Maternal Uterine Vascular Remodeling During Pregnancy

Sufficient uteroplacental blood flow is essential for normal pregnancy outcome and is accomplished by the coordinated growth and remodeling of the entire uterine circulation, as well as the creation of a new fetal vascular organ: the placenta. The process of remodeling involves a number of cellular processes, including hyperplasia and hypertrophy, rearrangement of existing elements, and changes in extracellular matrix. In this review, we provide information on uterine blood flow increases during pregnancy, the influence of placentation type on the distribution of uterine vascular resistance, consideration of the patterns, nature, and extent of maternal uterine vascular remodeling during pregnancy, and what is known about the underlying cellular mechanisms.

The clinical relevance of maternal uterine vascular adaptation during pregnancy is underscored by the fact that its aberrance is associated with several common gestational pathologies, including intrauterine growth restriction, gestational diabetes, and preclampsia.

In addition to the changes in vessel structure, uterine vascular reactivity is also altered during pregnancy, with the general pattern being one of reduced tone and enhanced vasodilation/blunted vasoconstriction (52, 72, 111, 112, 118). Space limitations preclude in-depth consideration of the ionic and enzymatic mechanisms that underlie reactivity, but it is worth noting that, in vivo, uterine vascular resistance (and, therefore, blood flow) is ultimately determined by the combination of vessel size and reactivity.

We also avoid examining the complex angiogenic mechanisms associated with implantation and placentation, other than to consider how hemochorial vs. epitheliocorial placentation influences uterine hemodynamics and vascular remodeling. Although the remodeling of spiral arteries by fetal trophoblast is considered, the main focus of this review is on upstream maternal uterine arteries and veins, since the processes involved in their remodeling have not been reviewed to date. Readers interested in endovascular trophoblast invasion and mechanisms underlying spiral artery remodeling are referred to several reviews on this subject (9, 31, 70, 101).

Nomenclature Used to Describe Vascular Remodeling

Circumferential remodeling is normally termed inward or outward to denote narrowing vs. widening of the vessel lumen. The term expansive remodeling has also been used and can be substituted for "outward" in describing an increase in circumference.

This classification was proposed by Mulvany (86) and is further refined to include consideration of wall mass, which can increase (hypertrophy), decrease (hypotrophy), or remain unchanged (euthrophy). Various patterns of arterial remodeling are shown in FIGURE 1, see legend for additional detail and for consideration of how changes in cross-sectional area, a two-dimensional quantity (e.g., μm²), relate to changes in wall mass, a three-dimensional quantity (e.g., μm³).

Uterine Hemodynamics During Pregnancy: Blood Flow Patterns and the Importance of Placentation Type

Uterine vascular anatomy

An overview of comparative uterine vascular anatomy is presented in FIGURE 2, which describes and illustrates the uterine circulation in humans (FIGURE 2A), rodents (FIGURE 2B), and ungulates, such as sheep and pigs. Please see legend for additional detail.

Uterine and placental blood flow during pregnancy

Early (1953–1960) human studies by Assali et al (3, 4) and Mercalle (78) utilizing the diffusion equilibrium principle (most often nitrous oxide, N₂O) or electromagnetic flow probes placed directly on the uterine artery reported that total uteroplacental blood flow (UPBF) increases from a baseline value of 20–50 ml/min to 450–800 ml/min in singleton pregnancies, with values in excess of 1 l/min measured in twin pregnancy. Subsequent measurements of uterine artery blood flow with 133Xe (106), placental metabolic clearance rate techniques (29), and most recently and directly transvaginal Doppler ultrasonography (96) support these early findings. For example, in the normal singleton pregnancy, blood flow averages 575 ml/min, total maternal blood flow is 750 ml/min, with the remaining estimate made from calculations of maternal cardiac output and placental extraction.

In experimental animal models, the changes of uterine blood flow during pregnancy have been reviewed to date. Readers interested in endovascular trophoblast invasion and mechanisms underlying spiral artery remodeling are referred to several reviews (9, 31, 70, 101). Since blood flow is regulated by arterial and venous pressure differences, the arterial blood pressure is somewhat lower, but the venous pressure is lower in sheep (112) than in primates such as rabbits and mice, and the venous pressure is lower in primates than in sheep. The influence of placental type on uterine blood flow has been examined in several species (86), indicating the importance of placental type on uterine hemodynamics. The influence of placental type on uterine blood flow has been examined in several species (86), indicating the importance of placental type on uterine hemodynamics.

Influence of uterine vascular remodeling on pregnancy outcome

Mice, rats, guinea pigs, and sheep are used as models of hemochorial placentation, presumably to avoid the complications inherent in studying the human or nonhuman primate. The role of hemochorial endovascular remodeling in pregnancy outcome has been studied in these species, with the exception of the rat. The role of hemochorial endovascular remodeling in pregnancy outcome has been studied in these species, with the exception of the rat. The role of hemochorial endovascular remodeling in pregnancy outcome has been studied in these species, with the exception of the rat.
Example, in the latter study, unilateral uterine artery blood flow at week 36 was calculated to be 353 ml/min; total UPBF would therefore be in excess of 700 ml/min, with some additional increase likely in the remaining few weeks of gestation (the authors’ estimate was 921 ml/min).

In experimental animals such as rodents or sheep, relative changes in UPBF are equal to or greater than those of humans, with increases in flow at term ranging from 10- to 100-fold above nonpregnant levels (6, 10, 15, 26, 37, 38, 44, 48, 56, 62, 112).

Since blood pressure normally decreases or is unchanged during pregnancy, uterine hemodynamic changes are principally affected by a profound decrease in uterine vascular resistance. This is accomplished by several different but complimentary mechanisms, including circumferential structural enlargement of the entire uterine vascular tree (including the veins), a reduction in vascular tone (vasodilation), and the creation of the placenta. From a systemic standpoint, increases in UPBF are facilitated by the combination of a substantially increased cardiac output and an expanded vascular volume that are characteristic of gestation in every species studied (129).

In humans (4, 127) and guinea pigs (6), the increase in UPBF is gradual and fairly linear, whereas in the rat, which has a 22-day gestation, increases in total uterine blood flow are first detectable on or around day 15, i.e., the last “trimester” of gestation (26). A similar pattern of augmented flow in the last trimester has been reported in sheep (112). Moreover, as pregnancy advances, there is a progressive increase in the proportion of blood directed to the placenta. This was shown by Dowell and Kauer in the rat (26), where <10% of uterine blood flow was placental on day 15 of pregnancy, near term (day 22), the value increased to 90%. Similar estimates have been made in sheep (112) and primates (65).

Absolute blood flow to the myometrium increases in proportion to uterine mass, whereas relative uterine blood flow (milliliter per minute per 100 g of tissue, excluding the placenta) may fluctuate and decrease somewhat (6, 112, 137) or remain fairly constant (26, 37) during pregnancy.

Influence of placental on distribution of uterine vascular resistance and blood flow

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both maternal and fetal blood flow through small vessels that are separate from but in close apposition to one another. The site of gaseous and nutrient exchange is therefore the intervillous space, which is lined by trophoblastic cells and, because of the greater resistance inherent in this anatomical arrangement and an increase in the number of cell layers (4 to 6) separating the two circulations, the inflow pressure to an epitheliochorial placenta is significantly higher than that of a hemochorial placenta, e.g., >80 mmHg in the ewe (81). Also, epitheliochorial placentation is less efficient than the hemochorial type (83), which may explain why UPBF in ungulates such as sheep and pigs is relatively higher than that of humans or rodents, with values in excess of 1 l/min reported in studies with sheep (312) and pigs (37). Thus differences in the type of placentation have a major influence on the pattern of afferent (arterial) remodeling and on the pressure head of blood as it enters the placenta.

FIGURE 2. Comparative anatomy of the uterine circulation in humans, rodents, and ungulates. In most mammals, including humans (A), blood is delivered to the uterus bidirectionally via a dual arterial anastomotic loop in which one end (the two ovarian arteries) originates from the aorta and the other (uterine arteries) from the internal iliacs. Unlike the linear, branching pattern of many vascular networks in which blockage leads to downstream ischemia, this bilateral anatomical arrangement provides the uterus with a dual source of blood and considerable redundancy in case of occlusion. Perpendicular vessels arise from the main utero-ovarian arteries and pass into the body of the uterus to form the arcuate arteries, which encircle the organ by coursing within a wall just beneath its serosal (outer) surface; vessels from each side Anastomose along the uterine midline. Smaller radial arteries (see inset) emanate from the arcuates and penetrate the myometrium centripeta]ly before ramifying into either straight (basal) or coiled (spiral) arteries at the myoendometrial border. The basal vessels spread to form a network along the myoendometrial border, while the spiral arteries penetrate further into the endometrium and terminate close to the uterine lumen in capillaries that are, in turn, drained by venules that coalesce into larger veins that eventually enter the inferior vena cava (not shown). Rodents (B) have a duplex uterus, with the main utero-ovarian (or parametrial) arteries and veins running parallel to, but well outside of, the uterine wall within a planar sheet of connective tissue called the mesometrium (shown by tan shading). The vessels of the mesometrium are perfused by arterial blood coming from either the uterine or the ovarian end; i.e., with bidirectional flow. Secondary vessels analogous to the arcuate arteries in humans may form redundant loops with the main artery, and tertiary radial arteries connect the arcuate loops with the uterine wall. These radial (also called mesometrial or segmental) arteries can be further categorized based on their destination as being either premyometrial or preplacental. The premyometrial radial arteries enter the uterine wall between placenta tion sites and ramify into an intradetrusor arterial plexus that supplies the myometrium, whereas preplacental radial vessels begin before entering the placenta through a process of endovascular trophoblast invasion. In addition to displaying distinctive patterns of remodeling during gestation, premyometrial vs. preplacental arteries have also been shown to have different patterns of reactivity (see text). In ungulates such as the sheep or pig, the main (middle) uterine artery originates from the umbilical branch of the internal iliac artery and divides into four primary branches that anastomose with contralateral vessels along the lesser curvature of the uterine horn. These vessels give rise to coiled, branching vessels that run along the ventral and dorsal surface of the uterus to form the arcuate arteries, with smaller branches (radial arteries) that penetrate the myometrium and terminate in arterioles within the endometrium. Most notably, whereas humans and rodents exhibit a hemochorial type of placentation (having low resistance), the placenta of sheep and pigs is epitheliochorial and therefore more analogous to a true microcirculatory bed. In humans, as well as other species (e.g., sheep, pig, rat, guinea pig), the uterus is drained by a venous system that parallels the arterial tree, with closely apposed arteries and veins.

Pattern, Nature, and Extent of Uterine Vascular Remodeling During Pregnancy

Pattern of circumferential remodeling and changes in vessel cellular properties

During pregnancy, the diameter of the main uterine artery approximately doubles in size in humans (95). This finding is supported by a host of published studies using sheep, pigs, guinea pigs, and rats, where uterine artery diameters also generally increase two- to threefold (2, 45, 46, 55, 75, 78, 83, 99, 132, 133). This expansion in arterial caliber occurs most often with little or no thickening of the vascular wall (2, 87), with the one apparent exception being the mouse, where media thickness increased significantly during the course of gestation (132, 134). With or without wall thickening, the increase in lumen diameter nevertheless results in an increased perfusion pressure head of blood as it enters the placenta.

Smaller arteries that display similar patterns of remodelling have a lumenal caliber of 25 to 50 μm (2, 45, 74, 80, 81). In one study, microangiography from precollagenase-treated uteri revealed a branching vascular network similar to that of the human uterine vasculature (116). This vascular network is built upon a system of arterioles and venules that form a series of loops originating from the interlobular arteries. In addition, these arterioles and venules form a terminal capillary network that is essential for the exchange of gases and nutrients across the uterine wall. The terminal capillary network is composed of small blood vessels that ramify within the myometrium and terminate in capillaries that are, in turn, drained by venules that coalesce into larger veins that eventually enter the inferior vena cava (not shown). Rodents have a duplex uterus, with the main utero-ovarian (or parametrial) arteries and veins running parallel to, but well outside of, the uterine wall within a planar sheet of connective tissue called the mesometrium (shown by tan shading). The vessels of the mesometrium are perfused by arterial blood coming from either the uterine or the ovarian end; i.e., with bidirectional flow. Secondary vessels analogous to the arcuate arteries in humans may form redundant loops with the main artery, and tertiary radial arteries connect the arcuate loops with the uterine wall. These radial (also called mesometrial or segmental) arteries can be further categorized based on their destination as being either premyometrial or preplacental. The premyometrial radial arteries enter the uterine wall between placenta tion sites and ramify into an intradetrusor arterial plexus that supplies the myometrium, whereas preplacental radial vessels begin before entering the placenta through a process of endovascular trophoblast invasion. In addition to displaying distinctive patterns of remodeling during gestation, premyometrial vs. preplacental arteries have also been shown to have different patterns of reactivity (see text). In ungulates such as the sheep or pig, the main (middle) uterine artery originates from the umbilical branch of the internal iliac artery and divides into four primary branches that anastomose with contralateral vessels along the lesser curvature of the uterine horn. These vessels give rise to coiled, branching vessels that run along the ventral and dorsal surface of the uterus to form the arcuate arteries, with smaller branches (radial arteries) that penetrate the myometrium and terminate in arterioles within the endometrium. Most notably, whereas humans and rodents exhibit a hemochorial type of placentation (having low resistance), the placenta of sheep and pigs is epitheliochorial and therefore more analogous to a true microcirculatory bed. In humans, as well as other species (e.g., sheep, pig, rat, guinea pig), the uterus is drained by a venous system that parallels the arterial tree, with closely apposed arteries and veins.
an increased cross-sectional area; thus the pattern of circumferential remodeling is outward hypertrophic. Smaller arcuate and radial arteries remodel in a similar pattern, with documented enlargements in luminal caliber ranging from 25 to 220% and with either no change or an increase in wall thickness (20, 21, 41, 74, 80, 91, 97, 119, 120).

In one study on human myometrial radial arteries from preeclamptic women (94), the pattern of remodeling was reported to be one favoring a smaller lumen and a thicker wall, with no change in cross-sectional area, suggesting rearrangement of existing wall elements around a smaller lumen, i.e., inward eutrophic remodeling. Since the media occupies the greatest proportion of the wall, luminal enlargement would be accomplished most simply by an increase in vascular smooth muscle cell length (axial hypertrophy), and this does indeed appear to be the case: e.g., unstimulated smooth muscle cell length in arcuate vessels from pregnant vs. virgin nonpregnant rats was increased by 28% in rats (20). In guinea pigs (48), smooth muscle cell length increased from 21 to 39 μm (80%), along with a comparable increase in cellular thickness (from 4.6 to 9.6 μm, or 108%). Morphometric measurements also suggest that elongation of vascular smooth muscle cells occurs in sheep (2). Surprisingly, no human data are available, although hypertrophy of myometrial smooth muscle is well established (e.g., Ref. 11).

In the main uterine artery of the sheep, vascular smooth muscle mass and protein content (including actin and myosin) doubled during pregnancy, with a corresponding (twofold) increase in cell volume (2). These changes in smooth muscle ultrastructure are associated with an increased force-generating ability (stress) per cross-sectional area, suggesting that the concentration of the contractile proteins (myosin and actin) may also increase. As noted by the authors, the magnitude of the increase in stress exceeded the magnitude of the increase in protein content, suggesting the existence of other mechanisms that augment force production, for example, changes in myosin duty cycle or force generation per stroke.

In addition to cellular hypertrophy, there is also strong evidence for hyperplasia within the vascular wall, since increased rates of smooth muscle cell division have been reported in uterine arteries and veins from rats and guinea pigs (20, 21, 47, 56, 57, 98). Although endothelial hyperplasia has been documented in the rat (20), changes in endothelial hypertrophy (increased cell area or mass) have not yet been detailed and await further study.

Changes in vessel biophysical properties

The biomechanical properties of uterine vessels also change significantly during pregnancy. In an early (1986) study by Gitendjing et al. (45), the incremental passive elastic modulus, which measures the relationship of stress to strain, increased from 4 to 29 dyn/cm² in main uterine arteries from near-term pregnant vs. nonpregnant sheep. Since this is essentially a stress-to-strain ratio, higher values indicate a less compliant material, and the authors interpreted their data as being indicative of increased arterial stiffness (decreased compliance). In the same study, however, arterial distensibility as a function of pressure was clearly increased, and this finding is consistent with other reports of increased distensibility of main uterine arteries from pregnant guinea pigs (56, 75). In rats, smaller arcuate and radial arteries are also more distensible than those from their nonpregnant counterparts (97, 98), and, in the rabbit, preplacental radial arteries were significantly more distensible than premyometrial vessels (21). In a different study, the distensibility of the main uterine vein was also increased in the rat, and associated with reduced elastin content (98).

Most commonly, changes in compliance are attributed to alterations in extracellular matrix volume, composition, and collagen and elastin fiber orientation. Some species differences may exist in this regard. In main uterine arteries from sheep (45) and pigs (46), collagen content decreased significantly, with no change in elastin; hence, the collagen-to-elastin ratios (presumably upstream uterine arteries, location not defined). In rats, we measured decreased elastin content in the uterine vein (collagen was not measured), and this correlated with significantly increased circumferential distensibility (98).

Spatial and temporal considerations: trophoblast invasion of spiral arteries

The time course and pattern of remodeling may also be specific to vessel size and location and may vary with species. For example, the results of one study in rats suggest that remodeling may begin in the smaller vessels proximal to the sites of placentaion or uterine wall and then, as pregnancy progresses, proceeds to the larger, more upstream vessels (20). This observation is based on the mitotic rates of vascular smooth muscle and endothelial cells, which were highest in smaller vessels in mid-pregnancy (day 16/22) and in larger upstream vessels later in gestation (day 20/22) and is consistent with the concept of trophoblast invasion of spiral arteries immediately proximal to the placenta initiating the remodeling process (9, 71, 101). Corroborative evidence can be found in other papers using guinea pigs as the experimental animal of choice (56, 124).

In addition to the influence of gestational age and species on the nature and extent of remodeling, differences in remodeling patterns have been noted in vessels of different size, type, and location. For example,
preplacental vessels enlarge more than premyometrial arteries in rabbits (21) and rats (41, 47) and may also show significant differences in rates of cell division, diastensibility, and reactivity. A photograph of a premyometrial vs. preplacental radial artery in the rat is shown in Figure 3 to illustrate the differences in structure.

As can be seen, mesometrial preplacental vessels widen progressively as they approach the placenta and may be several-fold wider at their distal vs. proximal ends. These changes are especially dramatic in the guinea pig, with thereafter increases in circumference (or diameter) occurring along the length of a single vessel during pregnancy. Guinea pig preplacental arteries show 50-fold increases in mass and 30-fold increases in nuclear DNA in addition to substantial changes in collagen breakdown (80). Fragmentation of elastic tissues and transformation of cellular wall constituents into a necrotic, homogenous, acellular fibrinoid was also noted (79), as reported in human spiral arteries as well (8, 105). Differences in the diameter along the length of the main uterine artery have also been noted, at least in the guinea pig, with a pattern of widening at each end (92). Localized differences in structure may be related to different rates of stress, a mechanism likely involved in the expansive remodeling process, as described below in Shear stress and NO.

Differences in the structure of spiral arteries immediately proximal to the placenta are normally assessed to the trophoblast invasion that occurs in association with placentation. In this unique endovascular process, fetal trophoblast cells migrate into the arterial lumen, ablate the endothelium and smooth muscle of the arterial wall, and reorganize the matrix elements (1, 7, 9, 14, 22, 31, 48, 71, 101). The involvement of other cell types, such as natural killer (NK) cells, is a type of lymphocyte, is also likely to play a role in placental and spiral artery invasion and remodeling (28, 115) and has been implicated in the development of preeclampsia (42, 116). This process of endovascular invasion in vessels that completely lose their ability to contract (41) and on a trumpet-like, splayed shape further decreases resistance and facilitates an increase in flow. Several studies have implicated a reduction in the depth and extent of this process in the genesis of hypertension associated with preeclampsia (9), suggesting that insufficient spiral artery remodeling leads to placental ischemia, triggering the release of placental signals that increase maternal blood pressure to provide more driving force (a higher perfusion pressure) for UPBF.

Axial (longitudinal) remodeling of uterine arteries

In humans, elongation (axial growth) of accreting arteries must occur as the uterus enlarges circumferentially to accommodate the fetoplacental unit. In women, it is not clear whether this is accomplished by actual longitudinal growth or by progressive straightening of coiled vessels. Tortuosity is characteristic of the human uterine vascular anatomy (32, 33), and there are no studies that have attempted to differentiate between vessel straightening due to altered mechanical forces and true growth, which would involve cell division and an increase in wall mass.

In rodents that bear young rat and mouse, significant axial growth of the main uterine artery is clearly evident, and the length of the main uterine-ovarian artery at term is double or triple that of the nonpregnant state in the rat. The guinea pig, which only gives birth to several young and has a much longer gestation than the mouse or rat (55 vs. 20 and 22 days, respectively), exhibits comparable elongation of the main uterine artery (92).

Rat and guinea pig mesometrial (arcuate and radial) vessels elongate as well, increasing three- to five-fold in length (80, 97). These measurements were made in the unstretched and unstressed state and thus reflect true increases in vessel mass. Taking both circumferential and axial remodeling into account, the actual increase in uterine artery wall mass in the rat is quite substantial, on the order of 300-700%, based on available measurements.

It is interesting to consider the influence of circumferential vs. axial remodeling on uterine hemodynamics, since increases in length would have opposite influences on resistance from those of increased diameter. With an approximate doubling of each parameter, as has been noted in several studies, the effect of widening of the vessel, whereas the increase in wall mass will decrease resistance in vessels that have a larger diameter. Whereas the increase in resistance in vessels of increased diameter can be represented as per Poiseuille’s law with increased blood viscosity and the resistance due to wall 

where R is resistance, ΔP is pressure difference, and R is radius of the vessel. Thus, as the length and the diameter of the vessel change, resistance changes in vessels that show increases in resistance due to changes in viscosity (111) and decreases in corresponding resistances due to changes that can result in increased flow to the placenta. Finally, axial growth makes it possible to accommodate the fetoplacental unit during pregnancy.

Remodeling during pregnancy

The process of remodeling of spiral arteries, since怀孕期螺旋动脉的重塑，may be more limited. Weaver et al. (59) found that the main uterine arteries of the pregnant guinea pig averaged 1,576±219 μm wide, along with a significant increase in wall thickness. Increased vascular remodeling is thought to be an adaptation to accommodate an increasing number of fetuses during pregnancy.

Mechanis of uterine vascular remodeling

The role of local uterine vascular remodeling in pregnancy

As pointed out above, vascular remodeling is not just a local process, but it is a complex process that involves at least four cells types. Each of these cells types secretes and interacts with factors such as prostanoids, sex steroids, hormones, and integrins. Interactions and outputs from the different cells types can lead to the changes in structure and function of the spiral arteries, including increased distensibility, increased reactivity, and increased resistance. The role of local uterine vascular remodeling in pregnancy is not well understood, and further research is needed to elucidate the mechanisms involved.
and smooth muscle cells to play a role in the process of uterine vascular remodeling that leads to the development of vasculature in the developing placental mass in the uterus. In women, expression of estrogen receptors for both estrogen and progesterone (66–68, 72, 73) has been investigated to date.

Mechanisms Underlying Gestational Uterine Vascular Remodeling

**The role of local vs. systemic influences on uterine vascular remodeling**

As pointed out by Poston and colleagues (55), vascular remodeling is an active process that is dependent on at least four cellular processes: growth, death, migration, and production/degradation of extracellular matrix. Each of these processes is subject to multiple regulatory and interactive influences, including physical forces such as pressure/stretch and shear stress, humoral/endothelial influences such as VEGF and the sex steroids, and local factors generated within the vascular wall, e.g., endothelial NO, angiotensin, and endothelin. Multiple linkages between cellular inputs and outputs further complicate understanding the precise mechanisms involved. For example, VEGF, estrogen, and shear stress all stimulate NO production, and both estrogen and NO regulate matrix metalloproteinase activity and, hence, passive mechanical properties and matrix composition (27, 43, 103).

In addressing the question of how uterine vascular remodeling is accomplished during pregnancy, one might first consider whether this process is due to the influence of local factors (e.g., those associated with implantation, placentation, and fetal growth), to systemic changes in hormonal levels, particularly those of estrogen and progesterone, or a combination thereof.

Three different experimental approaches have been utilized to investigate this concept. Induction of pseudopregnancy (in animals such as the rat and rabbit that are induced ovulators), hormone replacement in oophorectomized animals to mimic the steroid milieu of the pregnant state, and surgical ligation of (and, thereby, restriction of implantation to) one uterine horn in animals that have duplex uteri, such as the rat and rabbit.

**Pseudopregnancy.** In animals that are induced ovulators, sexual stimulation induces endocrine changes similar to those of pregnancy (pseudopregnancy), at least for the first half of gestation. Circulating estrogen and progesterone levels increase progressively during this time, allowing the evaluation of their influence without the complicating presence of fetoplacental units.

Peeters’ group from Maastricht explored this question in mice (34) and reported that pseudopregnancy resulted in a 25% increase in main uterine artery lumen radius and a 71% increase in cross-sectional area on day 11 of pseudopregnancy. Structural changes were accompanied by reduced smoothelin expression and an increased proliferation of uterine artery medial smooth muscle cells. The effects of pseudopregnancy paralleled changes in control pregnant animals at 5 days and were about half as large as those measured in pregnant animals on day 11.

These data support the idea that placental and ovarian steroids may initiate the process of circumferential remodeling, which then becomes more dependent on local (fetoplacental) factors as pregnancy progresses. Interestingly, despite early arterial enlargement, increases in UPBF are quite modest, or absent, until much later in normal pregnancy (26), perhaps because changes in length (not documented in the Peeters’ study) counteract those of increasing diameter. In addition, there may be an increased level of tone that maintains resistance and prevents an increase in blood flow, neither of these possibilities has been investigated to date.

**Hormone replacement.** Uterine arteries contain receptors for both estrogen and progesterone (66–68, 72, 73) and respond to these steroids via genomic and non-genomic mechanisms. Most attention has been directed at estrogen, especially in sheep (by Rosenfeld and Magnes, e.g., Refs. 72, 73, 111, 112), since its injection results in both acute and chronic increases in...
uterine blood flow related to vasodilation and increased cardiac output (19), and its in vitro application to isolated vessels induces vasoconstriction, albeit in concentrations that are several orders of magnitude higher than those present in vivo. Daily injections of estradiol benzoate (7–11 μg) for 3 wk induced a greater than twofold increase in the internal diameter of segmental mesometrial arteries of ovariectomized guinea pigs (85). Exogenous estradiol treatment in guinea pigs also stimulated DNA synthesis within the uterine artery (74) and increased cellular responsiveness to growth factors such as platelet-derived growth factor (PDGF) by a PKC-dependent mechanism (57). This latter study used isolated vascular smooth muscle cells from the guinea pig uterine artery and reported that cells from the uterine artery, but not the aorta of pregnant animals, showed enhanced spontaneous DNA synthesis and growth. Changes in pseudopregnancy (134), already discussed, are presumably due to an altered endocrine profile and, although more modest than those that occur during pregnancy, are nonetheless measurable and significant.

Exactly how estrogen increases arterial size is not known. Its actions may be indirect, via augmentation of endothelial NO synthesis (58, 59) since nitric oxide (NO) has been implicated in outward circumferential remodeling (96, 142) and by the induction of uterine artery vasodilation (123). Along with progesterone, it is also an important determinant of growth factor secretion, e.g., VEGF (50), and is known to affect matrix metalloproteinase (MMP) activity and arterial biomechanical properties (138, 139).

It thus appears that steroids promote uterine vascular remodeling through their modulation of numerous cellular processes associated with vascular contractility, growth, and matrix deposition. The reader is referred to a recent review by Chang and Zhang, which provides an excellent summary of steroidal influences on uterine vascular adaptation to pregnancy (19).

Unilateral horn ligation. In animals with duplex uteri, especially rodents, the two horns are physically separate so that one horn can be made to remain barren either by ligating the cervical end (which prevents the passage of sperm) or by tying off the ovarian end (which prevents eggs from entering the uterine lumen), and both experimental approaches have been used.

The uterine horn ligation model has been used to explore a variety of pregnancy-related questions in several species, including the cow (35), pig (36, 60), rabbit (137), guinea pig (128), rat (136), and mouse (34), and the available evidence points to local rather than systemic factors playing a primary role in gestational uterine vascular remodeling and increases in blood flow.

In a rat model, this can be readily seen in the photographs shown in FIGURE 4, where the increase in arterial length is clearly apparent (also in diameter, although this parameter is more difficult to evaluate visually without higher magnification). Vessel dimensions in the nonpregnant horn were similar to those of a nonpregnant animal in terms of the length and diameter of both large and small arteries. Consistent with this, uterine vein size was found to be increased only in the pregnant horn with values from pregnant animals to that of nonpregnant controls.

Shear stress and vascular remodeling

Shear stress appears to be an important determinant of vascular growth (16, 17). This was established through the observation that vascular remodeling is extensive in a number of species, including the nonpregnant rat, since virtually all of the increase in uterine vascular dimensions can be obtained using a fluid-filled uterine cast to observe vascular remodeling in situ.

Elevation in vascular pressure decreases vascular resistance and thereby normalizes blood flow (and, therefore, uterine vascular resistance). Vascular relaxation increases vessel diameter and thereby normalizes blood flow (and, therefore, uterine vascular resistance).

Yet, the velocity of blood flow in the uterine arteries is 20 times faster than in the aorta (8.4 cm/s), and it is not possible to measure it in vivo. MCMC analysis indicates that it is not possible to measure shear stress in vivo, as it is not measurable due to the microscopic nature of the vessel lumen. Yet, in vivo measurements of shear stress are necessary to establish a cause and effect relationship between shear stress and vascular remodeling.

The molecular mechanisms by which shear stress promotes vascular remodeling are not well understood. Although several mechanotransduction pathways, including endothelial NO synthesis (58, 59) and shear stress-induced NOS-3 (or eNOS) induction by this parameter, have been suggested, direct evidence for the importance of shear stress in vascular remodeling is still lacking. However, one recent study demonstrated that shear stress was an important determinant of pulsatile blood flow regulation in uterine arteries (114, 115). This study found that shear stress was a major determinant of pulsatile blood flow in uterine arteries, and that changes in shear stress were associated with changes in pulsatile blood flow.

This study supports the hypothesis that shear stress is an important determinant of vascular remodeling in the uterine arteries, and provides evidence for the importance of shear stress in regulating pulsatile blood flow in these vessels.

In conclusion, shear stress appears to be an important determinant of vascular remodeling in the uterine arteries, and it is likely that this parameter plays a role in regulating pulsatile blood flow in these vessels.

FIGURE 4. Local mechanisms predominate in uterine vascular remodeling in the rodent A: photograph of a 20-day pregnant rat uterus in which one uterine horn was ligated at the ovarian end, preventing oocyte descent and fertilization. Thirteen fetalplacental units are present in the pregnant uterine horn (PH); the nonpregnant horn is at the bottom of the picture (NPH). CERV, cervix. B: the arterial vasculature of the specimen in A was infused with a latex casting compound and allowed to harden. Uterine and fetalplacental tissues were digested in KOH, leaving a cast of the arterial network. The main uterine arteries (MUA) and the mesometrial arteries (MESOM, arcuate, radial) are labeled, as are two small tree-like structures that represent the maternal intraplacental compartment typical of rodent hemochorial placentation (FL).
injections of estrogen, progesterone, and oxytocin. These stimuli induced a rapid increase in ascending uterine artery diameter and velocity. Indeed, the increase in uterine artery diameter is in proportion to increases in local eNOS activity and NO synthesis (23, 100). In a study that utilized NOS-3 knockout mice (132), the growth of the main uterine artery was less than that of wild-type animals but still significantly greater than that of nonpregnant controls, suggesting that mechanisms other than those linked to shear stress-induced endothelial NO release play a role.

NO production by guinea pig extravillous trophoblast has also been described (88), raising the possibility that NO production by extravillous trophoblast may migrate into the periarterial space and stimulate NO production by neighboring smooth muscle cells. NO may also be produced by decidua and the myometrium, although several recent studies have indicated that endothelial NO may be an important mediator of this process (114, 130–132). This observation is pertinent to uterine gestational remodeling in view of the well-established upregulation of eNOS and NO signaling in the pregnant state and is supported by several lines of evidence. First, both message and protein levels of NOS-3 (or eNOS), the enzyme responsible for NO production by the endothelium, are increased by shear stress, as is the release of NO (131). Accordingly, NO synthase activity and expression (91) and relaxation to acetylcholine (96) are augmented in uterine arteries from pregnant women. Second, mice lacking the gene for NOS-3 show a reduction in uterine vascular remodeling and decreased uterine blood flow (132). And third, chemical inhibition of NO production by NO inhibitors such as L-NAME virtually abolished the expansive remodeling of the main uterine artery and of smaller radial arteries in the rat, although, notably, axial growth was completely unaffected (96).

There is also some evidence against a role for NO in flow-induced arterial remodeling. Other studies (23, 100) have indicated that other cell types such as macrophages or trophoblast may migrate into the periarterial space and stimulate vasodilation and remodeling of both the arterial and venous wall through mechanisms linked to NO signaling. Although NO is the most likely candidate, the precise mechanism(s) by which shear stress stimulates NO release remains to be elucidated.

Yet, the velocity of blood in the uterine artery of women in week 36 of pregnancy was nearly eight times faster than in the nonpregnant state (averaging 61.4 vs. 8.4 cm/s), whereas arterial diameter increased approximately twofold (98). These data do not support normalization of shear stress, although, unfortunately, it is not possible to calculate vascular wall shear without knowing the actual velocity and viscosity of blood at the endothelial surface—a difficult proposition for a non-Newtonian fluid delivered in a pulsatile and sometimes non-laminar fashion.

The molecular mechanism(s) by which shear stress leads to circumferential vessel growth is not known, although several recent studies have indicated that endothelial NO may be an important mediator of this process (114, 130–132). This observation is pertinent to uterine gestational remodeling in view of the well-established upregulation of eNOS and NO signaling in the pregnant state and is supported by several lines of evidence. First, both message and protein levels of NOS-3 (or eNOS), the enzyme responsible for NO production by the endothelium, are increased by shear stress, as is the release of NO (131). Accordingly, NO synthase activity and expression (91) and relaxation to acetylcholine (96) are augmented in uterine arteries from pregnant women. Second, mice lacking the gene for NOS-3 show a reduction in uterine vascular remodeling and decreased uterine blood flow (132). And third, chemical inhibition of NO production by NO inhibitors such as L-NAME virtually abolished the expansive remodeling of the main uterine artery and of smaller radial arteries in the rat, although, notably, axial growth was completely unaffected (96).
including vimentin (117), and membrane-associated tyrosine kinases such as PYK2 (125).

Matrix metalloproteinases in gestational vascular remodeling. Matrix metalloproteinases (MMPs) play a vital role in matrix turnover and are, in turn, subject to regulation by both sex steroids and NO. For example, both estrogen and progesterone, alone and in combination, have been shown to modulate smooth muscle cell MMP gene and protein expression, matrix turnover, and deposition (43, 89). The activity of several MMPs is elevated in vascular tissues during pregnancy (55) and MMP levels, particularly those of MMP-2 and MMP-9, are altered in preeclamptic women (87, 104). This combination of regulation by gestational signals and a broad spectrum of actions on the structure of the vascular wall (e.g., matrix reorganization and composition, and smooth muscle cell migration) has established a central role for MMPs in vascular remodeling (77). The linkage between estrogen and MMP activity was already discussed above, and several reviews highlight our understanding of these processes in greater depth and consider the role they may play in pregnancy under physiological and pathological conditions (55, 104).

Other mechanisms (e.g., the renin-angiotensin system and altered VEGF/PlGF signaling) in uterine vascular remodeling. If elevated shear stress secondary to decreased downstream vascular resistance (due to placentalization) were the only stimulus for remodeling, one might not expect to see any remodeling in vessels that deliver blood to the myometrium. Yet, although the extent of remodeling of premyometrial radial arteries is less than that of preplacental vessels, at least in rats (41, 47), these arteries are still clearly larger and longer than those of age-matched nonpregnant animals. Thus it is likely that other mechanisms are involved in the remodeling process.

For example, the renin-angiotensin system may play a role in view of the association between angiotensin II and smooth muscle cellular hypertrophy (39), and one current theory of preeclampsia posits that, at least in some women, this disease may have a nonimmunological component related to the production of auto-antibodies directed at the AT-1 receptor (25, 108). Exposure to auto-antibodies extracted from the serum of preeclamptic women resulted in the development of a preeclampsia-like syndrome in pregnant mice, and this syndrome could be prevented by co-administration of losartan, an AT-1 receptor blocker, or by an antibody-neutralizing seven-amino acid epitope peptide (140). Although uterine vascular remodeling was not measured in this study, placental abnormalities and small fetus size were reported, and uterine blood flow is a well-documented feature of the human (113), and this syndrome could be prevented by co-administration of losartan, an AT-1 receptor blocker, or by an antibody-neutralizing seven-amino acid epitope peptide (140). The linkage between estrogen and MMP activity was already discussed above, and several reviews highlight our understanding of these processes in greater depth and consider the role they may play in pregnancy under physiological and pathological conditions (55, 104).

A related observation was made in a study by St-Louis et al. (119), who showed that administering a low-sodium diet, which is associated with over-activation of the renin-angiotensin system (113), to pregnant rats during the last third of gestation attenuated the normal increase in arcuate artery diameter by ~50%.

In contrast, although a recent study (135) describing a transgenic rat model with an overactivated renin-angiotensin system reported fetal growth restriction, impaired uterine artery endothelial relaxation, and hyposensitivity to the constrictor effects of phenylephrine, the arterial resistance index decreased during pregnancy compared with control pregnant animals, suggesting unimpaired uteroplacental flow in the uterine artery. Unfortunately, arterial remodeling was not evaluated directly, and the differentiation of large vs. small, or premyometrial vs. preplacental artery adaptations as contributing factors was not evaluated.

Changes in vasodilator influences may also occur. For example, a number of studies (12, 53, 61, 70, 121, 126) have implicated abnormal VEGF/PlGF (placental growth factor) signaling in preeclamptic women due to overexpression of a soluble receptor for VEGF/PlGF (called sFlt-1 or sVEGFR-1). Bats injected with an adenovirus that overexpresses sFlt-1 develop several features associated with preeclampsia (76), although direct evaluation of uterine blood flow or vascular remodeling, either in women or animals, has not been carried out to date. Growth factors of the VEGF family are appealing candidates for mediating this process since they induce vasodilation, stimulate endothelial mitosis, and are associated with hypervascularization
and enlargement of existing vessels (at least in the mouse ear; Ref. 93), but their role in uterine pregnancy-induced uterine vascular remodeling and of effects on different segments of the vasculature (e.g., mesometrial vs. intraplacental, large vs. small, and preplacental vs. preponderential arteries, or in arteries vs. veins) has not been defined.

Vascular remodeling as a pathway for arterial remodeling. That the molecular signal or signals that induce remodeling originate from the uterus or placenta is an intriguing idea, especially since the latter is a local organ known to be a rich source of vasoactive and growth-promoting molecular signals. Involvement of periplacental maternal tissues, e.g., the decidua, is also possible and has yet to be investigated. The principal question, however, is: How can molecules secreted into the uterine or placental venous effluent affect the structure (and/or tone) of the arterial (arterial)?

One mechanism that deserves mention is venoarterial transfer. Illustrated diagrammatically in Figure 5, it posits that secreted placentally- and/or myometrial signals (such as growth factors) pass across the uterine venous wall and thereby influence the structure of adjacent uterine arteries. Since growth factors such as VEGF and PGF are potent stimulators of vascular smooth muscle, this mechanism could also provide a short loop pathway for regulating placental perfusion by inducing changes in arterial tone.
still largely defined in descriptive rather than mechanistic terms. The authors gratefully acknowledge the research support of the National Heart, Lung, and Blood Institute (NIH R01 HL-07253) and HL-073895).

References


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