CERVICAL LENGTH MEASUREMENT WITH TRANSVAGINAL ULTRASONOGRAPHY

USEFULNESS FOR PREDICTION OF SPONTANEOUS PRETERM DELIVERY

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Professional Procedures Assessment Department
This report was validated by the HAS Board on 21 July 2010.

THE TEAM

This assessment report was prepared by Dr. Olivier ALLAIRE, a dental surgeon and project head in the Professional Procedures Assessment Department.

The literature search was carried out by Mr. Aurélien DANCOISNE, information officer, with the assistance of Ms. Laurence FRIGERE.

The logistical organisation and administrative work were undertaken by Mr. Félix MULLER and Ms. Stéphanie BANKOUSSOU.

Contact details for any communication regarding this report:
Tel.: 01 55 93 71 12
Fax : 01 55 93 74 35
Email: contact.seap@has-sante.fr

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Professional Procedures Assessment Department

Head of department, Dr. Sun Hae LEE-ROBIN
Deputy head of department, Dr. Denis Jean DAVID, PhD

Documentation and Public Information Department
Head of department, Dr. Frédérique PAGES, PhD
Deputy head of department, Ms. Christine DEVAUD
INTRODUCTION

Preterm delivery is a major cause of perinatal morbidity and mortality. Determining the risk of preterm delivery is a matter of considerable importance in obstetrics. Several methods for trying to predict the occurrence of preterm delivery have been put forward. Measuring the length of the cervical canal of the neck of the uterus by transvaginal ultrasound is one of them. Use of this procedure appears widespread according to the health-insurance databases; hence the request for an assessment. The procedure’s potential to correctly distinguish patients who will give birth prematurely from those who will carry their baby to term meets two objectives: firstly, it allows effective preventive treatment to be put in place at an early stage, and secondly, it makes it possible to avoid inappropriate treatment and inappropriate hospitalisation, which result in side effects and considerable expenditure. This report is in response to a request made by the CNAMTS [French national health insurance] in May 2009 and aims to determine the extent to which the procedure is able to predict the occurrence of spontaneous preterm delivery (SPD).
BACKGROUND

The procedure to be assessed

- **General information**
  The procedure assessed in this report is measurement of the length of the cervical canal of the neck of the uterus by transvaginal ultrasound. This procedure is carried out according to a standard technique. It is included in the joint classification of medical procedures that are borne by health insurance. The health-insurance databases show it to be a frequent procedure.

- **Potential benefit of the procedure**
  An inverse relationship between the length of the uterine neck and the frequency of SPD has been demonstrated.
  Measurement of neck length by transvaginal ultrasound has therefore been proposed as a tool for predicting the occurrence of SPD, which a length below a predetermined threshold is reported to be predictive of.
  The benefit of the procedure depends on:
  - its power to predict SPD;
  - the risk/benefit ratio of measures aimed at preventing SPD or of measures whereby the neonate can be prepared for prematurity.
  Only the power of the procedure to predict SPD is examined in this report.

- **Alternative techniques**
  Changes in the neck of the uterus can be detected by a digital vaginal examination. This provides clinical information used as a basis for determining Bishop's score. From Bishop’s score it is possible to ascertain how imminent delivery is. The higher the score, the closer the delivery.
  The presence of foetal fibronectin, which is normally absent from vaginal secretions between the 21st and 37th week of pregnancy, is increased as preterm delivery approaches.

- **Recommendations**
  French recommendations on the management of threatened preterm delivery and on the management of twin pregnancies have been produced by the Collège National des Gynécologues et Obstétriciens Français [National College of French Gynaecologists and Obstetricians]. Measurement of the length of the neck of the uterus by transvaginal ultrasound is recommended in cases where there is a threat of preterm delivery and in the case of monochorionic twin pregnancies.
  There are also numerous foreign recommendations on the management of threatened preterm delivery and on ultrasonographic assessment of uterine neck length for the prediction of SPD. Except in regard to the indications in cases of threatened preterm delivery, these recommendations sometimes do not agree.

Preterm delivery

- **Definition**
  A preterm delivery is any birth occurring before the end of the 37th week of amenorrhoea, i.e. before the 259\textsuperscript{th} day of amenorrhoea. It can be spontaneous or induced and occurs in 7.2% of births.

- **Morbidity and mortality of premature babies**
Prematurity is a key factor in perinatal mortality and morbidity. Neonatal mortality and morbidity are closely linked to gestational age at birth and increase with increasing precocity of delivery. Prematurity is responsible for 70% of neonatal deaths and for considerable neonatal morbidity, including the possibility of psychomotor, visual, and respiratory sequelae.

- **Causes**
  Uterine and placental abnormalities and urinary, genital, and intra-amniotic infections are the main causes of SPD.

- **Risk factors**
  The risk factors for SPD are linked to:
  - socioeconomic parameters (age of the mother, smoking, alcohol consumption, socioeconomic level, etc.),
  - gynaecological and obstetric history (uterine malformations, uterine neck surgery, history of SPD or of late miscarriages, etc.),
  - the pregnancy itself (multiple pregnancy, incompetent cervix, placental haematomas, haemorrhagic disorders, maternal disease, etc.).

**Population affected by the procedure assessed**

Not all pregnant women are at the same risk of preterm delivery, and the treatment aimed at preventing the occurrence of SPD differs according to the clinical picture.

That is why the procedure’s performance was assessed in four clinical situations in which the measures proposed for preventing SPD differ:

- **Women who are symptomatic, i.e. show signs of threatened preterm delivery**
  Threatened preterm delivery is a condition combining cervical changes and regular, painful uterine contractions occurring between 22 and 36 weeks of amenorrhoea + 6 days, which can spontaneously develop into labour in the absence of treatment.

In 1998, 20% of pregnant women were hospitalised in the course of their pregnancy and in 38% of cases this was because of TPD. In France, where there are 800,000 births a year, the incidence of TPD is estimated at 60,000. Furthermore, it should be noted that the prevalence of SPD in these patients varies considerably from one study to another (20 to 40%).

In 2003 the rate of premature births was 7.2%, and 75% of these cases were spontaneous premature births. The number of SPD cases can be estimated at 43,000 per year. Bearing in mind that these SPD cases are almost always preceded by TPD and that 20 to 40% of women hospitalised for TPD give birth prematurely, the incidence of TPD is estimated at between 107,500 and 215,000.

In total, the incidence of TPD can be estimated at between 60,000 and 215,000 patients/year.

Treatment of threatened preterm delivery is initially directed at reducing uterine contractions. It is based on rest and tocolysis. Thereafter, maternal corticosteroid therapy is administered to allow foetal pulmonary maturation to take place prior to delivery.

In cases of threatened preterm delivery, it is important to know whether delivery is imminent or not. The treatments are no trivial matter. The tests that form the basis for the decision on whether or not treatment should be administered must be effective in order to avoid a situation in which treatment is given needlessly or, on the contrary, wrongly omitted.
- **Women who are asymptomatic but show an identified risk factor for SPD**
These are patients without contractions whose gynaecological and obstetric history represents a risk factor for premature delivery. They are patients with uterine malformations or with a history of late miscarriages, SPD, or uterine neck surgery.

In addition to rest and administration of progesterone, prophylactic stitching can be carried out. Use of stitching is not a procedure on which there is consensus, however.

- **Women who are asymptomatic and do not show an identified risk factor for SPD**
These are women with singleton pregnancies, without contractions, who do not have a history of preterm delivery or of uterine neck surgery or uterine malformation either.

In this group, prevention of SPD is based on monthly monitoring by means of the usual clinical examinations and, if necessary, adaptation of the workplace and journey patterns, and investigation and treatment of local infection.

- **Women with a twin pregnancy who are asymptomatic**
This group covers all twin pregnancies irrespective of their obstetric or gynaecological history. In France, between 1995 and 1998, 43.7% of live-born twins were born before 36 weeks.

Recent recommendations of the Collège National des Gynécologues et Obstétriciens Français [National College of French Gynaecologists and Obstetricians] on the prevention of premature birth in twin pregnancies state that bed-rest, oral tocolytic therapy, administration of progesterone, and prophylactic stitching are not recommended in asymptomatic patients who are pregnant with twins. The recommendations state that the means available for the prevention of SPD in asymptomatic twin pregnancies are very limited.

**The issues**
Measuring the length of the neck of the uterus would make it possible to identify women at risk of SPD and thus to give treatment where it is pertinent and to avoid wrongly administering treatment to patients who will not give birth prematurely.

From the public-health viewpoint, the hope is to reduce the number of SPD cases, neonatal morbidity/mortality, and needless hospital admissions and thus make good use of resources.

Practice in regard to the prediction of SPD through transvaginal measurement of the length of the neck of the uterus varies. This assessment could harmonise professional practice.
METHOD OF ASSESSMENT

Literature search

Method
The literature search was carried out by searching the computer databases, health-assessment sites, and sites of learned societies. It was carried out between 01/1999 and 06/2009. A watch was kept until 02/2010.

Results
Number of references identified: 431
Number of references analysed: 272
Number of references used: 68

Selection of the identified documents

General selection criteria
The studies had to present results compared with the reference: SPD. As the comparator is the event itself, SPD is the ideal reference.

In order to be able to calculate diagnostic performance, it had to be possible to produce a contingency table from the studies, according to the following model:

Below a selected length threshold, the test is deemed positive (true and false positives); above that threshold, it is deemed negative (true and false negatives). These results are then compared with the actual time of delivery – prematurely or at full-term – to identify the true positives from the false positives and the true negatives from the false negatives.

Data on gestational age at the time of measurement, on the definition of the prematurity threshold, and on the definition of the uterine neck length threshold are data that affect the results. The studies had thus to present these data too.

The inclusion and exclusion criteria for the study populations had to be clear and enable the study populations to be identified.

Retrospective studies were excluded from the selection.

Selection criteria specific to each population?
For symptomatic patients, the selection criterion was delivery within the 48 h and/or 7 days following admission.

For asymptomatic patients with an identified risk factor, only studies paying attention to risks based on obstetric and gynaecological history were used.

For asymptomatic patients without an identified risk factor, only studies including patients without an obstetric and gynaecological history were used.

Finally, in the case of twin pregnancies, only studies undertaken in asymptomatic twin pregnancies were used.

Analysis of the selected documents
The results were expressed as sensitivity (Se) values, specificity (Spe) values, positive predictive values (PPV) or negative predictive values (NPV), and positive or negative likelihood ratios (LR+ or LR-).
Working group
A working group was set up, with representatives from the following disciplines: gynaecology-obstetrics, midwifery, radiology, and neonatology. The working group met and gave a verdict on the analysis of the literature and on the utility of uterine neck length measurement by transvaginal ultrasound in the four populations investigated.
RESULTS OF THE ASSESSMENT

Predictive power in regard to preterm delivery in symptomatic patients

Presentation of the studies
The literature search identified 13 studies comprising a total of 2279 patients and a meta-analysis that looked at 2114 patients. Two studies that were found did not figure in the meta-analysis, 1 for an unidentified reason and 1 because the study was published after the meta-analysis.

All these studies were carried out using similar approaches in terms of the selection criteria, method of measurement, and expression of the results. Of these thirteen studies, only two presented results compared with digital vaginal examination (Bishop’s score). The results of one of these two studies were uninterpretable.

Results
In the meta-analysis, for delivery within 48 h and for a neck length of 25 mm, the positive likelihood ratio was 2.09 (result from 2 studies). For delivery within 7 days, the positive likelihood ratios were 5.7 for a neck length of 15 mm (6 studies), 3.74 for 20 mm (4 studies), and 2.77 for 25 mm (4 studies). The sensitivity values were between 60 and 93%.

The power of ultrasound was comparable to that of Bishop’s score (one study).

All in all, the data showed measurement of uterine neck length to be a good investigation for predicting SPD within 7 days but there were no data that would make it possible to say whether it was a good investigation for predicting delivery within 48 h.

Position of the working group
Measuring uterine neck length by transvaginal ultrasound facilitates identification of women who are at risk of a premature delivery and thus facilitates selection of those who might benefit from specific therapy.

The threshold recommended by the working group is 25 mm. However, this threshold:
- can vary depending on whether high specificity or sensitivity is given more importance
- can be modulated depending on the gestational age at which the measurement is performed or be expressed directly in the form of a Z score or a percentile for the term.

The measurement ceases to be of benefit after 34 weeks.

The measurement does not need to be repeated some time after the acute episode in the absence of new symptoms.

Predictive power in regard to SPD in asymptomatic patients with an identified risk factor for SPD

Presentation of the studies
The literature search identified 8 studies comprising a total of 1796 patients. The inclusion criteria of each of the studies stipulated populations at increased risk of preterm delivery. The investigated risks were not always the same.

The age at which measurement was performed, the definition of the prematurity threshold, and the definition of the neck length threshold were not absolutely the same from one study to another.
Results
The results were analysed for common neck length thresholds across the studies, and then pooled according to the definition of the prematurity threshold.

- Neck length threshold defined as 20 mm
  Sensitivity varied very considerably (10 to 83%) depending on the study. The positive likelihood ratios were always above 5.

- Neck length threshold defined as 25 mm
  Sensitivity varied from one study to another (19 to 83%), and a positive likelihood ratio that was generally between 2 and 8 was found.

- Neck length threshold defined as 30 mm
  Two studies showed sensitivity values of below 40% and positive likelihood ratios above 2 and below 5.

All in all, these data found a connection between neck length and SPD. The lower the thresholds, the higher the positive likelihood ratios. The investigation was informative at low length thresholds. However, the sensitivity values for low neck length thresholds showed that it was hard to identify with certainty the women who gave birth prematurely (numerous false negatives).

Position of the working group
A short uterine neck is associated with an increase in the risk of premature delivery. Measuring uterine neck length by transvaginal ultrasound, repeated if necessary, can help select patients who might benefit from specific therapy.

The threshold recommended by the working group is 25 mm. However, this threshold:

- can vary depending on whether high specificity or sensitivity is given more importance
- can be modulated depending on the gestational age at which the measurement is performed or be expressed directly in the form of a Z score or a percentile for the term.

The measurement is no longer useful after 34 weeks.

Predictive power in regard to SPD in asymptomatic patients without an identified risk factor for SPD

Presentation of the studies
The literature search identified 5 studies comprising a total of over 3343 patients. Heterogeneity factors that can influence interpretation of the results were found among the studies. These factors were the method of patient selection, the gestational age at the time of measurement, the definition of premature delivery, and the chosen neck length threshold values.

Results
The sensitivity values were moderate and heterogeneous: between 39 and 84%, with better specificity values, between 78 and 98%. The positive likelihood ratios were between 2.57 and 6.15.

As expected, the higher the neck length thresholds, the higher the sensitivity values. Measurements carried out or begun at lower gestational ages produced lower sensitivity results than measurements carried out or begun at higher gestational ages.
All in all, the literature data showed that measuring uterine neck length in a population of patients without an identified risk factor resulted in a diagnostic benefit (positive likelihood ratios above 2.5). However, fairly low sensitivity, even at thresholds above 30 mm, led to a considerable number of false negatives. It was thus not possible, with this investigation, to reliably identify the patients who gave birth prematurely.

- **Position of the working group**

A short uterine neck is associated with an increase in the risk of premature delivery. However, the low prevalence of prematurity and the low PPV of the investigation in this population of patients without an identified risk factor lead the working group not to recommend systematic measurement of cervical length in the current state of knowledge and outside the context of a research study.

**Predictive power in regard to SPD in twin pregnancies**

- **Presentation of the studies**

The literature search identified 6 studies comprising a total of 2466 patients. The ages at which measurement was performed, the neck length thresholds, and the definitions of the prematurity thresholds investigated varied. The inclusion criteria of each of the studies stipulated all asymptomatic twin pregnancies. None of the studies defined exclusion criteria based on obstetric history and consequently, in each of the studies, the results were expressed “all risks combined”.

- **Results**

The results were analysed for common neck length thresholds across the studies, and then pooled according to the definition of the prematurity threshold. Sensitivity at a given threshold varied very considerably. It was higher at higher neck length thresholds. The predictive power was greater at prematurity thresholds close to the age of measurement.

The sensitivity values, which differed excessively, were not readily exploitable and probably reflect substantial heterogeneity across the studies. The most favourable positive likelihood ratios (values and confidence interval) were observed at a neck length of 25 mm and at 33 or 34 weeks of pregnancy.

All in all, the literature data showed that measuring uterine neck length in twin pregnancies was of diagnostic benefit for prediction of SPD before 35 weeks.
Position of the working group

The working group subscribes to the December 2009 recommendations of the Collège National des Gynécologues et Obstétriciens Français [National College of French Gynaecologists and Obstetricians] on the management of twin pregnancies, which state that "using this investigation it is possible, with a negative predictive value of over 90%, to remove a risk of mechanical prematurity for the four weeks following the investigation. For this reason, it may permit a useful substantial reduction in the medical monitoring of a twin pregnancy. However, an ultrasonographic finding of short neck can be the source of potentially iatrogenic approaches, because the positive predictive value of this investigation is only half its NPV". Nevertheless, in cases of monochorionic twin pregnancies, the optimal term is less than the term of a dichorionic pregnancy. The Collège National des Gynécologues et Obstétriciens Français [National College of French Gynaecologists and Obstetricians] thus recommends monthly transvaginal ultrasonographic monitoring of the neck of the uterus.
CONCLUSION AND OUTLOOK

Conclusions:
The literature data show that there is a connection between uterine neck length and SPD, a very short neck being predictive of SPD and, conversely, a very long neck being predictive of a full-term delivery.

Between these two extremes there is an uncertain area, in which the diagnostic power of measuring uterine neck length – which depends on the neck length threshold selected – is insufficient for the occurrence of an SPD to be reliably predicted on that basis alone.

The literature data also show that the presence of a short uterine neck makes an SPD more likely to varying degrees depending on the population studied and on the neck length threshold chosen. Thus, although measuring uterine neck length does not permit the prediction of preterm birth, it does make it possible to estimate a level of risk for it.

Nevertheless, given the uncertainty that exists over occurrence of a preterm birth after measurement of the length of the neck, the utility of this measurement will depend on the risk/benefit ratio of the measures aimed at preventing SPD. These measures have not been assessed in this report.

Thus, after analysis of the diagnostic power of uterine neck length measurement and after consulting experts, HAS is of the view that:

- Measuring uterine neck length by transvaginal ultrasound in symptomatic patients is of benefit for helping to select the patients who might benefit from specific therapy.
  
The measurement does not need to be repeated some time after the acute episode in the absence of new symptoms.
- Measuring uterine neck length by transvaginal ultrasound in asymptomatic patients with identified risk factors is of benefit, subject to the measures for the prevention of SPD being effective.
  
The measurement can be carried out twice-monthly from week 12 to week 24.
- Measuring uterine neck length by transvaginal ultrasound is of no benefit in asymptomatic patients without an identified risk for SPD.
- Measuring uterine neck length by transvaginal ultrasound is of no benefit in twin pregnancies apart from monochorionic twin pregnancies. (Professional recommendations)
- Measuring uterine neck length by transvaginal ultrasound ceases to be of benefit after the 34th week.

Outlook
Defining a threshold below which a decision to treat is taken is of key importance. To improve the accuracy of prediction of SPD, studies are needed to better define a specific threshold as a function of term for each of the populations concerned.

The utility of the measurement depends on the risk/benefit ratio of the treatments envisaged. An assessment of the risks and benefits of these treatments is needed.