Corticosteroids for foetal lung maturation

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1. INTRODUCTION

Corticosteroid administration between the 23rd and 34th gestation week is an efficient method to decrease perinatal morbidity and mortality (respiratory distress syndrome, requiring oxygen therapy and ventilatory support, intraventricular haemorrhage and necrotizing enterocolitis) secondary to prematurity. This decrease of morbimortality has been proven with the following dosage: intramuscular betamethasone (12 mg/24 hours, 2 doses) or intravenous dexamethasone (6 mg/12 hours, 4 doses).

The maximum benefit from the administration of corticosteroids is obtained between 24 hours and 7 days post-administration. This fact forces most centres worldwide to carry out repeated treatments weekly in a “preventive” manner. However, in the last decade, different authors, based on animal studies and human observational studies, point out that the administration of repeated doses of corticosteroids can show adverse effects both on foetal development and growth, and on neurologic development.

Currently, the debate on the topic of corticosteroids for foetal lung maturation is focused on three points: a) using corticosteroids between weeks 22.0-23.6, b) restrictive use of multiple doses and c) including the use of predictive foetal lung maturity methods to support clinical decisions.

- Regarding the first point, we need to take into consideration that the advances in neonatal management have made it possible to move , foetal viability to below 24 weeks in some centres and in specific cases. Literature shows that prenatal corticosteroid treatment improves postnatal morbimortality at that gestational age. The morbidity cost is still high and, thus, clinical management must be agreed with the parents in every particular case.
- When it comes to the second point, it seems that the repetition of corticosteroid treatment leads to better short-term results, but without benefit, or even with potential long-term harm in neonates who will ultimately be delivered at term.
- And, finally, in relation to the use of tools like quantusFLM®, we need to add that the objective is the individualisation of each particular case to optimise corticosteroid usage. On one hand, to avoid corticosteroid overuse in those patients/foetuses that do not require them, as well as to plan, in *late preterm* pregnant women with non-urgent conditions where delivery is considered, the optimum moment and needs for a safe delivery for the baby.

2. MANAGEMENT

Given that corticosteroid administration has been shown to be of maximum benefit when birth takes place between 24 hours and 7 days post-treatment, its administration will only be suitable if a premature labour is foreseen (regardless of the cause) in the following 7 days.
Prophylactic administration of corticosteroids will **NOT** be suitable in gestations epidemiologically associated with prematurity (adverse obstetric medical history, multiple gestation, etc.) without the objective risk of an imminent birth.

When facing potentially severe but stable situations, in which an acute risk to the mother or the foetus is unlikely (e.g. stable severe preeclampsia without criteria for imminent induction of labour/c-section), delaying delivery 48 hours in order to administrate corticosteroids, should be taken into consideration. On the contrary, corticosteroid administration in situations with maternal or foetal instability (e.g. chorioamnionitis or non-reassuring foetal wellbeing) should not be the only reason to delay delivery.

If the decision involves using quantusFLM® to support a clinical decision, it should be done, if possible, 48 hours before the expected delivery date to allow for a corticoid treatment if there is a suspicion of foetal lung immaturity.

Dosage:
The chosen corticosteroid is intramuscular Betamethasone 12 mg.

The initial treatment will consist of administering one course = 2 doses 24 hours apart.

If there delivery is indicated after foetal lung maturation, induction should be considered from the next day onwards after the last dose (in order to obtain the maximum benefit from the corticoid treatment).

Repeat administration of corticoid dose:
The **maximum number of doses** administered shall not exceed **6 doses**.

In order to minimise repeat doses, doses or courses should **only** be repeated **if the risk of delivery during the following 7 days resumes or persists (with the evolution of the clinical conditions, and also considering blood tests and cervical ultrasound)**. Following this line of reasoning, it will NOT be necessary to administer repeat corticoid doses systematically in those patients in which there is a baseline risk of preterm labour throughout gestation (example: PPROM, cervical cerclage, etc.) unless there is a change suggesting clinical evolution (alterations in the laboratory tests, cervical shortening, regular uterine contractions, etc.).

- If the risk resumes 7-14 days after the first dose, only one dose of intramuscular Betamethasone 12 mg should be administered.
- If the risk reappears ≥ 14 days after the first dose, a full course should be administered.

If the risk reappears or persists during the first 7 days after the first corticosteroid dose, NO new dose is necessary.

Conditions for corticosteroid treatment depending on the gestational age:

2.1 Between 22.0 and < 24.0 weeks

In our centre, the periviable period is considered to be between 22.0 and 23.6 weeks. Despite the improvement in the neonatal management of these newborns, due to the high morbimortality at this gestational age, corticosteroid prescriptions should be **individualised**, bearing in mind the following:

- **22.5 – 23.6 weeks:** our neonatologists propose systematic reanimation from 23.0 weeks. In order to optimise the management, and as literature exists on the benefit of corticoids from the 23rd week, we propose to consider prescribing corticosteroids from 22.5 weeks when, following obstetric criteria, **the probability of labour in the following days is very high**. Its use should be limited to imminent labour as there is evidence of repeat doses of corticosteroids causing harm when the gestation is prolonged.
- **22.0 – 22.5 weeks:** corticosteroid use **should be an exception** during this period as, following clinical obstetric criteria, foetal expulsion is the most probable event in the hours following administration, and should only be prescribed following a discussion between obstetricians, neonatologists, and the parents.

If, after receiving the information, its administration is finally agreed, the dosage will be the same as for gestations between 24.0 and 34.0 weeks.

2.2. Between 24.0 and <34.0 weeks

Prenatal corticosteroid administration is recommended for all those gestations with a risk of preterm delivery in the 7 following days (regardless of whether this is spontaneous or medically induced).

2.3. *Late preterm*: between 34.0. and <37.0 weeks

The risk of respiratory morbidity decreases as gestational age increases. Therefore, delaying delivery must always be considered during the *late preterm period* (34.0 to <37.0) instead of using corticosteroids. Late preterm delivery may only be indicated if it is for maternal or foetal benefit.

There is data (ALPS study, Gyamfi-Bannerman NEMJ 2016) suggesting the benefits of corticosteroid administration between **34 and <37 weeks of gestation**, if delivery is expected within one week (for example, premature membrane rupture, advanced dilatation conditions, elective caesarean for some medical indication, etc.) and NO previous lung maturation method has been applied. In this study, administration of corticosteroids demonstrated a consistent benefit in decreasing respiratory morbidity (from 14% to 11%) at the expense of an increase in neonatal hypoglycaemia (from 15% to 24%). Therefore, there is **still a risk of respiratory morbidity even if corticosteroids are administered,** and the risk of hypoglycaemia increases instead. The authors highlight **avoiding** using corticosteroids in pregnant women who do not meet these conditions and therefore have a low risk of preterm labour. It should be noted that there is data suggesting a suboptimal neurodevelopment in those newborns exposed to corticosteroids during these gestational ages who were finally born at term. Therefore, unnecessary overtreatment is a relevant topic, and knowing lung maturity or immaturity can be helpful, as it encourages clinical re-evaluation and a delivery planned at the optimal timewith neonatologists at an adequate hospital level.

According to the published series, most *late preterm* respiratory morbidity is condensed in the first gestational age range (between 34.0 and 34.6 weeks), being rare over 35 weeks (especially when referring to vaginal birth). Hence, two scenarios are differentiated in this group of patients:

Delivery risk 34.0-34.6 weeks

A) If the patient **has never received corticosteriods for lung maturation** or the **lung maturation is unknown** (or not evaluable): lung maturation will be indicated.
B) If the patient **has previously received** lung maturation and it is possible to carry out quantusFLM®:
    - If there is high risk, evaluate according to clinical situation: a) repeat doses of corticosteroids (following the dosage in point 2), b) delay the elected caesarean by 3-7 days or c) if neither the delay nor maturation is possible, deliver under neonatologist surveillance.
    - If there is low risk: lung maturation should not be indicated.

Delivery risk 35.0-<37.0 weeks

In this situation the risk of respiratory distress syndrome is very low, so corticosteroids should only be administered if lung immaturity can be proven:

A) If the patient **has received** at some point during the gestation a course of corticosteroids for lung **maturation** or **if she has not received this and lung maturation is unknown**: corticosteroids **SHOULD NOT** be indicated (low risk does not justify random administration).
B) If the patient **has not received** any course of corticosteroids for lung **maturation** during this gestation and quantusFLM® is possible:
    - If there is high risk, evaluate depending on the clinical situation: a) administer one course of corticosteroids, b) delay delivery by 3-7 days or c) if neither the delay nor maturation is possible, deliver under neonatologist surveillance.
    - If there is low risk: lung maturation will not be needed.

Clinical management deriving from the application of quantusFLM® is proposed in the algorithm as an annex (except in PPROM situation that has a specific protocol).

Information about quantusFLM® in specific populations (multiple pregnancy, intrauterine growth restriction, diabetes, etc.) is limited. Hence, there are not any specific instructions, and the general recommendations should be applied (as the study included a proportion of patients with these characteristics).

If a revaluation of foetal lung maturity is needed, as there is no specific evidence on the impact of corticoids, **quantusFLM® will only be repeated once 7 days have passed since the last maturity test.**

From 35 weeks onwards, evaluating lung maturity should be a support tool and should never interfere in the clinical decision-making process. Therefore, evaluation of lung maturity is recommended, especially if it is going to be an elective caesarean delivery, in stabilised situations with planned delivery, taking into consideration the particular context (patient's situation, delivery date, quantusFLM® availability, etc.). In cases with medical-indicated delivery or contractions, delaying the delivery is NOT indicated (nor is tocolysis) in order to evaluate lung maturity.

3. SPECIAL SITUATIONS

"Emerging" treatment: there is literature that suggests that mortality and severe morbidity (respiratory distress syndrome, intraventricular haemorrhage, etc.) show a progressive decrease during the first 6 hours after corticosteroid administration, achieving the maximum reduction between 16-36 hours after administration. However, when it comes to severe neurological morbidity, slower benefits have been described, being a higher 24-48 hours after the administration.[1] Lung maturation should be initiated **in all the cases** because, except in imminent delivery, the time lapses for the delivery are difficult to determine. Even in very advanced obstetric conditions, the latency period is uncertain, as tocolysis and the inhibition of the uterine contraction through epidural (if indicated during labour), can delay the immediate delivery. On the contrary, in those deliveries that progress rapidly, **accelerating the dose**[2] to just 12 hours after the first one has NOT shown any benefits (and could even have the opposite effect) and it is not recommended. Therefore, there is no evidence to support administering the second dose any earlier than 24 hours after the first one.

Gestational diabetes screening: to avoid false positives, delay carrying out O'Sullivan screening tests or gestational diabetes diagnosis (oral glucose tolerance test) until one week has passed from the last dose of corticosteroids (see *Gestational diabetes* protocol).

Diabetic pregnant women: even though its effectiveness has not been proven, in situations with a risk of preterm birth, Betamethasone will be administered following the same protocol as in non-diabetic pregnant women. Metabolic control in these patients must be maximised.

Multiple pregnancies: there is no exhaustive evidence on the use of corticosteroids in multiple pregnancies and, as cited previously, there is no specific data on the use of quantusFLM® in this group. Therefore, the general recommendations cited in this protocol will be applied. If different maturation of the foetuses is confirmed, maturation criteria will be applied, repeating doses and evaluating lung maturation according to findings in the most immature foetus.

Pregnant women receiving chronic corticosteroid treatment: only Betamethasone and dexamethasone cross the placental barrier and therefore have an effect on foetal lungs. Any other corticosteroid treatments that the mother may receive as a baseline treatment, have NO effect on lung maturation.

Most patients following chronic corticosteroid treatment are administered prednisone or methylprednisolone 5-10 mg/24h. Betamethasone/dexamethasone are approximately 10 times stronger than other corticosteroids; therefore, if it was necessary to induce foetal lung maturation, the mothers' corticosteroid treatment would be fully covered by the betamethasone 12 mg/24h (equivalent approximately to prednisone or methylprednisolone 100 mg/day). Thus, the usual corticosteroid treatment will be suspended for the 48 hour of lung maturation, resuming the usual treatment the following day.

Pregnant women with suboptimal coagulation: treatment with prophylactic or therapeutic heparin (LMWH) or thrombocytopenia <100,000 platelets:
in patients being treated with prophylactic doses of LMWH, intramuscular corticosteroid treatment can be administered following the usual dosage. In patients following LMWH or other anticoagulant treatment in therapeutic doses or thrombocytopenia <100,000 platelets, there is a risk of haematoma due to the intramuscular injection. In these cases, the intramuscular injection must be administered avoiding the gluteal zone (preferably in the deltoid) and continuous compression should be carried out on the puncture zone for 1-2 minutes.

HELLP syndrome: in HELLP cases that require lung maturation with corticosteroids, Dexamethasone ev 10 mg/12h should be used for 48h (see *Hypertension and gestation* protocol, section 4.6 HELLP Syndrome).

BIBLIOGRAPHY

- ACOG Committee opinion. Number 713. ACOG. August 2017.
- [1] Norman M, Pledvache A, Borch K, et al. Association of short antenatal corticosteroid administration-to-birth intervals with survival and morbidity among very preterm infants. Results from de EPICE Cohort. JAMA Pediatr. 2017;171(7):678-686
- [2] Khandelwal M, Chang E, Hansen C, et al. Betamethasone dosing interval: 12 or 24 hours apart? A randomised, noninferiority open trial. AJOG. 2012 Mar; 201:1-11.

Delivery indication

If there is any indication of delivery following a specific protocol (FGR, PPROM, multiple gestation, etc.)
follow that protocol (do not delay the delivery for QuantusFLM if indicated)

If there is non-absolute indication of delivery, but reasonable option (1) **or need for information on** foetal lung **maturation**

34.0-34.6 weeks

Has NOT received corticosteroids or maturity is unknown (or cannot be checked):

Administer corticosteroids as the dosage indicates

Schedule the delivery for 24 hours after the last dose of CS

Has received corticosteroids and quantusFLM® is available

35.0 - 36.6 weeks

If lung maturation NOT previously received and quantusFLM® is available

If lung maturation previously received or quantusFLM® is NOT available

quantus FLM

HIGH risk of neonatal respiratory morbidity*

LOW risk of neonatal respiratory morbidity*

Based on indication and EG, 3 situations are possible:
- Delay the delivery 3-7 days and/or revaluate quantusFLM® one week later
- Round of corticosteroids or rematuration and delivery 24h after the last doses
- If delivery is required despite the immaturity: let neonatology know

Schedule the delivery

*neonatal respiratory morbidity = includes respiratory distress syndrome and neonatal transient tachypnea

(1) Examples of potential situations:
- -Chronical hypertension or diabetes that is difficult to control.
- -Positive fluid balance with severe maternal discomfort.
- -Highly symptomatic cholestasis without response to treatment.
- -Mild preeclampsia or late IUGR
- -Previous intermittent moderate bleeding of placenta and multiple admissions.