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Chapter 2

# Alternative Therapies for the Management of Respiratory Distress Syndrome

Alejandro González-Garay and
Vicente González-Bustamante

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**Abstract**

Respiratory distress syndrome (RDS) is a disorder caused by a deficiency of surface-active agent called pulmonary surfactant, in the pulmonary alveoli. This deficiency leads the alveoli to collapse, impeding air entry, gas exchange, and oxygenation in newborns. Conventional treatment involves exogenous surfactant administration, ventilation, and hydroelectrolytic management.

However, there are alternative treatments to prevent RDS that can be administered to pregnant women (steroids, thyrotropin-releasing hormone, and ambroxol) or to newborns in their first few hours of life (continuous positive airway pressure, prophylactic surfactant in single or multiple doses, and digoxin). These approaches may be effective and cost less than conventional treatment. Conventional treatment requires trained medical personnel to attend to the newborn, ventilation, temperature control, and electrolytic and nutritional support, which can cost up to USD 14,226 per event.

This chapter seeks to analyze the effectiveness of each of these alternative treatments in preventing RDS in preterm newborns, so that it can be applied in communities with limited resources.

**Keywords:** ambroxol, respiratory distress syndrome, antenatal steroids, preterm birth, alternative therapies

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## 1. Introduction

The lungs are composed of different structures. The alveoli are the functional units of the lungs that allow oxygen gas ($O_2$) from the environment to be exchanged for carbon dioxide ($CO_2$) from the bloodstream.

In order for this process to take place, contact between the air-filled alveoli and the capillaries of the lung is essential. However, certain conditions can affect this process by preventing air from entering the alveoli, diminishing blood flow in pulmonary capillaries, or impeding alveolus-capillary contact, which hampers gas exchange and leads to decreased $O_2$ and increased $CO_2$ levels in the blood [1].

Alveoli comprise (a) type I pneumocytes, cells that provide shape and support and (b) type II pneumocytes, cells responsible for producing the surface-active agent called pulmonary surfactant. A surfactant is a substance made up of phospholipids (80%), proteins (12%), and neutral lipids (8%). Surfactants decrease the surface tension inside the alveoli. When there is insufficient surfactant, the alveoli collapse, preventing air entry and gas exchange. This is accompanied by a decrease in $O_2$ in the tissues and a gradual increase in respiratory effort, leading to this disorder being known as respiratory distress syndrome (RDS) [1–3].

This disorder affects up to 30% of premature newborns (<37 weeks of gestation) and accounts for 9.3–12% of hospital admissions to neonatal intensive care units [4–6]. Some studies have reported that the following factors are linked to the development of RDS: birth by cesarean section, gestational diabetes, meconium aspiration, and neonatal asphyxia [7].

Conventional treatment, which has been shown to reduce mortality rates by up to 18%, involves the exogenous administration of natural or synthetic surfactant at a dose of 100 mg/kg, up to 2–3 times, once RDS is diagnosed. The treatment also involves the use of mechanical ventilation, temperature control in an incubator, and electrolytic and nutritional support. However, this treatment has multiple adverse effects, such as pneumothorax, bronchopulmonary dysplasia, and retinopathy secondary to ventilation support and the continuous administration of supplemental oxygen over prolonged periods, malnutrition, and infections [2, 8].

As a consequence, many researchers have studied alternatives to prevent the development of RDS and reduce the frequency of these complications.

## 2. Alternative treatments for the prevention of RDS

The following are some treatments designed to prevent the development of RDS in newborns.

### 2.1. Early administration of surfactant

Numerous studies have reported that the administration of surfactant in the first few hours of life prior to the development of RDS reduces the mortality rate of preterm newborns. In 2012,

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Bahadue and Soll carried out a systematic review of six clinical trials involving 3577 preterm newborns and analyzed the effectiveness of administering surfactant in the first 2 hours of life. The authors found a significant reduction in the risk of death [RR 0.84 (0.74–0.95)] compared to delayed selective surfactant administration with neonates with established RDS [9] (**Figure 1**).

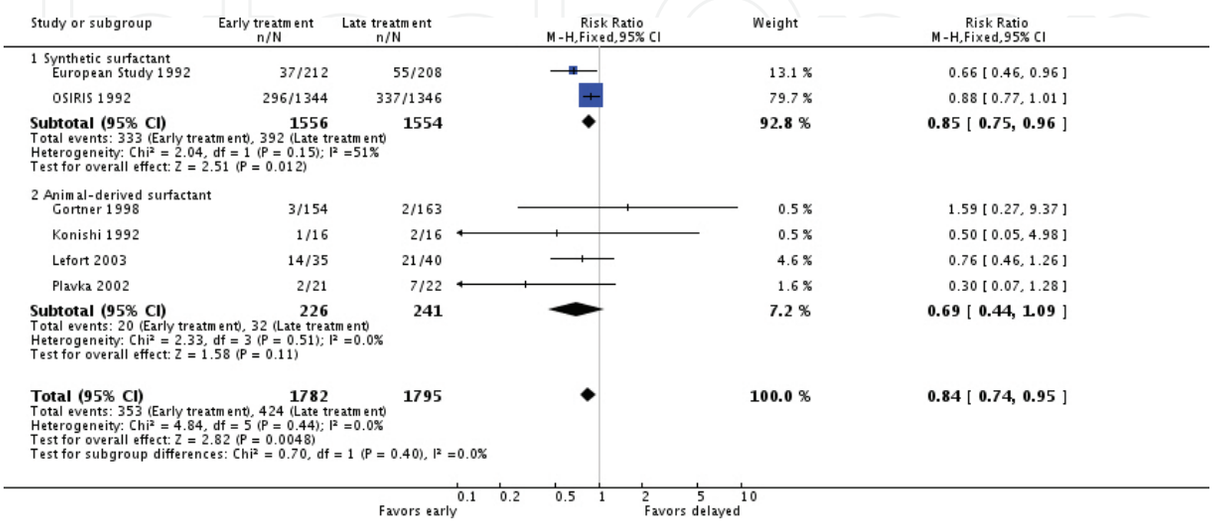



**Figure 1.** Early vs delayed administration of surfactant (risk of death).

Bahadue also analyzed adverse effects in patients that received early administration of surfactant and reported that there was a decrease in the risk of developing chronic lung disease [RR 0.69 (0.55–0.86)], pneumothorax [RR 0.69 (0.59–0.82)], pulmonary interstitial emphysema [RR 0.60 (0.41–0.89)], and bronchopulmonary dysplasia [RR 0.94 (0.88–1.00)] [9] (**Figures 2–5**).

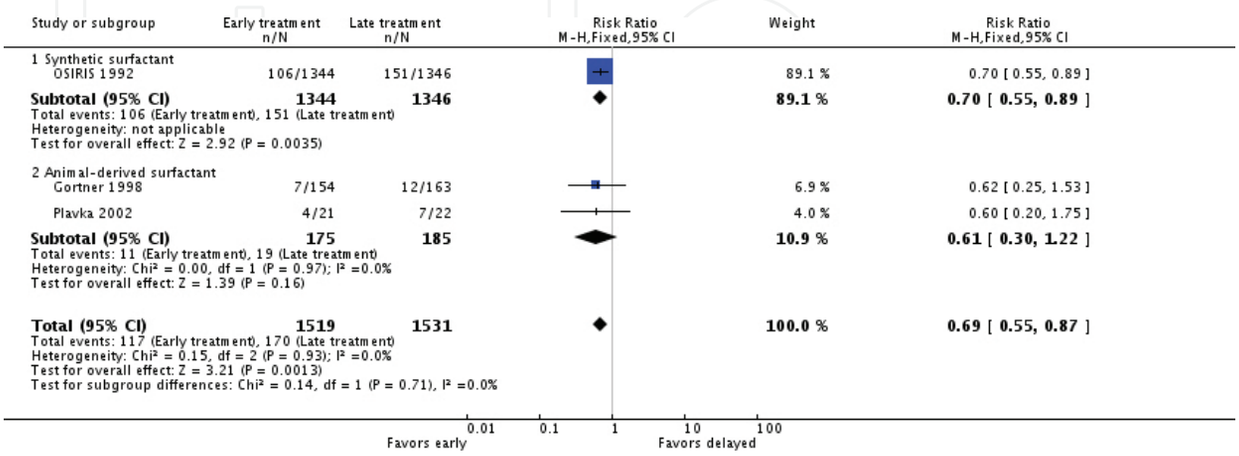



**Figure 2.** Early vs delayed selective surfactant treatment (chronic lung disease).

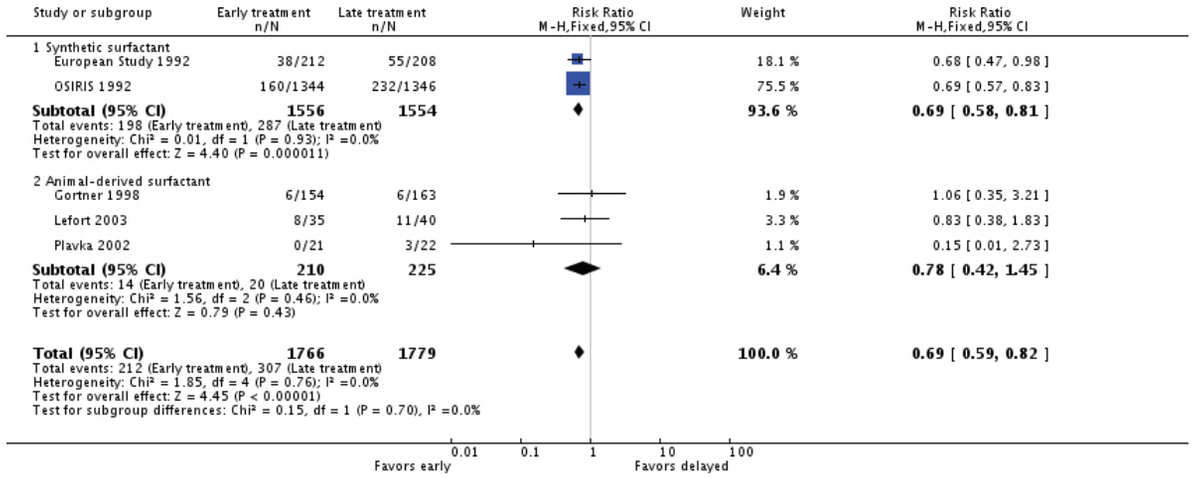



**Figure 3.** Early vs delayed selective surfactant treatment (pneumothorax).

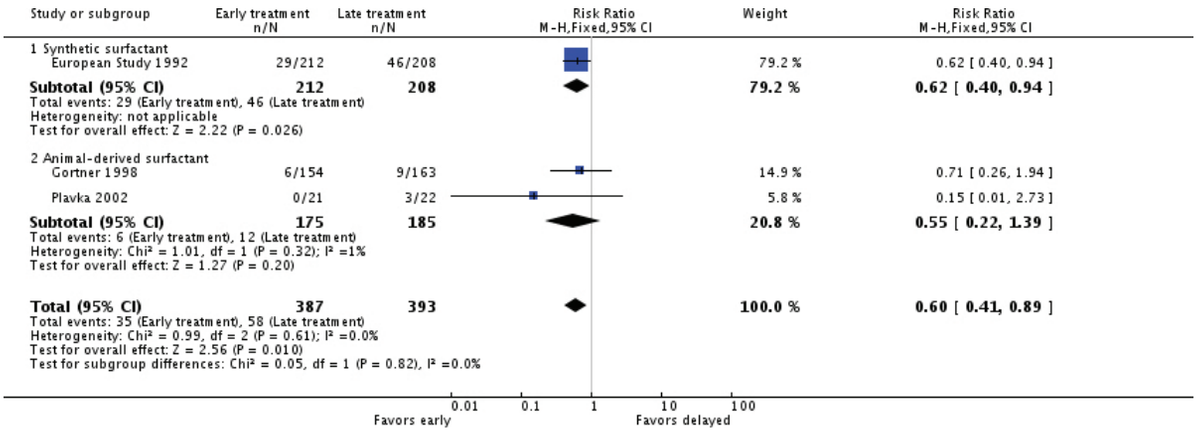



**Figure 4.** Early vs delayed selective surfactant treatment (pulmonary interstitial emphysema).

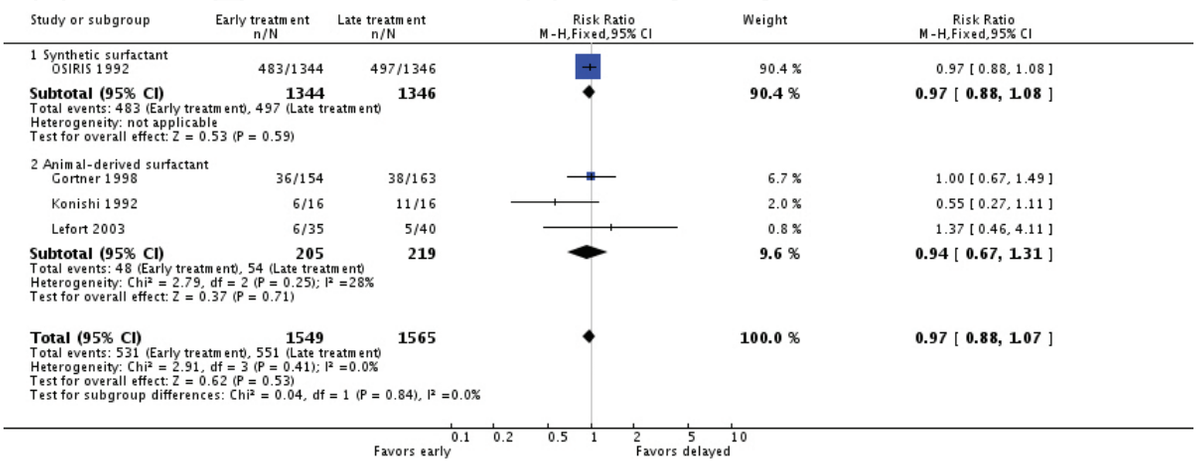



**Figure 5.** Early vs delayed selective surfactant treatment (bronchopulmonary dysplasia).

## 2.2. Administration of multiple doses of surfactant

Some researchers have carried out clinical trials to determine the effectiveness of administering multiple doses of surfactant to newborns to prevent RDS or reduce its complications. In 2009, Soll and Ozek carried out a systematic review to investigate whether this alternative treatment could decrease the risk of RDS and complications in preterm newborns. Only three clinical trials could be included in the review, but the authors concluded from these that there was a decrease in the risk of developing pneumothorax for neonates that received up to a maximum of four doses of surfactant spaced 6–12 hours apart compared to those who received single doses [RR 0.51 (0.30–0.88)]. There was a non-significant decrease in the risk of death for newborns who received multiple doses of surfactant [RR 0.63 (0.39–1.02)]. They concluded that the ability to give multiple doses of surfactant to infants with ongoing respiratory insufficiency leads to improved clinical outcome and appears to be the most effective treatment policy (**Figures 6** and **7**) [10].

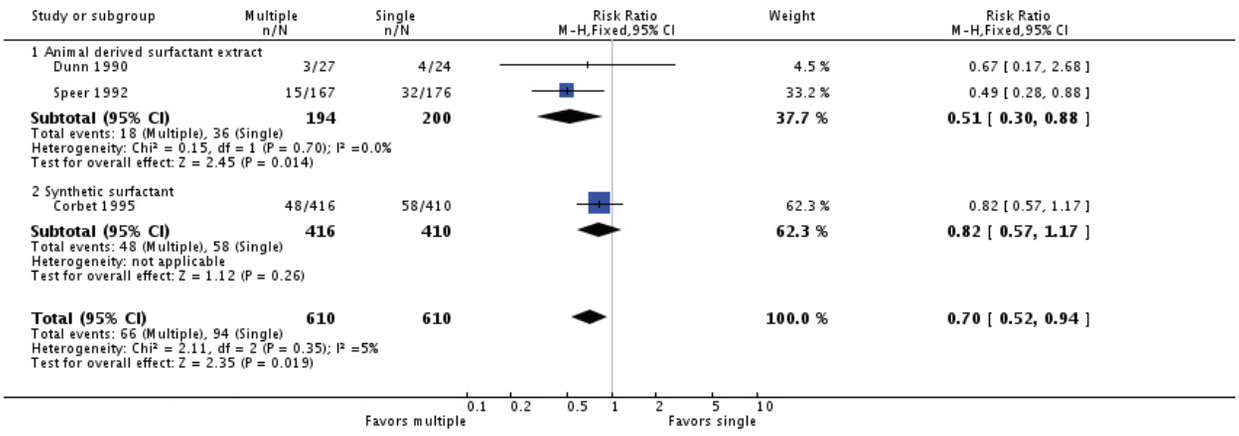



**Figure 6.** Multiple vs single doses of pulmonary treatment (pneumothorax).

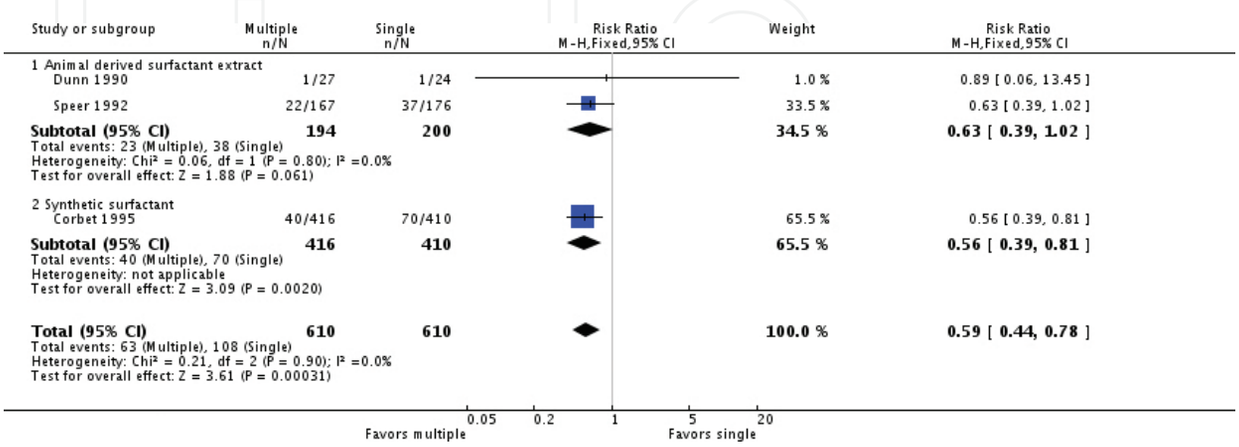



**Figure 7.** Multiple vs single doses of pulmonary surfactant (mortality).

### 2.3. Early application of continuous positive airway pressure (CPAP)

CPAP is an alternative treatment for newborns with RDS that involves the application of a type of respiratory support that applies air at low pressure in a continuous manner to keep the airway open. This treatment increases functional residual capacity and oxygenation with fewer secondary effects [11].

It has been observed that this type of respiratory support carries a lower risk of secondary complications such as barotrauma, pneumothorax, and pulmonary emphysema, among others. Recent studies of CPAP application in premature neonates in the first few minutes of life have shown that the risk of death is lower [RR 0.68 (0.5–1.92)] than for neonates who receive conventional ventilation. It has also been reported that the early application of CPAP in patients who developed RDS and received conventional treatment reduced the duration of mechanical ventilation (25 vs. 28 days) [12].

These findings were confirmed in a systematic review by Bahadue, who reported that the early application of CPAP and the selective administration of surfactants in preterm neonates reduced the risk of death compared to newborns who received only prophylactic surfactant [RR 0.84 (0.74–0.95)] [9].

To study long-term outcomes, Vaucher and colleagues carried out a follow-up assessment at 22 months of 1310 neonates that had been treated with CPAP to prevent RDS and found a decrease in the frequency of neurological and respiratory problems compared to patients treated with conventional therapy involving mechanical ventilation [RR 0.93 (0.78–1.10)] [13], similar findings were observed in the prospective study performed by Stevens and colleagues in 918 infants; those who received CPAP had fewer episodes of wheezing, respiratory illnesses, and visits to emergency room for breathing problems compared to infants who received conventional therapy [28.9% vs. 36.5%, 47.7% vs. 55.2%, and 68% vs. 72.9% ($p < 0.05$), respectively] [14].

On the basis of these results, the American Academy of Pediatrics recommends the early use of CPAP in conjunction with surfactant administration as an alternative to prevent RDS in preterm newborns [15].

### 2.4. Administration of digoxin

In 1955, Lendrum suggested that cardiac insufficiency secondary to pulmonary edema was a predisposing factor for RDS. Several clinical trials were carried out to determine whether the administration of digoxin in the first few hours of life would improve heart contractility and reduce the risk of developing RDS [16, 17].

As part of a systematic review in 2011, Soll and Ozek analyzed the efficacy of digoxin application in preventing RDS at doses of 0.01–0.06 mg/kg every 12 hours in 212 preterm newborns. They found that, despite improvements to cardiac insufficiency, there was no significant reduction in mortality compared to newborns who did not receive digoxin [RR 1.27 (0.78–2.07)]. The authors concluded that although hemodynamic disturbances play a role in the overall pathogenesis of RDS, the specific contribution of early congestive heart failure does

not appear to be significant factor in RDS, and the treatment with digoxin has no proven value in infants solely affected with RDS [18] (**Figure 8**).

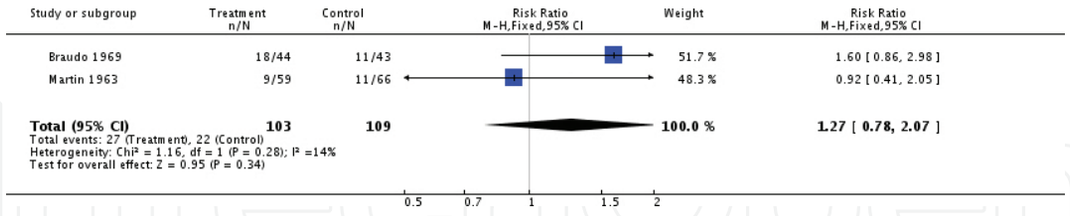



**Figure 8.** Digoxin vs placebo for preventing or treating respiratory distress syndrome (mortality).

## 2.5. Administration of thyrotropin-releasing hormone and antenatal steroids

In 1972, Liggins and Howie demonstrated that the administration of steroids (betamethasone) to pregnant women at risk of giving birth prematurely reduced the risk of their newborns developing RDS [RR 0.69 (0.59–0.73)] because the steroid passes through the placenta, reaches the fetal pulmonary alveoli, and stimulates the production of surfactant by type II pneumocytes. However, the use of this treatment did not become commonplace until 1987. It has since reduced the rate of neonatal mortality and is the preventive therapy of choice for obstetricians [19, 20].

Later, Liggins found that the administration of thyrotropin-releasing hormone (TRH) in combination with antenatal steroids increased the production of phospholipids and the distension of fetal sheep' lungs [19]. In 2013, Crowther carried out a systematic review analyzing 4600 pregnant women who were administered TRH and steroids prior to delivery. However, no significant differences were observed in terms of reducing the risk of death for premature newborns [RR 1.05 (0.86–1.27)] (**Figure 9**) or prevention of RDS compared to neonates born to women who received antenatal betamethasone therapy [RR 1.05 (0.91–1.22)] (**Figure 10**). However, it was observed that the administration of the combination of TRH and antenatal steroids did significantly increase the risk of adverse effects such as nausea, vomiting, and headaches [RR 3.92 (3.13–4.92), RR 2.35 (1.35–4.09), and RR 1.73 (1.36–2.22), respectively] (**Figures 11–13**) [21].

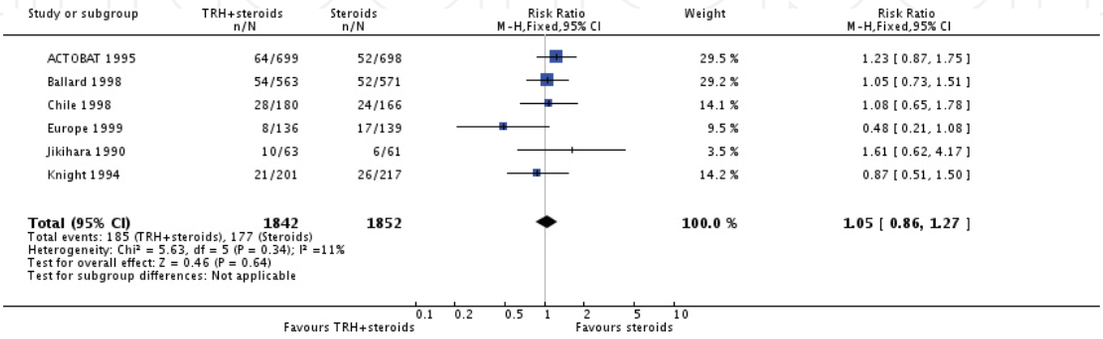



**Figure 9.** Thyrotropin-releasing hormone + steroids vs steroids alone for RDS (mortality).

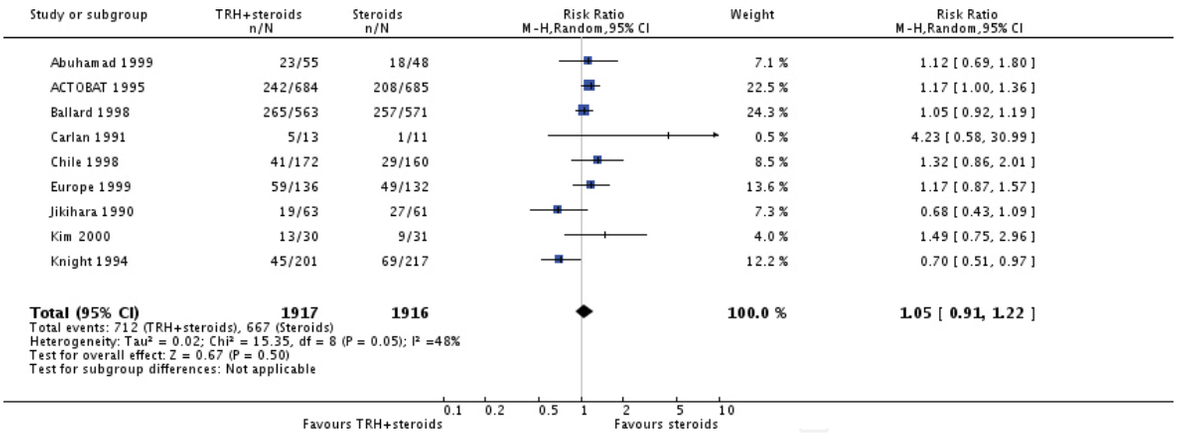



**Figure 10.** Thyrotropin-releasing hormone + steroids vs steroids alone for respiratory distress syndrome.

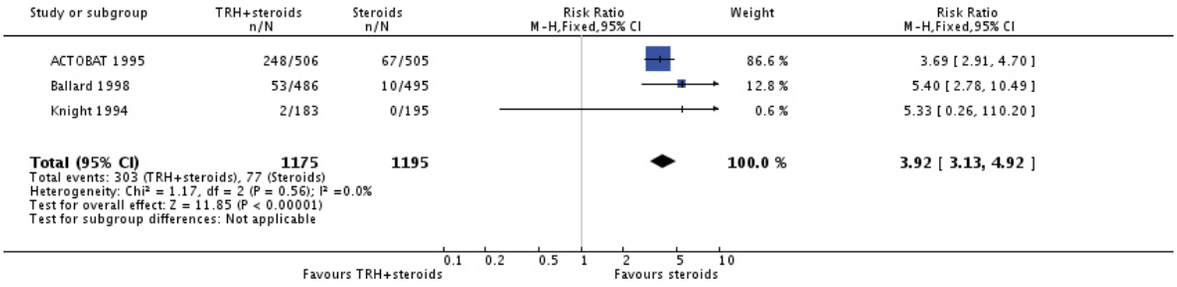



**Figure 11.** Thyrotropin-releasing hormone + steroids vs steroids alone for RDS (nausea).

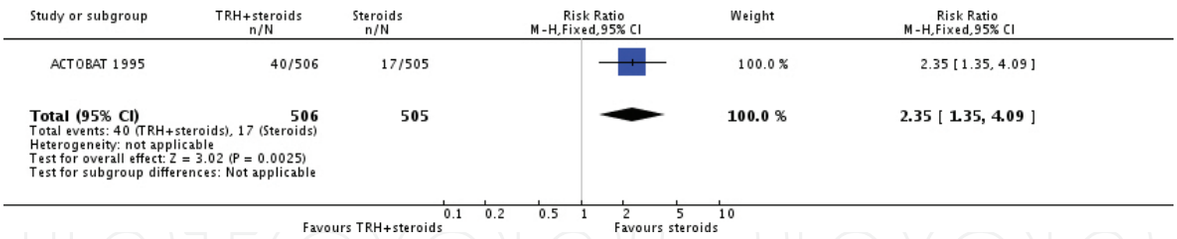



**Figure 12.** Thyrotropin-releasing hormone + steroids vs steroids alone for RDS (vomiting).

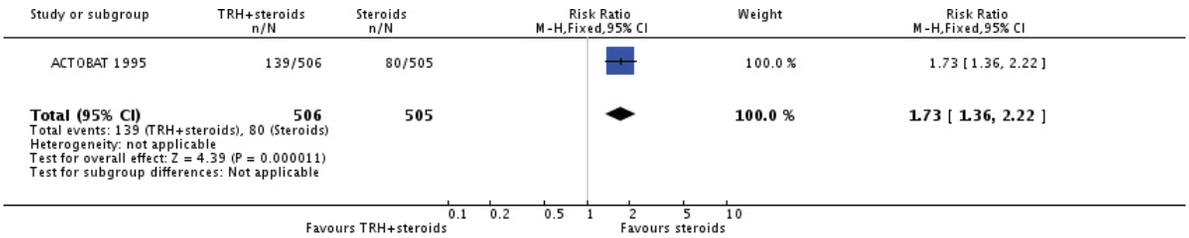



**Figure 13.** Thyrotropin-releasing hormone + steroids vs steroids alone for RDS (headaches).

## 2.6. Administration of magnesium sulfate

The administration of magnesium sulfate to pregnant women is used by obstetricians to inhibit labor and birth before 37 weeks of gestation by altering the union and distribution of calcium in the muscle fibers of the uterus, thus reducing the frequency of contractions [22].

In 2015, McNamara carried out a systematic review to analyze the efficacy and safety of magnesium sulfate (4 g loading dose and 2–5 g/h via infusion) administered to 360 pregnant women at less than 37 weeks of gestation to inhibit preterm labor. McNamara observed that this treatment reduces the risk of developing RDS [RR 0.31 (0.11–0.88)] and decreases the time that neonates spend in intensive care [MD −3.10 (0–5.48 to −0.72 days)]. However, there is too little evidence available to recommend the regular use of this treatment (**Figures 14** and **15**) [23].

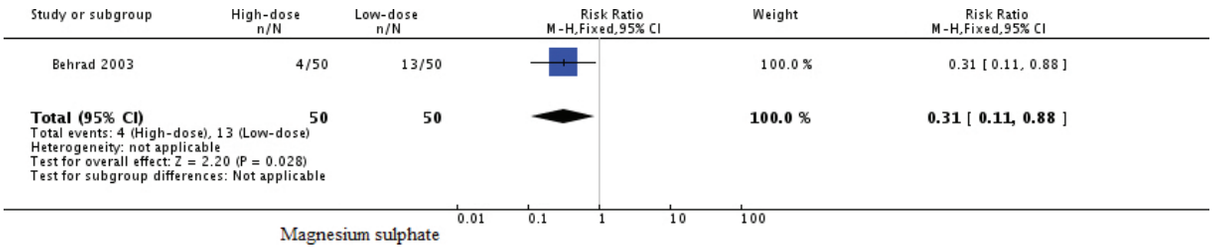



**Figure 14.** Magnesium sulfate for respiratory distress syndrome.

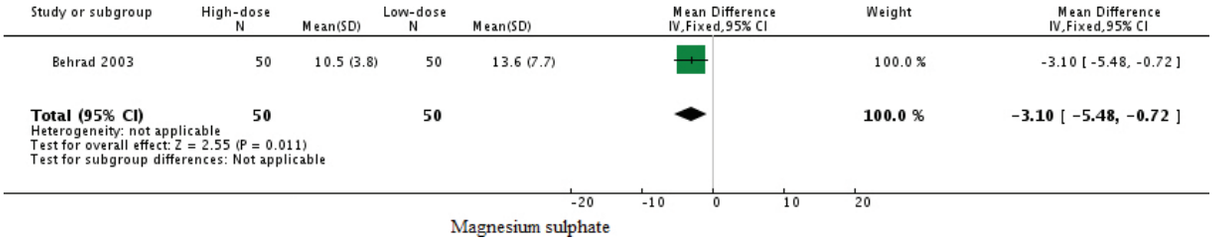



**Figure 15.** Magnesium sulfate for RDS (days of stay neonatal intensive care unit).

## 2.7. Administration of ambroxol

Ambroxol is a metabolite derived from bromhexine that increases the movement of cilia in the cells of the respiratory tract, facilitating the transport of mucus in the airway and inhibiting the activity of lysosomal phospholipase, the enzyme responsible for the degradation of pulmonary surfactant [24].

Laoag-Fernandez and Seifart carried out several clinical studies to analyze the effectiveness of ambroxol as an alternative treatment in the prevention of RDS because it allows easily reaching the fetus through placental circulation. These studies allowed Gonzalez to carry out a systematic review in 2014 [25].

The systematic review included 14 clinical trials analyzing 1047 pregnant women at risk of preterm birth who were administered a daily 1 g dose of ambroxol for a week.

The results of the review showed a reduction in the risk of neonates developing RDS compared to treatments in which women were administered antenatal steroids (betamethasone) or a placebo [RR 0.79 (0.59–1.07) and RR 0.74 (0.46–1.20), respectively] (**Figures 16** and **17**) [25].

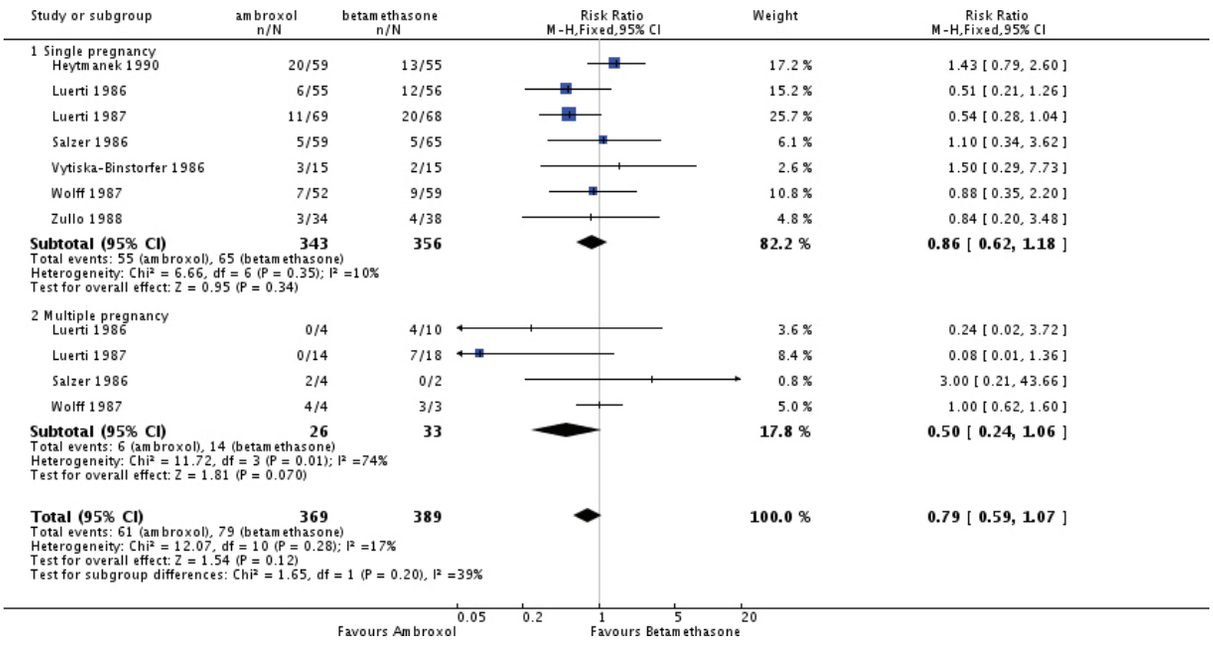



**Figure 16.** Ambroxol vs betamethasone for respiratory distress syndrome.

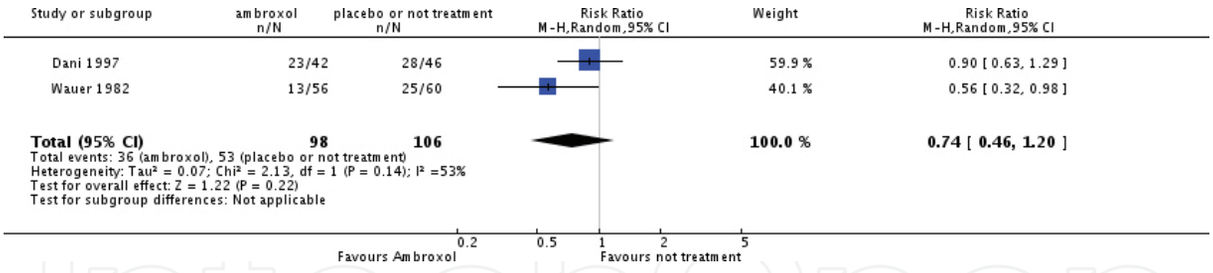



**Figure 17.** Ambroxol vs placebo or no treatment for respiratory distress syndrome.

## 3. Conclusions

We can see that although there are multiple alternative treatment options to prevent preterm newborns from developing RDS, their effectiveness has not yet been proven (with the exception of prenatal steroid administration) with evidence that is strong enough due to a lack of studies with larger numbers of participants and sound methodology. Nevertheless, it is possible that these might be viable treatments in communities that do not have the financial resources or the medical care required to attend to these patients. Conventional treatments

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require trained medical personnel who can attend deliveries and care for premature neonates in hospital units that have the necessary infrastructure as well as mechanical ventilators, temperature control systems, antibiotics for infection control, and intravenous solutions to maintain nutritional and hydroelectrolytic homeostasis.

In 2014, Martínez-Valverde and colleagues carried out a study to estimate the costs of providing care to newborns with RDS in public hospitals in Mexico and found that, on average, the cost per patient per event can reach USD 14,226, without accounting for the cost of treating secondary conditions [26].

Undoubtedly, more studies need to be carried out to strengthen the evidence supporting the use of these alternative treatments. However, they could be a sustainable option in communities with limited financial resources because they are more readily available and have fewer adverse effects and lower costs than conventional treatment.

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