Maternal and fetal adaptations during pregnancy: lessons in regulatory and integrative physiology

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PREGNANCY IS A COMPLEX PHYSIOLOGICAL condition that involves the integration of a variety of regulatory and organ systems. Many aspects of maternal and fetal adaptations during pregnancy have been addressed by recent publications in the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. Articles include investigations on cardiac, vascular, endothelial (1, 7), renal (17), respiratory, gastrointestinal (39), uteroplacental (12, 36, 38, 48, 55, 56, 63, 68, 71–74), and neuroendocrine changes during pregnancy. Cardiovascular (19) and neurohumoral (41, 49, 66) and metabolic (3, 4, 8, 18) adaptations in the fetus have also been a subject of great interest. Much attention has also been given to the impact of hypoxia, glucocorticoids, and other stressors on the development of the fetus and newborn.

Normal pregnancy is associated with marked hemodynamic alterations within the maternal circulation, including increases in cardiac output and plasma volume and reductions in vascular resistance and arterial pressure. Associated with these changes are marked alterations in the activity of various neurohumoral systems and in vascular and endothelial function. Hines and colleagues (33–35) recently reported that stimulation of volume-sensitive cardiac mechanoreceptors elicits an attenuated reflex effect on blood pressure and renal function. Furthermore, these investigators reported baroreceptor afferent as well as cardiac receptor afferent discharge is reduced during pregnancy (33–35). These investigators postulate these changes in reflex function are an important adaptation that allows plasma volume expansion during pregnancy.

The reduction in arterial pressure in the face of marked increases in cardiac output during pregnancy is due to a considerable decrease in vascular tone. An increase in nitric oxide (NO) during normal pregnancy has been suggested to mediate decreases in vascular resistance by direct actions and by blunting the vascular responsiveness to vasoconstrictors such as angiotensin II and norepinephrine (16, 57). This concept is supported by recent reports that the expression (2) and activity of NO synthases are elevated during normal pregnancy and that the plasma level and urinary excretion of cGMP, a second messenger of NO and a mediator of vascular smooth muscle relaxation, are increased during pregnancy. Moreover, pharmacological blockade or targeted disruption of NO synthases markedly attenuates the reduction in vascular resistance and blood pressure during pregnancy (11, 32). Inhibition of NO synthesis has also been recently shown to modulate the reduction in vascular smooth muscle intracellular calcium concentration (52) and protein kinase C activity (40) that normally occurs during pregnancy. Furthermore, the vascular responsiveness to vasoconstrictors such as angiotensin II is markedly enhanced during pregnancy when NO synthase is inhibited. Finally, recent studies in American Journal of Physiology-Regulatory, Integrative and Comparative Physiology have reported that the vascular actions of NO during pregnancy are attenuated by hyperlipidemia (53) and alcohol intake (15).

The renal circulation is particularly affected during normal pregnancy. Both renal plasma flow and glomerular filtration rate increase to 40–80% above normal in humans and 20–40% in pregnant rats. Mechanisms underlying the marked renal vasodilation during pregnancy have been a subject of intensive investigation. Although numerous factors may be involved in this renal hyperemia, recent studies have implicated NO as an important mediator of the renal hyperfiltration during pregnancy (27, 45). Pregnancy is associated with enhanced renal expression and activation of NO synthase (2). Nonselective and selective inhibition of NO synthase isoforms also attenuate the renal hemodynamic changes during pregnancy (1). Recent studies have suggested that the hormone relaxin is an important factor that mediates the enhanced renal hyperemia and production of NO during pregnancy (17). It
also appears that relaxin enhances NO production by an endothelin B receptor-mediated mechanism (17). The interaction between relaxin and the renal endo-
thelin system remains to be an important area of investigation.

The influence of various neurohumoral and metab-
olic factors on fetal physiology and development of the cardiovascular (7, 46, 60, 64, 69), renal, gastrointesti-
nal (14, 61, 62), neuroendocrine (42), hemopoietic (10, 65), and pulmonary (37, 54) systems has also been an important area of investigation. In particular, much attention has been directed toward studying the impact of various stressors such as hypoxia (5, 13, 28, 30, 43, 44, 70), malnutrition (25, 31, 67), glucocorticoids, infection (23, 29), alcohol, nicotine (26), and other factors (6) on the mother and the fetus. This is a clinically important area of investigation because maternal-fetal stress is a major factor for poor obstetric and infant outcomes, including spontaneous abortion, prematurity, and intrauterine growth restriction as well as susceptibility to cardiovascular and metabolic disease throughout life. Numerous epidemiological studies have reported an association between low birth weight and the risk of hypertension. The inverse relationship between low birth weight and hypertension suggests that factors present in the prenatal environment that affect fetal growth are responsible for the in utero programming of arterial blood pressure control.

A number of studies published in American Journal of Physiology-Regulatory, Integrative and Comparative Physiology have focused on the effect of glucocorticoids and other stressors on fetal development and its impact on blood pressure regulation later in life. Although antenatal glucocorticoid administration is used to improve lung function in human premature newborns, data emerging from humans and animal studies indicate antenatal glucocorticoid administration can significantly affect the cardiovascular, renal, and metabolic alterations essential to postnatal adaptation at birth. Although the mechanisms by which antenatal glucocorticoids impact postnatal circulatory function are unclear, abnormalities in vascular, cardiac, neurohumoral, and autacoid functions appear to be involved (20, 21, 51). Segar et al. (59) recently reported that postnatal increases in arterial pressure and renal symp-
thetic nerve activity seen with glucocorticoid treatment are not mediated by stimulation of peripherally accessible angiotensin type 1 receptors. They also sug-
gest that augmented cardiovascular function in glu-
corticoid-treated premature lambs is dependent, in part, on a generalized sympathetic excitatory response that is mediated by central mechanisms (59). Ervin and colleagues (24) reported that the alterations in postnatal blood pressure regulation in lambs exposed to glucocorticoids preterm occurs despite reductions in plasma cortisol, catecholamines, and circulating levels of angiotensin II. Interestingly, in another study by Brabham et al. (9), it was reported that the environment provided by a healthy mother during postnatal period can prevent the detrimental effects of prenatal glucocorticoid administration on cognitive function.

Because of its significant clinical implications, it is quite obvious that more studies are needed to deter-
mine the underlying mechanisms whereby antenatal exposure to glucocorticoids and other stressors such as malnutrition and hypoxia affect the physiology of the fetus and the newborn.

Because the renin-angiotensin system has been im-
plicated in the morphogenesis and growth of the kid-
ney throughout fetal development, investigators have also been interested in studying factors that regulate renin secretion in the developing fetus (22, 47, 50). Draper et al. (22) recently examined the role of renal nerves on renin secretion in the mature ovine fetus. They reported that renal nerves are required for the renin secretory mechanisms and responsiveness of renin mRNA to β-adrenergic stimulation but not for the basal expression of renin in the fetal kidney. In another study by Marsh and colleagues (47), insulin-like growth factor (IGF) was found to chronically enhance plasma renin activity and concentration, implicating IGF as another modulator of renin secretion during fetal development.

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