Mid-Trimester Endovaginal Sonography in Women at High Risk for Spontaneous Preterm Delivery

Protocol and
Manual of Operations

The National Institute of Child Health and Human Development
Maternal Fetal Medicine Units Network

Prepared by the

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Protocol Amendments

October 6, 1997

In order to ensure the total sample size of 235 patients will obtained, the limit that a single center couldn't enroll more than 55 patients was removed. This change was approved by the Steering Committee on October 6, 1997

April 27, 1998

Sample size assumptions were revised since it was found that most patients in the Cervical Ultrasound study were not enrolled in another clinical trial. The total sample size changed from 235 to 170.

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1. Introduction

1.1 Study Abstract

This protocol proposes endovaginal sonographic data collection in high risk women, defined as those with a prior spontaneous birth between 16^0 and 31^6 weeks gestation.

1.2 Objectives

The objective of the study is to determine whether endovaginal sonography can identify a group of high risk women whose mid-trimester cervical characteristics define them as candidates for a future clinical trial of cerclage or other intervention strategies. Cervical length will be the primary variable of interest, but the presence of funneling, response to fundal pressure, and other parameters will also be examined.

Other objectives are to determine whether:

- Cervical sonographic data at 16-23 weeks gestational age is predictive of subsequent spontaneous preterm birth at less than 35 weeks.
- Longitudinal assessment of changes in cervical characteristics will improve the predictive accuracy of endovaginal sonography for spontaneous preterm birth at less than 35 weeks.
- Analysis of other cervical characteristics (in addition to cervical length) will improve the predictive accuracy of endovaginal sonography for spontaneous preterm birth at less than 35 weeks.

1.3 Purpose of the Protocol

This protocol describes the background, design, and organization of the study and how it interfaces with the existing Randomized Clinical Trials of the Effect of Metronidazole on Pregnancy Outcome in Women Infected with *Trichomonas vaginalis* or Bacterial Vaginosis (the BV/TV study). It may be viewed as a written agreement between the study investigators. It is approved by the Steering Committee and the Institutional Review Board (IRB) of each clinical center before recruitment begins. Any changes to this protocol during the study require the approval of the Steering Committee and review by the Advisory Board.

2. Background of the Study

Endovaginal ultrasound (EVUS) has evolved as a reliable technology for imaging the cervix and lower uterine segment in pregnancy and has overcome essentially all of the technical limitations imposed by the transabdominal technique.[1,2,3] Using high frequency probes and defined techniques, image quality and reproducibility are consistently high. Several reports have demonstrated concordant relationships between cervical length and the risk of spontaneous preterm birth. Conversely, the utility of EVUS to predict cervical incompetence has also been investigated, but with conflicting results and recommendations. Thus, our ability to identify the woman who might reasonably benefit from a cerclage is currently limited.

2.1 Spontaneous Preterm Birth

From a study of 113 women, Anderson et al [4] concluded that a short cervix, (less than the median value of 39 mm) found prior to 30 weeks was a significant risk factor for spontaneous preterm birth (25% vs. 7%) and had a sensitivity of 76% and a specificity of 59%. Their incidence of spontaneous preterm birth was 15%. However, the timing of the endovaginal exam was not controlled and ranged from 8 to 30 weeks gestation, with only half of the scans performed prior to 20 weeks. Their study included an unselected but generally low risk population and they assumed that cervical length did not change over gestation. Logistic regression analysis confirmed that the risk of spontaneous preterm birth was inversely related to the cervical length.

More recently, Tongsong et al [5] (1995) studied 730 unselected women at 28 - 30 weeks and determined that the optimal cut-off for predicting spontaneous preterm birth was a cervical length < 35 mm based on ROC analyses (sensitivity = 66%, specificity = 62%). The definition of spontaneous preterm birth was less than 37 weeks, and the observed incidence of spontaneous preterm birth was 12.5%.

The NICHD MFMU Network recently completed an analysis of the relationship between cervical length and spontaneous preterm birth in approximately 3,000 women[6]: 2,915 women with a singleton gestation were examined at 24 weeks and 2,531 at 28 weeks. There was a strong inverse relationship between cervical length at both 24 and 28 weeks and the risk of spontaneous preterm birth < 35 weeks. The relative risk for spontaneous preterm birth was 2.1 at cervical lengths less 35 mm (determined at 24 weeks). This increased to a relative risk of 8.6 at lengths less 13 mm (determined at 24 weeks). The relative risk at less than or equal to the 10th percentile (26 mm) and the 5th percentile (22 mm) were 5.1 and 7.1 respectively. The logistic models developed by Dr. Iams in evaluating these study data were similar to Andersen's[4] results and confirmed a progressively increased risk of spontaneous preterm birth with a shorter cervix.

2.2 Cervical Incompetence

Cervical incompetence (CI) is usually considered when painless cervical dilatation and membrane prolapse have resulted in spontaneous pregnancy loss in the mid-trimester. Several reports have described the sonographic findings of CI.[7,8] Because the outcome of early or prophylactic cerclage is superior to emergent placement,[9] some efforts have been directed to determining the early sonographic signs of CI. More recently, investigators have attempted to define CI on the basis of sonographically determined parameters.[2]

Since the distinction between CI and other causes of early pregnancy loss (e.g., labor) is imprecise, several authors[10,11,12,13] have suggested that it more likely represents a continuum of pathology. On one end is the anatomically weak cervix which dilates before it shortens, resulting in predictable membrane prolapse and early delivery. In other cases uterine activity may predominate, possibly aggravated by the events which have caused the premature cervical ripening and effacement.

Podobnik et al evaluated 80 women "at risk" for CI using transabdominal sonography.[14] Although the use of cerclage was not controlled, or even defined, the authors concluded that a cerclage was indicated for women with a cervical length less than 34 mm at 15-19 weeks gestation or an endocervical canal dilated more than 10 mm. Conversely, Brook et al (1981) reported that a dilatation of ≥ 1.9 cm indicated CI.[7] Using transabdominal sonography in a selected population of 88 gravidas with historic risk factors for CI, Ayers et al suggested that a cervical length less than 4 cm represented CI and was an indication for cerclage.[10] Michaels et al also used transabdominal sonography to study 107 "at risk" patients.[15] They used undefined sonographic criteria, as well as suggestive histories or physical findings to diagnose CI and to recommend cerclage. While their study methodology was not reproducible, they suggested that herniation of the membranes greater than 6 mm into the endocervical canal was a particularly significant finding. Conversely Andersen et al concluded that shorter cervical lengths were more often associated with a risk of preterm labor than with CI.[2]

Quinn performed serial endovaginal sonography in 21 women who had a Shirodkar cerclage placed because of historic risk factors.[16] Membrane prolapse to level of the stitch was observed in four women and felt to be an ominous finding that preceded spontaneous delivery between 21 and 33 weeks gestation. Six women without sonographic evidence of membrane prolapse were also delivered preterm (mean = 28 weeks). Finally, they noted that in half of their population, there was no dilatation or effacement after cerclage removal, casting doubt on the original diagnosis. This small study suggests that the true benefits of cerclage may be limited in women without a classic history of CI. Clinically, this same conclusion was reached in a multicenter randomized trial performed by the Medical Research Council/Royal College of Obstetricians and Gynecologists.[17] These investigators studied nearly 1,300 women who were deemed to be "at risk" for CI and concluded that only one delivery prior to term would be prevented for every 25 women who received a cerclage. Thus our current ability to discriminate "real" CI from other conditions in women with a non-classic history is poor.

Sonek et al reported the concept of dynamic changes which were visible with transvaginal sonography in some patients.[18] This involved shortening of the cervix and the onset of "funneling." Since this phenomenon could be accentuated by gentle manual pressure on the fundus, they suggested investigation of this internal os "stress test". Recently Guzman et al examined the utility of transvaginal sonography as a screening test for CI and included the application of transfundal pressure as a provocative maneuver.[19] In 31 women "at risk" for CI, 14 demonstrated cervical dilatation or prolapse of the membranes with fundal pressure, while two women were felt to have had a "grossly incompetent" cervix during the scan. Of these 16 women, 15 received a cerclage and 10 (67%) of these went to term. Of the 15 with no sonographic evidence of CI, two received a cerclage after a false-negative scan with subsequent dilatation and prolapse of the membranes. In this group the term delivery rate was also 67%, confirming that women with historic risk factors but no anatomic evidence of CI are still at high risk for spontaneous preterm birth.

2.3 Summary

While there appears to be consistent data linking a short cervix (variously defined) to an increased risk of spontaneous preterm birth, it is not known if women who have spontaneous preterm birth related to a short cervix develop this finding over time or whether they begin the pregnancy with this “risk factor”. Conversely, the identification of women with CI who might benefit from cerclage appears to be very imprecise, and practically empiric, based on available reports. Additionally, there are several important limitations in the available literature. First, there has been a paucity of data obtained at less than 20 weeks of gestation, and much of this has resulted from a transabdominal technique. Similarly, because of earlier technical limitations and limited operator experience, available studies have usually included only cervical length and dilatation/funneling of the endocervical canal. Other characteristics, such as response to fundal pressure, may augment the predictive value for early loss. Second, the mechanisms by which these phenomena occur remain very speculative. Since extremely low birth weight infants represent the highest risk group and account for most of the morbidity and mortality associated with prematurity, better understanding of early pregnancy events will be crucial to the reduction in extremely preterm birth and midtrimester loss. Finally, essentially all sonographic data on cervical characteristics, has been cross-sectional in nature, and much of it poorly controlled or obtained from unselected populations. Thus, important trends which can only be defined with longitudinal studies are generally not detectable. This further limits our ability to better define possible mechanisms and plan effective treatment strategies (e.g. cerclage) for the prevention of spontaneous preterm birth and early pregnancy loss.

3. Study Design

3.1 Summary

The BV/TV study consists of two randomized, double-masked, placebo-controlled, multicenter clinical trials, each with 1,900 women who screen positive for the presence of either asymptomatic BV or TV. Women with TV enter the TV trial regardless of their BV status; BV positive women who are TV negative enter the BV trial. Exclusions include planned or previous antibiotic therapy, multiple gestation, indicated cerclage, and other significant medical problems. All obstetric patients will be screened to detect these microbiologic risk factors for spontaneous preterm birth, and the Cervical Ultrasound study will focus on a subset of this screened (positive or negative) population who have had a prior spontaneous preterm birth between 16^0 and 31^6 weeks gestation. Women in the treatment trial are randomly assigned to receive metronidazole or an identical placebo. Women receive a 2 gram dose of metronidazole, or an equivalent placebo dose, at randomization and the same study medication two days later. This treatment course is repeated two to four weeks later.

All patients who have been screened for the BV/TV study at less than 19^0 weeks and who also have had a prior spontaneous preterm birth between 16^0 and 31^6 weeks will then be approached for inclusion in the Cervical Ultrasound study. This group will ultimately include both BV/TV positive women (and who either have consented to or declined to participate in the BV/TV trials) and BV/TV negative women. Patients can still be considered for the Cervical Ultrasound study if they did not receive a screening pelvic exam for the BV/TV study because of vaginal symptoms, antibiotic use, or an allergy to metronidazole. After consent to the study, the first endovaginal scan will be performed between 16^0 and 18^6 weeks. Subsequent scans will be performed every two weeks, to end at 22^0-23^6 weeks gestation. No more than four exams will be performed on a patient. Based on an estimated 75% compliance with all visits, an average of three scans per patient will be completed. Women who enroll in the Cervical Ultrasound study will be followed to determine the subsequent obstetric course and outcome. For patients participating in the BV/TV trials, the outcome assessment will be performed as part of the primary trial. For women not enrolled in the BV/TV trials, clinical outcomes will be assessed in analogous fashion.

When the BV/TV trials end, screening for the Cervical Ultrasound study will continue until the sample size goal is met.

3.2 Eligibility Criteria

3.2.1 Inclusion Criteria

Patients who meet the following inclusion criteria will be eligible for the study:

1. Previous spontaneous preterm delivery anytime between 16^0 and 31^6 weeks gestation (inclusive). If the gestational age at this birth is uncertain, a prior pregnancy resulting in an infant weighing 1,500 grams or less is acceptable. Study nurses should attempt to obtain the records of the previous spontaneous preterm birth. Women whose previous records cannot be

obtained can be enrolled if the patient reports she is "certain" of the gestation (or birthweight) of her previous pregnancy. For example, a patient could be enrolled if she knows her previous date of delivery, her previous EDC, and recalls that first her water broke and then she was admitted to labor and delivery. Multifetal gestations are eligible, as are stillborn infants and neonates with anomalies. Study nurses who are unsure about whether a particular patient should be enrolled should contact Dr. Owen for further guidance.

2. Less than 19^0 weeks by project gestational age (see criteria below).

3. First cervical ultrasound can be performed between 16^0 weeks and 18^6 weeks gestation by project gestational age.

3.2.2 Gestational Age Determination

For the purposes of this and other MFMU Network studies, gestational age is determined in the following manner and is denoted 'project gestational age'. The 'project EDC', which is based on the project gestational age, cannot be revised once a correct determination has been made from data available at randomization. Because the project EDC depends on information from the earliest dating ultrasound, if no ultrasound has been performed previously, one must be performed before the patient can be enrolled. This is considered part of general clinical management of a high risk patient and will not be funded for.

1. The first day of the last menstrual period (LMP) is determined and a judgment made as to whether or not the patient has a 'sure' LMP date.

2. If the LMP date is unsure, the ultrasound measurements obtained at the patient's first ultrasound examination are used to determine the project gestational age, by the standard method of ultrasound gestational age determination at that institution.

3. If the date of her LMP is sure, and the ultrasound confirms this gestational age within the number of days specified in *Cutoffs for Using LMP to Determine Gestational Age*, the LMP derived gestational age is used to determine the project gestational age. When using the table, it is important to use the gestational age at the first ultrasound as calculated from the LMP.

4. If the ultrasound determined gestational age does not confirm the LMP generated gestational age within the number of days specified in the table below, the ultrasound is used to determine the project gestational age.

Cutoffs for Using LMP to Determine Gestational Age

Gestational age at first ultrasound by LMP	Ultrasound agreement with LMP
up to 19^6 weeks	$\pm$7 days
20^0 weeks to 29^6 weeks	$\pm$14 days
30^0 weeks or more	$\pm$21 days

3.2.3 Exclusion Criteria

All of the exclusion criteria in the BV/TV study apply, except for those relating to antibiotic use, vaginal symptoms, or allergy to metronidazole. Patients with the following medical conditions will be excluded from this study:

- Major fetal anomaly/death
- Multiple gestation
- Ethanol abuse
- Hypertension requiring medication
- Collagen vascular diseases
- Isoimmunization
- Tocolytic treatment/preterm labor
- Cervical cerclage
- Uterine anomaly
- Diabetes requiring insulin
- Renal failure or heart disease
- Asthma
- Delivery/prenatal care elsewhere

Women should not be enrolled in this study if they are enrolled in a study where the treatment could affect delivery gestation (such as the Asthma trial), with the exceptions of the BV/TV trials, the FFN trial, and the Progesterone trial. Once a women is enrolled in this study, she cannot be enrolled in this study in subsequent pregnancies. Women who were screened or randomized in the BV/TV study during a previous pregnancy, but not enrolled in the Cervical Ultrasound study, are eligible.

3.3 Informed Consent

If required by the center's own Institutional Review Board, written informed consent must be obtained before enrollment into the Cervical Ultrasound study. Full disclosure of the nature and potential risks of participating in the trial is to be made. Each center will develop its own consent forms according to the requirements of its own Institutional Review Board. A sample informed consent form is included in Appendix A.

Women who are not fluent in English will be enrolled by a person fluent in their language, and both verbal and written informed consent will be obtained in that language. If such is not available, they will not be enrolled.

3.4 Masking

In general, managing physicians will be blinded to the results of the endovaginal examinations. The consent form should make it clear that diagnostic sonography is not being performed. However, if the sonologist happens to notice either fetal death or complete placenta previa, the managing physician will be

notified. Since placenta previa and fetal death are conditions which are normally detected through other clinical indicators (such as bleeding, fetal heart rate assessment, or fetal movements), missing these conditions at a particular visit would not be catastrophic. The diagnostic accuracy of endovaginal sonography for these conditions is poor: the fetal chest can only be seen occasionally with endovaginal sonography, making the technique insensitive to the diagnosis of fetal death. Similarly, most cases of placenta previa diagnosed by ultrasound in the second trimester do not eventuate in a clinically important problem.

The principal investigator (Dr. John Owen) will be blinded to individual pregnancy outcomes and will be responsible for reviewing representative images from each examination.

3.5 Study Outcome

The primary study outcome is spontaneous preterm delivery at less than 35^0 weeks gestation, as defined by project gestational age.

3. Study Procedures

4.1 Screening

All patients at less than 19^0 weeks gestation who have had a previous spontaneous preterm delivery between 16^0 and 31^6 weeks should be considered for the Cervical Ultrasound study. At most sites, these patients will also be screened for the BV/TV study. Complete the screening/enrollment form (MB20) and review the patient's chart with the inclusion and exclusion criteria listed in the previous chapter.

4.2 Enrollment

Additional information on the previous spontaneous preterm birth between 16^0 and 31^6 weeks will be gathered from a patient interview followed by a review of the patient's medical record. Before enrolling a patient, check that all of the following have occurred:

1. Eligibility confirmed
2. Dating ultrasound performed
3. Project gestational age calculated to be less than 19^0 weeks gestation
4. Signed informed consent
5. First cervical ultrasound scheduled between 16^0 and 18^6 weeks gestation

Complete the screening/enrollment form (MB20) and baseline data form (MB04) just before the first cervical ultrasound. If the patient was randomized to the BV or TV trial earlier in her pregnancy and already has an MB04 completed, do not update the MB04.

4.3 Assigning a Network Number

The Network number is a unique identifier for all patients randomized to the BV/TV trials or screened for this study. The Network number is allocated by the computer system and should then be recorded on the top of each page of every data form. Acquiring a valid Network number is requisite to entering all patient forms into the computer system. Network numbers do not have to be assigned in chronological order, since it may be inconvenient to obtain Network numbers for study patients while randomizing patients to the BV/TV trials. The information required to create a "base" record in the computer system is patient initials and protocol number. The protocol number for the BV/TV trials ("12") should also be used for this study.

4.4 Scheduling Cervical Ultrasounds

After their initial scan at 16^0 - 18^6 weeks gestation, patients should have serial cervical ultrasound examinations at fourteen day intervals (acceptable range 11 - 17 days), with their final scan performed between 22^0 and 23^6 weeks gestation. No more than four exams should be performed on one patient. Conditions which should preclude cervical ultrasound examinations include ruptured membranes, the placement of an emergent cerclage, or any medical/obstetric condition which requires continued hospitalization. Note that prior treatment for preterm labor (if discharged home) would not be a contraindication to these scans.

4.5 Cervical Ultrasound Procedures

While each patient and examination will be unique, these guidelines are provided to standardize the examinations and increase the reproducibility of the findings. Throughout the procedure, the sonographer should not inquire about the patient's medical condition. As always, universal precautions should be used at all times. Cervical length and other parameters listed below will be measured with a real time, high frequency endovaginal probe in women with an empty bladder. Measurement with a transabdominal probe is not acceptable because the amount of urine in a full maternal bladder may affect the apparent length of the cervix.

4.5.1 Preparing for the Examination

Because bladder volume can significantly affect the lower segment anatomy, all patients must void within five minutes of their endovaginal scan. The bladder, with even a small amount of urine, becomes a very easy structure to visualize and makes a good landmark. If the bladder appears to be subjectively “full” after voiding, have the patient try to void again. If it still appears full, note this on the data form (MB21).

All exams will be videotaped to ensure that any dynamic changes which may not be noted by the sonologist can later be detected and ultimately analyzed by another reviewer. Before starting the videotape, make sure that the ultrasound image is correctly labeled with the patient's initials (first three letters of the last name followed by the first two letters of the first name). Also check that the date and time displayed are correct. All of the examinations for a patient should be on the same tape, and the exams should be recorded in chronological order. Using the pre-printed labels provided by the BCC, the videotapes should be labeled with center number, network number, patient initials, and date of enrollment.

In addition to the videotape, at least one hard copy photostat (of the best cervical length measurement) should be obtained during the exam. Additional hard copy photostats should be obtained if any of the following were noted during the exam: funneling, dynamic changes with fundal pressure, or unusual findings. If the ultrasound unit cannot measure the posterior cervical angle electronically, a hard copy of the image should be obtained for later analysis. Using the pre-printed labels provided by the BCC, the photostats should be labeled with center number, network number, patient initials, and date of ultrasound. If necessary, you may use Post-it notes to make comments on the photostats.

As an aid to these examinations, either a checklist (such as the one in Appendix C) or the data form (MB21) should be posted near the ultrasound unit. This should help minimize missing data. As demonstrated on the teaching videotape, not all examinations are completely cut and dry. Some subjective estimates may be necessary. Comments entered on the data form will be reviewed later by the study PI.

The “freeze” time of the exam should be minimized since it is important to spot dynamic changes. Once the image is frozen, the measurements should be made as efficiently and quickly as possible. The image should promptly be "un-frozen" in order to maintain the video progress. No more than two cervical characteristics should be measured per frozen image. The minimum examination time is five minutes. While a maximum length cannot be strictly defined, in general it should not exceed 10-12 minutes. With practice, the examinations will become more efficient and require less time, so be sure to pace your measurements so that at least five minutes of videotape are captured at each examination.

4.5.2 Obtaining a Clear Image

The basic exam should always stem from a good midline sagittal view of the cervix and lower uterine segment, which includes both the external and internal os. Although all measurements are generally obtainable from the adequate sagittal view, also note that angling the transducer up or down will improve visibility of the anterior lower uterine segment and bladder reflection, or conversely, better image the posterior lower uterine segment. The sagittal view should be maintained most of the time. Obtaining the optimal sagittal view involves some experience. In particular, excess probe pressure which can alter the lower segment anatomy should be avoided. This can be monitored by keeping the bladder reflection as a landmark on the screen; with excessive pressure, this landmark is generally lost.

The appropriate sagittal view for measurement is identified by finding the triangular echodensity at the external os, and a faint line of echodensity or echoluscency between the external os and internal os. The probe is inserted while watching the screen, and advanced along the anterior vaginal wall until the lower uterine segment and internal cervical os are identified. After inserting the transducer sufficiently to see the amniotic fluid, relax pressure to find the os. It should look like a small notch or indentation. The probe is then rotated slightly left or right, while relaxing further, to obtain a clear sagittal view of the long axis of the cervix. The intermittent echodensities of the canal are made by the interface between the anterior and posterior walls. Not every cervix is parallel with the vagina, in either anterior/posterior or lateral planes.

Once the internal os and the proximal canal are identified, keep them in the field of view until the entire length of the cervix is imaged. Undue pressure on the cervical canal, which might artificially create the impression of a longer cervix, will be avoided by withdrawing the probe until the image blurs, then reapplying sufficient axial pressure to restore the image and freeze it. The image begins to blur when the transducer tip loses contact with the anterior vaginal fornix. This step is the most likely to create interobserver variation, and should be done with great care. Undue pressure may also result in a false image of the posterior wall of the vagina, which may look a little like the cervical canal to the inexperienced examiner.

It is recommended that the following four steps be performed at the start of each exam:

1. Proper recognition of the internal os
2. Observation of the entire endocervical canal
3. Proper recognition of the external os
4. Minimizing the effects of excess probe pressure by recognizing its effect on cervical symmetry

It is very easy to miss either the internal os or external os while still maintaining a satisfactory view of (part of) the canal. Very small lateral excursions of the probe handle can cause an oblique section of the endocervical canal to be imaged. Thus, it is worth spending a little time up front focusing first on the best view of the internal os, then the external os, and finally trying to image these simultaneously. The endocervical canal should, in all cases, directly connect these anatomic landmarks.

Excess probe pressure may also cause problems by compressing the cervix. Thus, by subjectively ensuring that the "posterior" cervical width (which we are measuring and recording) equals the "anterior" cervical width, excessive pressure is probably not being applied. Loss of the bladder reflection out of the field of view is also a hint that the probe may be too closely applied to the cervix.

4.5.3 Assessing the Cervix

As part of each examination, the cervix is classified as primarily horizontal or vertical. While this depends in part on the angle of the transducer in relationship to the horizontal plane (floor), for the purposes of this study a cervix should be classified as vertical if the canal, beginning at the external os, appears to have an angle > 45° from the horizontal.

Record whether the lower segment is poorly developed. This is an uncommon finding at this gestational age, especially if the cervical length is less than 50 mm, but it will confound the measurements. It is characterized by both a very long cervix and difficulty obtaining a good standard image of the internal os. Two of the patients on the teaching tape demonstrate a poorly developed lower segment, which can be appreciated by noting a much longer than average cervical length and a large distance between the bladder reflection and the amniotic cavity. This finding may persist throughout the entire examination or may abate at some point. If this finding abates, the usual measurements may be obtained. If it persists throughout the entire exam, this should be noted on the data sheet and the cervical length and funneling measurements should not be obtained. However, a hard photostat copy of the best sagittal view should be obtained, even if the measurements are omitted.

For patients with a normal cervix, the internal and external os will be easily seen. The echodensity of a normal cervix is uniform, and the lower uterine segment is not thin. There is no true funnel, although there may be a small notch at the internal os. The calipers should be placed at the "notches", which are easy to identify.

In some patients, particularly mutiparas, it may be difficult to decide about placement of the calipers even though the cervix may be easy to see. This cervix is the source of a lot of variation. Minimum pressure on the cervix is necessary to be sure that this is just a loose, normal cervix, and not an abnormal cervix that will show true funneling when transducer pressure is relaxed. Some time should be spent with the image to be sure of this distinction. If the external os notch cannot be found, measure the confluence of the apparent canal.

Once the examiner is satisfied that a good image has been obtained, the cervical length will be measured by freezing the screen three separate times and each time measuring the line made along the interface of the mucosal surfaces and calipers placed at the notches made by the internal and external os[6] (see Figure 1, item A). The variation between the measurements should be no more than 2-3 mm (7-8% for a 30-35 mm cervix; normal is 45 mm ± 7). The first measurement is usually too long and the second and third measurements are usually 3 - 5 mm shorter. If the second and third measurements are not within 2 to 3 mm of one another, start over and make sure the correct structure is being measured. The cervical length recorded will be the <u>shortest</u> of the <u>best</u> measurements that were most clearly displayed. Be sure to submit a hard copy photostat of the cervical length recorded.

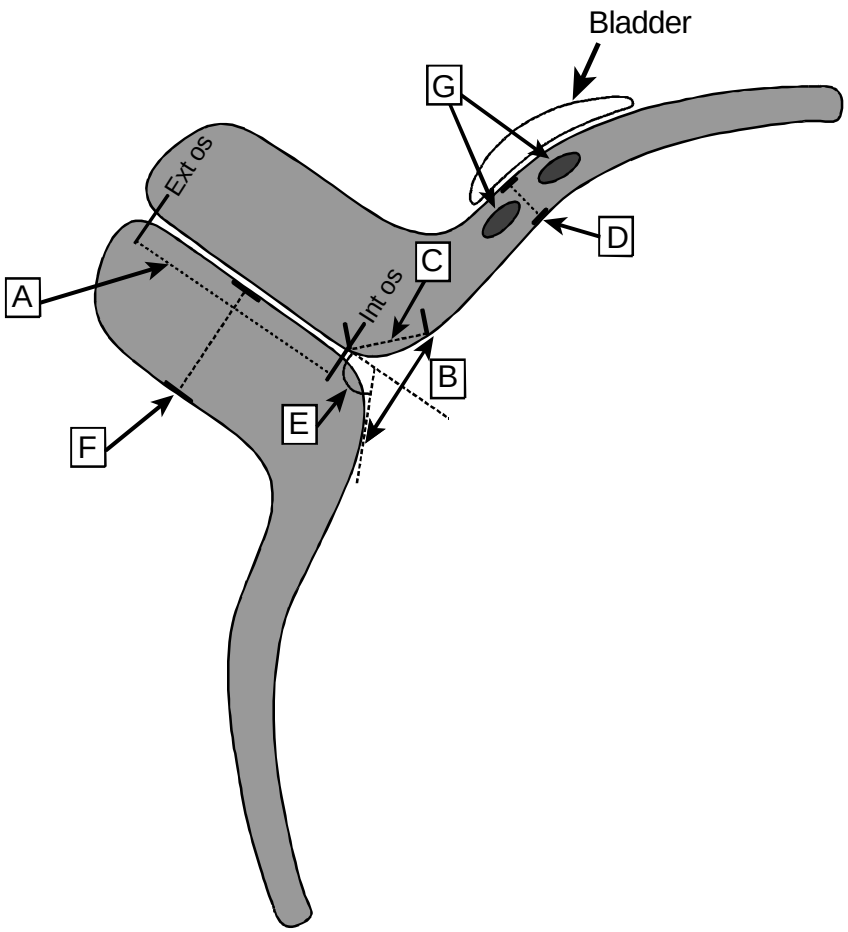

Figure 1. Anatomic Landmarks for Endovaginal Sonography

A. Cervical length (external os to internal os)
B. Funneling (absent/present)
C. Funnel depth
D. Thickness: lower uterine segment
E. Posterior cervical angle
F. Posterior cervical width
G. Vascular lower segment (absent/present)

JOCERV5A.AI

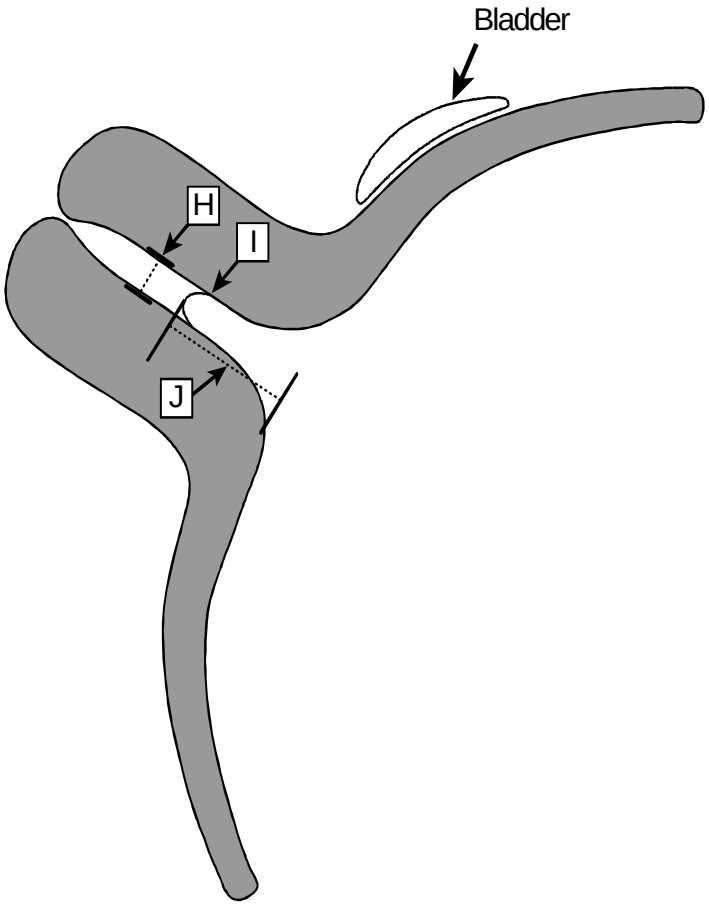

Figure 2. Anatomic Landmarks for Endovaginal Sonography: Canal Dilated

H. Maximum canal width
I. Membrane prolapse (absent/present)
J. Membrane penetration

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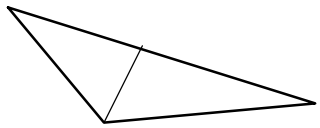
The cervical canal should be classified as primarily straight or curved. The canal should be measured in two sections if any subjective curvature is noted. Then a third line connecting the internal and external os should be added, and finally, the maximum excursion between the intersection of the first two lines and the middle of the third connecting line should be measured (as represented by the bisecting line in the diagram below). See the teaching tape for an example. If this excursion is 5 mm or greater, then this will define a curved cervix.



To allow sufficient time to observe the occasional patient with a "dynamic" internal os, in which a lower uterine segment contraction appears to occur, and to determine if a "funnel" develops, the remaining measurements will be made over a minimum of three minutes of observation.

A funnel is defined as protrusion of the amniotic membranes of ≥ 3 mm into the internal os, as measured along the lateral border of the funnel (Figure 1, item C). A true funnel is deeper than it is broad and is "dynamic". It will appear to change during the exam. Often it will be closed when the probe is first inserted, and is evident only by an unusually dark proximal cervical canal. With time and relaxation of pressure on the vaginal probe, it is seen to open up to involve the proximal half or two-thirds length of the cervix. This finding is NOT to be communicated to the care providers.

Be sure to differentiate between a true funnel and a pseudo-funnel. A pseudo-funnel may occur when the lower uterine muscles, sometimes with the placenta, form what appears to be a funnel above an otherwise normal cervix. If the length of the cervix is normal, and especially if the cervix is of the "normal" type, this is usually easy to recognize. If the cervix is multiparous, the distinction can be difficult. A pseudo-funnel may also occur when there is a broad notch at the internal os, with less depth to it (e.g., 5 mm across the opening but only 2-3 mm deep), or if the cervix is short with a broad, fairly large funnel of the lower uterine segment.

Be very careful when measuring the cervix of a patient with a funnel. Do not include the length of membrane protrusion in the measurement of cervical length. Be sure to obtain a hard copy photostat of the optimal funnel image.

Other aspects of the endocervical anatomy will be imaged and recorded as listed in Figures 1 and 2: posterior cervical angle, canal width, thickness of lower uterine segment, and posterior cervical width. If your ultrasound machine does not have the software necessary to measure cervical angle, it will be measured later off of the hard copy by the study PI.

When measuring the thickness of the anterior lower uterine segment, be sure to get as close as possible to the lower extent of the bladder reflection. Note that in some cases, the lower uterine segment will begin to visibly thicken as it joins the cervix, and the bladder reflection (particularly if more than scant urine is present) will appear to override the junction between the lower uterine segment and the cervix. In these cases, we wish to obtain a measurement as close as possible to the bladder reflection, but in an area of subjectively constant thickness. Do not incorrectly place the caliper above the bladder reflection. If the lower uterine segment appears subjectively vascular, record this on the data form.

Determine whether the chorioamnionic membrane is visible at the internal os, and if so, whether it is prolapsing into the canal. In many cases, the membrane is impossible to see distinctly. By reducing the overall gain, the membrane may become visible.

Following this, constant, moderate transfundal pressure will be applied for 15 seconds along the uterine axis and any cervical shortening, increase in funneling (or protrusion of the membranes into the endocervical canal), or overt canal dilatation will be considered a positive response to fundal pressure.[19] Label the screen just before pressure is applied (for example, with "FP") and erase the note from the screen once pressure is released. It is acceptable for the patient to place pressure on herself. If the cervix shortens or the canal dilates, measure it again. There is a place on the data form to record the revised measurements.

Finally, on the data form grade the overall exam difficulty on a 4 point scale, with 1 being minimal if any difficulty, and 4 being very difficult. If you notice something unusual during the scan, briefly describe the finding on the MB21 and make a hard copy photostat of the image. Also record the length of the exam and the number of hard copy images retained.

4.5.4 Notifying the Managing Physician of the Results

Because this is an observational study, the BV/TV Subcommittee has made it very clear that the Cervical Ultrasound study should interfere with the primary clinical trial as little as possible. Thus the sonographers should not inquire about abnormal symptomatology or make any comments concerning their sonographic findings or impressions. There are two exceptions to this rule. The managing physician should be notified if a fetal death or complete placenta previa is detected. A complete placenta previa is defined as a placenta that completely occludes the internal os and the edge of the implantation site extends at least one centimeter past the internal os. Therefore, if during your examination a view of the fetal thoracic cavity is obtained and if no fetal heart beat can be recognized, the managing physician should be promptly notified. Likewise, if the placenta appears to be completely occluding the internal os, this should also be reported.

4.5.5 General Comments

- Rarely, a satisfactory and reproducible image cannot be obtained. This occurs most often in the first and early second trimesters and in subjects with an unusual cervical angle. Most such subjects can be reliably imaged later in the pregnancy.
- After becoming oriented, it helps to enlarge the image 1.5 - 2 times.
- As well as lubricating the outside of the condom, put a lot of gel in the condom to get the probe away from the cervix. If the patient is scheduled to have a pelvic examination for the BV/TV or FFN study later in the day, the outside of the condom should be lubricated only with saline.
- If the probe has more than one frequency, use 5 to 6 MHz (not 7) for better depth.
- If the probe has variable viewing angles, open it as wide as it will go.
- An image is good if it can be easily explained to someone who doesn't do transvaginal scans.

4. Maternal and Neonatal Outcome Data Collection

Once the patient has delivered, the study coordinator should review the patient's and infant's records and complete outcome forms MB10 (Labor and Delivery Summary), MB11 (Neonatal Baseline Data), and, if necessary, MB12 (NICU Summary). If the patient is not randomized to the BV/TV trials, form MB07 (Record of Antibiotic Use) and form MB09 (Hospital Admissions) are not necessary, even if the patient has taken antibiotics or has been admitted to the hospital.

Patients who are randomized to the FFN or Progesterone trial will need to have two sets of outcome forms completed (one for the Cervical Ultrasound study and one for the trial). Be sure to note on the MB10 (Labor and Delivery Summary) that the patient participated in another Network study (question 2a).

5.1 Patient Withdrawal or Lost to Follow-up

If the patient delivers at another hospital, it is very important that every attempt is made to obtain as much maternal and neonatal outcome data as possible. At the very least, the date of delivery should be obtained. If the delivery date is permanently missing, form MB13 should be completed.

A patient who has less than three scans completed is considered withdrawn and needs to have an MB13 completed. Indicate the reason for withdrawal under Question 1b.

5.2 Adverse Event Reporting

Adverse events that could possibly be related to the cervical ultrasound examination should be reported promptly by completing the MFMU Network Adverse Event Form and mailing it to both Dr. McNellis and the BCC. Events that are serious and unexpected in nature, severity, or frequency should also be reported.

The BCC will inform the Data Monitoring and Safety Committee of any adverse effects experienced by study patients, and the Steering Committee will be informed of any problems associated with the interventions in this study.

5. Data Processing

6.1 Data Collection Forms

Data will be collected on standardized forms and data relevant to this study will be abstracted from the BV/TV database. The following two new forms will be added to those being used in the BV/TV trials:

- MB20 - Screening/Enrollment Form (will include supplementary baseline data)
- MB21 - Cervical Ultrasound Form

Once the BV/TV study ends, only the MB04, MB10, MB11, MB12 (if needed) and MB13 (if needed) data forms will be completed in addition to the MB20 and MB21.

6.2 Distributed Data Entry System

The microcomputer data entry system consists of a network of microcomputers, one at each clinical center and one at the BCC. Data entry software corresponding to the study forms will be developed and maintained by the staff of the BCC. Data will be entered by clinical center staff, and transmitted weekly via telecommunications link to the BCC. Detailed instructions for entering and transmitting data are provided in the MFMU Network Distributed Data Entry System Handbook (Users' Manual).

6.3 Centralized Data Management System

All created and updated forms are transmitted weekly from the clinical centers to the BCC where they are uploaded to the mainframe computer and merged with the existing data base. The data are automatically edited for missing, out of range and inconsistent values. After review at the BCC, edit printouts are returned to the center for correction or clarification on a weekly basis. At regular intervals, audits, which compare data across forms (inter-form) are run by the BCC on the entire database or on a specific subset of data. These reports are also submitted to the centers for corrections.

6.4 Performance Monitoring

The BCC will present regular reports to the BV/TV Subcommittee, the Steering Committee, and the centers. These include:

- Monthly recruitment reports: reports of the number of women screened and enrolled by month and by clinical center will be provided to the BV/TV Subcommittee and all other members of the Steering Committee.

- Quarterly Steering Committee reports: a report detailing recruitment, baseline patient characteristics, data quality, incidence of missing data and adherence to study protocol by clinical center, will be provided to the BV/TV Subcommittee and all other members of the Steering Committee.

7. Instructions for Completing Forms

The general guidelines for filling out forms outlined in the BV/TV Manual of Operations should be followed. Specific instructions for each of the forms unique to the Cervical Ultrasound follow.

7.1 Form MB20 - Screening/Enrollment Form

Patient Group: All patients screened for the study at less than 19^0 weeks gestation who have had a previous spontaneous preterm delivery between 16^0 and 31^6 weeks (inclusive). Some of the sites that are participating in the Cervical Ultrasound study are not screening patients for the BV/TV study. When the BV/TV study ends, screening for the Cervical Ultrasound study will continue until the sample size goal is met.

When completed: During the screening and enrollment process

Who completes: Study nurse

Other Documents: None

Related forms: If patient is enrolled, you will also need to fill out form MB04 (Baseline Data Form) and form MB21 (Cervical Ultrasound Form). If the patient was randomized to the BV or TV trial earlier in her pregnancy and already has an MB04 completed, do not update the MB04.

Special Instructions:

- All patients screened for the Cervical Ultrasound study will require a screening number and a Network number. While patients are still being randomized to the BV/TV study, the same series of screening numbers will be used for patients screened for the BV/TV study and/or the Cervical Ultrasound study. In addition, the same series of Network numbers will be used for patient randomized to the BV/TV Trials or enrolled in the Cervical Ultrasound study. Network numbers do not have to be assigned in chronological order, so you may want to wait until it is convenient for you to assign an ineligible patient a number. For example, you can hold all of the MB20s for ineligible patients and enter them all at one time each week.

- Be sure that the patient meets the gestational age and previous spontaneous preterm delivery criteria using study definitions, as well the other eligibility criteria in chapter three of the manual of operations.

Question 1 - Screening number

Enter the patient's five digit screening number as assigned on form MB01A. If the patient was screened more than once, enter the most recent screening number assigned. When screening for the BV/TV study ends, this question will not need to be answered.

Question 2 - Screening status

The chart of each selected patient should be reviewed to determine if she meets any of the exclusion criteria. Enter the appropriate status code.

1. Ineligible - Code "1" if the patient meets any of the exclusion codes listed on the form.
2. Refused consent - Code "2" if the study was discussed with the patient and she refused to participate.
3. U/S scheduled, but patient did not show - Code "3" if an ultrasound examination was scheduled, but the patient did not show.
4. Enrolled - Code "4" if the patient was eligible, signed informed consent, and had at least one cervical ultrasound performed.

Item a - If patient ineligible (1), give exclusion code

If status code 1 was used, meaning that the patient was ineligible, provide the exclusion code from the following list. If the patient was eligible, leave this field blank. If more than one exclusion code applies, use the first listed code. For example, if the patient had diabetes requiring insulin (code "14") in addition to a major fetal anomaly (code "2"), code "2" should be listed on the log.

1. Project gestational age > 18^6 weeks - Code "1" if the patient's project gestational age is more than 18^6 weeks. If the patient is clearly over 18^6 weeks, this form does not need to be completed.
2. Major fetal anomaly/death
3. Multiple gestation - Code "3" if patient has a multifetal pregnancy, even if only one fetus is viable.
6. Ethanol abuse - Code "6" if the patient is an active alcohol abuser.
8. Hypertension requiring medication - Code "8" if the patient requires medication to control her hypertension. This includes women with pulmonary hypertension. Patients who were taken off of hypertension medication because of the pregnancy are also eligible.
9. Collagen vascular diseases - Code "9" if the patient has a collagen vascular disease such as lupus or anti-phospholipid antibodies.
10. Isoimmunization - Code "10" if the patient has Rh sensitization documented by elevated antibody titers. This does not automatically exclude patients who are Rh negative or who have a situation of Rh incompatibility.
11. Tocolytic treatment/preterm labor - Code "11" if at the time of the assessment the patient has had or is planning to have tocolytic therapy in this pregnancy, or if she had preterm labor. This does not preclude tocolytic use later in pregnancy if indicated. Preterm labor is defined as having more than six contractions per hour *plus*:
    - documented cervical change *or*
    - cervix dilated > 2 cm *or*
    - cervical effacement > 80% *or*
    - documented change in effacement > 50%.
12. Cervical cerclage - Code "12" if the patient currently has or plans to have a cervical cerclage.
13. Uterine anomaly - Code "13" if the patient has a uterine anomaly such as uterus didelphys or a bicornuate uterus.
14. Diabetes requiring insulin - Code "14" if the patient has diabetes and requires insulin (including diabetes mellitus and gestational diabetes).
15. Renal failure or heart disease - Code "15" if the patient has renal failure (creatinine > 1.5 mg/dl) or heart disease requiring medication.
16. Asthma - Code "16" if patient has asthma requiring systemic prescription therapy.

17. Delivery/prenatal care elsewhere - Code "17" if outcome information cannot be obtained for this reason. If the patient is delivering elsewhere, but the follow-up visit can be made as scheduled and complete outcome information can be obtained, the patient may be randomized.
18. Cannot arrange visit/ultrasound between 16^0 - 18^6 weeks - Code "18" if either the dating ultrasound or the cervical ultrasound examination cannot be arranged within the gestational age window.
99. Other - Code "99" if the patient is being excluded from the study for another reason (such as mental retardation) and briefly explain in item b. Note that women should not be enrolled in the Cervical Ultrasound study if they are enrolled in the Asthma trial or any other study where the treatment could affect delivery gestation. The exceptions to this rule are the Progesterone, FFN and BV/TV trials. Once a women is enrolled in the Cervical Ultrasound study, she cannot be enrolled in the study again in subsequent pregnancies. Women who were screened or randomized in the BV/TV study during a previous pregnancy, but not enrolled in the Cervical Ultrasound study, are eligible.

Item b - If other (99), explain

If exclusion code 99 was used, give a brief explanation.

If patient is not enrolled, you may skip the remainder of the form.

Question 3 - Date of informed consent

Enter the date the patient signed the consent form for the Cervical Ultrasound study.

Question 4 - Randomized to BV/TV study?

Answer YES if the patient was randomized to the BV or TV trial during this pregnancy before she was enrolled in this study. Do not change the answer to this question if the patient is randomized later in the pregnancy. If the patient was, questions five through nine do not need to be completed. When randomization to the BV/TV study ends, this question will no longer need to be answered.

PROJECT GESTATIONAL AGE

Question 5 - LMP date

Record the start of the patient's last menstrual period (LMP). If the patient gives "first", "middle", or "end" of month, record 1, 15, or 30 respectively and answer NO to Question 6. If no date can be obtained, enter "11/11/11". If the patient knows only the month, record 15 as the date and answer NO to Question 6.

Question 6 - Is LMP date sure?

Answer YES if the patient provides an LMP date that she is sure of within plus or minus 3 days, had a 24-35 day regular cycle, and was not on oral contraceptives at the time of conception. The LMP date is also considered "sure" if there is a known date of conception (IVF, IUI, etc.) in which case the LMP date is 14 days before the conception date. Otherwise, answer NO.

Question 7- Date of first (dating) ultrasound:

Record the date of the first dating ultrasound done in this pregnancy. Measurements obtained at this ultrasound are to be used along with the patient's LMP to determine gestational age.

Question 8 - Gestational age by the first U/S:

Record the gestational age in weeks and days as it is shown on the printout from the earliest dating ultrasound. Record the gestational age determined ONLY by the ultrasound, not a combination of ultrasound measurements and LMP. For this question, DO NOT calculate the gestational age on the day of randomization based on the earliest ultrasound. This ultrasound may be done at any time during the pregnancy up to the point of enrollment.

Question 9 - Project EDC:

The project EDC field MUST be completed if the patient is enrolled. The project EDC will be determined by the combination of a reliable menstrual history and measurements obtained at the patient's first ultrasound examination. Once correctly obtained, the project EDC is not revised for the remainder of the patient's pregnancy. The Network software has an option (WHEEL) that may be useful when making this determination. This software is also available for use separately on other personal computers.

- If the LMP is not sure (Question 5 was answered NO), the ultrasound measurements obtained at the patient's first ultrasound examination should be used to determine project EDC.
- If the LMP date is sure (Question 5 was answered YES) and the ultrasound confirms this gestational age within the number of days specified in the table that follows, the LMP derived gestational age is used to determine the project gestational age. When using the table, it is important to use the gestational age at the first ultrasound as calculated from the LMP.
- If the ultrasound determined age does not confirm the LMP generated gestational age within the number of days specified in the table that follows, the ultrasound is used to determine the project gestational age.

Cutoffs for using LMP for determining gestational age

Gestational age at first ultrasound by LMP	Ultrasound agreement with LMP
up to 19^6 weeks	$\pm$ 7 days
20^0 weeks to 29^6 weeks	$\pm$ 14 days
30^0 weeks or more	$\pm$ 21 days

SUPPLEMENTAL BASELINE INFORMATION

Question 10 - Number of previous spontaneous preterm deliveries (between 16.0 and 31.6)

Record the number of times the patient has delivered a pregnancy between 16^0 and 31^6 weeks (inclusive) due to preterm labor or preterm PROM, regardless of pregnancy outcome.

For questions 11 - 15, if the patient has had more than one previous spontaneous birth, refer to the infant with the earliest gestational age at delivery or, if unknown, the infant with the smallest birthweight. Multifetal gestations are eligible, as are stillbirths and neonates with anomalies. Study nurses should attempt to obtain the records of the previous spontaneous preterm birth. Women whose previous records cannot be obtained can be enrolled if the patient reports she is "certain" of the gestation (or birthweight) of her previous pregnancy. For example, a patient could be randomized if she knows her previous date of delivery, her previous EDC, and recalls that first her water broke and then

she was admitted to labor and delivery. Study nurses who are unsure about enrolling a particular patient should call Dr. John Owen for further guidance.

If you enroll a patient based on information obtained through an interview, and later receive medical records that contradict the patient's statements, please update the answers to questions 10 - 17. The answer to question 2 (Screening Status = Enrolled) should not be changed.

Question 11 - Date of previous spontaneous preterm delivery

Record the date of the previous spontaneous preterm delivery. If the medical record cannot be obtained, and the patient gives "first", "middle", or "end" of month, record 1, 15, or 30 respectively. If no date can be obtained, enter "11/11/11". Remember that if the patient has had more than one previous spontaneous birth, refer to the infant with the earliest gestational age at delivery or, if unknown, the infant with the smallest birthweight.

Question 12 - Did delivery result in a live birth?

If the previous delivery resulted in at least one live infant, answer YES.

Question 13 - Gestational age at previous spontaneous preterm delivery

Record the best estimate of the gestational age at the delivery. It must be between 16^0 and 31^6 weeks (inclusive) for the patient to be eligible for the study.

Question 14 - Birthweight

Enter the infant's weight at delivery. In the case of multifetal gestations, enter the largest weight. If the gestational age is not known (Q.13 is blank), this question must be answered and the weight must be less than 1,500 grams.

Question 15 - Reason for spontaneous preterm delivery

Indicate the patient's reason for the preterm delivery.

1 Spontaneous preterm labor with delivery - Code "1" for patients who have a spontaneous preterm delivery due to preterm labor if the patient's membranes did not rupture more than an hour before the start of labor.

2 PROM leading to spontaneous preterm delivery - Code "2" for patients whose membranes ruptured at least one hour before the onset of labor and the patient subsequently had a spontaneous preterm delivery.

3 PROM leading to induction/C-section - Code "3" for patients whose membranes ruptured and they subsequently had an indicated delivery due to maternal indications (such as preeclampsia, abruptio, previa, or diabetes) or fetal indications (such as + CST, IUGR, oligohydramnious, or fetal death). Do not include C-sections prior to labor or prior to PPROM. Do not include therapeutic or elective abortions at any gestational age.

Question 16 - Length of labor

Enter the patient's best estimate of the number of hours she was in labor. The start of labor is defined as regular contractions accompanied by cervical change. If labor stopped and started, enter the length of the course of labor that lead to delivery.

Question 17 - Answers to Q11-16 based on

Enter the source of information used to obtain answers for questions 11 - 16.

1 Medical records
2 Patient interview
3 Both

7.2 Form MB21 - Cervical Ultrasound Form

Patient Group: All enrolled patients

When completed: At each biweekly cervical ultrasound

Who completes: Certified sonographer or study nurse

Other Documents: Videotape and hard copy photostats

Related forms: None

Special Instructions:

- The ultrasound date on the form should match the date that appears on the videotape.
- Label the videotape and hard copy photostats with the pre-printed labels provided by the BCC.
- All of the scans for a patient should be in chronological order on one videotape.

Question 1 - Ultrasound number

The first ultrasound after the Screening and Enrollment form (MB20) is completed is considered number one. The ultrasound numbers should be in sequential order, corresponding to the chronological sequence of cervical ultrasound dates. There should be no duplicates or gaps.

Question 2 - Date of ultrasound

Enter the date the cervical ultrasound was performed. The date of the first ultrasound is considered the date of enrollment into the Cervical Ultrasound study.

ULTRASOUND DATA

Question 3 - Does bladder appear full?

All patients must void within five minutes of their cervical ultrasound examination. If the bladder appears to be subjectively "full" by ultrasound, have the patient try to void again. Answer YES if it continues to appear full.

Question 4 - The cervix is primarily

Beginning at the external os, note the angle of the cervical canal from the horizontal. Code as follows:

1. Horizontal - Code "1" if the angle is 45 degrees or less.
2. Vertical - Code "2" if the angle is more than 45 degrees.

Question 5 - The lower segment is

A poorly developed lower segment is characterized by both a very long cervix and difficulty obtaining a good standard image of the internal os. There will be a large distance between the bladder reflection and the amniotic cavity. If this finding persists throughout the entire exam, obtain a hard copy photostat of the best sagittal view, but do not record the cervical length or funnel measurements. If the finding abates, the usual measurements can be obtained. Code as follows:

1. Not poorly developed
2. Initially poorly developed, but then improved
3. Poorly developed during the entire scan

If (3), skip to Q9.

Question 6 - Cervical length

Measure the length between the notches of the external and internal os on three separate frozen images. If any subjective curvature is noted, measure the canal in two sections (see Q7). If the external os notch cannot be found, measure the confluence of the apparent canal. If the measurements are not within 2-3 mm of each other, start over. Record the shortest of the three best measurements. Be sure to retain a hard copy photostat of the cervical length recorded.

Question 7 - The cervical canal is primarily

If the cervix appears curved, the canal should be measured in two sections. A third reference line should be formed by connecting the external and internal os directly. Measure the maximum excursion between the intersection of the first two lines and the center of the third line. Code as follows:

1. Straight - Code "1" if the cervix subjectively appears straight or the maximum excursion is less than 5 mm.
2. Curved - Code "2" if the cervix subjectively appears curved and the maximum excursion is 5 mm or more.

Item a - If curved (2), cervical excursion

Record the maximum cervical excursion, which should be at least 5 mm.

Question 8 - Funneling?

Answer YES if the amniotic membranes protrude 3 mm or more into the internal os, as measured along the lateral border of the funnel. Be sure to differentiate between a true funnel and a pseudo-funnel. A true funnel is deeper than it is broad and is dynamic. A pseudo-funnel may occur when the lower uterine muscles, sometimes with the placenta, form what appears to be a funnel above an otherwise normal cervix. A pseudo-funnel may also occur if there is a broad notch at the internal os with less depth to it (e.g., 5 mm across the opening but only 2-3 mm deep), or the cervix is short with a broad, fairly large funnel of the uterine segment. Do not include the length of membrane protrusion in the measurement of cervical length. Be sure to obtain a hard copy photostat of the optimal funnel image and measurements.

Item a - If YES, funnel depth

If there appears to be funneling, record the length of the lateral border of the funnel.

Question 9 - Posterior cervical angle

Record the angle made from the intersection between a line positioned along the cervical canal and a line positioned along the posterior side of the cervix. If the angle cannot be measured electronically by the ultrasound unit, submit a hard copy photostat of the image for later analysis.

Question 10 - Canal dilation (echoluscent area)?

Answer YES if the canal appears dilated along its entire length (not just a proximal segment).

Item a - If YES, maximal canal width

Record the maximum canal width measured at the largest, completely echolucent area.

Question 11 - Membranes visible at internal os?

Answer YES if the chorioamnionic membrane is visible at the internal os. It may be easier to see the membrane if the overall gain is reduced.

Item a - If YES, are membranes protruding into the cervical canal?

Answer YES if chorioamnionic membrane has prolapsed into the canal.

Part 1 - If YES, maximum penetration

Record the amount of membrane protrusion into the endocervical canal.

Question 12 - Thickness of lower uterine segment

Measure and record the thickness of the anterior lower uterine segment as close as possible to the lower extent of the bladder reflection. Note that in some cases, the lower uterine segment will begin to visibly thicken as it joins the cervix, and the bladder reflection (particularly if more than scant urine is present) will appear to override the junction between the lower uterine segment and the cervix. In these cases, we wish to obtain a measurement as close as possible to the bladder reflection, but in an area of subjectively constant thickness. Be sure not to incorrectly place the caliper above the bladder reflection.

Item a – Does the segment appear to be vascular at, or adjacent to, the point of measurement?

Answer YES if, at the point of measurement, the lower uterine segment appears subjectively vascular.

Question 13 - Posterior cervical width

Record the posterior cervical width.

Question 14 - Dynamic changes

The following are considered dynamic changes: cervical shortening, an increase in funneling, protrusion of the membranes into the endocervical canal, or overt cervical dilatation. If changes are noted, remeasure the cervical length, funnel depth, and canal width and submit a hard copy photostat of the measurements. After 15 seconds of transfundal pressure, code as follows:

1. Did not occur - Code "1" if no dynamic changes occurred during the exam.
2. Occurred with fundal pressure - Code "2" if dynamic changes occurred with fundal pressure.
3. Occurred without fundal pressure - Code "3" if there were dynamic changes, but not in response to fundal pressure.

Item a - Remeasurement of cervical length:
Record the revised cervical length.

Item b - Remeasurement of funnel depth:
Record the revised funnel depth.

Item c - Remeasurement of canal width:
Record the revised canal width.

Question 15 - Was the MD notified of any results from this ultrasound?

Answer YES if the managing physician was notified of any of your sonographic findings or impressions. If YES, code as follows:

1. Placenta previa - Code "1" if a complete placenta previa was noted and reported. A complete placenta previa is defined as a placenta that completely occludes the internal os and the edge of the implantation site extends at least one centimeter past the internal os.
2. IUFD - Code "2" if the fetal thoracic cavity was viewed during the examination and the absence of a heart beat was reported to the physician.
3. Other - Although this should generally never occur, code "3" if the physician was notified of another finding. Enter a short explanation in the field provided.

Question 16 - Difficulty of exam:

Code as follows:

1. None to minimal
2. Average
3. Slightly more difficult than average - Code "3" if the exam was more difficult than usual. Also use this code if one or two measurements could not be obtained.
4. Very difficult - Code "4" if the exam was very difficult. Also use this code if more than two measurements could not be obtained.

Question 17 - Anything unusual about the endovaginal scan?

Answer YES if there was something unusual about the scan that you would like to report. Enter a short explanation in the field provided. If possible, obtain a hard copy photostat of an image of the unusual finding.

Question 18 - Length of exam

Record the length of the examination, which should be at least five minutes.

Question 19 - Ultrasound recorded on videotape?

All examinations for this study should be videotaped. Answer YES if this was done. Be sure to label the video tape with the pre-printed labels provided by the BCC.

Question 20 - Number of hard copy images retained

Record the number of hard copy images that you will submit to the BCC. There should be at least one capturing the cervical length measurement. Additional hard copy photostat should be obtained if any of the following were noted: funneling, dynamic changes with fundal pressure, or unusual findings. If your ultrasound unit cannot measure the posterior cervical angle electronically, a hard copy of the image should be obtained for later analysis. Label the copies with the pre-printed labels provided by the BCC.

8. Statistical Considerations

It was estimated that from the approximately 11,000 women who are screened yearly for the BV/TV trials, about 3,000 will test positive for BV or TV. Similarly, it was estimated that approximately 6% of women screened yearly from the Network will have had a prior spontaneous preterm birth between 16^0 and 31^6 weeks.

8.1 Sample Size

Since this is not a treatment effect trial, and since appropriate mid-trimester ultrasonographic pilot data are currently lacking, the sample size is based on data from the recently completed Preterm Prediction Study. This study collected endovaginal sonographic data at both 24 and 28 weeks gestation.

The following assumptions and adjustments were made for the sample size calculation:

- The spontaneous preterm birth rate less than 35 weeks for women with a long cervix will be approximately 10%.
- The percentage of women with a short cervix will be approximately 20%.
- Power = 80%, alpha = 0.05, 2-tailed, desired relative risk = 3.0.

A total of 170 patients will be required for the study.

8.2 Analysis Plan

Since the primary outcome is dichotomous, standard statistical methods for rates and proportions will be appropriate. These methods include simple contingency table analysis, Mantel-Haenzel procedures for the combination of two-way tables, and regression techniques such as logistic regression. If a cervical characteristic is shown to be related to the incidence of the primary outcome, further subgroup analyses will be conducted to determine whether the effect prevails throughout particular subgroups of patients. All of the secondary analyses will be exploratory in nature, and statistical techniques such as type I error control and model validation methods will be used to assist in interpretation of the data where suitable.

9. Study Administration

9.1 Organization and Funding

The study is being conducted by the NICHD Maternal Fetal Medicine Units Network as an adjunct to the Randomized Clinical Trials of the Effect of Metronidazole on Pregnancy Outcome in Women infected with *T. Vaginalis* or Bacterial Vaginosis. The NICHD MFMU consists of thirteen clinical centers, the Biostatistical Coordinating Center and NICHD, and is administered under cooperative agreements between each of the centers and NICHD. Each of the funded institutions is represented by a Principal Investigator.

9.2 Participating Clinical Centers

The Principal Investigators of the following centers have agreed to participate in this study and abide by the standards set out in the BV/TV study protocol: University of Tennessee, University of Alabama, University of Cincinnati, Wake Forest, University of Texas – Southwestern, University of Texas – San Antonio, University of Utah, and Thomas Jefferson. The Biostatistical Coordinating Center (BCC) is responsible for all aspects of biostatistical design, analysis and data management of the study, in addition to the interim and final statistical analyses and preparation of publications based on the study results.

9.3 NICHD

In addition to its role as funding agency, the NICHD participates in the activities of the Network, including the development of protocols, administration and conduct of the studies and preparation of publications.

9.4 Network Advisory Board

Appointed by the NICHD, its members include the director of the Center for Research for Mothers and Children (CRMC), the NICHD Network program officers, chairpersons of the Network Steering Committees and outside experts and consultants. Its role includes assisting in the identification and prioritization of research projects and reviewing protocols.

10. Training and Quality Assurance

Cervical imaging will be standardized across participating centers by training and quality control programs similar to those used in the Preterm Prediction and HUAM Studies. Each participating center must have the appropriate equipment and an individual on site experienced in transvaginal sonography. Before the study can begin at a center, at least one sonographer at that center (but no more than four) must be certified.

10.1 Certification

Although there is no written quiz for the study, the study sonographers at each center must become certified by submitting a videotape of cervical ultrasounds to Dr. Owen. The University of Alabama has provided a teaching tape to each participating center. After viewing the tape with the study guide in Appendix D, each sonographer will perform ultrasounds on ten subjects between 16 and 24 weeks gestation, completing a Cervical Ultrasound form (MB21) for each exam and creating hard copy images as specified by protocol. A tape of the exams, the appropriate hard copies, and the completed forms will be sent to:

Dr. John Owen
Department of OB/GYN
University of Alabama at Birmingham
Birmingham, AL 35233-7333

The tapes will be reviewed for technique and graded as satisfactory or unsatisfactory. If eight or more of the exams are considered satisfactory, the sonographer will be certified. If less than eight exams are satisfactory, a second tape will need to be submitted. In some cases, the sonographer will be offered the opportunity to go to the University of Alabama or Ohio State University for "hands on" certification.

For sonographers who actively participated in the Preterm Prediction or HUAM studies, only five examinations will be necessary for certification (four of which must be satisfactory).

Sonographers should not begin videotaping exams until they feel comfortable with the procedure. In other words, the videotape should not represent the first ten cervical ultrasounds performed. Scans for certification should not be done on patients with a cerclage.

If necessary, two sonographers can use the same patient at the same visit for a certification examination. At least the last exam, however, should be completed independently. Be sure to clearly identify the sonographer of each exam.

10.2 Quality Assurance

Throughout the study, all cervical ultrasounds will be videotaped and hard copy photostats will be obtained of the cervical length and funnel measurements. Periodically, the BCC will randomly select a subset for review. If the videotape or hard copies show consistent errors in technique, further training will be arranged.

11. Study Timetable

11.1 Recruitment and Data Collection Period

The BV study is estimated to run until June 1998, at which point a decision will be made on whether or not the TV trial should continue. Both the BV and TV studies began enrollment in May 1995. The timetable for this study should be similar. It should take approximately 18 months to enroll 170 patients (3/97-9/98) and six months of follow-up will be need to obtain outcome data (3/99).

11.2 Final Analysis

After a two month period for completion of data entry, the data set will be locked and available for analysis. Approximately six months will be required to complete final analysis of results and to submit the primary report for publication (9/99).

12. Appendix A: Design Summary

13. Appendix B: Sample Consent Form

SAMPLE CONSENT FORM

Mid-Trimester Endovaginal Sonography in Women at High Risk for Spontaneous Preterm Delivery

Explanation of Procedures

I understand that I am being asked to participate in a study to determine if vaginal sonography will help to predict whether or not I am at risk for having a premature infant. I am eligible to participate in this study because I am currently less than 19 weeks gestation and I have previously had an infant at less than 32 weeks (8 months). In earlier studies, vaginal sonography was used to evaluate cervical length in pregnant women. In those studies, women with a short cervix were more likely to have premature infants.

I understand that if I decide to participate, I will have a vaginal ultrasound every two weeks beginning at 16 to 18 weeks gestation and continuing up to 24 weeks gestation.

Risks and Benefits

I understand that sonography has been used in pregnancy for many years and has not been shown to cause any harm to the mother or the unborn baby. Vaginal sonography is widely used to evaluate the cervix and lower part of the womb because these areas are otherwise very difficult to examine. Vaginal sonography is performed similarly to a pelvic examination, and therefore some women experience mild discomfort during the procedure. However, there has never been an increased risk of preterm delivery reported from the examination. I understand that I will receive no benefit from participating in this study, because the ultrasound is not being done for diagnostic purposes.

Alternative Treatments

I understand that if I do not wish to participate in this study, there are no other alternative treatments. Vaginal sonography is not performed as a part of routine prenatal care.

Confidentiality

I understand that the investigators working on this study know that confidentiality is an important concern to many people. My records will be kept in a secure place and only my health care providers will have access to them. Study personnel will examine my hospital records when I deliver and my name will be kept confidential. When the results of this study are published, I understand that I will not be listed by name and my identity will not be revealed.

Withdrawal Without Prejudice

I understand that I am free to withdraw my consent and to discontinue participation in this project at any time without prejudice against any future medical care I may receive at this institution.

Patient's Initials _____

Costs To Subjects From Participation

I understand that there are no costs to me for my participation in this study. The vaginal ultrasound examinations are performed free of charge.

Compensation Clause

I understand that neither UAB nor the National Institute of Child Health and Human Development has made provision for monetary compensation in the event of physical injury resulting from the research. In the event of such injury, medical treatment is provided, but not free of charge.

Questions

I acknowledge that I have been given an opportunity to ask questions about this study and that they have been answered to my satisfaction. If I have further questions about this study, Dr. John Owen or one of his associates will be glad to answer them at 934-1322. If I have questions about my rights as a study volunteer, Mrs. Tucker Slaughter, Director of Patient Representatives or one of her colleagues will be happy to answer them at 934-2273.

Agreement

I have read and understand the above information, and agree to participate in this study. I have received a copy of this informed consent and realize that I am not waiving any of my legal rights by signing this consent form. My signature below indicates that I agree to participate in this study.

_____ _____

Signature of volunteer Date

_____ _____

Signature of Father (if available) Date

_____ _____

Signature of Witness Date

16. Appendix C: Summary of Cervical Ultrasound Procedures

Total Exam Time: 5 - 12 minutes

1. Ask patient to void.

2. Label ultrasound image with patient's initials. Note the ultrasound number. Check that date and time displayed are correct. Start videotape.

3. Insert probe under direct vision. Look for familiar anatomy: bladder, amniotic fluid.

4. Find the midline sagittal plane. Look in proximal 1/3 of image for internal os.

5. Pull probe back until lightest touch consistent with a good image of cervical canal.

6. Angle probe slightly to get best long axis of cervix.

7. Check that bladder does not appear full.

8. Classify cervix as primarily horizontal or vertical.

9. Determine whether lower segment is poorly developed (this may change during exam).

10. Measure the cervical length (x3) by placing the calipers appropriately and recording the shortest distance between "notches". Submit a hard copy photostat of the best (shortest) measurement.

11. Classify the cervical canal as primarily straight or curved based on the maximum excursion at the center of the canal (> 4 mm defines a curved cervix).

12. Assess cervix for funneling, dilatation, and membrane protrusion. Measure the posterior cervical angle, the thickness of lower uterine segment, and the posterior cervical width. Record whether the lower uterine segment appears vascular at the point of measurement. Submit a picture of the posterior cervical angle if your ultrasound unit cannot measure the angle automatically. If funneling is present, submit a hard copy photostat of the measurement.

13. Note any dynamic changes with 15 seconds of moderate fundal pressure (should not cause patient discomfort). If cervix shortens or the canal dilates, remeasure cervical length, funnel depth, and canal dilation. Submit an image of the new length and funnel.

14. Check that form MB21 is complete and the exam was videotaped for at least 5 minutes.

15. Stop videotape. Make sure tape and hard copies are labeled correctly with BCC labels.

16. If necessary, notify physician of IUFD or complete placenta previa.

17. Schedule next appointment (preferably 14 days later, 11 - 17 days later is acceptable).

16. Appendix D: Study Guide for Teaching Video Tape

**STUDY GUIDE ACCOMPANYING THE TEACHING VIDEOTAPE
FOR THE CERVICAL ULTRASOUND STUDY
TO THE NICHD MFMU NETWORK BV/TV CLINICAL TRIAL**

This tape contains complete endovaginal examination details on eight mid-trimester gestations ranging from 15 to 23 weeks. Chapter 4 contains a schematic diagram of the cervix and lower uterine segment structures which are commonly visualized with endovaginal sonography. It is labeled to show the various landmarks and also to standardize our measurements. Cherry Neely, the research sonographer at the University of Alabama, performed all of these scans on a GE 3200 Advantage II unit using a 7 MHz 120° probe.

It is hoped that the tape will be of some benefit to the sonologists who are performing these scans. Once the study is underway, if you have any specific questions, or note some unusual findings which cannot be accounted for on the data sheet, please call Dr. John Owen at the University of Alabama anytime (205-934-7343).

A NOTE ON VIEWING THE TAPE: it is probably best to view the tape on your ultrasound monitor. Attempting to view this on a television screen is associated with reduced image quality, and may also truncate the edges of the scan. The resolution can be enhanced somewhat by adjusting the brightness and contrast controls on the ultrasound monitor.

SCAN ONE: This scan, labeled PT2 BRO.BR, was performed on 8-15-96 and began at 10:59. This patient was 23 weeks of gestation. The first step was to obtain a usable sagittal image. Then fundal pressure was applied for approximately 15 seconds, after which the canal length was measured in two sections, 21 plus 14 mm. Note that there were no significant dynamic changes which occurred during the fundal pressure. The reference line between the internal and external os was placed and a maximum excursion of 7 mm was noted. Thus, the cervix was classified as curved. Subjectively, it was also classified as vertical. The gain was adjusted to improve the chorioamnion visualization, and the canal width was measured at 4 mm (not labeled). Note that the canal width should be the largest, completely echolucent area. The posterior cervical width was measured next at 17 mm, and then the lower uterine segment thickness was measured. The first time, the cursors were incorrectly placed above the bladder reflection. The mistake was recognized, and the correct measurement was 6 mm. During the exam, there was no significant dynamic changes or funneling. The posterior cervical angle was also measured, and for those of you that have a GE3200 Advantage II, the hip dysplasia package is extremely useful for this measurement. The angle obtained was 73°. For those centers that do not have this or a similar package, the angle can be measured later off of the hard copies. Note that in this case, the chorioamnion was not visualized. Subjectively, the bladder was essentially empty.

SCAN TWO: The second scan, labeled PT3 VES.UZ, began at 9:14 on 8-21-96. This was a 15 week gestation, which is bit earlier than the 16 weeks specified in the protocol. However, it was felt that the findings were still applicable. Please note that there is fluid in the cul-de-sac and also an ovarian cyst. Subjectively, this was called a vertical cervix. Note also that this was a straight cervix with no appreciable excursion on the cervical length measurement, which was 31 mm. The canal width was 2 mm, and the cervical canal excursion was 4 mm. With fundal pressure there were no noticeable changes. The posterior cervical width was 16 mm, and the lower segment thickness was 8 mm. Note that the first time, the correct reference point at the bladder reflection was not used. Clearly, the bladder was essentially empty. The posterior cervical angle was 113°.

SCAN THREE: The third scan is labeled PT4 WRI.VE, performed on 8-21-96 starting at 10:04. This is a 23 week gestation. The initial view of the cervix showed it to be horizontal with some curvature. It was measured in two sections, 20 plus 18. A 5 mm excursion was noted, which met the minimum criteria for a curved cervix. Next, an anterior view revealed that the bladder was subjectively not full, however there were intravesical echogenicities which may represent varicosities. The lower segment thickness was 8 mm, after which fundal pressure was applied with no appreciable change. The posterior cervical width was 18 mm, and it is recommend that this be measured halfway between the internal and external os. The posterior cervical angle was 82°. The cervical length was remeasured in two sections (19 and 22 mm), and the excursion was again > 4 mm.

SCAN FOUR: The fourth scan, labeled PT5 LEE.ST, is from a 21 week gestation. The exam was performed on 8-21-96 beginning at 10:44. This is a more difficult curved vertical cervix confounded by an anterior low lying placenta. It was initially difficult to find the cervix and internal os. A funnel was not diagnosed for this patient, but it is probably debatable. The "funnel" was actually measured at one point as an example.

When in doubt, it never hurts to measure a suspected funnel and record it as such. It can be judge later when it is reviewed. The cervical length was hard to measure, and it was done in two sections (19 and 16 mm), with an excursion of 6 mm (curved). There were no changes with fundal pressure, and the posterior cervical width was 18 mm. Note that the placental edge was approximately at the level of the internal os (not a previa). The funnel measurement was taken, be it was probably due to ultrasound artifact or dropout. The membrane was visualized, but it was not prolapsing. The posterior cervical angle was 91°, and no dynamic changes were noted during the exam.

SCAN FIVE: The fifth scan, labeled PT6 MCK.FRA, was performed at 11:29 on 8-21-96. This is a 16 week gestation, with a horizontal cervix and a very good example of a poorly developed lower uterine segment which was labeled "contraction" on the screen. Thus, the cervical length and lower uterine segment thickness could not be measured. Note the increased distance between the bladder reflection and the amniotic cavity. With fundal pressure, the lower segment opened somewhat, but basically this finding persisted throughout the entire exam. The canal width was measured at 2 mm, and the posterior cervical width was 12 mm. The cervical angle could not be obtained.

SCAN SIX: The sixth scan, labeled PT7 YOU.TR, is a 16 weeks gestation performed on 8-22-96 at 9:41. Here a horizontal, curved cervix was noted, and the cervical length was taken in two sections, 17 and 18 mm with a 6 mm excursion. There were no changes with fundal pressure, and the posterior cervical width was 14 mm. The membrane became visible by dropping the gain, however, it was not prolapsed. No funnel was noted, and the posterior cervical angle was 105°. The lower uterine segment was 9 mm. Overall, the scan was a little too short (less than five minutes). However, it went well, with few technical problems.

SCAN SEVEN: The seventh scan, labeled PT8 CHE.AN, was performed on 8-22-96 at 10:53. This is a 21 week gestation, and represents a much more difficult than average exam. As seen in PT6, the lower uterine segment was poorly developed. There was no dynamic changes with fundal pressure, and the cervix was considered horizontal. It also appeared curved, and the cervical canal was measured at 27 plus 27, with a 9 mm excursion. This measurement would not, however, have been recorded on the data form. There was essentially no echolucent area in the canal to measure, and thus, this was omitted (record a zero). The posterior cervical width was 18 mm, and a small funnel was noted during the exam, however, this was not measured. The cervical angle was 95°, and the first measurement was rejected for technical

reasons. The placenta was anterior, and as the lower segment opened, a reasonable view was obtained. The segment thickness was then measured at 13 mm, and later the anterior lower segment was measured at 15 mm (preferred). Fundal pressure was reapplied, and an increase in funneling, was seen. It was measured at 18 x 11 mm. Thus, as the exam proceeded, the lower segment opened up, and the measurements could be obtained.

SCAN EIGHT: The eighth and last scan, labeled PT9 FAR.MI, is a 19 week scan performed on 8-22-96 at 11:17. This was a straight, vertical cervix. With fundal pressure, no changes were noted. The membrane was visualized, but was not prolapsing. The posterior cervical width was 19 mm, and the lower uterine segment thickness was 10 mm. The cervical length was measured several times, yielding 38, 44, and 42 mm. On the data form, 38 would have been recorded. The canal width was 2 mm, and it was noted that there was some dropout at the internal os that simulated a funnel. This was thought to be an artifact. The cervical angle was 84°.

16. Appendix E: References

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