Maternal Hypercholesterolemia Enhances Atherogenesis in Normocholesterolemic Rabbits, Which Is Inhibited by Antioxidant or Lipid-Lowering Intervention During Pregnancy

An Experimental Model of Atherogenic Mechanisms in Human Fetuses

Claudio Napoli, Joseph L. Witztum, Federico Calara, Filomena de Nigris, Wulf Palinski

Abstract—Maternal hypercholesterolemia during pregnancy is associated with a marked increase in aortic fatty streak formation in human fetuses and faster progression of atherosclerosis during normocholesterolemic childhood. However, the mechanisms responsible are unknown, and the contribution of genetic differences is difficult to assess in humans. The goal of this study was to determine whether maternal hypercholesterolemia per se may cause enhanced fatty streak formation in offspring and whether interventions during pregnancy can reduce it. During pregnancy, 1 group of New Zealand White rabbits was fed control chow and 8 groups were fed hypercholesterolemic diets Chol 1 (yielding plasma cholesterol of 153 mg/dL) or Chol 2 (yielding 359 mg/dL) without or with cholestyramine, vitamin E, or both. Offspring (n = 15 to 25 per group) were killed at birth. Maternal hypercholesterolemia enhanced mean lesion size in the aorta of their offspring at birth from $44 \pm 6 \times 10^3 \, \text{mm}^2$ per section in controls to $85 \pm 6 \times 10^3 \, \text{mm}^2$ in Chol 1 and $156 \pm 6 \times 10^3 \, \text{mm}^2$ in Chol 2 groups ($P < 0.0001$ for both). Cholestyramine or vitamin E treatment of mothers significantly reduced atherosclerosis at birth by up to 39% compared with controls on the same diet. Oxidized fatty acids and malondialdehyde in aortic atherosclerotic lesions and plasma were similarly affected by diets and treatment as atherosclerosis. Our results establish the causal role of hypercholesterolemia and peroxidation in fetal atherogenesis and demonstrate that both lipid-lowering and antioxidant interventions during pregnancy can reduce it. If it can be established that interventions in mothers also affect progression of lesions after birth, this may indicate a novel approach for the prevention of atherosclerosis. (Circ Res. 2000;87:946-952.)

Key Words: atherosclerosis ■ cholestyramine ■ vitamin E ■ oxidation ■ prevention

The atherogenic process in humans already begins in fetuses, and pathogenic events occurring during fetal development profoundly influence the progression of atherosclerosis later in life. In the past, atherogenesis was thought to begin during late childhood, even though fatty streaks had been observed in younger children. However, morphometric analysis of cross sections through the aorta of premature human fetuses showed that fatty streaks, the earliest stages of atherosclerotic lesions, already occur in fetal aortas and that their distribution reflects that of more advanced lesions in adults. Remarkably, the number and size of fatty streaks were much greater in fetuses of hypercholesterolemic mothers, including those in whom hypercholesterolemia was limited to pregnancy.

Although animal experiments and human studies had indicated that the placenta is relatively impermeable to large, cholesterol-carrying lipoproteins, hypercholesterolemia-induced events seemed to be a likely cause of lesion formation in fetuses. Fetal plasma cholesterol levels correlated significantly with maternal ones in fetuses younger than 6 months (but not thereafter). This indicated that maternal hypercholesterolemia itself contributes to enhanced fetal atherogenesis. However, we also observed a striking inverse correlation between fetal age and fetal plasma cholesterol, with very high levels in all younger fetuses (see Reference 1, Figure 3B). Thus, it was conceivable that fetal lesions would regress when cholesterol levels decrease toward the end of pregnancy or under normocholesterolemic conditions after birth.

The Fate of Early Lesions in Children (FELIC) study, designed to investigate the potential influence of fetal lesion formation on later atherogenesis, showed that fetal fatty streaks regress only partially (and not uniformly throughout the aorta) and that maternal hypercholesterolemia was asso-

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Received August 1, 2000; revision received September 7, 2000; accepted September 8, 2000.

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Maternal Plasma Lipid Oxidation During Pregnancy

<table>
<thead>
<tr>
<th>Group</th>
<th>MDA, μmol/L</th>
<th>10-OH Oleic Acid, 10⁻² ng/mL</th>
<th>12-OH Linoleic Acid, 10⁻² ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (regular chow)</td>
<td>0.47±0.03</td>
<td>1.37±0.10</td>
<td>0.71±0.08</td>
</tr>
<tr>
<td>Chol 1</td>
<td>0.68±0.04</td>
<td>1.52±0.11</td>
<td>0.85±0.07</td>
</tr>
<tr>
<td>Chol 1+cholostyr</td>
<td>0.62±0.03</td>
<td>1.42±0.09</td>
<td>0.74±0.05</td>
</tr>
<tr>
<td>Chol 1+vit E</td>
<td>0.33±0.02</td>
<td>1.08±0.05</td>
<td>0.48±0.04</td>
</tr>
<tr>
<td>Chol 1+cholostyr+vit E</td>
<td>0.34±0.04</td>
<td>0.95±0.05</td>
<td>0.31±0.04</td>
</tr>
<tr>
<td>Chol 2</td>
<td>0.85±0.03</td>
<td>1.78±0.08</td>
<td>0.93±0.05</td>
</tr>
<tr>
<td>Chol 2+cholostyr</td>
<td>0.68±0.03</td>
<td>1.59±0.08</td>
<td>0.80±0.03</td>
</tr>
<tr>
<td>Chol 2+vit E</td>
<td>0.43±0.02</td>
<td>1.42±0.05</td>
<td>0.51±0.02</td>
</tr>
<tr>
<td>Chol 2+cholostyr+vit E</td>
<td>0.40±0.05</td>
<td>1.20±0.03</td>
<td>0.32±0.03</td>
</tr>
</tbody>
</table>

Cholesterol indicates cholestyramine; vit E, vitamin E.

市场竞争 with accelerated progression of atherosclerosis during childhood and adolescence.3 In this study, normocholesterolemic children who died mainly of trauma were divided into two groups, depending on whether their mother had been normocholesterolemic or hypercholesterolemic during pregnancy. In each group, atherosclerosis in the aortic arch and abdominal aorta increased linearly with age, but progression of atherosclerosis was much faster in children of hypercholesterolemic mothers. All children had normal lipid profiles, and multiple regression analysis indicated that none of 13 risk factors determined in children and their mothers could account for this difference. We hypothesized that fetal lesion formation and enhanced susceptibility to atherosclerosis later in life were induced, at least in part, by maternal hypercholesterolemia and ensuing enhanced lipid oxidation.10,11 A corollary of this hypothesis is that lipid-lowering or antioxidant interventions in mothers during pregnancy may constitute a new approach to reducing atherosclerosis.1,3 However, direct experimental evidence for this hypothesis is still outstanding, and differences in the genetic background of normocholesterolemic and hypercholesterolemic mothers may also provide an explanation for both the fetal onset and the enhanced progression of the disease.

We now provide evidence for the causal role of maternal hypercholesterolemia in fetal atherogenesis by showing that in a genetically more homogeneous animal model, the New Zealand White (NZW) rabbit, diet-induced maternal hypercholesterolemia during pregnancy is sufficient to markedly enhance lesions in their offspring at birth. We also demonstrate the involvement of lipid oxidation and establish, in principle, that lipid-lowering and antioxidant interventions during pregnancy are effective in reducing the fetal onset of atherogenesis.

Materials and Methods

Rabbits

Seventy-seven female NZW rabbits (Harlan-Nossan), age 4.6±1.1 months, were divided into 9 groups (n=8 to 9) (Table). One group (control) was fed regular chow (4% fat, 18% protein, 60% carbohydrate, and 4% fibers). Four groups each were fed cholesterol-enriched diets Chol 1 or Chol 2 (Teklad adjusted calories diet; 9% fat, 19% protein, 55% carbohydrate, and 4% fibers, to which cholesterol dissolved in ether was added) to achieve total plasma cholesterol (TC) levels of about 150 and 350 mg/dL, respectively (in the absence of lipid-lowering drugs). Diets were started 2 weeks before mating and continued until 2 weeks postpartum. On the basis of preliminary experiments, the cholesterol content of the diet given to the Chol 1 group ranged from 0.132% to 0.156% (depending on each animal’s initial TC level), whereas animals of the Chol 2 group received 0.168% to 0.221% cholesterol. One group (Chol 1) received only the diet. A second group (Chol 1+CH) received Chol 1 diet plus a dose of cholestyramine (1% to 1.4%) (SIGMA) that was individually adjusted to match the average TC level of the chow-fed rabbits (<80 mg/dL). A third group (Chol 1+vitamin E) was fed Chol 1 plus 100 IU/d of vitamin E (α-tocopherol; SIGMA), and a fourth group (Chol 1+CH+vitamin E) was fed the diet together with both cholestyramine and vitamin E. The four groups fed Chol 2 received the same supplements, except that the dose of cholestyramine (1.8% to 3%) was adjusted to achieve the average TC level of the Chol 1 group. Cholestyramine was chosen as hypocholesterolemic drug because of the virtual absence of side effects during pregnancy.3 Vitamin E treatment did not result in any adverse effects in mothers or their offspring. The Table provides a summary of experimental conditions. After 2 weeks on the diet, females were bred with untreated males. TC levels were determined at week 2 and 3 of pregnancy by standard enzymatic method. About half of each litter were killed at birth (n=19 to 25 per group), and the remaining littersmates were killed at age 4 months, after about 3 months on regular chow (n=15 to 18). Experimental groups contained roughly equal numbers of males and females, and data for both genders were analyzed together, because previous studies in human fetuses and children had not indicated significant differences between sexes.1,3 All experiments were carried out under approved institutional animal protocols.

Tissue Preparation and Quantification of Atherosclerosis

Lesion sizes were determined by computer-assisted image analysis of 30 equidistant frozen oil red O-stained sections each from the aortic arch, thoracic, and abdominal aorta. Additional sections were pooled as lesion or nonlesion tissue. The rationale and methods for tissue preparation and analysis were identical to those previously used for arteries of human fetuses.1,2 Results are reported as cumulative lesion area per section (ie, the mean area of all lesions in each of the 90 aortic sections).

Immunocytochemistry

Additional sections (n=10) from each aortic segment were formaldehyde fixed and immunostained with 1:500 dilutions of NAS59, a
murine monoclonal antibody (Mab) against oxidation-specific 4-hydroxynonenal-lysine epitopes; EO6, a natural Mab cloned from atherosclerotic apolipoprotein E–deficient mice that recognizes oxidized phospholipid epitopes; NP1539, a Mab to human apolipoprotein B that also recognizes rabbit LDL (Boehringer Mannheim); and RAM11, a Mab against rabbit monocytocyte and macrophages (DAKO). Epitopes recognized by the primary antibody were detected by an avidin-biotin-peroxidase method.

Peroxidative End Products

Fatty acids (FAs) were isolated from plasma or aortic homogenates, as described. Concentrations of 10-OH oleic acid, 12-OH linoleic acid, and 10-OH arachidonic acid were determined by a combination of gas chromatography and mass spectrometry. Results are presented as absolute amount of individual oxidized FAs. The concentration of oxidized FAs in atherosclerotic lesions of each rabbit was determined by comparison of pooled normal and lesion tissue. The concentration of oxidized FA in plasma of different dietary groups was compared after Δ-differentiation of FA spectra. Plasma malondialdehyde (MDA) content was measured as thiobarbituric acid–reactive substances. In maternal plasma, these parameters were measured at the 2nd and 3rd week of pregnancy and in their offspring, plasma and aortic measurements were performed when they were killed.

Statistical Analysis

Data were analyzed by ANOVA and comparisons between groups by unpaired Student’s t test. Fifteen comparisons were done for each parameter: control versus Chol 1 versus Chol 2 and 6 comparisons each between groups on the same diet. All significances were Bonferroni-corrected. Correlations were tested by linear regression analysis. Results are presented as mean ± SEM.

Results

Mothers

Maternal plasma cholesterol levels are shown in Figure 1. As expected, Chol 1 and Chol 2 diets raised the average maternal TC levels during pregnancy to 157 and 359 mg/dL, respectively, compared with 58 mg/dL in controls. Cholestyramine, but not vitamin E treatment, significantly reduced TC in both groups to 77 and 171 mg/dL, respectively (P < 0.001). Plasma triglycerides were significantly raised only in the Chol 2 group compared with the control group (132.8 ± 41.3 mg/dL; P < 0.05); triglycerides in the Chol 1 group were 72.0 ± 26.4 mg/dL (P = 0.083). No significant differences were observed in all other plasma analyses. None of the diets significantly affected maternal body weights during pregnancy. Peroxidative compounds are shown in the Table. Groups with increased plasma cholesterol consistently showed significant increases in plasma MDA. When data for all groups not receiving vitamin E were pooled, maternal plasma cholesterol showed a significant correlation with plasma MDA (r = 0.755, P < 0.0001). Vitamin E reduced plasma MDA levels to normal levels in both diet groups, even though the TC level of the Chol 2 + vitamin E group was much higher than that of the control group. Although cholestyramine normalized TC level in rabbits fed Chol 1 and markedly reduced it in rabbits fed Chol 2, it only achieved a marginal decrease in MDA level in the latter. In analogy, the increase in principal oxidized FAs associated with either hypercholesterolemic diet (eg, 10-OH oleic acid and 12-OH linoleic acid) was completely prevented by vitamin E but not cholestyramine. Absolute 10-OH arachidonic acid levels were low but generally behaved similarly (data not shown). Combinations of cholestyramine and vitamin E yielded lower oxidized FA levels than vitamin E only groups, but the differences generally were not significant.

Effect of Hypercholesterolemia and Interventions during Pregnancy on Atherosclerosis in Offspring at Birth

Morphometric assessment of aortic cross sections revealed microscopic fatty streaks even in the control group (Figure 2). Maternal hypercholesterolemia during pregnancy increased lesion sizes by 94% in the Chol 1 group (P < 0.0001). Treatment with cholestyramine decreased atherosclerosis by 22% (not significant [NS]), but lesion sizes remained greater than in the control group, even though maternal plasma cholesterol levels of both groups were similar (Figure 1). Offspring of mothers with more marked hypercholesterolemia (Chol 2 group) showed a 253% increase in lesions (P < 0.0001) and a powerful antiatherogenic effect of cholestyramine (~30%; P < 0.01). Again, lesion sizes in the Chol 2 + cholestyramine group significantly exceeded those in the Chol 1 group, which had similar maternal TC levels (Figure 2).
Treatment of mothers with vitamin E, which did not lower their cholesterol, significantly reduced atherosclerosis in the Chol 2 group (39%; \( P, 0.0005 \)) but missed significance in the Chol 1 group (19%). Combination of cholestyramine with vitamin E resulted in modest, not significant additional reduction of atherogenesis.

Effect on Plasma Cholesterol and Lipid Oxidation in Offspring at Birth
All groups examined at birth had normal TC levels (48 ± 2.3 to 58 ± 1.5 mg/dL; NS) (Figure 3A), indicating that at the end of a regular pregnancy, the placenta is impermeable to maternal LDL and VLDL. Plasma triglycerides were also normal in all groups (32.8 ± 6.3 to 42.1 ± 8.5 mg/dL; NS).

However, plasma concentrations of peroxidative end products, such as 10-OH oleic acid (Figure 3B), 12-OH linoleic acid (Figure 3C), and 10-OH arachidonic acid (data not shown), as well as plasma MDA levels (Figure 3D), were significantly increased in the offspring of mothers fed hypercholesterolemic diets, particularly in those fed Chol 2. Treatment of either diet group with vitamin E significantly reduced peroxidation (Figures 3B through 3D), whereas cholestyramine caused only a much smaller reduction of oxidation.

Effect on Aortic Lipid Oxidation and Lesion Composition at Birth
Concentrations of oxidized oleic and linoleic acids (Figures 4A and 4B) and arachidonic acid (not shown) in early atherosclerotic lesions of the aorta were markedly elevated in rabbits of the Chol 1 and Chol 2 groups. Maternal treatment with vitamin E was associated with a highly significant reduction of oxidized FAs in the Chol 2 group. A reduction was also seen in the Chol 1 group, but this was significant only for linoleic acid. As in plasma, offspring of cholestyramine-treated mothers also showed significant reductions in oxidized FAs in early aortic lesions, and no additional significant reduction was achieved by combination therapy. Immunocytochemical detection of typical components of early lesions, i.e., oxidation-specific epitopes such as 4-hydroxynonenal-lysines detected by NA59 (Figure 4C) and oxidized phospholipid epitopes detected by EO6 (Figure 4D), as well as LDL (apolipoprotein B) (Figure 4E), and macrophages and foam cells (Figure 4F), showed similar protective effects of antioxidant and lipid-lowering interventions during pregnancy. As expected, aortic concentrations of nonoxidized linoleic, oleic, and arachidonic acids were also increased by hypercholesterolemic diets (data not shown).

Correlation Between Maternal Plasma Cholesterol Levels and Atherosclerosis at Birth
The above results suggested that the marked increase in atherosclerosis in the Chol 1 and Chol 2 groups was a direct result of maternal hypercholesterolemia. Indeed, linear regression analysis of all data indicated a correlation between the average maternal plasma cholesterol level during pregnancy and the size of lesions in their offspring at birth (Figure 5). Data of the cholestyramine-treated groups also were
consistent with the assumption that the reduction of lesions was mainly attributable to the reduction of TC. However, only 37% of atherosclerosis could be explained by the maternal cholesterol levels. Furthermore, treatment with vitamin E was associated with a marked reduction in lesion size (Figures 2 and 5) but did not affect cholesterol levels. When data from groups receiving vitamin E were excluded, the correlation coefficient increased to \( r = 0.78 \). The size of atherosclerotic lesions also significantly correlated with maternal plasma MDA, particularly when only groups not receiving vitamin E were analyzed (\( r = 0.62, P < 0.0001 \)).

**Effects of Hypercholesterolemia and Interventions During Pregnancy at Age 4 Months**

To detect whether fetal lesions progress in the absence of postnatal hypercholesterolemia, some of the offspring were fed regular chow and examined at age 4 months (Figure 6). Atherogenesis in the Chol 1 and Chol 2 groups was greater than in the chow group by 224% and 323%, respectively. Atherogenesis in the Chol 1 and Chol 2 groups was raised from a normal level of 58 mg/dL to 153 and 359 mg/dL, respectively (Figure 1). Both dietary and oxidationspecific epitopes (eg, \( P < 0.01 \) in all Chol 1 treatment groups) and oxidation-specific epitopes (eg, \( P < 0.001 \) to \( P < 0.01 \) in all Chol 1 treatment groups for EO6-positive sections), whereas aortic levels of nonoxidized FAs were similar in all groups.

An additional experiment following the same protocol showed that lesions and some differences between treatment groups still persisted at age 7 months. But, again, this did not indicate progression (data not shown).

**Discussion**

We previously showed that atherogenesis in human offspring of hypercholesterolemic mothers was more extensive at fetal age and progressed faster during childhood and adolescence. The present study investigated the mechanisms responsible for the formation of early lesions during pregnancy using an inbred rabbit model, in which genetic differences are far less prevalent than in humans. It provides two main findings. The first is that temporary induction of maternal hypercholesterolemia in NZW rabbits by dietary intervention enhances fatty streak formation in their offspring. This demonstrates that increased early lesion formation similar to that seen in human fetuses can be caused by events associated with maternal hypercholesterolemia and does not necessarily require genetic differences that are likely to exist between normcholesterolemic and hypercholesterolemic human mothers (and fathers). The fact that cholestyramine lowered cholesterol levels in mothers during pregnancy and decreased lesions in their offspring strongly supports a causal role of maternal hypercholesterolemia in fetal atherogenesis. The second main finding is that intervention with vitamin E during pregnancy also markedly reduced fetal lesion sizes. This provides evidence for the causal role of processes influenced by lipid oxidation in fetal atherogenesis. Together, these data demonstrate, in principle, that hypolipidemic and antioxidant interventions during pregnancy may constitute a novel approach to prevention of atherosclerosis.

In our study, maternal plasma cholesterol in the Chol 1 and Chol 2 groups was raised from a normal level of 58 mg/dL to 153 and 359 mg/dL, respectively (Figure 1). Both dietary and plasma cholesterol concentrations were much lower than those conventionally used to induce atherosclerosis in NZW rabbits. Therefore, it is not surprising that the average lesion area in the aorta at birth was very small in absolute terms. Our experimental conditions were designed to achieve cholesterol levels comparable to those of human mothers in the hypercholesterolemic groups of our previous studies (280 and 460

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**Figure 5.** Correlation between the maternal cholesterol level during pregnancy and the cumulative lesion area in their offspring at birth. VitE indicates vitamin E.

**Figure 6.** Cumulative area of all oil red O–positive lesions per section in the aorta of rabbits at age 4 months (ie, after 3 months on a normal chow diet). Diets and treatments refer to mothers during pregnancy. Data are mean±SEM of 90 sections per aorta of 15 to 18 rabbits per group. \( * P < 0.0001 \) vs control.
Maternal hypercholesterolemia of NZW rabbits resulted in marked increases in aortic lesion sizes in their offspring at term birth, which was greatest in the group exposed to the highest cholesterol levels (Chol 2) (Figure 2). Cholestyramine consistently reduced both maternal cholesterol and lesion sizes in offspring, indicating a direct correlation between the two parameters. Linear regression analysis of all groups not receiving antioxidants confirmed a substantial influence of the maternal cholesterol on lesion sizes (Figure 5). However, the extent of atherosclerosis in the cholestyramine groups was not quite reduced to that of untreated groups with matching cholesterol levels (Figures 1 and 4), indicating involvement of atherogenic mechanisms other than hypercholesterolemia. Although maternal hypercholesterolemia thus plays a major role in fetal atherogenesis, it remains unclear whether this means an increased transplacental passage of maternal LDL and VLDL, increased transfer of FAs, or increase passage of oxidized FAs, oxidized FA fragments, or other transducers or end effectors.

One of the potential mechanisms contributing to the atherogenic effect of maternal hypercholesterolemia is an increase of peroxidative end products in both mother and fetus. LDL oxidation not only occurs in atherosclerotic lesions of the adult animals and humans, but also in fatty streaks of human fetuses. Several pathways by which OxLDL may promote atherogenesis have been identified. These include accelerated foam cell formation by enhanced macrophage uptake of OxLDL via scavenger receptors and the recruitment of monocytes and T-cells into the intima. Oxidation also influences nuclear receptor pathways, such as nuclear factor-κB and peroxisome proliferator-activated receptor γ, which regulate expression of adhesion molecules, growth factors, and proinflammatory genes, and affect cell cycle and apoptosis. Regulation of vasotocin by nitric oxide is also impaired by OxLDL. Finally, OxLDL has profound immunological consequences that modulate atherogenesis. Extensive evidence indicates that hypercholesterolemia is accompanied by increased plasma levels of peroxidative products. (Conversely, in our study the cholestyramine-induced reduction of maternal TC was associated with a decrease of peroxidative end products in plasma and, more importantly, in early atherosclerotic lesions.) We had postulated, therefore, that oxidation-sensitive mechanisms play an important role in lesion formation associated with maternal hypercholesterolemia.

Antioxidant intervention during pregnancy markedly reduced early atherogenesis. The fact that this was not associated with a decrease in plasma cholesterol strongly supports the pathogenic role of oxidation, but we cannot rule out unrelated effects of vitamin E in the arterial wall. As expected, peroxidative end products, such as oxidized FAs and MDA, were markedly reduced in early lesions and plasma of vitamin E–treated groups. Cholestyramine also reduced lipid oxidation, albeit to a lesser extent, suggesting that substrate availability is a major determinant. However, shifts in placental passage of specific FAs resulting from the hypcholesterolemic intervention may also have played a role. Combinations of cholestyramine and vitamin E tended to be even more protective than cholestyramine or vitamin E alone, in particular in rabbits fed Chol 2, but failed to completely abolish the increase in lesion formation compared with normocholesterolemic controls, probably because of insufficient protection achieved under the present experimental conditions.

The present results demonstrate the role of maternal hypercholesterolemia in early atherogenesis in offspring and the efficacy of interventions with vitamin E or cholestyramine. The results also establish an experimental model of human fetal atherogenesis, but additional studies are needed to determine whether fetal hypercholesterolemia and lipid peroxidation also accelerate the progression of atherosclerosis and whether interventions in mothers affect this. Our first exploratory experiment indicated that fetal lesions and therapeutic effects persist for a prolonged time but could not test its long-term consequences in the absence of lesion progression. The absence of atherogenesis or regression of fetal lesions is probably attributable to the fact that cholesterol levels in chow-fed NZW rabbits are extremely low compared with what is considered normal in humans. This may be overcome in future experiments by exposing rabbits to a mildly hypercholesterolemic diet after birth. Nevertheless, the lack of progression suggests that other risk factors of atherosclerosis, including differences in genetic background, may be required for the faster progression of atherosclerosis seen in children of hypercholesterolemic mothers.

If it can be established that fetal lesion formation influences the rate of progression of atherosclerosis later in life, our results would indicate novel approaches for prevention. Dietary intervention in pregnant women may be one way to lower cholesterol. Cholestyramine also seems to be safe during pregnancy and is commonly used in pruritus associated with cholestasis. Antioxidant interventions significantly reduced atherosclerosis in experimental models but had only mixed success in preventing recurrent cardiovascular events in patients with preexisting coronary heart disease. However, it is possible that antioxidant protection is most effective in early stages of atherosclerosis and, therefore, may offer greater benefits to fetuses than to adults. We chose vitamin E and cholestyramine because of their safety during pregnancy and to prove, in principle, that lipid-lowering and antioxidant intervention may be beneficial, but more powerful hypolipidemic drugs and antioxidants may offer greater benefits. Finally, by demonstrating the role of maternal hypercholesterolemia, our results support the inclusion of maternal hypercholesterolemia during pregnancy among the risk factors that determine the need for more intense monitoring in children than currently recommended.

**Acknowledgments**

This work was supported by National Heart, Lung, and Blood Institute grant HL56989, ISNIH grant 56980/99, and MURST.
96.40%. We thank Dr F.P. D’Armentio and Dr P. Somma for participation in quantification of atherosclerosis.

References


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*Circ Res.* 2000;87:946-952
doi: 10.1161/01.RES.87.10.946

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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