ANTENATAL CORTICOSTEROIDS VERSUS PLACEBO IN LATE PRETERM INFANTS: MULTICENTER RANDOMIZED TRIAL

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January 2015
# TABLE OF CONTENTS

1. Abstract ................................................................................................................ page 3
2. Introduction .............................................................................................................. page 4
   2.1 Terminologies ..................................................................................................... page 4
   2.2 Epidemiology ..................................................................................................... page 5
   2.3 Prematurity causes ............................................................................................. page 7
   2.4 Neonatal late preterm issues ............................................................................. page 8
   2.5 Late preterm infants at higher risk than term infants ...................................... page 11
   2.6 Costs of prematurity ......................................................................................... page 12
   2.7 Management of spontaneous preterm ............................................................... page 13
3. Justification .............................................................................................................. page 17
4. Methods ................................................................................................................... page 19
   4.1 Question, objectives and hypothesis ................................................................. page 19
      5.1.1 Question ...................................................................................................... page 19
      5.1.2 Objectives ................................................................................................ page 19
      5.1.3 Hypothesis ................................................................................................ page 19
   4.2 Study design ....................................................................................................... page 20
      5.2.1 Conditions for stopping the trial ............................................................... page 20
   4.3 Study population ............................................................................................... page 21
      4.3.1 Inclusion criteria ....................................................................................... page 21
      4.3.2 Exclusion criteria ..................................................................................... page 21
      4.3.3 Sample size .............................................................................................. page 22
      4.3.4 Estimated time of recruitment ................................................................ page 22
      4.3.5 Diagnose of spontaneous onset of labor ................................................. page 22
   4.4 Enrollment and randomization procedures ....................................................... page 23
      4.4.1 Informed consent ..................................................................................... page 23
      4.4.2 Randomization ........................................................................................ page 23
      4.4.3 Degree of blinding ................................................................................. page 23
   4.5 Study treatment ................................................................................................ page 25
      4.5.1 Study treatment groups .......................................................................... page 25
      4.5.2 Practical considerations ........................................................................ page 25
4.6 Study variables ................................................................. page 26
  4.6.1 Dependent variable .................................................... page 26
  4.6.2 Independent variable .................................................. page 30
  4.6.3 Covariates ................................................................. page 30
  4.6.4 Measure instruments .................................................. page 31
4.7 Execution plan and schedule of events ................................ page 33
4.8 Adverse events ............................................................... page 35
4.9 Statistical analysis ............................................................ page 36
4.10 Opportunities and limitations of the study ........................... page 39
   4.10.1 Opportunities ........................................................ page 39
   4.10.2 Limitations ............................................................ page 39
4.11 Work plan ................................................................. page 41
4.12 Ethical aspects .............................................................. page 42
4.13 Budget ................................................................. page 43

5. Bibliography ....................................................................... page 44

6. Annexes ........................................................................... page 50
   Annex I: Management of threat of preterm birth .................... page 50
   Annex II: Study flow chart ................................................ page 51
   Annex III: Safety data collection ........................................ page 52
   Annex IV: Work plan ....................................................... page 53
   Annex V: Protocol management .......................................... page 54
   Annex IV: Informed consent .............................................. page 57
1. ABSTRACT

**Objectives:** The main objective of this study is to demonstrate that antenatal corticosteroids administration during a spontaneous onset of labor between 35 0/7 and 36 6/7 of gestation reduces respiratory distress in the late preterm infants.

**Design:** Randomized triple blind clinical trial.

**Setting:** Multicenter study. The study will involve 5 centers, which Hospital Universitari Josep Trueta (Girona) will be the reference center.

**Participants:** Pregnant women with a spontaneous onset of labor between 35 0/7 and 36 6/7 of gestation.

**Interventions:** 24mg of betamethasone or placebo intramuscularly in two doses separated by 24h. In order to that betamethasone has enough time to take effect on the fetus, a pattern of Atosiban, a tocolytic to delay the uterine dynamic will be administered.

**Main outcomes measures:** Primary outcome will be the incidence of respiratory distress in the late preterm infant. Secondary outcomes will include other complications in the late preterm infants.
2. INTRODUCTION

Late preterm infants, or infants who born between 34 \textsuperscript{0/7} and 36 \textsuperscript{6/7} weeks of gestation, often have a similar size and weight than term infants and therefore are treated as if they are mature and have less risk of morbidity \cite{1-3}.

But late preterm infants are at higher risk for infant mortality, morbidity during the first days of life, and neonatal morbidity that requires more hospital readmission than term infants. For this high risk late preterm infants should no longer be treated in the same way as term infants\cite{1,2}.

The objective of this study is to demonstrate that tocolytic agents and antenatal glucocorticoid administration also reduces respiratory distress in late preterm infants.

2.1 TERMINOLOGIES

The definition of term and preterm infant has change in the last years. In 1935, the American Academy of Pediatrics defined a preterm infant as a newborn weighting 2500g or less. In 1962, the World Health Organization added gestational age as criteria for the preterm infant, who happened to be defined as one who is born at 37 weeks or earlier. Others, like American College Obstetricians and Gynecologist in 1995 suggested to define a preterm infant as a newborn who is born before completing 37 weeks of gestation\cite{4}. Now, Term infant is defined as who is born on the first day of the 38\textsuperscript{th} week of gestation (37 \textsuperscript{0/7} or 260 days of gestation)\cite{1}.

The American College of Obstetricians and Gynecologist classified a term infant in 4 different groups to be more accurate describing the outcomes occurring at or beyond 37 \textsuperscript{0/7} weeks of gestation: early term (37 \textsuperscript{0/7} weeks of gestation through 38 \textsuperscript{6/7} weeks of gestation), full term (39 \textsuperscript{0/7} weeks of gestation through 40 \textsuperscript{6/7} weeks of gestation) late term (41 \textsuperscript{0/7} weeks of gestation through 41 \textsuperscript{6/7} weeks of gestation) and post term (42 \textsuperscript{0/7} weeks of gestation and beyond)\cite{5}.
Currently, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologist define a *preterm infant* as a newborn who is born before the end of the 37\textsuperscript{th} week (259\textsuperscript{th} day) of pregnancy, counting from the first day of the last menstrual period\textsuperscript{(1,2,6)}. There are different degrees of prematurity, that are defined by birth weight or gestational age\textsuperscript{(6)}.

Premature infants classified by birth weight:

- Low birth weight: birth weight less than 2500g
- Very low birth weight: birth weight less than 1500g
- Extremely low birth weight: birth weight less than 1000g

Premature infants classified by gestational age:

- **Late preterm**: defined as who is born between the gestational ages of 34 weeks and 0/7 days through 36 weeks and 6/7 days\textsuperscript{(1,2)}.
- **Very preterm**: defined as who is born before the 32 week of gestational age.
- **Extremely preterm**: defined as who is born before the 28 week of gestational age.

Some years ago *late preterm infants* were called *near-term infants*, but this term assumed that the infants were almost term and almost fully mature and made health care professionals underestimate the risks of these children\textsuperscript{(1,2)}.

### 2.2 EPIDEMIOLOGY

In 2005 was recorded 12.9 million preterm birth, representing 9.6\% of all births worldwide. Approximately 11 million (85\%) of them were concentrated in Africa and Asia. In Europe and North America (excluding Mexico) recorded 0.5 million in each case, and in Latin America and The Caribbean, 0.9 million. The largest number of preterm births were in Africa and North America (11.9\% and 10.6\% of all births, respectively) and the fewer were in Europe (6.2\%)\textsuperscript{(7)}.
In 2003, the prevalence of preterm births in US was 12.3%. The birth preterm rate increased 31% since 1981\(^1\). In 2005, of all preterm births, 70% were late preterm. The birth late preterm rate increased from 7.3% in 1990 to 9.1% in 2005\(^1\). We can conclude that much of the increase preterm birth rate is because the increase birth late preterm rate.

The exactly reason for this increase is unknown, but is believed that it could be due to in vitro fertilization or artificial insemination increase (increasing the number of multiple pregnancies) or technological improvements in obstetric practices that allow greater survival of fetuses considered high risk\(^1\).

In Spain, in the data available from the National Statistics Institute (INE) for the last 16 years, the overall rate of prematurity between 1996 and 2012 varied from 5.27% to 5.58%. In 2012, of all preterm births 87.54% were born between 32 and 36 weeks of gestation. In Catalonia, in 2014, of all births, 5.63% were between 32 and 36 weeks of gestation, this represented an increase of 2% since 1996\(^3\).

If we put our attention on the data obtained from the Hospital Universitari Josep Trueta from 1997 - 2014 we find about 15% of prematurity (birth between 22 0/7 - 36 6/7 weeks of gestation) of which about 60 % were late preterm (34 0/7 - 36 6/7 weeks of gestation) (Figure 1,2).

![Figure 1. Term and preterm labors between 1997-2014.](unpublished data)

![Figure 2. Term and preterm labors between 1997-2014.](unpublished data)
2.3 PREMATURITY CAUSES

The etiology of preterm births is multifactorial and includes a complex interaction between fetal, placental, uterine and maternal factors. Fetal factors are: Fetal distress, multiple pregnancy, erythroblastosis, anasarca nonimmune. Placental factor are: Placental dysfunction, placenta previa, placental abruption. Uterine factors are: bicornuate uterus, cervical incompetence (premature dilatation). Maternal factors are: pre eclampsia, chronic diseases (cyanotic heart disease, nephropathy), infection (Lysteria monocytogenes, streptococcus B, urinary tract infection, bacterial vaginits, corioamnionitis), drugs (cocaine)\(^9\).

Despite the large heterogeneity of etiologies of preterm birth, we can classify them into 3 main subtypes by its clinical presentation: spontaneous preterm birth, preterm premature rupture of membranes (PROM) and medically indicated preterm birth\(^{10}\) (Table 1).

<table>
<thead>
<tr>
<th>Medically induced preterm birth</th>
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<tbody>
<tr>
<td>Maternal</td>
</tr>
<tr>
<td>Pregnancy hypertension and vascular disorder</td>
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<tr>
<td>Medical acute illness or chronic conditions</td>
</tr>
<tr>
<td>Obstetrical complication</td>
</tr>
<tr>
<td>Antepartum bleeding</td>
</tr>
<tr>
<td>Maternal age &gt; 35 years</td>
</tr>
<tr>
<td>Fetal</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
</tr>
<tr>
<td>Unstable fetal condition</td>
</tr>
<tr>
<td>Fetal anomaly</td>
</tr>
<tr>
<td>Multiple pregnancies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preterm premature rupture of membranes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Urinary distension</td>
</tr>
<tr>
<td>Cervical anomalies</td>
</tr>
<tr>
<td>Afro-American ethnicity</td>
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<tr>
<td>Disadvantaged population</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Spontaneous preterm birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous preterm birth, preterm labour</td>
</tr>
<tr>
<td>Low body mass, poor weight gain</td>
</tr>
<tr>
<td>Strenuous physical workload, ergonomic factors</td>
</tr>
<tr>
<td>Uterine anomalies</td>
</tr>
<tr>
<td>Psychosocial stress</td>
</tr>
<tr>
<td>Lifestyle, smoking</td>
</tr>
<tr>
<td>Drug abuse</td>
</tr>
<tr>
<td>Maternal age &lt; 18 years</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

Table 1. Currently recognised aetiological risk factors associated with clinical presentation of preterm birth. Extracted from Moutquin J. Classification and heterogeneity of preterm birth. BLOG An Int J Obstet Gynaecol [Internet]. 2003 Apr

Medically indicated preterm birth includes the 25% of all preterm births. Medical indications are mainly related to maternal complications such as pre eclampsia, eclampsia, placental abruption, or fetal well-being endangered, such as intrauterine growth retardation, or reassuring fetal status ("suffering fetal")\(^{10,11}\).

Spontaneous preterm birth represents the 50% of all preterm births, and in most cases, don’t show any established risk factor. However, one study related spontaneous
preterm birth with some risk factors: personal obstetrical history, social factors and lifestyle\(^{(10)}\).

**Preterm premature rupture of membranes**, usually followed by preterm delivery, accounts for another 25% of all preterm births. Infection is usually regarded as the main cause of PPROM although, in some cases, it is preceded by spontaneous preterm labor\(^{(10)}\).

A epidemiological review described some well-established risk factors for preterm birth: precedent preterm labor, antecedent of low birth weight labor (less than 2500g), numerous abortions in the second trimester, cervical and uterine anomalies, in-vitro fertilization, multiple pregnancy, maternal complications, gestational bleeding, abnormal placentation, urogenital infection, Afro-American ethnic origin, low socio-economic status, standing up > 2 hours a day, social isolation, smoking and low body mass index (BMI) before conception\(^{(12)}\).

There are also lifestyles factors that influence preterm birth\(^{(4)}\). Some maternal factors involved include early or advanced maternal age at pregnancy, poverty, short stature, vitamin C deficiency, and occupational factors such as prolonged standing or walking, strenuous working conditions and long weekly work hours. Other risk factors are those psychological factors such as depression, anxiety and chronic stress also associated with preterm part\(^{(4)}\).

**2.4 NEONATAL LATE PRETERM ISSUES**

1. **TEMPERATURE INSTABILITY**

The gestational age and the physical size, the quantity of mature brown and white adipose tissue, and maturity of the hypothalamus affect the infant’s response to cold exposure after birth \(^{(1)}\). *In utero* begin the development of the adipose tissue, but is not until the term birth that the end of the brown adipose tissue accumulation, maturation and concentrations of hormones responsible for brown adipose tissue metabolism are
reached\textsuperscript{13}. For that explanation, late preterm can’t generate effectively heat from brown adipose tissue.

2. HYPOGLYCEMIA:

Hypoglycemia is usual to find in newborns (term and preterm infants) because until birth their glucose supply was maternal. Thus, in the birth they have an insufficient metabolic response\textsuperscript{14}.

Multiples studies confirmed that preterm infants have lower blood sugar values than term infants. Thus, the hypoglycemia incidence is inversely proportional to gestational age\textsuperscript{15}. Gluconeogenesis is limited in preterm infants, possibly due to the immaturity of the enzyme pathways\textsuperscript{14}.

Although the carbohydrate metabolism in late preterm infants is not well understood, exist immaturity in regulating glucose levels in them because they receive more intravenous infusions of glucose for hypoglycemia than at term\textsuperscript{3}.

3. RESPIRATORY DISTRES

The development of the respiratory system begins in the embryonic period, continues in the fetal period, some process end after birth and others in infancy\textsuperscript{16}.

It is known that physiological events in the last weeks of pregnancy with the spontaneous onset of labor are responsible for some hormonal changes that make a rapid maturation and preparation of the fetus for labor and neonatal transition. In the transition to air breathing, the fast removal of fetal lung fluid clearance plays a key role. A modification of this process promotes fluid retention in air spaces, leading to a situation of alveolar hypoventilation and respiratory distress. In late term labors, especially those who are delivered by pre-labor cesarean section, the fetus is deprived of these hormonal changes and the neonatal transition becomes more difficult\textsuperscript{17}.
4. APNEA OF PREMATURITY

Decreased central chemosensitivity to carbon dioxide, increased respiratory inhibition sensitivity to laryngeal stimulation, increased susceptibility to hypoxic respiratory depression, immature pulmonary irritant receptors and decreases upper airway dilator muscle tone are predisposing apnea in late preterm infants\textsuperscript{(1,16)}.

The incidence of apnea decreases inversely proportional to gestational age, and if we separate late preterm infants according gestational age (34 weeks, 35 weeks and 36 week of gestational age), each group has a significantly lower incidence than its predecessor\textsuperscript{(18)}.

The concentration of uridine diphosphoglucuronate glucuronosyltransferase is directly proportional to gestational age; thus, late preterm infants have a lower concentration than term infants. That enzyme is important because is the rate-limiting enzyme in the excretion of bilirubin, so if late preterm infants have a lower concentration will lead to reduced elimination of bilirubin and therefore a greater accumulation of this, giving jaundice and hyperbilirubinemia\textsuperscript{(19)}.

5. CARDIOVASCULAR

It is generally believed that structural and functional immaturity restricts the amount of cardiovascular reserve that is available during times of stress. Immature cardiovascular function also may complicate recovery of the late preterm infant with respiratory distress because of delayed ductus arteriosus clousure and persisten pulmonary hypertension\textsuperscript{(1)}.

6. GASTROINTESTINAL

The digestive absorption capability seems not to be a problem in late preterm infants; however, control of esophageal, stomach and intestinal sphincters; peristaltic functions and deglutition are probably less mature in late preterm infants than term
infants\textsuperscript{(20)}, which may delay successful breastfeeding and consequently be more likely to dehydration and a greater number of readmissions after discharge\textsuperscript{(21)}.

7. BRAIN

Term infants have more mature brains compared with late preterm infants; it is estimate that at 34 weeks weighs only 65\% of the term brain, the cortical volume in the late preterm infant is only 53\% of the term volume, and the “myelinated” white matter process increases dramatically in volume as term is approached\textsuperscript{(22)}.

8. IMMUNOLOGIC SYSTEM

The maturation of the immune system and its ontogeny in the late preterm infant should be better studied. Late preterm infants are between terms infants and extremely preterm infants referring to the immunologic maturation\textsuperscript{(23)}.

2.5 LATE PRETERM INFANTS AT HIGHER RISK THAN TERM INFANTS

Up until now we have described the complications of late preterm infants, but most important is to show that these complications are more prevalent in late preterm infants than in term infants.

Compared with term infants, late preterm infants are at higher risk of medical problems in the neonatal period. During the first hours of life, late preterm infants are much more likely than term infants to have at least 1 or more diagnoses of clinical problems and 2 times more likely to have 2 or more clinical diagnoses\textsuperscript{(3)}. Late preterm infants have an increased risk of suffering during the birth hospitalization temperature instability\textsuperscript{(3)}, hypoglycemia\textsuperscript{(3,24)}, respiratory distress\textsuperscript{(3,24,25)}, apnea\textsuperscript{(24)}, jaundice\textsuperscript{(3,24)}, feeding difficulties\textsuperscript{(3)} and hyperbilirubinemia\textsuperscript{(1)}. Late preterm are more likely to be rehospitalized for hyperbilirubinemia and other diagnoses such as feeding difficulties and sepsis than term infants\textsuperscript{(26)}.
In breastfed infants, late preterm infants who are discharged early experience significantly a higher risk of neonatal morbidity than term infants discharged early\(^{(27)}\).

Several studies have shown that late preterm infants have greater risk for more severe illness than full-term newborns\(^{(3,25,28)}\). For example, some study evidenced greatest need of mechanical ventilation in preterm infants who were born at 34 weeks of gestation\(^{(28)}\), or that late preterm infants are given discharged later in the initial stay or are more admitted to the NICU\(^{(3,24,26)}\).

Late preterm infants have a higher relative risk of death in childhood and are responsible for a significant fraction of infant deaths\(^{(29)}\).

We can conclude that late preterm infants are at higher risk for infant mortality and morbidity during the first days of life, and neonatal morbidity that requires hospital readmission than term infants and it’s the reason for stop treating them like term infants.

### 2.6 COSTS OF PREMATURITY

A California\(^{(28)}\) study observed that neonatal hospital costs reached $202,700 (163.376€) average for a delivery at 25 weeks, dropping to $2,600 (2.096€) for a newborn of 36 weeks and $1,100 (886,60€) for a newborn of 38 weeks. Also found excessive costs for births between 34 and 37 weeks compared with those born at 38 weeks\(^{(28)}\).

Another study\(^{(3)}\) showed a relative increase of the total costs of late preterm compared with term infants of 2.93 (mean) and 1.39 (median), resulting in an increase of $2.630 (2120€) (mean) and $429 (345,77€ ) (median).

With these data, it is logical to think that if we reduce the complications of late preterm will reduce the costs generated by their treatment, hospital stay, hospital care...
2.7 MANAGEMENT OF SPONTANEOUS PRETERM

Currently, the management of obstetric spontaneous preterm delivery is based on maternal treatment with glucocorticoids in less than 33 weeks gestation and tocolysis in under 34 weeks and group B streptococcus prophylaxis in under 37 weeks of gestation. Management of premature rupture of membranes at or beyond 34\(^{6}/7\) weeks of gestation is delivery and expectant management with maternal antibiotics in less than 34 weeks of gestation\(^{4}\). In Spain, the tocolysis and antenatal corticoids administration is indicated in under 34 6/7 weeks of gestation\(^{30}\) (see Management of threat of preterm birth from SEGO, Annex I).

The threat of preterm birth is defined as symptomatic clinical process without treatment or when it fails, can lead to preterm labor\(^{30,31}\). The diagnosis was based on the presence of persistent uterine contractions (at least 4 in 20-30 minutes in an hour or 8) mesured by a cardiotocography and cervical changes as a blurring of> 80% or cervical> 2cm dilated\(^{30,31}\).

The data of this meta-analysis\(^{32}\) suggest that cervical length measured by transvaginal ultrasound in symptomatic women may be used to discriminate between those pregnant women with high and low risk for preterm delivery, which can help rationalize treatment. This meta-analysis\(^{32}\) estimated that the negative predictive value of a cervix 15mm, 20mm and 25 mm is 94.8%, 96.3% and 95.8% respectively. For this reason, the Spanish Society of Gynecology and Obstetrics, recommended transvaginal cervical measurement to determine in pregnant women with threatened preterm labor, which are high risk for preterm delivery and avoid unnecessary interventions\(^{30}\).

One study\(^{33}\) found no significant relationship between the result of the fibronectin test and time to delivery. However, when it was associated with transvaginal ultrasound measurement of cervical greater specificity for prediction is obtained, both of preterm birth less than 35 weeks, and for the less than 37 weeks.
Gyetvai and Colleagues\textsuperscript{[34]} made a meta-analysis of tocolytic therapy concluded that although tocolytics were associated with significant decreasing of the likelihood of delivery within 24 hours, 48 hours, and 7 days; these were not associated with significantly reduced rates of perinatal death, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, patent ductus arteriosus, neonatal sepsis, seizure, hypoglycemia, or birth weight under 2500 g; and increased risk of maternal palpitations, nausea, tremor, chorioamnionitis, hyperglycemia, hypokalemia, and the need to discontinue treatment.

Different studies\textsuperscript{[35,36,36]} evaluated the benefits of antenatal corticoids and concluded that produces a global reduction of approximately 50% of the chance of developing neonatal distress syndrome, reduces the likelihood of periventricular hemorrhage, necrotizing enterocolitis, respiratory support, intensive care admissions, systemic infections in the first 48 hours of life and neonatal hyperbilirubinemia despite not reducing the incidence of patent ductus arteriosus or bronchopulmonary dysplasia. Most importantly, substantially reduces neonatal mortality\textsuperscript{[35]}.

In contrast to the views expressed previously, the beneficial effect of corticosteroids is not limited in babies born between 30 and 34 weeks of gestation\textsuperscript{[35]}. There has also been a reduction in risk of respiratory distress syndrome in less than 31 weeks and only 29 babies 8 trials had SDR after 34 weeks of gestation, but cannot tell if it was due to a beneficial effect of treatment on these babies or random variation\textsuperscript{[35]}.

The prolongation of gestation by tocolytic agents doesn’t improve the neonatal outcome, thus, these “golden hours” need to be optimized by the maternal antenatal administration of corticosteroids\textsuperscript{[37]}.

The table 2 describes the tocolytic most commonly used in the treatment of threatened preterm labor. However, the tocolytic ones that are authorized in Spain for the treatment of threatened preterm labor, are the Atosiban, Ritodrine and Nifedipin\textsuperscript{[30,38]}.
One study\(^{39}\) showed that although there are no significant differences in proportion of women undelivered by 48 hours, the side effect profile was significantly better for Atosiban versus beta-agonists.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse events</th>
<th>Contraindications</th>
<th>Surveillance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atosiban</strong></td>
<td>Hyperglycemia, headache, dizziness, tachycardia, blushing, hypotension, nausea, vomiting, chest pain</td>
<td>Hypersensitivity to product</td>
<td>No precise</td>
<td>Efficacy comparable to ritodrine with Efficacy comparable to ritodrine with minimal side effects.</td>
</tr>
<tr>
<td>Specific antagonist of oxytocin uterus</td>
<td></td>
<td></td>
<td></td>
<td>Little impact on perinatal outcome.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Approved in Spain for the treatment of threatened preterm labor.</td>
</tr>
<tr>
<td><strong>Ritodrine</strong></td>
<td>Tachycardia, palpitations, arrhythmia, tremor, nausea, vomiting, headache, chest pain, dyspnea, hypotension, hyperglycemia, hypokalemia, myocardial ischemia.</td>
<td>Multiple gestations, poorly controlled diabetes mellitus, maternal heart disease, poorly controlled thyroid disease, severe anemia.</td>
<td>Water balance, pulse, blood pressure, respiratory rate, electrolytes (K), glucose.</td>
<td>Its use as a tocolytic choice would have declined in favor of other drugs.</td>
</tr>
<tr>
<td>Sympathomimetic agonist B-2 receptors</td>
<td></td>
<td></td>
<td></td>
<td>Retired in some countries and contraindicated in twins.</td>
</tr>
<tr>
<td></td>
<td>Maternal death described.</td>
<td></td>
<td></td>
<td>It is not effective orally.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Approved in Spain for the treatment of preterm labor.</td>
</tr>
<tr>
<td><strong>Nifedipine</strong></td>
<td>Palpitations, flushing, headache, nausea, vomiting, dizziness, transient hypotension, flushing. Prudence if used with MgSO4.</td>
<td>Maternal heart disease, hypertension, severe hypotension, liver dysfunction. Increased risk of pulmonary edema if used in diabetes or multifetal pregnancy.</td>
<td>Blood pressure and heart rate.</td>
<td>Superior to the B-mimetics in meta-analysis. Efficacy comparable to atosiban but with more maternal adverse events.</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td></td>
<td></td>
<td></td>
<td>Approved in Spain for the treatment of preterm labor in oral solution.</td>
</tr>
<tr>
<td><strong>Indomethacin</strong></td>
<td>Nausea, heartburn. Fetal: oligohydramnios, premature closure of the ductus arteriosus, pulmonary hypertension, intraventricular hemorrhage, necrotizing enterocolitis, renal dysfunktion.</td>
<td>Hepatic or renal dysfunction, gastric ulcer, asthma drug-induced coagulation disorders or thrombocytopenia.</td>
<td>ILA daily if treatment&gt;48 hours (discontinue if ILA &lt;5) Ductus IP (discontinue if &lt;2 cm/ sec).</td>
<td>Control studies demonstrated efficacy in prospective randomized. Do not use in &gt; 32 weeks. It is not approved in Spain use as tocolytic.</td>
</tr>
<tr>
<td>COX inhibitor</td>
<td></td>
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</table>

Table 2. Types of tocolytics. Adapted from \(^{47}\)

If Nifedipine compared with Betamimetics, the first is associated with a decreased risk of delivery in the following 7 days after treatment and before 34 weeks, better neonatal outcome, reduced risk of complications associated with prematurity and minor maternal adverse effects\(^{40}\).
There are two studies comparing Atosiban with Nifedipine\(^{41,42}\). Both studies show that both drugs are equally effective, although Nifedipine appears to lengthen pregnancy and instead Atosiban seems less failures tocolysis within 48 hours. Although it appears that Atosiban has fewer maternal adverse effects.
3. JUSTIFICATION

As mentioned before, late preterm infants, or infants who are born between 34\(^{0/7}\) and 36\(^{6/7}\) weeks of gestation, often have a similar size and weight than term infants and therefore are treated as if they were mature and had less risk of morbidity\(^{1-3}\). But late preterm infants are at higher risk for infant mortality, morbidity during the first days of life, and neonatal morbidity that requires hospital readmission than term infants and it’s the reason for stop treating them like term infants\(^{1,2}\).

The management of obstetric spontaneous preterm delivery is based on maternal treatment with glucocorticoids in less than 33 weeks gestation and tocolysis in under 34 weeks\(^{4}\). In Spain, the tocolysis and antenatal corticoids administration is indicated in under 34 \(^{6/7}\) weeks of gestation\(^{30}\).

There is limited evidence of the effect on respiratory disorders or other complications by the antenatal corticosteroids in late preterm infants\(^{43}\). The study made by Porto and colleagues assessed the effectiveness of corticosteroids for reducing respiratory disorders in infants between 34 and 36 weeks’ gestation and concluded that antenatal treatment with corticosteroids at 34-36 weeks of pregnancy does not reduce the incidence of respiratory disorders in newborn infants but they said that in order to confirm these findings with a sufficient number of patients to detect small or occasional benefits of antenatal corticosteroids in cases of late prematurity, a large randomized multicenter clinical trial would be ideal\(^{44}\).

Moreover, in a study performed in Spain, the incidence of income in neonatology and neonatal intensive care, the presence of transient tachypnea, hypoglycemia, gastrointestinal intolerance, jaundice, respiratory support in the form of continuous positive pressure in the respiratory pathway, oxygen therapy, fluid therapy and phototherapy were significantly higher in the group not receiving antenatal corticoids and concluded that morbidity, especially respiratory, is significantly lower in those who
received antenatal corticosteroids, without adverse short-term effects in late preterm infants\(^{(45)}\).

Limited evidence of the effects of antenatal corticosteroids in late preterm is the motivation of this clinical trial. The goal of this study is to show that the protocol for preterm infants under 34 weeks gestation birth is also valid for late preterm infants.
4. METHODS

4.1 QUESTION, OBJECTIVES AND HYPOTHESIS

4.1.1 Question
Is the antenatal corticosteroids administration reducing respiratory distress in the late preterm infant?

4.1.2 Objectives
The main objective of this study is to demonstrate that antenatal corticosteroids administration during a spontaneous onset of labor between 35° 0/7 and 36° 6/7 of gestation reduces respiratory distress in the late preterm infants.

The secondary objective is to demonstrate that antenatal corticosteroids administration during a spontaneous onset of labor between 35° 0/7 and 36° 6/7 of gestation also reduces other complications in the late preterm infants.

4.1.3 Hypothesis
Antenatal corticosteroids administration during a spontaneous onset of labor between 35° 0/7 and 36° 6/7 of gestation reduces respiratory distress in the late preterm infant.

Antenatal corticosteroids administration during a spontaneous onset of labor between 35° 0/7 and 36° 6/7 of gestation reduced other complications in the late preterm infant.

*Late preterm* is defined as who is born between the gestational ages of 34 weeks and 0/7 days through 36 weeks and 6/7 days. The clinical trial does not include those between 34° 0/7 and 34° 6/7 weeks of gestation because in Spain the SEGO includes tocolysis and prenatal maturation in these weeks under its protocol. As the clinical trial is performed with betamethasone and placebo, would not be ethical to deny treatment to this population.
4.2 STUDY DESIGN

This is a multicenter randomized, triple blind, placebo controlled clinical trial designed to evaluate the efficacy and safety of antenatal corticosteroids administration during a spontaneous onset of labor between 35 $^{0/7}$ and 36 $^{6/7}$ of gestation for reducing respiratory distress and others complications in the late preterm infants.

The study will be conducted in the delivery room for the tocolysis and the corticoids administration and in the neonatal area for the data collection and treatment of the different morbidity of the late preterm infant in 5 centers that have NUCI. Hospital Universitari Josep Trueta will be the reference center.

In each of the involved centers we will assign a principal investigator (an obstetrician), and two co-investigators: a neonatologist and a nurse; and the hospital pharmacy.

4.2.1 Conditions for stopping the trial

- A non-justified case of maternal death (temporary stop until complete evaluation of the case by an external committee).
- Significant difference in perinatal death rate between the two groups.
- Significant difference between the two groups in the primary outcome that the External Data Monitor refers to the Ethical Committee to consider stopping the trial.
4.3 STUDY POPULATION

This is a multicentric study of pregnant women with a spontaneous onset of labor between 35 $^{0/7}$ and 36 $^{6/7}$ of gestation.

4.3.1 Inclusion criteria

- Minimal age of 18 years
- Women who are able to cooperate and have given informed written consent
- Gestational age between 35 $^{0/7}$ and 36 $^{6/7}$

4.3.2 Exclusion criteria

- Pregnant women who have received corticosteroids before 35 $^{0/7}$ weeks of gestation.
- Premature rupture of membranes at the time of randomization
- Major fetal abnormalities
- Incomplete medical record
- Maternal substance abuse
- Contraindications of tocolysis and antenatal corticoids administration
- Previous use of corticosteroids
- Preclampsia
- Eclampsia
- Placenta previa
- Uterine bleeding
- Placental abruption
- Cord prolapse
- Chorioamnionitis
- Women who will be discharged from hospital while still pregnant and who later still give birth in another hospital or woman who will give birth before receiving the second dose corticosteroids will be excluded from the study after randomization.
4.3.3 Sample size
To demonstrate a 50% reduction in the prevalence of respiratory distress in late preterm infants, on the assumption that the rate in the control group would be 28.9%, it would be necessary to randomize 332\(^\dagger\) patients (166 in each group) to demonstrate significance at the 5% level with a power of 90%.

4.3.4 Estimated time of recruitment
As we calculated before, 332 patients are needed for the study. Around 250 pregnant women with a spontaneous onset of labor between 35\(^0/7\) and 36\(^6/7\) of gestation are diagnosed per year in the 5 centers that are involved in the study. Considering that about a 10% of the candidate patients may not want to participate, we estimate that will need around 16 months to treat 332 patients.

4.3.5 Diagnose of spontaneous onset of labor
Regular uterine contractions (4 in 20 minutes) accompanied by substantial modification of the uterine cervix (effacement equal to or greater than 80% and cervical dilation of 1 cm or more) supplementing with ultrasound measurement of the cervix.

\(^\dagger\) Sample size calculated by GRANMO program.
4.4 ENROLLMENT AND RANDOMIZATION PROCEDURES

4.4.1 Informed consent

Women attending for a spontaneous onset of labor between 35\(\frac{0}{7}\) and 36\(\frac{6}{7}\) weeks of gestation will be asked to participate in the study if they have the inclusion and not the exclusion criteria. Then we will give them an information leaflet concerning the use of tocolytic agents to stop the uterine dynamic and the use of antenatal corticoids to favor fetal maturation so they can sign the informed consent with enough information for take that decision.

4.4.2 Randomization

After written informed consent was obtained, all women diagnosed of spontaneous onset of labor will receive Atosiban to stop the uterine dynamic and then they will be randomly allocated to antenatal corticoids administration (Betamethasone 12 mg IM / 2 doses 24 hours apart) or placebo in a 1:1 ratio. The randomization sequence will be computer-generated stratified for center, parity, maternal characteristics, maternal health problems and obstetrics complications.

4.4.3 Degree of blinding

A statistical\(^{\footnote{The statistical will be independent of the study and unrelated to the funder clinical trial to avoid any conflict of interest and alteration of the results.}}\) will prepare a table of random numbers with 166 women randomized to receive corticosteroids and 166 to placebo.

The hospital pharmacy will prepare 332 sealed cardboard boxes, each with four more blister of corticosteroids or placebo, identical in appearance, size and color, and numbered according to the table of random numbers. Each blister of corticosteroids will contain 6mg of betamethasone. Placebo blisters will contain a similar volume of 0.9% saline.

Only the pharmacist responsible of the preparation will be aware of the contents. Researchers, obstetricians who attend women, neonatologist who attend newborns,
statistical, nurses and women will not know the contents; this information will be revealed only after data analysis is completed.

Only after signing the informed consent form by these women, they will receive sealed cardboard box for your group randomization.

Researchers and the neonatologist who will continue to newborns prospectively will collect data on pregnant women and their children in a standardized form.

If a woman gives birth before receiving the second dose corticosteroids or if the woman completes the pattern programmed, but it is discharged, while still pregnant and will give birth to another hospital, will be considered a subsequent loss allocation random follow-up and not will be replaced.
4.5 STUDY TREATMENT

4.5.1 Study treatment groups

Women attending for a spontaneous onset of labor between 35 0/7 and 36 6/7 weeks of gestation will receive one of the following dose regimens:

1. Treatment group will receive: two blisters intramuscularly § with 6mg of betamethasone and two more 24 hours later.

2. Control group will receive: two blisters intramuscularly of placebo and two more 24 hours later.

In order to have enough time for betamethasone to take effect on the fetus, the following pattern of Atosiban, a tocolytic to delay the uterine dynamic will be administered: 0,9ml in 1 min (IV bolus) then continuous perfusion of 24 mL / h (iv) during 3h and finally 8 mL / h (iv) during 45h of Atosiban.

4.5.2 Practical considerations

The treatment used in the study should be kept in a safe place and only be administered by obstetricians with nurses.

It must be registered all the vials and syringes used to calculate the costs of the study.

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§ Intramuscular injection will be made in the right buttock, for both placebo and betamethasone.
4.6 STUDY VARIABLES

4.6.1 Dependent variable

Primary outcomes:

*Incidence of respiratory distress in the late preterm infant*: is a categorical variable and it will be estimated by measuring the presence or absence of the following aspects. It will be expressed by a percentage of late preterm with the following aspects.

- Respiratory morbidity defined as any of the following:
  
  o *Respiratory distress syndrome*: RDS diagnosed if a baby had a PaO2 of less than 50 mmHg or central cyanosis, in room air, or needed supplemental oxygen to maintain a PaO2 of more than 50 mmHg, and had a chest radiograph consistent with RDS.

  o *Transient tachypnea* of newborn defined as > 60 breaths/minute measured by auscultation.

  o *Apnea*: diagnosed if cessation of respiration was followed by bradycardia (<100 beats per min) measured by auscultation or desaturation (<88%) measured by oximeter, and after exclusion of other causes of apnea.

  o *Pulmonary hypertension*. The definitive diagnosis of neonatal pulmonary hypertension is made by echocardiography, watching the left-right shunt in the ductus arteriosus or in the oval foramen or both, and estimating the pressure in the pulmonary artery. Because not all NICU have a portable echocardiography, has established a point system (46) for establishing the diagnosis of disease, based in the following tests:

    a. Chest radiography: 1 point (radiological findings unrelated to the severity of hypoxemia).

    b. Lability of oxygenation (PaO2 of less than 50 mmHg despite FiO2 100%): 2 points.

    c. Test hyperoxia: 2 points (a FiO2 of 100% for 5-10 min is administered to the patient, then PaO2 is compared with the
PaO2 previously obtained. An increase in PaO2 > 150 mmHg suggests pulmonary parenchymal disease, but if PaO2 not increase and the newborn remains hypoxemic (PaO2 <50 mmHg) it is probably due to a true shunt from right to left and the differential diagnosis is limited to cyanotic congenital heart disease and pulmonary hypertension.

d. Difference in preductual and postductal oxygenation: 2 points (15-20 mmHg greater difference between the gases in the right radial artery (preductal) and umbilical artery (postductal)).
e. Hyperventilation test-hyperoxia: 3 points (with 100% of FiO2 you hyperventilate the infant to reach a critical PaCO2 (20-25mmHg) if an accelerated increase over 40 mmHg in the PaO2 when PaCO2 decrease, is suggested pulmonary hypertension.

Then we will define pulmonary hypertension when a score > 6 points obtained in previous tests.

- **Need of ventilatory support.** Ventilatory support will be initiated under the following conditions:
  - **Severe hypoxemia:** oxygen saturation < 88 %.
  - **Hypercapnia:** venus PCO2 > 55 mmHg.
  - **Respiratory effort.**

**Secondary outcomes:** will include other neonatal complications in the late preterm infants defined by the presence or absence of one of the following items:

- **Admission to the neonatal intensive care unit (NICU).** The criteria for admission to the NICU are:
  - **Birth weight less than 1800g.**
  - **Respiratory or cardiac disease.**
  - **Hypoglycemia** defined as blood glucose level of lees than 40 mg/dl in capillary blood sample.
  - **Suspected sepsis.**
- Significant hematologic abnormality (anemia, polycythemia, or thrombocytopenia).

- Requirement for close observation as assessed by neonatologist.

- Duration of hospitalization (days of hospitalization).

- Jaundice. Neonatal jaundice progresses cephalocaudal direction and can be roughly estimated and practical but not always accurate, serum levels of bilirubin in different body areas involved following Kramer scale. We will consider jaundice as yellowing of the skin that already appears in level 1 of the Kramer scale (Figure 3).

- Hyperbilirubinemia defined as the total bilirubin blood level of more than 5 mg/dl.
- **Need of phototherapy.** In order to standardize the right moment of starting treatment with phototherapy will use the guide clinical practice recommended by the American Academy of Pediatrics (Figure 4). It indicates bilirubin levels leading to starting treatment according to the time of life, weeks of gestation and risk factors of the newborn.

- **Hypoglycemia** defined as blood glucose level of less than 40 mg/dl in capillary blood sample.

- **Hypothermia** defined as newborn core body temperature of less than 36.0°C measured by an axillary thermometer.

- **Sepsis** defined by culture-proven sepsis, meningitis or pneumonia.

- **Necrotizing enterocolitis (NEC)** diagnosed using the modified Bell staging criteria for NEC (Table 3), being the characteristics described from stage IIA required for diagnosis.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Classification</th>
<th>Systemic signs</th>
<th>Intestinal signs</th>
<th>Radiologic signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Suspected NEC</td>
<td>Temperature instability, apnea, bradycardia, lethargy</td>
<td>Increased pregavage residuals, mild abdominal distention, emesis, guaiac-positive stool</td>
<td>Normal or intestinal dilation, mild ileus</td>
</tr>
<tr>
<td>IB</td>
<td>Suspected NEC</td>
<td>Same as above</td>
<td>Bright red blood from rectum</td>
<td>Same as above</td>
</tr>
<tr>
<td>IIA</td>
<td>Proven NEC – mildly ill</td>
<td>Same as above</td>
<td>Same as above, plus absent bowel sounds, with or without abdominal tenderness</td>
<td>Intestinal dilation, ileus, pneumatosis intestinalis</td>
</tr>
<tr>
<td>IIB</td>
<td>Proven NEC – moderately ill</td>
<td>Same as above, plus mild metabolic acidosis, mild thrombocytopenia</td>
<td>Same as above, plus absent bowel sounds, definite abdominal tenderness, with or without abdominal cellulitis or right lower quadrant mass</td>
<td>Same as IIA, plus portal venous gas, with or without ascites</td>
</tr>
<tr>
<td>IIIA</td>
<td>Advanced NEC – severely ill, bowel intact</td>
<td>Same as IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, and neutropenia</td>
<td>Same as above, plus signs of generalized peritonitis, marked tenderness, and distention of abdomen</td>
<td>Same as IIB, plus definite ascites</td>
</tr>
<tr>
<td>IIIB</td>
<td>Advanced NEC – severely ill, bowel perforated</td>
<td>Same as IIIA</td>
<td>Same as IIIA</td>
<td>Same as IIB, plus pneumoperitoneum</td>
</tr>
</tbody>
</table>

Table 3. Modified Bell staging criteria for NEC[^1].


- **Intraventricular hemorrhage** diagnosed by a head ultrasonography. We will consider intraventricular hemorrhage already gradated in level 1 of the Volpe scale.

- **Neonatal death.**
- **Composite neonatal outcome** is defined as the presence any of the following:
  - Respiratory morbidity.
  - Infectious morbidity.
  - Central nervous system morbidity.
  - Neonatal death.
  - Necrotizing enterocolitis.
  - Jaundice, Hyperbilirubinemia, Need of phototherapy.
  - Hypoglycemia.
  - Hypothermia.

All variables evaluated are categorical variables and will be expressed by a percentage of late preterm with that variable except *duration of hospitalization* that is a continuous variable and will be expressed by *the mean ± standard deviation of days of hospitalization of late preterm*.

### 4.6.2 Independent variable

The independent variable will be *being allocated in the antenatal corticoids administration group or in the placebo group*. It’s a categorical variable and will be expressed by a percentage of late preterm with antenatal corticoids administration and with the placebo.

### 4.6.3 Covariables

- Maternal characteristics:
  - Gestational age (weeks): determined by the first day of the woman’s last normal menstrual period (LMP) and this is confirmed by obstetric ultrasound in the Department of Gynecology and Obstetrics of the regional hospital.
  - Maternal age at delivery (age).
  - Smoking during pregnancy (yes or not).
  - Parity (number of labors).
  - Multifetal pregnancy (yes or not).
  - Previous cesarean section (yes or not).
- **Previous preterm births** (number of preterm births).
  - Maternal health problems (present or absent):
    - **Preexisting diabetes**
    - **Gestational diabetes**
    - **Chronic hypertension**
    - **Gestational hypertension/preclampsia**
    - **Infection during pregnancy** (any periodontal, urinary tract, vaginal or cervical infections)
  - Obstetrical complications:
    - **Breech presentation**
    - **Small for gestational age**
  - Neonatal characteristics:
    - **Birth weight**: will estimate fetal weight by ultrasound using the Hadlock formula, based on measurements of head circumference, abdominal circumference and femur length.
    - **Infant sex**

All items evaluated are categorical variable and will be expressed by a percentage of late preterm infants with that item except **gestational age, maternal age at delivery, parity, number of preterm births, weight** at birth that are a continuous variable and will be expressed by the **mean ± standard deviation of weeks of gestation, maternal age, number of labors, number of preterm births and birth weight.**

### 4.6.4 Measure instruments

The different measure instruments that we need will be ultrasound and obstetric ultrasoun, axillary thermometer (Thermoval basic), cardiotocography, neonatal oximeter, chest radiography, abdominal radiography and blood tests.

Specifically in the blood tests, for glycemic and total bilirubin measurement we will use a two different colimetric test, hexokinase glucose and 2-4 and 2-5 dichloroaniline diazotized test respectively. For the analysis of hematocrit we will use fluorescent flow
cytometry, direct current and hydrodynamic focusing and SLS free cyanide method for the leukocyte formula; platelet count, hematocrit and red blood cell count; and hemoglobin levels respectively. Finally, we will use potentiometric sensors (potentiometric) for PaCO2 and amperometric sensors (amperometry) for the PaO2.
4.7 EXECUTION PLAN AND SCHEDULE OF EVENTS

Each patient participating in the study must follow the next steps (Table 4):

1. Selection of subjects to be included in the study (according to the inclusion and exclusion criteria). The obstetrician who will attend the patient will determine who is selected for the study.

2. The patients must sign the informed consent.

3. Enrollment in the study, randomization, assignation to an identification number and allocation in one of the intervention groups.

4. Collection of baseline data about maternal or obstetric characteristics from the patients (covariables).


6. Collection of baseline data about the different morbidity of the late preterm infants.

7. Analysis of results.

During the study participation, women and late preterm will be treated according the established clinical standards.

After the trial ended results must be sent to the Asociación Española de Medicamentos y Productos Sanitarios (AEMPS), Sociedad Española de Ginecología y Obstetricia (SEGO), publish the article in the journal Progresos and present it in National Congresses.

<table>
<thead>
<tr>
<th>Tests and evaluations</th>
<th>Diagnose of APP</th>
<th>Treatment with tocolysis + Betamethason or placebo</th>
<th>Follow up the late preterm infants during the neonatal period</th>
<th>End of the neonatal period of the late preterm infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>x</td>
<td></td>
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<tr>
<td>Collection of baseline data from medical history</td>
<td>x</td>
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<tr>
<td>Randomization and treatment assignment</td>
<td></td>
<td>x</td>
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<tr>
<td>Evaluation of late preterm morbidity</td>
<td></td>
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<td>x</td>
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<tr>
<td>Adverse events</td>
<td>x</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Analysis of results</td>
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<td>x</td>
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</tbody>
</table>

Table 4. Work Plan
The study will finish when the last treated patient is discharged (see study flow chart, annex II)
4.8 ADVERSE EVENTS

An adverse event will be considered any adverse experience that happens to a patient during the clinical trial, it is considered or not related to the drug used in research. A serious adverse event will be any AE that is one of the following: death, imminent threat to life or severe permanent disability or any adverse event that the researcher considers important.

Unexpected adverse event will be not described any experience related to the drugs used in the clinical trial.

During the study, we will make every effort to be alert to possible adverse events. If an AE occurs, the first concern will be patient safety. If necessary, appropriate medical treatment will be provided.

A record of the different types of EA that occur during the clinical trial from the moment of signing the informed consent until late preterm are no longer in the neonatal period will be made. All EA will be collected in the safety data collection sheet (Annex III).

All important information regarding the safety of drugs in clinical trial will be notified to the “Asociación Española de Medicamentos y Productos Sanitarios” (AEMPS), the Autonomous Community and hospital ethics committee concerned.
4.9 STATISTICAL ANALYSIS

Firstly, a table (Table 5) will be done with the characteristics of the study population with the number and percentage for categorical variable or the mean ± standard deviation for continuous variable of each variable that we have registered.

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>N= OR MEAN ± SD</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Maternal Characteristics:</td>
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<td>Mean gestational age</td>
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<tr>
<td>Mean Maternal age at delivery</td>
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<tr>
<td>Smoking during pregnancy</td>
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<td>Parity</td>
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<tr>
<td>Multifetal pregnancy</td>
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<tr>
<td>Previous cesarean section</td>
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<td>Previous preterm births</td>
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<tr>
<td>Maternal health problems:</td>
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<td>Preexisting diabetes</td>
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<td>Gestational diabetes</td>
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<td>Obstetrical complications:</td>
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<td>Breech presentation</td>
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<td>Small for gestational age</td>
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<td>Neonatal characteristics:</td>
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<td>Mean birth weight</td>
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<td>Infant sex</td>
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<td>Female</td>
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<tr>
<td>Male</td>
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</table>

Table 5. Characteristics of the study population

Second, in order to know the distribution of the study population according to their allocation to treatment or placebo a bivariate analysis will be performed using the Student test to compare continuous variable between the groups, and the Chi² test for categorical variables and the proportions will be presented by absolute numbers and percentages (Table 6). This analysis is important to see if randomization is actually uniformly distributed in each population group. If groups aren’t uniformly distributed, the results of the study could be affected by this randomization error. Therefore, a multivariable analysis (explained below) adjusted for covariates that could skew the main association we want to analyze.
<table>
<thead>
<tr>
<th>COVARIABLE</th>
<th>Corticosteroids (n=166)</th>
<th>Placebo (n=166)</th>
<th>Risk Ratio</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N= %</td>
<td>N= %</td>
<td>(95% CI)</td>
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<tr>
<td><strong>Maternal Characteristics:</strong></td>
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</tr>
</tbody>
</table>

Table 6. Bivariate analysis

Then, a second bivariate analysis will be performed using the **Student test** to compare continuous variable between the groups, and the **Chi^2 test** for categorical variables and the proportions will be presented by absolute numbers and percentages (Table 7). The independent variable will always consist of two categorical components: the antenatal corticosteroids administration and the placebo administration. The primary dependent variable is the presence or absence of respiratory distress; and the second dependent variable is the presence or absence of other complications neonatal complications. A confidence interval of 95% will be assumed and we will consider p value <0.005 to consider that there is a significance difference.
Finally, a **Poisson regression** (a multivariante analysis) will be performed in order to add all the covariables that could skew the main association we want to analyze, for being a randomization error or a confounding factor. For categorical variables overall percentages will be estimated. For continuous variables, if we can assume a normal distribution, we will estimate the mean and standard deviation and, if we cannot assume it we will estimate the median, first and third quartile.

Data analysis will be performed with the Statistical Package for the Social Sciences (SPSS Windows®).
4.10 Opportunities and Limitations of the Study

4.10.1 Opportunities
The number of patients needed for the study is easy to obtain in a reasonable time in obstetrics and neonatology departments of different hospitals that are part of the study.

This is a multicenter study; therefore, we can generalize the findings. The team's research group has experience in conducting clinical trials. It is not the first study performed by administering antenatal corticosteroids for fetal maturation, however, previous studies did not extract extrapolate conclusions because they were not multicenter.

If antenatal corticosteroids prove effective in reducing respiratory distress and other complications in late preterm infants may become the treatment for those pregnancies that are put in labor for $35^{0/7}$ to $36^{6/7}$ weeks gestation.

4.10.2 Limitations
The limitations of this clinical trial are resolved through randomization and triple blind explained above.

A possible limitation could be the loss of the patient during treatment, but is resolved in the following way:
If a woman gives birth before receiving the second dose corticosteroids or if the woman completes the pattern programmed, but it is discharged, while still pregnant and will give birth to another hospital, will be considered a subsequent loss allocation random follow-up and not will be replaced.

A limitation of this study is that it is quite expensive due to the pattern of Atosiban ($425.77 \, \text{€ per patient}$).

Although there are other tocoytic marketed in Spain, such as Ritodrine or Nifedipine, the Atosiban is the one with fewer adverse effects. Ritodrine as Nifedipine are
contraindicated in multifetal pregnancy, diabetic women, heart disease women ... so its use in a clinical trial would involve having to exclude these women. We believe it is important to include women in the study such as, for example diabetes is quite prevalent in pregnant women, and we don’t want to exclude this large population to check that prenatal maturation reduces complications of late preterm infants.

With the data collected in the cost of prematurity paragraph we believe that the costs arising from the treatment of these pregnant women will be less than the costs incurred by treating the complications of late preterm infants without prenatal maturation.
4.11 WORK PLAN

Principal investigators: Judith Banegas, Josep Maria Ramos.

Like I said, in each of the involved, we will assign a principal investigator (an obstetrician), and two co-investigators: a neonatologist and a nurse; and the hospital pharmacy.

The trial has been designed in five phases (see work plan, annex IV).

1. **Coordination phase. Development of theoretical framework (4 months):** The principal investigators and research associates from each center along will be involved in this phase. Prior to the first meeting, the principal investigators will have conducted a literature search to prove the importance of this study. The first meeting of the study will be planned study design and methodology of data collection and protocol will be written and then evaluated by the CEIC (Comitè d’Ètica I Investigació Clínica).

2. **Field research (16 months):** All the study staff form each center will be involved. A second meeting will be made to remember all the steps of the study protocol and then, the study will begin and will finish 30 months later.

3. **Data extraction and processing database (16 months):** All investigators and collaborators will be involved. Data will be entered in the database every 4 months. An analysis of data will be performed regularly to control its evolution.

4. **Statistical analysis (4 months):** The principal investigators and research associates from each center along and statistical consultant will be involved. A third meeting will be done to evaluate the clinical trial execution and plan the statistical analysis. During the processing the database, all data collected will be analyzed, once a year, using the appropriate statistical test. So the statistical consultant will make an analysis during the study and a second one, a final analysis of data, at the end.

5. **Analysis of the results (4 months):** The principal investigators will be the only involved. An interpretation, discussion and conclusion of the outcomes will be performed in the last meeting.

6. **Finalization and results publication (4 months):** The principal investigators will be the only involved. We will elaborate the final report, publish the article in the journal Progresos and present it in AEMPS, SEGO and National Congresses.
4.12 ETHICAL ASPECTS

This trial is designed in accordance with the medical ethics requirements defined on the World Medical Association Declaration of Helsinki for Ethical Principles for Medical Research Involving Human Subjects (Asamblea General, Fortaleza, Brazil, October 2013).

This trial will be sent to the Clinical Research Ethics Committee (CEIC) of the Hospital Universitari de Girona Dr. Josep Trueta, in order to be accepted and to the AEMPS.

As it is now recommended, the trial has also been registered with an International Standard Randomised Controlled Trial Number (http://www.controlled-trials.com) and has been submitted to ClinicalTrials.gov (http://clinicaltrials.gov.com)

The information of clinical history, names and surnames, will be confidential, guaranteeing the anonymity of the patients involved in the study according to “Ley Orgánica 15/1999, 13 de Diciembre, Protección de Datos de Carácter Personal”.

In addition, patients will be informed about the protocol management (annex V) and they must sign an informed consent (annex VI) before being included in the trial.
### 4.13 BUDGET

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Quantity</th>
<th>Cost</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel cost</td>
<td>Statistical consulting and analysis of study data</td>
<td>3 analysis of 30h</td>
<td>40€/h</td>
<td>3.600,00 €</td>
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<tr>
<td>Material expenses</td>
<td>Guideline tocolysis with atosiban</td>
<td>332</td>
<td>425,77 €*</td>
<td>141.355,64 €</td>
</tr>
<tr>
<td></td>
<td>CELESTONE CRONODOSE 6MG/VIAL 1 VIAL 2ML SUSP INY</td>
<td>166</td>
<td>5,02 €*</td>
<td>833,32 €</td>
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<tr>
<td></td>
<td>0.9% saline</td>
<td>166</td>
<td>0,15 €**</td>
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<td></td>
<td>Food and miscelania</td>
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<td>≈ 100 €</td>
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<td><strong>TOTAL</strong></td>
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<td></td>
<td><strong>169.513,86 €</strong></td>
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</table>

*Prices of hospital pharmacy.

Table 8. Budget
5. BIBLIOGRAPHY


https://vpgateway.udg.edu/doi/pdf/10.1080/,DanalInfo=informahealthcare.com+14767050600965882


6. ANNEXES

Annex I: Management of threat of preterm birth

Figure 5. Management of threat of preterm birth extrated from APP Protocol SEGO (S1)
Annex II: Study flow chart

**Women between 35 0/7 and 36 6/7 with a spontaneous onset of labor**

Regular uterine contractions (4 in 20 minutes) accompanied by substantial modification of the uterine cervix (effacement equal to or greater than 80% and cervical dilation of 1 cm or more) supplementing with ultrasound measurement of the cervix.

**CONSENT FORM + Collection of baseline data from medical history**

**Tocolysis with atosiban:** 0.9ml in 1 min (IV bolus) then continuous perfusion of 24 mL / h (iv) during 3h and finally 8 mL / h (iv) during 45h of Atosiban

- **Grup A**
  - Antenatal corticoids administration

- **Grup B**
  - Placebo

**Randomization and treatment assignment**

**Birth: Evaluation of late preterm morbidity**

**Analysis of results**

Figure 6. Study flow chart
Annex III. Safety data collection

<table>
<thead>
<tr>
<th>Date and time:</th>
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<tbody>
<tr>
<td>Patient number:</td>
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<tr>
<td>Person collecting data:</td>
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</tbody>
</table>

### Atosiban adverse events

<table>
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<tr>
<td>Hyperglycemia</td>
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<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
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<tr>
<td>Tachycardia</td>
<td></td>
</tr>
<tr>
<td>Blush</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Unexpected adverse events:*</td>
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</tr>
</tbody>
</table>

### Bethametason adverse events

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<tr>
<td>Musculoskeletal</td>
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<tr>
<td>Gastrointestinal</td>
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<td>Dermatological</td>
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<td>Neurological</td>
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<tr>
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<td>Ophthalmic</td>
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<td>Metabolic</td>
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<tr>
<td>Psychiatric</td>
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</tr>
<tr>
<td>Unexpected adverse events:*</td>
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</table>

* Write any unexpected adverse occurred

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Table 9. Safety data collection
Annex IV: Work plan

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<td>2. Literature review</td>
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<td>3. Study proposal design</td>
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<td>4. Study research proposal evaluation</td>
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<td>5. Data collection</td>
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<tr>
<td>6. Consecutive data collection</td>
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<tr>
<td>7. Data entry</td>
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<tr>
<td>8. Statistical analysis</td>
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<tr>
<td>9. Consecutive data entry</td>
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<tr>
<td>10. Final report elaboration</td>
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<tr>
<td>11. Discussion</td>
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<td>12. Final analysis of the results</td>
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<tr>
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<td>14. Final publication in the journal</td>
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<td>15. Statistical analysis of data</td>
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<td>16. Final report elaboration</td>
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Figure 7. Work Plan
Annex V: Protocol management

FULL INFORMATIU PEL PACIENT

ADMINISTRACIÓ DE CORTICOIDES PRENATAALS VERSUS PLACEBO EN PRETAMURS TARDANS: ASSAIG CLÍNIC RANDOMITZAT MULTICENTRIC

Estudi multicèntric, randomitzat en dos grups, triple cec; en relació amb el maneig de l’amenaça de part preterm entre les 35 0/7 y les 36 6/7 setmanes de gestació, un grups es tractarà amb betametasona i el segon grup amb placebo.

Benvolgut pacient,

Ens dirigim a vostè per convidar-lo a participar en un estudi de recerca que s’està portant a terme en la unitat de ginecologia i obstetricia en diferents hospitals de Catalunya sobre el maneig de l’amenaça de part preterme entre les 35 0/7 y les 36 6/7 setmanes de gestació. Es vol investigar si la maduració fetal prenatal amb betametasona redueix el distrès respiratori i altres possibles complicacions en el nownat entre aquestes setmanes de gestació.

Abans que prengui la decisió de participar o no a l’estudi, es imprescindible que llegeixi i entengui el full informatiu i, davant qualsevol dubte, pregunti al doctor que li convida participar en l’estudi.

Participació voluntària:

És important que sigui concient que participar a l’estudi és voluntari, i que pot no fer-ho, canviar d’opinió o retirar el seu consentiment informat si ho desitja, sense que això alteri la seva relació amb el seu metge ni es produeixi cap prejudici en el seu tractament. Per tal que pugui prendre la millor decisió, li proporcionem la informació correcta i suficient per a que pugui valorar-ho adequadament.

Descripció de l’estudi:

El grups d’investigació de l’estudi és especialista en ginecologia i obstetricia i en nounats i les complicacions relacionades amb la prematuritat.
L’estudi es centra en aquelles gestacions amb amenaça de part preterm entre les 35\textsuperscript{0/7} y les 36 \textsuperscript{6/7} setmanes de gestació, on el protocol actual considera que se’ls hi ha de fer un maneig expectant, deixant evolucionar el part com si es tractes d’un part a terme. Actualment, s’ha comprovat que els nadons nascuts entre les 35 \textsuperscript{0/7} i les 36 \textsuperscript{6/7} setmanes de gestació tenen més riscos de patir complicacions postnatales que els nascuts a partir de les 37 \textsuperscript{0/7} setmanes, és a dir, a terme; pel que concluim que no maneig ha de ser diferent entre aquests dos grups.

L’objectiu de l’estudi és comprovar si la maduració fetal prenatal amb betametasona redueix el risc de desenvolupar dístres respiratori i altres possibles complicacions en el noulat nascut entre les 35 \textsuperscript{0/7} i les 36 \textsuperscript{6/7} setmanes de gestació. Per tal que la betametasona tingui el temps suficient per fer efecte al fetus, se li administrarà una pauta d’Atosiban, un tocolític per parar la dinàmica uterina durant 48h.

**Grups de tractament:** Hi haurà dos grups de tractament, seleccionats aleatoriament una vegada hagin firmat el consentiment informat. Ni vostè, ni el personal mèdic, seran coneixedors del grup al que serà assignat.

- **Grup 1:** es tractarà amb 2 dosis de betametasona intramuscular separades per 24h.
- **Grup 2:** es tractarà amb 2 dosis de placebo intramuscular separades per 24h.

Degut a que la pauta d’Atosiban es realitza de forma intravenosa, haurà d’ingresar durant 48h.

**Interrupció de l’estudi:**

Vostè podrà abandonar l’estudi quan ho consideri oportú o necessari, ja sigui per motius personals com mèdics; per patir esdeveniments adversos greus; si no es compleix amb la “Ley del medicamento” o amb els principis ètics del Reial Decret 223/2004. Abans de prendre dita decisió, seria convenient que ho parlés amb el doctor que li fa oferir participar a l’estudi.
**Beneficis:**
Esperem trobar el millor maneig davant l’amenaça de part preterm entre les 35 \( \frac{0}{7} \) i les 36 \( \frac{6}{7} \) setmanes de gestació per tal de disminuir les diferents complicacions que aquests nadons poden patir per la falta de maduració al néixer abans de les 37 \( \frac{0}{7} \) setmanes de gestació, és a dir, a terme.

**Riscos:**
Al ser un estudi en el que s’administren fàrmacs es possible l’aparició d’esdeveniments adversos. En el cas que apareguin, aquests seran tractats segons la pauta clínica establerta, tenint sempre com a prioritat el benestar del pacient.

**Responsabilitat i assegurança:**
El doctor responsable de l’estudi ha contractat una assegurança que coveria la responsabilitat legal per danys ocasionats a les persones que hi participen i als derivats d’aquesta investigació, realitzada conforme al protocol científic i la legislació vigent.

**Confidencialitat**
La informació mèdica i qualsevol informació recollida sobre vostè y el seu nadó durant l’estudi seran confidencials, en cap cas el seu nom o el del seu fill apareixerà en la publicació dels resultats.  
La seva privatitat està protegida y recollida en las Llei Orgànica 15/1999 sobre Protecció de Dades personals y el corresponent Reial decret nacionals 1720/2007).

**Compensació econòmica:**
La participació en l’estudi no serà beneficiaria de cap compensació econòmica.  
En cas de generar-se un desenvolupament comercial dels coneixements obtinguts, els possibles beneficis seran destinats a cobrir costos científics.

**Consentiment informat:**
En el cas que vostè decideixi participar en l’assaig clínic, haurà de firmar el següent consentiment informar per tal de evidenciar que coneixe les condicions de l’estudi i les accepta.
Annex VI: Informed consent

FORMULARI DE CONSENTIMENT INFORMAT

<table>
<thead>
<tr>
<th>ADMINISTRACIÓ DE CORTICOIDES PRENATALS VERSUS PLACEBO EN PRETAMURS TARDANS: ASSAIG CLÍNIC RANDOMITZAT</th>
</tr>
</thead>
</table>

Estudi multicèntric, randomitzat en dos grups, triple cec; en relació amb el maneig de l’amenaça de part preterm entre les 35 $^{0/7}$ y les 36 $^{6/7}$ setmanes de gestació, un grups es tractarà amb betametasona i el segon grup amb placebo.

Nom i Cognoms del pacient: ________________________________________________________________
Data de Naixement: __ / __ / ____ Número de telèfon: ________________________________

1. He llegit i entès el formulari informatiu sobre l’estudi.
2. He entès el que se’m demana en l’estudi.
3. He tingut temps necessari per pensar si vull o no participar en l’estudi.
4. He parlat amb el doctor encarregat de l’estudi o el seu personal per tal de preguntar dubtes i entendre millor en què consisteix l’estudi.
5. He rebut la informació suficient per entendre adequadament l’estudi.
6. He entès que puc abandonar l’estudi si ho desitjo informant al metge responsable.
7. He entès que tota la informació obtinguda durant l’estudi, tant meva com del meu fill, serà confidencial.
8. He entès que la meva participació o el meu desig a no participar no afectarà als meus drets legals.
9. He entès que puc tenir una còpia del consentiment informat i del formulari informatiu.
10. Estic d’acord en participar en aquest estudi de forma voluntària.

Firma del pacient o representant legal: Firma de l’investigador:

Nom: ____________________________________________________________
Data de la signatura: __ / __ / ____

Nom: ____________________________________________________________
Data de la signatura: __ / __ / ____