Published in final edited form as:

Am J Obstet Gynecol. 2006 January ; 194(1): 1–9. doi:10.1016/j.ajog.2005.12.002.

The role of cervical cerclage in obstetrical practice: can the patient who could benefit from this procedure be identified?

Roberto Romero[1], **Jimmy Espinoza**[1,2], **Offer Erez**[1,2], **Sonia Hassan**[2]

[1]Perinatology Research Branch, National Institute of Child Health and Human Development, National Institute of Health, Department of Health and Human Services, Bethesda, MD and Detroit, MI

[2]Wayne State University, Department of Obstetrics and Gynecology, Detroit, MI

Keywords

cervical cerclage; cervical insufficiency; incompetent cervix; prematurity; preterm delivery

Introduction

This editorial critically examines the definition of “cervical insufficiency.” The definition, the clinical ascertainment, efforts to develop an objective method of diagnosis, as well as the nature of cervical disease leading to spontaneous mid-trimester spontaneous abortion and preterm delivery are reviewed. The value and limitations of cervical sonography as a risk assessment tool for spontaneous preterm delivery are appraised. The main focus is on the role of cervical cerclage to prevent an adverse pregnancy outcome. The value of assessing the presence or absence of endocervical inflammation in the outcome of cerclage placement is discussed.

When and how cervical cerclage was introduced into obstetrical practice:

Cervical cerclage was introduced in 1955 by VN Shirodkar, Professor of Midwifery and Gynecology at the Grant Medical College in Bombay, India.[1] The procedure was developed in response to his observation that “some women abort repeatedly between the fourth and seventh months and no amount of rest and treatment with hormones seemed to help them in retaining the product of conception.”[1] Shirodkar referred to a group of 30 women who had had at least four abortions (some between 9 and 11 weeks). He stated that in his opinion, “95% of cases were due to a weak cervical sphincter and the other few to an underdeveloped or malformed uterus, etc.”[1] Shirodkar emphasized that his work was confined to women in whom he could prove the existence of weakness of the internal os by “repeated internal

Address correspondence to: Roberto Romero, M.D., Perinatology Research Branch, NICHD, NIH, DHHS, Wayne State University/ Hutzel Women’s Hospital, 3990 John R, Box 4, Detroit, MI 48201, USA .

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examinations."[1] Ian McDonald, from the Royal Melbourne Hospital, reported in 1957 his experience with 70 patients who had a suture of the cervix for inevitable miscarriage.[2] Since the publication of these reports, the ability of cerclage to prevent mid-trimester pregnancy loss has become part of obstetrical dogma. The history of cerclage is relevant since 50 years after its introduction it is being used for indications different from those originally intended, and there is conflicting evidence about its efficacy for the new indications (e.g., prevention of preterm birth in women with a sonographic short cervix).[3–31]

The initial recognition of cervical incompetence as a mechanism for pregnancy loss:

Cole, Culpepper and Rowland are credited with the first description of cervical incompetence.[32] In the "Practice of Physick," published in 1658, they wrote, "the second fault in women which hindered conception is when the seed is not retained or the orifice of the womb is so slack that it cannot rightly contract itself to keep in the seed; which is chiefly caused by abortion or hard labor and childbirth, whereby the fibers of the womb are broken in pieces one from another and the inner orifice of the womb overmuch slackened."[32] The term "cervical incompetence" was mentioned by Gream in an article published in the Lancet in 1865.[33] It took nearly 300 years from the first description for a surgical treatment to be developed. The biology of cervical ripening, a term describing the changes in cervical dilatation, effacement and consistency that generally precede the onset of spontaneous labor, is complex and involves degradation of extracellular matrix, as well as inflammation.[34–49] These changes are aimed at increasing cervical compliance, so that the conceptus can pass through the birth canal.

Cervical incompetence/"cervical insufficiency":

Authors have repeated, often uncritically, definitions of cervical incompetence proposed by others. Such definitions need to be examined, particularly in light of recent observations and results of clinical trials. For example, the expectation that pregnancy loss and/or preterm delivery can be prevented with a "prophylactic cerclage" is now opened to question based upon the results of randomized clinical trials[7,50–52] and some systematic reviews.[18–21] Moreover, the paper by Sakai et al, published in this issue of the Journal, raises the issue of whether cerclage can worsen pregnancy outcome in patients with endocervical inflammation.[53]

The lack of an objective diagnosis[54–56] and the lack of unequivocal efficacy of cerclage has created confusion about the standard of care in obstetrics and increased the number of medicolegal disputes. Moreover, the introduction of cervical sonography has further compounded the complexity of diagnosis and treatment of "cervical insufficiency" during pregnancy.

Although the term "cervical incompetence" has been used for many years,[33] we and others refer to this condition as "cervical insufficiency" to avoid the negative connotation that the term "incompetence" implies to patients.

Problems with the definition of "cervical insufficiency":

Harger defined "cervical insufficiency" as "the inability of the uterine cervix to retain a pregnancy in the absence of contractions or labor."[54] Yet, it is unclear how a clinician can objectively use this definition. For example: 1) How can an obstetrician identify "the inability of the cervix to retain the pregnancy?"; 2) What is the scientific evidence that the typical description of a patient with "cervical insufficiency" truly identifies a primary cervical disorder?; 3) What is the proportion of patients who meet the clinical definition of "cervical insufficiency" that will have an adverse pregnancy outcome (spontaneous mid-trimester abortion or preterm delivery) in future pregnancies without intervention?; and 4) What is the evidence that "prophylactic" cervical cerclage will change the natural history of "cervical insufficiency" and improve pregnancy outcome? The latter question is important because some authors have stated that "unless effectively treated, the condition tends to repeat in each pregnancy."[55]

Description of the typical patient with "cervical insufficiency":

The clinical diagnosis of "cervical insufficiency" is traditionally applied to patients with a history of recurrent mid-trimester spontaneous abortions and/or early preterm deliveries in which "the basic process is thought to be the failure of the cervix to remain closed during pregnancy."[33] The assumption is that cervical dilatation and effacement have occurred in the absence of increased uterine contractility.[33] The presenting symptom is reported to be a feeling of vaginal pressure caused by the protruding membranes and eventual membrane rupture in the mid-trimester of pregnancy. Typically, there is no vaginal bleeding, the fetuses are born alive, and labor is short.[2,33,57] However, we find difficulty in establishing a causal relationship between the clinical presentation outlined above and primary cervical disease (i.e., "insufficiency").

The lack of an objective test:

Although the existence of "cervical insufficiency" is widely accepted among obstetricians, there is no objective diagnostic test for this condition. Several methods have been proposed for the diagnosis of "cervical insufficiency" in the nonpregnant state, including the progressive passage of Hegar number 6 to 8 mm or Pratt dilators through the internal cervical os,[58–60] the use of balloon elastance test,[58] or the ability of the cervix to hold an inflated Foley catheter during hysterosalpingography.[61,62] However, there is a paucity of scientific evidence to support the value of these tests in predicting subsequent pregnancy outcome.[54] This area of clinical investigation has been overlooked.

Sonographic cervical length:

Digital examination of the cervix is the method used to determine cervical status (effacement, dilatation, position, and consistency). Cervical sonography has become an objective and reliable method to assess cervical length, which approximates cervical effacement. The shorter the sonographic cervical length in the mid-trimester, the higher the risk of spontaneous preterm labor/delivery.[63–67] However, there is no agreement on what is a sonographic short cervix. For example, Iams et al.[64] proposed that a cervix of 26 mm or shorter at 24 weeks of gestation increases the risk for spontaneous preterm delivery (relative

risk [RR]: 6.19, 95% confidence interval [CI]: 3.84–9.97). The prevalence of spontaneous preterm delivery (defined as less than 35 weeks) in this study was 4.3%, and the positive predictive value was 17.8% for a cervical length ≤ 25 mm at 24 weeks of gestation.[64] Thus, most women with a short cervix (defined as 25mm or less) and no previous history of preterm delivery will not deliver a preterm neonate. Other investigators have proposed a cut-off of 15 mm or less because a cervical length of 15 mm or less is associated with nearly a 50% risk of spontaneous preterm delivery at 32 weeks of gestation or less when neonatal morbidity is substantial.[65,67]

It is important to stress that sonographic cervical length is not a screening test for spontaneous preterm delivery because only a small fraction of all patients who will have a spontaneous preterm birth have a short cervix in the mid-trimester. Previous studies conducted at our institution have indicated that only 8% of all patients who will have a preterm delivery at less than 32 weeks of gestation have a cervical length of 15 mm or less in the mid-trimester.[67] Therefore, sonographic cervical length is a method for risk assessment for spontaneous preterm delivery and not a screening test. Cervical length can modify the *a priori* risk for preterm delivery.[68] For example, a woman with a history of preterm delivery or one with a twin or triplet gestation will have a higher risk for preterm delivery than a patient without such history and with the same cervical length.[69–77]

Cervical sufficiency/insufficiency as a continuum:

The hypothesis that cervical competence or sufficiency represents a spectrum was studied by Parikh and Mehta, who used digital examination of the cervix to assess sufficiency. The authors, however, concluded that degrees of cervical competence did not exist.[78] Iams et al., using sonographic examination of the cervix, suggested that cervical sufficiency/insufficiency is a continuum.[79] The authors reported a strong relationship between cervical length in pregnancy and previous obstetrical history. This relationship was nearly linear, and patients with a typical history of an incompetent cervix did not constitute a separate group from those who delivered preterm.[79] Similar results have been reported by Guzman et al.[80] Collectively, these studies suggest that there is a relationship between a history of preterm delivery and the cervical length in a subsequent pregnancy. Inasmuch as patients with a short cervix are at increased risk for a mid-trimester pregnancy loss (clinically referred to as “cervical insufficiency”) or spontaneous preterm delivery with intact or rupture of membranes,[6,10,11,13,28,29,63–65,79–89] a short cervix could be considered as the expression of a spectrum of cervical disease or function. However, it is noteworthy that some women with a short cervix have an adverse pregnancy outcome while others have an uncomplicated term delivery.[6,10,11,13,28,29,63–65,79–89] Indeed, approximately 50% of women with a cervix of 15 mm or less deliver after 32 weeks.[67] This indicates that cervical length may be only one of the factors determining the degree of cervical competence and that a short cervix should not be equated with “cervical insufficiency.”

Cerclage to prevent midtrimester abortion/preterm birth: a summary of the evidence:

The clinical value of cervical cerclage has been subject of many observational and randomized clinical trials,[4,6,7,10,12,13,17,23,27,50–52,90–103] and the studies have been subject to several systematic reviews.[18–20] The evidence suggests the following conclusions:

1. Cervical cerclage in women with a sonographic short cervix (15 mm or less) and at low-risk for preterm delivery (by history) does not reduce the rate of spontaneous preterm birth.[27]

2. The effectiveness of cervical cerclage in women with a sonographic short cervix and at high-risk (by history) for preterm delivery remains controversial.[7,9,11,23,99]

3. The role of prophylactic cerclage in high-risk patients without a sonographic short cervix for the prevention of preterm delivery/midtrimester abortion (by history) is unclear.[21,50–52,99] While the largest trial conducted before the introduction of ultrasound evaluation of the cervix suggested a modest beneficial effect,[52] other trials [50,51] and systematic reviews[33] before the use of ultrasound have indicated that the evidence of effectiveness is either weak or non-existent.

4. In patients at risk for preterm delivery, serial sonographic examination of the cervix followed by cerclage in those who shortened the cervix is a reasonable alternative to prophylactic placement of a cerclage based upon uncontrolled studies.[4,17,25]

5. In one trial, emergency cerclage combined with indomethacin administration appeared to reduce the rate of preterm delivery in patients with the clinical presentation of “cervical insufficiency.”[102]

This evidence indicates that patients with the clinical presentation of “acute cervical insufficiency” and those with a previous history consistent with “cervical insufficiency” and progressive shortening of the cervix demonstrated with ultrasound may benefit from cerclage placement. However, these conclusions are based on the results of one randomized clinical trial each.[99,102] In this issue of the Journal, Sakai et al. support that the inflammatory status of the endocervix may be an additional criteria to identify those patients who could benefit from cerclage placement and those in which this intervention may be harmful.[53]

Is “cervical insufficiency” a discrete condition or a syndrome?

In a similar manner to preterm labor, preeclampsia, small-for-gestational age, fetal death, preterm prelabor rupture of membranes, the clinical conditions that describe “cervical insufficiency” can be considered ‘‘an obstetrical syndrome.’’[104] Cervical ripening in the mid-trimester may be the result of: 1) the loss of connective tissue after a cervical operation such as conization;[105–107] 2) a congenital disorder such as cervical hypoplasia after diethylstilbestrol (DES) exposure;[108–111] 3) intrauterine infection;[112,113] and 4) a suspension of progesterone action[57] (There is experimental evidence that progesterone can reverse cervical compliance induced by the administration of dexamethasone to pregnant sheep.[114] Sherman et al have also generated evidence that the administration of 17 alpha hydroxyprogesterone may be beneficial in patients with clinically diagnosed ‘‘cervical insufficiency’’[115]); and 5) a cervical disorder that manifests itself with the clinical presentation of ‘‘cervical insufficiency.’’ Each of these different causes of the syndrome could be affected by genetic or environmental factors (Figure). Moreover, more than one mechanism of disease may be operative in a specific patient. The possibility that novel and yet undiscovered mechanisms of disease may play a role must also be considered.

"Cervical insufficiency" as a clinical manifestation of intrauterine infection

A proportion of patients presenting with asymptomatic cervical dilatation in the mid-trimester have microbial invasion of amniotic cavity (MIAC)[112,113] that can be as high as 51.5%.[112] MIAC may be caused by premature cervical dilatation with the exposure of the chorioamniotic membranes to the microbial flora of the lower genital tract. Microorganisms may gain access to the amniotic cavity by crossing intact membranes.[112] Under these circumstances, infection would be a secondary phenomenon to primary cervical disease. An alternative is that intrauterine infection (ascending, hematogeneous[116]), or one caused by activation of microorganisms present within the uterine cavity[117] in the second trimester of pregnancy produces myometrial contractility and cervical ripening. Because uterine contractions are usually clinically silent in the mid-trimester of pregnancy, the clinical picture of an infection-induced spontaneous abortion may be indistinguishable from that of an incompetent cervix.[39,112] Recently, we have established that 9% (5/57) of asymptomatic women with a short endocervix (less than 25 mm) have microbiologically proven intra-amniotic infection,[118] suggesting that these infections are subclinical and may precede the development of the clinical picture of acute "cervical insufficiency" (dilated and effaced cervix with bulging membranes).

Cervical mucus concentrations of interleukin-8 in the mid-trimester of pregnancy: a risk factor for preterm delivery:

Interleukin (IL)-8, a chemokine capable of inducing neutrophil chemotaxis,[119–121] is produced by cervical tissue[42,122] and is capable of inducing cervical ripening when applied topically.[123] The cervical mucus of normal pregnant women contains IL-8 and its concentration increases during the third trimester of pregnancy and labor, as do the number of granulocytes.[124] IL-8 concentrations in cervical mucus can reflect physiologic changes such as cervical ripening but also pathology: endocervical inflammation (i.e., cervicitis).[125–130]

An elevated concentration of IL-8 in cervical mucus (≥ 360 ng/ml) between 20–28 weeks is a risk factor for spontaneous preterm delivery (at <32, <34, and <37 weeks).[128] It is unknown whether the elevation of IL-8 in cervical mucus reflects premature cervical ripening or endocervicitis. However, elevated IL-8 in cervical mucus has been reported in women with bacterial vaginosis, MIAC, and intra-amniotic inflammation.[129] Moreover, a high concentration of IL-8 and IL-18 in the cervical mucus or cervical secretions has been associated with preterm labor and MIAC.[131,132]

A role for infection in the elevation of cervical mucus IL-8 concentration is suggested by the observation that treatment with vaginal washing with povidone iodine and vaginal tablets of chloramphenicol can "normalize" IL-8 concentration in the cervical mucus in 23.2% (195/840) of patients. In addition, this treatment has been associated with a lower rate of preterm delivery at less than 34 and 37 weeks in an uncontrolled study.[127]

Can the combination of cervical ultrasound and markers of endocervical inflammation identify the patient who may benefit from a cerclage?

The study by Sakai et al published in this issue of the Journal included 16,508 women with singleton pregnancies in whom sonographic cervical length was determined. A short cervix (defined 25 mm or less) was detected in 252 women, and 246 were eligible for the study. A cervical cerclage was placed in women with a short cervix at the discretion of the attending physicians (cerclages were placed in 165 and not placed in 81). Cervical mucus was collected at the time of ultrasound examination, but the results of IL-8 concentrations were not used for patient management. Cervical cerclage did not reduce the rate of preterm delivery or lengthen the procedure to delivery interval, an observation that is consistent with that of other investigators. However, two observations are novel and noteworthy. Among women with an IL-8 concentration of less than 360 ng/ml, those who underwent a cerclage had a lower rate of preterm delivery (defined as 34 weeks or 37 weeks) than those who did not have a cerclage. In contrast, among patients with an elevated IL-8, those who had a cerclage had a higher rate of preterm delivery (< 37 weeks) and a shorter procedure to delivery interval than those who did not have a cerclage. There are two messages to be taken from the series of studies reported by the group at the Toyama Medical and Pharmaceutical University in Japan.[53,127] First, patients with an elevated concentration of IL-8 and a short cervix (<25 mm) may not benefit from a cerclage. These patients may have an inflammatory or infection-related process in the endocervix and placement of a cerclage either does not improve the natural history of this process or worsens the outcome. Second, a subset of patients who may benefit from cerclage may include those with cervical mucus IL-8 concentrations less than 360 ng/ml.

These observations are important as it is becoming increasingly clear that the identification of the patient who can benefit from a cerclage cannot be made on the basis of either history or cervical ultrasound alone. We propose that the patient with severe endocervical inflammation may have subclinical intra-amniotic inflammation/infection or extra-amniotic inflammation/infection and may be in the advanced stages of the process that culminates in the expulsion of the conceptus to enhance maternal survival. On the other hand, the combination of a sonographic short cervix, a history of a previous preterm delivery, and the absence of endocervical inflammation (and vaginal inflammation) is more likely to identify the patient who has primary cervical disease. This patient may benefit from a cerclage or a similar intervention aimed at preventing or correcting a cervical disorder, which may lead to cervical ripening and pregnancy loss. Although cerclage is the focus of this article, it is worth mentioning that it is not the only therapy available for a cervical factor responsible for preterm birth. Others may include medical interventions (progesterone,[115] COX-2-selective non-steroidal anti-inflammatory agents,[133] or anti-chemokine agents), the use of devices such as pessaries, the injection of collagen into the cervix to strengthen the cervical scaffold, or total cervical occlusion, which was first reported by Professor Erich Saling.[134] Randomized clinical trials of cerclage may benefit from collecting information about the state of inflammation of the cervix and consider this as a factor for stratification. This subject is being addressed by a randomized clinical trial sponsored by the National Institute of Child Health and Human Development, National Institutes of Health. This trial is led by Dr. John Owen and his collaborators at the University of Alabama. The new information

published in this issue of the Journal is that assessment of the inflammatory state of the endocervix may add important information to the evaluation of risk for preterm birth and the identification of the patient who may benefit or be harmed by a cerclage. The new knowledge provided by Sakai et al improves the understanding of a very complex problem in obstetrics: the identification of the patient who may benefit from cerclage.

Acknowledgement

The authors wish to acknowledge the contribution of Dr. Jay Iams for the insightful discussions on the subject of cervical insufficiency and cervical cerclage.

Funding: This work was funded by the Perinatology Research Branch, Division of Intramural Research of the National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health. In addition, Dr. Sonia Hassan is a Women's Reproductive Health Research Scholar funded by NICHD.

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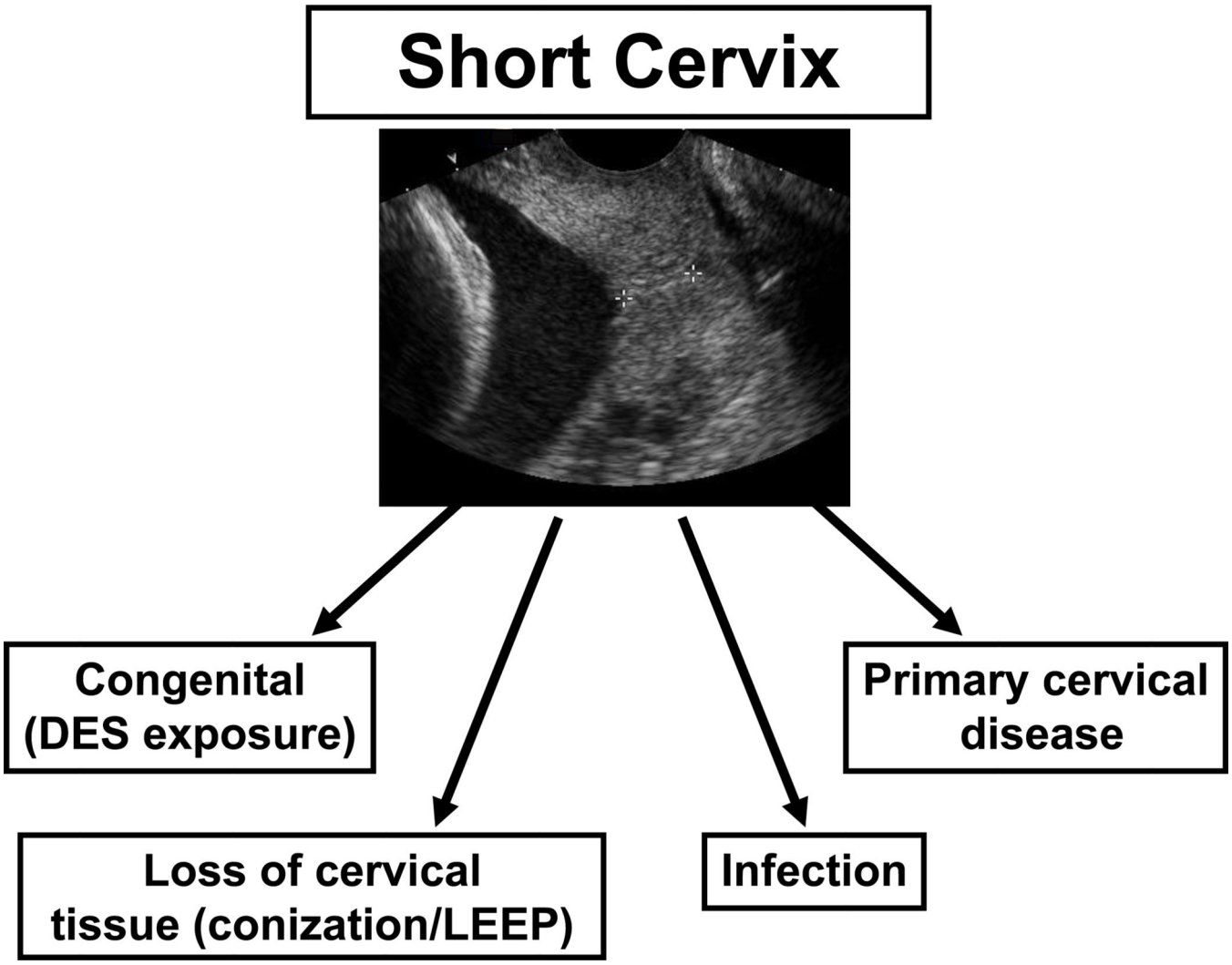

Figure:
The syndromic nature of a short cervix.