Elevations in triglyceride-rich lipoproteins constitute a substantial cardiovascular risk factor, perhaps as important as cholesterol (15, 29). Hypertriglyceridemia is associated with attenuated endothelium-dependent relaxation in human subjects with normal plasma low-density lipoprotein (LDL) cholesterol levels (16). Hypertriglyceridemia may promote vascular endothelial cell dysfunction or damage by several mechanisms, particularly those involving oxidative stress and formation of lipid peroxidation products (29). The clearance of lipoprotein triglyceride from the circulation is mediated primarily by lipoprotein lipase (LPL). Several common variations in the LPL gene exist that result in partial reduction in enzyme activity. Heterozygous carriers of these variants are predisposed to dyslipidemia and are at increased risk of coronary artery disease (37).

Interest in the relationship between dyslipidemia and cardiovascular disease has focused primarily on the general population, but effects during pregnancy also warrant evaluation. Normal pregnancy is associated with a progressive rise in plasma triglyceride concentrations, reaching a 200–300% increase relative to nonpregnant levels by the third trimester (17). This physiological hypertriglyceridemia is primarily due to increased hepatic production of very low density lipoprotein (VLDL) and decreased LPL activity (28, 30a). Normal pregnancy is also accompanied by lesser increases in free fatty acids and cholesterol. However, excessive hyperlipidemia frequently occurs during pregnancy. For example, the mild elevation of triglyceride levels characteristic of partial LPL deficiency can be greatly aggravated when the lipolytic system is additionally challenged by pregnancy. Although quite variable, triglyceride levels well in excess of 2,000 mg/dl, with lesser but significant increases in cholesterol, have been observed during pregnancy in women with LPL deficiency who were only mildly hypertriglyceremic in the nonpregnant state (18, 19). Women with non-insulin-dependent diabetes often present with fasting hypertriglyceridemia accentuated by pregnancy (8, 14). In women with the pregnancy disorder preeclampsia, mean plasma triglyceride and free fatty acid concentrations begin to show abnormal increases by 10–16 wk of gestation; term levels are approximately double relative to women with uncomplicated pregnancy; poloxamer 407; triglyceride; malondialdehyde; resistance vasculature
pregnancy (17). Several lines of evidence suggest that dyslipidemia contributes to the vascular dysfunction of preeclampsia (17). There is also evidence that women with genetic LPL deficiency are at increased risk of developing preeclampsia (11).

There has been ample demonstration that the rat is an appropriate model to study pregnancy-related cardiovascular adaptations. However, data are lacking regarding the effects of hyperlipidemia on vascular adaptation to pregnancy. A hyperlipidemic rodent model has recently been developed in which a single intraperitoneal injection of poloxamer 407 (P-407) results in a dose-dependent elevation of plasma triglycerides and cholesterol by inhibiting LPL and stimulating 3-hydroxy-3-methylglutaryl CoA reductase, respectively (13, 36). Release of free fatty acids from adipocytes is thought to cause the increases in circulating free fatty acids reported in this model (23). This has provided a useful model for the study of hyperlipidemia and atherosclerosis in the nonpregnant setting (12, 25, 26). We adapted this model for use in the late-pregnant rat to test the hypothesis that acute hyperlipidemia alters the normal vascular adaptation to pregnancy as observed by adverse changes in vascular behavior in isolated mesenteric arteries.

We chose myogenic reactivity as a characteristic to study because it is thought to play an important role in the modulation of vascular resistance and organ blood flow. Myogenic reactivity is defined as the active response of an artery (either constriction or dilation) to a rapid change in transmural pressure. This behavior is an integrative process that depends on the endothelium, vascular smooth muscle, and extracellular matrix (22, 30). Arteries that possess increased myogenic reactivity respond with greater constriction (or less dilation) in response to a given transmural pressure increase. Previous data have shown that myogenic reactivity is decreased during late gestation compared with virgin rats (6, 20, 21). Mesenteric arteries were chosen as a model of systemic resistance regulation because these arteries receive 30% of cardiac output and therefore contribute significantly to overall vascular homeostasis. Thus we hypothesized that the attenuation in myogenic reactivity that is normally present during pregnancy would be abrogated by P-407-induced hyperlipidemia. We also examined whether P-407-induced hyperlipidemia is associated with a marker of oxidative stress, namely plasma concentrations of the lipid peroxidation product malondialdehyde (MDA).

METHODS

Animal model. Sprague-Dawley rats (Taconic, New York, NY) were housed and bred in the Magee-Womens Research Institute animal care facility. The facility is accredited by the American Association for the Accreditation of Laboratory Animal Care. The entire protocol was reviewed and approved by the Institutional Animal Use and Care Committee of Magee-Womens Hospital.

Twelve- to fourteen-week-old virgin female rats were bred by placement with a male rat overnight. The presence of sperm in a vaginal lavage the following morning was used to designate day 0 of gestation (full term 23 days). Pregnant rats were then isolated for the duration of pregnancy. On days 13–15 of gestation, the rats were given a single intraperitoneal injection of either P-407 (0.75 g/kg; Sigma Chemical, St. Louis, MO), Pluronic F-88 (P-88; 0.75 g/kg; BASF Chemical, Mt. Olive, NJ), or vehicle (sterile water). P-88 was used as a control for P-407 because it possesses the same hydrophilic characteristics but without known lipase-altering effects. On day 4 postinjection (days 17–19 of pregnancy), the rats were killed by intraperitoneal injection of pentobarbital sodium (0.1 mg/kg body wt), and blood was collected by heart puncture. A section of the mesenteric arcade, 5–10 cm distal to the pylorus, was rapidly removed and placed in ice-cold HEPES-buffered (pH 7.4) physiological saline solution (HPSS). HPSS contained (in mM) 142 sodium chloride, 4.7 potassium chloride, 1.17 magnesium sulfate, 2.5 calcium chloride, 1.18 potassium phosphate, 10 HEPES, and 5.5 dextrose.

Arteriograph system. Resistance size artery segments were dissected from second-order branches of the mesenteric arcade and carefully cleaned of surrounding tissue. The mean diameter for all arteries studied was 268 ± 6.7 μm, and there was no difference in arterial diameters between groups. The arterial segments were then mounted on two microcannulas suspended in each chamber of an isobaric arteriograph (Living Systems, Burlington, VT). The arteriograph consists of two separate chambers, permitting the study of two artery segments in tandem. Residual blood was flushed from the lumen, and the distal cannula was occluded to prevent flow. The proximal cannula was attached to a solid-state pressure transducer, a pressure servo-controller, and a peristaltic pump. The servo-controller maintains a selected intraluminal pressure. Both arteriograph chambers were filled with HPSS, each chamber with inflow and outflow channels to allow for the circulation of fresh HPSS. The arteriograph system was placed on an inverted microscope stage. A video camera attached to the microscope provided a video image of each artery. A video dimension analyzing system (Living Systems) processed a selected video line to provide lumen diameter and wall thickness measurements. Transmural pressure and lumen diameter measurements were available by digital readout (Maclab, version 3). Further description of this system is reported elsewhere (7).

Transmural pressure was adjusted to 60 mmHg, and the inflowing HPSS was maintained at 37°C and pH of 7.4. After 60 min of equilibration, a conditioning stretch was performed by increasing the intraluminal pressure from 60 to 100 mmHg and then returning back to 60 mmHg (1–2 min total) followed by 15 min of equilibration before the beginning of the experiment.

Myogenic tone assessment. Before changes in intraluminal pressure were initiated for myogenic measurements, each artery was submaximally contracted to 75–80% of its initial diameter with the α-adrenergic agonist phenylephrine (PE). After stable tone was initiated, pressure was lowered to 20 mmHg, and the vessels were equilibrated at this pressure for 10 min. Pressure was then increased to 120 mmHg in 20-mmHg increments. A diameter measurement was taken 5 min after each pressure step or after maximal response to each pressure step was achieved. When finished, the baths were washed and filled with fresh HPSS. After a 15-min equilibration period, the nitric oxide synthase (NOS) competitive inhibitor Nω-nitro-L-arginine (L-NMA) was added to the arteriograph at a final concentration of 0.1 M and allowed to equilibrate an additional 15 min. The pressure step protocol was then repeated.

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To assess the endothelial influence on myogenic response, a separate set of arteries was denuded of the endothelial cell layer by transluminal passage of an air bubble while mounted in the arteriograph chamber. After the vessels were allowed to equilibrate for 60 min, responses to pressure increases were measured. Endothelial denudation was verified by lack of relaxation in response to the endothelium-dependent vasodilator methacholine (ME). PE-preconstricted arteries that relaxed >20% to 1.0 μM ME were not included in the study.

Responses to changes in intraluminal pressure were normalized as a percent of the initial diameter at 20 mmHg using the following equation: %change from starting diameter at 20 mmHg = D0 - D20/D20 × 100. D0 is the diameter at a given pressure step, and D20 is the diameter at 20 mmHg. By convention, a positive percent change in diameter is indicative of dilation, whereas a negative percent change denotes arterial constriction. Therefore, an artery with increased myogenicity displays a smaller positive percent change in diameter or a greater negative percent change in diameter relative to control.

Agonist concentration response. Arteries were exposed to cumulative concentrations of PE (0.10–10.0 μM). After the highest concentration of PE was administered, the vessels were rinsed three times with fresh HPSS. The arteries were allowed to equilibrate for 15 min before the NOS competitive inhibitor L-NMA was added to the arteriographs for a final concentration of 0.1 M and allowed to equilibrate for an additional 15 min. Concentration responses to PE were then studied as before. A separate set of arteries was preconstricted with PE to 80% of initial and then exposed to cumulative concentrations of the endothelium-dependent vasodilator ME (5 nM–10 μM). This protocol was also repeated in the presence of L-NMA (0.1 M) as described above.

Plasma and sera analyses. Plasma and sera samples were stored at ~80°C until assayed. Serum total cholesterol and triglyceride concentrations were determined by enzymatic methods (1, 3). Serum free fatty acids were measured using a commercially available kit (NEFA C; Wako Chemicals USA, Richmond, VA). The analyses were done in single runs to avoid intra-assay variation using an Abbott VP Biichromate Analyzer (Abbott Laboratories, Irving, TX) in the Heinz Nutrition Laboratory of the Department of Epidemiology at the University of Pittsburgh Graduate School of Public Health.

Plasma MDA concentrations were determined by high-pressure liquid chromatography (35). In this assay, the authentic chromagen produced by the reaction of MDA with thiobarbituric acid is separated from other chromagens and quantified. The assay measures preexisting MDA plus MDA generated by decomposition of plasma lipid hydroperoxides during the acid heating stage of the test. The antioxidant butylated hydroxytolulene (BHT; 3 mM) was added to the samples before the acid heating stage to prevent in vitro oxidation of endogenous plasma lipids.

Statistical analyses. Artery responses were compared using two-way repeated-measures ANOVA with post hoc Bonferroni’s test. Mean litter sizes, fetal weights, serum lipids, and plasma MDA were all compared using one-way ANOVA. Data are given as means ± SE. Statistical significance was accepted at P ≤ 0.05.

RESULTS

As shown in Table 1, the mean number of fetal pups did not differ by treatment group. Treatment with P-407 was associated with a decrease in mean fetal pup weight that approached statistical significance (P = 0.06). Serum concentrations of total triglyceride, total cholesterol, free fatty acids, and MDA were significantly elevated in P-407-treated rats compared with both control groups (Table 1). Serum lipids and MDA in the P-88 (control poloxamer)-treated group did not differ from vehicle-treated controls.

Myogenic responses. As shown in Fig. 1 by the smaller change in diameter on increases in pressure, myogenic responses were significantly increased in arteries from P-407-treated rats compared with those from vehicle- or P-88-treated control animals (P = 0.004 and P = 0.002).

Incubation with the NOS inhibitor L-NMA resulted in significant increases in myogenic responses for arteries from vehicle-treated (P = 0.045) and P-88-treated control (P = 0.05) animals (Fig. 2). In arteries from P-407 rats, L-NMA had no effect on myogenic tone generation; responses to increases in intraluminal pressure in these vessels did not differ before and after L-NMA (Fig. 3; P = 0.6). The myogenic response profile of control vessels after L-NMA exposure was no longer different from P-407-treated vessels (P-407 vs. vehicle, P = 0.4; P-407 vs. P-88, P = 0.6).

Myogenic reactivity increased in arteries from both P-407-treated and vehicle-treated rats after selective removal of the endothelial cell layer (Figs. 3 and 4, respectively). In both cases, myogenic tone generation after endothelial removal surpassed that achieved after L-NMA treatment, and the overall degree of myogenicity was similar between groups (P = 0.4).

Responses to PE and ME. Artery contractile responses to PE were not different between P-407-treated and control groups as percent of the maximum

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### Table 1. Data from vehicle-treated control, P-88-treated control, and P-407-treated rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>P-88</th>
<th>P-407</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean litter size, fetuses</td>
<td>13.3 ± 1.1</td>
<td>12.7 ± 0.8</td>
<td>13.2 ± 0.3</td>
</tr>
<tr>
<td>(n = 7)</td>
<td>(n = 7)</td>
<td>(n = 7)</td>
<td></td>
</tr>
<tr>
<td>Mean fetal wt, g</td>
<td>1.6 ± 0.5</td>
<td>1.35 ± 0.4</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>(n = 7)</td>
<td>(n = 7)</td>
<td>(n = 7)</td>
<td></td>
</tr>
<tr>
<td>Serum triglyceride, mg/dl</td>
<td>239.0 ± 0.5</td>
<td>228.0 ± 81.3</td>
<td>3,638.0 ± 1,005.3*</td>
</tr>
<tr>
<td>(n = 7)</td>
<td>(n = 6)</td>
<td>(n = 5)</td>
<td></td>
</tr>
<tr>
<td>Serum cholesterol, mg/dl</td>
<td>80.6 ± 2.2</td>
<td>83.5 ± 6.2</td>
<td>488.8 ± 43.4†</td>
</tr>
<tr>
<td>(n = 7)</td>
<td>(n = 6)</td>
<td>(n = 5)</td>
<td></td>
</tr>
<tr>
<td>Serum free fatty acids, mmol/l</td>
<td>1.6 ± 0.3</td>
<td>1.2 ± 0.4</td>
<td>5.0 ± 1.2‡</td>
</tr>
<tr>
<td>(n = 7)</td>
<td>(n = 6)</td>
<td>(n = 5)</td>
<td></td>
</tr>
<tr>
<td>Plasma MDA, μmol/l</td>
<td>1.7 ± 0.3</td>
<td>2.24 ± 0.5</td>
<td>5.7 ± 1.0§</td>
</tr>
<tr>
<td>(n = 7)</td>
<td>(n = 6)</td>
<td>(n = 7)</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE; n = number of animals used. *P = 0.004 poloxamer 407 (P-407) vs. vehicle control; P = 0.006 P-407 vs. pluronic P-88 (P-88); †P < 0.0001 P-407 vs. both vehicle control and P-88; §P = 0.02 P-407 vs. both vehicle control and P-88; ‡P < 0.001 P-407 vs. vehicle control; P = 0.002 P-407 vs. P-88.
constriction to the agonist (Fig. 5). There were no significant differences in the concentration of PE required to achieve a constriction equal to 50% of the maximum (EC50): vehicle control (EC50 = 2.0 ± 0.2 μM), P-88 control (EC50 = 2.6 ± 0.5 μM), and P-407

Fig. 1. Myogenic responsiveness of small mesenteric arteries from vehicle-treated controls (n = 9), pluronic F-88 (P-88)-treated (n = 6), and poloxamer 407 (P-407)-treated (n = 6) rats. Responses are displayed as a percent change in diameter (Dm) from initial diameter at 20 mmHg. *P < 0.005 for P-407-treated rat arteries vs. vehicle-treated control rat arteries. †P < 0.005 P-407- vs. P-88-treated control rat arteries.

Myogenic responsiveness of small mesenteric arteries from P-407-treated rats (n = 11). Included are responses from arteries incubated with L-NMA (n = 7) and arteries denuded of their endothelium (EC; n = 7). Responses are displayed as a percent change in Dm from initial diameter at 20 mmHg. *P ≤ 0.05 for endothelium-denuded P-407-treated rat arteries vs. endothelium-intact P-407-treated rat arteries. †P ≤ 0.05 for endothelium-denuded P-407-treated rat arteries vs. endothelium-intact P-407-treated rat arteries incubated with L-NMA.

Fig. 3. Myogenic responsiveness of small mesenteric arteries from vehicle-treated controls (n = 9). Included are responses from arteries incubated with l-NMA (n = 7) and arteries denuded of their endothelium (-EC; n = 7). Responses are displayed as a percent change in Dm from initial diameter at 20 mmHg. *P ≤ 0.05 for vehicle-treated control arteries incubated with l-NMA vs. without l-NMA. †P ≤ 0.05 for P-88 control arteries treated with l-NMA vs. without l-NMA.

Fig. 4. Myogenic responsiveness of small mesenteric arteries from P-407-treated rats (n = 9). Included are responses from arteries incubated with l-NMA (n = 9) and arteries denuded of their endothelium (n = 6). Responses are displayed as a percent change in Dm from initial diameter at 20 mmHg. *P ≤ 0.05 for vehicle-treated control arteries incubated with l-NMA vs. without l-NMA. †P ≤ 0.05 for endothelium-denuded vs. endothelium-intact vehicle-treated controls.
EC50 = 2.6 ± 0.4 μM). However, arteries from all groups displayed a significant leftward shift in concentration-response curves to PE (increased sensitivity) in the presence of the NOS inhibitor L-NMA (Fig. 5). Similar responses were observed from arteries incubated with L-NMA (n = 6 and 5 for vehicle-treated and P-407-treated rat arteries, respectively). Data are normalized as a percentage of maximal PE constriction. *P < 0.005 for vehicle-treated rat arteries incubated with L-NMA vs. without L-NMA. †P < 0.005 for P-407-treated rat arteries incubated with L-NMA vs. without L-NMA.

As shown in Fig. 6, arteries from vehicle-treated control and P-407-treated animals responded to the endothelium-dependent vasodilator ME with comparable dose-dependent relaxations that completely reversed the PE-induced preconstriction (vehicle control EC50 = 1.2 ± 0.15 μM, P-88 control EC50 = 0.7 ± 0.5 μM), and P-407 (EC50 = 1.16 ± 0.12 μM).

**DISCUSSION**

Myogenic reactivity is the degree of inherent contraction of an artery in response to intraluminal pressure changes and is a primary determinant of intrinsic vascular tone. The major finding of this study is that hyperlipidemia, induced by intraperitoneal injection of the nonionic surfactant P-407, leads to a marked increase in myogenic reactivity of small mesenteric arteries isolated from late-pregnant rats. The myogenic response of arteries from P-407-treated rats was not further increased by pretreatment with the NOS inhibitor L-NMA. In contrast, arteries from control (P-88 or vehicle treated) rats responded to L-NMA with significant increases in myogenic reactivity such that responses of control and P-407 groups converged. These results suggest that the myogenic effect of P-407 treatment involves selective destruction of the NO-vasodilatory modulation of the myogenic response during pregnancy. Myogenic reactivity is believed to play an important role in the modulation of vascular resistance and organ blood flow. Given that vascular resistance is proportional to the fourth power of the radius, the decreases in arterial diameter resulting from this model of hyperlipidemia, if occurring in vivo, would have a profound negative impact on blood flow. Further augmentation of myogenic reactivity occurred in both control and P-407-treated arteries after selective removal of the endothelium, suggesting that an endothelium-dependent but NO-independent vasodilator component of myogenic regulation is preserved during the hyperlipidemic challenge.

It was recently shown that a vasodilatory substance of endothelial origin, likely NO, mediates the reduced myogenic reactivity of small renal arteries from midgestation rats (6). Compared with mesenteric arteries of equivalent size from virgin rats (unpublished data), there is a substantial endothelium-dependent reduc-
tion in myogenicity in mesenteric vessels during late gestation. Endothelium-derived NO is likely partially responsible for the pregnancy reduction in myogenicity in these vessels as both NO blockade and endothelial removal resulted in a substantial myogenic increase. Small radial arteries from the rat uterus are robustly myogenic, especially during late pregnancy, and thus intrinsic myogenic reactivity is likely to be an important regulator of uterine blood flow (24). Although not examined in the present study, if hyperlipidemia-mediated decreases in blood flow were to occur in the uterine vasculature in vivo, it might explain the tendency for fetal growth restriction in the P-407-treated animals.

The single injection of P-407 (but not P-88 or vehicle) produces a rapid rise in circulating triglycerides, cholesterol, and free fatty acids; concentrations peak by 48 h postinjection (13) and in our study remained elevated until death of the animals 96 h later. The hyperlipidemia and increased myogenicity resulting from P-407 treatment were also accompanied by three-fold increases in plasma concentrations of the lipid peroxidation product MDA. In contrast, injection of P-88, an agent with similar surfactant and hydrophilic characteristics but without known lipase-altering effects, did not result in elevations of lipids or MDA. We used high-pressure liquid chromatography to separate the authentic thiobarbituric acid-MDA adduct from other chromagens, thereby minimizing artifacts resulting from reaction of thiobarbituric acid with other plasma constituents. In addition, the antioxidant BHT was added to the samples before assay at a dose previously shown to eliminate in vitro oxidation of unsaturated lipids (10).

The hyperlipidemic challenge was administered during late gestation in view of the fact that the greatest increase in maternal circulating lipids occurs in late pregnancy (17). Although ostensibly acute, the 4-day duration of exposure comprised a substantial percentage of the total gestational interval in the rat. There is substantial evidence that both acute and chronic hyperlipidemia impair endothelial cell function via enhancement of oxidative stress (28). For example, triglyceride-rich lipoproteins in the form of a single high-fat meal induce oxidative stress and endothelial dysfunction in a reversible manner (2, 27, 34). Hypertriglyceridemia may increase production of reactive oxygen species by several mechanisms, for example acutely by stimulation of leukocyte NADPH oxidase (2) or more chronically by lowering concentrations of protective high-density lipoproteins and by increasing formation of smaller, peroxidation-susceptible LDL particles (9, 29). Enhanced formation of reactive oxygen species can decrease the bioavailability of NO, either directly by destruction or indirectly by formation of oxidized lipids that subsequently either destroy NO or decrease NOS and release (4, 31). Further study will be required to determine if antioxidant supplementation restores the normal pregnancy myogenic response in P-407-treated hyperlipidemic pregnant rats.

Another plausible explanation for the abrogation of NO-mediated regulation in myogenicity by P-407-induced hyperlipidemia may be endothelial damage induced by the abnormal increase in free fatty acids. Experiments on cultured endothelial cells suggest that elevated levels of free fatty acids cause reductions in prostacyclin and NO production, which could result in diminished relaxation capacity (4, 5). Furthermore, both acute (2 h) and more prolonged (>4 h) increases in circulating free fatty acids, in the range observed in insulin-resistant patients (2- to 9-fold elevations), result in endothelial dysfunction in lean insulin-sensitive subjects (31, 32). As discussed by these authors, elevated free fatty acids may induce formation of reactive oxygen species, which could quench NO and thus attenuate NO-dependent vasodilatation (31). Although our data do not suggest an alteration in agonist-stimulated release of NO, interference of pressure-stimulated release of NO by elevated free fatty acids is a possibility.

Contractile responses to cumulative concentrations of PE were not significantly different in arteries from vehicle control and P-407-treated pregnant animals. Additionally, blockade of NOS by L-NMA produced comparable increases in PE sensitivity between groups. Similarly, relaxation responses to ME were not different between groups, and the attenuation of ME-induced relaxation after treatment with L-NMA did not differ. It is noteworthy that pressure-induced diameter changes of arteries bathed in calcium-free buffer medium were also not different between groups (data not shown). Thus it is unlikely that the passive mechanical properties of the arterial wall were significantly altered by hyperlipidemia within the time span of these studies. The mechanism by which the hyperlipidemic challenge selectively suppressed NO-mediated modulation of myogenic reactivity is unclear. It is possible that this involves regulation of myogenic reactivity via the endothelial endothelin B receptor (ETB). In small renal arteries, the release of NO that results in reduced myogenic reactivity during pregnancy is thought to occur via the ETB receptor (6).

In conclusion, P-407-induced hyperlipidemia during pregnancy in the rat increases myogenic reactivity due to selective attenuation of the NO-mediated vasodilator component of the myogenic response. Hypertriglyceridemia and related lipid alterations occurring during preeclampsia and other pregnancy conditions may likewise adversely affect NO-mediated modulation of vascular responses.

**Perspectives**

The changes in circulating lipids during pregnancy in the rat, although not identical to the human, bear several critical similarities. During late gestation, the most pronounced change is the increase in maternal triglyceride-rich lipoproteins (primarily VLDL), which in both species largely results from both increased hepatic production and decreased clearance from the circulation (14). Mean plasma triglyceride and free
fatty acid concentrations undergo near doubling in women with the pregnancy disorder preeclampsia relative to normal pregnancy. There are empiric and conceptual reasons to believe that these lipid changes may causally contribute to oxidative stress and vascular dysfunction in preeclampsia (9). The observation that the surfactant P-407 increases blood lipids in rats without the toxic effects of earlier methods, such as Triton X, has provided a unique model of hyperlipidemia in the absence of alterations in fuel sources (as occurs with fructose or high-fat feeding; Ref. 13). This model was thus used to study the effect of pronounced hyperlipidemia on vascular function during pregnancy. Our principal finding was that P-407-induced hyperlipidemia during pregnancy increases myogenic reactivity due to selective attenuation of the NO-mediated vasodilator component of the myogenic response. This was accompanied by increased serum MDA, suggestive of lipid peroxidation. Further refinements in this model may help to extend or clarify the necessarily published facts and attractive hypotheses. Clin Sci (Colch) 96: 313–320, 1999.

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