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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REFERENCES

1. Liguori A, D'Armiento FP, Palagiano A, Palinski W, Napoli C. Maternal C-reactive protein and developmental programming of atherosclerosis. Am J Obstet Gynecol 2008;198:e281-e285.
2. McGladdery SH, Frohlich JJ. Lipoprotein lipase and apoE polymorphisms: relationship to hypertriglyceridemia during pregnancy. J Lipid Res 2001;42:1905-12.
3. Brizzi P, Tonolo G, Esposito F, et al. Lipoprotein metabolism during normal pregnancy. Am J Obstet Gynecol 1999;181:430-4.
4. Hwang HS, Kwon JY, Kim MA, Park YW, Kim YH. Maternal serum highly sensitive C-reactive protein in normal pregnancy and pre-eclampsia. Int J Gynaecol Obstet 2007;98:105-9.
5. Marseille-Tremblay C, Ethier-Chiasson M, Forest JC, et al. Impact of maternal circulating cholesterol and gestational diabetes mellitus on lipid metabolism in human term placenta. Mol Reprod Dev 2008;75:1054-62.

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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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REFERENCES

1. Liguori A, D'Armiento FP, Palagiano A, Palinski W, Napoli C. Maternal C-reactive protein and developmental programming of atherosclerosis. Am J Obstet Gynecol 2008;198:281e1-5.

2. McGladdery SH, Frohlich JJ. Lipoprotein lipase and apoE polymorphisms: Relationship to hypertriglyceridemia during pregnancy. J Lipid Res 2001;42:1905-12.

3. Napoli C, Glass CK, Witztum JL, Deutsch R, D'Armiento FP, Palinski W. Influence of maternal hypercholesterolaemia during pregnancy on progression of early atherosclerotic lesions in childhood: Fate of Early Lesions in Children (FELIC) study. Lancet 1999;354:1234-41.

4. Napoli C, Palinski W. Maternal hypercholesterolemia during pregnancy influences the later development of atherosclerosis: Clinical and pathogenic implications. Eur Heart J 2001;22:4-9.

5. Mudd LM, Pham X, Nechuta S, et al. Prenatal care and delivery room staff attitudes toward research and The National Childrens Study. Matern Child Health J 2008;12:684-91.

6. Napoli C, D'Armiento FP, Mancini FP, et al. Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia: Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. J Clin Invest 1997;100:2680-90.

7. Napoli C, Witztum JL, Calara F, de Nigris F, Palinski W. 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. Circ Res 2000;87:946-52.

8. Napoli C, de Nigris F, Welch JS, et al. Maternal hypercholesterolemia during pregnancy promotes early atherogenesis in LDL receptor-deficient mice and alters aortic gene expression determined by microarray. Circulation 2002;105:1360-7.

9. Alkemade FE, Gittenberger-de Groot AC, Schiel AE, et al. Intrauterine exposure to maternal atherosclerotic risk factors increases the susceptibility to atherosclerosis in adult life. Arterioscler Thromb Vasc Biol 2007;27:2228-35.

10. Elahi MM, Cagampang FR, Anthony FW, et al. Statin treatment in hypercholesterolemic pregnant mice reduces cardiovascular risk factors in their offspring. Hypertension 2008;51:939-44.

 doi: 10.1016/j.ajog.2008.06.044