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Can physiologic hyperlipidemia during pregnancy be the culprit for atherogenesis in utero?

TO THE EDITORS: We read the article by Liguori et al[1] with great interest. However, there are some conflicting points that need to be clarified. The first thing that I want to mention is about the exclusion criteria that did not include gravids with polycystic ovary syndrome, diabetes, or gestational diabetes; patients with high body mass index or preterm labor; and smoking mothers.

These disorders are well known to be associated with increased lipid levels and/or C-reactive protein (CRP) during pregnancy.[2] To call something abnormal, the norm must have been defined. During pregnancy both CRP and maternal cholesterol levels (MCLs) increase as the gestational age advances.[3,4] Serum CRP levels vary widely in healthy pregnant women; however, there is a slow increase of mean CRP during pregnancy (Table 1).[4] MCLs in healthy pregnant women are shown in Table 2 according to trimesters.[3]

When we compared the range of values for CRP and MCLs in the study of Liquori et al[1] with values provided in the tables, they are still within the ranges of healthy pregnant women. And moreover, if we do not group the patients according to gesta-

TABLE 1
CRP levels among healthy pregnant women

	Mean	Range
5-9 wks	0.76	0.16-13.61
15-20 wks	1.53	0.39-20.31
24-30 wks	2.08	0.50-9.45
30-39 wks	2.28	0.44-8.11

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TABLE 2
Maternal cholesterol levels in healthy pregnant women

	Mean (mg/dL)	95% CI
Nulliparous women	177	139.2-216.6
First trimester	177	116-239.8
Second trimester	247.5	162.4-332.6
Third trimester	286.2	193.4-378.9

CI, confidence interval.

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TABLE 3
Maternal and fetal cholesterol concentrations from the study of Marseille-Tremblay et al[5]

	Maternal cholesterol level, mg/dL (95% CI)	Newborn venous cord blood cholesterol level, mg/dL (95% CI)
Low median cholesterol (n = 29)	213.5 (203.5-223.5)	67.3 (60.0-74.3)
High median cholesterol (n = 30)	299 (285.9-312.1)	65.4 (59.2-71.2)
Nongestational diabetes mellitus (n = 7)	256 (221.2-290.8)	70 (54.5-85.4)
Gestational diabetes mellitus (n = 7)	265.7 (219.2-312.1)	69.6 (55.4-85.8)

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tional age, patients in the second and third trimester will be falsely labeled as hypercholesterolemic.

The placenta and fetal compartment is a substantially different environment from the mother, although there are exceptions for a variety of substances. The syncytiotrophoblastic layer of the placenta acts as a physical barrier between the maternal and fetal circulations. To supply the fetus with maternal cholesterol, the placenta must receive the vast majority of those nutrients in the form of lipoproteins. Cholesterol and lipids then cross the placenta by either diffusion or protein-mediated efflux.

In their study, Marseille-Tremblay et al[5] showed that mild hypercholesterolemia does not appear to affect the newborn lipid profile, possibly as a consequence of the modulation of lipid metabolism in the placenta. The maternal and fetal levels of cholesterol in the study by Marseille-Tremblay et al[5] are shown in Table 3.[5]

When we take into account the data given here and the study of Liquori et al,[1] the question that occurs is that without causing any alteration of cholesterol levels in the fetal compartment, how does increased MCL lead to increased atherogenesis? And could metabolic changes that are physiologically observed during pregnancy be classified as pathologic?

In conclusion, the current study is lacking a cause-and-effect relationship, and statistically significant findings on the data sheets may not always translate into solid associations. ■

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REPLY

In his comment on our paper,[1] Dr Basaran raises the question why we did not exclude some conditions associated with increased C-reactive protein (CRP) and the need to define hypercholesterolemia and elevated CRP in dependency of the trimester. An impairment of CRP levels is not described in the paper[2] quoted by Dr Basaran.

The obvious response is that our recent paper[1] used the patient population of the retrospective Fate of Early Lesions in Children study.[3] The main criterion was to exclude pathologies suspected on the basis of epidemiological data to influence offspring cardiovascular disease by mechanisms independent of maternal hypercholesterolemia (ie, maternal diabetes and smoking).

In addition, there are other maternal clinical conditions, many of which are known to be associated with dyslipidemia and inflammation, for which no such evidence exists, including CRP.[4]

The National Children's Study will test whether they do and also provide valuable data on the threshold of risk factors in childhood.[5] However, it is not very relevant to understand a precise threshold of maternal hypercholesterolemia.

The same is true for CRP. Why define with rigidity the values of supposed normal ranges of maternal CRP levels? Again, the pathogenetically relevant question is whether increased CRP levels may indicate or promote subsequent vascular disease in children. It is well established that cholesterol levels may increase toward the third trimester and that the extent of this increase varies considerably from patient to patient.

Prospective studies should obtain cholesterol and related values, including CRP, at a defined gestational age.

Our retrospective studies utilized a composite value performed throughout pregnancy precisely to minimize the variability in the time of the prenatal exam. Dr Basaran states that "to call something abnormal, the norm must have been defined." Indeed, our early studies were the first to define levels of hypercholesterolemia associated with increased atherosclerosis in fetuses[6] and during childhood,[3] and the present paper does this for a surrogate parameter, CRP, but more practical definitions would have to be defined. Although it strikes us as exceptionally daring to expect evidence for causality from a human study on developmental programming,[4,6] extensive evidence for the atherogenic role of maternal hypercholesterolemia has been obtained in various experimental models.[7-10] ■

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