Vascular Control During Pregnancy
Extending Experimental Findings to Humans

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It has been known for more than 50 years that estrogen increases blood flow to uterine tissue. Indeed, perhaps one of the most dramatic effects of hormones on modulation of a circulatory system is change in uterine blood flow during pregnancy. Much has been learned about mechanisms contributing to these changes in blood flow from studies performed in experimental animals. For example, observations of nonneuronal vasodilatory effects of acetylcholine in uterine arteries and the time course for modulation of this response by pregnancy and estrogen preceded discovery of endothelium-derived relaxing factors. These original observations provided some of the first hints as to both an immediate, nongenomic and longer-term modulation of vascular responses by sex steroid hormones. Subsequently, nitric oxide was identified as one of the endothelium-derived factors modulated by estrogen in systemic blood vessels as well as blood vessels of the reproductive system. In this issue of Circulation Research, Nelson et al extend these observations by investigating expression of isoforms of nitric oxide synthase (NOS) in uterine arteries from women after normal pregnancies compared with those from multipara, nonpregnant women. Results of this study confirm observations in experimental animals: NOS expression increases in uterine arteries during pregnancy and NOS immunostaining increases in uterine arteries during the follicular compared with luteal phase of the menstrual cycle in nonpregnant women.

In the era of translational or bench-to-bedside research, studies involving human tissue are necessary to validate observations in experimental animals, because each type of study carries certain limitations. Results from animal studies reflect the combined genetic and environmental influences that have resulted from evolutionary survival of a particular species in an environmental niche. Molecular probes and antibodies developed for one species may not be appropriate for another and, when used without careful controls, may negatively influence outcomes and, therefore, conclusions.

On the other hand, in experiments using human tissue, legal and ethical issues of confidentiality, risk, and ownership must be considered in addition to the scientific issues that affect the outcome and interpretation of results. These issues, when the material is surgical waste, include the underlying condition or disease process that required the need for surgery, demographics of the patient (age, ethnicity, and gender), and medications for preexisting conditions and anesthesia. This type of information is especially important for studies in women, because their hormonal statuses change across the life span and physiology may be influenced by pregnancy.

Some of these points were brought to bear in the study by Nelson et al, because particular attention was paid to the source of the tissue being from multipara women and normal pregnancy. However, the authors indicate that additional studies were needed, because initial information regarding hormonal status and stage of menstrual cycle was not included in the original medical record. Information regarding use of hormonal replacements, supplements, and treatments must be considered as variables in studies using tissue from women. Handling and storage of tissue are also important considerations, and the authors of the present study have been careful to include preliminary studies to define storage limitations.

Although it is necessary to confirm observations from animal studies in human tissue, it is even more important that such studies go beyond the confirmatory to provide new and specific insights into mechanisms or disease processes that have not been made in animal studies. The accompanying study by Nelson et al does that by confirming increased expression and activity of endothelial but not inducible NOS in uterine arteries during pregnancy. In addition, results of the study provide new insights into the distribution of neuronal NOS in the adventia of uterine arteries. Although the immunostaining for neuronal NOS seemed to be similar in arteries from pregnant and nonpregnant women, estrogen has been shown to modulate neuronal NOS in other cell types. Emerging data indicate that adventitial cells may contribute to healing of vascular wounds. To what extent estrogen regulates neuronal NOS in uterine arteries may be of interest for future studies, especially to determine whether and how adventitial cells participate in vascular remodeling during and after pregnancy.

Several other questions arise from the study by Nelson et al. For example, are there other aspects of NOS regulation, such as arginine transport systems or enzyme cofactors, affected by hormones and pregnancy? Are there differences in NOS expression and regulation that are set by pregnancy, ie, enzyme from nullipara compared with multipara, nonpregnant women? How are such changes related to distribution of estrogen receptors within the blood vessel? Are there differ-
ences in NOS induction and regulation or estrogen receptor polymorphisms that contribute to infertility or inability to sustain pregnancies? Are other structural proteins, such as polyamines, altered in blood vessels during pregnancy? Investigators in clinical departments with access to human tissue are in an ideal position to creatively design experiments that go beyond confirming observations from studies in experimental animals. Such studies could lead the way by providing new information necessary to improve the health of women into the 21st century.

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References
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