Impact of Experimental Diabetes on the Maternal Uterine Vascular Remodeling During Rat Pregnancy

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Abstract

Normal pregnancy is associated with an increase in uteroplacental blood flow in part due to growth and remodeling of the maternal uterine vasculature. In this study, we characterized the effect of diabetic pregnancy on vascular growth of the maternal uterine vasculature and on the passive mechanical properties of the uterine resistance arteries. Diabetes was induced in pregnant rats by injection of streptozotocin and confirmed by development of hyperglycemia. Fetuses of diabetic rats were significantly smaller and placentas larger compared to controls. Pregnancy-induced axial elongation of the mesometrial uterine vasculature was not altered by diabetes. Vascular wall thickness was unchanged between groups. Wall distensibility was increased and the rate constant of an exponential function fitted to stress-strain curve was significantly reduced demonstrating decreased wall stiffness in diabetic uterine radial arteries compared to controls. We conclude that experimental diabetes in rat pregnancy does not compromise the growth of maternal uterine vasculature but alters passive mechanical properties of the uterine radial arteries.

Keywords

streptozotocin, uterine vascular growth, arterial wall distensibility, stiffness

Introduction

Normal pregnancy is accompanied by significant maternal cardiovascular adaptations. Plasma volume and cardiac output rise markedly, beginning in the first trimester of pregnancy. By the second half of pregnancy, the distribution of cardiac output changes substantially in favor of uteroplacental blood flow that increases from 20 to 50 mL/minute in the nonpregnant state to 450 to 800 mL/minute in term singleton human pregnancies.^{1,2} Additionally, systemic and uterine vascular resistance decrease with advancing gestation. Structural adaptations of the maternal vasculature, particularly of the uteroplacental circulation, are necessary to accommodate the normal cardiovascular changes during pregnancy and to ensure an adequate blood supply to the developing placenta and fetus.³⁻⁵

In species with a hemochorial placentation, including humans, both longitudinal and circumferential structural remodeling of the maternal uterine vasculature can be detected by late pregnancy. The uterine vessels undergo marked elongation during uterine growth that is a unique structural change in the uterine vasculature.⁵⁻⁷ The circumferential vascular remodeling associated with normal pregnancy has been characterized as outward hypertrophic, with increases in both lumen diameter and cross-sectional area via smooth muscle cell hypertrophy and hyperplasia.^{5,8,9} This phenomenon has been shown in both

the main uterine artery (MUA) as well as in the smaller uterine resistance arteries in multiple species including sheep, pigs, rats, and humans.^{7,8,10-15}

The uterine spiral arteries—the distal extensions of uteroplacental radial arteries supplying the placenta—further undergo trophoblast-induced remodeling, with trophoblast invasion into the vascular wall and widening of the vascular lumen.^{6,16-18} The spiral arteries become progressively larger and more tortuous with replacement of the normal musculoe-lastic wall with fibrous tissue and loss of their constrictor function. Therefore, the proximal unmodified portion of the uteroplacental radial arteries becomes the main site of vascular resistance in the uteroplacental circulation of humans and animals with a hemochorial placentation.^{6,15,16,19}

Arterial compliance and distensibility of the uterine vasculature are also affected by pregnancy. In the MUA of sheep,

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higher stress-strain ratios were found in late pregnant compared to nonpregnant animals, suggesting an increased arterial stiffness and decreased arterial compliance.¹² In other animal models, however, both the MUA and smaller arcuate and radial arteries are more distensible during pregnancy compared to the nonpregnant state.^{5,20}

Deficient structural remodeling of the maternal uterine vasculature is thought to contribute to pregnancy complications such as preeclampsia.^{21,22} Pregnancy in patients with diabetes is often complicated by uteroplacental insufficiency and adverse outcomes including hypertension, preeclampsia, intrauterine growth restriction (IUGR), and stillbirth. In a human study of pregestational diabetics with vasculopathy, abnormal uterine artery Doppler velocimetry demonstrated by higher vascular impedance has been shown to be associated with small for gestational age infants.²³ Abnormal uteroplacental hemodynamics have also been shown in animal studies as a result of experimental diabetes. Decreased placental blood flow, as measured by Doppler methodology on day 20 of pregnancy, has been shown in diabetic rat pregnancies.^{24–26}

The exact nature of the diabetes-associated increase in uterine vascular resistance remains unknown and may include insufficient structural remodeling and/or changes in the functional behavior of the maternal uteroplacental vasculature. The objective of this study was to characterize the impact of experimental diabetes in rat pregnancy on vascular growth of the maternal uterine vasculature and on passive mechanical properties of uterine radial arteries, the major site of regulation of vascular resistance in the maternal uterine circulation.

Materials and Methods

Animal Model of Diabetic Pregnancy

All experiments were conducted in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* (NIH Publications No. 85-23, Revised 1996), and the experimental protocols were approved by the Institutional Animal Care and Use Committee of the University of Vermont.

Virgin Sprague-Dawley rats (10–11 weeks of age) were purchased from Charles River Laboratories International (Wilmington, Massachusetts) and housed in the animal care facility at the University of Vermont which is accredited by the American Association for Accreditation of Laboratory Animal Care. Estrus cycle for female rats was determined by examination of vaginal smears, and rats in proestrus were used for breeding. Females were bred with Sprague-Dawley males overnight in isolated pairs using metabolic cages at the University of Vermont Animal Care Facility. If copulative plugs were observed the following morning that day was designated day 1 of pregnancy.

On day 2 of pregnancy, female rats were weighed and random blood glucose levels were determined from a tail nick using a Freestyle glucometer. Rats were briefly (3 minutes)

anesthetized with 4% isoflurane (VetEquip, Inc, Pleasanton, California), and 50 to 55 mg/kg streptozotocin (STZ) in 1 mL citrate buffer was injected intraperitoneally. Streptozotocin was weighed and dissolved in sterile citrate buffer 2 minutes before injection. Control pregnant rats were injected with 1 mL citrate buffer. Both STZ- and citrate buffer-injected rats were weighed every 2 days. Their blood glucose levels were determined every other day using a Freestyle glucometer. On day 20 of pregnancy, rats were anesthetized with 4% isoflurane and after a negative tail pinch test euthanized by decapitation in a small animal guillotine.

Experimental Measurements of Uterine Vasculature

The gravid uterus and uterine vasculature were carefully removed and placed in a dissecting dish containing cold, physiologic salt solution (PSS) aerated with 5% O₂, 10% CO₂, and 85% N₂. Morphometric measurements of the unstretched uterine vasculature of both uterine horns were completed first. We used a stereomicroscope (Zeiss Stemi 2000-C) with a calibrated reticule to determine the length of the MUA as well as the distance between the MUA and placenta or myometrium on the ovarian and cervical side and in the center of each uterine horn. Main uterine and second-order uterine radial arteries feeding the placenta (uteroplacental) or myometrium (premyometrial) were then carefully dissected free from the surrounding connective tissue and used for in vitro experimentation. Fetuses and their placentas were individually weighed without membranes and umbilical cords. Dimensions of the shortest (*a*) and the longest (*b*) axes of each placenta were determined under Zeiss stereomicroscope to calculate the placental surface area (*S*) using the equation: $S = 3.142 (ab/2)$. Litter size and number of resorptions were recorded for diabetic and control rats.

Arteries were cannulated in an arteriograph that was placed on the stage of an inverted microscope with an attached video camera. Arteries were pressurized using a Servo pressure system (Living Systems Instrumentation, Burlington, Vermont) and continuously superfused at 3 mL/min with aerated PSS at 37°C and pH = 7.4. To determine vascular distensibility (the change in lumen volume for a given change in pressure, corrected for size of the vascular lumen), after twice alternating the pressure between 10 mm Hg and 100 mm Hg for 1 minute at each pressure, lumen diameter changes in response to step-wise elevation in intraluminal pressure from 3(5) to 140 mm Hg were monitored with the SoftEdge Acquisition System (IonOptix, Milton, Massachusetts). Three and 5 mm Hg were the minimal pressure levels to record the diameter from unstretched uterine radial and main arteries, respectively. Arterial wall thickness was measured from images of pressurized arteries on the monitor screen after stabilization of the lumen diameter at each specific level of pressure (typically, 2–3 minutes for each pressure step). All measurements were taken in the presence of 20 μmol/L diltiazem and 50 μmol/L papaverine or Ca²⁺-free ethylene glycol tetraacetic acid (EGTA) containing solution to inhibit vascular smooth muscle

Figure 1. Marked elevation in average blood glucose levels in rats after intraperitoneal injection of streptozotocin (STZ) throughout pregnancy. Citrate buffer-injected animals maintained euglycemia. Note: Error bars are smaller than the size of the symbols.

contractile activity and to allow for maximal arterial dilation at each pressure.

In another set of experiments to determine wall stress-strain relations for arteries of diabetic and control rats, lumen arterial diameters (D) were recorded in conjunction with measurements of arterial wall thickness (h) at pressures (P) 3(5) to 140 mm Hg in Ca^{2+} -free 5 mmol/L EGTA-containing PSS using IonOptix-VesAcq acquisition module. For the calculation of circumferential wall stress, intraluminal pressure was converted from mm Hg to N/m^2 ($1 \text{ mm Hg} = 1.334 \times 10^2 \text{ N/m}^2$). Circumferential stress (σ) was calculated using equation: $\sigma = P \times D/2h$. Circumferential strain (ϵ) was calculated according to the following equation: $\epsilon = (D - D_3)/D_3$, where D_3 represents the lumen arterial diameter at the lowest intraluminal pressure.²⁷ The rate constant of an exponential function fitted to stress-strain curve (stiffness coefficient β) for each artery was determined using SigmaPlot program and used to compare stress-strain relationships between arteries of control and diabetic pregnant rats.

Solutions and Drugs

The PSS contained: 119 mmol/L NaCl, 4.7 mmol/L KCl, 24.0 mmol/L NaHCO_3 , 1.2 mmol/L KH_2PO_4 , 1.6 mmol/L CaCl_2 , 1.2 mmol/L MgSO_4 , 0.023 mmol/L EDTA, and 11.0 mmol/L glucose, pH = 7.4. All chemicals were purchased from Sigma Chemical Co (St Louis, Missouri). Diltiazem was prepared as a 10 mmol/L stock solution in deionized water and kept refrigerated until use. Papaverine was dissolved in deionized water on the day of the experiment. Ethylene glycol tetraacetic acid (1 mol/L stock solution) was prepared in deionized water and used after adjustment of pH to 7.4 with NaOH.

Statistical Analysis

Arterial diameter and pressure were simultaneously recorded with an IonOptix data acquisition program and imported into

Sigma Plot and Sigma Stat programs for graphical representation, calculations, and statistical analysis (an unpaired Student *t* test or 2-way repeated measures analysis of variance). Significance of differences was defined as $P < .05$. Data are expressed as means $\pm$ standard error of the mean, where *n* is the number of arterial segments studied. One to 2 arteries of each specific type were used from diabetic or control rats.

Results

The STZ injection produced sustained hyperglycemia in treated rats with an average glucose level at day 20 of pregnancy of $413.6 \pm 7.8 \text{ mg/dL}$ in diabetic rats ($n = 46$) and $79.6 \pm 1.2 \text{ mg/dL}$ in control rats ($n = 51$), $P < .001$ (Figure 1). Hyperglycemic pregnant rats gained significantly less weight than controls ($98.2 \pm 4.8 \text{ g}$ vs $126.5 \pm 2.9 \text{ g}$; $P < .001$). Diabetes during pregnancy resulted in significantly smaller fetuses ($1.9 \pm 0.04 \text{ g}$ vs $2.2 \pm 0.02 \text{ g}$; $P < .001$). In contrast, placental weights and placental surface areas were larger in the hyperglycemic animals ($0.53 \pm 0.08 \text{ g}$ vs $0.44 \pm 0.05 \text{ g}$; $P < .001$ and $171.1 \pm 5.1 \text{ mm}^2$ vs $142.5 \pm 4.8 \text{ mm}^2$, $P < .01$). There were no differences in the number of resorptions (0.68 ± 0.23 vs 0.29 ± 0.1 ; $P = .635$ in STZ- vs citrate-treated rats, respectively) or litter size (14.9 ± 0.34 vs 15.6 ± 0.23 ; $P = .086$) between the groups.

To characterize the effect of diabetes on the growth of the maternal uterine vasculature, specific measurements of the mesometrial uterine arcade were taken from both uterine horns of diabetic ($n = 12$) or control ($n = 16$) late pregnant (day 20) rats immediately after euthanasia (Figure 2A). The length of the MUA was not significantly different between the 2 groups. The distance from the MUA to the placenta and to the myometrium—lengths indicative of vascular axial elongation—was not altered in diabetic pregnancy when measured at the center, on the ovarian side, and on the cervical side of each horn (Table 1).

Figure 2. A, A photograph of a uterine horn and mesometrial uterine vasculature from a 20-day control pregnant rat.; A—the distance from MUA to uterine wall; B—the distance from MUA to the placenta. B, A photograph of the enlarged section of mesometrial vasculature showing anatomical location of uteroplacental (a) and premyometrial (b) radial arteries used in the current study. Arcuate (c) and main uterine (d) arteries are shown as well. MUA indicates main uterine artery.

Table 1. Axial Measurements of the Uterine Vasculature in STZ-Treated and Control Late Pregnant Rats

		Citrate (n = 16)	STZ (n = 12)	P value
Main uterine artery (MUA), mm		82.0 ± 10.6	77.8 ± 10.2	.3
Premyometrial artery, mm	Ovarian side	15.1 ± 2.2	14.1 ± 0.9	.06
	Center	17.5 ± 3.5	17.8 ± 2.2	.8
	Cervical side	14.1 ± 2.4	13.3 ± 2.1	.4
Uteroplacental artery, mm	Ovarian side	16.8 ± 2.4	16.2 ± 1.2	.4
	Center	19.2 ± 3.7	18.4 ± 2.0	.5
	Cervical side	16.0 ± 2.4	15.5 ± 1.4	.8

Abbreviation: STZ, streptozotocin.

Arterial wall thickness and passive lumen diameter, markers of circumferential remodeling, were then measured from pressurized main uterine, uteroplacental, and premyometrial radial arteries. The location of each type of maternal uterine vessel is shown in Figure 2B. Figure 3 illustrates the measurements of wall thickness (Figure 3A) and lumen diameter (Figure 3B) at 3 levels of intraluminal pressure obtained from the MUA of STZ-treated (n = 9) and control animals (n = 9). We found no significant effect of experimental diabetes on the wall thickness or lumen diameter of the MUA in late pregnancy. Similar studies were carried out using uteroplacental and premyometrial radial arteries from both groups. We found no statistically significant difference in uteroplacental arterial wall thickness between control and diabetic animals (Figure 4A), although there was a trend toward an increase in premyometrial wall

thickness from STZ-treated animals (Figure 4B). There was no significant change in uteroplacental artery lumen diameter between groups (Figure 5A). The passive lumen diameter of premyometrial arteries at the lowest intraluminal pressure of 3 mm Hg was also not different. However, at pressures greater than 40 mm Hg, passive lumen diameters of these vessels were significantly greater in diabetic compared to control animals (Figure 5B).

To further characterize the impact of diabetes on structural adaptations of the maternal uterine vasculature, we next examined vessel wall distensibility of the MUA, uteroplacental, and premyometrial arteries in late pregnant STZ treated versus control animals. There were no statistically significant changes in distensibility of the MAU (Figure 6A). However, as shown in Figure 6B and C, the distensibility of both uteroplacental and

Figure 3. Bar graphs demonstrating no significant changes in wall thickness (A) and lumen diameter (B) of main uterine artery from diabetic (STZ) compared to control (Citrate) 20-day pregnant rats. All measurements were performed from vessels in the presence of 50 μmol/L papaverine and 20 μmol/L diltiazem at the levels of intraluminal pressure of 5, 50, and 80 mm Hg.

premyometrial radial arteries was significantly greater in diabetic compared to control pregnant rats.

Finally, the effect of diabetes on mechanical properties of the resistance uterine arteries was also characterized in terms of the stress–strain relationship determined in Ca^{2+} -free EGTA-containing PSS. Significance of changes in stress–strain relationships for each type of artery was determined by comparing the rate constant of an exponential function fitted to stress–strain curve (stiffness coefficient β) for each artery. As demonstrated in Figure 7A and B, there were no changes in stiffness coefficient β and stress–strain relationship for the MUA. However, stiffness coefficients β determined for uteroplacental (Figure 7C and D) and premyometrial (Figure 7E and F) radial arteries were significantly smaller in diabetic versus control vessels resulting in a right shift in the circumferential wall stress versus strain relationships.

Figure 4. Experimental diabetes during pregnancy did not alter wall thickness of uteroplacental (A) and premyometrial (B) radial arteries at intraluminal pressures of 5, 50, and 80 mm Hg. All measurements were performed from vessels in the presence of 50 μmol/L papaverine and 20 μmol/L diltiazem.

Discussion

This study was designed to characterize the structural changes imposed by experimental diabetes, if any, on the rat maternal uterine vasculature. Although diabetes appeared to have no effect on axial remodeling of the maternal uterine vasculature in late pregnancy, an increase in vessel wall distensibility suggests altered mechanical properties of the uterine resistance arteries. We speculate that this selective remodeling may be a compensatory mechanism to partially restore maternal blood flow to the uteroplacental units in rat pregnancies complicated by short-term experimental diabetes.

Rat Model of Experimental Diabetes in Pregnancy

To induce diabetes, rats were injected with STZ on day 2 of pregnancy. STZ is an alkylating agent taken up by the

Figure 5. Effect of experimental diabetes on passive lumen diameters of uteroplacental (A) and premyometrial (B) radial arteries plotted as a function of intraluminal pressure. *Significantly different at $P < .05$ (2-way repeated measures analysis of variance).

pancreatic β -cells that leads to their destruction and causes subsequent maternal hyperglycemia. Streptozotocin-induced diabetes is a well-studied model for untreated, insulin-dependent, type 1 diabetes mellitus and has been used extensively in rodents to study the effects of diabetic pregnancy.^{28–30} In our study and others, STZ was injected on day 2 of pregnancy as administration of STZ prior to conception results in rapid loss of fertility.³¹ Development of infertility is also the largest obstacle for the use of other known animal models of type 1 and type 2 diabetic females.³² Although our model of diabetic pregnancy is short-lasting, it covers most of the duration of rat pregnancy and allows us to study the effect of hyperglycemia, the most damaging factor of diabetic pregnancy, on the development and mechanical properties of the maternal uterine vasculature.

Streptozotocin is an unstable chemical both in vitro and in vivo. [^{14}C]-labeled STZ is renally metabolized and excreted

Figure 6. Effect of experimental diabetes on wall distensibility of the main uterine artery (A), uteroplacental (B) and premyometrial (C) radial arteries. Distensibility is expressed as percentage of pressure-induced changes in lumen diameter relative to that of an unstretched artery at minimal intraluminal pressure of 3(5) mm Hg. *Significantly different between control (citrate) and diabetic (STZ) rats at $P < .05$ (2-way repeated measures analysis of variance).

in the urine within 6 hours of injection in the rat.³³ Therefore, injection of STZ results in minimal direct toxic effect on the growing rat embryo. We used the lowest effective dose of STZ (50–55 mg/kg body weight) to reliably induce sustained maternal hyperglycemia, which was accepted as indicative of the development of diabetes during rat pregnancy.

Effect of Diabetic Pregnancy on Maternal and Fetal Outcome

We found that STZ-treated hyperglycemic animals gained significantly less weight over the course of pregnancy compared with the control group. Lower maternal weight gain has been reported in previous studies and can in part be explained by significantly decreased fetal weight in diabetic compared with control pregnancies.^{34–36} However, a decreased increment in body weight following STZ-induced experimental diabetes has

Figure 7. Circumferential stress–strain relations and the rate constants (stiffness coefficient β) in the main uterine artery (A and B), uteroplacental radial arteries (C and D) and premyometrial arteries (E and F) of control (citrate) and diabetic (STZ) 20-day pregnant rats. *Significantly different between control (citrate) and diabetic (STZ) rats at $P < .05$ (unpaired Student t test).

also been reported outside of pregnancy and is most likely related to significant metabolic derangements in diabetic animals.^{37,38}

Fetuses from diabetic pregnant rats weighed significantly less than those from controls. These data are in agreement with the findings of others demonstrating fetal growth restriction in association with severe maternal hyperglycemia during rodent pregnancy.^{34–36,39} IUGR is also frequently reported in human pregnancies with poorly controlled pregestational diabetes,

particularly in patients with vascular disease.⁴⁰ Consistent with previous studies of STZ-induced diabetes, placental weights were significantly increased in our model of diabetic pregnancy.^{34,36,39} Placental glycogen deposits are characteristic of this model of diabetic pregnancy and may contribute to the increased placental weight.³⁴ However, in our study, the diabetes-induced increase in placental weight was also associated with a significantly increased placental surface area. It is noteworthy that in human poorly controlled diabetic

pregnancy, the placental weight is increased⁴¹ and this increase is accompanied by an enlarged surface area.⁴² It has been suggested that these compensatory changes may be important for providing an increased area for maternal–fetal exchange and an adequate oxygen supply to the growing fetus.⁴²

Both animal and human studies provide evidence for decreased maternal uterine blood flow in pregnancies complicated by diabetes.^{23,25,26} It is likely that decreased uteroplacental perfusion is the major cause of fetal growth retardation in STZ-induced diabetes in the rat. In 1 study, pretreatment of diabetic pregnant rats with nicergoline, an α -adrenoreceptor antagonist, significantly improved uteroplacental hemodynamics as well as restored normal fetal weight despite persistent hyperglycemia.²⁵

Effect of Experimental Diabetes on Uterine Vascular Growth and Remodeling

The etiology of impaired placental perfusion in diabetes is likely multifactorial involving placental pathology and increased uteroplacental vascular resistance due to abnormal structure and/or function of maternal uterine vessels. Despite the well-documented changes in other vascular beds, there is very little, if any, known on the effect of diabetes on pregnancy-induced remodeling of the maternal uterine vasculature. Extensive axial and circumferential growth of the uterine vasculature in human and animal pregnancy is critical for successful fetal growth and survival.^{4–6} In the present study, we found no effect of experimental diabetes on the development of the maternal mesometrial uterine vasculature (Table 1). The length of the MUA was not different in diabetic and control rats. Pregnancy-induced expansion of the maternal mesometrial vasculature was also not modified. In our study, relatively short-term (16–17 days) diabetes during rat pregnancy was associated with no significant change in vessel wall thickness in either the MUA or in the smaller resistance arteries of the maternal uterine circulation. Passive lumen diameters of uteroplacental and premyometrial radial arteries at minimal intraluminal pressure were not altered by experimental diabetes indicating that circumferential growth of maternal uterine vasculature is not compromised in diabetic pregnancy.

Passive Mechanical Properties of Uterine Vasculature in Diabetic Pregnancy

Decreased organ perfusion is characteristic of progressive diabetes and is associated with increased vascular resistance due to altered vascular reactivity and structural remodeling of resistance vasculature.^{43–45} There are significant variations in the modulation of mechanical properties of large and small arteries induced by experimental type 1 diabetes. Studies performed on the aorta and carotid artery demonstrate significant vessel wall hypertrophy and increased arterial stiffness in diabetic animals.^{46,47} Passive mechanical wall properties of smaller resistance size arteries and arterioles are also modulated by diabetes. Increased wall thickness and decreased vessel wall

distensibility were reported for cremaster arterioles from STZ-treated diabetic male rats.⁴⁸ Similarly, in femoral arteries from diabetic rats, wall stiffness was markedly increased in association with no change in internal vessel diameter and wall thickness.⁴⁹ The increased vessel wall stiffness was associated with increased levels of collagen.^{48,50} The formation of advanced glycosylation end products on connective tissue accounts largely for the increase in collagen cross-linking and is responsible for increased arterial wall stiffness in diabetes.⁴⁷

In contrast, small mesenteric arteries or intestinal arterioles from STZ-treated diabetic rats showed significantly increased arterial diameters with no change in vessel wall thickness. Increased arterial compliance or no significant change in vessel wall distensibility was also reported for these vessels.^{37,38,49} Additionally, human subcutaneous arteries exhibited no change in lumen diameter but an increased wall thickness and distensibility in response to type 2 diabetes.⁵¹ An enlargement of small arteries and their increased distensibility were more characteristic of early stage diabetes and may be considered as beneficial adaptive changes to improve organ perfusion.

Our present study shows that wall distensibility of uterine radial arteries was significantly increased, and the stress–strain relationships were shifted to the right due to a decrease in the rate constant (stiffness coefficient β) indicating decreased wall stiffness during diabetic pregnancy (Figures 6 and 7). These data are in agreement with similar studies of mechanical properties reported for mesenteric and intestinal vessels of STZ diabetic rats.^{37,38,49,51} However, distensibility and stress–strain relationships of the MUA were not modified by experimental diabetes in rat pregnancy. These data indicate that effect of diabetes is more evident in smaller arteries. Such differential effect may be related to more extensive growth of the smaller uterine radial arteries compared to the large MUA during rat pregnancy resulting in more significant changes in the composition of the vascular wall. The nature of decreased stiffness of uterine radial arteries in diabetic pregnancy remains to be defined. A change in the ratio of elastin and collagen content, rearrangement of elastin and/or collagen fibers, or an increase in formation of new, compared to mature, collagen fibers may be the underlying mechanism.^{52–54}

The fact that uteroplacental blood flow is impaired in STZ-induced diabetic pregnancy suggests that abnormal vascular reactivity rather than structural changes in the maternal vessels is most likely responsible for the increased vascular resistance in the uteroplacental circulation. Restoration of both uterine blood flow and fetal growth in STZ-induced diabetic pregnant rats with the α -blocking vasodilator nicergoline strongly supports this suggestion.²⁵ In this regard, we previously reported a significantly impaired endothelial-mediated vasodilation of uteroplacental radial arteries in the STZ model of diabetic pregnancy.⁵⁵ Further studies are required to explore the underlying mechanisms and causes of diabetes-induced endothelial dysfunction in the maternal uterine vasculature. With an understanding of the etiology of pregnancy-related vascular dysfunction, pharmacologic therapies may be developed to minimize the complications associated with diabetic pregnancy.

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Declaration of Conflicting Interests

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