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Maternal Uterine Vascular Remodeling During Pregnancy

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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 preeclampsia.

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. 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 (eutrophy). 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., μm^2), relate to changes in wall mass, a three-dimensional quantity (e.g., μm^3).

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 Metcalfe (78) utilizing the diffusion equilibrium principle (most often nitrous oxide, N_2O) 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 ^{133}Xe (106), placental metabolic clearance rate techniques (29), and most recently and directly transvaginal Doppler ultrasonography (99) support these early findings. For

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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 placentation on distribution of uterine vascular resistance and blood flow

Mice, rats, guinea pigs, rabbits, and humans share a hemochorial type of placentation, in which intraplacental pressure created by the maternal blood occupying the intervillous space must be kept low enough to avoid compression of the intravillous (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).

With hemochorial placentation, for a molecule 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,

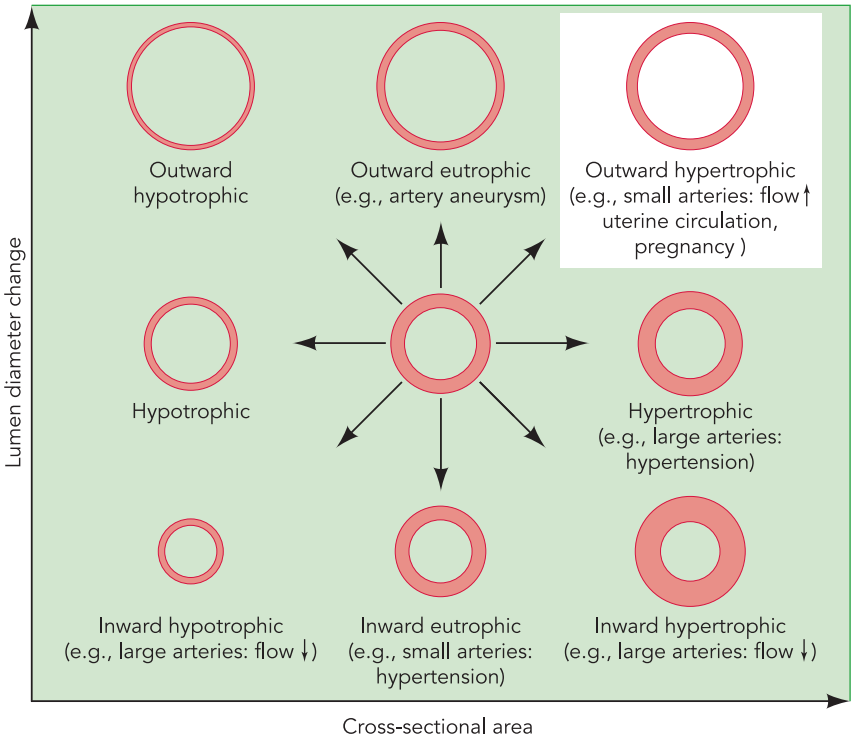

FIGURE 1. **Patterns of vascular remodeling**
This drawing relates changes in lumen diameter and cross-sectional area to illustrate the various two-dimensional patterns of arterial remodeling (adapted, with permission, from R. H. Hilgers). The remodeling of a vessel to a larger lumen with the same wall 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 eutrophic (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 "hypotrophic" 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 (112) 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.

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 (99). 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 three-fold (2, 45, 46, 56, 75, 79, 92, 99, 132, 133). This enlargement 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

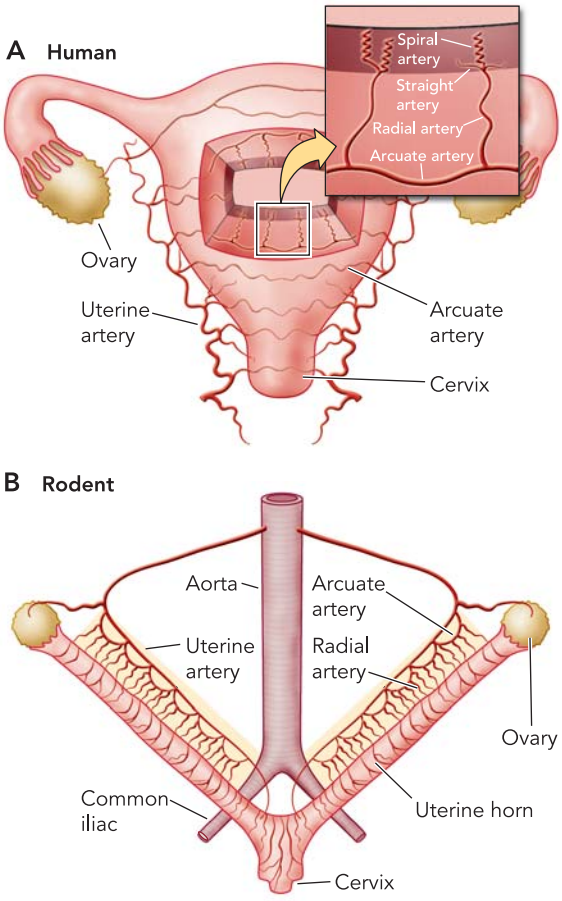

FIGURE 2. **Comparative anatomy of the uterine circulation in humans, rodents, and ungulates** In most mammals, including humans (*A*), blood is delivered to the uterus bidirectionally via a dual arterial anastomotic loop in which one end (the two ovarian arteries) originates from the aorta and the other (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 the myometrium 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 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 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 placentation 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 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 lumenal caliber ranging from 25 to 220% and with either no change or an increase in wall thickness (20, 21, 41, 74, 80, 81, 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, lumenal 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., unstressed smooth muscle cell length in arcuate vessels from pregnant vs. virgin nonpregnant rats was increased by 20% in rats (20). In guinea pigs (49), smooth muscle cell length increased from 21 to 39 μm (86%), 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 (1985) study by Griendling et al. (45), the incremental passive elastic modulus, which measures the relationship of stress to strain, increased from 4 to 29 dyn/cm^2 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 were decreased. Conversely, Robertson and Manning (109) found a decrease in the elastin content of spiral arteries of pregnant women, although there were no changes in vessels "remote from the placental bed" (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 placentation 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, 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, 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 threefold 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 constitutents 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 placentation and spiral artery invasion and remodeling (28, 115) and has been implicated in the development of preeclampsia (42, 116).

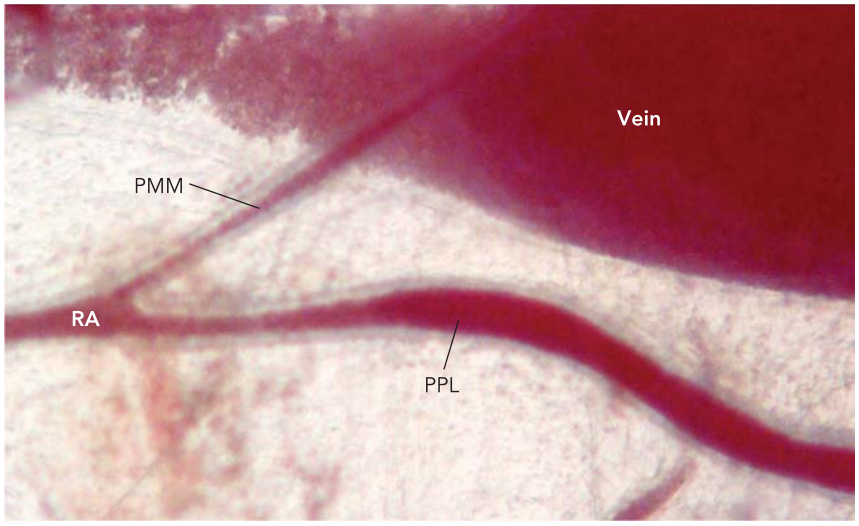

FIGURE 3. **Preplacental vs. premyometrial vessels in the rat**
Photograph of a segment of the uterine mesometrium from a 20-day pregnant rat. A proximal radial artery (RA) divides into two branches, both of which approach the uterine wall (not visible). The lower vessel perfuses the placenta [preplacental artery (PPL)] while the upper courses to and penetrates the myometrium between implantation sites [premyometrial (PMM)]. A segment of a vein draining the placenta is visible at *top right*. Note consistent shape of the PMM vs. significant (2–3×) widening of the PPL. The area of widening likely denotes the extent of endovascular trophoblast invasion. Once the vessel has widened, it loses the ability to contract or dilate due to ablation and/or de-differentiation of vascular smooth muscle in the arterial media.

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 arcuate 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 utero-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 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 should predominate, since the relationship between length and resistance is linear (i.e., a doubling of length equals a doubling of resistance), whereas the relationship of diameter (or radius) to resistance is inverse and quadratic (i.e., doubling of diameter theoretically decreases resistance 16-fold), as per Poiseiulle's Law. This mathematical formulation relates changes in vessel length, diameter, and blood viscosity to altered flow resistance by: $R = \epsilon L/r^4$, where R is resistance, ϵ is viscosity, L is length, and r is inner radius.

Thus, without considering changes in tone and reactivity, the combined effect of doubling both the length and the diameter of a tube would theoretically reduce resistance by a factor of 8 and, in the absence of changes in viscosity or growth of new vessels, induce a corresponding increase in blood flow. Clearly, expansive circumferential remodeling and decreased distal resistance due to placentation exert a synergistic effect that can result in the many-fold increases in UPBF.

Finally, additional rheological factors, such as a reduction in the viscosity of the blood (95), also occur during pregnancy and contribute to reducing blood flow resistance according to Poiseiulle's Law.

Remodeling of uterine veins

The process of expansive remodeling is not limited to arteries, since the veins also enlarge substantially during pregnancy, although the available data are much more limited. The fully distended diameter of the main uterine vein in pregnant vs. nonpregnant rats averaged 1,576 vs. 956 μm, respectively (an increase of 65%), along with a doubling in unstressed length (98). Increased venous diameter was also accompanied by increased distensibility and reduced elastin content, adaptations that would further enhance venous capacitance. Significant uterine venous enlargement during pregnancy was also reported in the mouse (34).

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/endocrine 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 steroidal 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 (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 (fetoplacental) 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 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 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.

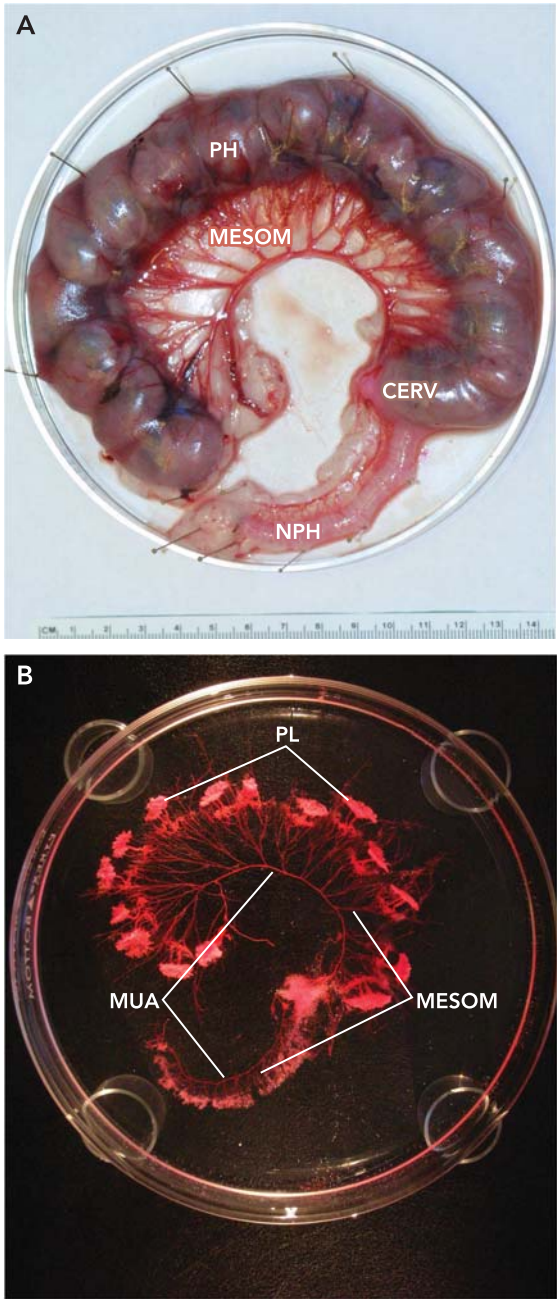

FIGURE 4. **Local mechanisms predominate in uterine vascular remodeling in the rodent**
A: photograph of a 20-day pregnant rat uterus in which one uterine horn was ligated at the ovarian end, preventing oocyte descent and fertilization. Thirteen fetoplacental units are present in the pregnant uterine 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 (PL).

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, 132) 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 of single horn ligated mice, with values from the nonpregnant horn being similar 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, 131) 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 number of citations, the species diversity is limited since virtually all of the data in these studies have been obtained using rodent models.

This mechanism is appealing from a physiological standpoint, since an increase in vessel caliber allows the maintenance of increased flow, while at the same time normalizing endothelial shear stress due to a decrease in blood flow velocity. A good discussion of the biophysical and theoretical aspects of shear stress in vascular tissues can be found in several recent papers (102, 107), and the inquisitive reader is also referred to a classic 1975 paper by Rodbard (110) for a more historic perspective of our understanding of the relationship between vascular caliber and flow.

Elevation in shear stress is a plausible mechanism for uterine arterial enlargement during gestation in view of its well established nature as a physiological mechanism and the fact that the reduction in downstream resistance that occurs secondary to placentation would be an effective stimulus for increasing the velocity of flow (and, therefore, shear stress) in upstream arteries. Vasodilation and/or vessel growth would allow the augmented flow to continue, but with a slower velocity, thereby normalizing shear stress in the process.

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 (99). 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 (90) 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 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),

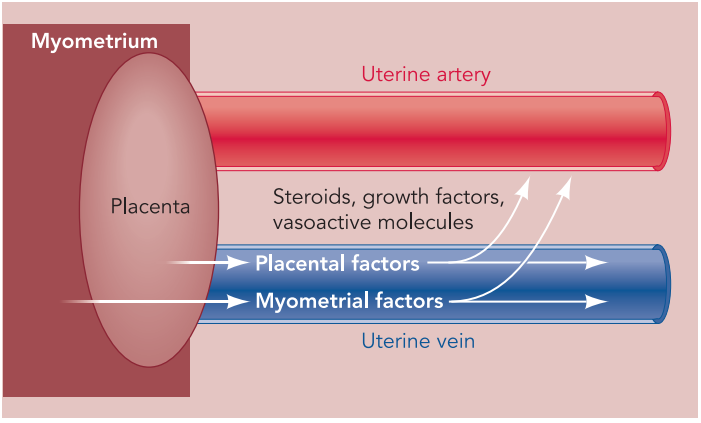

FIGURE 5. **Venoarterial exchange**
Signals secreted from the placenta, decidua, or myometrium (due to stretch) pass into the venous effluent, where their concentrations would be highest before dilution into the systemic circulation. Signals may be molecules that are vasoactive, mitogenic, or hypertrophic. 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 luteolysis (see text), its role in maternal uterine vascular remodeling during pregnancy is still hypothetical.

including vimentin (117), and membrane-asssociated 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 placentation) 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 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 automimmune component related to the production of agonistic 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 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 hypersensitivity 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). Rats 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

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

Processes
Implantation/placentation
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. premyometrial 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 PlGF are also potent vasodilators, this mechanism could also provide a short loop pathway for regulating placental perfusion by inducing changes in arterial tone.

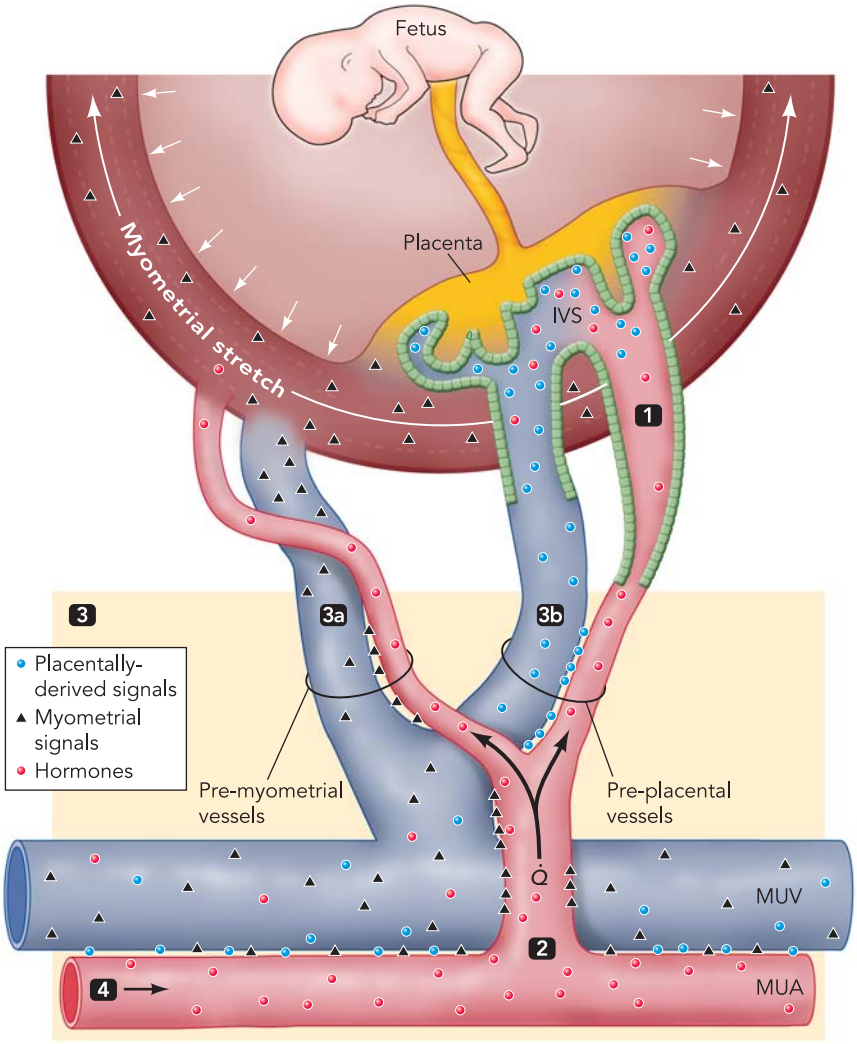

FIGURE 6. **Four physiological mechanisms that may play a role in uterine arterial and venous widening and elongation during pregnancy**
Note: This generalized drawing of the uteroplacental circulation with hemochorial placentation is not meant to be anatomically accurate; rather, it summarizes the four principal mechanisms likely to be involved in gestational uterine vascular remodeling, as discussed in the text. 1) **Placentation/endovascular trophoblast invasion**. Hemochorial placentation provides a low-resistance pathway for maternal blood flow by eliminating the intramyometrial microcirculation and creating an intervillous space (IVS). Flow resistance is further decreased by arterial widening secondary to endovascular trophoblast invasion (green cells) of the preplacental (in humans, spiral) arteries. Invasion of the veins has also been documented, at least in rodents, although to a lesser depth. The depth of invasion is exaggerated for purposes of illustration. *2*) **Increased shear stress**. Decreased resistance due to placentation and endovascular remodeling of distal (preplacental) arteries results in an acceleration of blood flow (Q) in proximal vessels, elevating shear stress at the endothelial surface (*2*, black arrows). Shear stimulates the release of endothelial NO and initiates outward circumferential (expansive) arterial remodeling. 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 circumferential enlargement and elongation clearly occur, although a role for shear stress in venous expansive remodeling has not yet been demonstrated experimentally. *3*) **Venoarterial exchange**. *3a*: placentally derived signals. 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, PlGF) 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. Mechanisms 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 arrows) 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 any combination thereof. In rodents, much of the vasculature is external to the myometrium and located in a planar mesometrium; in humans, arcuate and radial arteries are contained 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 estrogen and progesterone). Increased hormone concentrations may induce vasodilation, alter permeability, and stimulate both cellular and matrix remodeling.

An anatomical basis for venorterial transfer does exist in the uterine circulation, since arteries and veins are arranged in close apposition in a number of species (17, 18, 40) and in humans (122). Moreover, physiological plausibility derives from studies that have established this as a mechanism of luteolysis (40). Prostaglandins secreted by the uterus and carried in its veins are transferred to the ovarian artery, where they travel to the corpus luteum and induce a number of processes leading to luteal demise, with ischemic vasoconstriction among them.

Thus 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).

At the same time, evidence that conclusively demonstrates (or refutes) the importance of venoarterial transfer as an in vivo mechanism for uterine 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 defined in descriptive rather than mechanistic terms. ■

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