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VAGINAL PROGESTERONE VS CERVICAL PESSARY IN THE FIRST TRIMESTER OF PREGNANCY FOR PREVENTING PRETERM BIRTH:

A MULTICENTRE RANDOMIZED CLINICAL TRIAL

FINAL DEGREE PROJECT

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1. Abbreviations

PTB	Preterm birth
WG	Weeks of gestation
13^{+6} WG	13 weeks of gestation and 6 days (*as an example*)
SGA	Small for gestational age
IUGR	Intrauterine growth restriction
LBW	Low birth weight
IGFBP-1	Insulin-like grow factor binding protein
PPROM	Preterm premature rupture of the membranes
CAS	Chorioamniotic separation
HPA	Hypothalamus-pituitary-adrenal axis
CRH	Corticotrophin releasing hormone
AB	Asymptomatic bacteriuria
BV	Bacterial vaginosis
BMI	Body mass index
ART	Assisted reproductive technology
CRL	Crown-rump length
CRP	C-reactive protein

2. Abstract

Background: Preterm birth has increased in the last decades and it has a lot of negative consequences not only for the new-borns, but also for their families and for the health system. Several studies found evidence about doing a vaginal ultrasonography in the mid-trimester of pregnancy to those women with risk factors of preterm birth to measure their cervix length. If the cervix is ≤25 mm, preventive treatment will be recommended. This treatment would be vaginal progesterone or a cervical pessary. Some studies showed that the measure of the cervix length could be done earlier because there is a relationship between the short cervix in the 2nd and sooner in the 1st trimester. Thus, the prevention could be done since the 1st trimester of pregnancy.

Objective: To prove if the vaginal progesterone is a better preventive treatment than cervical pessary, both used since the 1st trimester of pregnancy, in those asymptomatic women with risk factors of prematurity, single gestations and a cervix length of ≤30 mm.

Design and methods: It is a multicentre randomized clinical trial, including 900 pregnant women that will be recruited in five hospitals of Catalonia for 20 months. They will be randomized in two different groups: 450 women will receive vaginal progesterone, and a cervical pessary will be inserted in 450 women. We will collect the preterm birth rate in each group to do a statistical analysis and compare the percentages adjusted for all the co-variables.

Participants: pregnant asymptomatic women, with single gestation, risk factors for preterm birth and a cervix length of ≤30 mm measured by vaginal ultrasound within 11-13^{+6} weeks of gestation.

Keywords: preterm birth, vaginal progesterone, cervical pessary, vaginal ultrasonography, weeks of gestation.

3. Introduction

The World Health Organisation (WHO) considers preterm birth as birth before 37 weeks or 259 days of gestation. (1) We can classify prematurity in different grades (*Fig.1*): extreme (less than 28 weeks of gestation, are 5% of preterm births), serious (from 28 to 31^{+6} WG, 15% of preterm birth), moderate (from 31 to 33^{+6} WG, 20% of preterm birth) and mild (from 34 to 36^{+6} WG, 60% of preterm births). (2)

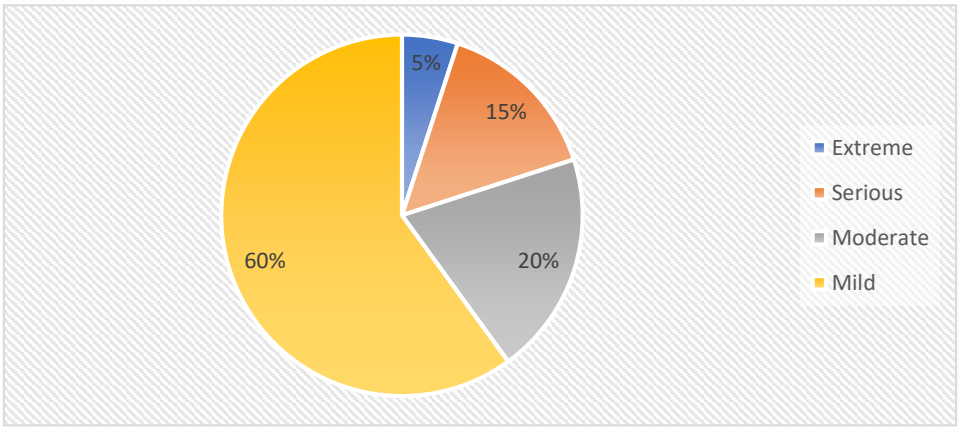

Figure 1: Grades of prematurity

The importance of considering 37 WG for the limit of preterm birth (PTB), is because there is high evidence that the new-borns before 37 weeks have higher morbidity and mortality than the full-term babies. Prematurity is the reason for approximately 70-85% of perinatal mortality not caused by lethal malformations. (3)

We must differentiate “preterm birth” from “low birth weight” (LBW) defined by the WHO as a weight of less than 2.500 g (up to and including 2.499 g) irrespective of the gestational age. Birth weight is the first weight of the fetus or new-born after birth and it should be measured in the first hour of life since a substantial postnatal weight loss takes places after that. (4) In Catalonia there were 5.205 new-borns with LBW in 2015. (5) Preterm birth and intrauterine growth restriction are the main causes of LBW. A new-born “small for gestational age” (SGA) is defined by the WHO as new-borns whose birth weight is less than 10 percentile for gestational age and it is caused by intrauterine growth restriction (IUGR) in most cases. (6)

3.1. Epidemiology

In most developed countries reported rates of preterm birth are generally 5-12%. In 2005 it was estimated that there were 12,9 million preterm new-borns worldwide (1), and in 2010 there were around 14,9 million preterm babies (uncertainty range 12,3–18,1 million), 11,1% of total births. (3,7). In Europe the rates are lower than in the U.S. (5-9% vs 12-13%). (2) In 1995 the Perinatal Medicine Section of "Sociedad Española de Ginecología y Obstetricia (SEGO)", took a national survey of perinatal mortality in Spain with results showing a preterm birth incidence of 6,94%. (8) Data from the "Instituto Nacional de Estadística" in Spain in 2015, showed 26.935 preterm births $<36^{+6}$ WG from a total of 420.290 deliveries (9). Despite the advancing knowledge in medicine in the last two decades, in the U.S. and as well as in Catalonia, the preterm rates have increased from 9,5% in 1981 to 12,7% in 2005 (U.S. rate) and from 5,5% in 1993 to 7,6% in 2002 (Catalonia rate). (2,8,10) This growth in the preterm rates could be influenced by the increased survival rates of the extreme preterm new-borns in the last decades (11), and also by the bigger number of preterm births caused by fetal suffering or maternal pathologies that a few years ago could not finish the pregnancy. However, nowadays comparing risks and benefits, is it better to provoke childbirth or do a caesarean section than extend the pregnancy. (12)

3.2. Diagnosis

It is important to clarify the difference between "risk of spontaneous preterm birth" in asymptomatic pregnant women, who are our trial population, from "threatened preterm labour," which is defined as the apparition of regular uterine dynamic associated with progressive dilatation of the cervix that occurs from the 22^{nd} to the 36^{th+6} weeks of gestation (8,13). If this process occurs before the 24^{th} week it is considered a miscarriage, and after the 37^{th} WG it will be the normal process of delivery at term.

However, the criteria defining “threatened preterm labour” has low sensibility and specificity to predict preterm labour, since the real risk in this cases that a preterm delivery occurs is only about 20-30%. There are some better objective predictors of preterm birth, like fetal fibronectin, a transvaginal ultrasonography, detection of IGFBP-1 (a glycoprotein that acts like an adhesive factor of the placenta and the amnion to the decidua; Partus test®) or PAMG-1 (Parto Sure®). (13) Fetal fibronectin, a glycoprotein of the extracellular matrix located between the chorion and the decidua, (*Fig. 2 & 3*) is a biomarker of choriodecidual disruption and membranes alteration when it is present in cervicovaginal fluid above 24 WG. Under normal circumstances, this biochemical substance is absent from cervicovaginal secretions in the 24th-37th weeks of gestational period, approximately. It has a predictive power of 48% and a specificity around 96-98%, but the most important feature of fibronectin is its negative predictive value because it is estimated that only around 1% of women who had a negative test will deliver within the next seven days. (14)

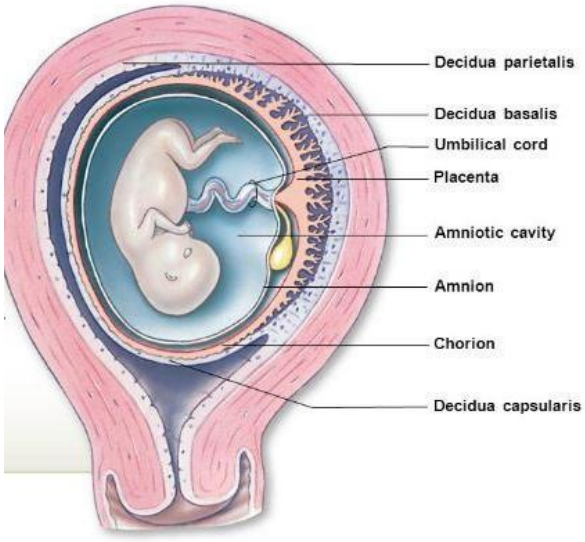

Figure 2. Scheme of the membranes in a pregnancy. (15)

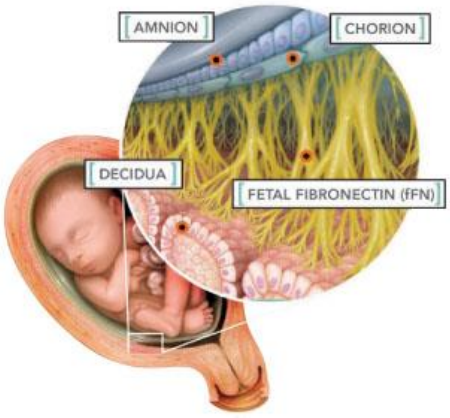

Figure 3. Fetal fibronectin between the chorion and the decidua. (16)

Transvaginal ultrasonography has the same efficacy, is more applicable and has less cost compared with the rest of objective predictors, so it would be the first election technique to determine the real risk of PTB. (17)

3.3. Etiologies

We can describe the following main causes (*Fig.4*) that lead to a preterm birth which are:

I. Spontaneous preterm labour divided in two categories:
   a. With intact membranes (40-45%),
   b. Preterm premature rupture of the membranes (PPROM) (25-30%);

II. Delivery for maternal or fetal indications (30-35%).

PPROM is defined as spontaneous rupture of the membranes before 37-WG and at least 1h before the beginning of contractions. In most cases, we cannot find the cause but it is frequently the consequence of an asymptomatic intrauterine infection, and infections and tobacco exposure are main risk factors. (2)

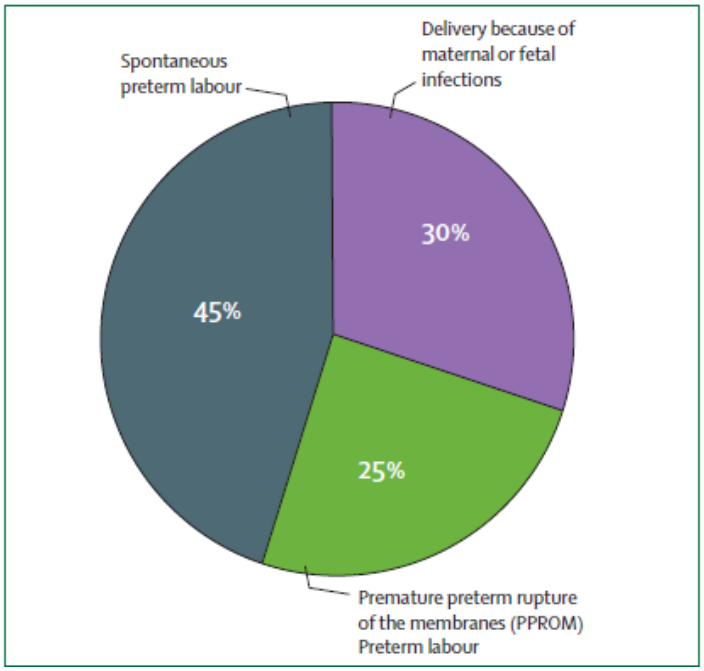

Figure 4: Obstetric precursors of preterm birth. (2)

Some main causes of preterm delivery for maternal indications are pre-eclampsia, pre-gestational and gestational diabetes, uterine anomalies (bicorne uterus, myomas that have been operated), placenta previa, fatty liver or other important maternal diseases that could improve after delivery. The most important etiologies of preterm delivery for fetal indications are multiple gestations, especially if they are monochorionic, congenital anomalies, intrauterine growth restriction (IUGR), suspicious of loss of fetal wellbeing, umbilical cord prolapse or macrosomia >4,5kg. (18)

The etiology of spontaneous preterm birth with or without intact membranes is considered multifactorial and we do not know the exact mechanisms that initiate the process in several cases, but there are some pathological processes that can cause preterm labour as (19):

- **INTRAAMNIOTIC INFECTION:**

It is known that an intraamniotic infection activates the innate immune system because microorganisms are recognised by the pregnant macrophages and leucocytes, and inflammatory chemokines, cytokines and vasoactive peptides are released. The proinflammatory chemokines and the microbial endotoxins by themselves stimulate the production of prostaglandins, which produce uterine contractility, and matrix-degrading enzymes that degrade the fetal membranes and leads to PPROM (2,20). Normally, the diagnosis of acute chorioamnionitis is done by amniotic fluid cultures but it can also be done by histological exam of the placenta when the gestation is ended, and we can make a further diagnostic. It is estimated to be the cause for approximately 25-40% preterm births (2), but these diagnosis techniques sub-estimate the real association of intraamniotic infection and preterm birth since there is another important amount of cases that could show negative cultures but positive PCR (polymerase chain reaction) detection of the microorganism in the amniotic fluid, and the chorion colonization is usually higher than the amnios colonization. (21)

Moreover, some studies showed that asymptomatic intrauterine infection could be the hidden cause of more than 14% of preterm births with intact membranes and around 28% of PPROM, data from "*Hospital Clínic de Barcelona*" in 2015 (22–24). Attending to these high rates of subclinical infection, there are important indicators that help the clinicians do an early diagnosis such as CRP (C-reactive protein) in maternal serum. (25) It is suggested to do an amniocentesis (*Fig.5*) in those "idiopathic" cases of threatened preterm birth in singleton pregnancies of ≤ 32 WG that we suspect asymptomatic intrauterine infection as the leading cause, to confirm it. The management of a chorioamnionitis would be antibiotic treatment and termination of the pregnancy. (13)

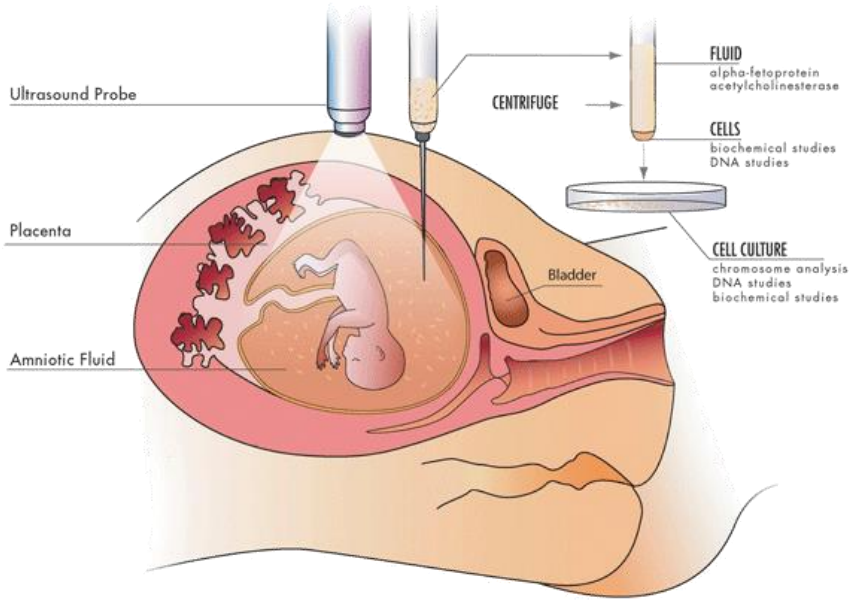

Figure 5. Amniocentesis procedure. (26)

The most common microorganisms involved in intraamniotic infection are genital *Mycoplasma spp* and *Ureaplasma urealyticum* that reach the amniotic cavity by the ascending route from the vagina and the cervix in the majority of cases. Pregnant women that have *Ureaplasma urealyticum* positive PCR (polymerase chain reaction) but negative cultures are also at risk of PTB and perinatal outcome, like the ones who have positive cultures.

Therefore, the classical technique to diagnose infection could be infra-estimating the infection rates. (21)

Some researchers analysed the membranes of pregnant women that were having an elective caesarean section at term and they detected bacteria in around 70% of them. Thus, the conclusion was that bacterial infection probably is an important risk factor and predisposes to preterm birth but is not sufficient by itself to produce it. (27)

- **UTERINE OVERDISTENSION**:

- **Multiple gestations** cause 15-20% of preterm births (2,24) and they have increased a lot its rate in the last few decades mostly due to assisted reproduction techniques. The increase of the uterine content produces overdistension of muscle fibres which causes the onset of contractions sooner than expected. (8) It is also important to note the number of twins that are born preterm because it is indicative of maternal disorders such as pre-eclampsia or fetal suffer. (2,20)
- **Polyhydramnios** produced in macrosomia, diabetes, multiple gestation, and infections (*Parvovirus B19*) is another cause of uterine overdistension and it can lead the onset of contractions and PPROM before 37 WG. Polyhydramnios may also be observed in fetal malformations or in severe isoimmunization, but it can also be spontaneous. (2,8)

  On the other hand, oligohydramnios is associated to preterm birth too. (2)

- **VASCULAR CAUSES**:

- **Ischemia** (hereditary or acquired thrombophilia). (24)
- **Haemorrhage** (previous placenta, abruptio placentae, bleeding in the 1st or 2nd trimester with unknown cause): vaginal bleeding in the 3rd trimester, caused by placenta praevia or abruptio placentae (*Fig.6*), is hardly associated with preterm birth with an odds ratio (OR) of 5,91 in P. Meis *et al* study (19) so it is considered to be

one of the factors with the highest risk. It is logical because many of those situations are emergencies ending in a caesarean section irrespective if it's term or preterm (2,19). However, bleeding in the first and second trimesters is also associated with preterm birth. In Williams MA *et al* study (29) women who experienced vaginal bleeding only in the first trimester (n = 1174) had double the risk of delivering a preterm new-born compared with those that did not bleed (adjusted risk ratio = 2,0; 95% confidence interval 1,6-2,5).

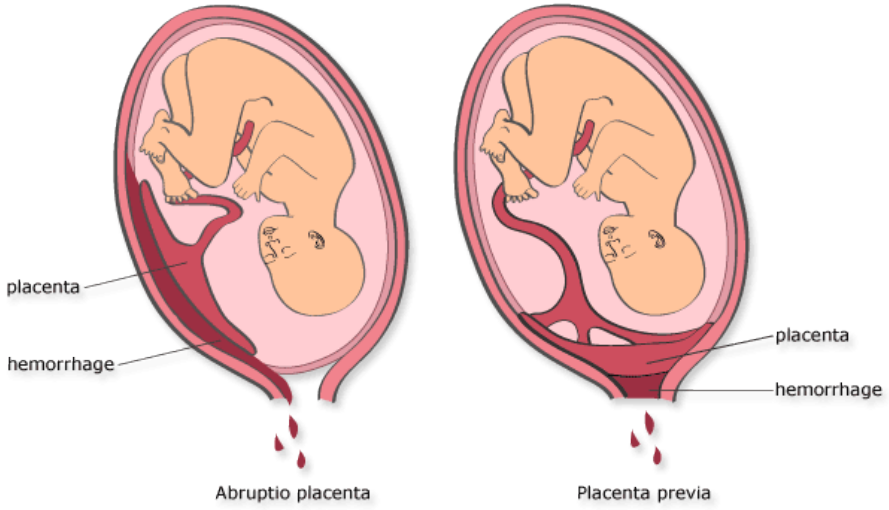

Figure 6. Vaginal bleeding in the third trimester without any traumatic event. (28)

- **UTERINE CAUSES**:

  - **Short cervix length**: the cervix of a pregnant women gets shorter as labour approaches. Measured by transvaginal ultrasonography in the second trimester, a cervix length of less than 25mm increased the risk of having a preterm birth of <34 WG around a 35%. The shorter the cervix, the higher the risk. (2) However, the prevalence of short cervix in low risk pregnant women is low, around 1-2% (17) and that is the reason why it is not recommended a vaginal ultrasound screening of all pregnant women.

- **Cervical insufficiency**: it can be congenital (abnormal development) or acquired by surgery or excessive dilatation. The inability of maintaining the fetus inside the uterine cavity leads to a progressive asymptomatic dilatation of the cervix with the membranes' protrusion or expulsion. The main treatment would be the insertion of a cervical cerclage. (8)
- **Chorioamniotic separation (CAS)**: the separation between the amnios and chorion can be physiologically normal if it is diagnosed before 14 weeks of gestation. After that time, any type of separation is pathological because both membranes usually fuse from 14 to 16 WG. (*Fig. 7*) Bibbo *et al* in a retrospective cohort study found that the rate of preterm delivery was significantly higher for those with chorioamniotic separation than for those without (57,5 vs. 17,1%, $p < 0.0001$). (30)

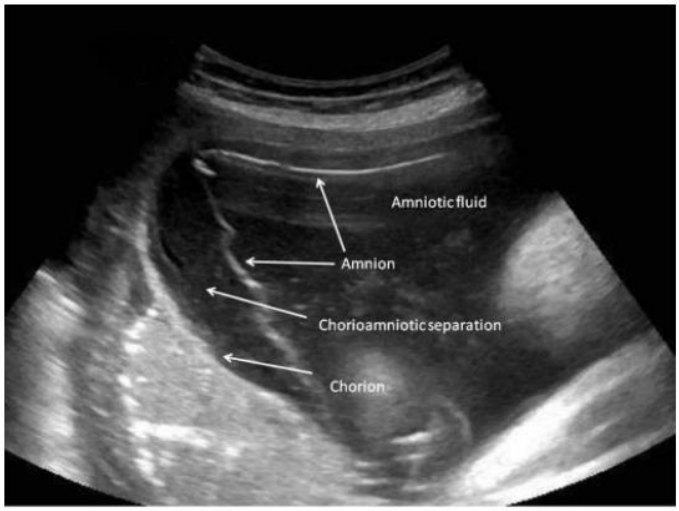

Figure 7. Chorioamniotic separation diagnosed by ultrasound evaluation at 39 weeks. The arrows point at the amniotic membrane that has separated from the chorion. (30)

- **Uterine malformation** (*Fig. 8*): congenital or acquired uterine anomalies can impede the normal growth and distention of the uterus during pregnancy and can restrict the normal development of the fetus, leading in a preterm delivery. The most common malformations are those derived from the abnormal development or uncomplete fusion of Müller's ducts that could end in a single hemi-uterus.

Another malformations could be bicorporal uterus (didelphys, bicorne), the existence of a uterine septum or a cervix hypoplasia. Uterine myomas that deform the uterine cavity, depending on their size and location, can also endanger the normal duration of a pregnancy. (2,8,24)

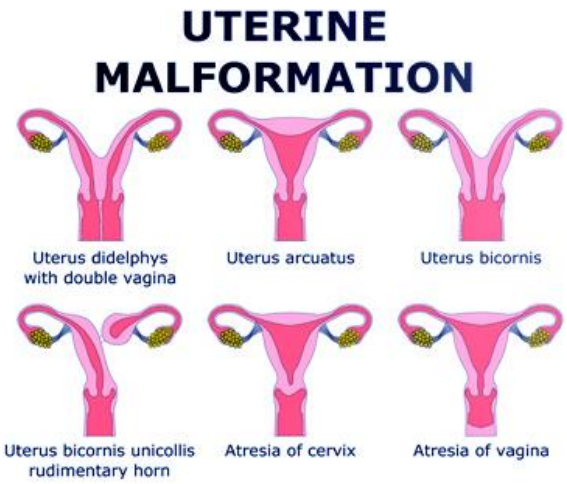

Figure 8. Uterine malformations (31)

- **Uterine surgeries**: trachelectomy and any type of treatment for cervix intraepithelial neoplasia (CIN), such as cervical cone biopsy and loop electrocautery excision procedure, are related with higher rates of preterm birth, which are especially severe and extreme preterm births. (2,24,32) Jakobsson *et al* (32) found in a retrospective cohort-study in Finland that the risk of any preterm delivery (less than 37 weeks of gestation), was increased after cervical conization with a relative risk [RR] of 1,99; 95% confidence interval [CI] of 1,81-2,20. The risk was especially higher to have a very preterm new-born (28-31 weeks of gestation), with a [RR] 2,86; 95% [CI] 2,22-3,70 and to have an extremely preterm baby (less than 28 weeks of gestation) [RR] 2,10; 95% [CI] 1,47-2,99.

- **MATERNAL FACTORS:**

Systemic maternal infections such as appendicitis, pneumonia or pyelonephritis are related to higher rates of preterm delivery (8). Other important maternal diseases like diabetes, thyroid disease, asthma, and hypertension, are associated with preterm labour sometimes due to maternal complications, but they are also related with an increased rate of spontaneous preterm deliveries. (2,8) Spontaneous preterm delivery in cases of maternal hypertension during pregnancy may be linked with vasospasm and ischemia producing placental abruption and preterm labour. (8) In a pregnant woman, every serious trauma can cause an onset of uterine dynamic because there is an adrenaline and noradrenaline realised by the maternal kidney glands that can activate the uterine muscles fibres culminating in contractions and preterm delivery. Also every surgery, specially abdominal surgeries and those in the 2nd and 3rd trimester, activate the adrenaline and noradrenaline realises, and are associated with higher preterm rates. (2,8)

3.4. Risk factors

Attending the multifactorial etiology of preterm birth, is primordial to know at least the risk factors and the different associations to try to prevent it:

- **Previous preterm delivery before 34 weeks of gestation:** Women with a previous preterm delivery have a recurrence risk of 15-50%, depending on the number and gestational age of previous deliveries, with an inverse relationship between the gestational age of the previous preterm birth and the risk of another preterm birth; reported by Mercer *et al*. (2,33) Women with previous preterm deliveries had a 2,5-fold increased risk in their next pregnancy, and with every PTB they acquire more risk to the future ones. (33) This higher risk could be explained by the underlying cause that could be, persistent or recurrent intrauterine infections in repetitive

spontaneous preterm births, or disorders like diabetes, obesity or hypertension in indicated preterm births (this maternal diseases often persists between pregnancies). (8,34)

- **Late gestational loss (≥ 17 WG)**: history of stillbirth and miscarriages, and poor obstetric history in general, are related with higher rates of preterm births (8), but miscarriages before 17 WG are not related with a future PTB. (24)
- **Parity**: nullipara women have higher risk of preterm delivery. However, those women who have three or more previous deliveries also have increased rates of preterm labour. (8)
- **Short interpregnancy interval**: intervals of less than 18 months were associated with higher rates of PTB, LBW and SGA even after adjustment for co-variables. (35)
- **Psychological or social stress**: mothers subjected to high levels of social or psychological stress have higher risk of preterm delivery even after adjustment for the effects of other sociodemographic, behavioural and medical risk factors. (36) Some studies found a relationship between the dysregulation of hypothalamus-pituitary-adrenal axis (HPA) produced in chronic stress situations and the higher rates of preterm births. The increased corticotrophin releasing hormone (CRH) and cortisol levels are suggested to be the linking factor. (37) Women exposed to chronic stress have a C-reactive protein (CRP) concentration increased in serum compared to those without exposition, so stress may increase the risk of preterm delivery by systemic inflammation. (2)
- **Depression during pregnancy**: maternal depressive symptoms have been linked with higher risk of preterm birth compared with women without or with minimal symptoms.(38)
- **Low socioeconomic and educational status** is related with higher rates of preterm delivery, but the association is less in a multivariable analysis because this situation is often related with other risk factors such as low maternal age and weight, and

smoking habit. Even so, low socioeconomic and educational status are risk factors by themselves. (8,39)

- **Genetic component:** if a pregnant woman has a sister who gave birth preterm, she has an 80% higher risk to do the same. (40)
- **Origin**: African-American and Afro-Caribbean women have approximately double risk of preterm birth and three-four times more likely to have an extreme preterm birth than Caucasian or Asian women. East Asian and Hispanic women typically have low preterm birth rates. (24,41)
- **Low and high maternal ages (<20 and >35 years old)**: in extreme maternal ages the risk is multiplied by a factor of 10 for a spontaneous preterm delivery. (24) Pregnant teenagers have higher risk of PTB, regardless of socioeconomic status or other variables. Pregnant women >35 years old have also higher rates of PTB but in most cases is due to medical indication because of maternal factors. (8)
- **Maternal body-mass index (BMI)**: low pre-pregnancy BMI is associated with higher risk of PTB with and OR 9,8 in <32WG and it can be related with a decreased blood volume and reduced uterine blood flow. (24,42) A maternal weight of less than 55kg in the 20th WG is hardly linked with PTB. (8) On the other hand, obesity has had opposite results in the association with PTB: Hendler *et al* found that obesity could be protective in order to have a preterm delivery (42) but Cobo *et al* found that obesity is associated with higher rates of prematurity not only for medical indications (pre-eclampsia or diabetes) but also for spontaneous reasons. (24)
- **Working long hours and hard exertion:** Saurel-Cubizolles *et al* found that working more than 42h a week or standing more than 6h a day were risk factors to have a PTB. (2,43)
- **Anaemia:** a haemoglobin of less than 9,5g/dl doubles the risk of PTB specially if it occurs in the 1st and 2nd trimester. The anaemia produces a chronic hypoxia that activates the realising of CRH by the placenta and the production of cortisol by the foetus with the consequent preterm delivery. (24)

- **Immunologic mechanisms**: autoimmune diseases, such as systemic lupus erythematosus and antiphospholipid syndrome, are related with a higher rate of preterm delivery and other obstetric adverse events like miscarriages and IUGR. (8)
- **Multiple gestation** (*described above*)
- **Uterine factors** (*described above*)
    - Conization
    - Uterine malformation
    - Cervical incompetency
    - Short cervix length
- **Asymptomatic bacteriuria (AB)**: it occurs in 2-10% of pregnancies and, if not treated, around 30% of them will develop an acute pyelonephritis. Asymptomatic bacteriuria is a risk factor for pyelonephritis, low birth weight and preterm birth. It is important to have a urine culture for screening during the three trimesters of pregnancy. In cases of AB, an antibiotic treatment is recommended, depending on the antibiogram, because there is evidence that it can reduce the incidence of development an acute pyelonephritis and also the rate of preterm births. The asymptomatic bacteriuria diagnosis needs an urine culture, it is not recommended to use the urine test strip because many AB may not have leucocytes in the urine and this is what the test strip identifies. (44,45)
- **Bacterial vaginosis (BV)**: is defined as an imbalance of the normal vaginal flora with a lack of normal lactobacilli flora and overgrowth of anaerobic bacteria. It is often asymptomatic but the most common symptom is a profuse white vaginal discharge with a fishy odour when the vaginal discharge is exposed to potassium hydroxide, which is easily to diagnose with a pH strip because it will appear >4,5. The BV has been associated with 1,5-fold to 3-fold increase in the rate of preterm delivery. (46) The early diagnosis and treatment of BV before 20-WG decreases the risk of PTB in asymptomatic pregnant women. However, the prevalence of BV is low, so the American College of Obstetricians and Gynaecologists (ACOG) and the Centres for

Disease Control and Prevention (CDC) do not recommend the population screening. If there are symptoms of BV, the treatment will be oral clindamycin 300mg/12h for 5-7 days. (24,47)

- **Assisted reproductive techniques (ART)**: in the last few decades the use of ART has increased a lot worldwide, according to the CDC there were 208.786 ART procedures done in 2014. The ART and the ovulation induction procedures are risk factors for prematurity not only because there are more cases of multiple pregnancies, but it is also a risk factor for single ones. ART is also related with higher rates of LBW, SGA and perinatal mortality. (48)
- **Smoking habit**: tobacco use increases the risk of PTB. This is perhaps caused by the systemic inflammatory response that leads to a spontaneous PTB, or vasoconstriction in other pathways, because nicotine and carbon monoxide are powerful vasoconstrictors and they can cause placental damage and decreased uteroplacental blood flow that could end in a IUGR and indicated PTB. (49) Smoking cessation is attributed with 20% risk reduction of PTB. (24)
- **Alcohol**: heavy consumption is associated with PTB. (2)
- **Drugs**: heroin and cocaine use is linked with an increase rate of PTB. (2,50)
- **Malaria**: *Falciparum malaria* after 24–28 weeks of gestation was linked with preterm birth (early from 28-32 WG, and also late from 32-37 WG) (OR range: 1,44–2,53; p range: <0,001–0,001). If a pregnant woman is infected at 24–28 WG by *Vivax malaria*, she has an increased risk of very preterm birth (OR: 1,79 [1,11-2,90]). If this occurs at 28–32 WG, the risk will be of late preterm birth (OR: 1,23 [1,01-1,50]). These associations are also true for asymptomatic malaria. (51)
- **Periodontal disease**: there is evidence of an association between periodontitis and PTB, and some randomized trials found that an accurate treatment of periodontitis will improve the perinatal results. (52)

- **Genital infections (trichomoniasis, chlamydia, syphilis, gonorrhoea)**: vaginal infection by *Trichomonas vaginalis* appears to be related with preterm delivery with a relative risk (RR) of 1,3 (CI 95% 1,1-1,4) (53). *Chlamydia trachomatis* is related with PTB but we do not know the exact risk, and there is not enough evidence to recommend the screening and treatment (24,54). Syphilis is associated with a RR of 4,8 (CI 95% 4,2-10,5) when RPR is positive and they no receive appropriate treatment; and gonorrhoea with a RR of 6 (CI 95% 1,5-34). (55)

  Vaginal group B Streptococcus is not related with PTB but it makes sense to do the screening in the 3rd trimester in order to reduce the risk of neonatal sepsis when the new-born goes through the birth canal. (24)

3.5. Prevention

Table 2. Strategies of PTB prevention

Primary prevention	Eradicate risk factors	Pre-gestational measures
Secondary prevention	Detection of high risk in asymptomatic period	Screening strategies
Tertiary prevention	Treatment in the symptomatic period	Diagnosis and treatment of threatened preterm birth
Quaternary prevention	Avoid iatrogenic	Do not recommend interventions that do not have enough evidence

The ideal would be to do **primary prevention** to diminish or eradicate the risk factors before the pregnancy occurs. However, in many cases, this is not possible because some of the risk factors like previous preterm births, multiple gestation, origin, low maternal BMI, age younger than 20 or older than 35 years old, uterine or cervical factors, vaginal bleeding, etc; cannot be altered. (8)

On the other hand, there are some risk factors that could be managed with strategies like:

- Control maternal weight and gestational diabetes to avoid macrosomia and polyhydramnios. (2,8)
- Accurate treatment of maternal diseases like diabetes, thyroid diseases, asthma and hypertension. (2,8)
- Recommend interpregnancy interval larger than 18 months, and get pregnant when the woman is 20-35 years old. (35)
- Social interventions to protect the pregnant women in lower socioeconomic and educational status. (8)
- Implant the embryos only one by one (single embryo transfer, SET) in fertilization programs, to diminish the number of multiple pregnancies. (56)
- Avoid stress situations (36) and hard exertion (2,43).
- Use iron supplements to treat anaemia if it is produced by iron deficiency. (24)
- Antibiotic treatment for the asymptomatic bacteriuria. (2,44,45)
- Oral clindamycin 300mg/12h for 5-7 days to treat bacterial vaginosis. (24,47)
- Antibiotic treatment for the genital infections. (53–55)
- Malaria accurate treatment. (51)
- Stop smoking and every drug use. (2,50)
- Try to maintain a good periodontal hygiene. (52)

Although these strategies worked, we must focus mainly on **secondary prevention**, trying to diagnose the pregnant women with higher risk when they are still asymptomatic. This early diagnosis must be done combining the anamnesis and clinical history of the pregnant woman and objective predictors such as vaginal ultrasonography to measure the cervix length or the fetal-fibronectin detection on vaginal exudate. Both techniques have similar efficacy so we will use vaginal ultrasonography because it lower cost and applicability. (17,24)

If we find a cervical length ≤25mm in an asymptomatic pregnant woman in the mid trimester (19^{+6}-21^{+6} WG) vaginal ultrasonography, she will have 35% more risk of a preterm delivery before 34 WG. (17) The population with high risk factors and short cervix will be candidates for preventive treatment with vaginal progesterone (57) or the implantation of a cervical pessary. (58,59) Several studies found evidence to recommend both treatments as different options for secondary prevention of PTB <34 WG, and there is no consensus about which one is better. (60)

The aim point is to do the cervix length screening earlier and start the preventive treatment as soon as possible with the objective of preventing more preterm deliveries than if the screening is done in the mid-trimester. (61)

Cervical Mc Donald cerclage is another preventive technique of PTB, but nowadays is reserved for cervical insufficiency and history of more than two miscarriages. (24) (*Figs. 9, 10*)

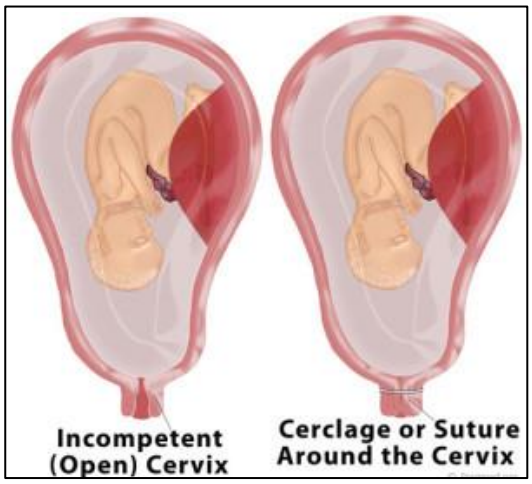

Figure 9. Cervical cerclage. (62)

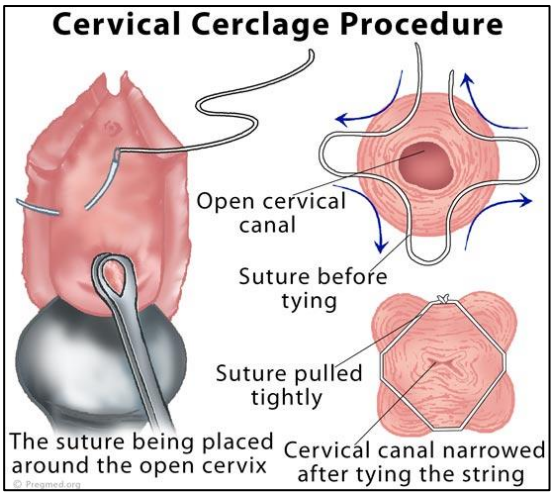

Figure 10. McDonald cerclage procedure. (62)

Although this strategies of secondary prevention have demonstrated a reduction in the PTB rates compared with no-intervention (57–59), there are still cases of **threatened preterm birth** that will need an accurate diagnose and treatment. The diagnosis process, as shown by *Hospital Clínic* and *Hospital Sant Joan de Déu* (13), will require:

- Gestational age dating (better if it was done in the 1st trimester).
- Precise anamnesis to identify if there is any situation that contraindicates the tocolytic treatment (abruptio placentae, chorioamnionitis).
- Physical exploration to check if there is another reason to explain the pain or the uterine dynamic.
- Obstetric exploration including:
    - Evaluation of the abdomen (uterine height, fetal static, uterine irritability, etc.).
    - Speculum: visualization of the cervix (discard amniorrhexis, metrorrhagia, etc.), take an endocervical smear to discard bacterial vaginosis.
    - Vaginal touch: cervical assessment using the characteristics of the Bishop's Score. (Annex 1)

- Abdominal ultrasonography to check: positive cardiac fetal frequency, fetal situation and biometrics, situation and characteristics of the placenta, amniotic fluid aspect and quantity, etc.
- Vaginal ultrasonography to measure the cervix length.
- NST (non-stress test) to evaluate the uterine dynamic and reject loss of fetal wellness.

- Blood analysis with an hemogram, CRP (to discard subclinical chorioamnionitis), basic biochemical and coagulation.
- Urine sediment and culture to discard asymptomatic bacteriuria and urine infection.
- Amniocentesis if ≤ 32 WG and we suspect asymptomatic intrauterine infection to confirm it. In the amniotic fluid we will check the glucose rate, and we will do a Gram stain, culture for aerobic and anaerobic bacteria, culture for mycoplasmas and QF-PCR (Quantitative Fluorescence – Polymerase Chain Reaction).

The management of threatened preterm birth will be done with tocolytics, magnesium sulphate for neuroprotection if the delivery is going to occur <32 WG and corticoid therapy if it happens from the 24th to 34+6th WG. It has been demonstrated that antenatal corticosteroids reduce not only the respiratory morbidity for distress respiratory syndrome, but also the global morbidity and mortality of premature new-borns. The corticoid therapy will be Betamethasone 12mg IM two doses separated between 24h. Also the pregnant woman will need to rest, and heparin treatment will be required. (13,63)

In order to avoid iatrogenic, as **quaternary prevention**, clinicians will not administer interpregnancy antibiotics in women with previous PTB with the objective of diminishing the risk of recurrent PTB because there is no evidence that it could help. (24) Vitamin C supplements are not useful to prevent PTB, so they are not recommended. (24,64)

3.6. Consequences

Prematurity has several consequences, the most common or severe are the following:

- Main cause of **perinatal and neonatal mortality**: around 75% of perinatal mortality (from 28 WG to 7 days after delivery) is caused by PTB and most preterm children have higher risk of death compared with others that were born at term. (2,65) Prematurity is also the principal cause of neonatal mortality that encompasses the period between labour and the first 28 days of life. (24)
- Main cause of **neonatal morbidity**: nowadays 80-85% of preterm babies survive, although there are huge differences among different countries. (2) Some of the multiple diseases that can appear in a preterm new-born are:
    - **Low birth weight**.
    - **Respiratory** (66): is the first cause of morbidity-mortality in preterm new-borns. There is a lack of maturity and alveolar development. The surfactant synthesis is not enough. There is also a central neurological immaturity and the respiratory muscles are weak.
        - Respiratory distress syndrome caused by the lack of surfactant.
        - Apnoea of prematurity.
        - Respiratory infections.
        - Bronchopulmonary dysplasia defined as oxygen dependency at 36 weeks postmenstrual age or oxygen dependency >21% for 28 days or more.
    - **Neurologic** (65,66): the damage is caused by immaturity and hypoxia.
        - Intraventricular haemorrhage: the vascular system in the germinal matrix is fragile and the cerebral mass is really susceptible to osmolarity, tension changes and hypoxia. Thus, the sub-ependyma tissue can bleed and cause an intraventricular haemorrhage.
        - Periventricular leukomalacia is the sign of hypoxia in the white substance.

- Hypoxic-ischemic encephalopathy (HIE) and intrapartum hypoxia, cause long-term neurodevelopmental problems.
- Kernicterus or neonatal encephalopathy could happen with low bilirubin rates because of the increased permeability of blood brain barrier.
- Cerebral palsy (CP) is the most common long-term neurodevelopment disability and with greater prevalence when the gestational age at delivery is lower. Around 5-15% of preterm new-born with a birth weight of <1.500g will develop CP (67). Nevertheless, prematurity is the cause of cerebral palsy in less than 50% of CP cases.
- Epilepsy is more common in preterm children than term ones.
- Cognitive impairment, disorders of attention and activity, and behavioural problems are more prevalent in preterm children.

- **Digestive** (66,68):
  - Necrotizing enterocolitis: the intestine gets necrotic with or without perforation because of ischemia, bacterial overgrowth and immune systemic response. Prematurity is the main risk factor to develop it.
  - Feeding problems because the suction and coordination with swallowing mechanism is not matured until 32-34 WG, and there are also problems of gastroesophageal reflux, gastric capacity limited and slow evacuation because the intestinal motility is not normal.
- **Ophthalmologic** (65,66):
  - Retinopathy of prematurity caused by the stop of retina vascularization and formation of disorganized neoangiogenic vessels.
  - Myopia and hypermetropia: children born before 28 WG have six-fold risk of develop them.
- **Hearing impairment** (69): prematurity and LBW are main risk factors to have neonatal hearing loss.

- **Infections and neonatal sepsis** (66,70): the immunity of preterm babies is not proficient, specifically the unspecific one. Due to the fact that the immune system of these new-borns cannot limit the infection in one organ, it is frequent that neonates develop sepsis.
- **Disability in renal function** (71): preterm new-borns have a lower number of nephrons because nephrogenesis is not completed until 34-36 WG. They also have a decreased vascularization of kidneys and tubular dysfunction. Preterm babies with these problems will develop renal injury faster than term ones who do not suffer these pathologies.
- **Hypothermia** (66): preterm new-borns have temperature regulation problems and tend to hypothermia because they have low metabolism, decreased fat reserve and poor vasomotor control.
- **Hypoglycaemia** (72): preterm babies have lower glycogen reserves, an immature hormonal response and feeding problems. Thus, the development of hypoglycaemias, that can be symptomatic or not, is frequent.
- **Admission to the neonatal intensive care unit (NICU)**.

In addition, preterm children have higher risk of short but also long-term morbidity (65), and there is evidence that early life events plays an important role in the development of adult diseases, concept known as “programming” (71):

- Adult hypertension.
- Early nephrolithiasis.
- Reduced forced expiratory flow at 25-75% of the forced vital capacity and distal airflow obstruction.
- Neurodevelopmental disabilities: cerebral palsy, visual and hearing impairment, language disorders, learning disabilities, behavioural problems, etc.

- Obesity: the preterm infants growth reaches the same point as term ones around the first 2-3 years of life, and this rapid weight gain is associated with increased adiposity and obesity.

The consequences of preterm birth are not only for the new-born, but also for the mother with infection complications when the cause of preterm delivery was an infection (for example a chorioamnionitis), and also caesarean section scar infection. Additionally, haemorrhage, for example, when the cause of preterm labour was a placenta praevia or abruptio placentae. (8)

4. Justification

In 2015 there were around 15 million preterm new-borns worldwide with huge differences between high-income and low-income countries. (7) Prematurity is one of the main causes of neonatal mortality with approximately 1.033.000 (720.000-1.222.000) deaths caused by complications of preterm birth. These number represents the 29-35% of total neonatal deaths in 2010 that they were approximately 3,6 million (73). Premature birth is also the principal cause of morbidity in children, with short and long-term sequels, and with an inverse relationship between the gestational age and the risk of complications. (65)

Another important aspect is the cost that prematurity carries for the health system and the patient's family. In 2005 in U.S., the Institute of Medicine (IOM) estimated that the cost of prematurity for the society was 26 billion dollars annually including the whole cost of the children until they are 5 years old, the delivery cost, the early interventions, special education, and lost productivity costs. (74)

The negative consequences of prematurity and the lack of measures to improve or cure the diseases related to that, puts the prevention as an aim point. Nowadays it is accepted and recommended, based on evidence, to do a vaginal ultrasonography in the mid trimester visit (19^{+6}-21^{+6} WG) for those pregnant women with high risk factors like previous preterm deliveries, cervix surgeries or uterine malformations. The risk of PTB is inversely associated with the cervix length. (17)

There is an average studies about the secondary prevention treatments of PTB, started after finding a cervix length ≤25 mm in the transvaginal ultrasonography performed in the mid trimester, with special interest in vaginal progesterone and cervical pessary:

Romero *et al*, in February 2018, published a meta-analysis of individual patient data (57) where they affirm that PTB and neonatal mortality and morbidity decreased with vaginal progesterone treatment in asymptomatic pregnant women with cervix length ≤25 mm.

There were not significant side effects on the treatment group. In addition, Werner *et al* (75) declared that universal cervical length screening and use of vaginal progesterone if cervix <15mm is a cost-effective measure because it could prevent 22 cases of neonatal deaths or long-term neurologic impairment and save 19,6 million dollars for every 100.000 women screened.

Goya *et al* (59), in 2012, published that PTB rate diminished in the pessary group versus the expectant management group with an odds ratio 0,18 (95% CI 0,08-0,37; p<0,0001), and without severe side effects associated. *Saccone et al* (58), in 2017, reaffirmed the pessary utility but proposed that further multicentre randomized clinical trials were needed to confirm it.

Multiple researchers have done randomized controlled trials to prove if one option of the two preventive strategies explained above is better than the other for singleton asymptomatic pregnant women with a short cervix ≤25 mm in the mid trimester, but for now there is no consensus. (60,76,77)

Our novelty approach is to do the vaginal ultrasonography in the first trimester visit (11-13^{+6} WG) because there is evidence that there is a significant association (r = 0,548, p <0,0001) between the endocervix measures done in 11-13^{+6} WG period and those at 19^{+6}-21^{+6} WG. The cervix length of women who later had a preterm spontaneous delivery was shorter, already in the 1st trimester, compared with those women who had a term baby. (78) Vaginal progesterone is demonstrated to decrease the PTB rate in singleton asymptomatic pregnancies with a short cervix ≤25 mm but it is not as effective if the cervix length reaches <10 mm. (57,61) The aim of this randomized clinical trial is to do the vaginal ultrasonography earlier, in the 1st trimester, to avoid those cases of pregnant women that have a cervix length of less than 10 mm in the 2nd trimester. If we do the screening sooner, we would probably avoid more PTB than if we do it in the 2nd trimester, because more population of pregnant women would benefit from the preventive treatments.

We assume that vaginal progesterone may be better to prevent PTB than cervical pessary used in the 1st trimester because it is proven that vaginal progesterone is effective to maintain the pregnancy when administered at the beginning of it, for example in programs of assisted reproductive technology (ART) to support the luteal phase, or in women with recurrent miscarriages. (79) The exact mechanism of the progesterone is unknown, but it has a relaxant action of the uterine muscles because it inhibits the releasing of cytokines and prostaglandins and it decreases the number of gap junctions, necessary to coordinate the contractions. (8) The mechanism of the cervical pessary that leads to a lower rate of PTB is not clear, but it is supposed to act mechanically bringing the cervix back, elongating it and changing the uterocervical angle. All of these measures protect the membranes to maintain contact with the vagina. (59)

We define the cervix length of ≤30mm as short cervix in the first trimester based on the publication of Greco *et al* (78) that found that the median endocervical length between the 11th and 13th WG was 32,4mm (5th centile 25,6mm and 95th centile 40,2mm).

In the first trimester (11-13+6 WG) when measuring of the cervix length, it is important to differentiate the endocervix length from the isthmus length (*Fig.11*); where both measured together is known as cervico-isthmic complex. The cervix evolves during pregnancy. In the first trimester, we can observe the uterine isthmus formed by a hypertrophied myometrium, just continuing the endocervix that is an area surrounded by glandular tissue with hyper-echogenicity. In the 2nd trimester, this area opens out and forms part of the uterus, so just the endocervix is visible. (61,78)

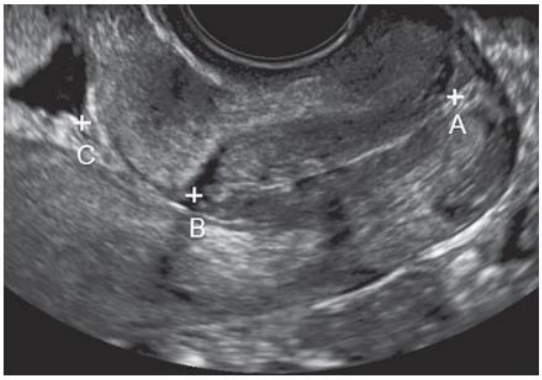

Figure 11. Ultrasound picture illustrating the measurement of the length of the cervix (A to B) and the isthmus (B to C). (61)

In conclusion, if our hypothesis is confirmed, prematurity could be prevented since the first trimester of pregnancy in those women with higher risk and more PTB could be avoided. Moreover, this trial will give scientific evidence about which preventive treatment would be better to use from the first trimester, even the vaginal progesterone or the cervical pessary.

5. Hypothesis

Vaginal progesterone has low rates of preterm birth compared with cervical pessary in singleton pregnancies in pregnant women with risk factors and short cervix length (≤ 30 mm) measured by transvaginal ultrasound in the first trimester control (11-13^{+6} WG).

6. Objectives

Compare vaginal progesterone with cervical pessary to prevent preterm birth in women with singleton pregnancies, high risk of preterm birth and a short cervix length (≤ 30 mm) in the vaginal ultrasound of the first trimester (11-13^{+6} WG).

7. Material and methods

7.1. Type of design

This is a multicentre randomized controlled clinical trial to check if vaginal progesterone is a better preventive treatment of PTB compared with cervical pessary, used after finding a short cervix (≤30 mm) in a vaginal ultrasonography in the 1st trimester (11-13^{+6} WG). It is an open-label trial because of the nature of the intervention.

7.2. Situations to stop the trial

- An increased number of unexpected side effects in one or both groups.
- An increased rate of maternal or fetal non-justified death in one or both groups.

7.3. Study population

The population of this trial will be the pregnant women who undergo the pregnancy under the control of the selected hospitals in Catalonia and meet the inclusion and not the exclusion criteria:

- **<u>Inclusion criteria</u>**
  - ✓ Asymptomatic pregnant women.
  - ✓ Gestational age at randomization within 11-13^{+6} WG.
  - ✓ Women older than 18 years old.
  - ✓ Single pregnancy.
  - ✓ Women with a cervix length ≤ 30mm measured by transvaginal ultrasonography in the first trimester between 11-13^{+6} weeks of gestation.
  - ✓ Women who have high risk of preterm birth:
    - Previous preterm births.

- Previous cervix surgeries.
- Uterine malformations.

✓ Women who want to participate and can give the informed consent.

- **Exclusion criteria**

⌦ Women younger than 18 years old.

⌦ Multiple pregnancies.

⌦ Cervical cerclage *in situ*.

⌦ Active vaginal bleeding.

⌦ Ruptured membranes at the time of randomization.

⌦ Painful regular uterine contractions.

⌦ Cervical length <2mm or cervical dilatation of more than 3 cm.

⌦ Major fetal abnormality.

⌦ Major maternal disease.

⌦ Women unable to give the informed consent.

⌦ Contraindication for progesterone use, for example, history of thromboembolic disorders.

⌦ Active treatment with progesterone at randomization.

⌦ Cervical pessary *in situ*.

- **Withdrawal criteria**

➢ Severe discomfort in the pessary group.

➢ Severe side effects of progesterone treatment.

➢ Onset of delivery (regular uterine dynamic with more than 2 contractions every ten minutes associated with cervix dilatation >2cm).

7.4. Sampling

- **Sample size**

In a bilateral contrast, with a 5% risk alpha, a statistical power of 80% and a drop-out rate of 15%, we need a sample size of 900 women (450 women per arm) supposing that the effect difference between the two preventive treatments is small.

Computations carried out with prof. Marc Saez' software based on the library "pwr" of the free statistical environment R (version 3.5.1).

Statistical analysis by intention to treat will be performed. When we calculated the sample size, we considered a 15% of dropout rate. Missing data will be imputed using the last observation carried forward approach.

- **Sample selection**

A consecutive non-probabilistic sampling will be followed in pregnant women with short cervix length ≤30mm who fulfil the inclusion criteria and not the exclusion criteria that undergo their pregnancy under the control of each selected centre.

This trial will be multicentre to recruit the whole sample and to have more external validity.

The centres that will be proposed to enrol this trial are:

- *Hospital Universitari de Girona Dr. Josep Trueta* (Girona)
- *Hospital Materno-Infantil Vall d'Hebron* (Barcelona)
- *Hospital Sant Joan de Déu* (Barcelona)
- *Hospital Universitari Arnau de Vilanova* (Lleida)
- *Hospital Universitari Joan XXIII* (Tarragona)

Hospital Universitari de Girona Dr. Josep Trueta will be the reference centre in this trial, and one researcher will be assigned as the representant in each participant hospital to set up a good communication between all of them.

- **Estimated time of recruitment**

Data from Idescat (80), in Catalonia in 2017, there were 66.495 new-borns: 48.832 in Barcelona (73,44%), 6.993 in Girona (10,52%), 3.714 in Lleida (5,59%) and 6956 in Tarragona (10,46%).

There isn't available data about the prevalence of pregnant women with risk factors for prematurity and a short cervix length in the first trimester, we only know that the prevalence of short cervix in the low risk population is about 1-2% (17), but this is not our trial population. In consequence, we will take into account the prevalence of preterm birth that is around 8-10%, as in Catalonia there are pregnant women from different origins and with different risk factors. We have calculated the 8% of the new-borns of 2017 to have the approximately number of preterm new-borns in 2017, that would be similar to those in 2019-2020 that will be our period of sample recruitment. The number of preterm babies that were born in Catalonia in 2017 was about: 3906 in Barcelona, 559 in Girona, 297 in Lleida and 556 in Tarragona.

Considering that the factor of having a previous preterm birth is the strongest one to have a future preterm new-born we think that we can achieve the 900 subjects in 20 months with the following numbers: 660 women in Barcelona (73,44% of 900), 330 in *Hospital Materno-Infantil Vall d'Hebron* and 330 in *Hospital Sant Joan de Déu*; 96 women in *Hospital Universitari Dr. Josep Trueta* in Girona (10,52% of 900); 50 women in *Hospital Universitari Arnau de Vilanova* in Lleida (5,59% of 900); and 94 women in *Hospital Universitari Joan XXIII* in Tarragona (10,46% of 900).

Per month will be: 16-17 women in each participant hospital of Barcelona, 4-5 women per month in Girona's hospital and the same in Tarragona's hospital; and 2-3 women per month in Lleida's hospital.

If we cannot achieve the whole sample in 20 months, the recruitment time will be prolonged.

7.5. Data collection

- **Enrolment procedures**

Pregnant women will usually have their first control visit with the midwifery service around 6-8 weeks after the last menstruation. The midwife will do a complete anamnesis and will calculate approximately the gestational age considering the date of the last menstruation that the woman is saying. If the woman has some risk factors maybe she will be directed in that moment to the obstetrician consultation to check if the pregnancy is going fine, but if the woman has not, maybe she won't go to the obstetrician appointment until 11-13^{+6} WG to do the routinely first trimester control.

If we receive a pregnant woman with risk factors but with a gestational age less than 11-WG, we would do a vaginal ultrasonography to check that the pregnancy is evolutive and the fetal heart rate is positive. We can inform her about our trial, but we will give her another appointment a few weeks later when she will be between 11-13^{+6} WG.

Other pregnant women will come directly when they will be between 11-13^{+6} WG to do the first trimester normal control. Maybe they already went to the midwifery service or not, but we will do the complete anamnesis to make sure they don't have risk factors for PTB (previous PTB, cervix surgeries, uterine malformations, etc).

Even if the visit between 11-13^{+6} WG is their first or their second visit to the obstetrician service, we will do the same protocol:

1. We will do the routine 1st trimester abdominal ultrasound: check if the pregnancy is evolutive and the fetal heart rate is positive, measure the CRL of the fetus to calculate the gestational age, measure the nuchal translucency, check the presence of nasal bone, prove the normal flux of venous ductus, describe the situation of the placenta and the umbilical cord insertion, and make sure that the quantity of amniotic fluid is normal. We will measure the basic biometric parameters like biparietal diameter (BPD), check the normal fetal anatomy and the presence of the stomach, the bladder, and the four extremities; and confirm the normal development of the cranium and it structures. Finally, we will check the doppler flux of the uterine arteries to evaluate the risk of pre-eclampsia.

   In case there is poor echogenic transmission through the abdominal route, we will check these first trimester markers vaginally.

2. Then if the woman has high risk factors of PTB, we will propose for her to do a transvaginal ultrasonography to measure the endocervix length, because it is another important risk factor for prematurity, and our population is only the ones with the cervix ≤30 mm.
3. If the pregnant woman accomplishes the inclusion and not the exclusion criteria, we will propose her to enrol our trial.
4. We will explain all the trial procedure, the two treatment strategies and that both have similar results as preventive methods, and all the information to understand the trial that would be written in a sheet and we will give her a copy to read at home.
5. If the woman meets the profile to enrol in our trial but she does not want to, we will explain to her that we would continue doing the normal control of the pregnancy. In case she wants it, we will do another transvaginal ultrasound in the mid trimester to measure the cervix length and if it is still short, we will offer her a preventive treatment

then. Of course, if she does not want to make any treatment, the expectant management is another option available.

6. If the woman agrees to enrol the trial, she will sign the informed consent and we will proceed to randomize her.

- **Randomization**

In order to avoid the selection bias, we will randomize the patients admitted in our study in a 1:1 ratio, after they have signed the informed consent. The technique used for the randomization will be the Statistical Package for the Social Sciences (SPSS) software for Windows® carried out by the obstetrician in the same moment that the patient is entered in the database. The obstetrician will be previously taught by the statistician to know the essential aspects of the program.

- **Intervention, follow-up and results collection**

To enter the patient in the database, the obstetrician will collect the clinical history of each subject with demographic, medical and obstetric history; and this database will be shared with the rest of participant hospitals. The patient will be identified with her trial subject identification number. We will proceed to do a physical examination before the start of the treatment, including a vaginal examination with speculum and we will take vaginal and cervical swabs to discard bacterial infection.

The pregnant women will be assigned by the SPSS to one treatment or the other:

- The cervical pessary will be placed by a trained obstetrician with the woman in the lithotomy position. The pessary will have a batch number and expiration date that will be registered with the trial subject identification number into the database of the trial.

- The vaginal progesterone capsules will be dispensed in the boxes prepared by the Pharmacy Unit of *Hospital Universitari Dr. Josep Trueta* and then distributed to the rest of participating hospitals. The boxes will have the trial code, batch number, expiration date and the trial subject identification number.

During the pregnancy the trial subjects will have the following appointments approximately: eight-ten in the midwifery service; five in the obstetrician service to do the ultrasounds, check the normal evolution of the pregnancy and measure the cervix length to assure that it is not shortening. They will also go to the appointments with High Obstetric Risk Service once a month to control more accurately the development of the pregnancy because those women have pregnancies with risk. In these appointments the obstetrician will report any side effect of the treatment in case it exists, and they will also check the normal evolution of the pregnancy and the cervix length with ultrasound.

In the 37^{th} WG, if the labour have not occurred yet, the obstetrician will remove the cervical pessary and the nurse will collect the medication that is left over.

Finally, when the women will give birth, we will report the gestational age of the new-born to know if the baby is preterm or not and which grade of prematurity. All the data reported in each hospital will be shared with the rest of participant hospitals in our database, and the statistical analysis will be done of all the data reported together.

- **Degree of blinding**

This randomized clinical trial will be open-label because both, the obstetrician and the patient herself, will know what treatment is applied to her by their own nature. The cervical pessary needs to be placed by the obstetrician and will not be removed until 37-37^{+4} weeks of gestation or until the start of labour, whichever comes first. On the other hand, the progesterone will be introduced by the patient herself into the vagina every night until 37-37^{+4} WG or until the start of labour.

The obstetrician that removes the pessary will also know the treatment of the woman. In most cases the clinician or midwife that would assist in the delivery will be aware of the treatment that the woman has received, so the data collectors will not be blinded. We can't divide the professionals of the Obstetric unit into two groups: one who implement the treatment and do the pregnancy follow-up, and the others to assist in the delivery and do the data collection; because the moment when the labour may occur is unpredictable, maybe it can happen at night or at the weekend and only one or two obstetricians will be on-duty.

We can only assure that the statistician who do the data analysis will be blinded.

7.6. Study variables

- **Independent variables** are dichotomic qualitative variables:
  - Cervical pessary placement after the discovery of short cervix (≤ 30 mm) on transvaginal ultrasound between 11 and 13^{+6} weeks of gestation.
  - 200 mg of vaginal progesterone every night after the discovery of short cervix (≤ 30 mm) on transvaginal ultrasound between 11 and 13^{+6} weeks of gestation.

- **Dependent variable** is a categoric quantitative variable:
  - Primary outcome: proportion of spontaneous preterm birth before 37 weeks of gestation in both treatment groups, measured in a percentage.
  - Secondary outcomes: proportion of spontaneous preterm birth before the 34^{th}, 32^{nd}, 30^{th} and 28^{th} week in each treatment group, measured in a percentage.

- **Co-variables**:
  - Maternal age at delivery (years), we will treat it like a categorical qualitative variable divided in 3 groups:
    - <25 years.
    - 25-35 years.
    - >35 years.
  - Maternal weight (kg)
  - Maternal height (m)

  } BMI before pregnancy (kg/m^2) = weight (kg) / height^2 (m^2)

  We will treat the maternal BMI before pregnancy like a categorical qualitative variable, divided in 4 groups:
    - <18,5 → low weight.
    - 18,5 – 24,9 → normal weight.
    - 25 – 29,9 → overweight.
    - >30 → obesity.
  - Origin, treated like a qualitative variable:
    - Caucasian.
    - African:
      - African-American.
      - Afro-Caribbean.
    - South Asian.
    - East Asian.
    - Mixed.
  - Parity (nulliparous vs multiparous), a dichotomic qualitative variable.
  - Number of previous preterm births (nº), a discrete quantitative variable.
  - Smoking habit (yes/no), a dichotomic qualitative variable.
  - Assisted conception (yes/no), a dichotomic qualitative variable.
  - Fetal CRL (mm), a continue quantitative variable.

7.7. Measure instruments

To measure the cervix length, we will need a transvaginal ultrasound, condoms and lubricating gel. Dust-free nitrile gloves will be required.

To do the vaginal ultrasound to measure the endocervix length, the obstetricians in each hospital will be trained by an external expert and they will need to pass a practical examination to demonstrate their abilities. The accepted methodology for the transvaginal ultrasound in the first trimester includes the following steps:

1. Ask the woman to empty her bladder and then place her in the dorsal lithotomy position.
2. Introduce the vaginal transducer (2,7-9,3 MHz) in the anterior fornix of the vagina and adjust to obtain a sagittal view of the entire length of the cervical canal, which can be translucent or echo-dense. The canal is bordered by the endocervical mucosa that, compared with the adjacent tissues, is usually of decreased echogenicity.
3. Remove the transducer until the image is blurred and then go ahead softly until you see the image clear again without pressing the cervix.
4. Manage the ultrasound machine settings to get the widest viewing angle, where almost the entire screen is occupied by the tissues between the external cervical os and the gestational sac.
5. Use the callipers to measure the linear distance between the external and the internal os (end points of the endocervix), without including the shortest distance between the glandular area and the gestational sac which corresponds to the isthmus in the first trimester.
6. Taking into account that the cervix is a dynamic structure, the measure must be done 3 times for 3 minutes and only the shortest one will be reported for the trial.

To collect our dependent variable, we will need the report of each delivery of our patients to know if the baby was born preterm or at term, and which grade of prematurity had. We will include this data in the database shared with all the participant hospitals.

7.8. Treatment

- **Study treatment groups**

This trial includes two treatment strategies with the following characteristics:

- One group will receive 200mg of micronized progesterone capsules by vaginal route. Every night the woman will self-administrate it before going to bed. The patients will get instructions of the vaginal progesterone use when they get the medication. It will be commercial progesterone “Progeffik” that will be bought and relabelled by the Pharmacy Unit of the *Hospital Universitari Dr. Josep Trueta* and then distributed to all participant hospitals. Each box of “Progeffik” has 60 capsules of 200mg of micronized progesterone, so the women will get the medication for 60 days, approximately 8 weeks, and then they will get another box in the next scheduled appointment.
- The other group will get a perforated-cerclage type pessary, a hypoallergenic silicon medical device certified by European conformity (CE0482, MED/CERT ISO 9003/EN 46003), Dr. Arabin®, size 65/17/32 (65mm external diameter, 17mm height and 32mm internal diameter) for nullipara, and size 70/17/32 for multipara. (81) It will be introduced by trained obstetricians at the participating hospitals, and before the insertion, swabs from the cervix and the vagina will be taken to make cultures and exclude bacterial colonization. It is perforated so it allows to pass the cervical/vaginal discharge, particularly useful in cases of increased discharge.

Both treatments will be initiated between the 11^{th} and the 13^{th+6} WG and discontinued the 37^{th}-37^{th+4} WG, but there are some situations for discontinuing the treatment before this time like:

- Vaginal bleeding.
- Severe patient discomfort.
- Onset of delivery.

During the 37^{th} WG until 37^{+4}, the cervical pessary will be removed by a trained obstetrician in the participating hospitals, and the other group of women will return the medication that they didn't use to the nurse, that will count it and then destroy it.

If while the patients are doing preventive treatment, a threat of preterm delivery is triggered, the appropriate protocol will be followed.

- **Adverse events**

The vaginal progesterone "Progeffik 200mg" doesn't have local intolerance and neither systemic side effects. (82)

The cervical pessary can produce and increased vaginal discharge, and in cases of bad collocation it can produce discomfort; but it is normally well-tolerated.

8. Statistical analysis

8.1. Descriptive analysis

We are going to summarize the variables with means and standard deviations if the variables are quantitative and they have a symmetric distribution (i.e. continuous variables), and with medians and interquartile range (IQR) if the distribution is not symmetric (i.e. discrete variables). To summarize the qualitative variables, we will use proportions.

8.2. Bivariate inference

We will compare the proportions of the dependent variables (primary and secondary) between the two treatment groups with *Chi-square* and the *Fisher exact test*.

The means of the continuous covariables between the groups of the dependent variables will be tested with *Student's t test*. The medians of the discrete covariables between the groups of the dependent variables will be compared using the *Mann-Whitney' U test*. Finally, for qualitative variables we will use the *Chi-square* and the *Fisher exact test*.

The analyses between the dependent and the independent variables will be stratified by the covariables. In case the covariables were quantitative these will be categorized.

8.3. Multivariate inference

Finally, we will use multivariate models to adjust for possible confounding. In particular, we will do a logistic regression where dependent variable will be preterm birth subdivided for weeks of gestation and independent variable will be the different preventive treatments, controlled by all the co-variables.

9. Limitations, strengths and impact of the study

This trial has some **limitations** that must be mentioned:

First, the open-label design of the trial. This could produce an observer-bias, but it can't be avoided because of the nature of the interventions. Not only the obstetrician, but also the woman must know which treatment is going to receive, so it can't be a blinded trial. The clinician that assists the woman in her delivery will be the same or another obstetrician of the hospital, that will also be involved in the trial, because all the Obstetric unit will participate in the study to enrol more patients, and the assistance in the delivery can't be chosen, because is unpredictable when it can occur. If the delivery occurs at term, and the treatments have been removed in the 37th WG, the midwife could not know in the moment of the labour which treatment had received this woman, but this won't occur in all the cases. In conclusion, the outcome collection will be done in most cases by the obstetricians or midwifes that will be involved in the trial. On the other hand, the statistician that will read the database and will do the data analysis will be blinded.

Second, the consecutive non-probabilistic sampling method used in this trial may produce selection-bias, nevertheless it can't be avoided, because the population of this study has some concrete characteristics. We can't select the sample from the general population, although every person will not have the same opportunity to be selected like if it was a probabilistic sampling.

Another limitation is that it has been estimated a period of 20 months to recruit the sample in the five participant hospitals, but in case it was not achieved, we will ask for an extension to complete the sample selection.

Finally, we have to consider the drop-out of the sample. During pregnancy period, the subjects can move to another place or give birth in other hospitals not involved in the trial. Also, the pregnant woman who refuse continuing in the project will not provide

results to the study. To deal with this, we have anticipated these losses and we have calculated the sample size with a drop-out rate of 15%.

On the other hand, this trial has some **strengths**:

First, we are proposing a preventive strategy of PTB, that is the most important cause of perinatal and neonatal morbidity and mortality; so, if our hypothesis is confirmed, a big breakthrough will be achieved.

Another important characteristic is that, the multicentric and randomized nature of the study will make it possible to generalize the results obtained if they are statistically significant.

The information bias has been avoided because all the obstetricians involved in the trial has been trained together to do the ultrasound with the same protocol, and all of them have passed a practical examination to demonstrate their ability.

To finalize is important to mention the **health impact** that could produce this trial in the management of prematurity, that has medical, social and economic important consequences. If our hypothesis is confirmed, this trial would give us evidence about which preventive strategy is better implemented in the first trimester, and also it would demonstrate that starting the preventive treatment earlier would end in lower PTB rates and that it would be cost-effective.

10. Ethical aspects and law

This trial has been proposed according the Basic Ethical Principles:

- Respect for the patient autonomy: represented in the informed consent, because the participation in the trial is absolutely voluntary; and in the confidentiality and anonymity of the patient data.
- Beneficence: the discomfort or the risks that could cause the treatments are very inferior compared with the benefits that could be obtained, and the importance of the evidence generated.
- Non-maleficence: not only the researchers, but also the places where the trial will be developed will be adapted to attend the trial patients.
- Justice: every woman that meets the inclusion and not the exclusion criteria will be asked to enrol the trial, without any discrimination. An insurance policy will be contracted.

This project respects the ethical criteria exposed in the Nuremberg Code, the Belmont Report, the Declaration of Helsinki (1964, last actualization in 2016) and the Convenio de Oviedo.

It has been done according to the "*Real Decreto Legislativo 1/2015, de 24 de julio"* and the "*Real Decreto 1090/2015, de 4 de diciembre"*.

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

The protocol will be sent to the *Agencia Española del Medicamento y Productos Sanitarios (AEMPS)*, to the *Comitè d'Ètica d'Investigació amb Medicaments (CEIm)* and to the *Clinical Research Ethics Committee (CEIC)* of *Hospital Universitari Dr. Josep Trueta* in Girona.

The protocol must have the conformity of all participant hospitals and the authorization of the *AEMPS* and the *CEIm* to start the trial. Also, an insurance policy will be contracted.

All the information from the subjects' trial will be confidential and their anonymity will be preserved, according the *"Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal"* and the last adaptation *"Real Decreto-ley 5/2018, de 27 de julio, de medidas urgentes para la adaptación del Derecho español a la normativa de la Unión Europea en materia de protección de datos"*.

The patients must be informed about all the details in the protocol and they must sign the informed consent to enrol the trial.

All the research team commits that, whatever the results of the trial are, all the data will be published with transparency, and they will not exclude unfavourable events or data.

This trial doesn't have a third arm of patients treated with placebo for ethical issues. Both treatments showed effectiveness compared with expectant management in the most recent publications, and it will not be ethical to leave a group of pregnant women without an effective treatment.

11. Feasibility

The selected hospitals to participate in this trial are reference hospitals in the 4 provinces of Catalonia, and they are at least level 2b or 3, so they have adequate resources available to attend the pregnant women with high risk of prematurity, and also the new-borns in case they were born premature.

The obstetricians involved in the trial have enough experience in their speciality and have passed a practical examination of the vaginal ultrasonography to demonstrate that all of them have the ability to do it and that everyone does it in the same way.

The work plan explains the steps that makes the trial feasible.

12. Work plan

This trial will be completed in three years. It is organized in the following steps:

1. **Protocol design and approbation** (4 months, October 2018 – January 2019):

   The obstetric unit of *Hospital Universitari Dr. Josep Trueta* in Girona, decided to do this randomized clinical trial and they review the bibliography published about this topic in PubMed database, Embase, the Cochrane Central Register of Controlled Trials, etc.

   They designed the protocol and it will be shared with the hole Gynecology and Obstetrics Service of their own hospital and it will be sent to the direction of the hospital to get their approbation.

   The protocol will be sent to the *AEMPS*, the *CEIm* and the *CEIC* and once we get the approbation, we will share the protocol with the respective services in the proposed participant hospitals.

2. **Organization** (1 month, February 2019):

   Each Obstetric Service in every participant hospital will have a meeting to talk about the trial, read and understand the protocol and assign someone to be the coordinator that will get in touch with the others to communicate all the trial information during the whole duration of it.

   The representants of each hospital will have a meeting in *Hospital Universitari Dr. Josep Trueta* in Girona to deal with any doubt or problem about the protocol or the organization before starting the interventions of the trial.

   The obstetricians of each hospital involved in the trial will meet in *Hospital Universitari Dr. Josep Trueta* in Girona to do a practical journal with an expert in ultrasound that will train them to do the vaginal ultrasound with the same protocol. The last two hours of the journal will be a practical examination where all the obstetricians will have to demonstrate their learned skills.

3. **Sample collection, intervention and first data collection** (20 months, March 2019 – October 2020):

   For 20 months, in the 5 participating hospitals, the Obstetric Services will be collecting patients, doing the intervention (cervical pessary placement or vaginal progesterone administration) and collecting the results of their deliveries (if there will be preterm or not, and which grade of prematurity).

4. **Last data collection** (7 months, November 2020 – May 2021):

   The last pregnant women included in the trial will be collected in October 2020 so the expected date of birth will be approximately in May 2021 because when they were enrolled they already were at 11-13^{+6} WG, and the pregnancy is maintained until 42-WG maximum, and moreover, in those cases we suppose it will happen a little bit earlier.

5. **Statistical analysis** (2 months, June – July 2021):

   After we will get the last results of the deliveries of the last pregnant women treated (estimated in May 2021), the statistician will proceed to recollect all the data from our database and do the statistical analysis.

6. **Results** (2 months, August – September 2021):

   The results, whatever they are, will be published in a journal article. The scientific evidence obtained from this trial will be shared in national and international congresses of Obstetricians.

13. Budget

	DESCRIPTION	QUANTITIY	COST (€)	SUBTOTAL (€)
MATERIAL	Vaginal progesterone (Progeffik 200mg, 60 capsules)	450 patients x 3 boxes each patient = 1350 boxes	41,96€ each box = 56.646 €	0 € [*]
	Cervical pessary Dr. Arabin ®	450	55,99€ x 450 = 25.155 €	0 € [*]
	Vaginal ultrasonography	900 in each appointment	50€ each one	0 € [*]
	Office material	15 sheets x 900	0,04€ each sheet	540 €
STAFF (subcontracted professional services)	Statistician	100h	35€/h	3.500 €
FEES	AEMPS	1	114,55 €	2.114,55 €
	Publication	1	2.000 €	
INSURANCE	Insurance policy	1	10.000 €	10.000 €
COORDINATION	Meeting of the representants of the different hospitals	1 meeting (including travel and diets) for 5 coordinators	100€ per person	500 €
	Ultrasounds practical journey	1 meeting (including travel and diets) for 60 obstetricians	100€ per person	6.000 €
PUBLICATION	Publication in a journal		2.000 €	2.000 €
PRESENTATION	National Obstetrics Congress	1	1.400 €	4.400 €
	International Obstetrics Congress	1	3.000 €	
TOTAL COST……29.054,55 €				

[*] The price of vaginal progesterone and the cervical pessaries has been calculated but it is not included in the final cost of the trial because the public health system covers the costs. The vaginal ultrasounds are also included in the normal control of pregnancy, so their cost is not included in the trial.

14. Conflict of interests

The authors declare no conflict of interest in any step of this trial.

15. Chronogram

WORK PLAN STEPS	DESCRIPTION OF THE ACTIVITY	STAFF	Oct-Dec 2018	Jan-Mar 2019	Apr-Jun 2019	Jul-Sep 2019	Oct-Dec 2019	Jan-Mar 2020	Apr-Jun 2020	Jul-Sep 2020	Oct-Dec 2020	Jan-Mar 2021	Apr-Jun 2021	Jul-Sep 2021
STEP 1	**Scientific research + drafting off the protocol**	Main researcher												
	Protocol approbation	– Direction of the hospital – AEMPS – CEIm and CEIC												
STEP 2	**Organization** – Coordinators meeting – Practical journey	Obstetricians												
STEP 3	**Sample collection**	Obstetricians												
	Intervention	Obstetricians + nurses												
	Follow-up	Obstetricians + nurses												
	Habitual appointments of the pregnancy control	Obstetricians + nurses												
	First data collection	Obstetricians												
STEP 4	**Last data collection**	Obstetricians												
STEP 5	**Statistical analysis**	Statistician												
STEP 6	**Results** – Publication – Dissemination	Main researcher												

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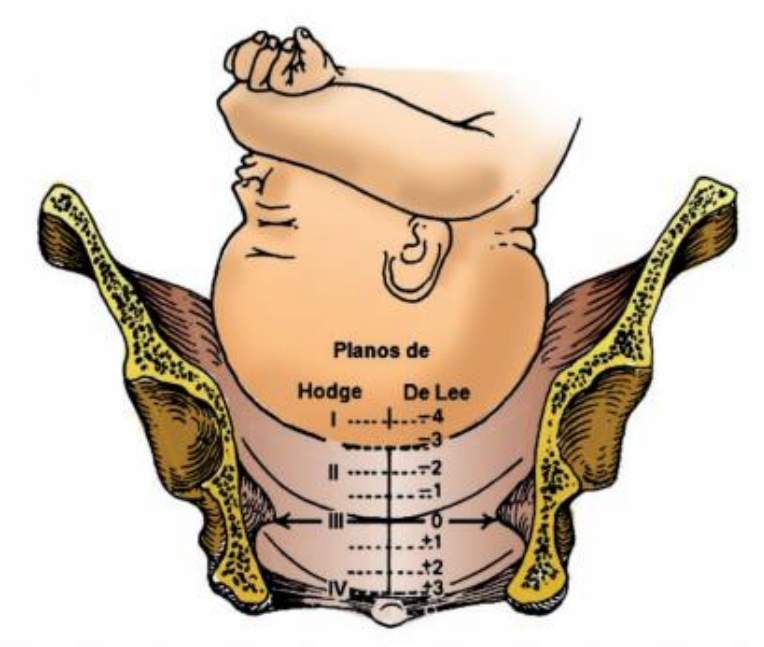
17. Annexes

- **Annex 1: Bishop Test** (8)

Punctuation	0	1	2	3
Position	Posterior	Mid	Anterior	
Consistency	Firm	Medium	Soft	
Effacement (cm)	3	2	1	Erased
Dilatation (cm)	0	1-2	3-4	>4
Hodge's planes [**]	I	II	III	IV

If the final score of the Bishop Test is >6, it suggests that the labour can occur soon because the cervix is prepared.



[**] *Figure 12. Hodge's planes and the correspondence with De Lee stations*. (83)

- **Annex 2: Protocol information sheet**

FULL D'INFORMACIÓ PER LA PACIENT

Títol de l'estudi: *Progesterona vaginal versus pessari cervical en el primer trimestre de l'embaràs per prevenir el part preterme*.

Investigador/a principal:

Centre:

Benvinguda,

Ens posem en contacte amb vostè per convidar-la a participar en un estudi d'investigació realitzat pels serveis de Ginecologia i Obstetrícia de diferents hospitals de Catalunya.

Aquest estudi ha estat aprovat per "*l'Agencia Española del Medicamento y Productos Sanitarios" (AEMPS)* i pel *Comitè d'Ètica i Investigació Clínica (CEIC)*, seguint la legislació vigent, *Real Decreto 1090/2015, de 24 de diciembre* i el *Reglamento Europeo 536/2014 de 16 de abril*; sobre la realització d'assaigs clínics amb medicaments.

Abans de tot, volem fer-li saber que la seva participació en aquest estudi és totalment voluntària i que en cas d'acceptar entrar-hi podrà revocar el consentiment en qualsevol moment que vostè ho desitgi sense que això tingui cap repercussió negativa en la seva relació assistencial amb el seu metge o la seva metgessa, ni en el seu tractament.

Abans de decidir participar o no en l'estudi, li demanem que llegeixi detingudament aquest document d'informació i nosaltres li resoldrem qualsevol dubte que tingui, per tal de que vostè pugui decidir disposant de tota la informació necessària.

DESCRIPCIÓ I OBJECTIU DE L'ESTUDI

Aquest estudi va dirigit a dones embarassades majors d'edat, que estiguin en el primer trimestre de l'embaràs entre les 11 i les 13^{+6} setmanes de gestació (13 setmanes i 6 dies), que tinguin factors de risc per tenir un part preterme i alhora presentin una longitud del cèrvix de 30 o menys mil·límetres, que considerem curta. La longitud cervical es mesurarà amb una ecografia transvaginal a la consulta d'Obstetrícia.

L'objectiu de l'estudi és posar en aquestes dones un dels dos tractaments preventius del part preterme, com són la progesterona vaginal en càpsules i la col·locació d'un pessari cervical, i valorar al final de la gestació amb quins dels dos tractaments hi ha hagut menys naixements prematurs; per tant quin dels dos tractaments preventius és més eficaç.

Per fer aquest estudi inclourem 900 dones en 5 hospitals de Catalunya, que seran dividides en dos grups de tractament, assignats a l'atzar:

- **GRUP 1**: Un grup de 450 dones rebran una caixa de medicació cada 60 dies que conté 60 càpsules de 200mg de progesterona cadascuna. En el moment de rebre la primera caixa, la dona serà instruïda per una infermera del Servei de Ginecologia i Obstetrícia que li explicarà com ha d'utilitzar el medicament per via vaginal. La dona haurà d'introduir-se ella mateixa una càpsula de progesterona al fons de la vagina, cada nit abans d'anar a dormir, fins a la setmana 37 de l'embaràs o fins que es desencadeni el treball de part.
- **GRUP 2**: A l'altre grup de 450 dones se'ls hi col·locarà un pessari cervical, que és un anell de silicona de fàcil col·locació i retirada. Un metge o metgessa del Servei de Ginecologia i Obstetrícia introduirà el pessari per la vagina de la dona fins a col·locar-lo al voltant del cèrvix uterí. El pessari serà retirat, per algun professional del servei, la setmana 37 de l'embaràs o quan es desencadeni el treball de part. Tant

la col·locació com la retirada es poden fer a la mateixa consulta d'Obstetrícia, no cal anestèsia i no sol ser un procediment gaire molest.

Degut a les pròpies característiques d'aquests dos tractaments, tant la pacient com la metgessa o metge que li posi i li tregui el tractament, sabran a quin dels dos grups de l'estudi pertany cada dona.

Actualment es mesura la longitud cervical, en aquelles dones amb factors de risc, en el segon trimestre de l'embaràs, entre les 19^{+6} i les 21^{+6} setmanes de gestació, i és en aquest moment que es posen algun d'aquests dos tractaments preventius del part prematur. Diversos estudis han demostrat que hi ha relació entre la longitud de cèrvix curta en el segon trimestre i en el primer trimestre, és a dir que ja en el primer trimestre es podria valorar si la longitud cervical està reduïda. El que volem és començar la prevenció abans, en el primer trimestre, per tal de reduir el nombre parts preterme.

ACTIVITATS DE L'ESTUDI

Si vostè accepta entrar en l'estudi, seguirem el seu embaràs amb els controls habituals i en aquestes mateixes visites, en el servei d'Alt Risc Obstètric, ens assegurarem que estigui fent bé el tractament amb progesterona o comprovarem que el pessari està correctament col·locat i no li provoca cap molèstia. També mesurarem la longitud cervical per assegurar-nos que no es redueix.

Al final del seu embaràs s'inclourà a la nostra base de dades l'edat gestacional amb la que el seu fill o filla hagi nascut, per veure si ha sigut prematur o no.

BENEFICIS I RISCOS DE L'ESTUDI

El benefici que esperem que es derivarà d'aquest estudi és una menor taxa de parts preterme que si es posa el tractament preventiu en el segon trimestre, ja que les dones

portaran el tractament més temps. El benefici de no tenir un fill/a prematur és primerament pel nadó en termes mèdics, però també a nivell social i econòmic; ja que un recent nascut prematur tindrà moltes més complicacions que un bebè nascut a terme. A la vegada, aquest estudi aportarà evidencia científica per escollir algun dels dos tractaments per davant de l'altre.

Segons la informació de l'*AEMPS* reflexada a la fitxa tècnica de la progesterona per via vaginal, aquesta no té cap efecte indesitjat ni a nivell local ni sistèmic. Per altra banda, el pessari sol ser molt ben tolerat però pot produir una mica de molèstia la seva introducció i la seva retirada, i s'han descrit casos d'augment del flux vaginal, sense més transcendència. Si està ben col·locat no produeix cap incomoditat.

ALTERNATIVES AL PROCEDIMENT

L'única alternativa a aquests tractaments és el maneig expectant. Es podrà realitzar l'ecografia transvaginal per mesurar la longitud cervical en el segon trimestre de l'embaràs i començar el tractament preventiu en aquell moment.

INTERRUPCIÓ DE L'ESTUDI

L'estudi seria interromput en casos de troballa de molts efectes indesitjats no esperats tant en la mare com els fetus, o de morts maternes o fetals.

Vostè podrà abandonar l'estudi en el moment que ho desitgi, però li preguem que ho comuniqui a algun dels professionals del Servei de Ginecologia i Obstetrícia del seu hospital.

CONFIDENCIALITAT

Totes les seves dades, tant personals com mèdiques, que vostè ens proporcioni per la realització d'aquest estudi, seran tractats amb la més absoluta confidencialitat segons l'establert a la *"Ley Orgánica 15/1999, de 13 de Diciembre, de Protección de Datos de Carácter Personal"* i la seva última modificació *"Real Decreto-ley 5/2018, de 27 de julio, de medidas urgentes para la adaptación del Derecho español a la normativa de la Unión Europea en materia de protección de datos"* que garanteixen la confidencialitat de les dades informatitzades. En cap moment ni les seves dades personals, ni les del seu fill/a que espera, seran publicades enlloc.

COMPENSACIÓ ECONÒMICA

Per participar en aquest estudi vostè no rebrà cap compensació econòmica, però tampoc li suposarà cap despesa. Cal remarcar que els investigadors d'aquest assaig clínic tampoc reben cap compensació econòmica per la realització de l'estudi.

RESPONSABILITAT I ASSEGURANÇA

Els promotors d'aquest estudi han contractat una pòlissa d'assegurança per la realització del mateix, com estableix la legislació vigent *(Real Decreto 1090/2015)*, que s'encarregaria de la seva compensació i indemnització en cas que el fet de participar en l'estudi li produís algun dany o perjudici.

CONTACTE

En cas de qualsevol dubte durant la realització d'aquest estudi, podrà contactar amb:

(espai per posar les dades de l'hospital i del responsable corresponent)

HOJA DE INFORMACIÓN PARA LA PACIENTE

Título del estudio: *Progesterona vaginal versus pesario cervical en el primer trimestre del embarazo para prevenir el parto pretérmino*.

Investigador principal:

Centro:

Bienvenida,

Nos ponemos en contacto con usted para invitarla a participar en un estudio de investigación realizado por los Servicios de Ginecología y Obstetricia de diferentes hospitales de Cataluña.

Este estudio ha sido aprobado por la *Agencia Española del Medicamento y Productos Sanitarios (AEMPS)* y por el *Comité de Ética e Investigación Clínica (CEIC)*, siguiendo la legislación vigente, *Real Decreto 1090/2015, de 24 de diciembre* y el *Reglamento Europeo 536/2014, de 16 de abril*; sobre la realización de ensayos clínicos con medicamentos.

En primer lugar, queremos comunicarle que su participación en este estudio es totalmente voluntaria y que, en caso de aceptar entrar en él, podrá revocar su consentimiento en cualquier momento que usted quiera sin que eso tenga ninguna repercusión negativa en su relación asistencial con su médico, ni en su tratamiento.

Antes de decidir participar o no en el estudio, le pedimos que lea detenidamente este documento de información y nosotros le resolveremos cualquier duda que tenga, para que usted pueda decidir disponiendo de toda la información necesaria.

DESCRIPCIÓN Y OBJETIVO DEL ESTUDIO

Este estudio va dirigido a mujeres embarazadas mayores de edad, que estén en el primer trimestre del embarazo entre las 11 y las 13^{+6} semanas de gestación (13 semanas y 6 días), que tengan factores de riesgo para tener un parto prematuro y además presenten una longitud del cérvix de 30 o menos milímetros, que consideramos corta. La longitud cervical se medirá con una ecografía transvaginal en la consulta de Obstetricia.

El objetivo del estudio es poner a estas mujeres uno de los dos tratamientos preventivos del parto pretérmino, como son la progesterona vaginal en cápsulas y la colocación de un pesario cervical, y valorar al final de la gestación con cuál de los dos tratamientos ha habido menos nacimientos prematuros; por tanto cuál de los dos tratamientos preventivos es más eficaz.

Para realizar este estudio incluiremos 900 mujeres en 5 hospitales de Cataluña, que serán divididas en dos grupos de tratamiento, asignados al azar:

- **GRUPO 1**: Un grupo de 450 mujeres recibirán una caja de medicación cada 60 días que contiene 60 cápsulas de 200mg de progesterona cada una. En el momento en que reciban la primera caja, la mujer será instruida por una enfermera del Servicio de Ginecología y Obstetricia que le explicará como ha de utilizar el medicamento por vía vaginal. La mujer tendrá que introducirse, ella misma, una cápsula de progesterona en el fondo de la vagina, cada noche antes de ir a dormir, hasta la semana 37 de embarazo o hasta que se desencadene el trabajo de parto.
- **GRUPO 2**: Al otro grupo de 450 mujeres se les colocará un pesario cervical, que es un anillo de silicona de fácil colocación y retirada. Un médico del Servicio de Ginecología y Obstetricia introducirá el pesario por la vagina de la mujer hasta colocarlo alrededor del cérvix uterino. El pesario será retirado, por algún

profesional del servicio, la semana 37 de embarazo o cuando se desencadene el trabajo de parto. Tanto la colocación como la retirada del pesario se pueden realizar en la propia consulta de Obstetricia, no requiere anestesia y no suele ser un procedimiento demasiado molesto.

Debido a las propias características de estos dos tratamientos, tanto la paciente como el médico que le ponga y le quite el tratamiento, sabrán a cuál de los dos grupos del estudio pertenece cada mujer.

Actualmente se mide la longitud cervical, en aquellas mujeres con factores de riesgo, en el segundo trimestre del embarazo, entre las 19^{+6} y las 21^{+6} semanas de gestación, y es en ese momento que se pone alguno de estos dos tratamientos preventivos del parto prematuro. Varios estudios han demostrado que hay relación entre la longitud de cérvix corta en el segundo trimestre y en el primer trimestre, es decir que ya en el primer trimestre se podría valorar si la longitud cervical está reducida. Lo que queremos es empezar la prevención antes, en el primer trimestre, para reducir el número de partos prematuros.

ACTIVIDADES DEL ESTUDIO

Si usted acepta entrar en el estudio, seguiremos su embarazo con los controles habituales y en esas mismas visitas, en el servicio de Alto Riesgo Obstétrico, nos aseguraremos de que esté haciendo bien el tratamiento con progesterona o comprobaremos que el pesario está bien colocado y no le provoca ninguna molestia. También mediremos la longitud cervical para cerciorarnos que no se reduce.

Al final de su embarazo se incluirá en nuestra base de datos la edad gestacional con la que su hijo/a haya nacido, para ver si ha sido prematuro o no.

BENEFICIOS Y RIESGOS DEL ESTUDIO

El beneficio que esperamos que se derivará de este estudio es una menor tasa de partos prematuros que si se pone el tratamiento preventivo en el segundo trimestre, ya que las mujeres llevarán el tratamiento más tiempo. El beneficio de no tener un hijo prematuro es primeramente para su hijo/a en términos médicos, pero también a nivel social y económico; ya que un recién nacido prematuro tendrá muchas más complicaciones que un bebé nacido a término. A su vez, este estudio aportará evidencia científica para escoger alguno de los dos tratamientos por delante del otro.

Según la información de la AEMPS reflejada en la ficha técnica de la progesterona por vía vaginal, ésta no tiene ningún efecto indeseado ni a nivel local ni sistémico. Por otro lado, el pesario suele ser muy bien tolerado pero puede producir un poco de molestia su introducción o su retirada, y se han descrito casos de aumento del flujo vaginal, sin más trascendencia. Si está bien colocado no produce ninguna incomodidad.

ALTERNATIVAS AL PROCEDIMIENTO

La única alternativa a estos tratamientos es el manejo expectante. Se podrá realizar la ecografía transvaginal para medir la longitud cervical en el segundo trimestre del embarazo y comenzar el tratamiento preventivo en ese momento.

INTERRUPCIÓN DEL ESTUDIO

El estudio sería interrumpido en caso de hallazgo de muchos efectos indeseados no esperados tanto en la madre como en los fetos, o de muertes maternas o fetales.

Usted podrá abandonar el estudio en el momento en que lo desee, pero le pedimos que lo comunique a alguno de los/las profesionales del Servicio de Ginecología y Obstetricia de su hospital.

CONFIDENCIALIDAD

Todos sus datos, tanto personales como médicos, que usted nos proporcione para la realización de este estudio, serán tratados con la más absoluta confidencialidad según lo establecido en la *"Ley Orgánica 15/1999, de 13 de Diciembre, de Protección de Datos de Carácter Personal"* y su última modificación *"Real Decreto-ley 5/2018, de 27 de julio, de medidas urgentes para la adaptación del Derecho español a la normativa de la Unión Europea en materia de protección de datos"* que garantizan la confidencialidad de los datos informatizados. En ningún momento sus datos personales, ni los de su hijo/a que espera, serán publicados en ningún sitio.

COMPENSACIÓN ECONÓMICA

Por participar en este estudio usted no recibirá ninguna compensación económica, pero tampoco se supondrá ningún gasto. Debemos remarcar que los investigadores de este ensayo clínico tampoco reciben ninguna compensación económica por la realización del estudio.

RESPONSABILIDAD Y SEGURO

Los promotores de este estudio han contratado una póliza de seguros para la realización del mismo, como establece la ley vigente *(Real Decreto 1090/2015)*, que se encargaría de su compensación e indemnización en caso de que el hecho de participar en el estudio le produjese algún daño o perjuicio.

CONTACTO

En caso de cualquier duda durante la realización de este estudio, podrá contactar con:

(espacio para poner los datos del hospital y del responsable correspondiente)

- **Annex 3: Informed consent document**

FULL DE CONSENTIMENT INFORMAT

Jo, _____, amb DNI/NIE_____ accepto voluntàriament participar en l'assaig clínic "*Progesterona vaginal versus pessari cervical en el primer trimestre de l'embaràs per prevenir el part preterme*" i confirmo que:

- He estat informada adientment pel Dr./Dra. _____
- He llegit tota la informació del full d'informació per la pacient i he entès el contingut.
- He preguntat qualsevol dubte relacionat amb l'estudi als responsables i me l'han resolt.
- He entès els possibles beneficis i riscos que se'n deriven de l'estudi.
- Se m'han exposat les possibles alternatives a aquests tractaments.
- He rebut una còpia del full d'informació per la pacient.

Comprenc que la meva participació és voluntària i que podré revocar el consentiment prèviament signat en qualsevol moment sense que això suposi cap conseqüència negativa pel meu futur tractament.

Signatura de la pacient Signatura de l'investigador/a

Lloc i data: _____, ____ de _____ del 20__

REVOCACIÓ DEL CONSENTIMENT INFORMAT

Jo, _____, revoco el consentiment prèviament signat per la participació en l'assaig clínic especificat a dalt.

Signatura de la pacient Signatura de l'investigador/a

Lloc i data: _____, ____ de _____ del 20__

HOJA DE CONSENTIMIENTO INFORMADO

Yo, _____, con DNI/NIE _____

acepto voluntariamente participar en el ensayo clínico "*Progesterona vaginal versus pesario cervical en el primer trimestre del embarazo para prevenir el parto pretérmino*" y confirmo que:

- He sido informada adecuadamente por el Dr./Dra. _____
- He leído toda la información de la hoja de información para la paciente y he entendido el contenido.
- He preguntado cualquier duda relacionada con el estudio a los responsables y ellos me la han resuelto.
- He entendido los posibles beneficios y riesgos que se derivan del estudio.
- Se me han expuesto las posibles alternativas a estos tratamientos.
- He recibido una copia de la hoja de información para la paciente.

Comprendo que mi participación es voluntaria y que podré revocar el consentimiento previamente firmado en cualquier momento sin que eso suponga ninguna consecuencia negativa en mi futuro tratamiento.

Firma de la paciente Firma del investigador/a

Lugar y fecha: _____, ____ de _____ del 20__

REVOCACIÓN DEL CONSENTIMIENTO INFORMADO

Yo, _____, revoco el consentimiento previamente firmado para la participación en el ensayo clínico especificado arriba.

Firma de la paciente Firma del investigador/a

Lugar y fecha: _____, ____ de _____ del 20__