

This Week's Citation Classic

Liggins G C & Howie R N. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics* 50:515-25, 1972. [Postgrad. Sch. Obstet. and Gynaecol., Univ. Auckland, Auckland, New Zealand]

Immature human fetuses responded with accelerated lung maturation when exposed for 24 to 72 hours to a synthetic corticosteroid. At birth, the treated infants in this doubleblind trial were less likely to develop respiratory distress syndrome (RDS) and more likely to survive. [The SC[®] indicates that this paper has been cited over 565 times since 1972.]

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"In 1967, while investigating the mechanism by which fetuses control the time of their birth, I noticed that lambs born very prematurely as a result of fetal infusions of ACTH or dexamethasone were able to breathe effectively. At autopsy, the lungs were found to be partly air-filled instead of having the liver-like appearance characteristic of immaturity. No sophisticated tests were needed to postulate a connection between adrenal activity and lung maturation. Because we were inexperienced at that time in pulmonary physiology and were preoccupied with parturitional physiology, it was decided to pass on this intriguing finding to better equipped colleagues elsewhere, particularly Mary Ellen Avery¹ in Montreal, and William Tooley and John Clements in San Francisco.² The preliminary observations were soon confirmed and greatly extended, encouraging us to plan a clinical trial to find out whether corticosteroid treatment would hasten pulmonary maturation in human fetuses about to be born prematurely. The medical staff and nurses of the National Women's Hospital, Auckland, New Zealand,

cooperated enthusiastically in a double blind trial which eventually included over 1,000 women. The study was organized with the help of my Coauthor, Ross Howie, a neonatologist who has a gift that I lack for meticulous attention to detail. The first patient was enrolled in December 1969. A paper describing a reduction in the incidence of RDS and early neonatal death in infants treated *in utero* with corticosteroids was offered to *Lancet* in 1972 but was rejected on grounds of lack of general interest. Whereupon the spelling was Americanized and an otherwise unamended manuscript was submitted with greater success to *Pediatrics*.

"Interest in the paper has come not only from clinicians who have confirmed our findings but more particularly from physiologists and biochemists to whom the work seems to have acted as a stimulus to the study of lung development, perhaps partly because of its appeal to mission-oriented granting agencies. Inevitably there are those who wish to record their dislike of fetal exposure to drugs in any shape or form. Reports in press of the long-term follow-up of surviving children now up to 11 years old show no adverse effects of their corticosteroid treatment as fetuses.

"It is an interesting reflection on the way that science progresses in fits and starts that 12 years after I first reported the relationship of the fetal adrenal to lung maturation, the nature of the relationship remains unclear. It seemed so simple then—cortisol induces an enzyme in the biosynthetic pathway to surfactant. Today, there is no agreement on what, if any, enzyme is induced, whether changes in structure or surfactant are more important, and whether the action of cortisol is dependent on other hormones. Fortunately, therapeutic success often is not dependent on a detailed knowledge of pharmacological action. The reason the paper is highly cited may stem partly from novelty but mainly from the fact that an equally well-controlled study was not published until five years later."³

1. DeLemos R A, Shermeta D W, Knelson J H, Kotas R & Avery M E. Acceleration of appearance of pulmonary surfactant in the fetal lamb by administration of corticosteroids. *Amer. Rev. Resp. Dis.* 102:459-61, 1970.
2. Plazker A C G, Kitterman J A, Mescher E J, Clements J A & Tooley W H. Surfactant in the lung and tracheal fluid of the fetal lamb and acceleration of its appearance by dexamethasone. *Pediatrics* 56:554-61, 1975.
3. Papageorgiou A N, Desgranges M F, Masson M, Colle E, Shatz R & Gelfand M M. The antenatal use of betamethasone in the prevention of respiratory distress syndrome: a controlled double-blind study. *Pediatrics* 63:73-9. 1979.