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# Cervical Length and Progesterone: Contribution of Ultrasonography to Decide to Whom Administer the Progesterone

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# Cervical Length and Progesterone: Contribution of Ultrasonography to Decide to Whom Administer the Progesterone

Luis Raúl Martínez González

**Abstract- Introduction:** Preterm birth is considered a worldwide problem having multifactorial causes showing a high rate of morbidity and mortality, even in this 21<sup>st</sup> century; researchers are working in the proteomics field searching for new solutions to its prophylaxis.

**Objective:** This article is aimed at reaching a review of the most recent aspects concerning the use of progesterone to the specialists who follow up pregnant women having short cervix and history of preterm births.

**Development:** A transvaginal cervicometry is performed in the 18<sup>th</sup> and 24<sup>th</sup> weeks of gestation, which can also be performed trans-abdominally to determine the length of cervix, the internal cervical os(ICO), the existence or not of cervical funneling, the presence of complete, partial or non-presence of mucous plug, and if sludge is observed in the amniotic fluid or the so-called muddy fluid; in this case, a cervix length lesser than 25 millimeters, in a single pregnancy, helps us to predict a high risk of preterm birth, worsening if the other factors mentioned before are observed; which can be previously explored using this technique. Henceforth, considering these results and evidences, the treatment with progesterone can be established following the recommended scheme.

**Conclusions:** The cervicometry and the assessment of other factors in the cervix, together with the evidences found aid establishing prophylactic measures to avoid preterm births using progestins.

**Keywords:** cervicometry, progesterone, preterm birth.

## I. INTRODUCTION

According to WHO the birth of 130 millions of infants are expected in a year, and thirteen (13) millions will be preterm births approximately, of them 68% die in the fetal component and 70% die in the first week of life and those surviving (50%) will suffer from neurological problems and by 26% learning disabilities. Regarding these figures, there are no doubts about, that preterm birth was in the last and it is still a health problem in this current century<sup>1</sup>.

With the purpose of explaining and solving this difficult problem worldwide, a number of factors that are linked to a higher risk of a preterm birth have been identified: uterine overdistension, vascular factors, and infections, hormonal disorders, immunological, genetic and cervical; by 40-50% of idiopathic causes, it is true

that all these factors, one way or another, can lead to the causes, it is written and proved that to maintain pregnancy the mechanical power of cervix is always necessary, as it provides a barrier between the inferior genital tract and the intrauterine space<sup>2</sup>.

Increase of interleukins secretion and nitric oxide (NO) in vaginal secretions have been reported, which are associated with preterm birth, since these mediators stimulate the apoptosis, the activation of proteases and as a result the disintegration of collagen fibers which leads to a shortening of cervix<sup>3</sup>.

In consequence, preterm birth is defined as an entity having multifactorial causes that can be a trigger for the early maturing of the physiological processes, normally occurring at the end of pregnancy, as a result, cervical alterations before the end of pregnancy could predict a third part of patients with preterm birth<sup>3</sup>.

In consequence, a conclusion can be stated; the risk of prematurity is inversely proportionate to the length of cervix, but a modified cervix is another one link in the sequence of risk factors which determine the preterm birth<sup>4</sup>.

The cervicometry is valid as a screening for a preterm birth, but it is only justified in a population at risk, where the competence of a *sharp-eyed* observer can be taken into consideration as well as the control of quality of the equipments; this then, is the only way to find an answer to this complex health problem<sup>5</sup>.

There are many ways to prevent preterm births and they can vary depending on the case, and on important antecedents such as cervical conization, associated diseases and if it is a single or a multiple pregnancy. But in this review article we are trying to provide an outlook on how cervicometry and the use of progesterone can contribute to the prevention of preterm births.

## II. DEVELOPMENT

Prematurity is still the great problem of the 21<sup>st</sup> century, as a consequence researches related to proteomic are in increase into the first world, which are aimed at finding protein biomarkers that could foresee the possible pathogenesis<sup>5,6</sup>.

These protein biomarkers aid us to determine the possible preterm birth that can include predictable

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and valuable factors to determine its onset, which will then imply demographic causes, personal behaviors along with the findings in physical examinations. These basic sources, to carry out proteomic study, as the searching for these biomarkers are basically found in

plasma, placenta and amniotic fluid (Fig.1). Proteomic has developed new pathways in the knowledge of preterm birth pathogenesis, regarding inflammatory and hemorrhagic patterns, when they are not as well present<sup>6</sup>.

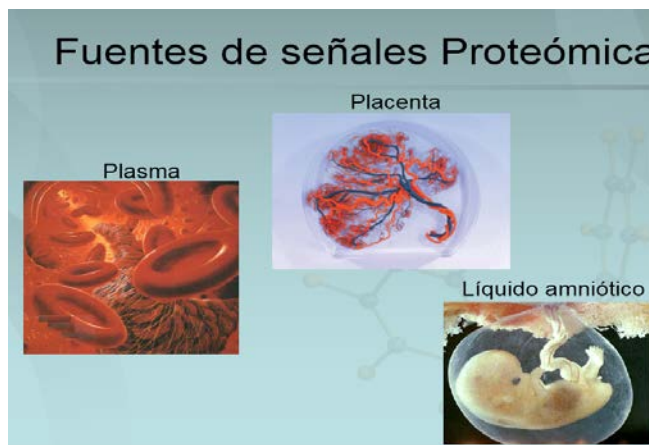


Figure 1 : Images of sources with the proteomic signals are shown: plasma, placenta and the amniotic fluid

Until the researches comprising these markers end, doctors of medicine involve with the treatment of pregnant women must learn very well the points previously proved in recent studies, this way the ultrasonography of the cervix plays its role, therefore between the 18<sup>th</sup>-24<sup>th</sup> weeks of gestation an assessment of the cervix is recommended.

Other different features of the cervix can be assessed, and will be shown in this article, even though it is demonstrated that a short cervix with small amount of mucous plug and *sludge*-amniotic fluid (*muddy*), can be particularly important to identify the pregnant women who are destined to have a preterm delivery<sup>7</sup>.

The *sludge* is the immune response of the organism as protection before a microbial invasion in the internal environment; the microorganisms find different ways of protection, one of them has been defined as the introduction of polyhedral compounds, known as biofilms. The bacteria can stay viable within these structures and the leukocytes penetrate inside them; which has been proved in vitro; however, they are not able to phagocytize the microorganisms there<sup>7-9</sup>.

### III. INDICATIONS FOR THE CERVICOMETRY<sup>5, 10-12</sup>

There are different indications to perform a cervicometry that not only can be reduced to measure the cervix; other variables can also be observed, which will be subsequently discuss.

### IV. AMONG THE MAIN INDICATIONS FOR THE CERVICOMETRY

Previous preterm delivery, which is considered the most important.

1. A patient having a cervical conization.
2. A multiple pregnancy.
3. Repeated artificial abortions.
4. Uterine malformation.
5. Bleeding on the second half of pregnancy.
6. Worrying socio- hygienic conditions.

It is known that a history of preterm delivery predisposes to 20% of repetition in another pregnancy with a precedent of presenting a two-fold increase of probability of its occurrence; but when a delivery takes place before the full-term pregnancy and another at full-term, it is an intermediate risk.

A multiple pregnancy constitutes one of the causes for the increase of preterm deliveries, as a result of the medical development; the use of fertility medications, where the stimulators of ovulation get involved, along with the assisted reproduction, which favors the onset of its presentation, and therefore between 3-6 times more frequent<sup>12,13</sup>.

It is said, nowadays, that as the single pregnancies increase preterm deliveries in 61%, multiple ones make 168% and even in 615% when there are 3 or more products of conception. In equal respects, it is said that 30-50% of the multiple pregnancies and 75% of triplets, come from not so young infertile women treated to procreate, which is considered another element of risk. In some regions of the world, up to 56% of multiple pregnancies were delivered before full term<sup>13, 14</sup>.

### V. VARIABLES TO BE CONSIDERED IN THE ASSESSMENT OF CERVIX (SEE FIG. 2)

The majority of the authors suggest a transvaginal examination of the cervix, because of the

advantage of avoiding the artifacts provoked by the entrance of the sound in the skin to approach to the cervix, keeping away the inconvenient that trans-abdominal ultrasound has, where the bladder must be full of urine, though not as much, because the measures could be distorted when exerting pressure on the cervix, in lengthening it, it does not happen by using transvaginal ultrasound, where full urinary bladder-preparation is not necessary and the transducer approaches the cervix and measures it, along with the rest of the examination performed with better definition<sup>15,16</sup>.

Then, in this examination we can make the measures of the cervix to find out its length, assessment of the internal cervical os, the existence of funneling, where the length is measured and the presence of this last element may be calculated from the internal cervical os (ICO), which requires at least 5 mm dilatation of this funnel-like, with a vertex in the cervical canal. The amplitude of the tunnel corresponds with the dilatation of the ICO and it is possible to measure the functional length of the cervix, measuring the total length of the cervix and subtracting the funneling part, whether the presence or not of *sludge* in the amniotic fluid<sup>15</sup> can be observed from the echographic point of view, and where this definition indicates the presence of a dense aggregate of floating particles in the amniotic fluid, so close to the ICO, as a sign of invasion of microorganisms in the internal environment, generally composed of mucous slug portions, cervical epithelium, fragments of chorion-amniotic membranes, considered as an immune response of the organism before a microbial invasion<sup>7,8,17</sup>, where cells from numerous structures participate: amnion, chorion, deciduas, neutrophils, macrophages, trophoblasts and taking them as germ-free.

During the examination of the cervix, whether the mucous plug is or it is not complete is also explored, which constitutes a well-established structure to protect the internal environment, which is basically composed by water together with organic and inorganic compounds. When the cervical length is reduced, it turns into a small and short slug, almost surpassing its internal and external extremes, this way it loses the protective function and can be easily associated with subclinical infections<sup>10, 11</sup> and for few supporters, the measurement of cervical volume with 3D-echography.

It must be considered that the cervix is an important biomechanical structure to maintain the balance with the uterine body to provide the chronologic end of pregnancy. The majority of the studies suggest that this measure progressively decreases as the pregnancy develops; others, that it increases; and another third part thinks, it has no changes, but the trend of acceptance indicates that its length shortens<sup>10, 12</sup>.

During pregnancy, although normally, the cervix measures 3-5 cm, placing 35 mm in 50 percentile, as much during the second trimester as at the beginning of the third, it has been demonstrated that, for the third months of pregnancy, the elongation of the isthmus starts occurs, helping to differentiate the structures, so that, by the fifth months, delimitations of the inferior segment and the cervix become evident; having a very great importance to interpret echographic images accurately<sup>17-19</sup>.



Figure 2: Echographic images to examine the cervix: length, presence of mucous plug, cervical internal os, funneling and the presence or not of *sludge* in the amniotic fluid.

### VI. ADVANTAGES OF CERVICOMETRY <sup>8,20</sup>

Concerning the data previously exposed it will be necessary to perform a cervicometry having the following advantages.

- It:
1. helps to reduce false positives which are causes of admissions in hospitals.
  2. shortens hospital stays.
  3. reduces the iatrogenic tocolysis.
  4. helps to identify patients having a true need of cervical cerclage.
  5. makes possible the screening of a group of asymptomatic pregnant women with high risk of preterm birth without other evident risk factors.

### VII. INCISION-POINT OF THE CERVICAL LENGTH TO PREVENT PRETERM DELIVERY <sup>10,12,21,22</sup>

With the practice of cervicometry and the advantages it has, adding this is not an invasive technique; incision-point of the cervical length should be determined to carry out the screening for preterm delivery, where the majority of the authors affirm the following conclusions:

1. To use an incision-point for a cervical length of 25 mm to identify preterm delivery in a single fetus during the 2<sup>nd</sup> trimester of pregnancy, starting it at the 20 weeks.
2. To use the measure of the incision-point for a cervical length of 20 mm to screen the possible anticipation of a multiple pregnancy, considering that during the third trimester a marked decrease of 10 mm takes place.
3. To use the measures of incision-point for a cervical length of 15 mm in patients with evident clinical risk of preterm delivery to establish this diagnosis.

It has been proved that, the length of the cervix between the 18<sup>th</sup> and 24<sup>th</sup> weeks of pregnancy lesser than 25 mm and prior to 32<sup>nd</sup> week, pregnant women have a six-fold increase in preterm birth, in relation to pregnant women having a cervix length over the 75 percentile<sup>23,24</sup>.

Then, a cervicometry is performed in a twin pregnancy at 20<sup>th</sup> week approximately; an incision-point of 23 mm seems to establish a population at risk with an increase of preterm delivery-probability<sup>25,26</sup>.

The findings of a short cervix not always results in cervical incompetence or preterm delivery and the length of the cervix must be assessed as a screening in patients at risk.



## VIII. PROGESTERONE ADMINISTRATION AND ITS INDICATIONS

If it is known that one or more previous preterm deliveries, in present pregnancy this condition exists because a short cervix is observed, then it is feasible to administer progesterone supplementation in this patient, which is available of a pharmacotherapy since 1934 and it has been in use for different gynecological diseases, such as: menstrual disorders, infertility, recurrent abortions and other complains<sup>27</sup>.

Progesterone can be found as synthetic and natural progestins or micronized and improved with better bioavailability as oral, vaginal and intramuscular (17  $\alpha$ -hydroxyprogesterone), the last two presentations are the most employed all over the world<sup>27, 28</sup>.

As progesterone can be administered to prevent preterm delivery, it is time to question which the possible mechanisms of actions are<sup>29</sup>:

- ❖ It blocks the oxytocic effect of F2 $\alpha$ -prostaglandin.
- ❖ It avoids the development of gap unions that are formed by two hemi-channels inserted between two contiguous cells where the lumen of one of them continues with the other allowing, when they open, the passage of ions from cytoplasm to cytoplasm of the adjoining cell makes possible the electric synapses without chemical messengers.
- ❖ It blocks the prostaglandins that induce the contractions.
- ❖ It relaxes the smooth myometrium-musculature.
- ❖ It is a suppressant of the action of calcium-calmodulin in the system of kinases diminishing the influx of calcium. It should be remembered that, the calmodulin is an intracellular protein which is one of the regulators in the transduction of the signal of calcium in the cell; besides it intervenes in other metabolic processes.

Other individual and meta-analyses studies sustain the administration of intramuscular 17  $\alpha$ -hydroxyprogesterone (17  $\alpha$  OH P) reduces the incidence of recurrent preterm delivery in women with history of spontaneous preterm delivery.

Taking as a whole, the review of the data pointed out that the prophylactic use of progesterone results beneficial in reducing preterm delivery and low-weight at birth. Data also indicate, in a minor concluding way, that progesterone can improve the rates of neonatal morbidity and mortality<sup>30</sup>.

Intramuscular route-progesterone is associated with a reduction of premature delivery before the 37<sup>th</sup> week, and with a newborn infant inferior to 2500 gram-weight, observing a lesser degree of cervical shortening, confirming that the use of 17  $\alpha$ -hydroxyprogesterone (17  $\alpha$  OH P) was related with a reduction of premature delivery (OR: 0,15; IC 95%, 0,04-0,58)<sup>31,32</sup>.

Hassan and Romero, et al. stated in their work that the use of intramuscular 17-hydroxyprogesterone

caproate or vaginal micronized during 18<sup>th</sup> and 22<sup>th</sup> week up to the 36<sup>th</sup> week in patients with history of premature delivery or a cervix shorter than 15 mm reduces by 50% the risk for another preterm delivery<sup>33</sup>. It was demonstrated in 2011, that the finding of a cervical length between 10-20 mm at the beginnings of the second term, constitutes an indicator to administrate progesterone as well, and that its use not only could reduce the incidence of prematurity, but also its associated morbidity<sup>34</sup>.

## IX. THERAPEUTIC APPROACH<sup>35-40</sup>

To date, when progesterone is used to prevent preterm delivery, the following approach can be applied based on the available data:

1. For women having a previous spontaneous premature delivery: to administer 17 $\alpha$  OH P (250 mg) weekly, starting at 16<sup>th</sup> and 24<sup>th</sup> weeks.
2. For women having a short cervix (<25 mm): vaginal progesterone suppositories of 200mg can be administered in reasonable doses of 250mg weekly of 17 $\alpha$  OH P.
3. For women having a twin pregnancy: progesterone is not systematically indicated, even though its use can be effective in the context of a previous spontaneous premature delivery or a very short cervix: 250 mg of intramuscular 17 $\alpha$  OH P weekly or 200 mg vaginal suppositories.
4. For women having preterm labor arrest: the administration of progesterone could be considered (400 mg daily in vaginal suppositories or 250 mg of intramuscular 17 $\alpha$  OH P, twice a week), but the available data are so limited because of the lack of blind trails.

However, results have been satisfactory with the administration of progesterone in some of its presentations (intramuscular or vaginal) for many authors, and there are recent articles published from 2013, along with multicenter studies carried out in United States and Great Britain along with a study done in Spain with pregnant women having short cervix detected by cervicometry and history of preterm delivery. Cervical cerclage was performed to a group of 142 pregnant women, 59 of them were administered progesterone and to 42 a silicone device (pessary) was placed around the cervix, the conclusions of this study did not contribute to significantly statistical results<sup>40</sup>, showing that an only therapy or behavior will not solve the problem and that in occasions two therapies should be applied, as cervix cerclage and progesterone could be, even though researches must continue.

## X. CONCLUSION

Preterm delivery is a health problem even in the middle of 21<sup>st</sup> century due to the high levels of morbidity and mortality, which has a multifactorial etiology, but

almost a third of births before a gestational age of 37 complete weeks are consequences of an early modification of cervix, therefore prophylactic measures can help, an ultrasonography cervicometry must be performed to predict preterm delivery where the different features of cervix can be assessed, comprising: the length of cervix, existence of funneling or amniotic fluid with *sludge*, performing these assessments between 18<sup>th</sup> and 24<sup>th</sup> weeks of pregnancy. In the case a shortening of cervix is confirmed or the patients refer one or more previous preterm deliveries, then a progestin therapy by vaginal route or intramuscular 17-hydroxyprogesterone should be established, preferably up to the 36<sup>th</sup> week if necessary, as a result different therapeutic approaches in both aspects are explained, as well as in twin pregnancy and with limited results, in cases presenting arrested preterm deliveries. The greater part of works support the weekly injections of 17-hydroxyprogesterone, a supplementation that also reduces the frequency of recurrent preterm delivery, particularly in patients presenting high risks for premature births reducing the probabilities of numerous complications in newborn infants.

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