MANAGEMENT OF PATIENTS AT RISK OF PRETERM DELIVERY

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The objective of this protocol is to describe the management of pregnant women at risk of spontaneous preterm delivery in singleton pregnancies. The management of multiple gestations is described in a specific protocol.

1. OBJECTIVES OF THE PRETERM BIRTH PREVENTION CLINIC

The main objectives of the Prematurity Unit are the following:

1.1. **Management of pregnant women at risk of spontaneous preterm delivery (sPTD)**, integrating transvaginal ultrasound to evaluate the cervix, a microbiological examination and an assessment of foetal wellbeing.

1.2. Offering **therapeutic alternatives** in the event of a high-risk situation.

2. PREGNANT WOMEN SUSCEPTIBLE TO FOLLOW-UP IN THE PRETERM BIRTH PREVENTION CLINIC

Patients with indication for follow-up in the Prematurity Unit will be those who present:

2.1. **Previous history of spontaneous preterm delivery or history of preterm premature rupture of membranes (PPROM) <34 weeks**. Prematurity due to medical reasons (hypertensive disorders, intrauterine growth restriction), poorly controlled diabetes, twin pregnancies, foetal pathology, etc. is excluded.

2.2. Obstetric history suggesting cervical insufficiency in the second trimester and/or spontaneous miscarriage ≥16 weeks of gestation.

2.3. **Threatened preterm labour (TPL)** episode or **preterm prelabour rupture of membranes (PPROM)** episode in the current pregnancy.

2.4. **Short cervix for the gestational age** (cervical length <25 mm before 26 weeks of gestation) in asymptomatic pregnant women with no history of preterm delivery (sPTD).

2.5. Uterine factors:

2.5.1. **Previous cervical surgery**: cervical conization, trachelectomy.

2.5.2. **Uterine malformations**: bicorporeal uterus (didelphys or bicornuate), septate uterus, hypoplastic cervix secondary to medical treatment with diethylstilbestrol.

2.6. **6-week post-partum assessment in patients with** spontaneous singleton **preterm delivery** <34.0 weeks.

3. MONITORING PREGNANT WOMEN AT RISK IN THE PRETERM BIRTH PREVENTION CLINIC

In patients with a history of spontaneous preterm delivery or with other risk factors for preterm birth, obstetric follow-up will begin in our preterm birth prevention clinic at around 13-14 weeks, after confirming normality in the ultrasound of the first trimester and in the prenatal aneuploidy screening or from the moment at which the risk is detected in other patients.

- **Vaginal culture/Vaginal gram stain and urine culture** will be performed at the first visit or before 20-22 weeks of gestation. In the presence of a positive urine culture, the management will be the same as in the case of asymptomatic bacteriuria (see specific protocol).

If the vaginal culture/vaginal gram stain confirms the diagnosis of bacterial vaginosis (according to Nugent's criteria), the treatment of choice will be clindamycin 300 mg/12 hours orally for 5 days. After 22 weeks of gestation, a gram stain will not be performed if there are no symptoms of vaginosis. Once the vaginosis has been treated, there will be no screening again unless the patient presents symptoms that suggest doing so.

- **Cervical length will be monitored** frequently according to the risk of prematurity (every 1-3 weeks).
- From week 26 (according to the patient's clinical and social context), the frequency of visits will be individualised, as well as possible follow-up in their reference centre (if the situation stabilises and the risk of prematurity is low).
- Screening for group B streptococcus (GBS) vagino-rectal sampling for Streptococcus agalactiae will be carried out earlier than in other pregnant women, around 34-35 weeks. GBS infection will only be treated if asymptomatic bacteuria.

According to the patient's history, the management of the pregnancy will be individualised. The following clinical situations will be differentiated:

3.1. Bad obstetric history

3.1.1. Pregnant women with a history of two or more foetal losses during the second trimester or early third trimester.
3.1.2. History of a foetal loss during the second or early third trimester after a cervical conization.
3.1.3. Pregnant woman who underwent an ultrasound-indicated cervical cerclage in the previous pregnancy and who, despite this, presented a premature delivery.

In these cases, a **history-indicated cervical cerclage** will be indicated between the 13-16 weeks of gestation (after confirming normality through ultrasound screening and aneuploidy in the first trimester). In very selected cases, performing an abdominal cerclage might be proposed (e.g. recurrent gestational losses despite cervical cerclage).

3.2. Women at potential risk of preterm delivery due to obstetric history or clinical factors

3.2.1. One or two foetal losses (NOT documented) in the second or the third trimester.

3.2.2. History suggesting cervical incompetence.

3.2.3. History of previous preterm labour or premature rupture of membranes before 34 weeks.

3.2.4. Uncertain diagnosis of cervical incompetence.

3.2.5. Other risks of prematurity (e.g. uterine, cervical factors).

In this group of women an ultrasound control will be considered every 2-3 weeks, from week 13-16 to week 26. If cervical length <25 mm is observed, treatment will be started with:

- **Vaginal progesterone 200 mg/24h**. The cervical length will be reassessed after a week. Progesterone is the first-line treatment, reassessing cervical length after a week.
- **Pessary** can be an alternative to vaginal progesterone (e.g. if cervical shortening was observed in the previous pregnancy despite treatment with progesterone, as well as for those pregnant women with cervical pessaries indicated in their reference centre).
- In the cases where a **progressive cervical shortening** is observed, despite treatment with progesterone (or cervical pessary), a **(therapeutic) ultrasound-indicated cervical cerclage** will be indicated.

3.3. Short cervix found in asymptomatic patients with no history of prematurity

Although, according to our own data, the finding of a short cervix (cervical length <25 mm) is less than 1%, **screening of the cervical length** coinciding with the morphological ultrasound of the **second trimester (20-22 weeks)** to identify those asymptomatic patients with a short cervix should be considered. This screening will be the managed as follows:

- If cervical length is found to be between 20-25 mm, the pregnant woman will be referred to the Preterm Birth Prevention Clinic for reassessment in 1-2 weeks. Sick leave with maternity rest may be recommended until the assessment by the Unit.

- If cervical length <20 mm, treatment with progesterone 200 mg/24h vaginally will be started from that moment and the pregnant woman will be referred to the Preterm Birth Prevention Clinic in approximately 1 week.

Once at the Preterm Birth Prevention Clinic, the procedure will differ according to the clinical situation:

- If cervical length ≥25 mm: Discharge from the Preterm Birth Prevention Clinic and follow-up by their reference centre or in a general outpatient obstetrics consultation.
- If cervical length ≥20 mm and <25 mm: follow-up in the Unit without need for progesterone treatment. If stable after 2 consecutive visits, consider discharging them from the Unit.
- If cervical length <20 mm:
    - Vaginal progesterone treatment 200mg/24h will be maintained until week 34-37 of gestation.
    - Consider that, in these asymptomatic women with no history of spontaneous preterm labour, the cervical pessary may be an alternative to progesterone in the case of finding a short cervix (<20 mm).
    - In gestations <24 weeks in which cervical shortening is persistent despite progesterone treatment (or cervical pessary), **ultrasound-indicated cerclage** will be indicated. Between 24-26 weeks, the management will be individualised.

3.4. Threatened Preterm Labour (TPL) in the current pregnancy

The risk will be reassessed in the Preterm Birth Prevention Clinic 1-2 weeks after hospital discharge:

3.4.1. If the cervical length is normal for the gestating age, (≥25 mm in gestations <28 weeks; ≥20 mm between 28 and 31.6 weeks or ≥15 mm if ≥32 weeks)(1) and the pregnant woman is clinically stable, the risk of preterm labour is low, therefore the patient will be referred to their reference centre or to a general obstetrics outpatient clinic.

3.4.2. In any other cases, the obstetrics follow-up will be individualised and controls will be performed every 1-2 weeks, assessing the cervical length.

It has not been proven that **prophylactic tocolysis** reduces the risk of preterm labour nor the risk of perinatal morbimortality. Therefore, it will not be administered systemically. Only in exceptional circumstances, where the uterine contractions preclude normal life, may this strategy be evaluated for the safety of the patient.

3.5. Preterm prelabour rupture of membranes

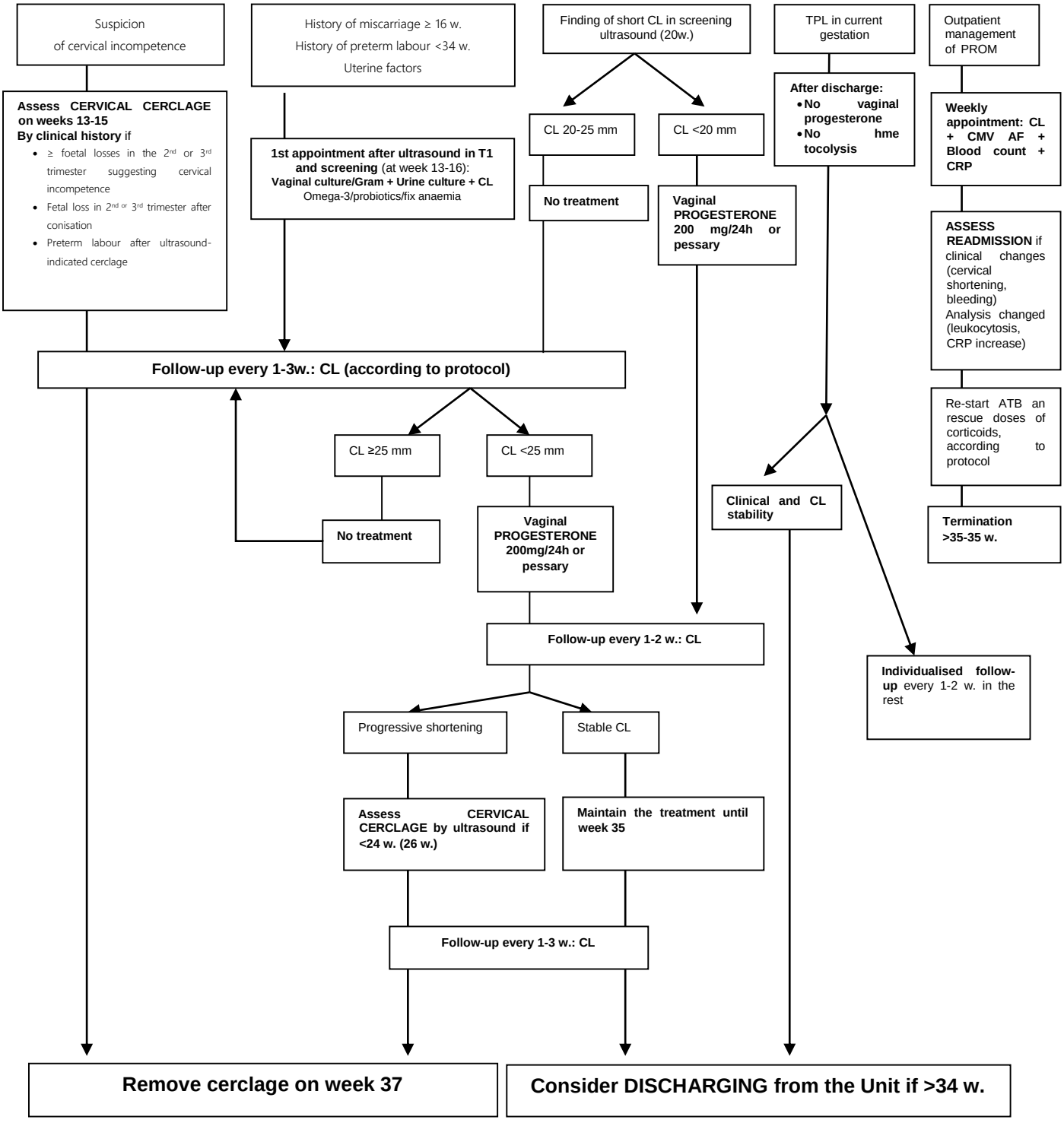
The clinical management of pregnant women with PPROM who are susceptible to outpatient management will include a clinical assessment, blood test (haemogram + C-reactive protein) and ultrasound (amniotic fluid maximum vertical pocket and cervical length) every 1-2 weeks.

Corticosteroids for foetal lung maturation will not be considered routinely (neither full course nor repeated dose), but they should be considered if clinical changes appear or there is an indication for hospital readmission. As in TPL, prophylactic tocolytic treatment will not be performed.

Hospital **readmission** will be considered based on clinical changes (e.g. cervical shortening, bleeding) or blood test changes (increased CRP) that suggest an evolution of the condition.

Antibiotic treatment will only be resumed if there is suspicion of a clinical (e.g. fever, onset of labour), blood test or microbiological infection.

Management of patients at risk of preterm labour



4. MANAGEMENT OF THE 6-WEEK POSTPARTUM APPOINTMENT

The purpose of the postpartum appointment is to summarise the episode that caused the preterm birth and report the results pending upon discharge, the placental cultures and the anatomopathological study of the placenta (if applicable), offering a series of preconceptional assessments in order to improve the prognosis of a new pregnancy.

A gynaecological ultrasound will be indicated if uterine malformation is suspected (extreme prematurity in which no infectious factor is observed) and in those patients referred due to the presence of a uterine malformation (septate uterus) or without a well-established diagnosis. In these cases, a 3D ultrasound and/or hysteroscopy might be indicated by the gynaecology team.

5. FOR PATIENTS AT RISK OF PRETERM LABOUR

Recommendations DURING GESTATION

5.1. **Partial bed rest and intercourse**. There are no differences between bed rest at home versus rest in the hospital with respect to the risk of preterm labour (2)(3). The effect of rest or sexual intercourse on pregnant women with a short cervix has not been studied. Overall, it seems prudent to recommend a sick leave and abstinence from sexual intercourse to pregnant women with a cervix <25 mm before 26 weeks.

5.2. **Antibiotics**. It has not been shown that the administration of prophylactic antibiotics during the second or third trimester in patients with a history of prior preterm labour reduces the risk of recurrent prematurity, poor perinatal outcomes, or morbidity (2); nor in patients with threatened preterm labour and an intact sac with unknown infectious factors.

5.3. **Tocolysis or progesterone**. Outpatient treatment with tocolytics or vaginal progesterone is not indicated after stabilisation of the PTL or PPROM episode.

PRECONCEPTION recommendations

A history of premature labour is the main factor for recurrence. The risk of recurrence is determined by the weeks of pregnancy at the moment of labour and by the number of previous births. That is why women with a history of preterm labour benefit from a follow-up of their subsequent pregnancy in the Preterm Birth Prevention Clinic, since, in case of recurrence, the planning of a strategy is useful for delaying or optimising labour conditions. As preconception measures, the following will be recommended:

5.4. **Intergenesic period**. After the preterm delivery, an intergenesic period (from the delivery to the new pregnancy) of 12 months (minimum of 9 months) will be recommended. However, in case of a caesarean section, 18 months will be recommended.

5.5. **Iron**. Iron supplement therapy improves perinatal outcomes when the mother has iron-deficiency anaemia, but prophylactic supplementation does not affect the risk of preterm labour. However, it does increase the risk of gestational diabetes and oxidative stress. Therefore, it will not be recommended in prophylactic form, except for cases in which iron-deficiency anaemia is detected.

5.6. **Vitamin supplements**. Vitamin C, E or calcium supplements do not have an effect on reducing preterm deliveries (2). Zinc supplementation has not been shown to reduce preterm labour in areas where there is no malnutrition. Vitamin D supplementation without calcium seems to possibly reduce the risk of preterm delivery, although the clinical meaning of the increase in 25(OH) vitamin D is unknown. For this reason, this supplementation is not recommended if sun exposure is normal.

5.7. **Omega 3 fatty acids.** A high supplementation in Docosahexaenoic acid (DHA) (600-900 mg/day) has not been shown to reduce the risk of preterm delivery and thus it will not be recommended (4). The general guidelines are to supplement pregnant women with 200 mg/day of DHA. There are commercial mixtures that contain exclusively omega 3 oils, as well as other multivitamin formulas that contain the recommended dosage for the

general population. Omega 3 fatty acids inhibit the production of arachidonic acids and thus reduce concentrations of cytokines, which help with the inflammatory factor of prematurity. It is important to insist on the consumption of fruit, vegetables and oily fish.

5.8. **Probiotics**. In the absence of further scientific evidence, the consumption of dairy produce rich in probiotics will be recommended. However, the use of oral probiotics will be individualised for those women at higher risk of dysbiosis of the vaginal microbiome. Numerous studies show that the combined treatment of antibiotics and probiotics is effective in treating bacterial vaginosis and reducing recurrences, since they act by reducing vaginal pH, inhibiting the adhesion of pathogens and modulating immunity. There are also observational epidemiological studies that have observed a reduction in spontaneous preterm labour in women who consume dairy products rich in probiotics regularly.

6. Annexes

6.1. PRETERM LABOUR DEFINITION AND AETIOLOGY

Preterm labour is defined as the labour that takes place before the 37th week of gestation. It is considered to be the main cause of neonatal morbimortality.

In reference centres like ours, prematurity is classified in our centre as follows, according to the gestational age at which it occurs (5):

6.1.1. ***Extreme prematurity*** (which occurs before the 28th week of pregnancy): represents 14% of premature births.
6.1.2. ***Severe prematurity*** (Between 28.1 and 31.6 weeks):represents 15% of premature births.
6.1.3. ***Moderate prematurity*** (Between 32.0 and 33.6 weeks): represents 20% of premature births.
6.1.4. ***Mild prematurity*** (Between 34.0 and 36.6 weeks): represents 60% of premature births.

The introduction of prenatal improvements, such as the use of corticosteroids, neuroprotection and antibiotics in preterm prelabour rupture of membranes, and postnatal improvements, such as the introduction of surfactant, more effective ventilatory therapies and neonatal nutrition, have improved survival and decreased neonatal morbidity. However, the prevalence of preterm labour has remained unchanged, or has even increased in recent years, representing approximately 7-9% of childbirths according to national records, although in centres such as ours it represents up to 12% of deliveries.

The creation of the Preterm Birth Prevention Clinics allows a more specialised antenatal care with an individualised risk assessment and the possibility to apply general and specific preventive measures to prevent preterm labour in this group of women.

There are three types of preterm labour:

6.1.5. **Spontaneous preterm labour**: represents 31-40% of premature births.
6.1.6 **Preterm premature rupture of membranes**: appears in 3-5% of pregnancies. Represents 30-40% of premature deliveries.
6.1.7. **Elective delivery** due to maternal and/or foetal pathology (gestational hypertension, intrauterine growth restriction, gestational diabetes). Represents 20-25% of premature deliveries.

The aetiology of spontaneous preterm labour with sac intact or not is considered multifactorial. As known causes, we highlight:

- **Subclinical intra-amniotic infection**: in our centre, it is responsible for 14% of the cases of preterm labour with intact sac (6) and 28% of the cases of preterm rupture of the membrane (7).
- **Vascular case**: ischemia (inherited or acquired thrombophilia) or haemorrhagic (placenta previa, placental abruption, 1st or 2nd trimester haemorrhage of unknown cause).
- **Uterine overdistention**: multiple pregnancy (responsible for 15-20% of premature deliveries), polyhydramnios.
- **Uterine cause**: short cervix, chorioamniotic detachment, uterine malformation.
- **Psychological or physical stress**.

6.2. PRETERM LABOUR RISK FACTORS

6.2.1. **Prior premature delivery:** this is the most important risk factor related to prematurity. Miscarriages before 16 weeks do not increase the risk of preterm labour recurrence. The recurrence risk in these women is 15%-50% depending on the number and gestational age of the previous preterm labours. Preterm labour is directly proportional to the number of previous preterm labours and inversely proportional to the gestational

age of the previous labour. Pregnant women with an obstetric history of spontaneous preterm labour before 35 weeks have a 2.5 times higher risk of preterm labour in a new pregnancy. If 2 previous occurrences, the risk increases by 3.7 times, and if there are 3 previous occurrences, it increases by 5 times. If they have a history of a delivery <28 weeks, the risk of a new preterm delivery increases by 10.5 (8).

6.2.2 **Uterine factors**: such as **previous uterine surgery** (conisations, trachelectomy, uterine curettage) or **uterine malformations** (hypoplastic cervix, bicorporeal uterus (didelphys, bicornuate), uterine septum).

6.2.3. **Race**: more frequent in the black race (the risk of spontaneous preterm labour increasing by 3 times).

6.2.4. **Nutritional state**: a low body mass index (<19) increases the risk of preterm delivery (relative risk (RR) 9.8 <32 weeks).

6.2.5. **Extreme ages**: at extreme ages, the risk of spontaneous preterm labour increases by 10 times (9).

6.2.6. **Tobacco and other drugs**: a correlation between tobacco or other drugs (heroin, cocaine) and poor perinatal results has been shown. Tobacco is linked to inflammatory responses. Quitting smoking reduces the risk of preterm labour (RR 0.84, 95% CI 0.72-0.98) as well as the percentage for the baby being underweight when born (10).

6.2.7. **Intergenesic period <12 months**: it is associated with poor obstetric results, including prematurity (especially if there is a history of previous preterm labour).

6.2.8. **Stress at work**: there is some controversy here. There is some correlation between the number of hours worked with a significant degree of physical activity and psychological stress conditions. Women exposed to stress conditions have increased levels of inflammatory markers, such as CRP. This suggests that the inflammatory pathway is the cause of the risk of preterm labour in these cases.

6.2.9. **Periodontal disease**: possible hematogenous transmission. The relationship with preterm labour is controversial because randomised studies have not shown a reduction in preterm rates in women treated for periodontal disease during their pregnancy.

6.3 THERAPEUTICAL OPTIONS IN THE PREVENTION OF PRETERM LABOUR

6.3.1 **Progesterone**: progesterone reduces the risk of preterm labour by approximately 32%, both in women with and without a history of preterm labour (11). Given the possibility of monitoring cervical length in the Prematurity Unit, progesterone use is recommended in patients with cervix <25 mm in the second trimester. Overall, treatment with vaginal progesterone 200 mg/24h will be initiated and maintained until week 34-37.

6.3.2. **Cervical pessary**: the efficacy of the Arabin cervical pessary, inserted before week 24 in asymptomatic patients with a short cervix, has been evaluated in numerous studies. Its efficacy in preventing preterm labour is still controversial and pending new evidence (12).

6.2.3 **Uterine cerclage**: uterine cerclage is indicated for the prevention and treatment of cervical incompetence. Its indications are detailed in the specific Protocol for Uterine Cerclage.

6.4 PREDICTIVE MARKERS FOR PRETERM LABOUR

6.4.1. **Ultrasound cervical assessment**: there is evidence that, in the absence of uterine contractions, ultrasound measurement of the cervical length is an effective method to detect the population at risk of preterm labour (13). In asymptomatic patients, the presence of a cervix <25 mm increases the risk of preterm labour <34 weeks by 35%, despite the fact that the prevalence of a short cervix in the low-risk population is very low (1-2%).

6.4.2. **Fibronectin**: in our environment, the use of fibronectin will be reserved for cases of uncertain diagnosis. In daily clinical management, both ultrasound and fibronectin have a similar efficacy. Due to greater access to and the lower cost of the ultrasound in our setting, cervical length measurement (by transvaginal ultrasound) will be used as a predictive element for patient follow-up.

Fibronectin is an extracellular matrix protein located between the chorion and the decidua and is a marker of choriodecidual disruption. Under normal conditions, it is absent from cervicovaginal secretions above 24 weeks of gestation. It presents a prediction of preterm labour of 48%. Like the cervix, the most important thing is its high negative predictive value: only 1% of women with a negative test will give birth in the following 7 days

(14).

6.4.3. **Screening and treatment of asymptomatic bacteriuria**: treatment with antibiotics of pregnant women with asymptomatic bacteriuria is effective at reducing the risk of pyelonephritis and preterm labour. There is no evidence regarding the duration of the treatment (single dose or long therapy).

6.4.4. **Detection and treatment for bacterial vaginosis in the second trimester**: in our centre, a vaginosis screening will be carried out in pregnant women at risk of preterm labour before week 20. In these pregnant women, bacterial vaginosis increases the risk of preterm labour by more than double, even increasing by 4 times if vaginosis is detected before week 20.

Although there is some controversy regarding the impact of antibiotics in reducing preterm labour, the early use of antibiotics in bacterial vaginosis is recommended (15). Oral treatment with Clindamycin has shown to be more effective than treatment with metronidazole (15). Oral administration with 600 mg/day for 5 days leads to the eradication of 90% of the cases. No culture will be performed after treatment if the pregnant woman remains asymptomatic.

Vaginosis will not be screened in the third trimester because antibiotic treatment during the third trimester has been shown to treat the infection but does not reduce the risk of preterm labour. Screening will only be indicated in these cases if suggestive clinical signs.

6.5.5. **Detection and treatment for Chlamydia trachomatis, Ureaplasma and S. agalactiae**: there is not enough scientific evidence to integrate screening and treatment with Chlamydia, Ureaplasma or SGB as an attempt to reduce the risk of prematurity. But SGB S. agalactiae in the third trimester does make sense in order to reduce the risk of intrapartum neonatal sepsis.

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