Universitat de Girona
Facultat de Medicina

Cervical consistency index as a valid predictor of spontaneous preterm birth in pregnant women

A PROSPECTIVE COHORT STUDY

FINAL DEGREE PROJECT

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1. Abbreviations

PTB: Preterm birth

sPTB: Spontaneous preterm birth

WG: Weeks of gestation

25^4 WG: 25 weeks and 4 days of gestation (as an example)

LMP: last menstrual period

PROM: preterm rupture of membranes

IPI: inter-pregnancy interval

CCI: cervical consistency index

HUJT: Hospital Universitari de Girona Doctor Josep Trueta

CIO: Cervical internal orifice

CEO: Cervical external orifice

2. Abstract

BACKGROUND

Preterm birth is a major cause of morbidity and mortality in perinatal population, and its incidence has increased in the last decade. The current methods to predict if a pregnancy will end up in a spontaneous preterm birth have been demonstrated not to be accurate. Cervical consistency index by ultrasound is a new tool created with the aim to predict accurately if spontaneous preterm birth will occur or will not occur, but more studies need to be conducted in order to introduce it to regular clinical practice and pregnancy follow-up.

OBJECTIVE

The aim of this study is to evaluate the performance of the second-trimester cervical consistency index (CCI) to predict spontaneous preterm birth in pregnant women.

STUDY DESIGN AND POPULATION

It is a prospective cohort study including all kind of pregnancies between $19 - 22^6$ WG, performed in the *Hospital Universitari Doctor Josep Trueta*. The sample size is of 419 women.

METHODS

The main variables will be CCI —calculated by doing the ratio between the anteroposterior diameter of the cervix at maximum compression and at rest— by ultrasound and the occurrence or not of spontaneous preterm birth. Patients will be followed up until delivery, so the maximum time will be 23 weeks.

KEYWORDS

Uterine cervix, Ultrasound, Cervical consistency index, spontaneous preterm birth

3. Introduction

3.1 Preterm birth

Preterm birth was defined by the World health Organisation (WHO) as the delivery before 37WG completed or 259 days counted by the LMP. It is a major determinant of neonatal mortality (28% early neonatal deaths are due to it) and a high morbidity, which often extends to later life, resulting in enormous consequences for health, both physical and psychological, as well as economic costs (1).

Figure 1. Adjusted odds of death by gestational age, US 1995-2001. Source: (3)

Preterm birth can be classified depending on different criteria, for example, the cause of the beginning of the labour (idiopathic, preterm rupture of membranes or iatrogenic) or the gestational age at delivery.

It is important to differentiate the cause of the beginning of the labour because some maternofoetal diseases may lead to stopping the pregnancy in order to protect the mother and/or the foetus, but spontaneous preterm labour may often lead to maternofoetal complications both in a short and a long term (2).

We can classify the preterm new-borns due to the gestational age in extreme prematurity ($20 - 27^6$ WG), severe prematurity ($28 - 31^6$ WG), moderate prematurity ($32 - 33^6$ WG), and mild prematurity ($34 - 37^6$ WG) (3). This classification reveals significant differences between the stages of pregnancy related to the probability of survival, the need for intensive care, long term health, disability outcomes and costs.

It is important to take into account the method of measuring the gestational age, because different methods can lead to committing bias. The most commonly used measurement tool is the first day of a woman's last menstrual period (LMP), but it is only accurate within about 2 weeks. The current gold standard is based on first-trimester ultrasound with specific foetal crown-rump length (CRL) measurements. If it is not possible to measure the gestational age in the first trimester, biparietal diameter and femur length measures are used as measure tools. The maximum accurate period for this method is prior to 20 weeks in order to avoid the confounders associated with variations in intrauterine growth of the foetus. CRL is accurate within about 5 days (3–5).

In nearly all of the cases, there exists a correlation between the weight and the weeks of gestation, so most of the new-borns with low weight are premature. Even though it is important to consider that this parallelism does not always occur, we have to differentiate "low birth weight" babies from "preterm birth" babies (2). Low birth weight is defined by the WHO as weight under 2500g (not included) and it has to be measured in the first hour of life (6). In Catalonia there were 5205 low birth weight babies during 2016 (7).

3.2 Epidemiology

The global incidence of preterm birth in 2010 was estimated to be an 11.1% rate resulting in almost 15 million preterm births worldwide. Countries defined as "developed" had an 8.6% rate, and it seems to be increasing (3,4).

In Europe the rates are lower than in the U.S. (5.8-6.7% vs 10.5-10.6%) (1).

According to data from the *Instituto Nacional de Estadística (INE)* in 2015 there were 26,935 preterm births from a total of 420,290 deliveries in Spain, resulting in a 6.41% rate (8). Despite the advancing knowledge in medicine in the last two decades, in the U.S. and also in developed countries and Catalonia, the preterm rates have increased from 9.2% in 1981 to 12.8% in 2006 (U.S. rate), from 7.2% in 1990 to 8.6% in 2010 (developed countries) and from 5.5% in 1993 to 7.6% in 2002 (Catalonia) (3,9). This growth in the preterm birth rates could be contributed to different factors such as the increasing trend of multiple births rates, greater use of assisted reproduction techniques, increases in the proportions of births in women over 34 years of age, higher rates of preterm inductions and caesarean deliveries and changes in clinical practices (4,5). The increase in survival of extreme preterm births (in concomitant reduction of stillbirths) and the reduction of the lower threshold of foetal viability —which was settled up to 28 WG (according to the WHO) and can now be considered that a livebirth is when birth happens from 24 WG onwards— could also be cause of the increased rate of prematurity (1,4).

However, nowadays it is better to induce labour or practice a caesarean section than to extend pregnancy in order to protect the mother and/or the foetus (10).

3.3 Risk factors

Even though presenting risk factors does not imply that the pregnancy will result in a preterm birth, it is important to know them and detect them to establish a more thorough obstetric monitoring.

The main risk factors are:

- **Preterm birth in a previous pregnancy**: It is the most important risk factor related to PTB, settling the recurrence risk in a 15-50% rate, depending on the number and the gestational age of the previous deliveries. Those pregnant women with only one previous spontaneous preterm birth before 35 WG have a 15% more risk in a later pregnancy. If the woman has 2 records the risk increases up to a 41% rate, and with 3 backgrounds it rises up to a 67% rate. If a medical history of delivery <28WG exists, the risk of PTB in a new pregnancy is 10 times higher (RR 10.5) (11).
- **Less than 12 months inter-pregnancy interval (IPI):** Several metanalysis have demonstrated that a <6 months IPI increases all the PTB risk, with an OR of 1.41 (IC 95% 1.20-1.65). For the IPI 6-11 months the OR was 1.14 (IC 95% 1.10-1.17). A short IPI has also been related to other obstetric complications (12).
- **Uterine factors**
    - **Short cervical length:** measured by transvaginal ultrasonography, it is associated to preterm birth —a length <25mm at 20 WG is a commonly used cut-off—. The shorter the cervical length, the greater the risk is (4).

- **Cervical incompetence:** Whether it is caused by congenital cervical weakness, surgery or trauma, several studies have shown its implication as a prematurity cause (13).
- **Leiomyoma:** Leiomyomas are benign tumours that affect women in reproductive age. Both their location and size have been related to prematurity (9).
- **Uterine malformation:** The most common anomalies are those which derive from a Müller conduct malformation, and they can be found in approximately 10% of women that suffer a threatened preterm labour (9). A probable explanation for these findings may be the smaller uterine cavity and higher rates of cervical incompetence associated with Müllerian anomalies (14). Women that suffer from a Müllerian malformation and have a precedent of preterm birth are more likely to suffer recurrent preterm birth than women that do not suffer the malformation (15,16).

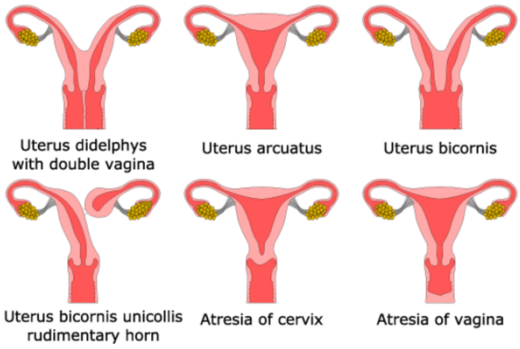

Figure 2. Uterine malformations. Source: (16)

- **Conisation and other uterine surgeries:** Women who have undergone through a cervical excision procedure of any kind have significantly increased odds for preterm birth, especially for preterm birth before 28 weeks and before 32 weeks of gestation (17). There is some evidence to suspect that the risk increases as it increases the cone size (18).

- **Extremes in the volume of amniotic fluid:** Polyhydramnios or oligohydramnios are associated with preterm labour and PROM.
- **Multiple gestations:** 15-20% of all preterm births result from a multiple gestation. Nearly 60% of twins are born preterm, whether due to PROM before 37 WG or due to an indicated preterm delivery because of pre-eclampsia or other maternal or foetal disorders. Nearly all higher multiple gestations will result in preterm delivery. Uterine distention, resulting in contractions and PROM is believed to be the cause (13).
- **In vitro fertilisation (IVF):** Singletons and twins formed through IVF suffer a higher risk (10.9%) than those spontaneously conceived (6.4%). In vitro fertilisation is also related with other perinatal complications, such as low birth weight or small for gestational age (19).
- **Infectious conditions**
    - **Bacterial vaginosis:** It is defined as a change in the microbial ecosystem of the vagina. Bacterial vaginosis is diagnosed clinically by the presence of clue cells, a vaginal pH greater than 4.5, a profuse white discharge, and a fishy odour when the vaginal discharge is exposed to potassium hydroxide (13). Bacterial vaginosis confers risk for intra-amniotic infection and spontaneous preterm delivery (20).
    - **Asymptomatic bacteriuria (ASB):** It is recommended to perform a routinary screening by mid-stream urine culture early in pregnancy, because treatment of ASB reduces the risk of pyelonephritis and PTB (21).

- **Genital infections:** It has been demonstrated that *Chlamydia trachomatis* infection, HIV and *Syphilis* are risk factors for PTB (4).
- **Chorioamnionitis:** One of every four preterm infants is born to mothers with an intra-amniotic infection that is largely subclinical. Microbial-induced preterm labour is mediated by an inflammatory process. Microorganisms and their products are sensed by pattern recognition receptors which induce the production of chemokines, cytokines, prostaglandins, and proteases leading to activation of the common pathway of parturition (20,22).

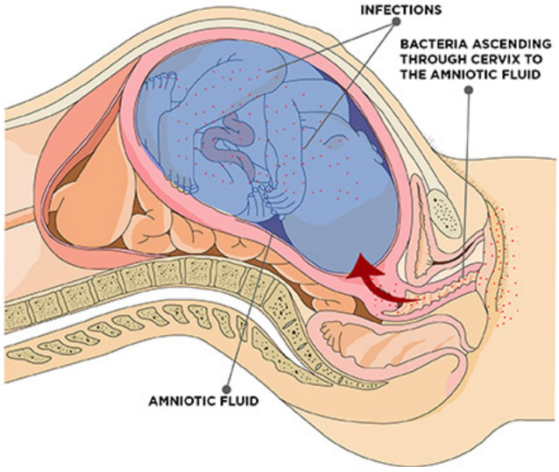

Figure 3. Chorioamnionitis. Source: (22)

- **Urinary tract infections:** Untreated pyelonephritis is a recognized risk factor for preterm birth. Lower urinary tract infections also are a risk factor for PTB (21).
- **Malaria:** from a global health perspective, malaria may be a major contributor to preterm birth in endemic areas. The mechanisms whereby malaria leads to preterm labour remain undetermined (20).

- **Maternal factors:**
  - **Black ethnicity:** A systematic review assessed the association between ethnic groups and prematurity and reported an OR (95% CI: 1.8-2.2) for black ethnicity. No significant associations were seen for Asian, Hispanic, or Caucasian women (23).
  - **Adolescent pregnancies and advanced maternal age:** Preterm birth occurs at rate ten time higher in extreme maternal ages (11). Pregnant teenagers have higher preterm birth rates than those who get pregnant at the age of 20-35, and the younger the woman is, the higher the rate will be. A plausible biological explanation may be incomplete maternal physical growth and relative malnutrition, which is related to the mother's gynaecological age rather than chronological age. For women aged ≥35, the preterm birth association may be attributed to greater incidence of chromosomal or congenital abnormalities, or confounded by maternal morbidities such as gestational diabetes, pre-eclampsia, and hypertension, as well as chronic diseases, which may be more common among older mothers. Age has a dose-response relation with PTB risk (24).
  - **Parity:** Nulliparous women have a higher risk of preterm labour, mainly if they are under 18 years old. However, women that have had 3 or more previous deliveries have also an increased PTB risk (24).
  - **Low maternal social status:** Low social status is also strongly related to prematurity. It could be a cause because of its relation

with other risk factors, such as low maternal age, low weight or toxic habits (9).

- **Maternal nutritional status:** A low body-mass index (BMI) —stablished in <19— increases the prematurity risk. Obesity also increases the preterm birth risk not only at the expense of iatrogenic causes but it also increases the spontaneous PTB risk by affecting the inflammatory pathway (11).
- **Maternal short stature:** A height <155cm has also been related to prematurity (9).
- **Maternal stress:** Mothers experiencing high levels of stress, both psychological and social, suffer from an increased risk of prematurity even after adjusting to the effects of sociodemographic, medical and behavioural risk factors. In the same way, exposure to objectively stressful conditions has been associated with preterm birth. The underlying mechanism is unknown, but it has been proposed a role for corticotropin releasing hormone and the inflammatory pathway, that in stress conditions remains activated (13).
- **Intimate partner violence during pregnancy:** A metanalysis performed by *Hill et all* demonstrated that intimate partner violence during pregnancy has significant increased odds of preterm birth. It is thought that the mechanism that leads to

preterm birth is by the stress pathway, the direct trauma and the genital infections (25).

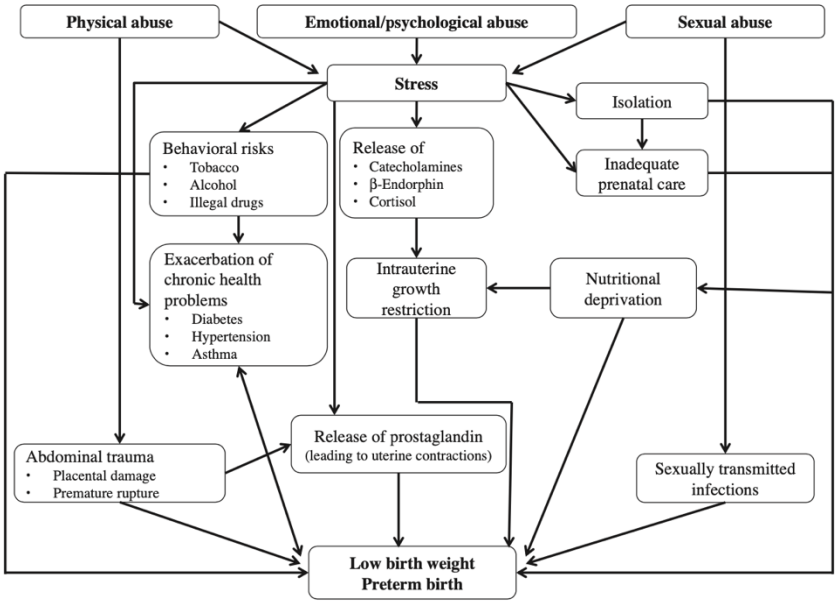

Figure 4. Potential pathways linking IPV to PTB and low birth weight. Source: A. Hill et al.

- **Periodontal disease:** There is evidence of an association between periodontal disease and PTB, and some randomized trials found that an accurate treatment of periodontitis will improve the perinatal results (26).
- **Immunologic mechanisms:** Autoimmunological diseases usually appear in women of reproductive age, so its association with pregnancy is not rare. Some of these diseases, such as systemic lupus erythematosus, have demonstrated their link with prematurity. The 12-30% —depending on the series— of women who had a preterm delivery suffered from an autoimmunological disease (9).

- **Maternal anaemia:** Anaemia's treatment has a positive effect, as anaemia may contribute to increase the preterm birth incidence (9).
- **Gestational hypertension and pre-eclampsia:** Hypertension whilst pregnancy has been related to PTB due to medical induction or due to spontaneous PTB. The mechanism is not clear, but it is suggested that vasospasms, with its consequent endothelial vascular rupture that happens in pre-eclampsia, lead to an ischaemia. This ischaemia produces a placentation defect, a placental abruption, and preterm labour (9).
- **Pregestational and gestational diabetes** increases the risk of birth <37 WG. Women who suffer from pregestational diabetes present an OR 3.8 (95% CI 2.5-5.9) (27).
- **Smoking:** Smoking is related to the inflammatory response. The tobacco reduction and/or withdrawal during pregnancy reduces the PTB risk. To stop smoking has been demonstrated to reduce up to 20% of preterm birth risk (11).
- **Use of recreational and illicit drugs:** Cocaine and heroin consumption during pregnancy have been associated with preterm birth (13).
- **Heavy alcohol use:** Women reporting an alcohol intake of 10 ≥ drinks/week have a 3 times higher risk of preterm delivery comparing to women drinking <1 drink/week even after adjusting for covariates (28).

- **Vaginal bleeding:** Bleeding in the first or second trimester is associated with preterm birth. If the bleeding occurs in the third trimester or the cause is placenta abruption or placenta praevia the associated risk of preterm birth is very high (13).
- **Foetal malformations:** The presence of birth defects is associated with prematurity because of the malformation by itself and because of the increased ratio of induced preterm delivery. Foetal malformations often lead to polyhydramnios —which is a risk factor, as we previously explained— or to a big tumour that grows up with pregnancy and provokes uterine distention. Foetal malformations have been related to PTB in 6% of the cases (9).
- **Outdoor air pollution:** High levels of sulphur dioxide, nitrogen dioxide and carbon monoxide in the air have been related to PTB (2,4).

3.4 Cervical remodelling during pregnancy and parturition

Along pregnancy, the uterine cervix suffers a remodelling process, consisting in changes at microstructural level and in water concentration. It starts during the first trimester and it progresses until term in normal pregnancies (29,30).

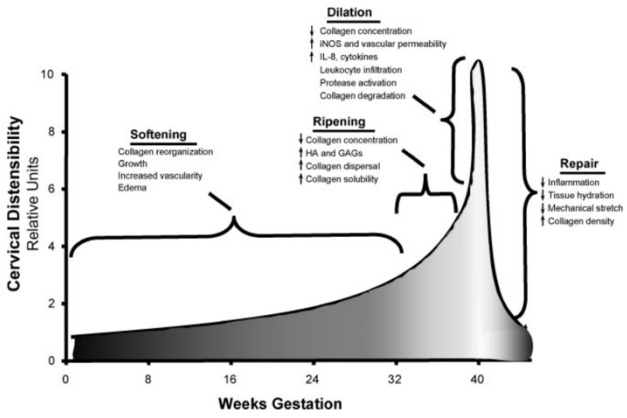

Figure 5. Stages of cervical remodeling during pregnancy. Source: WORD et al.

Cervical remodelling can be divided into four distinct but overlapping stages: softening, ripening, dilatation and postpartum repair.

Softening can be defined as the first measurable decline in the tensile strength or tissue compliance compared to non-pregnancy. It is a slow, progressive process of increased renewal of matrix components, resulting in reorganisation of the collagen fibrillar network, that begins in the first trimester of pregnancy and takes place in a progesterone rich environment. An increasing of vascularity, hypertrophy of the cervical stroma and hypertrophy and hyperplasia of the cervical glands also happen. Despite the progressive increase in compliance, tissue competence is maintained (29–31).

Cervical ripening is a more accelerated phase characterized by maximal loss of tissue compliance and integrity. It precedes the uterine contractions by weeks and involves increased synthesis of proteoglycans, glycosaminoglycans, and collagen. Collagen concentrations decrease and collagen fibrils are widely dispersed, due to the increase in the synthesis of hydrophilic glycosaminoglycans. Tensile strength is decreased and the cervix becomes thin and pliable (29,31).

The third phase is cervical dilatation during labour, until the cervix is wide enough to allow passage of a term foetus. This phase involves leukocytes and release of protease and collagenase into the extracellular matrix (29,31).

In the immediate postpartum period, rapid increases in repair processes ensures recovery of tissue integrity and competency (29,31).

Pregnancy is maintained by the absence of forceful uterine contractions and a closed, competent cervix. Contractions in presence of a competent cervix are not enough to bring about delivery; in contrast, cervical incompetence,

caused by an incorrect remodelling process, leads to preterm birth even without forceful uterine contractions (29).

3.5 Preterm birth screening and prevention strategies

3.5.1 Ultrasonographic cervical length (CL)

To date, the measurement of cervical length is the most accurate indicator of premature cervical remodelling and sPTB. The shorter the cervix, the higher the risk (9,32).

Transvaginal ultrasound measurement of cervical length is safe, reliable and highly reproducible when performed by trained obstetricians (32). The accepted threshold of significance for the prediction of sPTB in asymptomatic mid-term pregnant women is a CL <25mm (11). Nevertheless, the sPTB risk not only depends on cervical length, but also depends on the a priori risk factors.

Because the resultant risk also depends on the previous risk factors, cervical length screening recommendations set by professional societies differ. In women with high-risk of preterm birth, screening with serial cervical length will be performed between the gestational weeks 14-26. In asymptomatic low-risk women, no screening will be done by routine, because its cost-effectiveness has not been demonstrated (11,32).

It must be highlighted that CL presents a limited predictive capacity, which can be understood by the fact that it only describes one of the multidimensional changes associated with cervical remodelling (33).

The cervical length measure is, nowadays, the gold standard measure in spite of its weaknesses.

3.5.2 Foetal fibronectin

Foetal fibronectin (fFN) is a glycoprotein that is usually found in amniotic fluid and the placenta, thus its presence in the cervix or the vagina is an indirect sign of membrane alteration. It has been observed that its level significantly increases in the vaginal secretions of women in threatened preterm labour, so fFN may be valid to predict if a woman will have a PTB (9).

Its sensibility and positive predictive value are low, but a negative fFN test (<50ng/ml) has a high negative predictive value and strongly suggests that sPTB will not happen in the next weeks (32).

In the daily management, ultrasonographic cervical length and fibronectin test have a similar efficacy. Due to a greater access and lower cost of sonography in HUJT, transvaginal ultrasonography is the predictor element chosen to be performed (11).

3.5.3 A new tool: Cervical consistency index

The initial changes in the cervical ripening do not affect length, but they do affect consistency, because the cervix must first soften and then shorten. The cervical consistency index is a sonographic measurement tool that intends to estimate the cervical softness by measuring the maximum compressibility with a vaginal ultrasound probe; the lower the CCI, the higher the compressibility and consequent major softness.

CCI was firstly described by *Parra-Saavedra et al.* and the main aims of that study were to describe this new technique and to determine if statistically significant differences occur between non-pregnant woman, pregnant woman in the first, second and third trimester and stablish reference ranges to asses the potential value of CCI to predict sPTB (34).

The authors showed that the CCI decreased with advancing gestation and that in women who suffered preterm births, it was lower than in women that gave birth at term.

They finally suggested that CCI will enable to detect early stage patients at risk of preterm delivery, and it will also allow the evaluation of proposed treatments (34).

3.5.4 Prevention strategies in high-risk population

In high-risk pregnant woman, a closer follow-up will be started after the first-trimester sonography has been performed and the first-trimester screening has had normal results.

- Endocervical cultures and urine cultures will be done, in the 14WG and 22WG, in order to diagnose bacterial vaginosis and treat it if the results are positive.
- The cervical length will be monitored by doing controls every 2-3 weeks.

Regarding the clinical history of the pregnant woman the follow-up and the prevention strategies will be personalized:

- **Very unfavourable clinical history:**

  We classify a woman under this group when she has suffered two or more late foetal losses, understanding a late loss as those that happen after 16 WG.

  - Prophylactic cervical cerclage will be offered at 13-16WG to this group of women.

- **High preterm birth risk:**
  - If in the controls a short cervical length is found, vaginal progesterone treatment will be started, and a new control will be settled a week after. We define short cervix in singleton pregnancies as those shorter than 25mm in pregnancies <30 WG or shorter than 15mm in pregnancies >30 WG. In multiple gestations, short cervix is defined as shorter than 20mm in pregnancies <30 WG or shorter than 10mm in pregnancies >30 WG.
  - If the cervical length keeps on decreasing even the progesterone treatment, therapeutic cervical cerclage or pessary will be offered.
- **Casual short cervix length found in asymptomatic women**
  - The measure will be repeated in the specific unit after keeping some relative rest at home.
  - If the measure <20mm is confirmed, vaginal progesterone treatment will be started.

Keeping rest at home and avoiding sex are general recommendations to pregnant woman with a cervical length <25mm (11).

4. Justification

Preterm birth is a major cause of mortality and morbidity worldwide: it represents the cause of 28% of early neonatal deaths —late preterm babies have a mortality rate 9 times higher than those born at term— and the morbidity associated with preterm birth often extends to later life, resulting in enormous physical, psychological and economic costs (1,35). Two thirds of preterm births are attributed to spontaneous preterm birth; the remaining third is associated to medical indication due to maternofoetal complications (32). The global incidence of preterm birth in 2010 was estimated to be an 11.1%, and the trend is to increase (3).

Nowadays, what is done to try to prevent preterm birth is to take into account their historic and current pregnancy risk factors, and if a high-risk is determined, increase the surveillance during pregnancy by doing controls every 2-3 weeks. The cervical length is monitored, and if it is <25mm, progesterone treatment should be started. If the cervical length keeps on decreasing with the progesterone treatment, cervical cerclage or cervical pessary should be considered to implement (11,32).

Advances have been made to identify women at high risk of sPTB, but there are currently no effective diagnostic measures for preterm labour resulting in preterm birth, and no effective early interventions for prevention. There remains a lack of consistent and cost-effective screening modalities to early recognise patients who subsequently develop sPTB (1,32).

It has been demonstrated that some changes in the cervix occur all pregnancy long, such as softening and ripening. The process of the latter

starts one month before the onset of the labour (29,31). Premature remodelling of the cervix most likely increases the risk of sPTB, and objective detection and quantification measurement of its components (softening and ripening) is required (36).

Cervical consistency index was firstly described in 2011 by *Parra-Saavedra et al.* as a measure tool to measure the cervix consistency throughout pregnancy and it was suggested that it could be useful to early identify women at high risk of preterm birth (34).

Some researchers have done prospective cohort studies to prove that cervical consistency index performed in mid-trimester, is a valid predictor of sPTB, but all of them have separated the high-risk population and the low-risk population. Moreover, mostly all of them have had positive results in favour of the CCI. Seeing that, our proposal of a prospective cohort study with unselected pregnant woman should be done in order to validate the CCI as a screening tool and valid predictor of sPTB.

It is important that the population of the sample is unselected women, to be able to extrapolate the results to general population and make them valid. It is also important that the design is prospective, because we can control the co-variates that could act as confounders and give validity to our study. If cervical consistency index is proven to be a valid predictor of spontaneous preterm birth, a twist in preterm birth prediction and prevention could happen, because obstetricians will be able to apply preventive treatments to more selected people and reduce the preterm birth incidence.

5. Hypothesis

Cervical consistency index by sonography, performed at second-trimester screening, is a valid predictor of spontaneous preterm birth in pregnant women.

6. Objectives

Determine the validity of the cervical consistency index (CCI) by sonography to predict spontaneous preterm birth in second-trimester screening.

7. Subjects and methods

7.1 Type of design

The study is designed to be a prospective cohort study with the purpose of demonstrating the validity of cervical consistency index in mid-trimester sonography as a preterm birth predictor. It will be performed in the gynaecology and obstetrics department of *Hospital Universitari de Girona Doctor Josep Trueta.*

7.2 Study population

The population of this trial will be the pregnant women who undergo second-trimester pregnancy sonography control at *Hospital Universitari de Girona Doctor Josep Trueta.*

7.2.1 Inclusion criteria

Patients must meet all the following criteria to be part of this study.

- Pregnant women
- Gestational age at the moment of inclusion within $19 - 22^{6}$
- Women older than 18 years-old
- Women who can participate and have read, understood and given the informed consent

7.2.2 Exclusion criteria

Patients cannot meet any of the following criteria to be part of this study.

- Ruptured membranes at time of inclusion
- Painful and constant uterine contractions
- Unavailability to follow-up

7.2.3 Withdrawal criteria

- Preterm birth for iatrogenic intervention
- Delivery in a different hospital

7.3 Sampling

7.3.1 Sample size

In a bilateral contrast, with an alpha risk of 5%, a potency of 80%, assuming a clinically significant difference of 5%, the sample size that would be needed would be 349 subjects without drop-outs, and 419, assuming a drop-out of 20%.

The computations were carried out using the Prof. Dr. Marc Saez' software based on the library "pwr" of the free statistical environment R (version 3.6.2).

7.3.2 Data collection

A non-probabilistic consecutive sampling method will be followed in the gynaecology and obstetrics department of HUJT.

According to unpublished data from the gynaecology and obstetrics department of *Hospital Universitari de Girona Doctor Josep Trueta*, an average of 10 second-trimester sonographies are performed every day. Regarding that amount of daily mid-term sonographies and taking into account that not all the proposed women will accept to sign the informed consent, we have calculated that 35 women will be enrolled every week.

Therefore, we will need about 3 months to complete the inclusion of our sample size.

Every woman seen at *Hospital Universitari de Girona Doctor Josep Trueta* to complete the second-trimester sonographic control who fulfil the inclusion

criteria and not the exclusion criteria will be proposed to be enrolled in this trial.

The information document (see Annex I) and the informed consent (see Annex II) of the study will be given to all participants. They will only be included in the study if they sign and agree with the conditions of the research.

In the same visit the cervical consistency index will be measured, and the data will be collected in our database.

Afterwards, the patients will be followed-up until the delivery, when we will record in our database if the birth was at term or preterm.

7.4 Variables

7.4.1 Independent variable

The independent variable of the study is the Cervical consistency index measured by ultrasound.

It is a continuous quantitative variable. It will be expressed as a percentage.

7.4.2 Dependant variable

Preterm or term delivery.

It is a dichotomous nominal qualitative variable. It will be expressed by yes (Preterm birth) or not (Term birth). Any birth in HUJT will be recorded by medical history.

7.4.3 Co-variables

There are other variables that could affect our dependent and independent variables, but they are not the object of our study. As these variables could

act as confounders, we will have to control them in order to increase the internal and external validity of our study.

Among those variables we find:

- **Maternal age:** In years. A continue numeric variable.
- **BMI before pregnancy:** 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
- **Ethnicity:** Treated like a qualitative variable divided into 4 categories:
  - Caucasian
  - African
  - Asian
  - Mixed
- **Parity:** A dichotomic qualitative variable, divided into nulliparous and multiparous.
- **History of sPTB:** Measured in number, a discrete quantitative variable.
- **Smoking:** A dichotomic qualitative variable, divided into smokers and non-smokers.
- **Assisted conception:** A dichotomic qualitative variable, divided into yes or no.

7.5 Measure instruments

7.5.1 Cervical consistency index

Cervical consistency index will be measured at second-term sonographic control visit, so no extra visits will be needed.

We will need an ultrasonographic equipment with a transvaginal ultrasound probe, condoms and ultrasound gel. Dust-free nitrile gloves will be required.

To carry out the vaginal ultrasound to measure the cervical consistency index, the obstetricians will be trained by an external expert and they will need to pass a practical examination to demonstrate their abilities. To perform the measurement technique, it is needed that the woman has an empty bladder and that she is in a lithotomy position. The accepted methodology for the cervical consistency index measure, proposed by *Parra-Saavedra et al.* includes the following steps (34):

1. Cervical length taken according to standard technique.
2. The screen is divided into two, leaving fixed in one side the cervical length previously measured, and on the other side in real time. A pressure is made softly and progressively until there is no visual observation of a greater shortening in the anteroposterior (AP) diameter or the cervix moves due to pressure. Cervical length must be measured in the new image at maximum compression.

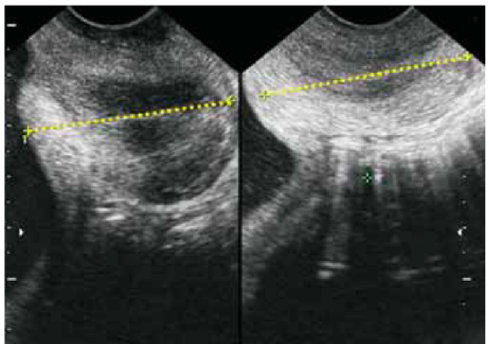

Figure 6. A line is drawn joining CIO to CEO in both sides of the screen. The left side is without pressure and the right side at maximum pressure. Source: Parra-Saavedra et al.

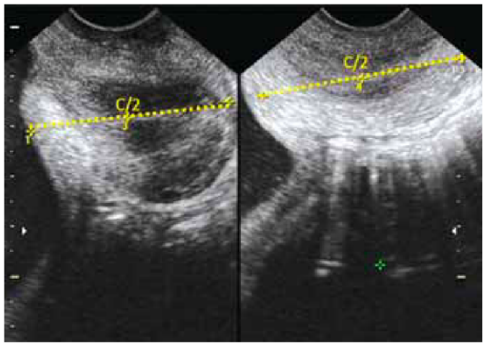

Figure 7. The half point of the cervical lenght is calculated. Source: Parra-Saavedra et al.

3. A half point of the cervical length transported to the center line of the longitudinal axis of the cervix is calculated in both sides of the screen.
4. In the half point a perpendicular line with an angle of 90º is built. On this perpendicular line, the distance of the most anterior lip point until the most posterior point of the lip is measured. This will be the measure of the anteroposterior diameter without (AP) and with maximum pressure (AP').

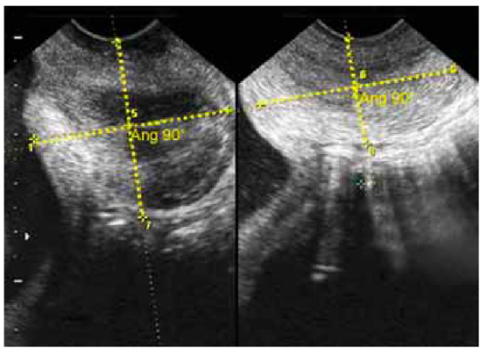

Figure 8. A perpendicular line is drawn to measure the anteroposterior diameter in both sides. Source: Parra-Saavedra et al.

5. Finally, the AP' distance is divided by the AP distance and it is multiplied by 100, obtaining the CCI. The equation is: $CCI = \frac{AP'}{AP} \times 100$.

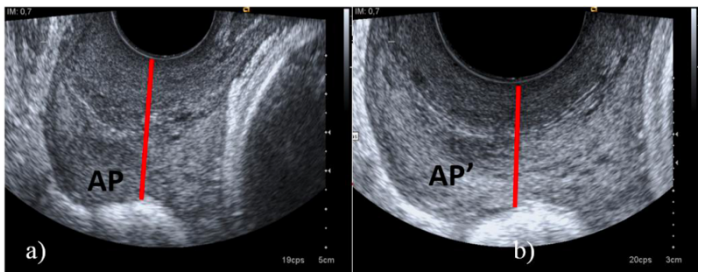

Figure 9. Cervical consistency index measurement. Source: N. Baños Lopez

The duration of the examination is calculated to be approximately 5 minutes.

8. Statistical analysis

8.1 Univariant analysis

The independent variable will be summarized by proportions and stratified, the dependent variable will be classified by the groups of the independent variable (a group each 5%).

The quantitative co-variables will be summarized using means (standard deviations) and medians (interquartile range IQR), again stratifying by independent variable groups.

8.2 Bivariate analysis

We will compare the proportions of the independent variables between the two birth groups (preterm and at term) with *Chi-square* and the *Fisher exact test*.

And we will contrast the difference of means, and of medians for the quantitative covariables, between the independent groups by the t-Student —when the variable follows a normal distribution— and the U of Mann-Whitney —when the variable does not follow a normal distribution—, respectively.

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 analysis

Finally, multivariate models will be used to adjust for possible confounding.

In particular, we will do a logistic regression where dependent variable will be preterm birth and independent variable will be the cervical consistency index -subdivided by groups of 5%-, controlled by all the co-variables.

9. Limitations, strengths and impact of the study

This study has some potential **limitations** that have to be taken into account in order to reduce them:

- The consecutive non-probabilistic sampling method could lead us to a selection bias; however, it cannot be avoided because of the specific characteristics of the study population. All the women who fulfil the inclusion criteria and do not meet any of the exclusion criteria will be proposed to be part of the study.
- We could have an observer bias because not all the sonographies will be performed by the same obstetrician. It is difficult to avoid, but we will try to minimize it by recording all the images and recalculating the CCI; and we will also do some formation with the aim of reducing the bias due to the technique.
- We can have a bias due to possible loss of participants, mainly because women can move to another place or give birth in another hospital. Also, women who have to give birth preterm because of iatrogenic causes will be considered as losses and they will not give results to our study. To deal with that possible bias, a 20% drop-out rate has been taken into account when calculating the sample size, in order to anticipate the losses.

This study also has some **strengths**:

- We are proposing a strategy to predict spontaneous preterm birth, that is the most important cause of perinatal mortality and morbidity. If our hypothesis is confirmed, the obstetrics services will be able to apply

earlier preventive strategies to avoid the occurrence of the preterm birth.

- The study population are all the pregnant women (not only the high-risk or low-risk groups) so if the hypothesis is confirmed, the technique could be implemented as another routine control in the normal pregnancy follow-up. It could also be seen as a sieving control in the second-trimester sonography visit.
- The information bias has been avoided with the team meetings and the ultrasound technique formation. All the team has been trained together, follow the same vaginal sonography protocol and have been required to demonstrate their ability.

It is important to mention the **impact on the National health system** that this study could produce. As explained in the introduction, preterm birth is a major determinant of neonatal mortality and morbidity —with all the costs and impact that it has on the National health system and in the future life of the preterm-born babies— and preventing it remains a big obstetrics challenge. If the hypothesis was confirmed, the study would give us evidence about a new tool that will allow us to predict spontaneous preterm birth and applicate the current scientifically demonstrated strategies to prevent it. By predicting (and preventing) spontaneous preterm birth we could find a cost-effective strategy to decrease the PTB rates and, as a direct consequence, the morbidity and mortality rates in perinatal population.

10. Ethical aspects and law

The study protocol will be sent to the *Comitè d'ètica d'investigació clínica (CEIC)* of *Hospital Universitari Doctor Josep Trueta* to be reviewed. If the project fulfils the required criteria, it will be approved. All the recommendations given by the CEIC will be taken into account.

All the information from the women included at the 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"*.

Women participants will be given the information sheet (annex I) and they will be asked to sign the informed consent (annex II) in order to be included in the study. Participants have the right to withdraw the consent without having a negative effect on the relationship with their assigned doctor. The principle of autonomy will be respected in all the process.

The study has been developed following the principles of the World Medical Association in the Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects (last amened in the 64th General Assembly, Fortaleza, Brazil, in October 2013).

The whole team will have to declare no conflict of interests, and to agree to publish all the results whatever are negative nor positive.

11. Work plan

11.1 Study Stages

This cohort study will be completed in 15 months following the hereunder steps:

- **Protocol design and approbation** (3 months, September 2019-November 2019)

Bibliography research about the topic, protocol processing and presentation to the *Comitè d'ètica d'investigació clínica (CEIC)* for its approval. The main researcher will be the responsible.

- **Organisation** (1 month, December 2019)

An organizer meeting will be convened with the research team. The main researcher will explain the objectives, methods and data collection, use of the patient data sheet and working plan. The chronogram will be modified regarding the team requirements.

A training journey will be organised. An ultrasound expert will explain how to do the CCI measurement following the protocol and practice will be done. At the end of the journey all the assistants will have to demonstrate that they have acquired the necessary skills to perform the technique.

- **Data collection** (8 months, January 2020-August 2020)

For 3 months, the Obstetrics service will be collecting patients, doing the sonography exploration procedure and collecting their results.

Once the women are recruited, they will keep on doing the normal pregnancy control until the delivery.

Once the women have given birth, the team will collect the data about the delivery (if it was preterm or at term, and which grade of prematurity).

The last data collection is expected to be in August 2020. The last pregnant woman will be included in March 2020, and the gestational age at that moment will be $19 - 22^{6}$ WG. Taking into account that pregnancy is maintained until a maximum of 42WG, the last woman in our study will give birth in August 2020.

- **Statistical analysis** (1 month, September 2020)

Once the last women in our cohort study has given birth (estimated in August), the whole data will be organised and sent to a statistician who will proceed to do the statistical analysis.

A final meeting with all the research team will be held with the aim to discuss the results and draw conclusions.

- **Publication and dissemination of results** (2 months, October 2020-November 2020)

Once the data has been analysed and conclusions have been drawn, the research team will write articles, with the aim to publish them in an Obstetrics journal to share the results with the scientific community.

We will attend a national and an international obstetrics conference about preterm birth, to present the results and share our experience.

11.2 Chronogram

Chronogram																
Work plan steps	Year	2019				2020										
	Months	Sept	Oct	Nov	Dec	Jan	Feb	March	April	May	June	July	August	Sep	Oct	Nov
Step 1	Scientific research + protocol writing															
	Ethical approval															
Step 2	**Organisation:** – Organisation meeting – Training journey															
Step 3	Patients recruitment															
	Data collection															
	Follow-up routine															
Step 4	Statistical analysis															
Step 5	**Results:** – Publication – Dissemination															

12. Budget

	DESCRIPTION	QUANTITY	COST (€)	SUBTOTAL
MATERIAL	Vaginal ultrasonography	419	20€ each	8380€
	5 extra minutes in ultrasonographic obstetric 2nd term control	419	12.75€	5342.25€
	Office material	5 sheets x 419	0.04€ each sheet	83.8€
STAFF	Statistician	120h	35€/h	4200€
FORMATION	Ultrasounds practical journey	1 meeting for 15 obstetricians (including diets)	100€ per person	1500€
PUBLICATION	Publication in a journal		2000€	2000€
PRESENTATION	National obstetrics congress	2 people (including transport and diets)	500€ per person	1000€
	International obstetrics congress	2 people (including transport and diets)	1000€ per person	2000€
TOTAL.....24.506.05€				

13. Feasibility

13.1 Medical team

The medical team in this study will be compounded by obstetricians and midwives, hired by *Hospital Universitari de Girona Doctor Josep Trueta*, so additional doctors or nurses will not be needed. The sonography to calculate the CCI will be performed by the obstetricians and the midwives will intervene during the labour.

An expert statistician will be contracted to process the statistical analysis implicated and help us to do the discussion and publication of the results.

13.2 Resources

Necessary means such as personnel salaries, sonograms, labour rooms and medical material will be provided by the National health system. The material required for this study is the standard material used in the usual pregnancy follow-up in hospital, so no extra material would be needed.

13.3 Patients

Assuming referral of patients from *Hospital Universitari de Girona Doctor Josep Trueta* we approximate an inclusion of 35 patients weekly. So, we believe that in about 3 months of data collection we will reach our sample size. However, the sampling will last until we achieve the sample needed. The follow-up will last until delivery, so we will follow those women a maximum of 23 weeks (assuming that pregnancy lasts until a maximum of 42 weeks) from the day they were included in our study. Thus, 8 months will be needed to get the sample size and know if the delivery was at term or preterm.

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Annex

Annex I: Information document

Information sheet for the patient

Study title: Cervical consistency index as a valid predictor of spontaneous preterm birth in pregnant woman.

We intend to inform you about a study in which you are asked to take part in. The study has been revised and approved by the *Comitè Ètic d'Investigació Clínica*. Our intention is that you can read and understand the information that is right and sufficient in order to evaluate and decide if you want to take part in our study. Please read this information sheet carefully. If any doubts come to you, please do ask us and we will try to solve them.

Voluntary participation

You must know that your participation in this study is totally voluntary and that you can decide not to take part or change your decision and withdraw your consent at any given moment, without any consequence in your relationship with your doctor nor treatment.

General description of the study

The main objective of the study is to determine if the cervical consistency index is a valid predictor of spontaneous preterm birth.

Preterm birth happens in around 11% of pregnancies and it carries out huge short-term and long-term consequences. Nowadays, preterm birth is predicted with the cervical length, but this tool can only predict accurately when a woman will not have a preterm birth; but there are still a lot of mistakes while predicting when a woman will have a preterm birth.

Cervical consistency index is a new vaginal ultrasound measure that gives us important information about changes in uterine cervix consistency and it has demonstrated a good sensibility and specificity. This index is obtained by performing a vaginal ultrasonography in the routinary second-trimester sonography control.

For all that, cervical consistency index helps us to predict more accurately if a pregnancy will end-up in a preterm or in at term birth. By predicting it we will be able to perform preventive strategies before the preterm labour threat happens, and as a consequence reduce the preterm birth rate.

In this study we intend to demonstrate that the cervical consistency index is a valid spontaneous preterm birth predictor and act consequently to improve the results both in the mother and the foetus.

This study will be performed in *Hospital Universitari de Girona Doctor Josep Trueta* and 419 women will be included.

Procedures during the study

In this study we pretend to validate a new predictive tool for preterm birth. If you take part into this study a vaginal sonography will be performed to you and the cervical consistency index will be calculated. A complete clinical history will also be done and a detailed physical exploration. The vaginal sonography will be performed at the same visit that the regular mid-term sonography control is done.

At the moment of birth, we will register if the birth was at term or preterm.

Your participation in the study will be from the moment you sign this document until 5 days postpartum.

Benefits:

It is possible that you do not obtain a direct benefit from your participation in the study. However, the evaluation of new predictive preterm birth techniques could contribute to improve the prognostic in future patients.

Inconveniences and possible risks:

No risks or inconveniences are foreseen for participating in this study, since the interventions that will be carried out are usually carried out in a standard high-risk pregnancy follow up. Vaginal sonography may be a little uncomfortable, but performed in the correct way it does not bother.

Personal data protection:

In order to ensure the compliment of *Llei Orgànica de Protecció de Dades de Caràcter Personal (5/2018)*, the information gathered during this study will keep confidential and will only be used for investigation purposes. Your name will not appear in any report. You will also have right to access and consult all the information about yourself and modify any mistake.

Accomplishing the prevailing legislation, you have the right of being informed about the relevant data for your health that could be obtained from the study. This information will be explained to you in the case you wanted to know it, if you prefer not no to know it your decision will be respected.

Economical compensation:

Your participation in this study will carry no cost and bring no economical compensation to you.

Thank you for your attention and collaboration

Annex II: Informed consent

Informed consent formulary

Study title: Cervical consistency index as a valid predictor of spontaneous preterm birth in pregnant woman.

Me (Name and surname) _____

with ID number _____

I declare that:

- I have read the information sheet that has been given to me.
- I was able to ask questions and doubts about the study and they have been correctly answered.
- I have been given enough information about the characteristics of the study and the possible risks and I understand the importance of my contribution to the progress of medicine.
- I have spoken to _____ (Name and surname of the investigator)
- I understand that my participation is voluntary
- I understand that I can withdraw my informed consent at any time, without the need of explanations and without repercussions in my future medical care.

I voluntarily agree to give my consent to be included in the study about the cervical consistency index as a valid predictor of spontaneous preterm birth, and I agree to give the personal information needed to perform the study.

_____ _____

Patient's signature | Investigator's signature

Date: | Date: