PRETERM LABOUR

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1. INTRODUCTION

Preterm labour (PTL) is classically defined as the presence of regular uterine contractions associated with progressive cervical modifications from 22.0 to 36.6 weeks of gestation with intact amniotic membranes[1][2]. However, these parameters have low sensitivity and specificity for predicting preterm delivery. In most cases in which the patient is admitted with the classical diagnosis of threatened preterm labour, the real risk of triggering the labour in the following 7 days is very low (10%)[3].

There are objective methods that assess this risk with better predictive capacity and with high specificity, allowing false positives to be ruled out. Among these methods, we can highlight transvaginal ultrasound and biochemical method. Due to its low cost and its ease of clinical application in our context, our centre will use the measurement of cervical length as first choice.

Threatened preterm labour can have a multifactorial origin [4]. The main causes are:

- Uterine **overdistention** (multiple gestation, polyhydramnios).
- Extra-uterine infection in other parts of the organism (appendicitis, pyelonephritis).
- **Subclinical intra-amniotic infection and/or inflammation (IAI)**: It is the most frequent known cause of PTL in early gestational ages (< 32 weeks)[5][6]. According to BCNatal data and very similarly to what is reported in the literature, 18% of the total of women that are admitted for PTL will have an intra-amniotic infection and/or inflammation (IAI). The prevalence of intra-amniotic infection/inflammation is 40% when the debut is before the 32 weeks. Since the literature refers to a higher risk of spontaneous preterm delivery and, consequently, of associated neonatal morbidity, the identification of this aetiology may be important for improving the overall prognosis of gestation in these cases. It is for this reason that we will include the performance of an amniocentesis in the diagnostic process in those cases in which the triggering aetiology is unknown.

This protocol is applicable in single and multiple gestations. However, this chapter excludes preterm prelabour rupture of membranes, the diagnostic suspicion/diagnosis of chorioamnionitis (triple I) and third trimester uterine bleeding.

2. DIAGNOSIS

General considerations

When a patient presents a clinical profile compatible with preterm labour (sensation of uterine contractions, continued low back pain, sensation of pressure in the pelvis, mild vaginal bleeding or spotting, etc.), it is important to:

2.1. Calculate gestational age, if possible, according to the first trimester crown-rump length.

2.2. Rule out the presence of other **risk factors** by anamnesis. Exclude other pathologies that contraindicate tocolysis (placental abruption, chorioamnionitis, etc.).

2.3. Perform physical examination aiming to rule out other possible focus at origin of pain and/or uterine contractions (e.g. fever, peritoneal irritation, fist percussion of the kidney).

2.4. Obstetric examination

- Check positive fetal heart frequency.
- Assessment of the abdomen (uterine heigh, fetal presentation, uterine irritability, etc.).
- Speculoscopy: visualisation of the cervix (rule out amniorrhexis, vaginal bleeding, etc.).
- Vaginal examination: It will not be done systematically but will be done if there are ultrasound doubts or suspicion of established delivery according to the Bishop index (see annex 1)[1]. We will avoid serial vaginal examinations as they increase the risk of infection.

2.5. Additional tests:

- **CTG (fetal cardiotocography):** assess uterine contractions and rule out nonreassuring fetal status.
- **Transvaginal ultrasound:** measurement of the cervical length (see annex 2).
- **Biochemical markers** (only if we do not have transvaginal ultrasound): fibronectin, detection of IGFBP-1 (Partus test®) or PAMG-1 (Parto Sure®). The systematic combination of biochemical markers and cervical length have not been observed to improve the prediction of spontaneous preterm delivery (2)(7).

Risk assessment

We will individualise the management of pregnant women **with symptoms of preterm labour** based on the risk of presenting a spontaneous labour.

- **High risk** patients:
  - Short cervix for gestational age (see Table 1) and/or Bishop ≥ 5 and/or
  - Presence of any risk factor of preterm labour: previous history of spontaneous preterm labour before week 34.0, late gestational loss (> 16 weeks), multiple gestation, has cervical

cerclage, uterine malformation, history of cervical conization.

- **Low risk** patients: do **NOT** present **ANY** of the aforementioned criteria.

Table 1. Cut off points for cervical length [5].

Cut-off points for short cervical length		
Gestational age	**Singleton pregnancy**	**Multiple pregnancy**
<28 weeks	<25 mm	<20 mm
28.0-31.6 weeks	<20 mm	<10 mm
≥32 weeks	<15 mm	<10 mm

3. MANAGEMENT AT THE EMERGENCY AREA

When we observe **regular uterine contractions** in a patient that has consulted for symptoms compatible with preterm labour, we will act according to the risk:

- In **LOW risk** patients and in those who are **HIGH risk without short cervix**: observation 2-3h in emergencies department to assess whether there are changes in cervical conditions considering the possibility of administering one dose of oral tocolysis (nifedipine).
  - **If uterine contractions subside and there are no cervical changes**: home discharge with relative rest in the following 24h and routine obstetric control.
  - **If uterine contractions do not subside but there are no cervical changes:** hospital admission under observation for 12-24h. Initially, tocolysis or corticosteroids will NOT be administered systematically. Tocolysis will only be used as a symptomatic treatment and with a 12-24 hours schedule if needed. Early discharge when symptoms subside.
  - **If there are cervical changes:** hospital admission.
- The rest of **HIGH risk patients due to short cervix** or **cervical changes** will be admitted with diagnosis of threatened preterm labour.

In the **absence of regular uterine contractions or when cervical modifications have been found in an asymptomatic patient,** the parameters considered to be high risk must be assessed with caution, since they may not be related to the preterm labour. These findings (for example, short cervix), in the absence of symptoms, are NOT amenable to tocolysis due to the fact that they may represent the

extreme of normality. In these cases, assess at follow-up in 1-2 weeks in the Preterm birth prevention clinic. However, it could be recommended to restrict activity, avoiding prolonged standing until the clinical progression is evaluated, as well as the treatment with natural micronized progesterone (200 mg/24h vaginally) if < 26.0 weeks of gestation.

4. HOSPITAL ADMISSION

Admission includes relative rest for 24h (permitting personal hygiene if the clinical history allows it) and maternal-fetal control.

4.1. ADDITIONAL TESTS. Plus the CTG and the emergencies transvaginal ultrasound:

- **Basic fetal ultrasound:** fetal presentation, amniotic fluid, placenta and fetal growth assessment.
- **Blood test:** hemogram, basic biochemical, blood clotting and C-reactive protein (CRP).
- **Vaginal-rectal sampling for screening of Streptococcus agalactiae** (of the external third of the vagina and the rectum) if it had not been performed in the previous 5 weeks.
- **Urine sediment analysis and urine culture.**
- **Vaginal sampling:** will ONLY be performed in women with symptoms suggestive of bacterial vaginosis, vaginal inflammation (e.g. vulvovaginal candidiasis). CRP will not be performed for Chlamydia spp., gonococcus or vaginal culture of genital mycoplasma except if there is a risk of sexual transmitted diseases.
- **Endocervical culture** will only be performed if the patient has cervical cerclage.
- **Diagnostic amniocentesis**: in singleton gestations and ≤ 32.0 weeks, the convenience of performing an amniocentesis will be proposed to rule out intra-amniotic infection in cases in which there is no other aetiology that justifies uterine contractions. The risks of the test are minimal (≤ 0.7% of PPROM). It will be performed prior to informed consent and evaluating the maternal serologic state (annex 3) with a 22G (or 20G) needle. 20 cc will be extracted to determine:
  - Glucose
  - Gram stain
  - Aerobic and anaerobic cultures. If Gram negative bacilli such as *Klebsiella spp.* or *Escherichia coli* are isolated, the microbiology service will test whether they are β-lactamase-producing germs, aiming to adjust the antibiotic treatment of ESBL (β-lactamase producing Gram negative bacteria or extended-spectrum β-lactamases-producing Gram negative bacteria).
  - Culture or PCR for genital mycoplasma (*Ureaplasma spp, micoplasma hominis*)
  - Interleukin 6

- QF-PCR (at previable gestational ages and/or suspicion of fetal pathology)

In singleton gestations **> 32.0 weeks or multiple gestations,** amniocentesis will NOT be proposed systematically, because the prevalence of intra-amniotic infection in these cases is low, although it will have to be assessed if there is clinical suspicion of infection (e.g. leucocytosis, high CRP, fever.).

4.2. CORTICOSTEROIDS: between 23.0 and 34.6 weeks, fetal lung maturation will be performed (8). The corticosteroid of choice is betamethasone 12 mg IM and the initial treatment will consist of a course (2 doses at 24 hours apart). Lung maturation may be considered between 22.0 and 23.0 weeks (after consensus with the couple and neonatology) if obstetric conditions suggest that the delivery may occur around 23.0 weeks.

4.3. TOCOLYSIS: The objective of tocolytics is the inhibition of uterine contractions to complete fetal lung maturation and/or neuroprotection (provided there are no reasons to allow the labour to progress). If uterine contractions recommence, reintroduction will be considered.

Tocolysis should not be used if there is any contraindication to prolong the pregnancy: confirmed diagnosis of chorioamnionitis or triple I, suspicion of placental abruption, decompensation of maternal disease, etc.

In suspected cases of **subclinical intra-amniotic infection** (glucose ≤ 5 but NO germs seen in Gram stain), maintaining tocolysis to complete fetal lung maturation may be considered while awaiting the final culture result (always in the absence of a diagnosis of chorioamnionitis or triple I).

In the case of a diagnosis of **confirmed subclinical intra-amniotic infection** (germs in Gram stain or positive LA culture), gestational age is of great importance when considering delivery:

- If **< 23.0 weeks**, our recommendation will be delivery, given the poor fetal prognosis at these weeks of gestation and the maternal infectious risk.

- Between **23.0-26.0 weeks**, tocolysis will be allowed until fetal maturation is complete under antibiotic coverage, and ALWAYS provided that there is no diagnosis of chorioamnionitis or triple I. Depending on the germ, gestational age and maternal condition, decision after fetal lung maturation will be individualised in agreement with the Preterm birth prevention clinic.

- If **> 26.0 weeks**, antibiotic coverage and lung maturation will be started but tocolysis will NOT be administered. If the birth does not progress spontaneously, an individualised decision based on the germ, gestational age, and maternal status with the Preterm birth prevention clinic will be

taken.

The different types of tocolytics are described in Annex 4. The use of tocolytics will be individualised **based on gestational age**:

≥ 36.0 weeks	All types of tocolysis treatment will be discontinued.
35.0-35.6 weeks	A less aggressive approach will be chosen. The intravenous tocolysis treatment will be suspended and relative rest will be indicated. Optionally, if necessary, tocolysis will be administered orally to improve symptoms.
< 35.0 weeks	**First line of tocolysis:** ▪ < 24.0 weeks: INDOMETHACIN. ▪ ≥ 24.0 weeks: NIFEDIPINE or ATOSIBAN. If cardiovascular risk/antihypertensive medication, we will use ATOSIBAN.

Furthermore, in the use of **tocolysis** we must value the **following <u>considerations</u>:**

COMBINATION TOCOLYSIS THERAPY

If, despite treatment with monotherapy, uterine contractions persist, the possibility of combination therapy will be assessed considering gestational age, cervical changes, and whether the pulmonary maturation regimen has been completed. Since combination therapies have a higher number of adverse effects (9), their regular use must be justified, and under maternal monitoring. In these cases of introduction of combination therapy, it is especially important to have ruled out intra-amniotic infection. It is recommended to preferably use the combination of **nifedipine with atosiban**. The combination therapy **will be avoided** beyond 32 weeks of gestation.

MAINTENANCE TREATMENT

Since the benefit of maintenance treatment has not been demonstrated, **all** tocolysis treatments will be discontinued **after 48 hours** of treatment.

In case of resumption of regular uterine contractions, the patient will be reassessed before reintroducing a new treatment cycle. The reintroduction must be justified. It is recommended not to use maintenance treatment beyond 32 weeks.

OUTPATIENT TREATMENT

Oral tocolysis treatment given at home will not be prescribed after discharge, except in very specific situations in which the symptoms persist despite no observed cervical changes or risk of infection.

4.4. LOCO-REGIONAL ANAESTHESIA

In patients with persistent painful uterine contractions despite tocolysis, loco-regional anaesthesia will be considered for analgesic purposes. If uterine contractions subside and labour does not progress, loco-regional anaesthesia will be withdrawn once fetal lung maturation is complete. If labour is established, it can be maintained for delivery coverage.

4.5. ANTIBIOTICS

Threatened preterm labour does not justify the administration of antibiotics. The exposure of membranes (unless there are positive cultures) "per se" is not an indication for antibiotic therapy either, since there is insufficient evidence in the literature, and no specific recommendation in national or international clinical guidelines on its prophylactic use.

Antibiotic treatment will be considered for:

- Patients with **imminent delivery and vagino-rectal sampling for Streptococcus agalactiae positive or unknown**.
- In case of **positive urogenital cultures** (urinoculture, vaginal smear, endocervical smear).
- Patient with **a suspected diagnosis of subclinical intra-amniotic infection** (due to glucose ≤ 5 mg/dL), a broad-spectrum antibiotic treatment will be started with ampicillin 2 g/6h IV + ceftriaxone 1 g/12h IV + oral clarithromycin 500 mg/12h waiting for amniotic fluid culture results. Antibiotic treatment will be suspended if cultures are finally negative.
- If **amniotic fluid cultures are positive for genital mycoplasmas**, the treatment of choice will be clarithromycin 500 mg/8h orally for 7-10 days. In these cases, an electrocardiogram will be performed in the initial days of diagnosis, since cases have been described of an increase in the Q-T interval after prolonged use in multipathological patients. **In all other cases,** if an expectant management is chosen, antibiotic treatment will be individualised based on the antibiogram until completing 7-10 days.

4.6. NEUROPROPHYLAXIS WITH MAGNESIUM SULPHATE

Fetal neuroprophylaxis with magnesium sulphate will be performed in case of suspicion of imminent delivery or progression of obstetric conditions in pregnancies < 32.0 weeks (See protocol: *Neuroprotection with magnesium sulphate*). For a fetus with intrauterine growth restriction and monochorionic twins, magnesium sulphate will be maintained as a neuroprotector until 33.6 weeks. An hourly maternal monitoring will be required.

4.7. ASSESSMENT OF FETAL WELL-BEING (during admission and if clinical stability)

- Weekly ultrasound and prior to discharge.

- Daily auscultation of fetal heartbeat or daily CTG (starting from week 28). If < 28 weeks and asymptomatic patient, it is not necessary to perform CTG (only monitoring of fetal heartbeat and uterine contractions).

4.8. GENERAL CARE

- In general, **absolute rest is contraindicated** unless cervical conditions justify it. Except for very individualised cases (for example, complete dilation), if the uterine contractions have subsided, relative rest will be allowed, allowing mobilisation for hygiene and meals.

- Diet rich in residues +/- fibre orally or, if necessary, osmotic or lubricant laxatives. Once the intestinal rhythm is re-established, reduce the dose.

- Prophylactic low molecular weight heparin according to the specific local protocol from the third day of admission, unless thromboprophylaxis was given for other reasons prior to admission.

4.9. DISCHARGE FOLLOW-UP

Prior to discharge, the patient will be allowed to wander around the room and move for personal hygiene for 24 - 48 hours depending on the risk, gestational age, and cervical conditions. Oral maintenance treatment will not be considered except for justified exceptions. The patient will be referred for a follow-up in 1 - 2 weeks in the Preterm birth prevention clinic for risk reassessment and with instructions to return to the emergency room if the symptoms reappear.

5. BIBLIOGRAPHY

1. NICE. Preterm labour and birth Preterm labour and birth Contents. NatlInstClinHealExcellGuidel.2015:1–12.
2. Sego GAP, Perinatal M. Preterm Delivery. Practical Assistance Guide updated in February 2020 Index. SEGO, Practical Asist Guide, MedPerinat [Internet]. 2020;1–62. Available from: www.prosego.com.
3. Defranco EA, Lewis DF, Odibo AO. Improving the screening accuracy for preterm labour: Is the combination of foetal fibronectin and cervical length in symptomatic patients a useful predictor of preterm birth? A systematic review. In: American Journal of Obstetrics and Gynecology.2013;p.233.e1-233.e6.
4. Romero R, Dey SK, Fisher SJ. Preterm Labour: One Syndrome, Many Causes NIH Public Access.Science.2014;345(6198):760–5.
5. Palacio M, Cobo T, Bosch J, Filella X, Navarro-Sastre A, Ribes A, et al. Cervical length and gestational age at admission as predictors of intra-amniotic inflammation in preterm labour with intact membranes. UltrasoundObsGynecol.2009;34:441–7.
6. R G, R R, JK N, T C, L M, YM K, et al. A short cervix in women with preterm labour and intact membranes: a risk factor for microbial invasion of the amniotic cavity. Am J ObstetGynecol.2005;192(3):678–89.
7. Biomarker tests to help diagnose preterm labour in women with intact membranes Diagnostics guidance. NatlInstClinHealExcellGuidel. 2018. Available from: www.nice.org.uk/guidance/dg33
8. E M, F S, R P, SR D. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane database SystRev.2020Dec25;12(12).
9. De Heus R, Mol BW, Erwich JJHM, Van Geijn HP, Gyselaers WJ, Hanssens M, et al. Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study. BMJ. 2009Mar28;338(7697).
10. Conde-Agudelo A, Romero R, Kusanovic JP. Nifedipine in the management of preterm labour: a systematic review and meta-analysis. Am JObstetGynecol.2011[;204(2):134.e1-134.e20.
11. SM L, L S-R, AM K. Assessing the neonatal safety of indomethacin tocolysis: a systematic review with meta-analysis. ObstetGynecol.2005;106(1):173–9.

1. BISHOP TEST

Score	0	1	2	3
Dilation (cm)	0	1-2	3-4	5-6
Shortening (%)	0-30	40-50	60-70	≥80
Position	Posterior	Medium	Centred	
Consistency	Hard	Medium	Soft	
Presentation height	-3	-2	-1/0	1/2

2. CONDITIONS FOR CARRYING OUT THE CERVICAL LENGTH MEASUREMENT

Measurement of cervical length using transvaginal ultrasound
• Recommended position for patient in **dorsal lithotomy.** • **Urinary bladder** of the pregnant patient **empty.** • Measurement of the cervix in its **longitudinal axis:** - The cervix should occupy approximately **50-75% of the image**. - **Excessive pressure** on the cervix with the **ultrasound probe** should be **avoided** since this artificially lengthens the cervix and also makes it difficult to visualise *funnelling*. - **The cervical canal and surrounding cervical mucosa** should be visualised. • The **examination** should **last** between **3 and 5 minutes**, and it is advisable to take **several** (at least three) **measurements** of the cervical length and **use the smallest size** to advise the patient and decide on the management of the pregnancy.

3. CONDITIONS TO PERFORM AN AMNIOCENTESIS

- Prior to the procedure, the Rh(D)-red blood cells and the serological status for HIV human immunodeficiency virus and hepatitis B virus must be known, which have to be requested urgently if they are unknown.
- The serological status for the hepatitis C virus will be requested only in patients at risk:
  - History of parenteral drug use
  - History of transfusion or transplantation
  - HIV or HBV infection
  - HCV-infected partner

- Chronic elevated transaminases
- Wearer of tattoos
- Piercings made with non-sterile or single-use material.

- In general, it is preferable to avoid a transplacental amniocentesis whenever there is feasible extra-placental access. It should be avoided in pregnancies with positive serologies for HIV, Hepatitis B virus, HCV and in isoimmunisation.
- In the case of maternal infection with HIV, Hepatitis B virus or HCV, the main peculiarities are summarised here:

  - The risk-benefit of diagnostic amniocentesis should be considered when assessing an intra-amniotic infection. It can be limited to cases with clinical suspicion of intra-amniotic infection. If it is considered proper to perform it, **transplacental passage should be avoided in case of HIV, Hepatitis B virus or HCV infection**.
  - HIV positive: perform the procedure under **combined antiretroviral treatment** and, ideally, with an **undetectable viral load**. In case of untreated HIV infection or detectable viral load, try to delay the procedure and reassess together with the Perinatal Infections Unit. If it is not possible to delay it, start the zidovudine protocol and consider an urgent initiation of combination antiretroviral treatment.
  - Hepatitis B virus positive: in case of hepatitis B-e antigen (HBe-Ag), positive viral load (DNA HBV), unavoidable transplacental puncture or third-trimester amniocentesis, a post-procedure HBV-specific immunoglobulin (600 IU IM. single dose within 24 hours) will be administered.
  - HCV positive: the risk of vertical transmission of HCV through an amniocentesis has been very poorly evaluated. If possible, have RNA-HCV available before the procedure.

4. TOCOLYSIS

NIFEDIPINE (calcium-channel blocking agent)

As orally administered tocolysis, it has been proven to be as effective as atosiban (1) but with a greater number of side effects, and superior to β2-adrenergic agents because it is more effective with fewer side effects.

- **Oral capsule regimen**: 20 mg initially, followed by a regimen of 20 mg/6h for 48h. If there is no response to the initial treatment: add 10 mg of rescue dose 20 minutes after the first dose and 10 mg more after 20 minutes (maximum 40 mg during the first hour). If after this second rescue dose there is no response, a switch to an intravenous

tocolysis is indicated. The conventional regimen will be 20 mg/6h but there is a margin of 20 mg/4-8h, without exceeding a maximum dose of 120 mg/day.

- **Side effects**: headache and hypotension (mainly if > 60 mg/d) (10).
- **Contraindications:** patients with renal, hepatic or cardiac dysfunction, concurrent use of antihypertensive medication or transdermal nitroglycerin betamimetics, drug allergy or clinical hypotension at baseline.
- **Monitoring**: heart rate (HR) and blood pressure (BP) control every 30 minutes for the first hour or while intensive therapy is used. Afterwards, every hour. If the chart stabilises, control of constants every 8 hours.

INTRAVENOUS ATOSIBAN (oxytocin receptor antagonist):

Drug of choice in patients with heart conditions and those patients with basic antihypertensive treatment. It is administered in 48h cycles, with possibility of repetition. If there is a very good response to treatment, and the risk of preterm labour is not very high, consider doing short cycles of 24 hours instead of 48 hours.

- **Guideline**: administered intravenously in three successive stages:

Stage	Regimen	Infusion speed	Atosiban dose
1	0.9 ml of 7.5 mg/ml solution in cud administered over a minute	Not applicable	6.75 mg
2	Infusion loaded with 2 vials of 5 ml (7.5 mg/ml) diluted in 100 ml administered over 3 hours	24 ml/h = 300 mcg/min (or 18 mg/h)	54 mg
3	Continuous maintenance infusion with 2 vials of 5 ml (7.5 mg/ml) diluted in 100 ml administered for a maximum of 45 hours	8 ml/h = 100 mcg/min (or 6 mg/h)	Up to 270 mg

- **Side-effects:** nausea, hyperglycaemia, headache, tachycardia, hypotension, vomiting.
- **Contraindications**: Allergy to the drug.
- **Potential risks**: Chest pain. The concomitant use of atosiban together with other tocolytics such as calcium blockers or betamimetics is associated with an increased risk of acute pulmonary oedema and should therefore be used with caution.
- **Monitoring**: BP and HR control every 8 hours.

INDOMETHACIN (Prostaglandin synthesis inhibitor)

Especially useful in early PTL < 26 weeks, although in this protocol it will be the tocolysis of choice in gestations <24.0 weeks.

- **Guideline**: initial dose of 100 mg rectally +50 mg orally; later 50 mg/6h orally.
- **Potential risks**: early constriction of the fetal ductus arteriosus, oligohydramnios.

- **Side effects**: Headache, dizziness, vomiting, diarrhoea, constipation, irritation of the rectum.
- **Monitoring**: Fetal echocardiography is not indicated if administered in gestations below 27 weeks. Observations regarding treatment with indomethacin at other gestational ages:
    - If gestational age between 27.0 - 31.6 weeks: amniotic fluid index (AFI) together with a fetal Doppler study every 48h to control a possible constriction of the ductus arteriosus and continue according to the results.
    - If > 32.0 weeks: avoid as tocolysis treatment (11). If it is used as a treatment for polyhydramnios, it requires strict control of AFI and Doppler of the ductus arteriosus/24-48h (possible irreversible closure of the ductus from week 32).