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 placenta 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 vasodilatation/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. epitheliochorial 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, 71, 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 (eutyrophy). 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 Mecalf (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 ¹³¹I Xe (106), placental metabolic clearance rate techniques (29), and most recently and directly transvaginal Doppler ultrasonography (99) support these early findings. For example, in the human, total blood flow at term has been reported to range from 700 ml/min, total uterine vascular resistance (TVR) varies widely from 0.5 to 6.0 units.

In experimental animals, the relative changes in uterine blood flow are similar to those observed in humans. For instance, in sheep (112), uterine blood flow is reduced by 10–30% during the last trimester, and uterine vascular resistance is increased by 10–30% during pregnancy. Absolute blood flow is increased by 30–50% in pregnant rats as compared with nonpregnant controls (23), and, in general, absolute uterine blood flow increases by 2–3 l/min during pregnancy in most species, with the exception of the rabbit (50). In this species, uterine blood flow is reduced by 5–10% during pregnancy.

Influence of uterine vascular resistance on placental hemodynamics

Mice, rats, guinea pigs, and rabbits have a hemochoiral type of placentation and the uterine circulation is essentially a true systemic vascular bed. In these species, hemodynamic changes in the uterine circulation are associated mostly with an increase in blood flow, while changes in uterine vascular resistance are relatively small.

In contrast, in sheep, cows, and mares, the uterine circulation is structured more like a true intraabdominal vascular bed, with the uterine circulation closely linked to the systemic circulation via the uterine veins. As a result, hemodynamic changes in the uterine circulation are associated with significant changes in uterine vascular resistance, as well as blood flow.

In primates, uterine blood flow is increased by 300–600 ml/min, total uterine vascular resistance is reduced by 10–40% during pregnancy, and uterine vascular resistance does not change appreciably during lactation.
Intravillous (human) or intervillous space must be kept low enough for the intervillous space to pass from the maternal to the fetal compartment, only two fetal cell layers (trophoblast and intravillous endothelium) need to be traversed. Conversely, in animals with epitheliochorial placentation such as sheep, the value increased to 90%. Similar estimates have not been carried out in humans, the values are likely similar, since a subsequent study by the same group showed that pressures within the spiral arteries of primates (Rhesus monkeys) were also quite low, ranging from 9 to 15 mmHg (84).

Mice, rats, guinea pigs, rabbits, and humans share a hemochorial type of placentaion, in which intraplacental pressure created by the maternal blood occupying the intervillous space must be kept low enough to avoid compression of the intervillous (human) or intralabyrinthine (rodents) fetal vessels, necessitating the contribution of significant resistance by upstream vessels (83).

To examine this concept directly, Moll and colleagues measured the blood pressure in premyometrial arteries in a number of species (guinea pig, rat, rabbit, sheep) under anesthetized conditions by direct arterial puncture (81, 82). A substantial pressure drop occurred in the arcuate and radial arteries of rodents, such that the arterial pressure of maternal blood entering the placenta in rats, rabbits, and guinea pigs was only 8–14 mmHg. Based on this finding, they determined that the majority of uterine vascular resistance was localized in the upstream vessels of the mesometrial arcade. Although comparable measurements have not been carried out in humans, the values are likely similar, since a subsequent study by the same group showed that pressures within the spiral arteries of primates (Rhesus monkeys) were also quite low, ranging from 9 to 15 mmHg (84).

Patterns of vascular remodeling

This drawing relates changes in lumen diameter and cross-sectional area to illustrate the various two-dimensional patterns of arterial remodeling (adapted, with permission, from R. H. Hilgers). The remodeling of a vessel to a larger lumen with the same wall thickness, such as occurs in the uterine circulation during pregnancy (white shaded box), is termed "outward hypertrophic," since cross-sectional area is increased. Conversely, vessel narrowing with increased wall thickness occurs in chronic hypertension and may be inward hypertrophic (smaller lumen with a somewhat thicker wall), but the same cross-sectional area, characteristic of smaller resistance arteries or inward hypertrophic (smaller lumen with sufficient wall thickening to increase cross-sectional area, characteristic of larger conduit vessels). A common assumption is that changes in cross-sectional area indicate changes in wall mass (as implied by the terms "hypertrophic" or "hypertrophic"). This, of course, is only correct if vessel length is not altered. Although changes in venous or arterial length rarely occur in the adult and are therefore rarely measured, the uterine circulation during pregnancy is one notable and pertinent exception since existing vessels do undergo considerable elongation, thereby increasing wall mass further. Thus changes in both cross-sectional area and axial length must be considered to evaluate true changes in mass.
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 between two microvasculatures 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 enucleate the organ by courting with each other just beneath the 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 centripetally before ramifying into either straight (basal) or coiled (spiral) arteries at the myoendometrial border. The basal vessels spread to form a network along the myometrial 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 placental sites and ramify into an intrauterine arterial plexus that supplies the myometrium, whereas preplacental radial vessels widen 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 arteries within the endometrium. Most notably, whereas humans and rodents exhibit a hemochorial type of placentation (having low resistance), the placentas 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, 65, 67, 75, 99, 132, 133). This remodelling in arterial caliber occurs most often with little or no thickening of the vascular wall (2, 97), 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 cross-sectional arterial area.

Smaller arteries show similar patterns of luminal caliber change, either no change (21, 41, 74, 80, 81), or remodeling with either lumen narrowing or widening (45, 99), from precircumferential to circumferential remodeling. In the rat, remodeling involves an increase in the cross-sectional area of the wall elements (21). In an additional study, the epitheliochorial placenta of the ewe exhibited substantial remodeling with an increase in the cross-sectional area (37).

Since the media thickness of the wall, luminal area, and wall thickness are all measured in two dimensions, the percentage increase in area (or cross-sectional area, if it involves an increase of this magnitude) can be calculated using the formula for the area of a circle: 

\[ \text{Area} = \pi r^2 \]

where \( \text{Area} \) is the area of the circle, \( \pi \) is the mathematical constant approximately equal to 3.14159, and \( r \) is the radius of the circle. The percentage increase in area for the uterine artery can be calculated as follows:

\[ \% \text{increase} = \left( \frac{A_{\text{new}} - A_{\text{old}}}{A_{\text{old}}} \right) \times 100 \]

\[ \% \text{increase} = \left( \frac{\pi r_{\text{new}}^2 - \pi r_{\text{old}}^2}{\pi r_{\text{old}}^2} \right) \times 100 \]

\[ \% \text{increase} = \left( \frac{r_{\text{new}}^2 - r_{\text{old}}^2}{r_{\text{old}}^2} \right) \times 100 \]

or

\[ \% \text{increase} = \left( \frac{r_{\text{new}} - r_{\text{old}}}{r_{\text{old}}} \right) \times 100 \]

where \( r_{\text{new}} \) and \( r_{\text{old}} \) are the new and old radii, respectively.

Changes in the vasoactive state of the uterine arterial wall, since the existence of the existence of the vasoactive products, force generation is mediated by smooth muscle and involves the changes that occur in the contractile state of the smooth muscle cells of the arterial wall. Changes in the concentration of actin and myosin resulting from the change in tension within the cell (stress) is also associated with changes in the force generated by the cell. The force generated by the cell is proportional to the magnitude of the stress within the cell, the existence of the stress, the size of the cell, the existence of the force generated by the cell. In addition, the smooth muscle cells of the arterial wall may change in response to changes in the concentration of actin and myosin resulting from the change in tension within the cell (stress). These changes may be mediated by changes in the concentration of actin and myosin resulting from the change in tension within the cell (stress).

The biomechanical properties of the uterine arterial wall also change significantly during pregnancy, as has been documented by Gertler et al. (21). Rigidity and elasticity during Pregnancy
published studies where uterine 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 (23). 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 also increased in the rat, and associated with reduced elastin content (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 being an initiating event in the remodeling process (9, 71, 301). Corroboration 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, distensibility, 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 thencefold 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 shear 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 ascribed 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, 54, 71, 101). The involvement of other cell types, such as natural killer (NK) cells, 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 take 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 accuate 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 many 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).

Rad and guinea pig mesometrial (accuate and radial) vessels elongate as well, increasing three- to fivefold 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 is likely to overwhelm the widening of the lumen, whereas the attendant increases in resistance is presumably the result of an increased wall mass, which decreases lumen diameter theoretic resistance (as per Poiseuille’s law). Resistance is constant if blood viscosity (R) is inversely proportional to diameter squared. The main uterine artery in guinea pigs has an axial and distal radius of 0.86 and 0.59 mm, respectively, and the theoretical increase in resistance is 500%, assuming that the diameters increase by 100%.

Remodeling in response to pregnancy

The process of uterine arterial remodeling during pregnancy, since it is necessary for the uterus to accommodate the growing weight of the gestational sac and the fetoplacental unit, is the subject of many studies. The main uterine artery of both guinea pig and rabbit uteri increased more than two-fold in diameter (33, 54) during pregnancy. Mean diameter averaged 1.57 ± 0.3 mm during pregnancy vs. 0.7 ± 0.2 mm in nonpregnant rabbits (33), with a more than fourfold increase in the circumferential and axial remodeling of the main uterine artery (92).

Increased vascular resistance may reflect increased distensibility, adaptations to increase uterine blood flow resistance during pregnancy, and a reduction in axial growth.

Mechanisms of uterine vascular remodeling

The role of local humoral/endothelial factors in the process of uterine vascular remodeling is not entirely clear. Although there have been at least four cells types and dozens of factors described recently, it is generally accepted that local mechanotransduction is produced by such factors as pro-inflammatory cytokines, sex steroids, and cyclic nucleotides, among other factors. The local actions and outputs of these factors are complex and interact to alter uterine blood flow resistance during pregnancy.

As pointed out elsewhere (56), the remodeling of uterine arteries is not limited to the distal end vessels. In rodents, most uterine arteries undergo both circumferential and axial remodeling, whereas large arteries, such as the internal carotid, may remodel only circumferentially and with much greater changes in distensibility. The question of whether these differences in remodeling reflect differences in the local factors that stimulate remodeling or differences in the sensitivity of different vascular beds to the same factors remains unresolved.
Mechanisms Underlying Gestational Uterine 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/endothelium 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 ovariectomized animals to mimic the steroidal milieu of the pregnant state, and genetic engineering 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 feto-placental units. Peeters’ group from Maastricht explored this question in mice (134) 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 (feto-placental) factors as pregnancy progresses. Interestingly, despite early arterial enlargement, increases in UPBF are quite modest, or absent, until much later in normal pregnancy in rodents (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 prevent an increase in blood flow, neither of these possibilities has been investigated to date. Hormone replacement. Uterine remodeling contains receptors for both estrogen and progesterone (66-68, 72, 73) and respond to these steroids via genomic and nongenomic mechanisms. Most attention has been directed at estrogen, especially in sheep (by Rosenfeld and Magness, 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 vasorelaxation, 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, 112) 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 pregnancy side, with values from that side being greater than twofold higher than those from the nonpregnant side.

To determine the nature of this remodeling, the role of shear stress, as is then considered.

Physiological remodeling

Shear stress and uterine vascular remodeling. There is now significant evidence that shear stress plays a primary role in uterine vascular remodeling. Shear stress is elevated during pregnancy (102, 103), and this important determinant of vascular biology is also an important determinant of vascular biology and is known to affect matrix metalloproteinase (MMP) activity and arterial biomechanical properties (138, 139).

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 fetoplacental tissues were digested in KOH, leaving a cast of the arterial circulation of each horn. 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).
Potential mechanisms by which shear stress could influence uterine vessel growth during pregnancy include the increased blood flow as pregnancy progresses, changes in the uterine vascular bed, and increased production of nitric oxide (NO) due to shear stress. The velocity of blood in the uterine artery of pregnant females is nearly eight times higher than in nonpregnant controls (34). These changes in velocity are thought to be an effective stimulus for increasing the velocity of flow (and, therefore, shear stress) in upstream arteries. Accordingly, NO inhibitors such as L-NAME virtually abolished the augmentation of NO production by guinea pig extravillous trophoblast (88), raising the possibility that NO production by guinea pig extravillous trophoblast may migrate into the periarterial space and stimulate other cell types such as macrophages or trophoblast. Interestingly, despite the expansive remodeling of both large and small arteries during pregnancy, there is no significant increase in arterial diameter relative to that of nonpregnant controls (34). Physiological mechanisms of uterine vascular remodeling during pregnancy Shear stress and NO. Studies by Langille, DeMey, and others (5, 13, 16, 30, 63, 64, 69, 117) have firmly established that an increase in shear stress stimulates expansive remodeling of both large and small arteries in a number of vascular beds. Interestingly, despite the numerous signaling pathways that may contribute to flow-induced remodeling (16), although the focus of this paper was not on gestation, and observations were limited to the mesenteric circulation, which does not undergo expansive remodeling during pregnancy and may develop different, and sometimes even opposite, patterns of reactivity (23, 24). Differences in regional vascular responses have also been documented in other studies (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 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. A number of other signaling pathways have been implicated in flow-induced arterial remodeling (although not in the setting of gestational remodeling) including MMP activation (130), adrenergic influences (30), toll-like receptors (51), cytoskeleton (69), and PPAR-β (115). Figures 5. Venoarterial exchange Signals secreted from the placenta, decidua, or myometrium (due to stretch) pass into the venous effluent, where their concentrations would be highest before dilution into the systemic circulation. Signals may be molecules that are vasoactive, mitogenic, or hypertrophic. These, in turn, pass across the venous wall to the adjacent artery to alter arterial tone and/or structure. This pathway could provide a mechanism for fetoplacental regulation of maternal blood flow. Although venoarterial exchange has been documented in the uterine circulation of a number of species as a mechanism for lutetolysis (see text), its role in maternal uterine vascular remodeling during pregnancy is still hypothetical.

**FIGURE 5.** Venoarterial exchange

Signals secreted from the placenta, decidua, or myometrium (due to stretch) pass into the venous effluent, where their concentrations would be highest before dilution into the systemic circulation. Signals may be molecules that are vasoactive, mitogenic, or hypertrophic. These, in turn, pass across the venous wall to the adjacent artery to alter arterial tone and/or structure. This pathway could provide a mechanism for fetoplacental regulation of maternal blood flow. Although venoarterial exchange has been documented in the uterine circulation of a number of species as a mechanism for lutetolysis (see text), its role in maternal uterine vascular remodeling during pregnancy is still hypothetical.
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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 secondarily to decreased downstream vascular resistance (due to placenta) were the only stimuli 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 radial 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 an autocrine component related to the production of angiogenic 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 pregnancy-like syndrome in pregnant mice, and this syndrome could be prevented by co-administration of 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 established determinant of fetal growth (62). Presumably, this is a humoral mechanism that would therefore have a similar effect on both preplacental and premyometrial vessels.

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 hyporesponsivity to the constrictor effects of phenylephrine, the Doppler 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 developed several features associated with preeclampsia (75), 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 mouse uteri. Induced uterine remodeling is different from renal remodeling; thus is not considered in this review. However, despite these differences, it is likely that mechanisms within the myometrium may play a role in the regulation of uterine blood flow and may contribute to the changes in resistance that occur in pregnancy.

Table 1. Processes, pathways, signals, and events implicated in maternal uterine vascular remodeling during pregnancy

| Processes Implantation/placenta Endovascular trophoblast invasion Myometrial stretch Altered endocrine regulatory mechanisms Pathways Local Physical (e.g., increased shear stress on endothelium) Molecular (e.g., venoarterial exchange) Systemic (humoral/endocrine) Signals Sex steroids Nitric oxide Prostaglandins Growth factors and angiogenic molecules Angiotensin Other (?) Events occurring within the vascular wall Vasodilation Cellular hypertrophy Cellular hyperplasia Matrix remodeling Recruitment of periadventitial cells (?)
and enlargement of existing vessels (at least in the mouse ear; Ref. 93), but their role in 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. pre-uterine arteries, or in arteries vs. veins) has not been defined.

Venoarterial signaling 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 fetal 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 afferent (arterial) circulation?

One mechanism that deserves mention is venoarterial transfer. Illustrated diagrammatically in FIGURE 5, it posits that secreted placental- 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 also potent angiogenic molecules, this mechanism should also provide a short loop pathway for regulating placental perfusion by inducing changes in arterial tone.

FIGURE 5 Four physiological mechanisms that may play a role in uterine arterial and venous widening and elongation during pregnancy. Note: This generalized drawing of the utero-placental circulation with hemochorial placentaion is not meant to be anatomically accurate; rather, it summarizes the four principal mechanisms likely to be involved in gestational uterine vascular remodeling, as discussed in the text. 1) Placental/endothelial trophoblast invasion. Hemochorial placentation provides a low-resistance site for fetal blood flow. As vessels enlarge, higher flow can be maintained at a slower velocity, thereby normalizing shear stress at the endothelial surface. Venous shear stress must increase as well (since inflow must equal outflow), and venous circulatory enlargement and elongation clearly occur, although a role for shear stress in venous expansion remodeling has not yet been demonstrated experimentally. 2) Venous-arterial exchange. At placentalized sites, the fetoplacental unit secretes a variety of signals (blue circles) into the IVS. These pass into the venous outflow, where they are most concentrated before systemic dilution and may 1) induce changes in venous structure and 2) enhance venous permeability through molecular mechanisms (e.g., VEGF, PGF) and altered physical forces secondary to growth (e.g., increased wall tension). Both mechanisms have been described in the uterine circulation of rodents (see text), where arteries and veins are often in close apposition and would affect vessels within the area shown by the tan shaded box and indicated by the placement of symbols between the arteries and veins. Placental signals may include molecules that reduce arterial tone and stimulate cell division and/or hypertrophy, leading to vessel widening. 3b) myometrial signals. Signals involved in the axial remodeling (elongation) of arteries and veins have not been identified to date. Here, we postulate that increasing volume of the conceptus (white arrow) leads to myometrial stretch. This, in turn, induces the release of mitogenic signals (black triangles) into the venous outflow, stimulating hyperplasia within the venous wall, and in the adjacent arterial wall via venoarterial exchange and leading to structural elongation. Human arteries must also elongate during pregnancy, since the volume of the uterus increases approximately 1,000-fold, although it is not clear whether lengthening is due to arterial growth, elastic stretch, straightening of tortuous segments, or some combination thereof. In rodents, most of the vascularization is axially oriented to the myometrium and occurs in regions that are not innervated. This process also involves intimal proliferation within the myometrium and may therefore be subject to direct stretch. 4) Humoral factors. The endocrine milieu of pregnancy results in altered systemic concentrations of hormones and growth factors (red circles). The source of hormones may be placental, although this is species dependent (e.g., in rodents, the ovary, not the placenta, produces estradiol and progesterone). Increased hormone concentrations may induce vasodilation, alter permeability, and stimulate both cellular and matrix remodeling.
An anatomical basis for venoarterial transfer does exist in the uterine circulation, since arteries and veins are arranged in close apposition in a number of species (17, 18). In humans (122) Moreover, physiological plausibility derives from studies that have established this as a mechanism of luteolysis (40). Proteoglycans sequestered by the uterus and carried in its veins are transferred to the ovarian artery, where they travel to the corporeal luteum and induce a number of processes leading to luteal demise, with ischemic vasoconstriction among them.

This venoarterial exchange is plausible from both an anatomical and a physiological standpoint. The venous permeability of isolated rat uterine veins is considerable, even to large molecular weight signals (70 kDa), significantly enhanced during pregnancy, and regulated by physical forces such as wall tension and molecular signals such as VEGF (17, 18).

The same time, evidence that conclusively demonstrates (or refutes) the importance of venoarterial transfer as an in vivo mechanism for uterine vascular-vascular gestational remodeling is currently lacking, and the determination of whether this mechanism is physiologically important awaits further research.

Summary

Coordinated and sufficient uterine vascular remodeling must occur to facilitate the many-fold increase in uteroplacental blood flow that is required for normal pregnancy outcome. This physiological process is unique in the adult vascular system and likely occurs via a combination of mechanisms. Table 1 and Figure 6 are intended to provide a summary of the pathways, signals, and physiological processes that may be involved in uterine vascular remodeling during gestation. This table and figure also provide a basis for the consideration of future research, since the evidence implicating the involvement of these pathways and signals is largely indirect and inferential, i.e., based on other studies conducted in settings outside of the subject of this review.

Further investigations whose experimental design is clever enough to provide more specific, definitive information would help us bridge the theoretical with the real and provide deeper understanding of a process that is, at this point in time, still largely described in descriptive rather than mechanistic terms.

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