

[Corticosteroids' Effect on Fetal Lung Maturation \(1972\), by Sir Graham Collingwood Liggins and Ross Howie](#) ^[1]

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In a clinical trial from 1969 to 1972, Sir Graham Collingwood Liggins and [Ross Howie](#) ^[4] showed that if doctors treat pregnant women with corticosteroids before those women deliver prematurely, then those women's infants have fewer cases of [respiratory distress syndrome](#) ^[5] than do similarly premature infants of women not treated with corticosteroids. Prior to the study, premature infants born before 32 weeks of [gestation](#) ^[6] often died of [respiratory distress syndrome](#) ^[5], or the inability to inflate immature lungs. Liggins and Howie, then both at the University of Auckland in Auckland, New Zealand, published their results in "A Controlled Trial of Antepartum Glucocorticoid Treatment for Prevention of the Respiratory Distress Syndrome in Premature Infants," in 1972. The study built on Liggins's earlier experiments with [sheep](#) ^[7]. Liggins' corticosteroid experiments changed the way doctors treated pregnant women experiencing preterm labors, and they improved the life expectancies of prematurely born infants.

Liggins spent much of his life researching preterm labor, beginning with his tenure as a senior lecturer in obstetrics and gynecology at the National Women's Hospital in Auckland, New Zealand in the late 1950s. In an effort to learn how to halt [premature labor](#) ^[8], Liggins researched the factors responsible for the initiation of labor. Liggins also tested his hypothesis that the [fetus](#) ^[9], rather than the mother, caused the initiation and timing of labor. Liggins used [sheep](#) ^[7] as his [model organism](#) ^[10] because of their prevalence in New Zealand.

At the time, observations suggested that pregnant [sheep](#) ^[7] experienced abnormally long pregnancies if they carried fetal lambs that had damaged pituitary glands. Liggins hypothesized that fetal lambs with damaged pituitary glands due to anencephaly or hypothalamic lesions failed to initiate the normal processes of labor in the pregnant ewes. To test his hypotheses, Liggins traveled 80 miles south of Auckland to the Agricultural Research Station to learn how to remove pituitary glands (hypophysectomies) and adrenal glands (adrenalectomies) in fetal [sheep](#) ^[7]. In 1960, Liggins took sabbatical to study at the [University of California at Davis](#) ^[11] Veterinary School in Davis, California to further perfect his surgical and research techniques on [sheep](#) ^[7].

Upon his return to Auckland, Liggins wanted to continue his research on preterm birth in [sheep](#) ^[7], but money was tight so he was given an abandoned shed and limited funds to continue his experiments. Liggins began injecting pregnant ewes with corticosteroids to observe the effect on the timing of labor. One morning, Liggins discovered that a pregnant [sheep](#) ^[7] treated with corticosteroids had delivered a lamb overnight. The lamb was so premature that it should not have survived, but it was alive and breathing. However, the breathing was irregular and strained, and the lamb soon died. Liggins performed an autopsy and discovered that the newborn lamb's lungs had fully inflated, rather than being brittle as would be expected in such a premature lamb. The corticosteroids given to the pregnant [sheep](#) ^[7] had crossed the [placenta](#) ^[12] and accelerated fetal lung maturation, allowing the lamb to breathe and continue life outside the [womb](#) ^[13], if only for a brief time.

Liggins postulated that corticosteroids induced one or more enzymes responsible for surfactant synthesis in premature lungs. Just prior to normal-term birth, fetal lungs begin to produce surfactants, which lubricate the interior of the lungs and help to prevent collapse by lowering the surface tension of the lung's tissues. Without surfactant, the wet surfaces of the lung's alveoli stick together and do not expand, so oxygen cannot be captured and absorbed into the blood stream. A lack of surfactant causes a condition in prematurely born infants called infant [respiratory distress syndrome](#) ^[5]. Liggins published his experiments with lambs and corticosteroids in 1969, "Premature Delivery of Foetal Lambs Infused with Glucocorticoids," before directing his attention to human [pregnancy](#) ^[14] and surfactant production.

Between 1969 and 1972 Liggins created a double-blind, controlled clinical trial in collaboration with his pediatric colleague [Ross Howie](#) ^[4]. In their study, Liggins and Howie included women experiencing [premature labor](#) ^[8] at 24 to 36 weeks of [gestation](#) ^[6], or for whom premature delivery before 37 weeks was planned because of obstetric complications.

Upon admission to the trial, each patient received either an injection of the corticosteroids betamethasone phosphate and betamethasone acetate, or a placebo identical in appearance to the treatment drug. Unless delivery already occurred, a second injection was given to each woman 24 hours later. In the study, Liggins and Howie suggested that delivery be delayed for 48 to 72 hours from the time of the first injection. In cases where fetal membranes had spontaneously ruptured before the patients entered the study, doctors administered antibiotics and attempted to suppress labor for at most 48 hours. In patients for whom doctors planned to induce labor early due to obstetrical complications, the first injection was given three days before doctors

induced those labors.

Liggins and Howie recruited 287 pregnant women into the study over the course of twenty-two months. When necessary, they recommended the use of ethanol or salbutamol infusions to delay delivery, a technique that allowed doctors to administer the steroid or placebo therapy. Early neonatal mortality was 3.2 percent in the steroid-treated group and 15 percent in the control group. Respiratory distress syndrome occurred less often in treated babies (9.0 percent) than in the control group (25.8 percent), and there were no deaths due to hyaline membrane disease or intraventricular cerebral hemorrhage in infants of mothers who received corticosteroids at least 24 hours prior to delivery.

The experimental results on antepartum corticosteroids sparked a twenty-five year exploration of the hormonal [regulation](#)^[15] of fetal lung maturation. The manuscript created from the study, "A Controlled Trial of Antepartum Glucocorticoid Treatment for Prevention of the Respiratory Distress Syndrome in Premature Infants," was offered to *Nature* and *Lancet*, but both journals hesitated to publish the results, and in 1972, *Pediatrics* published the article. Despite the double-blind, controlled study and publication in a credible scientific journal, it took more than twenty years for corticosteroid intervention to become a routine clinical practice in the US. The efficacy and benefits of antenatal corticosteroid therapy, as well as the impact on the survival of premature infants, contributed to a drastic decrease in neonatal mortality.

Sources

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Subject

[Liggins, G. C.](#)^[16] [Liggins, G. C.](#)^[16] [Adrenocortical hormones](#)^[17] [Pregnancy](#)^[18] [Respiratory distress syndrome](#)^[19] [Premature infants](#)^[20] [Premature labor](#)^[21] [sheep](#)^[22] [Fetus](#)^[23] [Fetal development](#)^[24] [Birth](#)^[25] [Female Urogenital Diseases and Pregnancy Complications--Pregnancy Complications--Obstetric Labor Complications--Obstetric Labor, Premature--Premature Birth](#)^[26]

Topic

[Experiments](#)^[27]

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