Homer Smith, the father of renal physiology, marveling at motherhood, stated in 1956, "to a renal physiologist, a pregnant woman is a very interesting phenomenon. I do not know of another way to increase the filtration rate by 50 per cent or better for prolonged periods" (1). In human pregnancy such striking increments in glomerular filtration rate (GFR) and renal plasma flow (RPF) are already present in the first trimester and are maintained throughout gestation (2). The relevance of these changes to gestational outcome is unclear, though there are indications that women labeled "poor reproducers" have suboptimal increases in GFR. Of greater importance, gravidas developing preeclampsia, a complication associated with significant morbidity and mortality for both mother and fetus, experience substantial decrements in renal hemodynamics (~30–50% compared to normal gestation), and on occasion they develop frank renal failure (2). Nevertheless, and despite the wonderment of Homer Smith, research on the physiology and pathophysiology of the kidney during pregnancy has been sporadic, and currently we do not know why GFR increases during gestation. In this issue, Danielson and Conrad (3) attempt to explain the mystery behind hyperfiltration in pregnancy.

These authors measured GFR and RPF at mid-pregnancy in awake, chronically instrumented, Long-Evans rats during the period when gestational increments in renal hemodynamics most resemble those observed in humans (4). Acute inhibition of nitric oxide synthases (NOS) decreased GFR and RPF and increased renal vascular resistance (RVR) to a greater extent in gravid than virgin rats, eliminating the differences in renal hemodynamics between groups. The authors took care to include key controls often omitted in analogous studies. They confirmed that basal renal and vascular NO synthesis was, indeed, inhibited by the doses of $N^{\omega}$-substituted arginine analogues used in their protocols. Further, they infused angiotensin II (AII) to exclude nonspecific renal vasoconstriction as a cause of their observations. AII proved a less effective renal vasoconstrictor in gravid rats; filtration fraction increasing only in virgin animals. The authors concluded cautiously that augmented NO synthesis mediates the reduced RVR and hyperfiltration which characterize rat pregnancy. Is their hypothesis valid and what is the pertinence of their findings to human gestation?

Their conclusion would be strengthened if supported by other "vasoconstrictor controls." True the experiments comparing effects of infused AII with those of $N^{\omega}$-substituted arginine analogues appear convincing. But we do not know whether other renal vasoconstrictors, especially those which, like NOS inhibitors but unlike AII, selectively increase preglomerular arteriolar resistance in non gravid animals, would have similarly led to the conclusion that nonspecific renal vasoconstriction fails to reproduce the effects of NOS inhibition in this model. As well, while it is tempting to speculate, as the authors did, that gestational refractoriness to AII-induced renal vasoconstriction is mediated by NO, no data are yet available to rigorously test that hypothesis.

There is convincing evidence that NO synthesis and resulting cGMP accumulation and urinary excretion are augmented during pregnancy (5), but the tissue and cellular sites of increased NO synthesis, the responsible enzyme isoform, the mechanisms of NOS activation, and the relevance of increased NO synthesis to gestational vasodilation have remained elusive (5). In the present report the contributions of NO are inferred from measuring hemodynamic changes which follow acute NOS inhibition. This classic approach assures physiological relevance, but sacrifices specific mechanistic insights, especially in complex intact systems such as the control of glomerular hemodynamics (5). Some may also be uncomfortable drawing insights into chronic adaptations from acute interventions, but here such an approach was preferable as it wisely avoided the complex compensatory responses and renal damage which follow continued administration of NOS inhibitors (5).

Renal vasoconstriction due to NOS inhibition is selectively increased during gestation, yet the increase in blood pressure produced by these inhibitors is similar in gravid and virgin animals (5, 6). Assuming that increments in systemic vascular resistance are also similar, then there must be regional vascular heterogeneity in the mechanisms that mediate gestational vasodilation. In the study by Danielson and Conrad the NOS isoform contributing to renal vasodilation in pregnancy might have been revealed by using inhibitors which have greater selectivity or by studying the response to augmented substrate delivery. In fact, a recent survey of NOS activity and transcripts from gravid guinea pigs suggests increased expression of the calcium-sensitive isoforms in various tissues including the kidney (7). Although the hormonal stimulus for this effect in pregnancy remains obscure, the NOS induction was mimicked by administration of exogenous estradiol, but not progesterone (7). While such transcriptional activation of the physiologically regulated, calcium-dependent NOS isoforms during gestation has not been localized to cells which might relate to the rise in GFR they would be consistent with the authors' failure to detect increases in basal cGMP (an index of NO exposure) in either renal cortical slices or aorta ex vivo. The latter observations also suggest that augmented synthesis of NO in the renal vasculature of the pregnant rats may depend on continued exposure to humoral, neural or mechanical (i.e., flow-induced shear stress) factors present only in the intact animal.

What are the physiologic determinants of hyperfiltration in pregnancy? Micropuncture studies in the rat suggest that the increase in single nephron GFR (sngfr) results exclusively from increments in glomerular plasma flow (snpf), due to balanced afferent and efferent vasodilation, and without changes in either the ultrafiltration coefficient or in glomerular capillary pressure ($\Delta p$) (4). There is a resetting of renal blood flow autoregulation and tubuloglomerular feedback mechanisms, so that the renal vasodilation and hyperfiltration are sensed as normal (4). There is also evidence that increased renal hemodynamics of pregnancy is submaximal as GFR and RPF can be increased further by amino acid infusions (2, 4, 8). Of particular note, failure of $\Delta p$ to rise during rat pregnancy despite increments in snpf and sngfr is comforting to those concerned whether gestational hyperfiltration might harm the kidney. In this respect, Roberts, Lindheimer, and Davison (unpublished observations) have

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measured fractional dextran clearances and RPF in gravid women. Their preliminary data support conclusions that hyperfiltration is due primarily to increments in RPF without evidence of increased $\Delta p$ in humans.

Finally, renal vasodilation by endogenous NO appears due to prominent and selective relaxation of afferent arterioles and mesangial cells (4, 5). NO also influences the control of intrarenal blood flow as well as paracrine and endocrine regulatory pathways contributing to renal volume homeostasis (5), and may lead to changes in the glomerular capillary membrane (9). How these many NO responsive elements interact and produce the gestational changes described by Danielson and Conrad remains a fertile ground for future investigation, perhaps even more exciting in view of publications speculating that preeclampsia is due to decrements in the production of NO.

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