INTRODUCTION

Infants of diabetic mothers have an elevated incidence of respiratory distress syndrome of the newborn (RDS), a disease which is caused by pulmonary surfactant deficiency associated with inadequate numbers of differentiated alveolar type II cells in the lung (1,2). Pulmonary surfactant, which functions to reduce surface tension at the air–alveolar interface, is made up of glycerophospholipids (approx 80% by weight), cholesterol (approx 10%) and the surfactant-associated proteins (approx 10%) (3). The fetus of the diabetic mother tends to have high serum glucose and insulin levels as a result of maternal hyperglycemia (4). Robert et al. (1) first advanced the hypothesis that high levels of insulin might delay lung development in the fetus of the gestational diabetic woman. In this chapter, we will review the literature concerning the effects of maternal diabetes, glucose, and, in particular, insulin on fetal lung development.

RESPIRATORY DISTRESS SYNDROME IN THE INFANT OF THE DIABETIC MOTHER

It has been estimated that 100,000 infants of diabetic mothers are born in the United States every year, a large group of infants at risk for developing RDS and other morbidities.
associated with a diabetic pregnancy (5). Using the White classification system, infants born to mothers with type A diabetes (gestational onset diabetes) and types B and C have been found to have a higher incidence of RDS than infants born to mothers with more severe, insulin-dependent diabetes mellitus (classes D, E, F, and R) (6). More recently, it has been shown that infants of mothers whose diabetes is well controlled have a risk for RDS that is no different than that of the general population (7,8). While universal screening of pregnant women for gestational onset diabetes is recommended, women who receive inadequate prenatal care and develop uncontrolled diabetes still exist in the population (9).

Pathophysiology of Delayed Lung Maturation in the Diabetic Pregnancy

Two physiologic situations exist in diabetic pregnancies in which the diabetes is poorly controlled, namely, hyperinsulinemia and hyperglycemia (4). Diabetic mothers whose diabetes is poorly controlled with persistent hyperglycemia have been shown to have infants who are hyperinsulinemic at birth, with elevated proinsulin and C-peptide levels in cord blood when compared to levels in control infants (10–12). The levels of plasma insulin in infants of pregnancies complicated by diabetes have been reported to be as high as 112 μU/mL vs 11 μU/mL in control infants (13). In diabetic pregnancies with a glucose load, insulin levels in infants may rise to 200–300 μU/mL (14). Maternal blood glucose can reach levels greater than 150 mg/dL in diabetic pregnancies that are poorly controlled as compared to approx 90 mg/dL in controls (13,15). Infants of diabetic mothers have significantly higher blood glucose levels than control infants (13).

Lecithin: Sphingomyelin Ratio

Toward the end of gestation, fetal lung type II cells differentiate and begin to secrete surfactant into the amniotic fluid (16). Lecithin (specifically dipalmitoylphosphatidylcholine, a disaturated phospholipid produced by the fetal lung and is secreted into amniotic fluid in greater amounts toward the end of gestation (16). By contrast, the concentration of another lipid, sphingomyelin, remains constant in amniotic fluid throughout gestation. Thus, the ratio of lecithin to sphingomyelin (L:S) can be used to determine fetal lung maturity, with a ratio of greater than 2:1 predictive of maturity (6,17). In early studies, several investigators observed delayed fetal lung maturation as assessed by L:S ratios in diabetic pregnancies (Table 1) (6,18,19). By contrast, in more severe classes of diabetes, D, E, F, fetal lung maturity was accelerated (Table 1) (6). It was proposed that chronic intrauterine stress experienced by fetuses of severely diabetic mothers contributed to the accelerated lung maturation observed in this group (6). There are many more studies in which no evidence of delayed lung maturation in diabetic pregnancies was observed when using the L:S ratio as a guide (Table 1) (20–34). In many of the latter studies, good metabolic control of the diabetic pregnancies was reported (Table 1) (24,28–31,33). However, several investigators have described a high incidence of false-positive L:S ratios in diabetic pregnancies, that is, infants who develop RDS at birth despite L:S ratios predictive of pulmonary maturity (Table 1) (18,20,22,23,26,27,31,35–38). Thus, the L:S ratio may not be a reliable predictor of fetal lung maturity in the diabetic pregnancy.

Phosphatidylglycerol

When surfactant secretion begins in the fetus, at about 30–32 wk of gestation, the major anionic phospholipid present in surfactant is phosphatidylinositol (PI) (39). Then, as gestation proceeds, the level of PI falls while the level of phosphatidylglycerol (PG)