Universitat de Girona

FINAL DEGREE PROJECT

Neuroprotection with antepartum Magnesium Sulphate in preterm birth between 32 and 34 weeks´ gestation: multicentre randomized clinical trial

Author: Marta Díaz Vázquez
Clinical Tutor: Sara Torrent Bosch
Methodological Tutor: Mª Teresa Puig Miquel

2017/2018
HOSPITAL UNIVERSITARI DOCTOR JOSEP TRUETA
Universitat de Girona. Facultat de Medicina

Quiero dar las gracias al servicio de Ginecología y Obstetricia del Hospital Dr. Josep Trueta y CAP Güell por transmitirme su pasión por la especialidad en estos meses.

Al profesor Marc Saez, por su paciencia y tiempo resolviendo mis dudas.

Finalmente, a mi familia y a mi compañero de viaje. Gracias por nunca dejar de confiar en mí.

Index

Abbreviations

PTB	Preterm Birth
WG	Weeks' Gestation
BDP	Broncho-Pulmonary Dysplasia
WK	Weeks
$MgSO_4$	Magnesium Sulphate
fFN	Fibronectin Test
phIGFBP-1	Phosphorylated insulin-like growth factor binding protein-1
PAMG-1	Placentary α-microglobuline 1
CF	Cardiac Frequency
RF	Respiratory Frequency
AP	Arterial Pressure
CP	Cerebral Palsy
GMFCS	Gross Motor Function Classification System
MACS	Manual Ability Classification System
CFCS	Communication Function Classification System
QOL	Quality of Life
NMDA	N-Methyl-D-Aspartate

Abstract

Background: Preterm birth is increasing each year. These children have more adverse outcomes due to the early birth, including neurodevelopmental outcomes. Cerebral palsy is one of that. Some studies have shown the protective effect of antepartum administration of magnesium sulphate in this event, but the high evidence is only in preterm labor before 32 weeks´ gestation.

Objective: To prove the neuroprotective effect with the antepartum administration of magnesium sulphate in women with risk of spontaneous preterm labor between 32-34 completed WG, without secondary outcomes.

Design and methods: It is a multicentre, randomized, double blind clinical trial involving 3524 women with spontaneous threat of preterm labor between 32 and 34 completed weeks´ gestation. These women will be randomized to be or not be treated with magnesium sulphate. It will be evaluated the presence of secondary outcomes in women and children in that moment and cerebral palsy in these children at two years. It will be executed in 7 Catalonia´s Hospitals.

Key words: Preterm birth, Cerebral palsy, Magnesium Sulphate, Secondary outcomes.

Introduction

Preterm birth

Preterm birth (PTB) is defined as a delivery before to 37 completed weeks of gestation (prior to 259 days since the first day of the last menstrual period) (1,2).

The PTB can be assorted in spontaneous (preterm rupture of membranes or preterm labor with cervical dilation) and indicated (because of maternal or fetal complication in absence of delivery or membrane rupture) (1).

Besides, it is commonly separated based on gestational age (2–4):

- Extreme preterm: <28 weeks gestation (WG).
- Very preterm: 28-31 WG.
- Moderate and late preterm: 32-37 WG.

When gestational age data is not available, it can be used birth weight proxies because it does exist a relationship with the morbidities (2,5):

- <1.000g for extremely low weight
- 1.000 to <1.500g for very low weight
- < 2.500d for low weight

Epidemiology

There were around 15 million preterm births worldwide in 2010, 8.2 million were males. It means that more than 1 of each 10 births were premature (1–4,6,7).

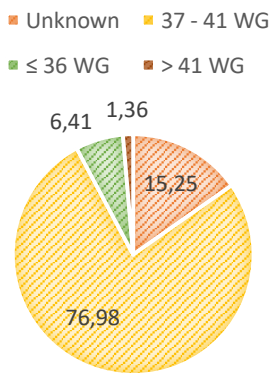


Figure 1. 2015 Born incidence in Spain

In 2015, in Spain, the preterm birth rate was 6,41% of all births (8).

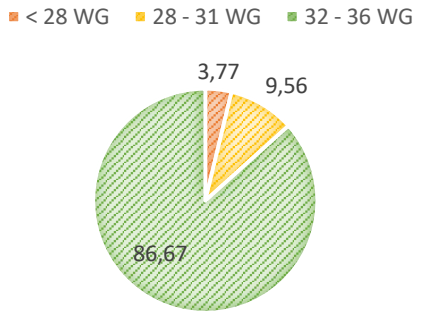


Figure 2. 2015 Preterm birth by gestational age in Spain

According to the gestational age, most preterm deliveries (75%) happen in the moderate and late preterm period (1–4,6,7); in 2015, in Spain, a 86,67% (8). The majority of global preterm birth happens in Africa and Asia, where their health systems are the poorest (9).

During the last century, the PTB rate has increased because of multiple factors (1,2), but the improvement of fertility therapies and the preterm birth prevention are decreasing this trend (10).

Causes

The most frequent causes of premature birth are multiple gestation, infections and chronic diseases, like diabetes and hypertension,… but the majority are idiopathic (3,9,11).

There are different factors which may increase the PTB rate such as maternal age, more use of assisted reproductive technologies, previous preterm labor (1,10)…

One factor that affects to PTB is the racial and ethnic background, in which non-Hispanic Black women delivered prior to 37 weeks more often than other women. It can be interacted by social and economic inequalities, but it is not well evidenced. However, some studies propose that there is a genetic predisposition to have a preterm labor(1).

There are evidences about the significant association between environmental exposures (environmental tobacco smoke, air pollution, chemicals) and preterm birth (12).

On the other hand, other factors like iron consumption, history of caesarean section, prenatal care… could be considered as protective (9). Furthermore, women with more advanced education levels have lower rates of PTB (1).

Table 1. Risk and protective factors of preterm birth

Risk Factors	Protective Factors
•Assisted reproductive technologies •Misbirth history •Previus preterm birth •Short time from last delibery •Multiparite •Preeclampsia •Fetal anomaly •Intercourse in the previous week •Rupture of membranes •Ambiotic fluid leak or polyhydramnios •Hypertension or diabetes •Maternal smoking •Intra-uterine infection •Extremes of maternal age (≤18 years or ≥40) •Maternal low weight or BMI <18,5 •Lower socio-economic status •Enviotonmental exposures •Ethniticty: Afro-American	•Iron consumption •Cephalic presentation •Hystory of cesarean section •Women´advanced education level

Adverse outcomes

Events happened in the early life have been recognized to play a key role in the children´s development. The term “programming” means that an insult in a sensitive or critical period may have long term effects on function and organism´s structure (13). An

opposite relationship exists between gestational age at labor and the risk of neonatal morbidity and mortality (1,2,4,7).

Most preterm birth survive the neonatal period, but children who survive are associated with many acute and long-term complications (*Figure 3*) (1–3,7,10). These preterm are more susceptible to be readmitted to hospital because of a higher number of complications, chiefly due to respiratory outcomes (4,6,7).

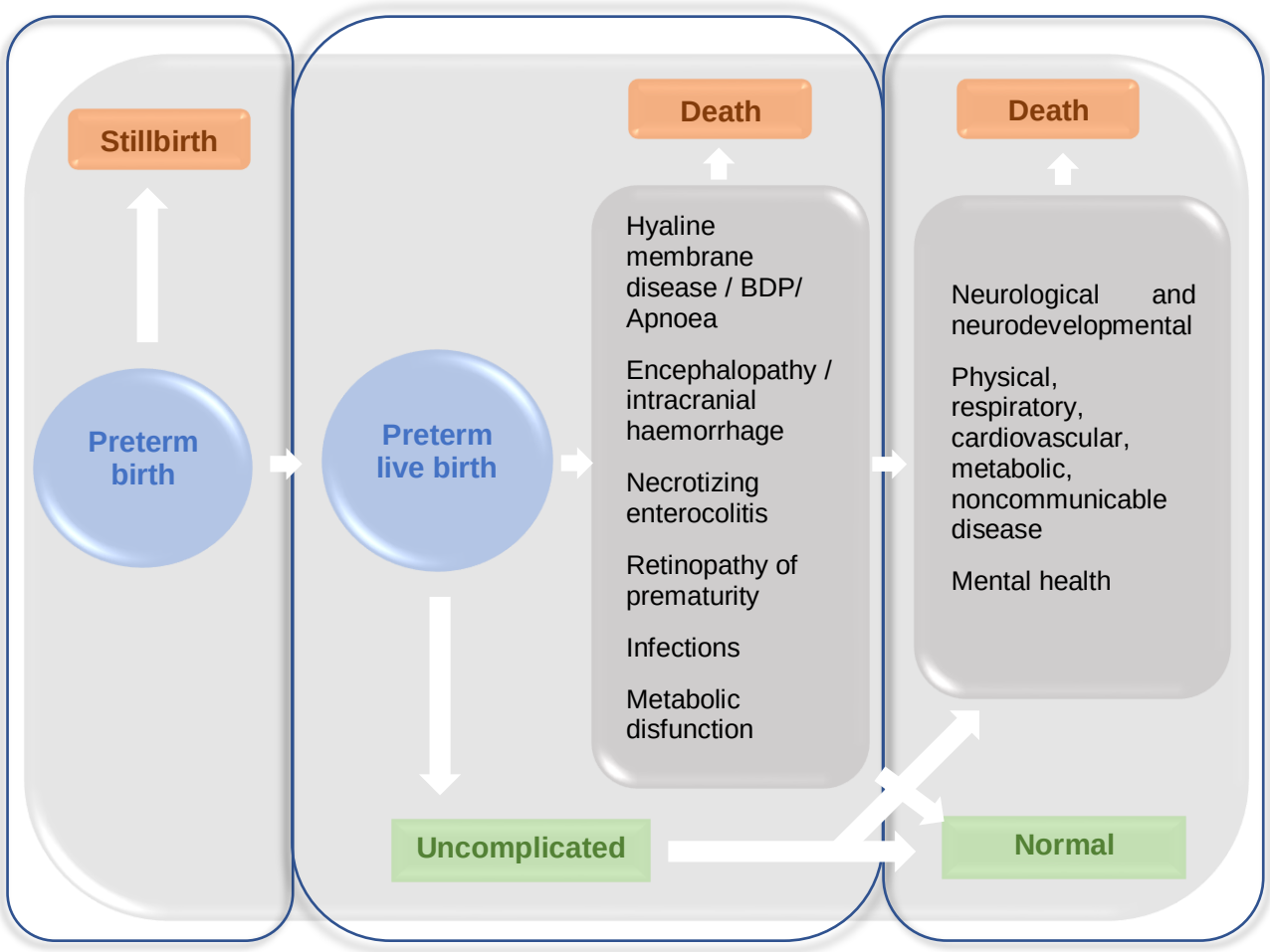


Figure 3. Disease schema for sequalae of preterm birth. (Adapted from Figure 1 of Preterm birth–associated neurodevelopmental impairment estimates at regional and global levels for 2010 (2))

An estimated 35% of the 3 million neonatal deaths in the world in 2010 were caused like as direct complications of preterm birth (2,3,6). It is in the main causes of death in children aged <5 years worldwide (1,3,4,9), this rate also increases due the higher risk of

neonatal infections (2). In recent years, these deaths have been decreasing due to the improvement of the health care (11).

More than 75% PTB can survive with an easy and cost-effective attention. For example, a basic health care, prenatal corticosteroids, the kangaroo technique and the use of antibiotics in the preterm infections can be useful (3).

Infections (6,7)

The immaturity of preterm immunological system entails an increased rate on infections in these children. Gram-positive organisms have caused most of these episodes, but the most dangerous episodes are caused by Gram-negative.

The risk of **meningitis** and **pneumonia** is higher in this group.

Temperature and glucose regulation (6,7)

There is more **temperature instability** in preterm infants, especially in the first hours of life. In addition, they are more brittle to cold stress. These children also have less brown and subcutaneous fat, a nonkeratinized skin and large surface area which made them lose more temperature. It may be prevented with the active management of hypothermia, with the use of incubators, for example.

According to glucose regulation, preterm children have reduced the glycogen stores and the activity of glucogenic and glycogenolytic enzimes. It can bring on **early postnatal hypoglycaemia**, which may be exacerbated by sepsis, stress or inadequate glucose intake. Almost 65% requires intravenous fluids.

Respiratory (4,6,7,13)

Preterm infants are at higher risk of **transient tachypnoea of the new-born**, **respiratory distress syndrome**, **pulmonary hypertension** and **pneumonia** in the neonatal period.

Some causes of respiratory distress syndrome are immature surfactant and antioxidant systems and delayed intrapulmonary fluid absorption.

A common adverse outcome of premature birth is chronic respiratory disease, particularly **bronchopulmonary dysplasia** (BPD), with up to 40% of preterm survivors. There is an oxygen dependency beyond 36 weeks gestation caused by a developmental disorder where the fact that the lung fails to reach full structural complexity bring on a decrease of the gas interchange´s area.

Also, due to the poor immunity system of preterm, they have more **respiratory infections**, such bronchiolitis due to respiratory syncytial virus.

The immaturity of brainstems regions and imperfect control of breathing, in addition of the collapse of the west wall and the upper airways, causes **apnoea of prematurity**.

The pulmonary function improves with the growth, but the airflow limitation persists in these children. It produces a higher prevalence of **asthma** in adolescents, and more if children are female.

Some changes, like reduced lung attenuation, decreased bronchus to pulmonary artery diameter ratio, bronchial wall thickening…, can be seen in computerized tomography (CT) scan.

Some respiratory outcomes can be reduced with the use of antenatal steroids for pregnant women between 24 and 34/36 weeks of gestation, but the week limit is still not clear.

Cardiovascular (13)

There is an increased risk of **adult hypertension** in subjects born preterm. It is because of an altered development due to the interruption in angiogenesis of the vascular tree. In addition, the endothelial dependent relaxation and the quantity of elastin are affected. These events produce an increased arterial stiffness and a reduced flow-mediated dilatation. Moreover, there is also a diminished density of arterioles and increased capillary rarefaction.

In preterm infants there is **retinopathy of prematurity**, which reflects a potential blinding disease caused by an anomalous growth of retinal blood vessels in preterms under 32 WG.

Also, it may be a higher risk of **stroke coronary disease** and **glomerulosclerosis** caused by reduced arterial diameters of major vessels.

Renal (13)

Nephrogenesis finalises at 34-36 weeks of gestation. Consequently, preterm subjects are born with a reduced number or nephrons compared with term infants. This reduction may cause a hyperfiltration: **proteinuria**, **hypercalciuria**, **hyperuricosuria**, **hyperoxaluria** and **kidney injury**.

These children are more sensitive to of potentially toxic drugs because of the kidney injury.

As previously mentioned, it has been reported a reduction in the glomerulus vascularization.

The tubular dysfunction may increase the occurrence of early **nephrolithiasis**.

Neurodevelopmental disabilities (4,6,7,13)

Preterm birth is associated with a high index of neurodevelopmental disabilities in all ages.

Preterm brain injury is caused for the developmental vulnerability given because the brain weighs a 65% of its full-term weight at 34 weeks (WK) and glial cell migration is not ended until 36 WK. In addition, other complications like respiratory distress, hypoxemia, infection, hyperbilirubinemia or hypoglycaemia increase this damage (2).

Myelination is uncompleted in these preterms. smaller brain biparietal diameter, corpus callosum, basal ganglia, thalami and cerebellar measurements can be seen more frequently in nuclear magnetic resonance (NMR) in preterm infants.

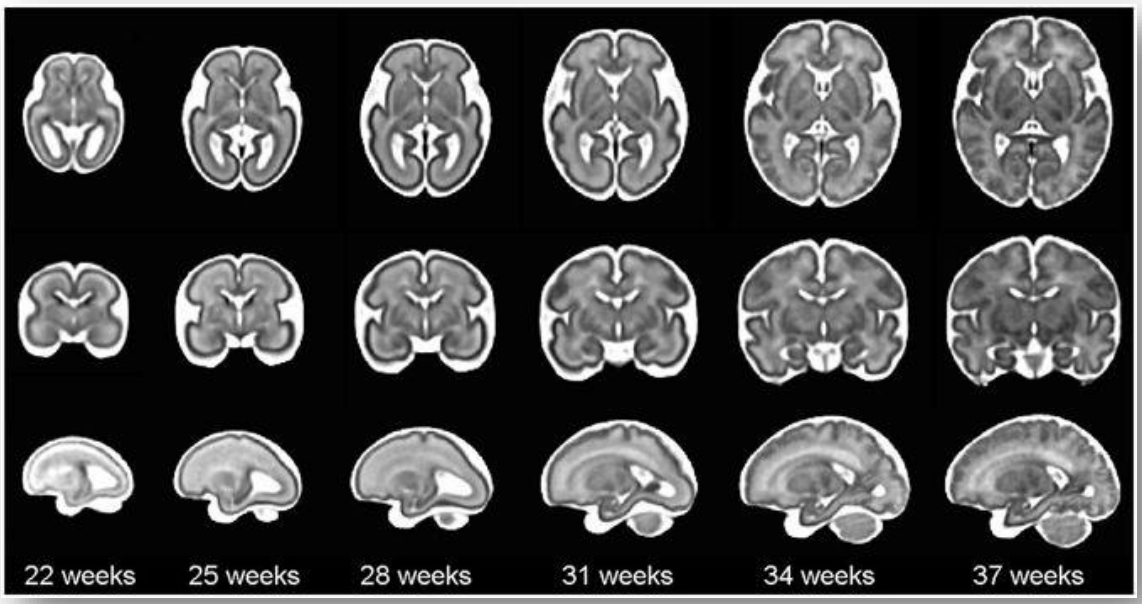


Figure 4. Spatiotemporal fetal brain MRI atlas (39)

Hypoxic-ischaemic encephalopathy is a complication of preterm birth, but the most common long-term disability is **cerebral palsy**. Other outcomes are **intracranial haemorrhage** and **periventricular leukomalacia**.

Epilepsy, **cognitive delay** and **developmental co-ordination disorders** are also more frequent in preterm infants. At preschool age, these children perform worse in neuropsychological domains, even in preterm children with no major disabilities (14).

Also, it has been observed more **behavioural disorders** in these infants and adolescents.

It is recommended follow-up until at least 18 months of age because of the risk of neurodevelopmental outcomes.

These outcomes may be prevented with the antenatal neuroprotection using Magnesium Sulphate ($MgSO_4$).

Digestive (4,6,7)

Necrotizing enterocolitis is seen more often in preterm infants. This pathophysiology is still unclear, but children who survive this illness are at higher risk of other long-term complications associated with preterm birth.

Other complication is the **neonatal jaundice**, but nowadays is less frequent. It may be produced by a higher bilirubin production and/or decreased bilirubin uptake and conjugation due to the immaturity of the liver and an increase of the enterohepatic circulation.

This hyperbirubinemia is more severe in preterm children than in term neonates. In addition, the response to treatment is lower. This situation increases the risk of **bilirubin encephalopathy**, which makes a neonatal screening recommended.

Feeding difficulties are an extra outcome related to suck-swallow incoordination and sphincter control mechanisms and immature peristalsis. Most infants routinely have nasogastric feeds, especially if they were born at 32-33 WK.

***Senses* disabilities** (4)

Children born before 28 weeks have more risk of **myopia** and **hypermetropia**.

There is also an increased tax of **hearing impaired**.

Growth and body composition changes (13)

Poor growth in early life is experimented for infants born preterm. However, there is a **catch-up growth** in the first 2-3 years of life until adolescence. This catch-up has been associated with an increase of adiposity and **obesity** rate in adulthood. Some studies have looked a **reduction of insulin sensitivity** in these adolescents.

Diagnosis and management (15)

The preterm birth threat is the clinic process that becomes a preterm delivery if there is not any treatment or the treatment is unsuccessful. The symptomatology is unspecific, it can be menstrual pain, continuous lumbar pain, regular and continuous uterine contractions and limited haemorrhage.

Traditionally, the diagnosis consists of (10,11,16):

- Cervical modifications: it means a cervical dilatation ≥2 cm or a blurring of ≥80%.
- Uterine contractions: at least 4 in 20-30 minutes or 8 in an hour. It may be with pain or not.

In addition, there are complementary markers such the cervical length (measured by transvaginal ultrasound), the fibronectin test (fFN >50ng/ml), the phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) and the placentary α-microglobuline 1 (PAMG-1). These elements have high negative predictive value.

According to the cervical length, <25mm until 32 WG and <15mm since 32 WG show high risk of preterm birth.

The Spanish Gynaecology and Obstetrics Society [15] recommends the following treatment guideline if there is a true preterm birth threat with cervical modification and uterine contractions previously defined and without any contraindication of tocolytic treatment or of gestation prolongation (it is also supported by more evidences [10,16,17])(*Annex 1*):

- **Tocolytic therapy** extends the pregnancy from 48 hours (h) until 7 days to complete the fetal pulmonary maturation and/or the neuro-prophylaxis. However, it is not demonstrated the reduction of preterm delivery.

  In Spain, different tocolytics are used: nifedipine, atosiban, indomethacin or ritodrine; but only ritodrine IV, atosiban IV and nifedipine OS have authorized indication (*Annex 2*). Last recommendations, published in 2015 by the WHO, mentioned nifedipine like first option [11].
- **Antenatal corticosterids** reduce the neonatal morbidity and mortality, the intraventricular haemorrhage and the distress respiratory syndrome. It may be used in women with 24-34^{6} WG with preterm birth theat. This is an exception the use of this treatment during 23rd WG.

  The treatment guideline is Betamethasone 12mg/24h for 2 days or Dexamethasone 6mg/12h for 2 days.
- **Magnesium sulphate** [18,19] decreases the nervous system damage in preterm birth.

  The dose and timing to administration is debated, but all studies used a dose between 4 and 6 mg with or without a maintenance infusion (1g/h, 2g/h or 2-3g/h). The University of Adelaide guideline wind up an IV 4g/20-30min loading dose followed by 1g/h maintenance dose to continue for 24h or until labor. The

American Congress of Obstetricians and Gynaecologists recommends the use of 6g loading dose and 2g/h maintenance infusion [18]. In Spain, the SEGO recommends the use of a 4g/30min initial dose followed by 1g/h maintenance dose in imminent preterm birth until 32 WG. However, in Hospital Universitari Josep Trueta, another guideline is followed using 4,5g/30min initial dose followed by 1g/h maintenance dose (*Annex 3*). The Australian guideline establishes that infusion should be started at least 4 hours before birth, but there may still be a benefit if the treatment is ended before when the delivery must not be delayed [20].

It must be controlled the cardiac frequency (CP), arterial pressure (AP), respiratory frequency (RF), oxygen saturation (Sat O_2) and patellar reflex when the treatment starts, 10 minutes after and when it ends. In addition, diuresis and the other parameters should be revised every 4 h. It is no needed to monitor the magnesemia if the renal function is correct.

The treatment should be suppressed if RF <12/min or RF >4/min respect the basal frequency, the diastolic arterial pressure decreases >15 mmHg respect the basal pressure, the patellar reflex disappears, or the diuresis becomes <100ml/4h.

The neuroprotection can be halted if the delivery does not start beyond 12 or 24 hours; if it seems that the labor stars again, the treatment will start anew, with a new initial dose if have passed more than 6 h.

The combined use of tocolytics and $MgSO_4$ is not contraindicated, but if nifedipine is used like tocolytic, women must be monitored every 2 hours [19].

This treatment is contraindicated in some situations:

- Fetal: prenatal decision of therapeutic effort limitation and lethal fetal malformations.

- Mother: severe cardiopathy, myasthenia gravis, respiratory insufficiency, renal failure or hydro-electrolytic alterations.

Some studies have showed that mother´s secondary outcomes are peripheral vasodilatation, nausea, vomiting, headache, palpitations, oliguria or renal failure, sensation of warmth and flushing... Respiratory depression and hypotension are the most severe risk. Also, $MgSO_4$ acts like neuromuscular blocker that causes abolition of reflexes and it can aggravate the muscular side-effects of other drugs (betamimetics, calcium-channel blockers and gentamicin). Besides, concentrations above recommended can produce cardiac and respiratory arrest leading to death. However, the studies are heterogeneous, so it is difficult to contrast the results [21,22]. It is true that this adverse outcomes start when the women are hypermagnesemic (>5mmol/L) during MgSO4 treatment [22], so it is important to control blood $MgSO_4$ blood levels to prevent it [18].

For the preterm, the high level of magnesium in blood can lead to poor sucking, hyporeflexia and respiratory depression that needs assisted ventilation, but this last one is uncommon. A 2016 revision affirms that there is not significant difference in the increasement of negative effects on neonates treated with $MgSO_4$, so this effects cannot be attributed to the $MgSO_4$ [21,22].

- **Prophylaxis** to **Group B Streptococcal infection** with **antibiotic** if the vaginal culture was positive or unknown.
- It is recommended to **reduce the physical** and **sexual activity** beyond the preterm birth threat. Also, it is suggested to **avoid the prolonged standing**.

Costs

The costs are high. It was estimated the societal cost of PTB in USA in 2005 was $26 billion. It included medical care costs up to 5 years for children, maternal delivery costs and the cost of early intervention [1,2].

Cerebral palsy

The first time that Cerebral palsy (CP) was defined by clinical description was in the 19th century; for over more than 100 years, there has been a debate about the term, and nowadays the international definition is "*group of permanent but not unchanging disorders of the development of movement, motor function and/or posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain*".

Disturbances of cognition, communication, hearing, vision, perception and behaviour are often accompanied by the motor disorders of cerebral palsy. Also, there are epilepsy and secondary musculoskeletal problems (23–26). During the first two years of life, cognitive impairment is the most common and severe disability, more than neuromotor, visual or other impairments (14).

CP can be filed in two ways (23):

- Motor type: spasticity, dyskinesia, ataxia and hypotonia.
- Body parts distribution (topography): monoplegia and hemiplegia (unilateral involvement), diplegia (bilateral involvement, with the lower limbs more affected than the upper limbs), triplegia (bilateral involvement, with only one upper limb affected) and quadriplegia (bilateral involvement with the upper limbs involved).

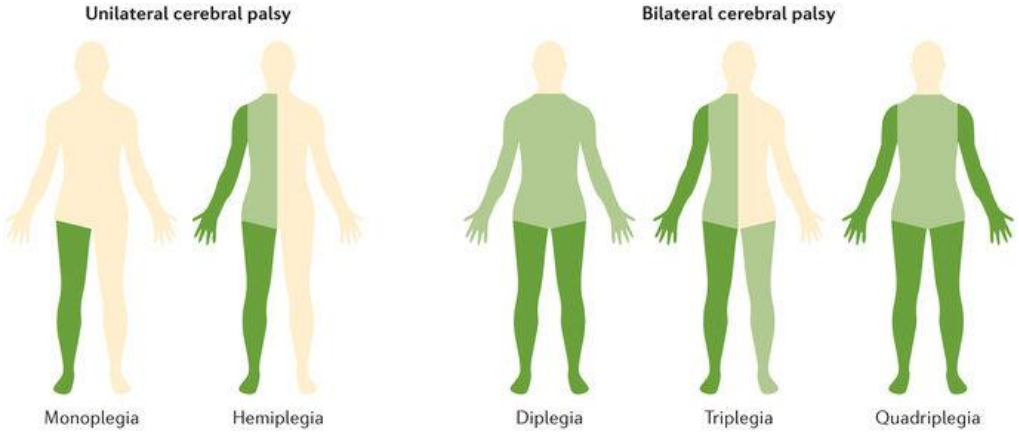


Figure 5. Topography distribution of cerebral palsy (24)

CP can be diagnosed around 18 months of age seeing changes in the brain NMR and ultrasonography, observing the child foot 5-20 minutes and assigning a qualitative rating of the quality of the children´s spontaneous movements. It is important that a low percentage of the infants with cerebral palsy will have normal NMR images. In addition, the gait analysis is used to support the clinical decision (24).

Recent evidence proposes that cerebral palsy may be detected in high-risk infants as early as three to four months corrected gestational age, using test and medical resonance imaging (23).

The functional performance in daily life for individuals with CP can be assessing by using the Gross Motor Function Classification System (GMFCS) (*Annex 4*), the Manual Ability Classification System (MACS) (*Annex 5*) and the Communication Function Classification System (CFCS) (*Annex 6*) (23,24).

The GMFCS is the internationally classification to the motor function in CP. It describes the gross movement ability of children five levels, and provides descriptions for each level across five age bands. The GMFCS in conjunction with the Gross Motor Function Measure are good predictors of motor function in cerebral palsy at 2 years old (23).

The MACS evaluates the ability of children with CP to handle objects, and the CFCS assists in appraising the communication capacity in real-life situations for these children (23).

Epidemiology

Worldwide, CP is the most common physical disability in the first life period. The prevalence is around 2 per 1.000 live births (23,24,26). In an incidence Swedish study was found that in 241 children with CP around a 2,5% was born at 32-38 WG (27).

Physiopathology and risk factors

Type and site of lesions is defined by the stage of brain maturation when the pathogenetic event occurs and it varies with the gestational age (24).

For the 94% of individuals with cerebral palsy, their **brain injury** is believed that it has occurred during the **antenatal** or the **neonatal** period of **infant development**, that is during pregnancy or in the first 28 days of live. For the remaining 6%, the brain injury must be acquired during a recognized event at least 28 days after birth and before the age of two to five years old (23).

The pathogenesis is still not well-known; the brain injury can be caused by multiple events like hypoxia-ischaemia, haemorrhage, infection, maldevelopment, autoimmunity or metabolic derangement that contribute to cellular dysfunction and death cell. These pathways are a collection of reactive oxygen species, the loose of excitatory amino acids, energy depletion and apoptosis. The final event is an inflammation that induces a microglial activation and demyelination (23,24).

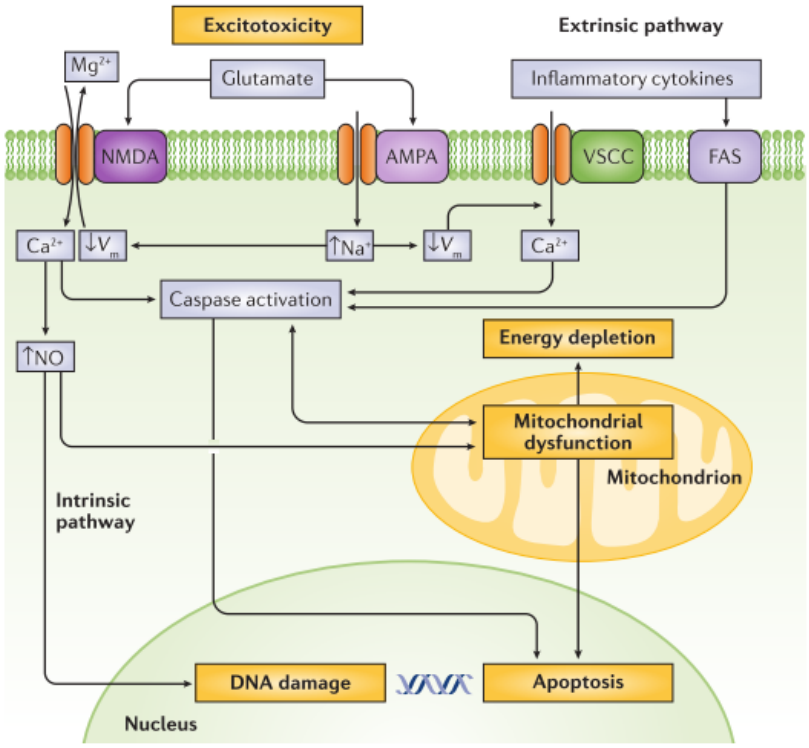


Figure 6. Cell death pathways (24)

It is known that mitochondrial failure causes ATP depletion which disrupts some processes resulting in cell death. One of the ATP-dependent process is the Na^{+}/K^{+}-ATPase whose disruption alters neuronal membrane potential, increasing a massive Ca^{+2} influx into the cytoplasm with glutamatergic N-methyl-d-aspartate (NMDA) receptor, leading to necrosis and apoptosis because of the oxidative stress (24).

Structural NMR and ultrasonography abnormalities like leukomalacia, hydrocephalus, congenital cerebral cyst, anomalies of the corpus callosum…, suggest the neural substrate of the illness. Periventricular leukomalacia is the characteristic lesion pattern showed in preterm birth with CP; in contrast, events happened in full-term infants affect the cerebral cortex and, basically, subcortical and periventricular white matter (14,24,25,28).

The **principal risk factor** for CP is **preterm birth**, which is related with the degree of prematurity, but other individual risk factors are (9,14,23,24,26):

- Prior to conception: maternal age, number of labors, the inter-pregnancy interval, a history of stillbirth, neonatal death, family history of cerebral palsy, genetic predispositions, low socioeconomic status, pre-existing maternal condition…
- During pregnancy: maternal disease like hypothyroidism, pregnancy complications, intrauterine infections or chorioamnionitis, intrauterine growth restriction, placenta abnormalities, maternal Rhesus alloimmunisation, congenital malformations such microcephaly, early-onset preeclampsia, multiple gestation, male gender …
- Around the part: acute intrapartum hypoxic event, encephalopathy of prematurity, stroke, seizures, hypoglycaemia, infection, errors of metabolism, chromosomal abnormalities, meconium passage, respiratory difficulties after birth, hyperbilirubinaemia…
- After the birth: infections, trauma, asphyxia, poisoning, severe dehydration…

The most important risk factors for CP in term children are low birthweight, congenital anomalies and birth asphyxia (25).

Secondary outcomes

CP is the leading cause of **physical disability** in children (23). Even though CP results from a primary lesion in the central nervous system, clinical symptoms take place in the peripheral neuromuscular system (muscular contractures, dystonia, spasticity…) (24).

Their life expectancy can be similar to the general population´s if a child reaches adolescence (23). Almost all children survive to adulthood (24).

Cases of antenatally or neonatally acquired CP have a strong association with more **motor** and **intellectual impairments** (language, memory, attention, visuomotor and visuoperceptual processing and executive function) (9,14,28); also with **early mortality** (23).

In addition, there are several **long-term sequelae**, including sight, speech, hearing and behavioural disorders, seizures and intellectual disabilities (23).

In general, the quality of life (QOL) of children and young people with cerebral palsy is like the other population, but adolescents and adults refer lower QOL in some domains, for example, because of the disadvantages in social life and employment. Also, parents of these children experience stress and depression (24).

It is important an early diagnosis of these disabilities because it can predict problems that will continue later in life or cause late development. In addition, the absence of intellectual disability does not involve the non-appearance of specific cognitive impairments. Neurodevelopmental follow-up during the first 2 years is essential in order to identify it (14,28).

Treatment and prevention (24,26)

Nowadays, there is **no cure** for CP, but the progress is becoming with the prevention and the improvement of the brain injury.

Some procedures may enable to reduce de incidence of CP. First, **secondary preventive strategies** may **reduce prematurity**: cervical cerclage or pesary, 17 α-hydroxyprogesterone caproate, tocolytic medication... Also, recent studies are showing that **antepartum magnesium** before 34 weeks of gestation can reduce around a 30% CP in premature infants. In addition, some trials have demonstrated that 72 hours of **brain or body cooling** in full-term infants with birth asphyxia decrease the number of children with cerebral palsy.

The neuroprotection´s mechanism of action of $MgSO_4$ is unclear. Such it is said before, the fetal and neonatal brain are more vulnerable to glutamate lesions and magnesium sulphate may block cerebral glutamate receptors (NMDA receptors), which acts as a calcium antagonist and reduces the calcium influx into the cells. It may prevent post-hypoxic brain damage in perinatal age, attenuates cytokines and has anti-apoptotic actions. In addition, it may increase cerebral blood flow and stabilise blood pressure during the first 2 days of preterm´s life. Magnesium with adenosine triphosphate is also needed to implement the activity of some body proteins, such as membrane transporters (20,21,29).

On the other hand, free-radical-scavening agents, like melatonin, may offset the reactive oxygen species production, which is marked early in brain maturation (24).

The CP **treatment** includes reducing and improving the complications with the use of physiotherapy, BoNT-A (treatment of spasticity), intrathecal baclofen therapy (to spasticity and dystonia), ankle foot orthoses, rehabilitation managing of non-motor

symptoms (epilepsy, nutrition, gastro oesophageal reflux, chronic lung disease, osteopenia, pain) …

There are some trials that check the use of stem cells in the treatment of cerebral palsy, but efficacy studies have not yet been published.

Costs

It has been estimated the lifetime costs of this illness, including social care, productivity and healthcare costs as 860.000€ for men and 800.000€ for women in Denmark in 2000, and 921.000$ for individuals in USA in 2003. In Australia, the financial cost was estimated around 1,47billions AUD in 2007 (23).

Justification

Worldwide, each year, 11% of all births are preterm births. These children have more risk of dying in their early life, and those who survive are most commonly affected by cerebral palsy compared with other population [29]. Around a 50-60% of CP cases occur in infants born at less than 34 WG [27], it may be related with the fact that the brain does not accomplish their full weight at that time.

As it has been said before, cerebral palsy is the most frequent reason of severe motor disability and neurological impairments, requiring more intensive postnatal medical care, expensive developmental services… with a considerable economic and social costs (800.000€ CP/year)[21] . These children can survive to more than 20 years, increasing expenses.

Nowadays, there is no cure for this illness, which makes very important to implant preventive interventions.

The hypothesis about the use of antenatal $MgSO_4$ to reduce the cerebral palsy started in the 90s, Nelson et all. published the first study of the possible effect of $MgSO_4$ like neuroprotector (OR 0,14; 95% CI: 0,05-0,51) [30]. In 2009, Cochrane published a review assessing this use for the first time (RR: 0,68; 95% CI: 0,54-0,87) [31].

The neuroprotection´s mechanism of action is unclear. However, as it is said before, the fetal and neonatal brain are more vulnerable to glutamate lesions. $MgSO_4$ may block cerebral glutamate receptors, prevent post-hypoxic brain damage in perinatal age, attenuate cytokines, increase cerebral blood flow and has anti-apoptotic actions [20,21,29].

Nowadays, there are enough evidences that the protective effect of $MgSO_4$ [(RR: 0,55; 95% CI 0,32-0,95)[26] - (RR: 0,63; 95% CI 0,44-0,90)[29]], without an statistical significant increase of the secondary outcomes [20,22,29]; however, it was unable to

concrete what is the gestational age when the benefit is higher or when the benefit disappears, if it is more effective by the reason of their risk of preterm birth, what is the best dose and whether maintenance treatment is necessary [18,29].

In the last publication about this topic in 2017, Crowther et all.[29] conclude their metanalysis saying that neuroprotection benefit is seen despite the range of preterm gestational ages, the reason for preterm labor and the different treatment guidelines. This review has some limitation such small sample sizes, low blinding and different objectives in each study.

According to the gestational age, a Cochrane revision affirms that the NNT increase with that; it is 46 at less than 30 WG and it increases until 56 before 32-34 WG [20,32,33], but only the antenatal neuroprotection on imminent threat of preterm birth at less than 30 or 32 WG is based in high evidence [19,21].

Actually, there are any study about the efficacy of antenatal neuroprotection between 32-34 WG. Some of the evidence reviewed talks about neuroprotection until 34 WG, but… Is this benefit real? Could it be because of birth <32 WG was included?

Actually, there are 2 ongoing placebo-controlled trials of neuroprotection with $MgSO_4$: one in women at risk of preterm labor from 24 to 32 WG [34] and other between 30 to <34 WG [21], that expected to be reported in 2018 and 2021 respectively.

The aim of this study is to show that the actual neuroprotection protocol for preterm birth under 31^6 weeks gestation using $MgSO_4$ is also effective for preterm birth between 32- 34 completed WG.

Hypothesis and objectives

Hypothesis

The antepartum administration of magnesium sulphate in spontaneous preterm birth between 32-34 completed weeks of gestation reduces the incidence of cerebral palsy, without induces secondary outcomes.

Objectives

Principal

The primary objective of this study is to prove the neuroprotective effect (survival free of cerebral palsy) with the antepartum administration of magnesium sulphate in women with risk of spontaneous preterm labor between 32-34 completed WG.

Secondary

The secondary objective is to demonstrate that $MgSO_4$ does not produce secondary outcomes in the mother or children.

Material and methods

Study design

This is a randomised, multicentred, double blind, placebo controlled trial designed to check the safety and efficacy of antenatal magnesium sulphate administration in a imminent threat of preterm labor between 32 and 34 completed weeks´ gestation for decrease the cerebral palsy incidence without induce secondary outcomes.

Conditions for stopping the trial

We consider that this trial must be ended if when the mid-term analysis will be performed:

- There are several adverse effects.
- There is a high rate of non-justified maternal death or significant difference between the two groups.
- There is a high rate of non-justified perinatal death or significant difference between the two groups.

Study population

Inclusion criteria

- Women that are at risk of preterm birth between 32 to 34 completed weeks´ gestation whose delivery is expected or planned within 24 hours.
- Women with more than 18 years old.
- Women who are able to cooperate and sign the informed written consent

Exclusion criteria

- Women who have received antenatal magnesium sulphate in the actual pregnancy because other reasons.
- Women who suffer myasthenia gravis, severe heart disease, respiratory failure, hydro-electrolytic alterations like hypokalemia or hypocalcemia or kidney failure.
- Hypersensibility to $MgSO_4$ or Atosiban.
- Obstetrical contraindications of tocolytic therapy.
- Vaginal haemorrhage with unknown origin.
- Placenta abruption.
- Major fetal malformations.
- Severe Intrauterine Growth Restriction.
- Fetal death.
- Placenta infection or chorioamnionitis.
- Previous decision of therapeutic effort limitation.

Sample size

With a risk alpha of 5%, statistical power of 80%, and the assumption of a RR = 0,63, the sample sizes are shown below:

Table 1. Sample size according to the precision

		FULL SAMPLE (EACH GROUP)	DROP-OUT (15%) (EACH GROUP)
PRECISION	10%	17561	20196
	20%	3915	4502
	30%	1532	1762
	40%	747	859
	50%	406	467

We have chosen a precision of 30%, that is to say n=1532 in each group, n=1762 assuming a drop-out of 15%. The whole sample is 3524 women. Whit this quantity and a 95% probability the RR will be between 0,44-0,82 [1].

Sample selection

A consecutive non-probabilistic sampling will be followed in women with imminent threat of preterm birth between 32 and 34 completed WG who accomplish the inclusion and not exclusion criteria in each assigned centre.

This study will be multicentre to achieve the whole sample and a high external validity in less time.

The centres that will be asked to participate in the trial are:

- Hospital de Sant Pau i Santa Tecla
- H. Universitari de Girona Dr. Josep Trueta
- H. Univ. Germans Trias i Pujol
- H. de Sant Joan de Déu
- H. Materno Infantil Vall d´Hebron
- H. Clinic i Provincial de Barna
- Hospital del Mar

To establish a good communication, we will assig the Hospital Universitari Dr. Josep Trueta like reference centre and a main investigator in each hospital participating.

[1] The sample size was computed using the software of Prof. Marc Saez, based in the package pwr, of the free statistical environment R (versión 3.4.2).

Estimated time of recruitment

In Catalonia, there are around 4000 labors between 32 and 36 WG each year. We select the main hospitals with preterm services there.

It is expected to get the whole sample of 3524 women with preterm labor between 32 and 34 completed WG in 3 years. However, it will be prolonged if it cannot achieve the predefined sample.

Enrolment and randomization procedures

Diagnose of spontaneous onset of labor

The women will come to the hospital with unspecific symptomatology, it can be menstrual pain, continuous lumbar pain, regular and continuous uterine contractions or limited haemorrhage.

The diagnosis consists in the next combination:

- Regular uterine contractions, at least 4 in 20-30 minutes or 8 in an hour.
- Cervical modifications: blurring of ≥80% or a cervical dilatation ≥2 cm.

It can be supplemented with the measurement of the cervical length with ultrasound (< 15mm), the fFN > 50ng/ml, the phIGFBP-1 ≥ 10µg/l and the PAMG-1 test positive.

Participation and Informed consent

It will be asked to participate in this trial all women with spontaneous onset labor between 32 and 34 completed weeks´ gestation who accomplish the inclusion and not the exclusion criteria.

They will obtain all the trial information in a written document concerning the use of tocolytic treatment to reduce the uterine dynamic and the use of antenatal neuroprotection with $MgSO_4$ and inviting them to join. (*Annex 7*)

Finally, they must sign the informed consent document with all the information necessary to take the decision to participate. (*Annex 8*)

Randomization

Statistical will prepare a table random numbers with 1762 women who receive $MgSO_4$ (A) and 1762 who receive placebo (B) in a 1:1 ratio

Degree of blinging

Statistical will be independent of the study and unrelated to the funder clinical trial.

Hospital pharmacy will prepare 3524 boxes, 1762 with the $MgSO_4$ treatment and 1762 with placebo, with the same appearance, size and colour. It will be numbered according the table with random numbers. The contents of each box, $MgSO_4$ treatment or placebo, only will be exposed after the statistical analysis.

The obstetrician who gives the treatment and the paediatrician who evaluates the children do not know what was the treatment received.

Moreover, the pregnancy will not know what treatment will going to receive.

Study treatment

Study treatment groups

Magnesium sulphate study group are treated with 4,5g $MgSO_4$ in 3x10ml phial[2] diluted in 100ml infusion bag containing isotonic sodium chloride solution 0,9% trough intravenous infusion line over 30 minutes like initial dose.

Then, the maintenance dose is 1g/h $MgSO_4$ iv. The preparation is 8x10ml $MgSO_4$ phial diluted in 420ml infusion bag containing isotonic sodium chloride solution 0,9% trough intravenous infusion line over 12 hours or until the labor.

Placebo study group are administered 3x10 ml isotonic sodium chloride solution 0,9% phial diluted in 100 ml infusion bag containing isotonic sodium chloride solution 0,9% trough intravenous infusion line over 30 min like initial dose.

Then, the maintenance dose is 8x10 ml isotonic sodium chloride solution 0,9% phial diluted in 420ml infusion bag containing isotonic sodium chloride solution 0,9% trough intravenous infusion line over 12 hours or until the labor.

According to the actual protocol (11,19), Atosiban will be administrated in **both groups** to delay the labor and to allow that $MgSO_4$ acts. The suggested guideline is 6,75 mg/1min IV like initial dose and then 300 µg/min over 3 hours or 100 µg/l over 45 hours in maintenance.

If the labor did not happen, both groups may be re-evaluated in 12 hours. The $MgSO_4$ / placebo maintenance dose will continue if the imminent preterm labor threat persists. If the treatment was completed and stopped and then there is a new imminent preterm labor threat, the treatment must be started again; but if it was ended less than 6 hours ago, it starts with the maintenance dose.

[2] $MgSO_4$ (Sulmetin®): 1 phial = 10ml = 1.5g

In addition, both groups will be monitored:

1. Before starting the treatment: AP, CF, RF and patellar reflex.
2. Just after starting the treatment: AP, CF, RF, patellar reflex and Sat O_2.
3. Every 4 hours during the maintenance dose: AP, CF, RF, patellar reflex, Sat O_2 and diuresis. $MgSO_4$´s blood levels are no needed in women with good renal function.

The **treatment** should be **suppressed** if RF >4 respirations per minute respect the basal frequency, RF <12/min, the diastolic arterial pressure decreases >15 mmHg respect the basal pressure, the patellar reflex disappears, or the diuresis becomes <100ml/4h.

Practical considerations

Each treatment will be in a closed box to preserve the triple blinding.

All material needed should be registered to calculate the study´s costs.

Study variables

Dependent variables

The main dependent variable is the *incidence of cerebral palsy* in children around 2 years. This variable will be estimated by measuring in a percentage the presence or absence of this diagnosis.

The clinical diagnosis will be get with an algorithm proposed by the National Institute of Child Health and Human Development (*Annex 9*) which allows evaluate the motor function according the GMFCS (*Annex 4*). Any motor disfunction can be progressive.

Despite the fact that there are different levels of CP in this algorithm, the results will be classified:

- Absence of CP: level 0.
- Presence of CP: level ≥ 1.

Other dependent variables are the *secondary outcomes related with the treatment* (35). It will be defined by the presence or absence of any of the following items´ group, stratifying by mother and preterm:

- Mother:
    - *Low risk outcomes:*
        - *Local pain* or *reactions* in the injection point.
        - *Peripheral vasodilatation* is the widening of blood vessels in peripheric areas. The symptomatology can be redness, rubor, warmth and tenderness.
        - *Nausea and vomiting.* Nausea refers to the sensation vaguely referred to the epigastrium and abdomen, with an urge to vomit.
        - *Headache* is a pain in the head.
        - *Palpitations* are the sensation of rapid, strong or irregular heartbeat.
        - *Sensation of warm.*
        - *Flushing* is the sudden redness of the skin.
        - *Hyporeflexia* is a condition in which the reflexes are weakened.
    - High risk outcomes:
        - *Muscular weakness.*
        - *Oliguria* is the low output of urine. It is clinically defined as an output less than 400 ml/day but more than 80 ml/day.

- *Renal failure* is the inability of the kidney to maintain their normal function wasting products and metabolites accumulate in the blood. It often results in systemic symptoms such oedema, hypertension, metabolic acidosis or uraemia.
- *Respiratory depression* is a rate below 12 breaths per minute or that fails to provide full ventilation and perfusion of the lungs.
- *Hypotension* means a blood pressure under 90/60 mmHg.
- *Cardiac arrest* is the sudden stoppage of effective heart action.
- *Respiratory arrest* is the sudden stoppage of effective breathing.
- *Death.*

– Preterm:

  - *Poor sucking* refers to the ineffective suction by the mouth.
  - *Hyporeflexia* is a condition in which the reflexes are weakened.
  - *Neuromuscular depression* in any body system.
  - *Respiratory depression.*
  - *Death.*

Independent variable

The independent variable will be the *$MgSO_4$ administration* in the experimental group or the *not administration* in control group.

Covariables

The covariables will be some of the risk factors to preterm birth that can variate the $MgSO_4$ effect.

- *Maternal age* at delivery measured in years. It will be subdivided in three groups:
  - ≤18 years.
  - 19 - 39 years.
  - ≥40 years.
- *Maternal body max index (BMI)* defined by $Weight\,(Kg)/Height^{2}(m)$ before the pregnancy. It can be approximated. It will be categorized:
  - <18,5.
  - 18,5 – 24,99.
  - ≥ 25.
- *Parity* is the number of previous labors. It will be categorized:
  - 0 previous labors.
  - ≥ 1 previous labors.
- Presence of *Maternal disease* during pregnancy, like hypertension or diabetes.
- *Maternal smoking* during pregnancy.
- *Single or Multiple pregnancy.*
- Children *gender*: male or female.

Measure instruments

The different measure instruments needed to examine some of the variables are 24h urine collection container to measure the mother´s diuresis, sphygmomanometers to measure the arterial pressure, thermometers to measure the temperature and reflex hammers to evaluate the reflexes.

Adverse events

All hostile experience, which is considered or not related to the drug used in research, that happens to a patient during the clinical trial will be considered an adverse event. Any of the following will be considered like serious adverse events: severe permanent disability, imminent threat to life, death or other adverse event that researchers consider important.

During the study, we will make every effort to be alert to possible events. If one of these occurs, the first solicitude will be patient safety and an optimal treatment will be provided if it is required. All these adverse events will be recorded in the safety data collection.

Every information relating to the safety of drugs in the clinical trial will be notified to the Autonomous Community and hospital ethics committee and to the “Asociación Española de Medicamentos y Produtos Sanitarios” (AEMPS).

Statistical analysis

Descriptive analysis

In the main objective, the response variable will be descripted using the proportion of cerebral palsy in 2 years old children whose mothers were treated with $MgSO_4$ or placebo. This **contingency table** will be stratified attending the covariables previously cited (*Table 2*). If the variable is quantitative, it will be categorized as explained above.

According to the secondary objective, it will be descripted with the presence of any high/low risk secondary outcomes in the mother and/or any secondary outcomes in children in each group, intervention or control group respectively (*Table 3*).

Bivariant inference

The proportions will be compared using **Pearson´s Chi^2 test**. These proportions will be expressed by absolute numbers and percentages. In addition, it will be also stratified according the covariables.

Multivariant inference

A **logistic regression** will be used to evaluate the intervention success controlled by the covariables.

Moreover, it will be useful to estimate the probability of the intervention success, conditioned to the covariables, to assess the cost-effectiveness of this intervention.

Table 2. Stratified contingency table of cerebral palsy´s proportions

			TREATMENT	
			$MgSO_4$	Placebo
CEREBRAL PALSY	**Yes**	Maternal age ≤18 y		
		Maternal age 19–39 y		
		Maternal age ≥40 y		
		Parity 0		
		Parity ≥ 1		
		Maternal disease Yes		
		Maternal disease No		
		Maternal Smoking Yes		
		Maternal Smoking No		
		Single or multiple pregnancy Single		
		Single or multiple pregnancy Multiple		
		Children gender Male		
		Children gender Female		
		BMI <18,5		
		BMI 18,5–24,99		
		BMI ≥ 25		
		Total		
	No	Maternal age ≤18 y		
		Maternal age 19–39 y		
		Maternal age ≥40 y		
		Parity 0		
		Parity ≥ 1		
		Maternal disease Yes		
		Maternal disease No		
		Maternal Smoking Yes		
		Maternal Smoking No		
		Single or multiple pregnancy Single		
		Single or multiple pregnancy Multiple		
		Children gender Male		
		Children gender Female		
		BMI <18,5		
		BMI 18,5–24,99		
		BMI ≥ 25		
		Total		

Table 3. Secondary outcomes .

				TREATMENT	
				$MgSO_4$	Placebo
SECONDARY OUTCOMES	Mother	Low risk	Yes		
			No		
		High risk	Yes		
			No		
		Total	Yes		
			No		
	Preterm		Yes		
			No		

Limitations, opportunities and impact of the study

This proposed study has some **limitations**.

These one includes the drop out of sample in the data analysis because of different reasons. The drop out may be due to the main dependent variable it will be valuated after 2 years. In this time, some people can change their city, or they can have other reasons which difficult this following. The sample size has been estimated keeping in mind this fact, assuming a drop out of a 15% of the sample.

Other limitation is the Atosiban´s price which is 60€ per women. The choice of this tocolityc is due to that it has less contraindications than others like Nifedipino, Ritodine or Indometacina. Indometacina should be the first option, as it is said before, but it is not recommended after 32 WG and this use is not approved in Spain. However, despite this price, Atosiban is used in the usual management of preterm birth without neuroprotection.

The study´s budget is also incremented because of the insurance policy. Pregnant women are the sample who is going to receive the treatment, so the insurance increases their price. It is compulsory an insurance policy because of the law, so this limit can not be avoided.

Limitation due to the study will be solved with the randomization and the double blinding of the design.

On the other hand, the main and most important **opportunity** of these trial is the possible prevention of cerebral palsy, an illness without cure.

Other advantages of this study are that it is a multicentre trial and it is possible to generalize the findings. Moreover, the research´s group will be trained in the same way, which reduces the information bias.

This trial can have an important **heath impact** because studies about the efficacy on this group of women/children have not been published yet; so, if the hypothesis is confirmed, the treatment could be extended until 34^6 without doubts.

In addition, hearing in mind that around 50% of CP happens in PTB until 34WG, $MgSO_4$ is a relatively inexpensive treatment (3€/patient) and CP results in a high cost (800.000€ CP/year) … if the hypothesis was confirmed, neuroprotection until 34 completed WG should be a cost-effective measure.

Ethic and law

This research has been proposed according the *Basic Ethical Principles* (respect for the patient autonomy, beneficence and justice) and the *Real Decreto 1/2015, 24 de Julio*.

The protocol will be sent to the *Agencia Española de Medicamentos y Productos Sanitarios (AEMPS*), to the *Comité de ética de la Investigación con medicamentos (CEIm*) and to the *Clinical Research Ethics Committee (CEIC)* of the Hospital Josep Trueta to review that the protocol design respects *Nuremberg Code*, the *Belmont Report*, the *Convenio de Oviedo*, the *Declaration of Helsinki* and the *Real Decreto 1090/2015*.

All the research team agrees to all the data and the results will be published with transparency and clarity. They must not exclude unfavourable events or data.

This trial is registered in the *International Standard Randomised Controlled Trial Number* registry (https://www.isrctn.com) in the *EudraCT* (https://eudract.ema.europa.eu/) and sent to *ClinicalTrials.gov.*

Following the *"Ley Orgánica 15/1999, 13 de Diciembre, Protección de Datos de Carácter Personal"*, all the patient information will be confidential and it their anonymity will be guaranteed.

Finally, it is necessary that all patients are informed about the protocol and that they must sign the informed consent to be part of this research.

Work plan

This clinical trial will be completed after 6 years and a half *(Annex 11*). It is organized in different steps to get the best results. These phases will be:

1. **Design and approbation of the protocol** (9 months, October 2017-June 2018).
    a. *Approach and drafting of the protocol*. To get this step, it was reviewed and analysed different bibliography about this topic.
    b. *Presentation and approbation by the hospitals proposed*. With the target of get the whole sample in less time, is needed a multicentred design. This project will be put forward in the hospitals to show the importance of this fact. It will encourage these hospitals to approbate and participate in the trial.
    c. *Protocol´s approbation by the AEMPS, the CEIm and by the CEIC*.
2. **Organizational step** (3 months, July-September 2018).
    In this time, it will be established the coordination protocol of all the researchers. In addition, all the staff involved will be trained to carry out the protocol in the same way.
3. **Sample collection** (36 months, October 2018-2021).
    Sample collection will be get according the appearance sequence and it will be randomized into the groups. This period will be 3 years to get the whole sample, but it will be prolonged if it cannot achieve the predefined sample.
4. **Intervention** (36 months, October 2018-2021).
    Drug or placebo administration.
5. **Follow-up visits and data collection** (60 months, October 2018-2023).

a. *The first data collection appertains with the secondary outcomes.* It will be in the immediate period of the drug administration or hospitalization.
b. *The ultimate data collection is due to the cerebral palsy diagnosis.* It will be when children will be around 2 years old.

All the information will be registered every 6 months.

6. **Statistical analysis**
    a. *A first statistical analysis* will happen after one year to start the drug/placebo administration. The goal of this analysis is to detect possible severe adverse effects which can stop the trial. (January-March 2020).
    b. *The ultimate statistical analysis* will happen when the last children whose mother was treated will be or not diagnosed of CP. (January-March 2024).
7. **Results** (April-June 2024).
    a. *Drafting the final results and publishing that* in a journal article.
    b. *Dissemination of the results* in national and international congresses.

Budget

Table 4. Trial´s budget

		Nº	COST (€)	TOTAL (€)
MATERIAL	Atosiban 6.75 mg/ 5 ml bolus	3.524	14,65	51.626,60
	Atosiban 37,5 mg/ 5 ml perfusion	3.524	45,68	160.976,32
	Sulmetin® 1 phial = 10ml = 1.5g	19.382	0,30	5.814,60
	Isotonic sodium chloride solution 0,9%	3.524	0,15	528,60
	Intravenous infusion set	3.524	0,05	176,20
STAFF	Statistic	100h	35€/h	3.500
FEES	AEMPS	1	113,42	113,42
INSURANCE	Insurance policy	1	100.000	100.000
PRESENTATION	Publication cost	1	2.000	2.000
	National Obstetrics Congress	1	1.000	1.000
	International Obstetric Congress	1	3.000	3.000
TOTAL				**328.735,77 €**

Conflict of interest

The authors declare no conflict of interest

References

1. Frey HA, Klebanoff MA. The epidemiology, etiology, and costs of preterm birth. Semin Fetal Neonatal Med [Internet]. 2016 [cited 2017 Nov 24];21(2):68–73. Available from:

   http://dx.doi.org/10.1016/j.siny.2015.12.011

2. Blencowe H, Lee ACC, Cousens S, Bahalim A, Narwal R, Zhong N, et al. Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels for 2010. Pediatr Res. 2013;74(SUPPL. 1):17–34.

3. Nacimientos prematuros [Internet]. WHO. Geneve: World Health Organization; 2017 [cited 2017 Nov 24]. p. 6. Available from:

   http://www.who.int/mediacentre/factsheets/fs363/es/#.Whh7BryyjiM.mendeley

4. Platt MJ. Outcomes in preterm infants. Public Health [Internet]. 2014 [cited 2017 Nov 27];128(5):399–403. Available from:

   http://dx.doi.org/10.1016/j.puhe.2014.03.010

5. Rellan Rodríguez S, Garcia De Ribera C, Aragón García M. El recién nacido prematuro. In: Protocolos Diagnóstico Terapéuticos de la AEP: Neonatología [Internet]. Madrid: Asociación Española de Pediatría; 2008 [cited 2017 Dec 1]. p. 68–77. Available from:

   http://www.aeped.es/sites/default/files/documentos/8_1.pdf

6. Girija Natarajan M, Seetha Shankaran M. Short- and Long-Term Outcomes of Moderate and Late Preterm Infants. Am J Perinatol. 2016;33(3):305–17.

7. Boyle JD, Boyle EM. Born just a few weeks early: does it matter? Arch Dis Child - Fetal Neonatal Ed [Internet]. 2013 [cited 2017 Nov 22];98(1):85–8. Available from:

   http://fn.bmj.com/lookup/doi/10.1136/archdischild-2011-300535

8. INE. Nacimientos por tipo de parto, tiempo de gestación y grupo de edad de la madre [Internet]. Madrid: Instituto Nacional de Estadística; 2015 [cited 2017 Dec 5]. Available from:

   http://www.ine.es/jaxi/Datos.htm?path=/t20/e301/nacim/a2015/l0/&file=01011.px

9. Halimi Asl AA, Safari S, Parvareshi Hamrah M. Epidemiology and Related Risk Factors of Preterm Labor as an obstetrics emergency. Emerg (Tehran, Iran) [Internet]. 2017 [cited 2017 Nov 27];5(1):e3. Available from:

   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5325899/pdf/emerg-5-e3.pdf

10. Tenorio NS, Seguro CC De, Costarricense C, Social DS, Costarricense C, Social DS.

TEMA 2-2016 : Amenaza de Parto Pretérmino ISSN. Rev Clínica la Esc Med UCR - HSJD. 2016;1(I):75–80.

11. Salazar L, Guirior C De, Alcalde P, Bermejo R, Nieto C. Alternativas terapéuticas para la tocólisis en el manejo de la amenaza de parto pretérmino. Rev Of la Soc Española Ginecol y Obstet. 2016;59(2):112–8.

12. Nieuwenhuijsen MJ, Dadvand P, Grellier J, Martinez D, Vrijheid M. Environmental risk factors of pregnancy outcomes: a summary of recent meta-analyses of epidemiological studies. Environ Heal [Internet]. 2013 [cited 2017 Nov 20];12(1):6. Available from:

http://ehjournal.biomedcentral.com/articles/10.1186/1476-069X-12-6

13. Roggero P, Giannì ML, Garbarino F, Mosca F. European Journal of Internal Medicine Consequences of prematurity on adult morbidities. Eur J Intern Med [Internet]. 2013 [cited 2017 Nov 30];24(7):624–6. Available from:

http://dx.doi.org/10.1016/j.ejim.2013.01.011

14. Pugliese M, Rossi C, Guidotti I, Gallo C, Della Casa E, Bertoncelli N, et al. Preterm birth and developmental problems in infancy and preschool age Part II: cognitive, neuropsychological and behavioural outcomes. J Matern Neonatal Med [Internet]. 2013 [cited 2017 Nov 20];26(16):1653–7. Available from:

http://www.tandfonline.com/doi/full/10.3109/14767058.2013.794205

15. SEGO. Amenaza de Parto Pretérmino. Madrid: Sociedad Española de Ginecología y Obstetricia; 2014. 1-21 p.

16. Cobo T, Ferrero S, Palacio M. Protocolo : Amenaza de Parto Pretérmino. Barcelona: Hospital Clinic; 2016. 1-12 p.

17. Stock SJ, Morris RK, Chandiramani M, Shennan AH, Norman JE. Variation in management of women with threatened preterm labour. Arch Dis Child Fetal Neonatal Ed [Internet]. 2015 [cited 2017 Dec 11];100(3):2013–4. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/25526911

18. SEGO. Sulfato de magnesio para neuroprotección fetal: revisión de la literatura [Internet]. Madrid: Sociedad Española de Ginecología y Obstetricia; 2014. 1-6 p. Available from:

http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S0034-74342014000300003&lang=es

19. Hernández S, Palacio M. Protocolo: Neuroprotección fetal con sulfato de magnesio en mujeres con riesgo de parto prematuro. Barcelona: Hospital Clinic; 2014. 1-4 p.

20. Magnesium Sulphate to Prevent Cerebral Palsy following Preterm Birth. Scientific Impact Paper. London: Royal College of Obstetrician & Gynaecologist; 2011.

21. Crowther CA, Middleton PF, Wilkinson D, Ashwood P, Haslam R. Magnesium sulphate at 30 to 34 weeks' gestational age: neuroprotection trial (MAGENTA) - study protocol. BMC Pregnancy Childbirth [Internet]. 2013 [cited 2017 Dec 1];13(1):91. Available from:

http://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/1471-2393-13-91

22. Zeng X, Xue Y, Tian Q, Sun R, An R. Effects and Safety of Magnesium Sulfate on Neuroprotection. Medicine (Baltimore) [Internet]. 2016;95(1):1–12. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00005792-201601050-00034

23. Shepherd E, Salam RA, Middleton P, Makrides M, Mcintyre S, Badawi N, et al. Antenatal and intrapartum interventions for preventing cerebral palsy: An overview of Cochrane systematic reviews. Cochrane Database Syst Rev [Internet]. 2017 [cited 2017 Nov 28];2017(8). Available from:

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012077.pub2/pdf

24. Graham HK, Rosenbaum P, Paneth N, Dan B, Lin JP, Damiano DiL, et al. Cerebral palsy. Nat Rev Dis Prim. 2016;2.

25. Jystad KP, Strand KM, Bjellmo S, Lydersen S, Klungsoyr K, Stoknes M, et al. Congenital anomalies and the severity of impairments for cerebral palsy. Dev Med Child Neurol. 2017;(2):1–8.

26. Stavsky M, Mor O, Mastrolia SA, Greenbaum S, Than NG, Erez O. Cerebral Palsy—Trends in Epidemiology and Recent Development in Prenatal Mechanisms of Disease, Treatment, and Prevention. Front Pediatr [Internet]. 2017;5(February):1–10. Available from:

http://journal.frontiersin.org/article/10.3389/fped.2017.00021/full

27. Rufo-Capos M, Rufo-Muños M. Parálisis cerebral infantil. An Peditría Contin. 2005;3:73–8.

28. Hielkema T, Hadders-Algra M. Motor and cognitive outcome after specific early lesions of the brain - a systematic review. Dev Med Child Neurol. 2016;58:46–52.

29. Crowther CA, Middleton PF, Voysey M, Askie L, Duley L, Pryde PG, et al. Assessing the neuroprotective benefits for babies of antenatal magnesium sulphate: An individual participant data meta-analysis. PLoS Med. 2017;14(10):1–24.

30. Nelson KB, Grether JK. Can Magnesium Sulfate Reduce the Risk of Cerebral Palsy in Very Low Birthweight Infants? Pediatrics [Internet]. 1995 [cited 2017 Dec 7];95(2). Available from:

http://pediatrics.aappublications.org/content/95/2/263

31. Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. In: Doyle LW, editor. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2009 [cited 2017 Dec 10]. Available from:

http://doi.wiley.com/10.1002/14651858.CD004661.pub3

32. Costantine M, Weiner S. Effects of Antenatal Exposure to Magnesium Sulfate on Neuroprotection and Mortality in Preterm Infants: A Meta-Analysis. Obs Gynecol. 2009;114:254–364.

33. Bowes Jr W, Heyborne K. The use of antenatal magnesium sulfate for neuroprotection for infants born prematurely. F1000 Med Rep [Internet]. 2010;(November):4–7. Available from:

http://www.f1000.com/reports/m/2/78

34. Wolf HT, Hegaard HK, Pinborg AB, Huusom LD. Does Antenatal Administration of Magnesium Sulphate Prevent Cerebral Palsy and Mortality in Preterm Infants? A Study Protocol. AIMS Public Heal. 2015;2(4):727–9.

35. AEMPS. Ficha técnica: Sulmetin simple 150 mg/dl [Internet]. Madrid: Asociación Española de Medicamentos y Productos Sanitarios; 2017 [cited 2017 Dec 18]. p. 1–8. Available from:

https://www.aemps.gob.es/cima/pdfs/es/ft/23622/23622_ft.pdf

36. SENeo. 9.3. Desarrollo motor. In: Protocolo de seguimiento para el recién nacido menos de 1500g o menor de 32 semanas de gestación. Madrid: Sociedad Española de Neonatología; 2017. p. 24–7.

37. Arner M, Eliasson AC, Rösblad B, Rosenbaum P, Krumlinde S, Becking E, et al. Manual ability classification system for children with cerebral palsy [Internet]. Manual Ability Classification System for children with cerebral palsy. Sweden; 2005 [cited 2017 Dec 10]. p. 317–9. Available from:

http://www.macs.nu/files/MACS_English_2010.pdf

38. Hidecker MJC, Paneth N, Rosenbaum PL, Kent RD, Lillie J, Eulenberg JB, et al. Communication Function Classification System for individuals with cerebral palsy [Internet]. Vol. 53, Developmental Medicine and Child Neurology. Wyoming: The University of Wyoming; 2011 [cited 2017 Dec 12]. p. 704–10. Available from:

http://cfcs.us/?page_id=8

39. Gholipour A, Rollins CK, Velasco-Annis C, Ouaalam A, Akhondi-Asl A, Afacan O, et al. A normative spatiotemporal MRI atlas of the fetal brain for automatic segmentation and analysis of early brain growth. Sci Rep [Internet]. 2017 [cited 2018 Jan 15];7(1):1–13. Available from:

http://dx.doi.org/10.1038/s41598-017-00525-w

Annexes

Annex 1: Management of preterm birth

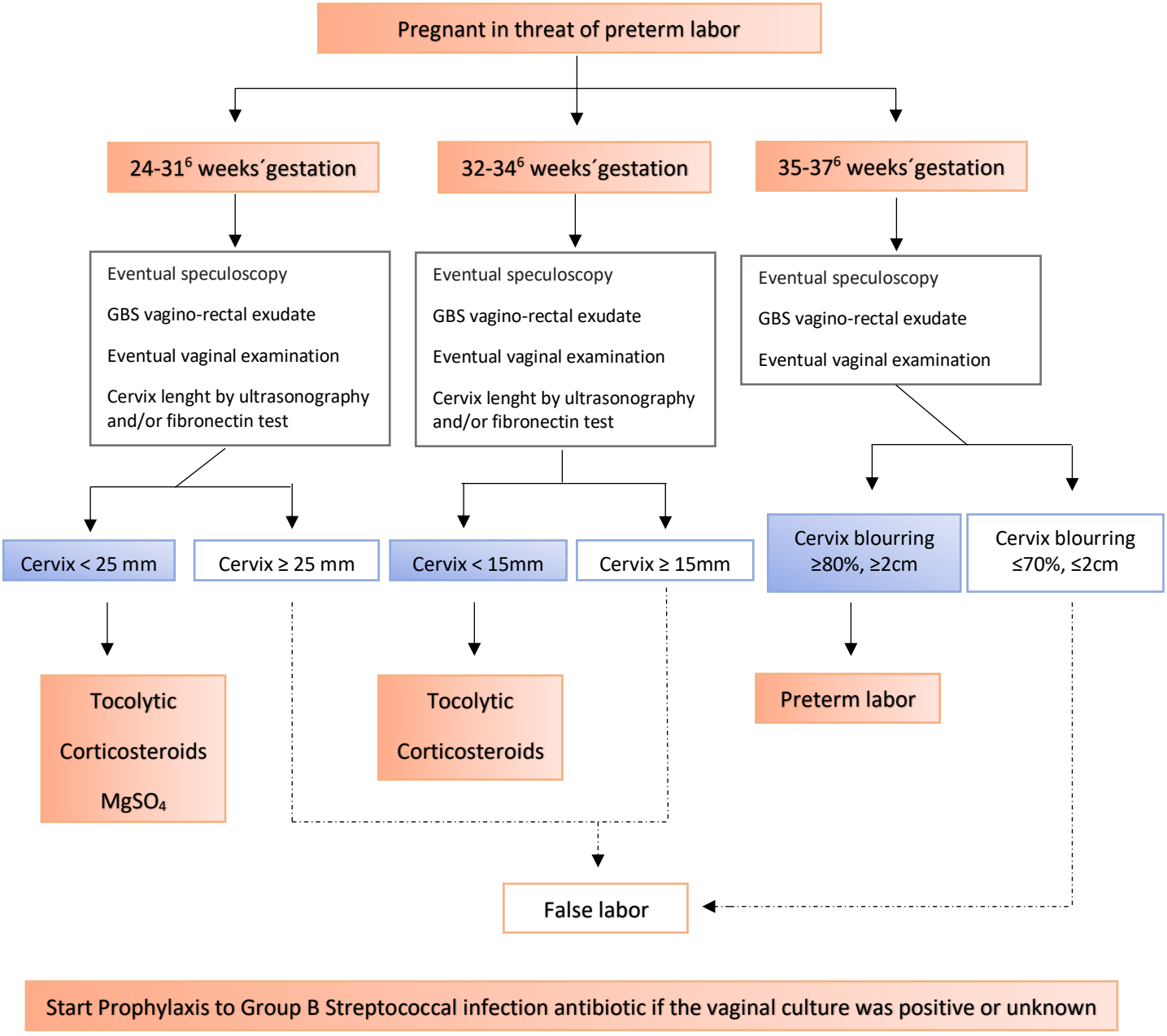


Figure 7. Management of preterm birth (Adapted from Figura 1. Actuación ante una gestante con sospecha de APP. SEGO. Amenaza de Parto Pretérmino (15)*)*

Annex 2: Tocolityc therapy (15)

Fármaco	Pauta sugerida	Efectos secundarios y riesgos potenciales	Contraindicaciones	Precauciones	Comentarios
Atosiban (intravenoso) Antagonista de la oxitocina útero específica	Dosis de ataque: Bolo 6,75 mg. IV a pasar en 1 minuto. Dosis de mantenimiento: 300 µg/min, 3 horas. 100 µg/min, 45 horas.	Náuseas, vómitos. Cefaleas, mareo, insomnio. Reacción en lugar de inyección. Pirexia. Hiperglucemia. Taquicardia, hipotensión, rubor. Prurito, erupción. Atonía y hemorragia uterina. Reacción alérgica.	Hipersensibilidad al producto. Situaciones que indican finalizar embarazo, tales como: muerte fetal, eclampsia, etc.	Monitorización de las contracciones uterinas y de la FCF. Si persisten contracciones durante el tratamiento, considerar un tratamiento alternativo. Precaución en pacientes con insuficiencia hepática, en casos de embarazos múltiples y administración concomitante con otros tocolíticos.	Eficacia comparable al nifedipino y al ritodrine Aprobado en España para el tratamiento de la APP.
Nifedipino (solución oral) Bloqueante de los canales de calcio	Dosis inicial de 2 ml (10 mg) vo, seguido de 1,5 ml (7,5 mg)/15 min si persiste la dinámica, hasta un máximo de 40 mg la primera hora. Dosis: 3 ml (15 mg)/6-8 h	Cefalea, mareo, vértigo, migraña, temblor. Parestesias, disestesias Edema periférico, edema alérgico, prurito, exantema, eritema. Alteración del sueño, nerviosismo, ansiedad. Taquicardia, palpitaciones, angina de pecho. Hipotensión, síncope Epistaxis, congestión nasal, dolor torácico, disnea, edema pulmonar.	Situaciones que indican finalizar embarazo, tales como: muerte fetal, eclampsia, etc. Enfermedad cardiaca materna, hipotensión severa <90 mmHg, hipertensión, insuficiencia cardiaca y estenosis aórtica. Hipertiroidismo.	Monitorización frecuencia cardiaca y tensión arterial materna. Registro cardiotocográfico externo una hora después de la primera dosis, y mantener o repetir según la evolución de la dinámica uterina a las 24 horas. Precaución en embarazos múltiples y en la administración concomitante con: fármacos vasoactivos como ritodrine, sulfato de magnesio o atosiban; o con rifampicina.	Eficacia comparable al atosiban y al ritodrine. Aprobado en España para el tratamiento de la APP.
Ritodrine (intravenoso) Simpaticomimético agonista de los receptores β-2	Inicial: 50-100 µg/min Aumento: 50 µg/min/ 10 min Máxima: 350 µg/min (iv)	Edema pulmonar Hipopotasemia, hiperglucemia. Taquicardia, palpitaciones, arritmias. Hipotensión.	Situaciones que indican finalizar embarazo, tales como: muerte fetal, eclampsia, etc. Hipertensión pulmonar y trastornos cardiacos como cardiopatía isquémica, miocardiopatía obstructiva, o cualquier tipo de obstrucción del tracto de salida del ventrículo izquierdo (estenosis)	Supervisar la función cardiorespiratoria y monitorización electrocardiográfica. Monitorizar tensión arterial, frecuencia cardiaca, balance hídrico y electrolitos (K), glucosa y lactato en diabéticas. Precaución en embarazos múltiples y en la administración concomitante con otros tocolíticos.	Aprobado en España su presentación inyectable para el tratamiento de la APP. No utilizar durante más de 48 horas, ni por debajo de las 22 semanas de gestación. Monitorizar los parámetros cardiovasculares y bioquímicos.
Indometacina (comprimidos orales) Inhibidor de la COX	Inicial: 50-100 mg oral o rectal, seguido de 25-50 mg cada 6 horas oral o 100 mg/12 h rectal	Náuseas, pirosis. Fetales: oligoamnios, cierre precoz del ductus arterioso, hipertensión pulmonar, hemorragia intraventricular, NEC.	Disfunción hepática o renal, úlcus gástrico, asma inducida por fármacos, alteraciones de la coagulación o trombopenia.	ILA diario si tratamiento de >48 horas de duración (suspender si ILA<5) IP del ductus (suspender si <2cm/seg)	Eficacia demostrada en estudios control, *randomizados* y prospectivos. No usar en ≥32 semanas No está aprobado en España su uso como tocolítico.

Annex 3: Actual neuroprotection´s protocol (19)

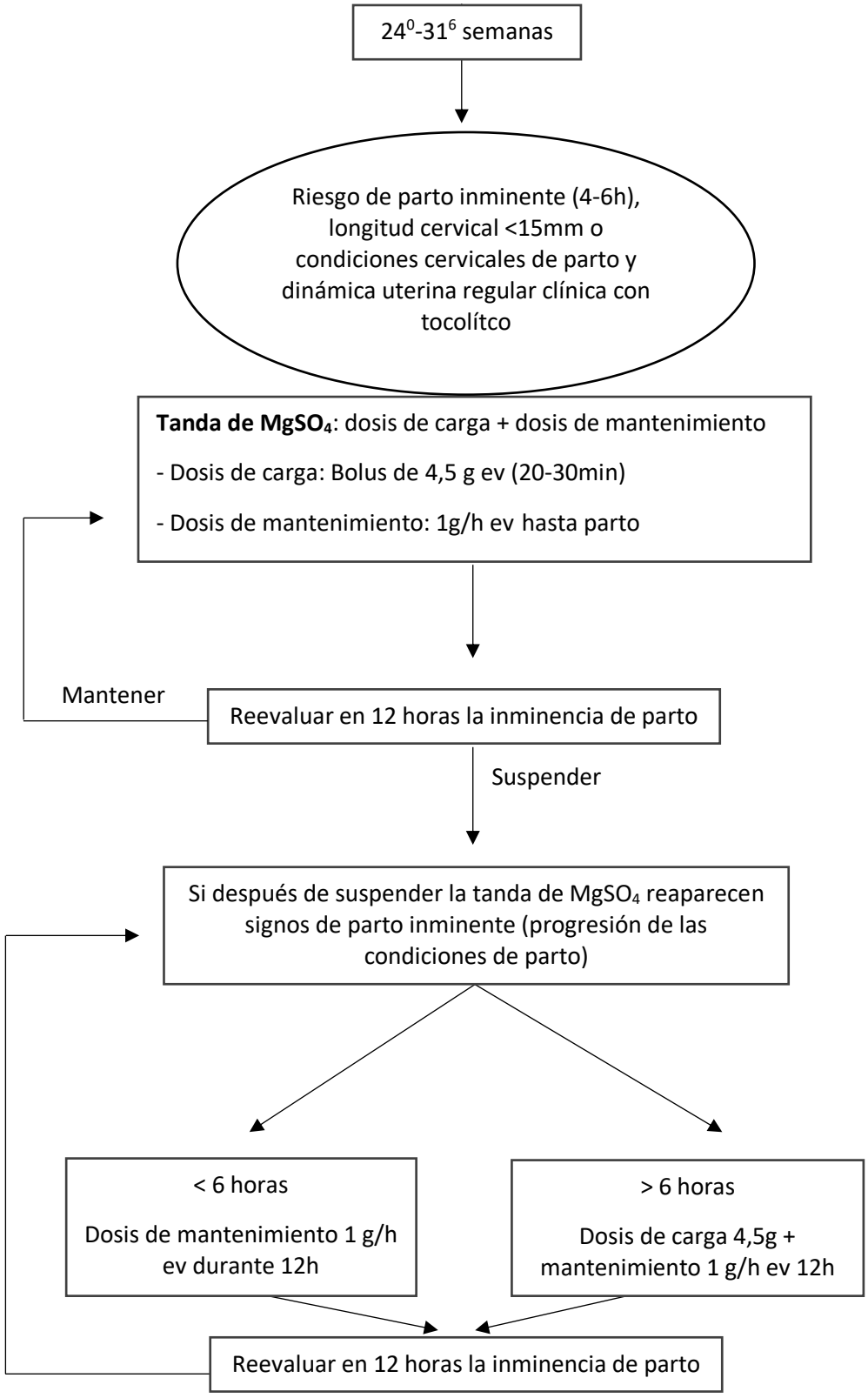


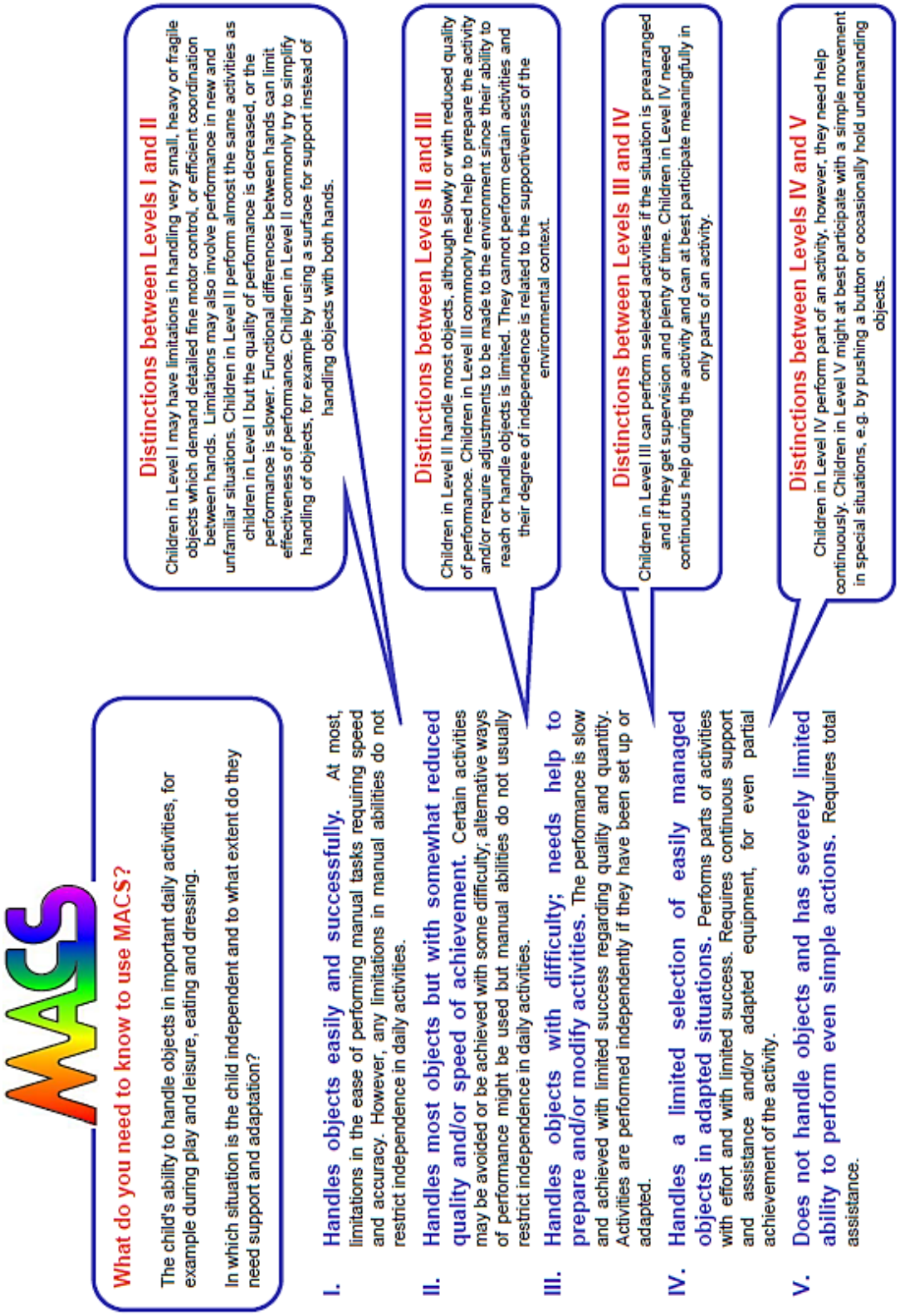
Figure 8. Neuroprotection´s protocol

Annex 4: GMFCS (36)

GMFCS para niños de 2 a 4 años	
Nivel 1	Los niños se mantienen sentados en el suelo con las dos manos libres para manipular objetos. Los niños se pueden sentar, mover del lugar de asiento y ponerse de pie sin ayuda del adulto. Para desplazarse prefieren caminar y no necesitan ayudas técnicas
Nivel 2	Los niños se mantienen sentados en el suelo, pero pueden desequilibrarse cuando manipulan objetos con las dos manos. Se sientan y se ponen de pie sobre una superficie estable agarrándose a algo sin la ayuda de un adulto. Gatean con manos y rodillas con un patrón recíproco, pasan de un mueble a otro agarrándose y para desplazarse prefieren caminar utilizando una ayuda técnica
Nivel 3	Los niños se mantienen sentados, adoptando frecuentemente una posición en "W" (sentados con rotación interna de las caderas y las rodillas flexionadas) y pueden necesitar ayuda de un adulto para sentarse. Para desplazarse de forma autónoma, preferentemente reptan o gatean sobre manos y rodillas (con frecuencia, sin movimientos recíprocos de las piernas). Los niños pueden agarrarse a algo para ponerse de pie sobre una superficie estable y recorrer distancias cortas. Pueden caminar pequeñas distancias en espacios cerrados con una ayuda técnica manual (andadores) y la asistencia de un adulto para dirigir y girar
Nivel 4	Los niños tienen que ser sentados en el suelo y no son capaces de mantener la alineación ni el equilibrio sin usar sus manos para apoyarse. Suelen necesitar adaptaciones para estar sentados y mantenerse de pie. Para desplazarse pequeñas distancias de forma autónoma en espacios cerrados, se voltean, reptan y gatean con manos y rodillas, sin movimiento recíproco de las piernas
Nivel 5	Las deficiencias físicas limitan el control voluntario del movimiento y la capacidad de mantener cabeza y tronco contra la gravedad. Todas las áreas de la función motora están limitadas. Las limitaciones funcionales para sentarse y ponerse de pie no se compensan totalmente con el uso de adaptaciones y ayudas técnicas. En el nivel 5 los niños no son independientes para desplazarse y tienen que ser transportados. Algunos niños logran ser autónomos para desplazarse usando una silla de ruedas eléctrica con numerosas adaptaciones

Figure 9. GMFCS evaluation in children between 2 - 4 years old

Annex 5: MACS (37)



Annex 6: CFCS (38)

Communication Function Classification System (CFCS)

I. Effective Sender and Receiver with unfamiliar and familiar partners.
The person independently **alternates between sender and receiver** roles with most people in most environments. The communication occurs easily and at a **comfortable pace** with both **unfamiliar and familiar conversational partners**. Communication misunderstandings are quickly repaired and do not interfere with the overall effectiveness of the person's communication.

II. Effective but slower paced Sender and/or Receiver with unfamiliar and/or familiar partners. The person independently **alternates between sender and receiver** roles with most people in most environments, but the **conversational pace is slow** and may make the communication interaction more difficult. The person may need extra time to understand messages, compose messages, and/or repair misunderstandings. Communication misunderstanding are often repaired and do not interfere with the eventual effectiveness of the person's communication with both **unfamiliar and familiar partners**.

III. Effective Sender and Receiver with familiar partners. The person **alternates between sender and receiver roles with familiar** (but not unfamiliar) conversational partners in most environments. Communication is **not consistently effective** with most **unfamiliar partners**, but is **usually effective** with **familiar partners.**

IV. Inconsistent Sender and/or Receiver with familiar partners. The person does **not** consistently alternate **sender and receiver** roles. This type of inconsistency might be seen in different types of communicators including: a) an occasionally effective sender and receiver; b) an effective sender but limited receiver; c) a limited sender but effective receiver. Communication is **sometimes effective** with **familiar partners**.

V. Seldom Effective Sender and Receiver even with familiar partners. The person is limited as both a **sender and a receiver**. The person's communication is difficult for most people to understand. The person appears to have limited understanding of messages from most people. Communication is **seldom effective** even with **familiar partners**.

Annex 7: Protocol information

Hoja informativa para la paciente.

Bienvenida,

Nos dirigimos a usted para invitarla a participar en un estudio de investigación llevado a cabo por la unidad de ginecología y obstetricia en diferentes hospitales de Cataluña sobre la neuroprotección fetal entre las 32 y 34 semanas completas de gestación.

Se está investigando si el uso de sulfato de magnesio administrado previo al parto reduce la incidencia de parálisis cerebral en los niños entre estas semanas de gestación.

Antes de que tome la decisión sobre si participar o no en el estudio, es imprescindible que lea detenidamente es siguiente formulario y resuelva cualquier duda que se le plantee. Después ha de entregar el consentimiento informado correctamente cumplimentado en el servicio.

Descripción

Este estudio se centra en las pacientes con amenaza de parto prematuro entre las semanas completas 32 y 34 de gestación. En protocolo actual se administra tratamiento neuroprotector fetal de manera segura a aquellas gestantes con amenaza de parto prematuro y una edad gestacional menor a 32 semanas. Diversos estudios han demostrado que los recién nacidos prematuros de hasta 36 semanas presentan un riesgo incrementado de sufrir parálisis cerebral, sobre todo hasta las 34 semanas; por lo que concluimos que el manejo actual neuroprotector podría ser ampliado hasta las 34 semanas completas de gestación.

El objetivo de este estudio es demostrar la reducción de parálisis cerebral en aquellos niños que nacieron con menos de 34 semanas completas de gestación que sus madres han recibido sulfato de magnesio antes del parto.

Para ello, y para que el sulfato de magnesio disponga de un tiempo mínimo de actuación, se le administrará una pauta de Atosibán, un tocolítico que detendrá la dinámica uterina un mínimo de 4h.

La evaluación de su hijo/a se llevará a cabo por un neurólogo pediátrico cuando este tenga 2 años. En dicho momento, recibirán una llamada telefónica para concertar la cita.

Grupos de tratamiento

En este estudio habrá dos grupos de tratamiento, pero ni el paciente ni los facultativos serán conocedores de a qué grupo pertenecerá. En cualquier caso, esta distribución será aleatoria. Los grupos consisten:

Grupo 1: será tratado mediante infusión intravenosa de 30ml de sulfato de magnesio diluidos en 100ml de suero salino isotónico al 0,9% durante 30 min. Posteriormente, 80ml de sulfato de magnesio diluidos en 420ml de suero salino isotónico al 0,9% en 12h o hasta el parto.

Grupo 2: será tratado mediante infusión intravenosa de 30ml de placebo (suero salino isotónico) diluidos en 100ml de suero salino isotónico al 0,9% durante 30 min. Posteriormente, 80ml de placebo diluidos en 420ml de suero salino isotónico al 0,9% en 12h o hasta el parto.

Beneficios del procedimiento

Esperamos encontrar un efecto beneficioso del sulfato de magnesio en el manejo del parto prematuro entre las 32 y 34 semanas completas de gestación reduciendo en número de casos de parálisis cerebral mediante esta prevención.

Alternativas al procedimiento

Actualmente no existen alternativas a este tratamiento, ya que la opción actual es el manejo expectante.

Riesgos generales y específicos del procedimiento

Al tratarse de un estudio en el que se administran fármacos es posible la aparición de efectos adversos. Siendo los siguientes:

Frecuentes y leves en la madre: vasodilatación periférica, náuseas, vómitos, dolor de cabeza, palpitaciones, sensación de calor, hiporreflexia, flushing…

Poco frecuentes y graves en la madre: fallo renal, fallo respiratorio, hipotensión, parada cardíaca, debilidad muscular…

Poco frecuentes en el recién nacido: succión débil, hiporreflexia, fallo respiratorio…

En caso de aparecer alguno de estos, serán tratados según la pauta clínica establecida, teniendo siempre como prioridad la salud del paciente.

Interrupción del estudio

El estudio será interrumpido si en el análisis a medio plazo se describa un aumento injustificado de tasa de mortalidad materna o infantil, así como también de efectos adversos.

Usted podrá abandonar el estudio en el momento que lo desee. Se recomienda consultar al facultativo y explicar los motivos de la decisión.

Participación voluntaria

Es importante que entienda que la participación en este estudio es completamente voluntaria, y que, en caso de participar, podrá desistir el consentimiento en cualquier momento, sin que esto altere su atención sanitaria.

Confidencialidad

La información médica recogida en este estudio, así como cualquier otro tipo de información serán confidenciales. En ningún caso aparecerá su nombre o el de su hijo en la publicación de los resultados.

Su privacidad está protegida por la Ley Orgánica 15/1999 sobre Protección de Datos personales y el correspondiente Real Decreto Nacional 1720/2007.

Compensación económica

En este estudio no se recibirá ningún tipo de compensación económica.

Cualquier tipo de beneficio obtenido en caso de resultar exitoso irá destinado a cubrir los gastos ocasionados por la realización del estudio.

Responsabilidad y seguro

Los responsables de este estudio han contratado un seguro que cubre la responsabilidad legal por daños ocasionados a las personas que participan y derivados de esta investigación según la legislación vigente.

Annex 8: Inform consent

Consentimiento informado.

D./Dª. **, con DNI**

F. Nacimiento **, NSS**

y teléfono/s

Manifiesto que

He sido informado por el Dr./Dra.

Y que me ha sido entregada una copia de la información sobre este estudio y el tratamiento que voy a recibir (**neuroprotección fetal**) e igualmente de los beneficios que cabría esperar y el tipo de riesgos que comporta su administración (complicaciones más frecuentes) y su no realización, así como las posibles alternativas según los médicos asistenciales de este centro. Además, me comprometo al posterior seguimiento de mi hijo/a para completar el estudio.

He comprendido toda la información que se me ha proporcionado y mis dudas han sido aclaradas satisfactoriamente.

Consiento

Formar parte de este estudio, que se me practique dicho procedimiento y las pruebas complementarias necesarias.

Soy conocedor/a de que en caso de urgencia o por causas imprevistas podrán realizarse las actuaciones médicas necesarias o detener el tratamiento.

Sé que en cualquier momento puedo revocar mi consentimiento.

Firmo dos ejemplares en , a día .

Firma del paciente **Firma del facultativo**

Annex 9: Diagnosis evaluation of CP at 2 years (36)

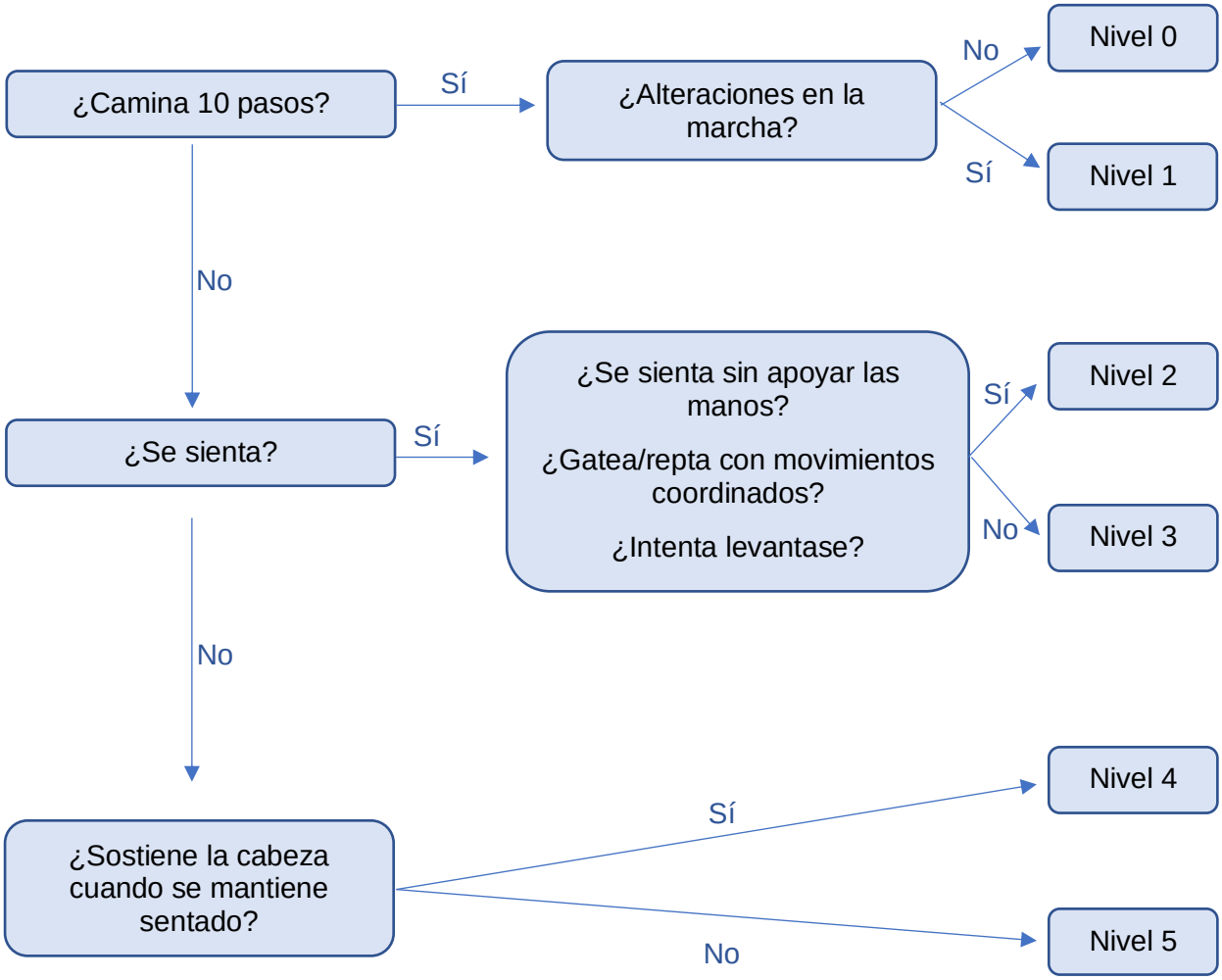


Figure 10. Diagnosis evaluation of CP at 2 years

Annex 10: Study member´s information

Treatment box number:

Mother:

Age , BMI , Diseases

Smoking , Parity

Single or multiple pregnancy

Children:

Gender , Cerebral palsy diagnoses (level)

			Yes	No
Mother	Low risk	Local pain/reaction		
		Peripheral vasodilatation		
		Nausea/ vomiting		
		Headache		
		Palpitations		
		Warm sensation		
		Flushing		
		Hyporeflexia		
	High risk	Muscular weakness		
		Oliguria		
		Renal failure		
		Respiratory depression		
		Hypotension		
		Cardiac arrest		
		Respiratory arrest		
		Death		
Children	Poor sucking			
	Hyporeflexia			
	Neuromuscular depression			
	Respiratory depression			
	Death			

Other considerable information:

Annex 11: Chronogram

	Staff	2017	2018				2019				2020				2021				2022				2023				2024	
		O-D	J-M	A-J	J-S	O-D	J-M	A-J	J-S	O-D	J-M	A-J	J-S	O-D	J-M	A-J	J-S	O-D	J-M	A-J	J-S	O-D	J-M	A-J	J-S	O-D	J-M	A-J
Design and approbation of the protocol																												
Approach and drafting of the protocol	Main researcher																											
Presentation and hospitals´ approbation	Main researcher																											
Protocol´s approbation	AEMPS, CEIm and CEIC																											
Organizational step	All the staff																											
Sample collection	Obstetrician																											
Intervention	Obstetrician and nurse																											
Follow-up visits and data collection																												
Secondary outcomes	Obstetrician							✖		✖		✖		✖		✖		✖										
Cerebral palsy diagnosis	Paediatrician															✖		✖		✖		✖		✖		✖		
Statistical analysis																												
First statistical analysis	Statistician																											
Ultimate statistical analysis	Statistician																											
Results																												
Drafting and publishing the final results	Main researcher																											
Dissemination of the Results	Main researcher																											

✖ All the information will be registered every 6 months