause occlusion of branches or even main arterial stems. The basic venous pattern in the endometrium is a grid with dilatations into venous lakes at the junction of vertical and lateral limbs. These relationships continue into pregnancy with certain of the vertical channels increasingly distended as they are required to accommodate the ever increasing volume of placental blood. Other channels are passively obliterated by external compression. On the physiological side there is again continuity between prepregnant and pregnant states. From the standpoint of circulation, this is most apparent in the persistence of an intrinsic contractile potential in the spiral arteries. The opposite number to uteroplacental circulation is of course fetoplacental circulation. Propelled by the vis a tergo of fetal blood

pressure, fetal blood courses through the umbilical arteries into the subdivisions which run laterally through the chorionic plate. Finally, the vessels dip into the substance of the placenta and travel through the arborizations of the fetal villous tree. There the fetal capillary bed, coming into its closest proximity to maternal blood in the intervillous space, forms the ultimate area of matemalfetal exchange. Oxygenated blood returns via vessels running through the same villous stems to the umbilical vein and thence to the fetal body Martin and Ramsey, Maternal Placental Artery Remodelling.