UNDERSTANDING the physiologic and hormonal changes in pregnancy involves challenges and, sometimes, surprises. Foremost among the challenges is the mechanism that regulates the volume of extracellular fluid. In human pregnancy, there is a marked expansion of extracellular fluid volume, associated with a cumulative retention of 500 to 700 mEq of sodium and a 1.5-fold increase in plasma volume. Concurrently a pronounced dilation of the peripheral vasculature begins early in pregnancy and persists until term, resulting in a 40% decrease in total peripheral arterial resistance. Blood pressure declines modestly in the second trimester and returns to baseline values near term. Additional hemodynamic changes include a 50% increase in cardiac output and similar rises in blood flow to visceral organs, such as the kidney and uterus. It is assumed that these changes occur to provide an optimal environment for the growth and development of the fetus, but the mechanisms that cause these changes are not fully understood.

The renin-angiotensin-aldosterone system has attracted attention for its possible role in the control of sodium balance in pregnancy. A striking increase in the adrenal secretion of aldosterone is observed by the 8th week of gestation and continues to rise throughout pregnancy to achieve plasma aldosterone levels of 80 to 100 ng/dL by the third trimester, 4 to 6 fold above the upper level observed in euvolemic nonpregnant adults. Although renin activity also increases, this change does not correlate with aldosterone secretion. Special interest is directed toward progesterone, produced by the placenta, because the progressive rise during gestation parallels that of aldosterone and reaches a level of about 200 ng/dL by term and because progesterone is an antagonist for aldosterone. Evidence for its inhibitory action includes the capacity of progesterone to bind to the mineralocorticoid receptor (MR), albeit at a lower affinity, and to inhibit the action of aldosterone to stimulate sodium transport in amphibian epithelium. The administration of progesterone, in physiologic amounts, to adults with normal adrenal function induces natriuresis, but not in subjects with adrenal insufficiency.

Some investigators suggest that high plasma levels of aldosterone during pregnancy reflect a compensatory response to salt losing factors, such as the 50% increase in filtered sodium and the inhibitory action of progesterone. An alternative proposal suggests that aldosterone secretion is adjusted to support the expanded peripheral vasculature as a result of the direct action of a vasodilating factor. Studies in the rat model of pregnancy suggest that that factor may be relaxin, a peptide hormone belonging to the insulin family, which stimulates vascular dilation by inducing the production of nitric oxide in vascular endothelial cells. Relaxin normally is produced in the corpus luteum and in larger amounts by the placenta and decidua during pregnancy.

Notwithstanding evidence that progesterone can antagonize the action of aldosterone, numerous studies indicate that aldosterone is poised to maintain sodium balance and extracellular fluid volume at a level appropriate for the stage of
pregnancy. When sodium balance is perturbed by decreases or increases in dietary sodium, there are immediate and appropriate changes in plasma aldosterone levels and corresponding changes in sodium excretion. At high sodium loads, the aldosterone level falls to values observed in euvolemic nonpregnant adults. The administration of mineralocorticoids to pregnant women stimulates sodium retention and an increase in body weight, showing that the MR is capable of responding to the ligand by activation and that the signaling mechanism to stimulate the epithelium sodium channel is intact. All of these responses occurred in the presence of high plasma levels of progesterone. Taken together, these data support the notion that aldosterone is crucial in maintaining sodium balance in pregnancy.

A report by Geller et al. provides a surprise. They showed that in at least one family progesterone acts as an agonist to activate the MR and cause pregnancy-related hypertension. Geller et al. identified a family in which 11 of 23 relatives experienced severe hypertension before age 20. The afflicted individuals were heterozygous for a missense mutation, resulting in the substitution of leucine for serine at codon 810 in the MR. The S810L mutation lies in the hormone-binding domain of the MR. Normally, activation of the wild-type MR (MRWT) requires steroids bearing 21-hydroxyl groups, such as aldosterone. Some steroids, which lack 21-hydroxyl groups, such as progesterone and spironolactone, can antagonize mineralocorticoids via competitive inhibition when they bind but fail to activate the receptor. When the mutant MR_{L810} was studied, however, progesterone and aldosterone were equally effective in activating the receptor. MR_{L810} was shown to be partially active in the absence of the steroid, perhaps explaining hypertension in carriers younger than age 20.

Two of the carriers experienced a total of five pregnancies. In each pregnancy, severe hypertension occurred in the latter half of gestation, in the absence of signs of preeclampsia. When measured, plasma aldosterone was undetectable. Hypertension resolved promptly after delivery. The authors proposed that hypertension developed in these pregnancies because progesterone activated MR_{L810}. This discovery identifies another cause of hypertension that, similar to Liddle’s syndrome, results from unregulated reabsorption of sodium across the collecting tubule, which causes volume expansion, inhibition of renin and aldosterone secretion, and hypertension. In contrast to Liddle’s syndrome, caused by constitutive activation of the epithelium sodium channel, female carriers for MR_{L810} are uniquely vulnerable to develop hypertension during pregnancy because it is the only condition associated with high levels of progesterone.

The story of the mutant MR_{L810} is extended in this report by an explanation of how a single amino acid replacement allows progesterone to act as an agonist. Because the crystalline structure of the progesterone receptor was known and differed from MRWT by only three residues in the cavity of the hormone-binding domain, it was possible to model the mutant and wild-type structures of the MR. This analysis showed that in the model of MR_{L810}, the L810 side chain in helix 5 projected into the ligand-binding cavity, potentially forming van der Waals interactions with helix 3 and the steroid. A similar interaction was not found in the model of MRWT. The prediction that the additional van der Waals interactions resulted in receptor activation by steroids lacking 21-hydroxyl groups was confirmed by site-specific mutagenesis. Progesterone and spironolactone showed increased competition with aldosterone, indicating higher affinity for the mutant receptor.

This study shows the usefulness of selecting individuals with unusual phenotypes, such as severe hypertension at an early age, to uncover mechanisms of disease. The clinical importance of this discovery is not obvious because the mutation is probably rare. It seems likely, however, that lessons learned from this study will have long-term usefulness because insights derived for understanding the mechanism of receptor activation and inhibition are likely to have general applications for the family of nuclear receptors.

This is not the first demonstration of a missense mutation in a receptor resulting in clinical disease during pregnancy owing to a placenta-produced agonist. Rodien et al. investigated a mother and daughter with recurrent hyperthyroidism in pregnancy. Although hyperthyroidism in pregnancy can result from excessive stimulation of the thyrotropin receptor by high plasma levels of gonadotropin, because of the close structural
relationship between chorionic gonadotropin and thyrotropin and between their receptors, these women had normal levels of chorionic gonadotropin for pregnancy. Both women had a missense mutation on codon 183 of the thyrotropin receptor where there was a replacement of a lysine residue with arginine in one allele. The position 183 is in a region of the receptor that constitutes the putative surface of interaction with thyrotropin. The authors suggested that the mutant substitution might have increased the stability of the illegitimate complex between chorionic gonadotropin and thyrotropin receptor enough to stimulate signal transduction secondary to increased levels of the hormone present in pregnant women.

REFERENCES