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# Uterine Vascular Control Preconception and During Pregnancy

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## Abstract

Successful pregnancy and reproduction are dependent on adequate uterine blood flow, placental perfusion, and vascular responsivity to fetal demands. The ability to support pregnancy centers on systemic adaptation and endometrial preparation through decidualization, embryonic implantation, trophoblast invasion, arterial/arteriolar reactivity, and vascular remodeling. These adaptations occur through responsiveness to endocrine signaling and local uteroplacental mediators. The purpose of this Comprehensive Physiology review is to highlight the current knowledge associated with vascular remodeling and responsivity during uterine preparation for and during pregnancy. We will focus on maternal cardiovascular systemic and uterine modifications, endometrial decidualization, implantation and invasion, uterine and spiral artery remodeling, local uterine regulatory mechanisms, placentation, and pathological consequences of vascular dysfunction during pregnancy.

### Keywords

placenta; decidualization; implantation; arteries; trophoblast

## INTRODUCTION

The vascular system plays critical roles in oxygen transport, nutrition, excretion, fluid balance, homeostasis, and immune functions. It is a complex system regulated by hormones and growth factors alongside inflammatory, adhesion, cytoskeletal and extracellular proteins. These molecules have direct and indirect effects on vascular remodeling and reactivity (97, 157, 188). During pregnancy, the functions of the cardiovascular system and its regulatory factors are heightened to promote fetal growth and development (66, 110). Successful reproduction hinges upon vascular growth and accommodations throughout the menstrual cycle and pregnancy.

The purpose of this review is to give an overview of the uterine vasculature and unique vascular physiology accompanying the transition of the uterus from non-pregnant to

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pregnant. These modifications take place through uterine decidualization in preparation for embryonic implantation, trophoblast invasion, and spiral artery transformation to successfully sustain pregnancy. The process of placentation and maternal adaptations to pregnancy will be examined. Uterine vascular remodeling and reactivity and their influence on uteroplacental blood flow will be discussed. The mechanisms regulating postpartum uterine vascular repair after deliver will be addressed. Finally, we will review pathological consequences of aberrant maternal vascular adaptation and placentation during pregnancy.

## UTERINE VASCULATURE AND REPRODUCTIVE CYCLE

### Uterine Vascular Tree

The shape of the human uterus has been described as an inverted pear (Figure 1a). A hollow muscular organ, it is comprised of three tissue layers (40). Epithelial cells make up a thin outer sheath of tissue called the perimetrium. Smooth muscle cells are the primary component of the muscular middle layer, the myometrium. The innermost layer, the endometrium, is vital to reproduction and menstruation, and is a complex mixture of parenchymal and stromal tissues (155).

The uterus receives blood from the right and left uterine and ovarian arteries. Each uterine artery branches from the ipsilateral internal iliac artery and descends toward the uterus (34). Undulations in the mid and distal regions of the descending uterine arteries are thought to provide reserve arterial length to accommodate rapid expansion during pregnancy (1). Evidence from ultrasound and angiographic studies indicate that, in non-pregnant women, the diameter of the uterine artery ranges between 1.5 and 5.0 mm (167, 211). The ovarian arteries originate from the abdominal aorta and display undulations like those observed in the uterine arteries (162). Branches of the uterine artery anastomose with the ovarian arteries to provide blood flow to the female reproductive organs, an evolutionary adaptation to provide adequate and continued uterine blood flow (172).

Within the human myometrium, the uterine artery branches into smaller vessels that span and penetrate the muscle tissue (Figure 1a). The arcuate arteries assume a circumferential pattern of growth, within the myometrium close to the uterine serosa, and give rise to the radial arteries. The radial arteries course deeper into the myometrium and bifurcate at the myometrial/endometrial border (Figure 1a). Radial arteries give rise to short, straight, basal arterioles that supply the basal layer of the endometrium, and pre-placental spiral arterioles that supply blood to the upper functional layer of the endometrium (94). The spiral arterioles possess a distinctive coiled architecture that is more pronounced during the secretory phase of the menstrual cycle (54). Each spiral arteriole supplies blood to support an estimated 4 to 9 $mm^2$ of uterine luminal surface area (131). The terminal regions of the spiral arterioles assemble to form a capillary plexus that extends beneath and runs in parallel with the uterine epithelium (26). The capillary plexus is coupled to a venous drainage network that passes through the endometrium and the myometrium to return blood to the heart (94).

Animal models are commonly used in laboratory reproductive studies; therefore it is imperative to identify anatomical differences between human and laboratory animal uterine anatomy. The rodent and rabbit have a bicornuate or duplex uterus that is comprised of a

left and right tubular uterine horn to permit multiple fetus litters. The rat or mouse uterus is shaped like a “V” unifying at the cervix (Figure 1b) (162), while the rabbit uterus is shaped like a “T”, unifying at the cervix and a longer vaginal canal (Figure 1c) (177). Sheep have a bicorneal uterus that is heart shaped (Figure 1d) (55). Some differences are noted between the with the uterine vasculatures. As in humans, the uteri of the rodent, rabbit, and sheep receive blood from the left and right ovarian and uterine arteries (55, 106, 162, 177). In all models these primary arteries branch into arcuate arteries to increase uterine perfusion. In the mouse and rat, arcuate networks allow for blood flow to implanted pups along the uterine tube to be in parallel, not in series (162). The arcuate arteries give rise to the radial arteries, which branch to form the basal and spiral arterioles (87, 162). The basal arterioles provide blood to the myometrium, whereas the spiral arteries are considered pre-placental vessels. Placentation is also similar between the human and laboratory models. The human, rodent, and rabbit employ hemochorial placentation, wherein the maternal blood comes in direct contact with the fetal trophoblast cells; alternatively, sheep develop a more superficial epitheliochorial placentation wherein the separation between the maternal and fetal tissues is maintained (64). Overall, while there are many similarities between human uterine anatomy and physiology and laboratory models, the differences between the species must be considered.

## Angiogenesis and Vascular Remodeling Preconception

The menstrual cycle may be divided into two phases under distinct hormonal control: (1) the follicular/proliferative and (2) the luteal/secretory phase. The former ranges from 10 to 20 days, with an average duration of 14 days, culminating in ovulation (50). Ovulation is triggered by a surge in luteinizing hormone (LH) via a positive feedback signal of estrogen stimulating hypothalamus and pituitary action (45, 142). The onset of the luteal phase begins after ovulation and concludes on the first day of menstruation. This period lasts approximately 14 days in most women.

Angiogenesis, the growth of new blood vessels, occurs throughout all stages of the menstrual cycle, with the exception of menstruation (71). The menstrual cycle is predominantly influenced by increasing levels of estrogen and is characterized by substantial uterine angiogenesis and vascular elongation (65, 189). New vessel growth within the endometrium is initiated during the follicular phase; while angiogenesis in the forms of branching, elongation, and vascular maturation occur during the luteal phase of the menstrual cycle (72, 181, 182).

Progesterone and estrogen directly control endometrial angiogenesis and vascular remodeling, moreover these hormones act indirectly with other regulators. Progesterone regulates vascular elongation and maturation of the subepithelial capillary plexus and the growth and coiling of spiral arterioles (56, 72). Members of the vascular endothelial growth factor (VEGF) family and their receptors are critical for estrogen-induced endometrial vascular remodeling (231). Estrogen treatment *in vivo* is known to impact both temporal and spatial VEGFA expression in the endometrium (122). Decidual angiogenesis is stimulated by VEGF-A secreted from the PR-expressing decidual stromal cells that are up-regulated via estrogen during the proliferative phase. VEGF and it’s tyrosine kinase receptors induce

the proliferation of endothelial cells and increase vascular permeability (152). During the mid-secretory phase, when progesterone peaks, the production of VEGF by endometrial epithelial cells increases significantly, suggesting a requisite for the coordinated actions of estrogen and progesterone for maximal production (231). VEGF-A, VEGFR2 and uterine natural killer (uNK) cells regulate the enlargement and elongation of endometrial blood vessels. Further information on the roles of VEGF and their receptors in endometrial vascular remodeling can be found here (33, 72).

Presumably, additional vasoactive substances influence preconceptive uterine remodeling. Relaxin is a peptide hormone produced by the corpus luteum, a transient endocrine organ which forms from the remaining ovarian follicle after ovulation. This hormone has been shown to promote vascular remodeling and angiogenesis through the upregulation of matrix metallopeptidases (MMP) (102), and upregulation of VEGF (139). Furthermore, prostaglandins likely modulate reproductive function as studies have shown that genetic cyclooxygenase knockout mice suffer severe reproductive failure (98, 111). Together, these physiologic changes increase uterine vascular surface area in preparation for implantation (31).

## Vascular Reactivity Preconception and Influence of Sex Hormones

Vascular reactivity and tone are related to the local responsiveness of arteries and arterioles. Under normal, homeostatic conditions, arterial and arteriolar vascular smooth muscle (VSM) cells remain at a partially constricted state, referred to as tone. Endothelial cells, which form the lining of blood vessels, react to luminal changes in chemical signaling agents and mechanical influences (138). The endothelium acts as a paracrine organ to promote relaxation or contraction of the VSM cells culminating in blood vessel dilation or constriction, respectively. Alternatively, molecular signaling may influence VSM activity directly, in an endothelium-independent manner. Therefore, vascular reactivity and tone are determined by the balance between vasodilator and vasoconstrictor factors within the endothelium and VSM of the vascular wall. Sex hormones are also known to influence endothelial cells directly, or indirectly by endothelium-dependent or -independent mechanisms (195). Therefore, the fluctuation in levels of estrogen and progesterone during the reproductive cycle is thought to play a role in uterine vascular reactivity and tone (207).

Studies using intravital microscopy in the rat demonstrate alterations to basal arteriolar reactivity in response to locally-infused endothelium-dependent (i.e., acetylcholine) and endothelium-independent (i.e., sodium-nitroprusside) chemical agonists during the rat estrous cycle (Figure 2) (46, 208). These studies also demonstrated that if maternal homeostasis is perturbed (e.g., environmental exposure) during oestrous, arteriolar responsiveness and myogenic reactivity shift toward vasoconstriction, thereby limiting blood flow to the uterine myometrium and potentially impairing decidualization (Figure 2) (44, 208, 218).

**Estrogen—**Estrogen concentrations are highest during the follicular phase of the reproductive cycle. The most pronounced effects of estrogen on vascular reactivity are mediated through endothelial function (144). Elevated estrogen concentrations are known to

increase mean blood flow to many vascular beds (79, 80, 124, 125); occurring likely through reduced uterine vascular resistance and arteriolar vasodilation (207). Estrogen receptors (ER), ERα and ERβ have been identified in endothelial cells and VSM cells within uterine vascular beds (120). Accumulating evidence suggests that an increase in uterine artery blood flow is an ER-mediated phenomenon, leading to increased nitric oxide production and VSM cell relaxation (146, 187). Local infusion of estradiol in non-pregnant ovariectomized ewes also showed an increase in uterine artery blood flow, without systemic changes, suggesting estrogenic changes within the uterus are mediated locally

Numerous studies in humans demonstrate that estrogen-mediated vasodilation occurs through endothelial nitric oxide synthase (eNOS)-dependent mechanisms (30, 109, 144). Protein expression of eNOS in uterine artery endothelial cells (127) and endogenous uteroplacental nitric oxide (NO) (215) is known to increase during the estrogen-dominant follicular phase of the menstrual cycle and decrease during the progesterone-dominant luteal phase in both sheep and humans. This phenomenon is unique to the uterine vasculature, particularly the uterine arteries, due to the presence and concentrations of ERα and ERβ receptors that are differentially regulated by estrogen (120). Previous studies have demonstrated that estrogen augments endothelium-dependent and - independent vasodilation within the microcirculation during mid-cycle in pre-menopausal women and in post-menopausal women taking estrogen replacement therapy (8). Unfortunately, the exact mechanism responsible for estrogen-enhanced endothelial function remains unclear and requires further study. Further reading pertaining to the systemic vascular actions of estrogens can be found here (143).

**Progesterone—**The corpus luteum produces progesterone, with the primary function of preparing the estrogen-primed endometrium for implantation. Previous studies report that concentrations of progesterone, in combination with estrogen (as detailed above) may be responsible for the regulation of uterine blood flow (126). This understanding is based on findings that elevated estrogen-to-progesterone ratios, characteristic of the follicular phase of the estrous cycle, correspond with elevated uterine blood flow (126). Alternatively in ruminants, the luteal phase is characterized by high plasma progesterone and low estrogen concentrations, restoring uterine blood flow to basal levels (59). Similar to estrogen, progesterone may also promote endothelium-dependent relaxation (157); nonetheless this may be species dependent. In sheep models, exogenous progesterone fails to produce vasodilation in the uterine vascular bed when administered alone (4). In contrast, when progesterone is infused in combination with estrogen it produces an inhibitory effect (29, 79, 175). Results from studies using rodent models describe progesterone as a vasoactive hormone that acts to inhibit vasoconstriction through modulation of $Ca^{++}$ concentrations (15). At peak levels of progesterone, VEGF and cognate receptors are upregulated within the uterine microvasculature, leading to subsequent increases in vascularity and blood flow, thereby optimizing conditions for implantation (231). Unfortunately, the mechanisms of action supporting progesterone-induced vascular reactivity remain unknown and require future study.

**Luteinizing Hormone—**As its name implies, LH is responsible for the transformation of the follicular remnant cells to form the corpus luteum. Few studies have evaluated the modulation of uterine vascular responsivity to increased concentrations of LH. One study evaluated porcine vascular responsiveness to norepinephrine, a potent vasoconstrictor, in a high LH environment (200). Using wire myography to assess uterine artery vascular smooth muscle tension generation, these studies concluded that LH mitigated norepinephrine contractility (200). Therefore, more work is needed to understand the impact of LH on uterine vascular reactivity.

While significant work has been conducted on the influence of estrogen and uterine vascular responsiveness, further studies pertaining to the cyclic effects of estrogen, effects of progesterone, LH, relaxin, and testosterone require further study.

### Decidualization and Menstruation

Decidualization is the process by which the endometrium thickens in preparation for pregnancy, providing a nutritive matrix for implantation. In humans, decidualization occurs with each menstrual cycle and involves vascular sprouting and elongation, increased surface area of the spiral arterioles, influx of specialized uNK cells, and secretory transformation of the uterine glands (Figure 3) (68, 151). These physiological processes occur in response to coordinated estrogen and progesterone secretion. There is a positive correlation between the degree of endometrial decidualization and trophoblast invasion of maternal uterine vessels during implantation and pregnancy (58). Consequently, pathological manifestations such as infertility, preeclampsia, and fetal growth restriction may result secondary to physiological complications during this phase.

Menstruation occurs naturally in humans and very few other species; rodent models do not menstruate. In the absence of an implanted blastocyst the sprouted and elongated vessels degenerate and are lost during menstrual shedding (234). Humans are thought to undergo vaginal bleeding as a physiological adaptation of invasive placentation; building of the uterine wall increases the success of pregnancy but is not energetically favorable to maintain (136). Protective mechanisms to limit blood loss during menstruation are initiated. These include the local production of potent vasoconstrictors, prostaglandin F2α and endothelin-1 (ET-1) (12, 132). Vasoconstriction is accompanied by the activation of the coagulation cascade within the endometrium to achieve hemostasis (136). Spiral arteries constrict to limit blood flow to the endometrium to prevent excessive blood loss and permit scar-free tissue repair. In species that do not undergo menstruation, the endometrium is extensively reabsorbed and remodeled (136). More information regarding the mechanisms of menstruation can be found here (121).

## INITIATING PREGNANCY: IMPLANTATION AND TROPHOBLAST INVASION

In humans, adhesion of the blastocyst to the endometrial surface marks the completion of the process of decidualization. This includes extracellular matrix remodeling, balancing the local immune response, maintenance of an antioxidant environment, and vascular maturation (113). Progesterone and estrogen, via activation of their cognate receptors, coordinate these processes (76, 179). The marked increase in neovascularization during early pregnancy is a

result of hormonal actions on estrogen and progesterone receptor expressing stromal cells along with an increase in the expression of VEGF-A and VEGF-R2 by local immune cell populations (19, 107). Trophoblast invasion into the spiral arteriole lumen ramifies the spiral pre-placental arterioles (231). In late pregnancy, this process is critical for establishing blood supply to the developing fetus.

## Implantation

There is a short period of time when the endometrium is receptive to a conceptus for implantation (Figure 3) (151). The implantation window begins approximately 6 days after ovulation, when endometrial thickness and vascularization peak, lasting for about 4 days. In humans, implantation of a fertilized ovum occurs about 9 days after ovulation. At this stage of development, the conceptus is referred to as a blastocyst (Figure 3) (151). Implantation describes the process of attachment to the uterine epithelium and invasion into the uterine endometrium by the blastocyst. Trophoblast cells form the outer layer of a blastocyst. These cells physically connect the embryo to the uterine wall (39). This connection deepens with trophoblast invasion into the uterine endometrium, establishing vascular connections with the uterine pre-placental spiral arteries (39). Invasion of the uterine spiral arteries is discussed in detail below. This connection deepens with trophoblast invasion into the uterine endometrium, establishing vascular connections with the uterine pre-placental spiral arteries (39). Invasion of the uterine spiral arteries is discussed in depth below. There is a positive correlation between the degree of uterine thickening and extent of trophoblast invasion during implantation/placentation (58). Impaired implantation is associated with multiple gestational complications, including pregnancy failure and uteroplacental disorders (156). Further review of the mechanisms and molecular interactions associated with embryologic implantation can be found here (108).

## Invasion, Spiral Artery Remodeling, and Placentation

Maternal-embryo crosstalk including molecular signaling between immune cell receptors, extravillous trophoblasts, and uterine spiral arteriolar endothelial cells is initiated at implantation (113). By the time a blastocyst meets the endometrium, it consists of two major parts; the inner cell mass (which will become the embryo), and the outer layer of trophoblast cells called the trophectoderm (which is destined to become the placenta) (198). The trophoblast layer proliferates and differentiates into the cytotrophoblast, which gives rise to the villous syncytiotrophoblast and invasive syncytiotrophoblast lineages. Differentiation of trophoblast layer is tightly controlled by molecular crosstalk between maternal and fetal tissues, including oxygen tension, transcription factors, hormones, growth factors, and alternative signaling molecules (103).

**Invasion—**Trophoblast cell invasion into the inner third of the myometrium requires the exchange of biological signals between maternal and fetal tissues. Cell colocalization studies from uterine bed biopsies reveal the presence of immune cells at the wall of the spiral arterioles (90). Invading trophoblast cells interact with maternal immune cells (70% being decidual NK cells, 20% macrophages, and 10% T-cell lymphocytes). Immune cells disrupt endothelial and VSM cells, increasing vascular permeability, before trophoblast invasion (202). Infiltrated immune cells, namely the macrophages, express a wide range of, proteases,

and angiogenic factors (e.g., angiogenin, keratinocyte growth factor, fibroblast growth factor B, VEGF A, and angiopoietin-1 and -2) against the vessel cell walls (114). Fetal trophoblast cells also generate immune signals, through the expression of HLA-C, HLA-E and HLA-G for decidual NK cell receptor interaction. HLA-G binds to inhibitory decidual NK receptors to suppress the maternal immune response and permit fetal invasion (7, 89). There is considerable interplay between immune cells, decidual cells and invading trophoblasts.

Invasion of the endometrium requires fetal trophoblasts to penetrate the uterine epithelium and invade endometrial stroma to gain access to the spiral arterioles. Trophoblast cells penetrate the matrix layer under the epithelium, known as the basement membrane, invading through the intercellular gaps between endometrial epithelial cells without destroying them (28). Expression of MMPs from perivascular uNK cells and macrophages initiate trophoblast invasion of the spiral arterioles (241). The decidua contains high amounts of pro-invasive factors including interleukin (IL) -1β, IL-5, IL-6, IL-7, IL-8, IL-9, IL-13, IL-15, Eotaxin, CCL11, IP-10 and RANTES, as well as anti-invasive factors IL-10, IL-12 and VEGF (198). The coordinated influence of these decidual factors promote invasion by regulating protease pathways and integrin expression via STAT signaling pathways in trophoblasts (198). Simultaneously, tissue inhibitors of MMPs reduce fetal trophoblast proliferation and restrain over-invasion (114).

This process stimulates the expression of VEGF and other proangiogenic factors such as placental growth factor (PGF) by extravillous cytotrophoblasts. Preimplantation factor (PIF) is a peptide secreted from blastocyst and placental tissue and detected in the maternal circulation. The function of PIF is to modulate local uterine immunity, enhance the expression of adhesion molecules within the decidua, and facilitate trophoblast invasion (16). Invasive trophoblasts utilize molecular mediators (e.g., epidermal growth factor, VEGF, MMP-9, phosphatidylinositol 3’-kinase (PI3K), AKT) that comply with precise spaciotemporal boundaries in normal pregnancy (57). Failure of fetal invasive trophoblasts to express necessary molecules, such as cadherin, integrin and immunoglobulin superfamily members, is associated with poor invasion and inability to mimic a vascular endothelial phenotype necessary for successful invasion (242). The inability to moderate trophoblast invasion becomes evident in placental disease conditions; therefore, proper regulation of trophoblast invasion is paramount for both maternal health and proper fetal development. The replacement of spiral artery endothelium with fetal trophoblast cells exerts several effects on vascular control which will be further discussed in the following subsections.

**Spiral Artery Remodeling—**Species with hemochorial placentation, which includes humans and laboratory rodents, undergo trophoblast invasion and spiral artery transformation (204). This facilitates both maternal and fetal control of local hemostasis. During early pregnancy, extravillous cytotrophoblasts invade through the decidualized endometrium and migrate retrograde through the distal ends of the spiral arterioles, acquiring an endothelial cell-like thromboregulatory gene expression profile (Figure 4) (203, 206). A rise in maternal procoagulant activity occurs to defend against maternal endometrial hemorrhage imposed by the trophoblast invasion; in turn, trophoblast cells elicit an anti-coagulation response by protease-activated surface receptors (217). The regulation

of hemostasis at the maternal-fetal interface by trophoblast cells is protective against local coagulation that may compromise nutrient-rich blood flow to the fetus.

As trophoblasts invade and migrate into the spiral arteriole lumen, they diminish the endothelium and supplant the smooth muscle of the vessel wall to ablate sensitivity and limit vascular smooth muscle action (Figure 4) (162, 203). In humans, NK cell targeting of the vascular smooth muscle limits vascular reactivity (24, 180), followed by displacement of the endothelial layer of the spiral arterioles by trophoblasts. This action eliminates endothelium-dependent vascular signaling and modifies the extracellular matrix, restricting vascular smooth muscle reactivity and responsiveness (162). Further, NK cells are integral in the regulation of trophoblast invasion, as identified using an immunocompromised *in vivo* rat model (174). While the mechanisms of NK cell functions in remodeling of spiral arteries are not fully understood (Figure 4), more information on the temporal dependence of molecular signaling may be found here (203).

During invasion, extravillous trophoblasts penetrate the maternal spiral arteries and form temporary “plugs” in the lumen of the vessels, decrease the flow of maternal blood, and establish an oxygen gradient between the mother and fetus (Figure 5) (178, 203, 230). Trophoblast plugs are present in the spiral arteries until gestational weeks 10–12. The maternal-fetal oxygen gradient is essential for differentiation, growth, and development of the placenta, whereas premature “unplugging” is associated with miscarriage (96). It is unclear if maternal blood cells can penetrate the trophoblast plugs, or if a few cells are able to pass into the intervillous space. It is increasingly accepted that at the $6^{th}$ week of pregnancy, the trophoblast plugs begin to slowly loosen to permit the gradual infiltration of maternal blood cells into the placenta, with the vessels being clear of any obstruction near the end of the first trimester (148, 230). Intervillous blood flow increases at gestational weeks 10–12, and thus early placentation occurs in an environment characterized by low oxygen tension (17–18 mm Hg compared to endometrial 39–40 mm Hg) (243). It is estimated that between 30 and 60 spiral arterioles open to serve as carrying maternal blood to the intervillous space of the placenta (25, 26).

Furthermore, the invaded trophoblast cells reconfigure the distal ends of the pre-placental arterioles into a widened, trumpet-like opening; the vessels are splayed open to further decrease vascular resistance and increase blood flow to the early intervillous space of the placenta (203). Widening of the spiral arterial lumen also dampens the pulsatile nature of blood flow entering the intervillous space. This function ensures slow percolation of maternal blood into the intervillous space around the fetal villi. Turbulent blood flow may damage the delicate villous tree tissue and promote fibrin deposition, precluding efficient nutrient exchange; however, the blood must enter at a rate sufficient to ensure deep perfusion of the maternal blood into the intervillous space (Figure 6) (173). As pregnancy progresses, placental vascular resistance decreases progressively from approximately 0.65 mmHg/mL/min at mid-gestation; to 0.15 mmHg/mL/min at term (2). Blood flowing through the uterine, arcuate, and radial arteries increases progressively throughout pregnancy, approaching values of 750 – 900 ml/min by term. By week 20, the arcuate arteries become larger than the vessels that feed them and may enlarge up to 220% over the course of pregnancy. Progressive remodeling of the spiral arteries occurs during the first 22 weeks of

gestation (234). The trumpet-like mouth of the arterioles at the time of opening is about 200 to 350 μm in diameter and expands to 2 to 3 mm by the third trimester. Remodeling of the spiral arteries continues into the second and third trimesters (Figure 5) (178).

**Placentation—**Placentation is the process that includes attachment of fetal trophoblasts to the uterine wall and growth, development, and organization into the mature organ. Ultimately, placentation allows the critical function of nutrient transfer to fetus and fetal waste to the mother. The capacity of the placenta for nutrient/waste exchange is due to the receipt of blood from two separate circulations, the maternal uterine vasculature and fetal systems (224). In hemochorial placentation, blood enters the intervillous space as a high volume, high throughput, and low velocity flow (Figure 6) (173). Thus, the fetal villi are continuously bathed in maternal blood, and nutrient and waste exchange with fetal blood occurs through a combination of mechanisms that include simple diffusion, facilitated diffusion, and active transport.

During pregnancy, maternal hemodynamic accommodations and regional control establish and maintain placental perfusion such that there is a tremendous increase in systemic blood volume directed toward the uterus. During pregnancy plasma volume may increase from 4L to 5 or 6L in women, and by term, nearly 1L is directed to the uteroplacental circulation with 90% going to the placenta and only about 10% to the uterine tissues (23, 162). In ewes, the progression of pregnancy is accompanied by a preferential increase in the proportion of uterine blood flow directed to the placenta (Figure 7) (81).

The placenta features a pressure gradient with high pressure in the maternal spiral arterioles (70 mmHg) and low pressure within the placenta intervillous space (10 mmHg) (224). A decreasing pressure gradient, in combination with remodeling of the spiral arterioles, which lowers distal resistance, permits efficient perfusion of the intervillous space. The blood pressure gradient between the uterine arteries and the placental intervillous space is quite steep, highlighting the activity of the resistance vasculature and assuring the continual but slow movement of maternal blood through the intervillous space, providing an optimal environment for nutrient and waste exchange across the fetal villi.

Oxygenated blood is provided to the fetus from the placental intervillous space via the umbilical vein within the umbilical cord (Figure 8) (42, 43). In return the fetoplacental circulation supplies the placenta with deoxygenated blood via umbilical arteries contained in the umbilical cord (Figure 8) (42, 43). It extends from the fetal umbilicus and inserts onto the chorionic plate of the placenta. At the interface of placental insertion, each umbilical artery branches into at least 8 stem arteries, which then branch into 4 to 8 horizontal vessels spanning varying lengths and curving towards the intervillous space (224). Here, branching occurs into terminal capillary beds within villous trophoblastic cell encapsulations. This brings fetal blood into proximity with the maternal blood, which are separated by two cell layers: the villous trophoblast and the fetal capillary endothelium. Fetal blood pressure is approximately 50 mmHg in the umbilical arteries and 20 mmHg in the umbilical vein (224).

Placentation mechanisms, trophoblast invasion, and spiral artery remodeling are modeled using *in vitro, ex vivo*, and *in vivo* approaches (203). Mechanistic and genetic screening

of trophoblast stem cells or immortalized human trophoblast cell lines provide molecular targets of differentiation, transporter function, and barrier functions. Despite species differences, mouse, rat, hamster, and guinea pig models provide laboratory evidence of anatomical invasion and physiological remodeling in attempts to gain a better understanding of human hemochorial placentation (203).

## PREGANCY

Maternal systemic and uterine adaptations are vital to support uteroplacental blood flow and crucial for successful pregnancy outcome. A combination of expansive vascular structural remodeling, and changes in blood vessel reactivity regulate uterine vascular resistance to accommodate increased uteroplacental blood flow during pregnancy and satisfy the needs of the developing fetus. Blood flow increases as pregnancy progresses, especially toward the end of pregnancy where fetal demand is greatest. In a cyclical fashion, the placenta matures, and in turn, the uterine circulation adapts through altered vessel structure, reduced vascular tone, and enhanced vasodilation/blunted vasoconstriction (162).

### Maternal Systemic Modifications

In order to support gestational tissue growth and fetal development, maternal physiology must expand rapidly and precisely. The profound hemodynamic adaptations of pregnancy extend beyond the uterine vasculature to the systemic circulation (61). As mentioned above, in normal pregnancy, maternal blood volume increases by an average of 30–50% over non-pregnant values (205). Heart rate and stroke volume increase in the first trimester (weeks 1 to 12). Heart rate continues to gradually rise until term, whereas stroke volume reaches a plateau near gestational week 20 (212). As a product of stroke volume and heart rate, cardiac output increases by 50%, reaching a peak between gestational weeks 20 to 28 (49). This leads to increased metabolic coronary demand and the development of reversible maternal cardiac hypertrophy to support increased coronary demand. Unlike pathological cardiac hypertrophy there is no coronary fibrotic tissue deposition (118). Further reading pertaining to the clinical development, physiological development, or metabolic coordination of coronary hypertrophy can be found here (69, 85, 161, 192, 205).

Primary systemic vasodilation in early pregnancy occurs in parallel with renal vasodilation. Renal vasodilation leads to a 30–50% increase in renal blood flow and glomerular filtration rate (GFR) (214). A fall in effective arterial blood volume activates the renin-angiotensin-aldosterone-system (RAAS), and stimulates the production of renin, angiotensin II, and aldosterone. A rise in circulating levels of water and sodium-retaining hormones leads to renal sodium and water retention in order to compensate for early arterial under filling (214).

### Maternal Circulating Clotting and Fibrinolytic Factors

Pregnancy produces a hypercoagulable and hypofibrinolytic state to protect the mother from postpartum hemorrhage. A progressive rise in plasma volume associated with pregnancy stimulates protein synthesis to maintain normal concentrations of clotting factors. Despite changes in protein synthesis, maternal platelet count during gestation is reduced by 10% from pre-pregnancy values (48). Spontaneous platelet aggregation, activation, and adhesion

have been reported during the third trimester in normotensive women, suggesting enhanced platelet reactivity (48).

## Uterine Vascular Modifications: Remodeling and Reactivity

Adjustments to uterine vascular structure and reactivity is critical for maintaining a successful pregnancy. Research has suggested that there are local and systemic factors that induce and maintain these processes. Vascular hyperplasia, hypertrophy, anatomical reconfiguration, and changes in extracellular matrices occur cooperatively to remodel the uterine circulation and establish a new transient vascular organ: the placenta. Furthermore, vascular reactivity is altered by systemic and local molecular signaling and mechanotransduction elements. Together these factors augment vascular compliance (162). The temporal relationship between macrovascular and microvascular changes associated with pregnancy is not well understood in humans. However, studies in rats and mice show that small artery remodeling precedes that of larger upstream vessels, suggesting that proximity to the placenta may be an important factor in spatial regulation of vascular function (130).

**Remodeling—**Remodeling is accomplished by both physical and chemical mechanisms; pressure/stretch and shear stress, humoral/endocrine factors such as VEGF and sex steroid hormones, and local endothelium-derived factors such as NO, angiotensin and endothelin (62, 130). During the first trimester (i.e., gestational week 1 – 12) the uterus rises out of the pelvic cavity to accommodate the developing fetoplacental unit. Substantial growth of the uterus is concurrent with axial growth (i.e., lengthening) of uterine arteries, but whether this is a result of uncoiling of tortuous vessels or of true longitudinal growth is uncertain, and may be species dependent (Figure 9) (130). Axial remodeling of the uterine arteries is well established in rodent models of pregnancy. In rats, the length of the main uterine artery and vein increases 2-fold (Figure 9) (130, 158) while downstream arcuate and radial arteries increase 3 to 5-fold in rodents by term; the situation in humans is less clear (160).

While major transformations are occurring at the level of the spiral arterioles at the maternal-fetal interface, the modifications to the upstream uterine vasculature cannot be overlooked. The vascular system directs more blood towards the uterus during pregnancy by increasing the circumference of the main uterine artery 2- to 3-fold, with little to no increase in vascular wall mass (95). This increase in cross sectional diameter appears to be achieved by wall mass hypertrophy (162). Pregnancy-related structural remodeling of the uterine circulation, characterized by vascular smooth muscle axial elongation, increased vessel caliber and wall cross-sectional area, is consistent with a pattern of outward hypertrophic arterial remodeling and has been identified in rats, guinea pigs, and sheep (Figure 10) (6, 35, 70, 91, 162). Outward hypertrophic arterial remodeling is characterized by an increase both in lumen cross-sectional area and wall thickness. This increase in luminal cross-sectional area allows for an increase in blood flow during pregnancy, in contrast to other pathological hypertrophic remodeling as described in hypertension or atherosclerosis where the luminal area remains the same (i.e., eutrophic) or narrow (i.e., inward hypertrophy) (Figure 10) (150, 162). Outward expansion of the uterine circulation in early pregnancy occurs, in part, through the concerted influence of VSM cellular hypertrophy and hyperplasia. VSM

cells isolated from radial uterine arteries Sprague-Dawley rats in late pregnancy (e.g., gestational day 20 to 21) exhibited substantial axial hypertrophy (21%) compared with values in non-pregnant animals (35). In guinea pigs, smooth muscle cell length measured in myometrial vessels increased from 21 μm in virgin animals to 39 μm in pregnant animals at gestational week 9 (91). Evidence from rodent studies suggests a role for hyperplastic processes in uterine arterial growth and elongation during pregnancy. Cellular proliferation rates of VSM cells and endothelial cells isolated from uterine and radial arteries were low in non-pregnant Sprague-Dawley rats but increased significantly during pregnancy (35). Moreover, the mitotic index values for endothelial and VSM cells were greatest in the smaller radial arteries at mid-pregnancy (e.g., gestational days 9 to 11) and in the larger upstream uterine arteries in late pregnancy (35). Regional variation in the pattern of cell division rates over time implies spatial and temporal regulation of gestational growth of the uterine vasculature. Unfortunately, this has not yet been well-documented in humans.

In combination with the several-fold increases in unstressed uterine artery length, total wall mass increases approximately 400% to 1000% (130). The smaller arcuate and radial arteries also undergo significant outward circumferential and axial remodeling characterized by both, hypertrophy and hyperplasia of endothelial and VSM cells (162). Although the mechanisms are not well defined, multiple influences on the vascular wall such as increased shear stress, sex hormones, and uterine deformation are likely at play.

Furthermore, uterine wall mechanics are altered during pregnancy, resulting in reduced compliance and increased distensibility in sheep, guinea pigs, rats, and rabbits (36, 84, 105, 135, 160). This may appear contradictory as reduced compliance often results in increased stiffness and increased distensibility is associated with reduced stiffness. Measures of compliance traditionally reported as direct measurements (e.g., diameter, area) when challenged by increased intralumenal pressure; whereas measures of distensibility are normalized to a percent change, often from baseline, allowing blood vessels of different sizes to be compared (73). Therefore, is it possible after outward hypertrophic arterial remodeling during pregnancy (Figure 10) for vessels of the uterine circulation to present greater stress-strain ratios (i.e., increased compliance), while also reporting increased percentage change from baseline (i.e., increased distensibility). It is likely that the alterations in compliance are associated with decreased vascular extracellular matrix collagen and elastin (162). Some studies have indicated a role for MMPs, particularly elevation in MMP-2 and -9, in extracellular matrix differentiation during pregnancy (32, 104, 141, 221). Further reading pertaining to uterine vascular remodeling during pregnancy can be found here (130, 161–163).

Although there is little research within this area, uterine veins also adapt to enhance their capacity for blood flow. In rats, there is a 65% increase in uterine vein diameter during pregnancy, along with a doubling in length (165). Additional venous adaptations include increased distensibility and decreased elastin to further augment capacitance for overall increase in blood volume during pregnancy and venous return to the heart (86).

**Reactivity—**Normal pregnancy is associated with significant physiological adaptations to meet the increased metabolic demands of the mother and fetus and to ensure optimal

uteroplacental circulation for fetal development. Local tissue blood flow is regulated primarily by dynamic changes in myogenic tone and arteriolar diameter to meet these metabolic requirements. Interestingly, the majority of altered vascular reactivity during pregnancy is unique and localized to the uterine circulation, differential to non-reproductive vascular beds (i.e., mesenteric circulation and carotid) of rats and guinea pigs (38, 41, 93, 226–228). In the first weeks of gestation global vascular compliance increases in parallel with a decline in peripheral vascular tone. Peripheral vasodilation leads to a 25–30% fall in systemic vascular resistance (SVR) by gestational week 6 (205). The collective effects of neural, endocrine, and local regulatory mechanisms mediate changes in arteriolar diameter.

**Neural Input:** Sympathetic and parasympathetic branches of the autonomic nervous system are critical constituents of neural control of vascular tone. The coordinated functions of the sympathetic nervous system and the parasympathetic nervous system allow for rapid adaption to physiological conditions. Actions of the autonomic nerves are mediated at target sites by the release of neurotransmitters that bind to adrenoreceptors and initiate signal transduction pathways that regulate cellular function (225). Uterine arterioles are highly innervated by sympathetic adrenergic nerve fibers (176). Norepinephrine (NE), the neurotransmitter released from adrenergic nerves, binds to α-adrenergic receptors located on the surface of VSM cells. NE binding and activation of receptors causes sympathetic-induced constriction of VSM cells. At rest, arterioles exhibit vascular tone due to the partial contraction of smooth muscle, this consistent level of vascular smooth muscle tone allows for vascular regulatory flexibility. Although the uterine circulation is highly sensitive to sympathetic influence, during pregnancy, there is reduced tone in the uterine vasculature, which may be attributable to reduced neural sympathetic signaling or increased mediators of vasodilation (165, 185). Interestingly, there is increased neurogenic tone in the peripheral circulation during pregnancy in sheep, attributed to increased nerve firing as opposed to increased neural density (9).

## Endocrine

***SEX HORMONES:*** As mentioned above in the pre-conceptive section, sex hormones are vasoactive factors. During pregnancy, circulating and local concentrations of sex steroid hormones are increased, which act to facilitate uterine blood flow. Greiss and Marston demonstrated in 1965 that direct infusion of estrogen in sheep led to uterine dilation in late pregnancy (83). Estrogen concentrations in pregnant ewes dramatically reduce uterine vascular resistance in both conduit and resistance arteries, permitting increased uteroplacental blood flow (207).

While many groups have demonstrated uterine hyperemia in ewes in response to different estrogenic compounds (31), estradiol −17β increases dramatically during pregnancy; therefore it is likely a major contributor to increased uteroplacental blood flow during gestation. In non-pregnant ovariectomized ewes, local infusion of estradiol −17β produced local uterine hyperemia without a systemic hypotensive reaction (125); thus indicating the response is mediated locally within the uterine vasculature.

It has been suggested that increased uteroplacental blood flow in response to estrogen is receptor-mediated (31). Further, estrogen receptors have been identified on the endothelial and VSM cells of the uterine artery (27). However, while stimulation of the estrogen receptors results in increased uterine blood flow, the functional mechanisms linking the stimulation to the response have yet to be elucidated (31).

It is also likely that estrogen modulates NO bioavailability by increasing endothelial and inducible NOS activity (229). Pharmacological inhibition of NOS activity has been shown to decrease estradiol −17β induced uterine hyperemia in non-pregnant ewes (216), this result was not reflected in the pregnant animal (184). Increased eNOS activation may be attributed to $Ca^{2+}$ handling, estrogen receptor activation, or caveolin-1 colocalization; however, these theories have yet to be confirmed. Further reading pertaining to steroid hormones and uterine vascular adaptations during pregnancy can be found here (31, 233).

***RELAXIN:*** Relaxin is also an important regulator of vascular adaptations during pregnancy (101). Circulating concentrations of relaxin are highest at the end of the first trimester and subsequently fall to intermediate levels throughout pregnancy (194). In a study of pregnant women, elevated serum concentrations of relaxin in early gestation were related to lower mean systolic blood pressures in the second and third trimesters of gestation, suggesting this hormone plays a potential role in endothelium-dependent vasodilation in pregnancy (9). Relaxin deficiency in mice led to a maintenance of uterine artery myogenic tone, whereas wild type animals produced an attenuated responsivity during pregnancy (133). Others, using pregnant and non-pregnant rats, theorize relaxin acts to mediate arterial VSM wall relaxation or compliance remodeling, possibly through continued modulation of MMPs (102, 220). Mechanisms responsible for relaxin-mediated vasodilation outcomes during pregnancy include increased NO (47), activation of the endothelin B receptor (52), upregulation of MMPs (102), and upregulation of VEGF (139, 168). Overall, relaxin has been shown to augment uterine blood flow during pregnancy through mechanisms that regulate maternal uterine vasodilation, vascular remodeling, and responsiveness during pregnancy. These mechanisms are not widely accepted, nevertheless, more detailed information can be found in recent literature (37, 116, 134).

***RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM:*** Endocrine regulation of vascular homeostasis also includes the influence of circulating catecholamines, NE and epinephrine, RAAS, and antidiuretic hormone. The collective actions of important humoral mechanisms contribute to the regulation of arterial blood pressure through changes in systemic vascular resistance.

A decline in systemic peripheral vascular resistance results in a net decrease in mean arterial blood pressure (MAP). To promote volume expansion and maintain MAP, the activity of the RAAS increases and remains elevated throughout pregnancy to retain salt and water. The decline in peripheral vascular resistance throughout pregnancy is associated with an increased production of vasodilators, and with the development of a refractoriness to α-adrenergic stimulation (115). In rodents, a pressor hyporesponsiveness was observed at gestational days 15 and 20, marked by substantial blunting of the pressor response to graded doses of angiotensin (ANG) II, NE, and arginine vasopressin (166). Similar results have

been reported during uncomplicated pregnancy in humans exhibiting a reduced vascular responsiveness to $\alpha$-adrenergic stimulation (115, 153) and ANG II infusion (18, 123). Liu et al. examined responses to NE and ANG II in isolated uterine artery rings from non-pregnant and pregnant women (34 – 40 weeks gestation) and observed increased sensitivity to NE compared with ANG II in non-pregnant and pregnant uterine arteries. Increased sensitivity to ANG II has been reported in the uterine, but not femoral, arteries of rabbits (147). Further, ANG II receptor subtype expression in uterine artery VSM was unchanged throughout reproduction suggesting the predominance of the type 2 ANG II receptor contributes to attenuated sensitivity to ANG II in uterine arteries from non-pregnant and pregnant women (186).

**Local Vascular Regulatory Mechanisms:** Local regulation of blood flow to satisfy tissue metabolic demand is achieved through the balance between mediators of vasodilation and vasoconstriction released from the vessel or from surrounding tissues. Intrinsic mechanisms crucial for regulation of local vascular tone include locally produced vasoactive factors (e.g. metabolites of arachidonic acid, histamine, bradykinin, NO, and endothelin-1) and myogenic autoregulation, an intrinsic capacity of vascular smooth muscle to regulate vascular tone in response to changes in intraluminal pressure (99, 159). Under normal physiological conditions, the vascular endothelium produces mediators of vascular hemodynamics in response to physical and chemical stimuli. Endothelial cells contribute to the regulation of blood pressure and blood flow through the production and release of vasodilators including NO and prostacyclin (PGI2), as well as vasoconstrictors including ET-1 and thromboxane A2 ($TXA_2$) (21, 193). In this section we review the main endothelial-derived factors for local uterine vascular control. Information regarding local ligand-receptor control of uterine blood flow through estrogen and relaxin may be found here (119, 154, 169).

The uterine artery responsiveness to local factors shifts toward increased dilation during pregnancy (Figure 11) (63). In isolated rat arteries, pressure myography studies demonstrate vascular dilation to the NO-donor sodium-nitroprusside is enhanced (Figure 11a), while vasocontraction to phenylephrine (PE) is delayed (Figure 11b), occurring independently from endothelial signaling (Figure 11c) (63, 235). Furthermore, pregnancy has been shown to enhance uterine artery myogenic tone, likely to protect the fetus from changes in blood pressure (238). An augmented myogenic tone is likely attributed to upregulation of local endothelium-independent calcium-handling mechanisms (75).

During pregnancy, NO plays a central role in maternal vascular adaptation and control of uterine and placental blood flow (201). eNOS protein expression increases by nearly 200% in uterine arteries of pregnant sheep, compared with non-pregnant controls (240). NO blockade throughout pregnancy in rats increased vascular tone and reduced maximal arterial dilation (236). A deficiency of NO and other important mediators of vasodilation in pregnancy may contribute to impaired uteroplacental blood flow by reducing both vasodilation and remodeling, and the genesis of pathological events including hypertension, preeclampsia, and intrauterine growth restriction (190, 215).

The balance between endothelial-derived relaxing factors and contracting factors represents a major determinant of basal vascular smooth muscle tone and subsequent downstream

blood flow. Uterine arteries have been shown to be less sensitive to the effects of serotonin, norepinephrine, ANG II, and thromboxane during pregnancy in a wide variety of animal models (129). These effects may be mediated by increased circulation, affinity, or action of NO. Experimental NO blockade or endothelial denudation in isolated rat uterine arteries increased sensitivity to serotonin, but did not return reactivity to control levels, indicating the likelihood of a nonendothelial source of NO (129).

As mentioned in the placentation section above, with profound increases in uterine blood flow during pregnancy (i.e., 10 to 50-fold) to support fetal growth and development, the uterine vasculature undergoes anatomic adaptation to maintain adequate uterine blood flow to the placenta (23). Beginning at mid gestation, maintaining uteroplacental blood flow becomes highly dependent on the capacity of the uterine vasculature to sustain vasodilation. Responsivity to humoral mediators of vasodilation and mediators of vasoconstriction is differential to the uterine vasculature, compared with systemic tissue beds. Endotheium-independent vasodilation is enhanced in uterine arteries, but not in mesenteric arteries during pregnancy (38).

Moreover, vasoconstrictor mechanisms are attenuated during pregnancy, compared with non-pregnant controls and other vascular beds. In pregnant uterine arteries isolated from rats, responsiveness to PE and ANG II declined early and remained diminished throughout pregnancy, while response to ET-1 moderated in late pregnancy (93). Similarly, significant reductions in responsiveness to thromboxane, norepinephrine, epinephrine, and PE have been reported in uterine arteries isolated from guinea pigs (227, 228). Pregnancy has also been demonstrated to reduce cortisol-mediated vascular smooth muscle contractility in the uterine artery of gravid sheep (239). Some theorize that pregnancy alters adrenergic signaling through enhanced α-adenoreceptor and impaired β- adenoreceptor activity, further modulating myogenic tone and responsivity in rats (159, 222). It is also likely that the reduction in vasoconstrictor actions are due to enhanced endothelium-dependent and -independent signaling (38, 226–228, 239). These differential responses may allow for increased blood flow to the uterus while preventing systemic hypotension during pregnancy (93).

During pregnancy, there is an increased production of vasodilator signals by the vascular endothelium (20). The concerted effects of circulating hormones, growth factors, and shear stress associated with pregnancy augment the expression and activity of endothelial NOS, prostacyclin, and endothelium-derived hyperpolarizing factor; the production of these factors may override vasoconstrictive signaling in the uterine vasculature during pregnancy (146).

Existing studies indicate a differential uterine vasoresponsiveness during pregnancy as compared to non-pregnant females. Importantly, most studies are conducted in late-stage pregnancy as the “experimental” group compared with controls (78, 129, 159). While the mechanisms controlling vascular reactivity during late pregnancy remain unclear, the time course associated with these modifications between trimesters during pregnancy also remains unexplored. Furthermore, while it is widely accepted that pregnancy elicits divergent responses between reproductive and systemic vascular beds, (38, 41, 93), the

anatomical differential within the myometrial, endometrial, placental, and umbilical arteries and arterioles remains unclear despite historical interest (5, 60, 78, 82, 93).

## Delivery

Multiple factors contribute to the detachment of the placenta from the uterine wall. Toward the end of gestation, sources of immune suppression at the maternal-fetal interface are reduced. The effects of immune stimulation is twofold; by the 9$^{th}$ month of gestation maternal immune cells induce apoptosis of trophoblast and endometrial epithelial cells, beginning placenta release, and creating a pro-inflammatory environment that promotes contraction of the uterus, delivery of the fetus and overall rejection of the semi-allogenic placenta (183). While the fetal signals that initiate maternal labor remain under investigation, it is reported that fetal-derived hormones (adrenocorticotropic hormone, oxytocin) and other biological signals trigger myometrial pathways and stimulate myometrial contraction (140).

Contractions during labor and delivery impart mechanical separation and slow, progressive detachment of the placenta. During contractions, the muscular uterine wall begins to atrophy. It rapidly transitions from being very taut at term pregnancy, to a reduced tension after the fetus is delivered, and thereby alters the diameter and circumference of the placental attachment. The placenta cannot reduce in size or contract along with the myometrium, and as a result, vascular attachments begins to separate. The placenta ultimately separates at the natural cleavage site of the basal plate and the decidual basalis. Oftentimes, the placenta is delivered quickly after the fetus. Manual removal of retained placental tissue involves risks of hemorrhage and infection (232).

Placental detachment leaves behind an “open wound” of deserted blood vessels, leading to hemorrhage after delivery. A peak in clotting activity occurs at the onset of labor and delivery. Thromboplastin is released during placental expulsion and initiates disseminated intravascular coagulation in the uterus to protect the mother from hemorrhage. Approximately 1-hour postpartum, depressed activity of tissue plasminogen activator (t-PA), a serine protease responsible for catalyzing the conversion of plasminogen to plasmin, returns to pre-pregnancy levels to maintain uterine blood flow (213). Firm uterine contraction and intertwining muscle bundles squeeze around branches of uterine arteries to slow blood flow and to compress the vessels shut (81). If the uterus fails to contract, bleeding continues, and may result in a possible emergency hysterectomy (11). The uterine mucosa heals without scarring. Fibrotic tissue inhibits decidualization and invasion, making future implantations at or around the initial site impossible (237). The uterus undergoes a healing process called “involution” that transforms the tissue matrix to a non-pregnant state. The endometrial lining becomes covered by fibrin and blood clots. Within 24-hours post-partum, the spiral arterioles of the implantation site disintegrates, becomes hyalinized, and necrotic (11). Endometrial veins undergo thrombosis and arteries develop arteritis, leading to overall necrosis of the decidua. The endometrial glands that paused with the menstrual cycle hiatus, regrow, and extend through the stroma. Within three to four weeks post-partum, the endometrial tissue of the implantation site has regenerated and uterine vessels have recanalized (11).

## PATHOLOGICAL CONSEQUENCES OF VASCULAR DYSFUNCTION IN PREGNANCY

Pregnancy outcome is affected by maternal vascular capability to support gestation and the region of uterine wall where the blastocyst implants. For example, anterior placental attachments are associated with a greater risk of pregnancy-induced hypertension (i.e., preeclampsia), gestational diabetes, placental abruption, intrauterine growth retardation, and intrauterine fetal death (244), while implantation on the posterior uterine wall is associated with preterm labor. Therefore, the site of implantation and placentation may be an important determinant of placental perfusion throughout pregnancy. Furthermore, uneven uterine blood distribution may result in the overperfusion of some regions and under-perfusion of others; thus contributing to positional effects, variable success in placentation, and negative pregnancy outcomes. A brief overview of placental disruptions may be found below. Further readings for each condition are presented within respective section(s).

### Placental Abruption

Placental abruption is the premature separation of the placenta from the uterine wall, an event that compromises its vascular integrity and reduces fetoplacental perfusion. The pathophysiology of placental abruption involves maternal blood vessels tearing away from the placenta prior to labor (197). Bleeding occurs, and blood accumulates between the space of the wall of the uterus and placenta, further separating the uterine wall and placenta. Abruption of the placenta may occur secondary to substance abuse by the mother, hypertension, physical trauma to the abdomen, or conditions that cause the uterus to overstretch (10, 145, 197). The uterus is a muscle that can withstand lengthening; however, the placenta is less flexible and therefore myometrial elongation may tear away at the vascular connections between endometrium and the maternal side of the placenta. Placental abruption can vary in severity from mild to severe depending on extent and location of separation and can be assessed by maternal clinical presentation. Separation can be complete, partial, central or marginal (197). If sufficiently severe, the fetus will not receive enough oxygen and nutrients, and intrauterine death may occur. A systemic review pertaining to placental abruption can be found here (51).

### Placenta Previa

Placenta previa occurs when implantation is low in the uterus and, as the placenta develops, it grows to cover the cervical opening. Cervical tissue is not primed for an implantation and is incapable of providing the vascular support necessary to support fetal needs. Consequently, placental perfusion is impaired, and the pregnancy may be compromised. Further, placentation in this area will overlap the cervical opening to the vaginal canal for birth. Upon initiation of labor, contractions can cause extensive hemorrhaging as cervical dilation will disrupt the placenta’s vascular connections and lead to fetal distress (164).

### Placenta Accreta, Increta, and Percreta

Placenta accreta is defined as a spectrum of abnormal adherence to the uterine wall, becoming inseparable at the risk of massive maternal blood loss. In normal pregnancy,

the placenta does not invade past the inner third of the myometrium. In these disorders, the placenta invades through the myometrium, or through all layers of the uterus and into the peritoneum, leading to compromised perfusion and increased risk of hemorrhage (17). This pathology is a result of imbalanced decidualization and trophoblast invasion (100). A review pertaining to the clinical implications of these conditions can be found here (199).

## Preeclampsia

Preeclampsia is a specific and multifactorial maternal hypertensive disorder that occurs during pregnancy. Clinically, the diagnosis of preeclampsia occurs with acute onset hypertension and proteinuria (171). This syndrome threatens the life of the both the mother and the developing fetus.

While there are many theories regarding the cause of preeclampsia, including maternal health conditions or fetal genetics, no single mechanism has been established (171). Therefore, the development of preeclampsia is associated with both maternal hypertensive conditions and abnormal placental formation/invasion (196). Pregnancy-exacerbated maternal hypertension may lead to the development of end-organ damage with long-term, postpartum consequences to maternal health (170).

Proposed mechanism of preeclampsia include increased expression of antiangiogenic influences, as well as reduced expression of proangiogenic VEGF and PGF (92). Failure of fetal invasive trophoblasts to express necessary molecules and appropriately engage with uterine spiral arteries likely contributes to the development of preeclampsia in humans (242). These may occur in conjunction with factors secreted from the placenta and fetus including soluble endoglin (sEng) and soluble fms-like tyrosine kinase 1 (sFlt1) -1 (170). Upregulation of sEng and sFlt-1 is reported in preeclamptic women. Excess sFlt placental may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia (137, 219). Increases in reactive nitrosative or oxidative radicals may trigger or exacerbate the development of maternal preeclampsia (210). Preeclampsia may occur with reduced circulating maternal estrogen, improper uterine remodeling, reduced NO bioavailability, and reduced heme oxygenase (128, 170).An in depth review of preeclampsia is outside the scope of this presentation; however, further reading on preeclampsia and the associated the vascular perturbations can be found here (20, 22, 26, 170, 171).

## Placental Insufficiency

A reduced blood supply and fetal undernourishment may occur when trophoblast invasion of the spiral arteries is not sufficiently robust, or if the upstream maternal vasculature is unable to respond appropriately through a combination of vasodilation and expansive remodeling, thereby compromising blood flow to the placenta and the developing fetus (Figure 5) (178). This results in reduced fetal growth and culminate in intrauterine growth restriction (IUGR). Placental function is insufficient because of compromised uteroplacental blood flow and this, in turn, effects the growth and development of the fetus. As a consequence of impaired blood flow, the placenta may be unable to fully develop and will have weight and dimensions less than those women without IUGR (191).

### Miscarriage

Miscarriage, defined by the loss of a pregnancy, is the most common pregnancy complication. Some 12%–24% of medically recognized pregnancies end in miscarriage, and it is estimated that one third of all pregnancies are lost due to miscarriage (223). Etiologies of miscarriage include genetic, endocrine, anatomic, immunological, infectious, environmental and metabolic factors (13). Decreased expression of angiogenic and vasoactive factors IL-10, VEGF and eNOS contribute to uterine vascular dysfunction at the time of blastocyst implantation, leading to early loss of pregnancy (13, 67). Insufficient blood supply to the endometrium may develop into fetal ischemia, and is thought to contribute to spontaneous miscarriage within 24 weeks of gestation (14). Lastly, recurrent pregnancy losses have been attributed to improper placental vascularization and spiral arterial remodeling during invasion and placental maturation (53).

## FUTURE DIRECTIONS AND KNOWLEDGE GAPS

The development of novel and innovative methodologies in vascular physiology permit greater scientific understanding of the uterine vascular bed, including the gravid uterus. The development of catheterization and implantation of flow probes grant the identification of pressure and flow variation (78, 83). The utilization of pressure myography techniques allows for further understanding of the molecular signaling mechanisms attributed to vasodilation and constriction in the uterine vascular bed (88, 159, 160). Isolation techniques are used to investigate vascular reactivity within a single utero-placental unit (43, 74, 77) or the utero-placental-fetal unit as a whole (112). Development and optimization of intravital microscopy techniques allow *in vivo* investigation of the uterine circulation without impairing neural or humoral input (3, 117, 209) alongside advances in ultrasound technologies to visualize rodent vascular modifications and Doppler blood velocity (149). These and future technological advances are critical to gain a comprehensive understanding of the mechanisms and molecular signaling pertaining to uteroplacental vascular control.

Uteroplacental vascular function remains a widely understudied field. The temporal relationships between systemic macrovascular and local microvascular modifications remain unclear. The physiological mechanisms supporting increased uterine perfusion without systemic hypotension remain clouded. Many studies are limited by evaluating uterine hyperemia in a non-pregnant ovariectomized animal and extrapolating those outcomes to pregnancy. The physiological modifications and hormonal milieu during pregnancy must be taken into consideration. Currently, we lack a basic understanding of the primary and compensatory mechanisms pertaining to uterine vascular control during pregnancy. Without this background, it is difficult to develop pharmacological interventions to treat pathological conditions during pregnancy, understand the sequelae of maternal-fetal environmental exposures, or identify the molecular mechanism associated with the fetal or developmental onset of disease in progeny (i.e., the biological mechanisms supporting the Barker Hypothesis/Developmental Onset of Health and Disease model) (44).

Lastly, the majority of pre-clinical studies are performed utilizing a rodent model of pregnancy. While these studies are important to identify likely mechanistic pathways, the laboratory models do not readily mimic human pregnancy-related diseases (e.g.,

preeclampsia). These differences impair the testing of novel therapeutic strategies in pre-clinical models.

## CONCLUSION

The menstrual cycle and pregnancy both present unique challenges to the maternal cardiovascular system that require considerable adaptation. In addition to systemic changes in cardiac output and blood volume, pressure, coagulability and composition, the circulation of the uterus must respond in varied and specific ways to accommodate placentation and, as pregnancy progresses, to provide sufficient placental perfusion to assure normal fetal growth and development. Failure of early events such as implantation and spiral artery invasion is associated with early pregnancy loss and miscarriage, as well as with subsequent development of gestational diseases such as preeclampsia and IUGR. As discussed in this review, proper placentation is essential for normal pregnancy outcome, and involves a complex interplay of spatial and temporal changes that provide for normal fetal nutrient delivery and waste removal. Furthermore, uterine artery and arteriolar responsivity and remodeling are paramount to the vascular control of pregnancy and to ensure placental and fetal perfusion. Overall, the basic science and mechanistic literature in these areas are lacking, leaving the immediate demand for further laboratory, translational, and clinical understanding of vascular control of pregnancy.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| **ANG** | angiotensin |
| **eNOS** | endothelial nitric oxide synthase |
| **ER** | estrogen receptors |
| **ET-1** | endothelin-1 |
| **GFR** | glomerular filtration rate |
| **IL** | interleukin |
| **IUGR** | intrauterine growth restriction |
| **LH** | luteinizing hormone |
| **MAP** | mean arterial blood pressure |
| **MMP** | matrix metallopeptidases |

| | |
|---|---|
| **NE** | Norepinephrine |
| **NO** | nitric oxide |
| **PE** | phenylephrine |
| **PGF** | placental growth factor |
| **PGI2** | prostacyclin |
| **PIF** | preimplantation factor |
| **RAAS** | renin-angiotensin-aldosterone-system |
| **sEng** | soluble endoglin |
| **sFlt1** | soluble fms-like tyrosine kinase 1 |
| **SVR** | systemic vascular resistance |
| **t-PA** | tissue plasminogen activator |
| **$TXA_2$** | thromboxane A2 |
| **uNK** | uterine natural killer cells |
| **VEGF** | vascular endothelial growth factor |
| **VSM** | Vascular Smooth Muscle |

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## DIDACTIC SYNOPSIS

**Major Teaching Points**

- The uterus receives blood from bilateral uterine and ovarian arteries. The dual perfusion of the uterus is a unique evolutionary adaptation to provide adequate uterine blood flow and its redundant architecture assures continuation of blood flow in case of blockage.
- Decidualization is the process by which the endometrium thickens in preparation for pregnancy, providing a nutritive matrix for implantation. In humans, decidualization occurs with each menstrual cycle.
- Vascular reactivity and tone are related to the local responsiveness or functionality of the arteries and arterioles. Under normal, homeostatic conditions, arterial and arteriolar vascular smooth muscle (VSM) cells remains at a partially constricted state, referred to as tone. Uterine artery and arteriolar tone are significantly reduced during pregnancy, allowing for uteroplacental hyperemia.
- During early pregnancy, trophoblasts invade through the decidualized endometrium and migrate retrograde to blood flow to the distal ends of the spiral arterioles. Later in pregnancy, trophoblasts supplant the spiral arteriolar endothelial cells, thereby ramifying and widening the arteriolar lumen.
- A combination of expansive vascular structural remodeling and changes in blood vessel reactivity regulate uterine vascular resistance to accommodate increased uteroplacental blood flow during pregnancy and satisfy the needs of the developing fetus.
- Vascular dysfunction in the forms of remodeling or responsivity during pregnancy has pathological consequences for the mother and developing fetus.

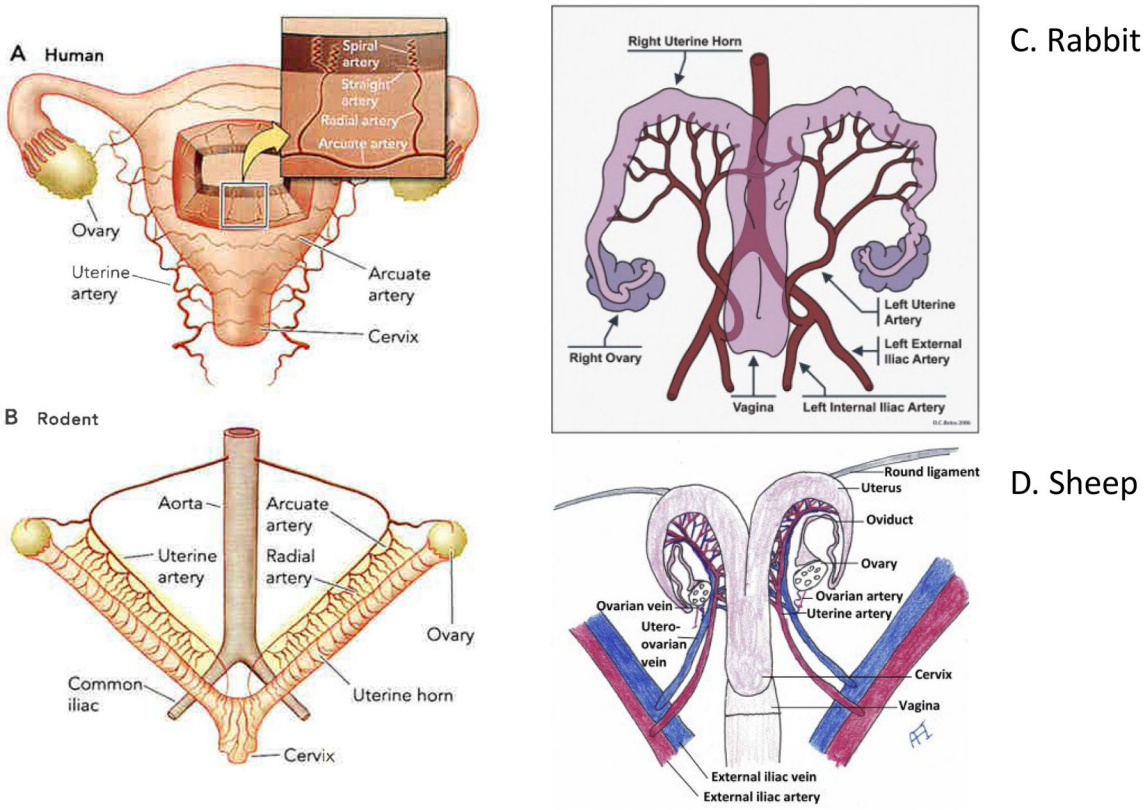


**Figure 1. Uterine gross anatomy and blood supply.**

**(A) Human Uterus.** View of the human female reproductive tract. Human uterine blood flow is derived from the ovarian and uterine arteries. These arteries branch to form the arcuate artery, allowing for greater tissue perfusion. The arcuate arteries subsequently branch to the radial artery, straight/basal arterioles, and spiral/preplacental arterioles. **(B) Rodent Uterus.** The rodent uterus is a dual-horn, bilateral organ allowing for multiple pup litters. The vascular architecture between the human and rodent uteri are very similar, making the rodent an ideal model to assess reproductive physiology. **(C) Rabbit Uterus.** The rabbit also has a duplex uterus, with two independent uterine horns combining at the cervix to allow for multiple fetus. The vasculature is very similar to that of the rodent, with their main artery supply via the ovarian artery, with bifurcates to the ovarian and uterine branches, the uterine artery supplying the distal uterine horn, and the vaginal artery. Secondary arteries may form analogous to human arcuate arteries arcuate and radial arteries provide blood supply to the myometrium and preplacental arterioles. **(D) Sheep Uterus.** The sheep uterus consists of two conjoined cavities with a short uterine body. The vasculature is similar to that of humans with the main source of blood flow supplied by the uterine artery. The ovary is supplied by the ovarian artery. The uterine artery branches, giving rise to anastomose, which act in a similar fashion to human arcuate arteries. These branches give rise to coiled secondary radial arteries that supply the myometrium and preplacental vessels.

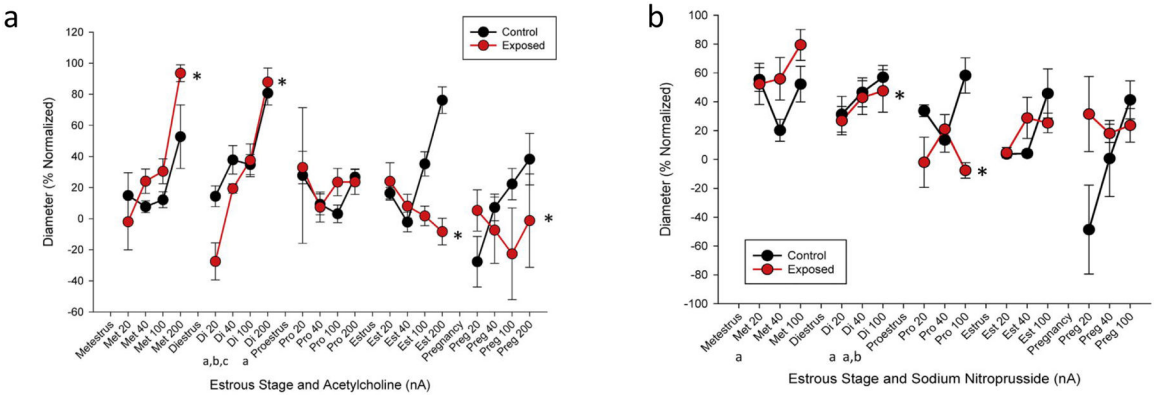


**Figure 2. Vasodilation during the estrous cycle and pregnancy.**

Vascular reactivity to endothelium-dependent (a) or -independent (b) modulators of vascular smooth muscle relaxation varies during the phases of the rodent estrous cycle (black lines). Perturbations to maternal homeostasis through natural (e.g., circadian rhythm disturbances or noise pollution) or chemical (e.g., air or water pollution) exposures may make these variations more pronounced (red lines). Reprinted with permission (208).

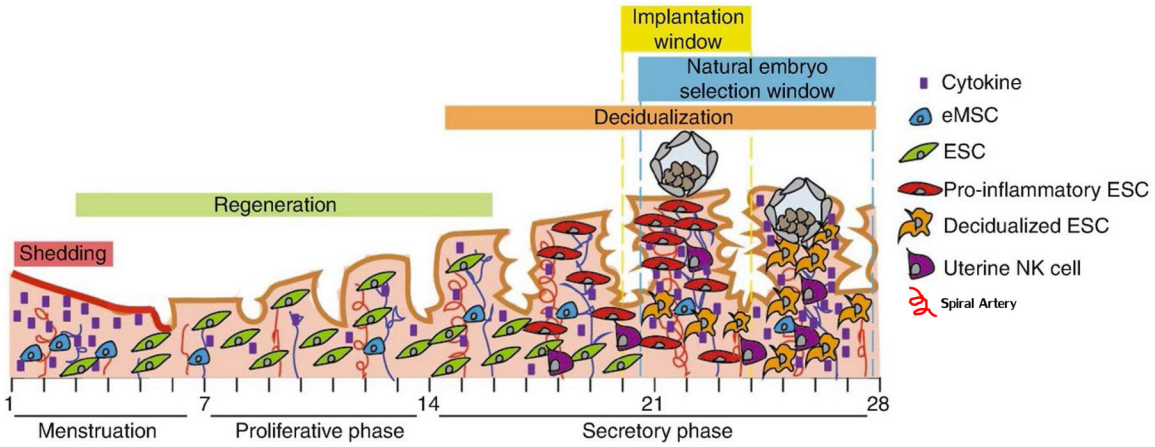


**Figure 3. Decidualization.**

Representation of decidualization of the human endometrium. Morphological and functional differentiation of endometrial stromal cells (ESCs), especially during the implantation window, is required for successful pregnancy outcome. Reprinted with permission (151).

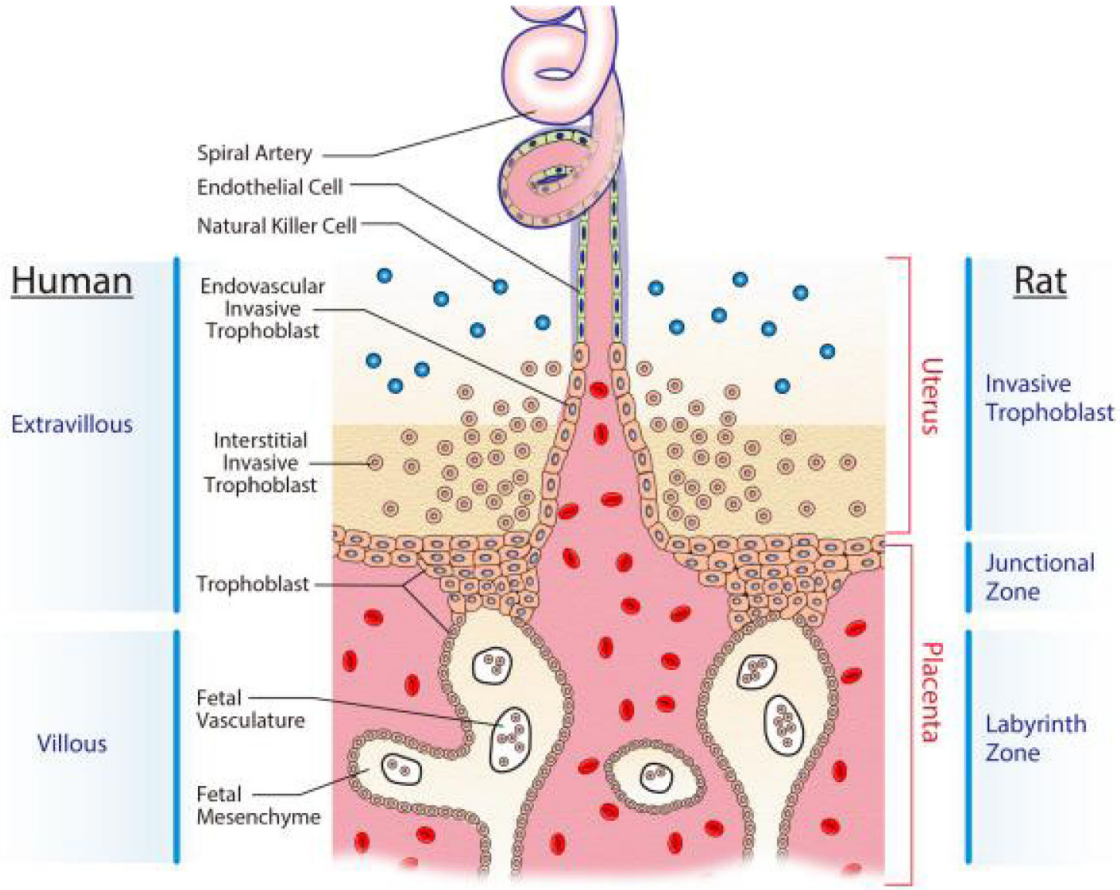


**Figure 4. Trophoblastic Invasion.**

Trophoblast invasion and spiral artery remodeling in healthy pregnancy. Reprinted with permission (203).

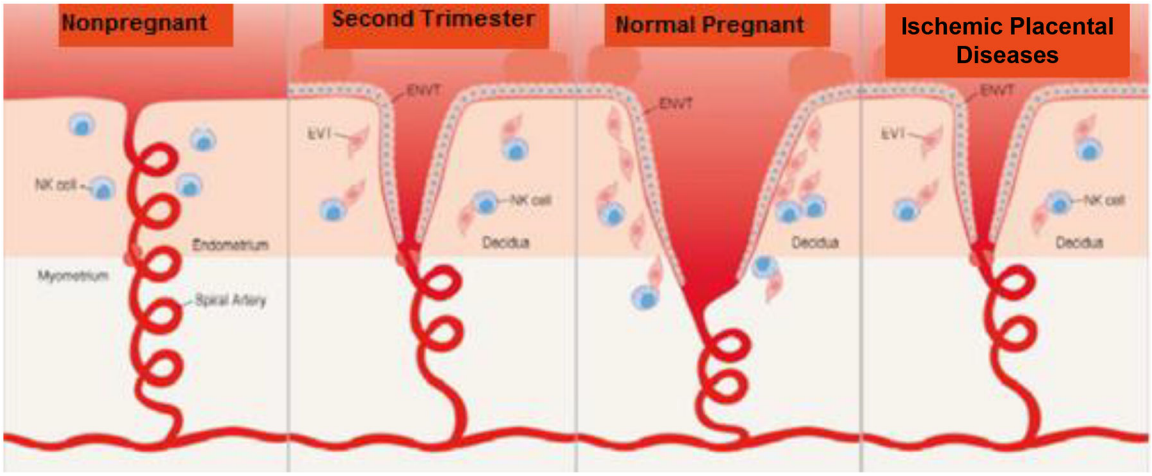


**Figure 5. Spiral Artery Remodeling.**

Spiral artery remodeling continues throughout pregnancy, into the second and third trimesters to provide increased blood flow to the growing fetus. Pregnancies that suffer from ischemic placental disease may demonstrate shallow trophoblast invasion and defective vascular remodeling; thus, leading to reduced maternal blood flow and compromised fetal growth. Reprinted with permission (178).

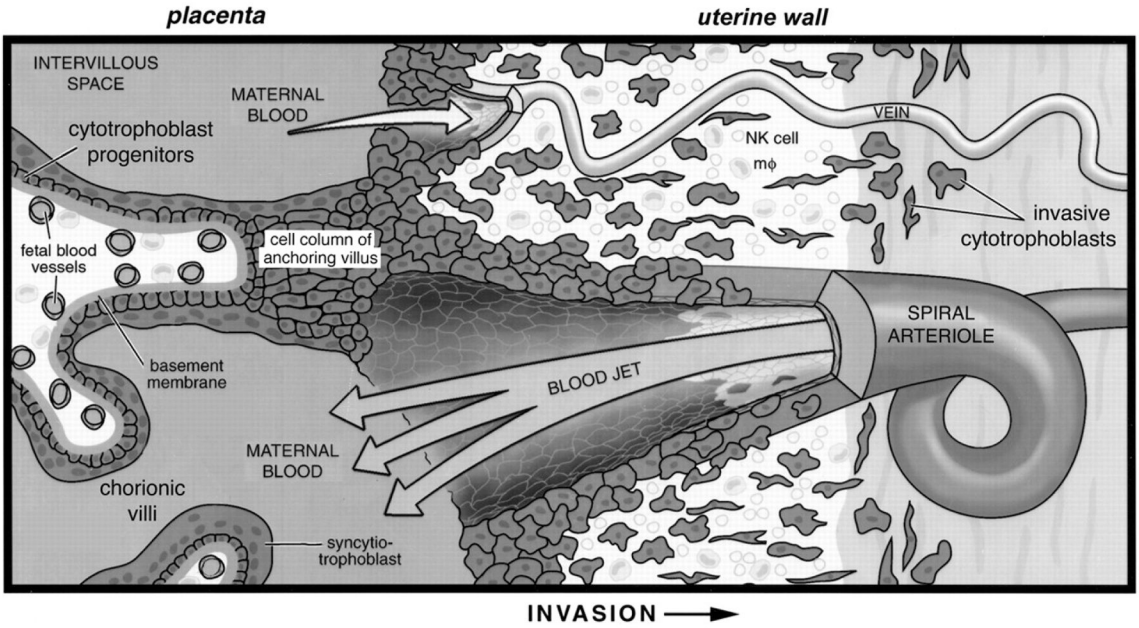


**Figure 6. Circulation of the Intervillous Space.**

Maternal blood enters the intervillous space from uterine spiral arteries and flows around terminal villi. After the exchange of oxygen and nutrients, the umbilical vein carries oxygenated and nutrient-rich fetal blood to the fetal circulation. Reprinted with permission (173).

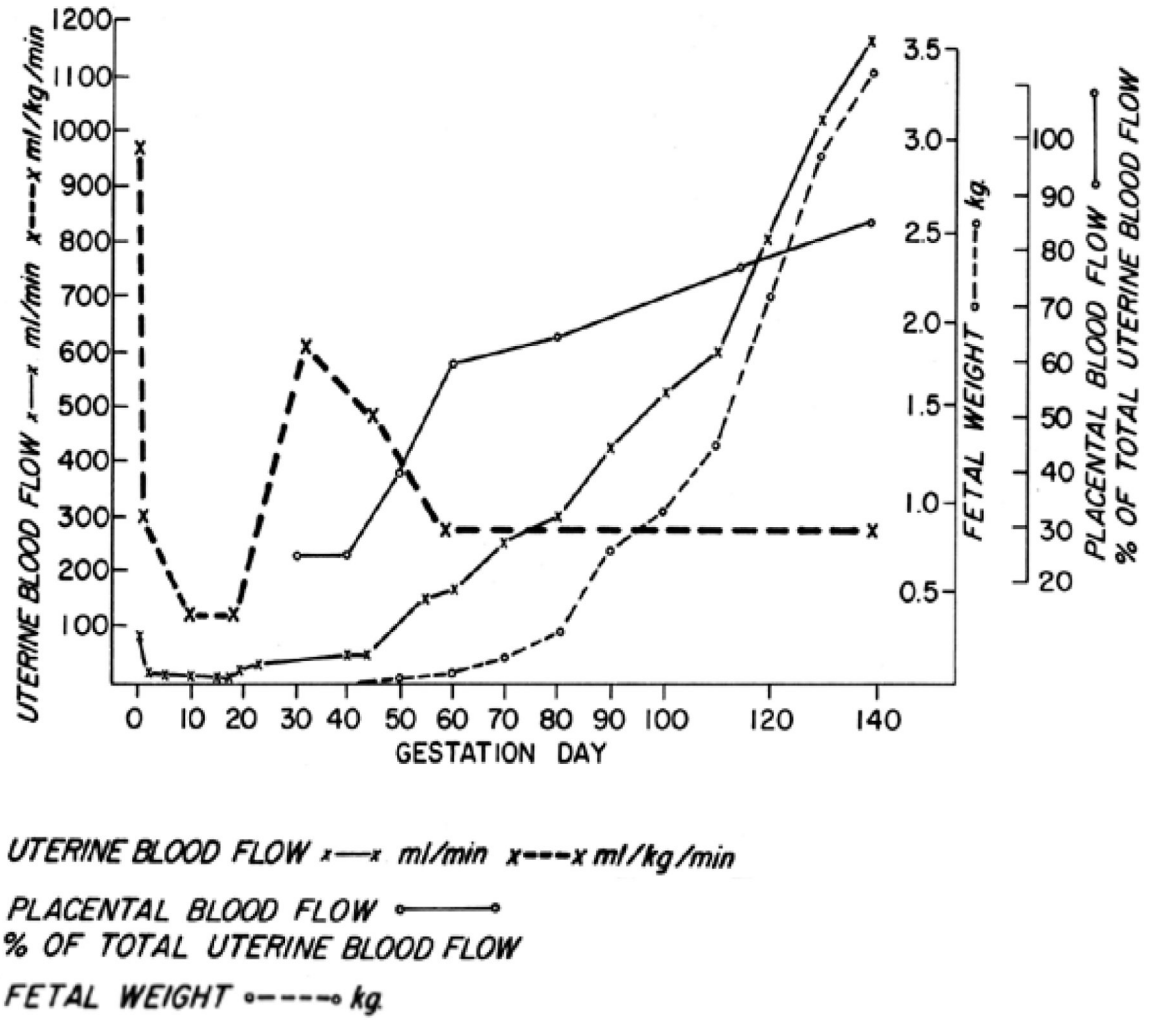


**Figure 7. Uteroplacental Blood Flow.**

Schematic depicting the increase in uterine blood flow through gestation in response to fetal growth. Reprinted with permission (81).

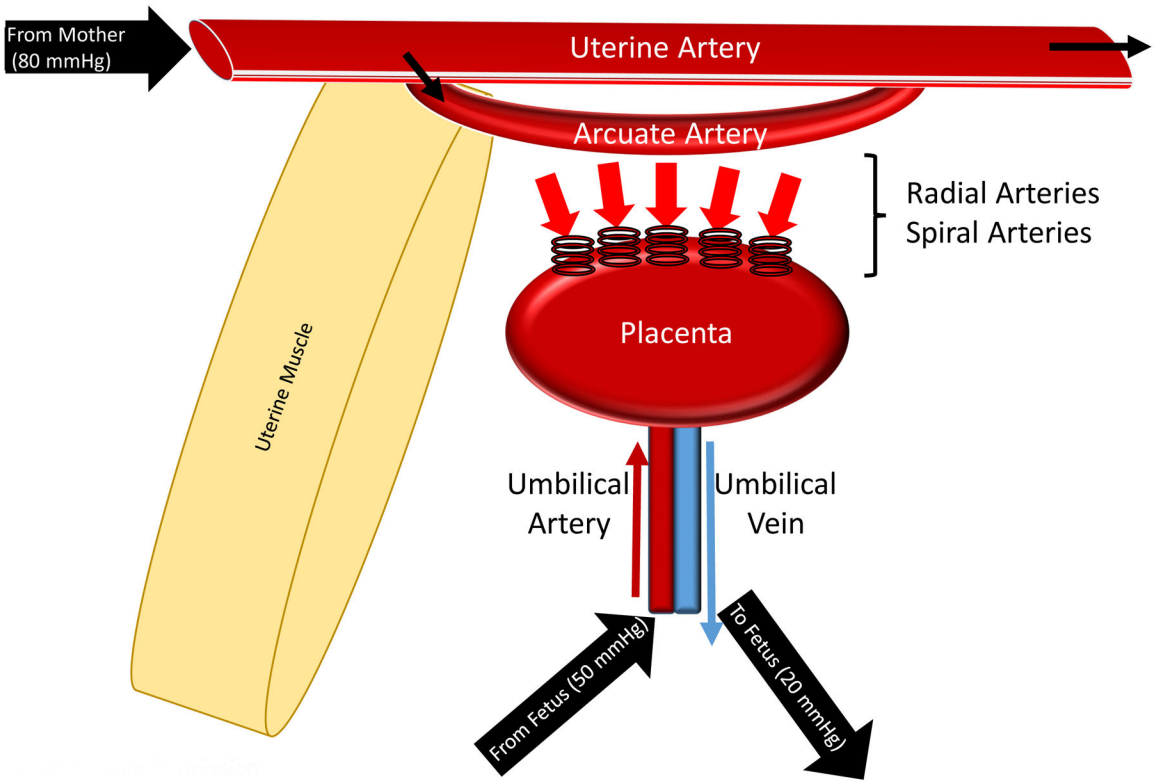


**Figure 8. Uteroplacental and Fetoplacental Circulation.**

The uterine, radial, and spiral arteries/arterioles perfuse the placental with nutrient-rich blood. The fetoplacental circulation includes the umbilical cord and the blood vessels within the placenta that carry fetal blood. Umbilical arteries carry deoxygenated and nutrient-depleted fetal blood from the fetus to the villous core fetal vessels where the exchange of oxygen and nutrients takes place. The umbilical cord returns oxygenated and nutrient-rich fetal blood to the fetal circulation. Adapted with permission (42, 43).

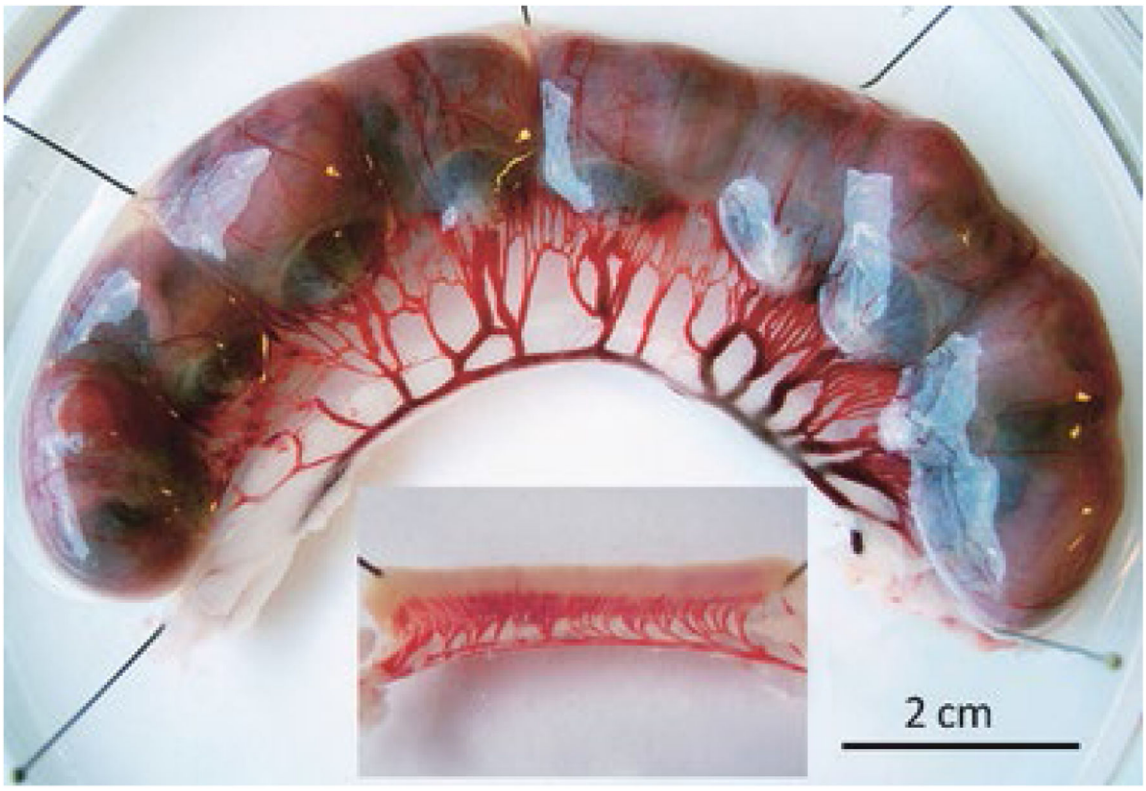


**Figure 9. Uteroplacental Growth.**

The uterine vasculature and muscle remodel significantly to sustain a successful pregnancy. This photograph showing age-matched uterine horn from pregnant (top) and non-pregnant (bottom) rats to depict vascular growth during pregnancy. Reprinted with permission (130).

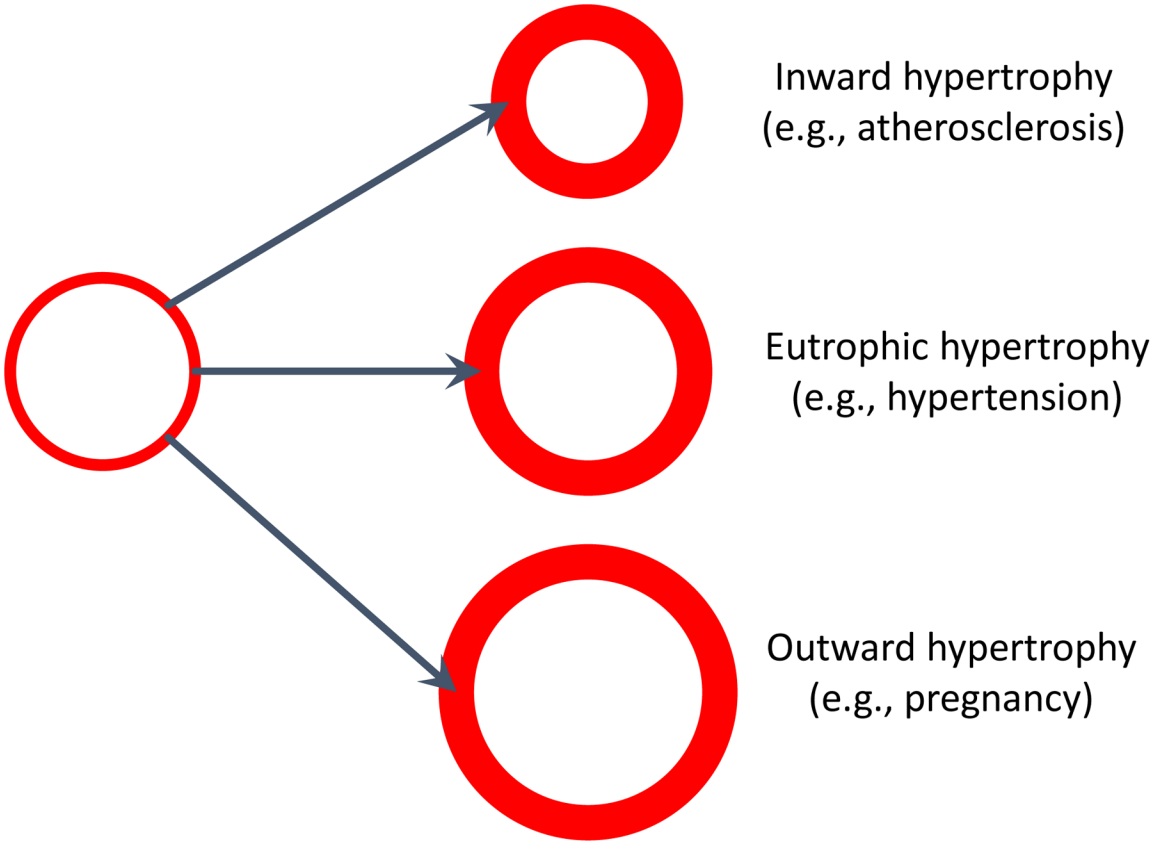


**Figure 10. Uterine Vascular Hypertrophic Remodeling.**

Vascular remodeling may be normal or pathologic. Hypertrophic vascular remodeling describes an increase in luminal wall thickness. This remodeling may be inward (i.e., narrowing the vascular lumen), eutrophic (i.e., maintaining luminal circumference), or outward (i.e., expanding the vascular lumen). The remodeling in the uterine circulation during gestation may be described as outward hypertrophic, thereby increasing both wall area and luminal cross-section.

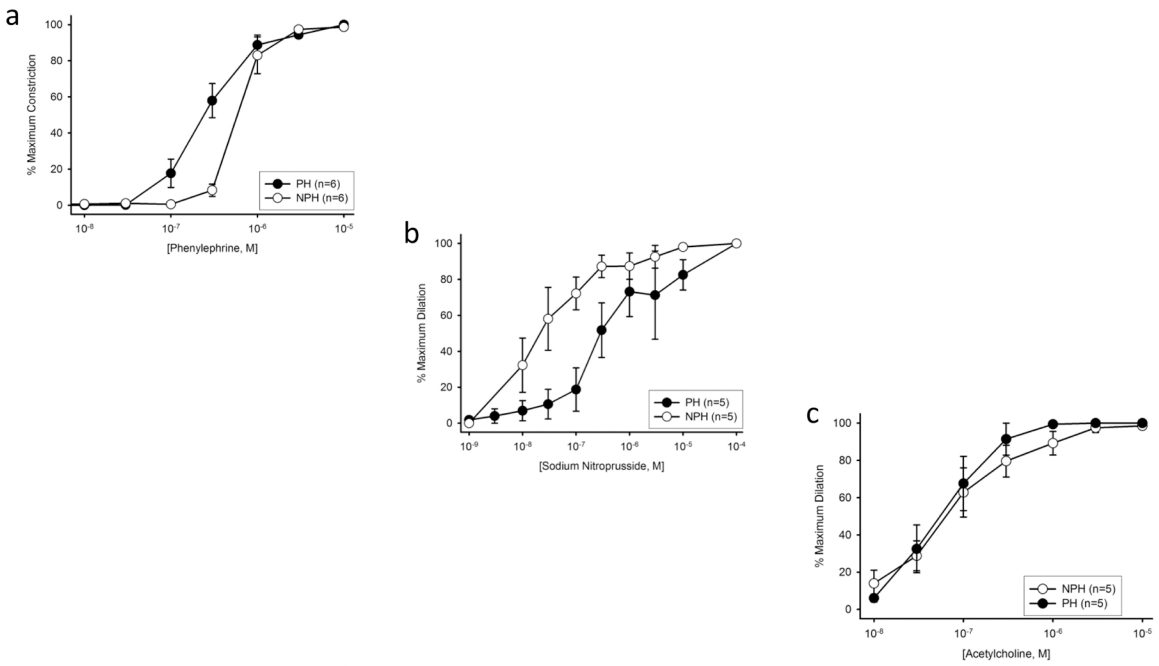


**Figure 11. Uterine Vascular Reactivity.**

Local vascular responses are altered during pregnancy, shifting toward vascular smooth muscle (VSM) relaxation and subsequent vasodilation. This shift is depicted by: (A) reduced responsiveness to phenylephrine, a vasoconstrictor, (B) heightened response to sodium-nitroprusside, an endothelium-independent vasodilator in arcuate arteries from pregnant rats compared to nonpregnant, and (C) no change in responsivity to acetylcholine, an endothelium-dependent vasodilator between arteries excised from pregnant and non-pregnant rats. Reprinted with permission (63).