

## **A Controlled Trial of Antepartum Glucocorticoid Treatment for Prevention of the Respiratory Distress Syndrome in Premature Infants<sup>1</sup> (1969-1971)**

### **Purpose**

- Primary research question(s):
  - Does intrafetal glucocorticoid infusion prevent Respiratory distress syndrome (RDS) among infants born at <37 weeks gestational age (GA)?
- Primary outcomes:
  - Neonatal mortality
  - RDS ('hyaline membrane disease'), as defined by clinical respiratory observation and evaluation (Silverman score), and radiology.
  - General condition at birth measured by Apgar score (1 and 5 minute)
- Perceived clinical importance:
  - RDS can lead to death in premature infants because of incomplete lung maturation. Acceleration of fetal lung development could prevent RDS and RDS-associated death.

### **Background and Context**

- RDS is a serious complication of premature birth (<37 weeks GA) and can lead to long-term morbidity (e.g., brain damage), as a result of insufficient oxygen. It affects one fifth of low birthweight babies and two thirds of extremely low birthweight babies.<sup>2</sup>
- Risk of RDS is inversely proportional to the GA and the maturation of fetal lungs. Attempts to prolong pregnancy past the age of greatest risk (<28 weeks GA) are not always successful.
- In the late 1960s, driven by an interest in understanding the biology of prematurity and the cause of labor, Mont Liggins and Ross Howie, discovered that pulmonary immaturity in lambs was

offset by an infusion of steroids in utero.<sup>3</sup>

- They hypothesized that steroids induced the early release of surfactant thereby enhancing alveolar development. Soon after, other researchers confirmed their hypothesis in further animal studies.
- Conveniently, Mary Ellen Avery, a leading RDS researcher was visiting New Zealand, allowing Liggins and Howie additional input and discussion, and further motivating them to attempt a clinical trial in humans.

### **Date and Place Conducted**

- Dates: December 1969 to October 1971
- National Women's Hospital, Auckland, New Zealand

### **Principal Investigators**

- GC Liggins and RN Howie, Postgraduate School of Obstetrics and Gynecology, University of Auckland, New Zealand.

### **Sponsored by/source of funding**

- Wellcome Trust

### **Size and Design**

- Number of participants: 282 women admitted to the maternity hospital presenting in premature labor at 24-36 weeks GA (74%) or planning premature delivery because of obstetric complications.
  - Those with contraindications to corticosteroids were excluded
- Participant characteristics:
  - Specific disorders related to the pregnancies were: 'hypertension-edema-proteinuria syndromes' (32), Rh isoimmunisation (21), major fetal malformation (14), placenta previa (2), and unplanned premature labor (213).
- Design:
  - Women were randomized to two groups:
    - Treatment (high dose corticosteroid) group: 2 intramuscular doses of betamethasone phosphate plus 6mg betamethasone acetate
    - Placebo group: 6mg cortisone acetate (a 1/70 weaker (1/70) placebo steroid)

- The pharmacist was the only one who was unmasked to treatment assignment.
- Dose administration depended on the timing of labor and delivery:
  - For women in labor, Dose 1 was administered at trial entry, 24 hours later they were given dose 2.
  - Between doses, IV ethanol or salbutamol was administered to delay delivery up to 72 hours.
  - Those planning a premature delivery received dose 1 at 72 hours before induction.
  - Those with premature membrane rupture received antibiotics.
- RDS cases received oxygen via umbilical arterial catheters.

### Issues Encountered During the Trial<sup>3</sup>

- It was noted that the ease and speed with which the trial was implemented was both spurred by another researcher with interest to do a similar trial at the same hospital as well as facilitated by the lack of a formal ethics committee (trial approval was given by the senior medical staff committee).
  - Several early US investigators of the period (1976) attempted similar trials but were unable to proceed for lack of ethical consent.
- Although the most often cited preliminary findings of the trial include the first 282 women, the study continued recruitment to involve 1218 infants. Given the positive findings from the first 717 women, the dose of corticosteroid was doubled.

### Findings

- Infant outcomes tended to be better for women in the treatment group although subgroup comparisons were not always statistically significant.
  - Among the 21 babies born to mothers with Rh hemolytic disease, perinatal mortality was lower (2/8) in the treatment group versus the control group (5/13) but not statistically significant.
  - Among the 32 infants born premature due to edema-hypertension-proteinuria complications there were more perinatal deaths in the treatment (6/19) than the control

- group (2/13). RDS less frequent among those who survived (1/14 treatment versus 4/13 control group).
- Among 226 infants delivered unplanned and premature, perinatal death rate was lower in the treatment group 8/126 versus 18/100, as was the incidence of RDS (11/122 versus 25/97) among all live births. The greatest benefit in preventing RDS occurred among those born at <30 weeks GA (2/17 treatment versus 16/23 control).
- No maternal adverse events appeared to be caused by steroid treatment. No adverse events among infants appeared to be caused by steroid treatment. No differences were found between groups in Apgar score at birth or other clinical signs or symptoms.
  - Although the major findings were published in 1972, the completed study findings were not presented until 1977, with continued long-term follow-up considered of importance to neonatal studies by Liggins.<sup>3</sup> A long-term tracing of participants was done 30 years following the trial.

## Impact

- The paper was originally rejected for publication, and appeared to be met with disinterest by the greater scientific community.
- However, several interested investigators continued to examine the issue. This included P Crowley, who began working with the National Perinatal Epidemiology Unit (UK) and the Oxford Database of Perinatal Trials, first cumulative database of trials from which formal meta-analyses were developed. Crowley began with unstructured reviews, later becoming more structured, and finally utilizing more modern meta-analysis technologies as they were invented.
  - By the late 1980s, with Crowley's meta-analysis and the continued data from the Liggins trial, there was clearly a difference between steroid-receiving versus control group infant mortality.
  - The large US multi-center NIH Collaborative Group on Antenatal Steroid Therapy randomized trial (1984) stressed the results of their subgroup analysis over their main finding of a reduction in RDS among a steroid group over a placebo group. "The effect was ...mainly attributable to discernible differences among singleton female infants, whereas no treatment effect was observed in male infants. Non-Caucasians were improved whereas Caucasians showed little benefit".<sup>4</sup>

- It is thought that this interrupted widespread public dissemination of steroids.<sup>3</sup>
- The image of the first seven trials for prenatal corticosteroids (Crowley's 1981 meta-analysis diagram ) was chosen as the Cochrane collaboration's logo.<sup>5</sup> This was because "within 10 years of the Liggins and Howie trial, there had been crystal-clear evidence that this was a very important way of reducing neonatal deaths.... Tens of thousands of babies had suffered and died unnecessarily.... Because information had not been assembled in a systematic review and meta-analysis to show the strength of evidence".<sup>3</sup>
- In practice, steroid use varied substantially throughout the decades.<sup>5</sup> However, by 1994 several publications advocated the use of steroids including the UK guidelines (British Association of Perinatal Medicine, 1992)<sup>6</sup> and those from an NIH Consensus Conference (1994)<sup>7</sup> incorporating all prior evidence. Following this, use eventually rose to be widespread.

### Unresolved issues

- Some reasons thought to be behind the lack of initial response include:<sup>3</sup>
  - A lack of respect to research done in New Zealand.
  - Conservatism in interpreting the results of a single trial by Howie, who stressed the need for more research (including their own) rather immediate uptake of the practice.
  - The interest of the pharmaceutical industry in drugs to prolong pregnancy and a narrow focus by the obstetric community on controlling the timing of labor rather than treating or altering the status of the fetus.
  - Conflict and disconnect between obstetricians and pediatricians in terms of professional territory and responsibility.
- Further issues surround why decades ensued before steps were taken to guide clinicians to incorporate corticosteroids into standard clinical practice. This includes:
  - "Professional failure to disseminate and implement evidence" (P Crowley)<sup>3</sup>
  - Concern over adverse unintended risk of therapy (e.g., hypertension) outweighing the potential benefit.

### Summary

The "Liggins Trial" was serendipitous in its fruition, was visionary in

conceiving a paradigm shift from maternal treatment (i.e. prolonging labor) to treating the fetus as a patient, and was courageous in its translation from animal to human research. Respiratory distress syndrome remains a major concern for obstetricians and pediatricians alike. The impact of the trial was not immediate. Some reasons for its delayed impact may have included (1) the cautionary nature of the authors own discussion, (2) the perception of the authors on the part of the larger scientific community, (3) the juncture of fields (obstetric and neonatal) for whom the trial had implications and (4) following trials that confused rather than clarified the issue. The "Liggins trial" also has a unique place in the evolution of evidence-based medicine: through unrelenting individual efforts to systematically collect randomized trials, evidence on the effectiveness of steroids to prevent RDS finally became undisputable. It took a systematic collection of evidence and national guidelines and consensus to finally move forward the widespread clinical use of steroids, as some would argue to be decades delayed.

## References

1. Liggins GC and Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics* 50[4], 515-525. 1972.
2. Crowley P, Roberts D, Danziel S, and Shaw BNJ. Antenatal corticosteroids to accelerate fetal lung maturation for women at risk of preterm birth (Protocol). *The Cochrane Database of Systematic Reviews* 4[CD004454], DOI: 10.1002/14651858. CD004454. 2003.
3. Wellcome Trust Centre for the History of Medicine at UCL. Prenatal corticosteroids for reducing morbidity and mortality after preterm birth. Reynolds LA and Tansey EM. 25, 1-149. 2005.
4. Collaborative Group on Antenatal Steroid Therapy. Effect of antenatal dexamethasone therapy on prevention of respiratory distress syndrome. *Am J Obstet Gynecol* 141, 276-287. 1981.
5. Crowley P, Chalmers I, and Keirse M. The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. *British Journal of Obstetrics and Gynaecology* 97, 11-25. 1990.
6. British Association of Perinatal Medicine (BAPM) and the Research Unit of the Royal College of Physicians (RCP) Joint Working Group. Development of audit measures and guidelines for good practice in the management of neonatal respiratory distress syndrome. *Archives of Disease in Childhood* 67, 1221-1227. 1992.

7. NIH Consensus Development Panel. Effect of corticosteroids for fetal maturation on perinatal outcomes. JAMA 273, 413-418. 1994.

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