Sex Differences
in Fetal Lung Development
Biology, Etiology, and Evolutionary Significance

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HISTORICAL PERSPECTIVE

Interest in the relationship between sexual dimorphism and lung maturation emerged in the late 1970s for one specific reason: it had been observed among pregnant women treated antenatally with glucocorticoids for lung immaturity that the risk of respiratory distress syndrome (RDS) was halved in females, but had no effect on males (1). Because of our mutual interest in fetal lung development, particularly its relationship to fetal endocrinology (2), we decided to determine the biologic basis for this phenomenon, thinking that if there were a sex-specific steroid effect, that this experiment of nature could be exploited as a means of discovering the underlying nature of the cellular machinery that mediates the processes of lung development. The global strategy we used was
to exploit the spontaneous sex difference in fetal lung development that occurs across species in utero. This “tool” would allow us to tease out the clinically significant, albeit small, differences in the timing of fetal lung maturation. With the advantage of 20/20 hindsight, we should have realized that this phenomenon comprises the “small, incremental steps” that typify self-organizing systems with respect to both their ontogeny and their homeostatic control (3). Our hope was that such extensive studies would reveal the mechanisms underlying this process to better predict and prevent neonatal lung disease.

A PRIORI EVIDENCE FOR THE EXISTENCE OF A SEX DIFFERENCE IN THE DEVELOPMENT OF PULMONARY SURFACTANT

Our first step in the study of sexual dimorphism of fetal lung development was to scour the literature for prior empiric evidence of such a phenomenon, particularly with respect to pulmonary surfactant ontogeny, since this process would provide a mechanistic link between lung development (4), steroid therapy (5), and RDS (6). At that time there was fairly extensive literature documenting the interrelationship between the structural development of the fetal lung and its direct relationship to the ontogeny of the surfactant system (7). The causal nature of this structure–function relationship has subsequently been elucidated, in large part, by using steroids and other hormones to influence the timing (8) and extent (9) of surfactant ontogeny. For example, glucocorticoids (10), thyroid hormone (11), and retinoic acid (12) will all accelerate both the structural maturation of the lung and the rate of surfactant production; in contrast to this, such hormones as insulin (13) and testosterone (14) delay lung development pathophysiologically; antiglucocorticoids (15) do so pharmacologically. Liggins' seminal observation of a dramatic effect of exogenous steroid treatment on lung maturation and precocious survival of fetal sheep was rapidly translated to human subjects, demonstrating an effective reduction in the risk of RDS (17).

A large number of randomized controlled trials demonstrated that prenatal glucocorticoid treatment reduced the risk of RDS in premature infants, generally between 28 and 32 wk. These trials culminated in an NIH-sponsored multicenter collaborative double-blind, randomized trial that showed an overall 30% reduction in the risk of RDS after prenatal dexamethasone therapy (1). One serendipitous finding in the Collaborative Trial was the observation that the statistical effect of prenatal steroids was stronger in females than in males. Others also evaluated their studies for evidence of a male–female difference in response; a stronger effect in female infants than in males was noted by some (18–20) but not by all (21). Overall, the beneficial effect of prenatal glucocorticoid was strongly substantiated by a metaanalysis of all randomized, blinded controlled trails (22), and supported by a recent NIH consensus conference and official NIH Consensus Statement (22).

DIRECT EVIDENCE FOR A SEX DIFFERENCE IN HUMAN FETAL LUNG DEVELOPMENT

The first empiric evidence of a link between fetal sex and lung maturation came from our observational study of sex-specific surfactant ontogeny in human amniotic fluid (23). Gluck had previously demonstrated the principle that surfactant phospholipid kinetics in amniotic fluid could be used to predict the risk of RDS in the newborn (24). We (J.T.) expanded on the precept by devising a more sensitive and specific assay to measure the major surface-active component of the surfactant complex (24), saturated phosphati-