3 Cervical insufficiency

Sonia S. Hassan, Roberto Romero, Francesca Gotsch, Lorraine Nikita, and Tinnakorn Chaiworapongsa

INTRODUCTION

The uterine cervix has a central role in the maintenance of pregnancy and in normal parturition. Preterm cervical ripening may lead to cervical insufficiency or preterm delivery. Moreover, delayed cervical ripening has been implicated in a prolonged latent phase of labor at term. This chapter will review the anatomy and physiology of the uterine cervix during pregnancy and focus on the diagnostic and therapeutic challenges of preterm cervical ripening and the role of cerclage in obstetrics.

ANATOMY AND FUNCTION OF THE UTERINE CERVIX

The uterus is composed of three parts: corpus, isthmus, and cervix. The corpus is the upper segment of the organ and predominantly contains smooth muscle (myometrium). The isthmus lies between the anatomical internal os of the cervix and the histologic internal os and, during labor, gives rise to the lower uterine segment. The anatomical internal os refers to the junction between the uterine cavity and the cervical canal, while the histologic internal os is the region where the epithelium changes from endometrial to endocervical (1). The term “fibromuscular junction” was introduced by Danforth, who identified the boundary between the connective tissue of the cervix and the myometrium. The fibromuscular junction is in close proximity to the histologic internal os (2) (Figures 1A–D) (3).

Function of the Uterine Cervix

The main function of the uterine cervix is to serve as a barrier to the expulsion of the conceptus. The endocervical glands generate mucous, which forms the mucous plug, an anatomical and biochemical barrier to microorganisms. “Cervical ripening” is a term used to describe the changes in cervical dilatation, effacement, and consistency, which generally precede the onset of spontaneous labor. This process is associated with complex changes in the extracellular matrix aimed at increasing cervical compliance. The conventional view has been that uterine contractions lead to cervical change, a concept based on the relationship between increased uterine contractility and cervical dilatation during spontaneous labor at term. However, the process of cervical ripening begins weeks before the onset of labor. Similarly, preterm cervical ripening can occur without a demonstrable increase in uterine contractility. Experimental evidence indicates that cervical changes can occur even if the cervix is transected from the myometrium; therefore, these two components of the uterus

(fundus and cervix) can undergo changes in the preparation for labor, which are independent from each other.

A Brief Summary of the Biology of Cervical Ripening and Remodeling

The uterine cervix is essentially a connective tissue organ. Smooth muscle accounts for <8% of the distal part of the cervix (4). Cervical competency, defined as the ability of the cervix to retain the conceptus during pregnancy, is unlikely to depend upon a traditional muscular sphincteric mechanism. Experiments in which strips of human cervix have been incubated with vasopressin (a hormone that induces smooth muscle contractility) indicate that the contractile response of the cervix is substantially lower than that of the tissue obtained from the isthmus of the uterine fundus (5). It is now well established that the normal function of the cervix during pregnancy depends upon collagen synthesis and extracellular matrix.

The connective tissue remodeling of the uterine cervix during pregnancy has been proposed to occur in four stages: (i) softening, (ii) ripening, (iii) dilatation, and (iv) repair (6). These phases are overlapping and cannot be sharply separated during gestation (Fig. 2). The interested reader is referred to the reviews and original work by numerous authors (2,6–31) for a detailed discussion of the biochemical and cellular events underlying cervical remodeling during pregnancy and labor.

Word et al. have proposed that early in pregnancy, tensile strength of the softened cervix is maintained by increasing collagen synthesis and cervical growth (6). Collagens type I and III confer tensile strength. During cervical ripening, the cervix becomes thin and pliable, and the collagen concentrations are decreased. This decrease is due to a relative increase in hydrophilic glycosaminoglycans and non-collagenous proteins. The increased expression of aquaporin water channels leads to tissue hydration; this, in turn, disperses collagen fibers and increases collagen solubility and its susceptibility to endogenous proteases. The primary glycosaminoglycan involved is decorin, which protects collagen fibers; however, later in gestation, decorin decreases and hyaluronan increases. The latter can weaken the interaction between collagen and fibronectin, contributing to collagen dispersal (6). Hyaluronan has been found in human endocervical mucous (32). Mahendroo’s laboratory has demonstrated that, in mice, the hyaluronan content of the cervix is increased with advancing gestational age along with the expression of the

This work is based on several chapters that were published previously by the authors in other textbooks. This work has been modified and adapted for this textbook. The original chapters are referenced and contain a more extensive discussion of the subject. This chapter has a clinical emphasis. The work has been primarily done by Roberto Romero, who is a government employee, and therefore, is not subject to copyright.

Figure 1(A–D) Ultrasound images and schematics representing the location of the fibromuscular junction and the cervical changes seen throughout pregnancy and labor. Source: From Ref. 3.

Figure 2 Stages of cervical function during pregnancy and the puerperium as proposed by R. Ann Word et al. (6). Abbreviations: GAG, glycosaminoglycan; HA, hyaluronan; IL-8, interleukin-8; iNOS, inducible nitric oxide synthase. Source: From Ref. 6.

enzyme hyaluronan synthase 2 (28). Low-molecular weight hyaluronan can bind CD44 and activate macrophages to produce chemokines that attract inflammatory cells (33). Thus, the current understanding is that once collagen is solubilized, an inflammatory cascade is initiated. Studies in humans are necessary to determine the biochemistry of these processes. Strong evidence suggests that a suspension of progesterone action can lead to cervical ripening (34,35).

ORIGIN OF THE CONCEPT OF CERVICAL INCOMPETENCE/INSUFFICIENCY

One of the first descriptions of “cervical incompetence” has been attributed to Cole, Culpepper, and Rowland in 1658 (36), who wrote in a chapter on the state of being barren: “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” (37). The term “cervical incompetence” was mentioned by Gream in an article published in the *Lancet* in 1865 (38). Interestingly, the earliest observations were made nearly 300 years before surgical treatment was developed by Shirodkar (39) and, subsequently, McDonald (40). Although the term “cervical incompetence” has been used for many years (41), this condition is now referred to as “cervical insufficiency” to avoid the negative connotation that the term “incompetence” may imply to patients (42).

Defining Cervical Insufficiency

Definitions of cervical insufficiency have been proposed by many authors and vary slightly. Such definitions need to be examined critically, particularly in light of recent observations with ultrasound and results of studies that have reframed the concept of cervical insufficiency.

The clinical diagnosis of cervical insufficiency has been traditionally applied to patients with a history of recurrent midtrimester 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” (41). The assumption is that cervical dilatation and effacement have occurred in the absence of increased uterine contractility (41). The presenting symptom is sometimes considered to be a feeling of vaginal pressure, possibly caused by protruding membranes in the midtrimester of pregnancy. Sometimes the membranes rupture. Typically, there is no vaginal bleeding, the fetuses are often born alive, and the labor is short (40,41,43).

We find it difficult to establish a causal relationship between the clinical presentation outlined above and its attribution to a primary cervical disease (i.e., “insufficiency”) (42). Clearly, a condition exists in which patients present before 24 weeks of gestation with a dilated and effaced cervix in which the membranes protrude into the vagina (Fig. 3). This condition can often be visualized on ultrasound as illustrated in Figure 4.

Harger, in a review of the literature, defined “cervical insufficiency” as “the inability of the uterine cervix to retain a pregnancy in the absence of contractions or labor” (44). However, the use of this definition in clinical practice is problematic. How can an obstetrician identify “the inability of

Figure 3 A patient who presented prior to 24 weeks of gestation with a dilated and effaced cervix in which the membranes are protruding into the vagina. Roberto Romero, MD and Karim Kalache, MD. Cover Image - American Journal of Obstetrics and Gynecology, Jan 2006 – Dec 2006 (Vol 194.1–195.6).

Figure 4 An ultrasound image demonstrating a dilated cervix in a patient with suspected cervical insufficiency.

the cervix to retain the pregnancy”? There is no clinical test that would allow this determination. Some have proposed that the response to treatment offers criteria for the diagnosis.

Namely, a patient with a history of recurrent midtrimester pregnancy losses who is subsequently treated with a cerclage and delivers at term could be considered to have cervical insufficiency, and hence, the claim that such patient needs a cerclage in every subsequent pregnancy; yet, observational studies do not support this conclusion.

One approach by some authors to examine the accuracy of the diagnosis of cervical insufficiency is to determine pregnancy outcome in patients with this diagnosis who did not have treatment in subsequent pregnancies. In 1961, Dunn and Dans (45) reported the outcome of 30 patients who had two or more consecutive midtrimester abortions without an intervening first-trimester abortion. Interestingly, 13 of the 30 patients had three consecutive midtrimester abortions. The authors reasoned that if cervical insufficiency was the operative mechanism for pregnancy failure, it would be expected that all subsequent untreated pregnancies would result in pregnancy loss; however, this was not the case. Indeed, in 50% of cases, patients delivered neonates who exceeded 28 weeks of gestation and weighed >1000 g. Thus, the authors proposed that the spontaneous "cure rate" of this entity would be 50%. The editor of *Obstetrical and Gynecological Survey* published a commentary (46) in which he argued that a more appropriate endpoint for spontaneous cure would be delivery at term in the subsequent pregnancy. Although he recalculated the spontaneous "cure rate" to be 20%, a clear message of the study is that even in patients with two and sometimes three midtrimester abortions, term pregnancy is possible without a cerclage.

In 1984, Socol et al. (47) reported the outcome of a group of patients who had previously delivered a live-born infant between 20 and 32 weeks of gestation. In the subsequent pregnancy, some patients were treated with a cervical cerclage and others were not (at the discretion of the practitioner). The rate of preterm delivery was 36% (5/14) in patients who had a cerclage and 38% (10/26) in those managed expectantly. One interpretation of this data is that delivery at term was frequently possible in patients with a previous midtrimester pregnancy loss or early preterm delivery without a cervical cerclage.

Yet obstetricians often face the clinical dilemma of how to manage a patient who had a previous successful pregnancy with a cervical cerclage. Was the first cerclage truly necessary? Would the patient have delivered at term regardless of the placement of the cerclage? These questions are pervasive because of the subjective nature of the diagnosis. For example, some obstetricians place a cerclage after a midtrimester pregnancy loss with rupture of membranes, while others consider that this is not enough evidence of cervical insufficiency to justify the operation.

In a 1994 article entitled "Once a cerclage, not always a cerclage," Fejgin et al. (48) reported the pregnancy outcome of patients who had a history of at least one pregnancy in which a McDonald cerclage had been placed and the physician caring for the subsequent pregnancy was uncertain as to whether the procedure was necessary. A committee of three obstetricians reviewed the history, a hysterosalpingogram when available, and the results of a pelvic examination. There were 35 patients who had 58 pregnancies with a cerclage, and 52 subsequent pregnancies without the procedure. The outcome of pregnancies without a cerclage was better than those with a cerclage.

Collectively, these retrospective studies question the accuracy of the diagnosis of cervical insufficiency and/or the effectiveness of cerclage. The results of these studies (and others) are at the root of the controversy about the nature of this clinical entity, its diagnosis, and the precise role of cerclage in clinical medicine.

There is no objective diagnostic test for cervical insufficiency. The diagnosis is often made in a patient in the midtrimester who presents with dilatation of the cervix and different degrees of membrane prolapse. The evaluation of the nonpregnant patient represents an unsolved challenge. Several methods have been proposed for the identification of the patient at risk for cervical insufficiency, including (i) the passage of Hegar dilators (6–8 mm) or Pratt dilators through the internal cervical os (49–51), (ii) the use of a balloon test (52), or (iii) the ability of the cervix to hold an inflated Foley catheter during hysterosalpingography (53). However, there is a paucity of scientific evidence to support the value of these tests in predicting subsequent pregnancy outcome (44).

SONOGRAPHIC CERVICAL LENGTH

Digital examination of the cervix was the method used to determine cervical status (effacement, dilatation, position, and consistency) before the introduction of ultrasound. Bishop developed his cervical scoring system primarily to predict when spontaneous labor at term would occur and found that the higher the score, the sooner the labor would start (54). Wood et al. (55) were the first to report that a short cervix was a risk factor for preterm labor and delivery. A large study reported by Papiernik consisted of serial digital examinations in 8303 women, where dilatation of the internal os was the strongest risk factor for preterm delivery. A short cervix (≤ 1 cm) also increased the risk (56). These findings have been confirmed by others (57–62). However, digital examination is subjective and has limitations. For example, the coefficient of variation for effacement has been reported to be 26% (63). Moreover, evaluation of effacement requires placing the examining finger in close proximity to the fetal membranes. Sonographic imaging of the cervix is less invasive and more objective in assessing cervical length as well as changes in the anatomy of the internal os (64).

Transvaginal sonography is superior to transabdominal for examination of the cervix (64,65). Numerous studies have proven that the shorter the sonographic cervical length in the midtrimester, the higher the risk of spontaneous preterm labor/delivery (66–70). However, there is no agreement concerning what constitutes a sonographic short cervix. For example, Iams et al. (67) proposed that a cervix of 26 mm or shorter at 24 weeks of gestation increases the risk of spontaneous preterm delivery (Relative Risk (RR) 6.19, 95% CI 3.84–9.97). The prevalence of spontaneous preterm delivery (defined as <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 (67). Thus, most women with a short cervix (defined as 25 mm or less) will not deliver a preterm neonate. Other investigators have proposed a cut-off of 15 mm, 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 (68,70).

It is important to stress that sonographic cervical length is not a screening test for spontaneous preterm delivery, because

only a fraction of all patients who will have a spontaneous preterm birth have a short cervix in the midtrimester. Sonographic cervical length is only 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. 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 with the same cervical length, but without such history (71–80). It is now possible to provide women with an individualized estimation of risk for preterm delivery based upon cervical length and whether they have a history of preterm birth (81).

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 and concluded that degrees of cervical competence did not exist (82). Iams et al., (83) using sonographic examination of the cervix, concluded that cervical competence was a continuum. The authors reported a strong relationship between cervical length in pregnancy and previous obstetrical history. This relationship is nearly linear. However, patients with a typical history of an incompetent cervix appear to represent a different group than those who delivered preterm (83). Similar results have been reported by Guzman et al. (84). 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 midtrimester pregnancy loss or spontaneous preterm delivery with intact or ruptured membranes, a short cervix could be considered as the expression of a spectrum of cervical diseases or functions. However, it is noteworthy that some women with a short cervix have an adverse pregnancy outcome, while others have an uncomplicated term delivery (65–70,83–97). Indeed, approximately 50% of women with a cervix of 15 mm or less deliver after 32 weeks (70). This indicates that cervical length is only one of the factors determining the degree of cervical competence and that a short cervix should not be equated with “cervical insufficiency.”

CERVICAL INSUFFICIENCY IS A SYNDROME

In a manner similar to preterm labor, pre-eclampsia, small for gestational age, fetal death, and preterm premature rupture of membranes (PROM), the clinical conditions that describe cervical insufficiency can be considered “an obstetrical syndrome” (98). Cervical ripening in the midtrimester may be the result of (i) the loss of connective tissue after a cervical operation such as conization (99–101) or loop electrosurgical excision procedure (LEEP) (101), (ii) a congenital disorder such as cervical hypoplasia after diethylstilbestrol (DES) exposure (102–105), (iii) intrauterine infection (106–108), (iv) a suspension of progesterone action (34,35): there is experimental evidence that progesterone can reverse cervical compliance induced by the administration of dexamethasone to pregnant sheep (109). Moreover, recent studies have indicated that progesterone administration to women with a short cervix can reduce the rate of preterm birth (110,111), or (v) a cervical disorder. Each of these different causes of the syndrome could be affected by genetic or environmental

Figure 5 The proposed causes of the “cervical insufficiency syndrome.” Abbreviations: DES, diethylstilbestrol; LEEP, loop electrosurgical excision procedure. Source: From Ref. 42.

factors (Figure 5) (42). Moreover, more than one mechanism of disease may be operative in a specific patient. The possibility of novel and yet to be discovered mechanisms of disease playing a role must also be considered.

PREVIOUS TRAUMA AS A CAUSE FOR CERVICAL INSUFFICIENCY

Procedures such as laser ablation, LEEP, and cold-knife conization may increase the risk of a preterm birth (100,112–118). In a recent retrospective study by Shin et al., the rate of preterm delivery was significantly higher in women with a history of a conization when compared with those without one [32.1% (18/56) vs. 15.2% (3355/22,070), $p < 0.001$]. Yet the use of a McDonald cerclage ($n = 25$) was not associated with a reduction in the rate of preterm delivery when compared with those without cerclage ($n = 31$) (expectantly managed group vs. cerclage group; <28 week, 6.5% vs. 8.0%, $p = 1.000$; <34 week, 19.4% vs. 20.0%, $p = 1.000$; <37 week, 29.0% vs. 36.0%, $p = 0.579$) (119).

CONGENITAL CERVICAL INSUFFICIENCY

Exposure to DES in utero has been reported to increase the risk of second-trimester pregnancy loss fivefold (6.3% in DES exposed vs. 1.6% in the control group) (120).

There is evidence of familial aggregation in cervical insufficiency. In one study, approximately 25% of patients with cervical insufficiency had a first-degree relative with a similar diagnosis (121). This has been attributed to genetic factors involved in the regulation of extracellular matrix, specifically, polymorphisms in the genes encoding for collagen 1 alpha 1 (COL1A1) and transforming growth factor beta (TGF β) (121), and recently IL-10 (122). A genetic predisposition to cervical insufficiency has been reported in women with Ehlers–Danlos syndrome (123,124) and Marfan syndrome (125–128).

“CERVICAL INSUFFICIENCY” AS A CLINICAL MANIFESTATION OF INTRAUTERINE INFECTION

A proportion of patients presenting with asymptomatic cervical dilatation in the midtrimester have microbial invasion of the amniotic cavity (MIAC) (106,107) that can be as high as

51.5% (106). MIAC may be due to 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 (106). Under these circumstances, infection would be a secondary phenomenon to primary cervical disease. An alternative is that intrauterine infection or one caused by activation of microorganisms present within the uterine cavity (129) in the second trimester of pregnancy produces myometrial contractility and cervical ripening. Since uterine contractions are usually clinically silent in the midtrimester of pregnancy, the clinical picture of an infection-induced spontaneous abortion may be indistinguishable from that of an incompetent cervix (106,130). The most frequently isolated organisms from the amniotic fluid in women with suspected cervical insufficiency include *Ureaplasma urealyticum* and *Ureaplasma parvum* (106,131,132). We have established that 9% (5/57) of women with a short endocervix (<25 mm) have microbiologically proven intra-amniotic infection (108), 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).

CERCLAGE

Cervical cerclage was introduced in 1955 by V. N. Shirodkar, Professor of Midwifery and Gynecology at the Grant Medical College in Bombay, India (39). 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” (39). 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” (39). 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 examinations” (39). 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 (40). The history of this procedure is relevant since 50 years after its introduction: cerclage 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) (39,40,90–92,95–97,133–154).

There are several approaches to cervical cerclage: (i) the Shirodkar method (39), (ii) the McDonald method (40), (iii) the Wurm procedure (155), and (iv) transabdominal (156). The latter has been performed using a laparotomy approach and later described, laparoscopically (157,158). The most widely used procedure is the McDonald cerclage.

Complications of Cerclage

The risks associated with the use of cerclage include those that can occur intra-operatively (anesthetic complications, blood loss, rupture of membranes), in the post-operative period (subclinical or clinical chorioamnionitis, preterm PROM, cervical laceration, preterm contractions), and at the time of labor and delivery (cervical laceration, cervical dystocia, sepsis,

uterine rupture) (159–170). The rate of each complication varies as a function of the indication for the cerclage, type of cerclage, and the state of the cervix and amniotic membranes at the time of surgery (161,164,167). Complications commonly reported include preterm PROM (elective 2.8–36.3%, emergency 2.8–52.2%) (162,167–170), preterm contractions (36–39%) (168), cervical lacerations (elective 0–14%, emergency 0–23.8%) (166–169, 171), uterine rupture (<0.1%) (172), chorioamnionitis (elective 5.2–14.9%, emergency 4–39.1%) (162,167,169,170,172), sepsis (0.34%) (166), and bleeding (14.9%) (168).

Harger (169) reported the outcome of 251 patients; 202 who underwent a cerclage placed based upon history and 49 in which cerclages were placed due to cervical dilation. The mean blood loss was 30 ml in those patients who underwent a McDonald cerclage and 44 ml in those who had a Shirodkar procedure. Two patients who had undergone an emergency cerclage lost 150 ml of blood. The risk of pregnancy loss “apparently caused by elective procedures” was 2% (4/202). Acute chorioamnionitis occurred in 1.2% of patients. Cervical lacerations occurred more frequently at the time of labor in women who had a Shirodkar or McDonald cerclage than in those without a cerclage ($n = 55,688$) (Shirodkar: 11% and McDonald: 14% vs. control group: 2.18%, $p < 0.001$). Furthermore, the authors argued that some cesarean sections in women who underwent cerclage (McDonald or Shirodkar) may be attributed to cervical scarring as a result of the surgery.

Charles and Edwards noted an increased risk of complications in patients undergoing cerclage after 19 weeks of gestation. The rate of rupture of the membranes within 5 days of the procedure was 19.5%, preterm PROM (26–34 weeks of gestation) 52.2%, and chorioamnionitis 39.1% in these patients (162).

In a retrospective review of 482 singleton pregnancies who underwent cerclage placement [McDonald cerclage ($n = 377$), Shirodkar ($n = 104$)] over a 6-year period, Treadwell et al. (167) reported that PROM occurred in 38% of patients and was the most frequent complication. The prognostic factors determining gestational age at delivery were gestational age at the time of cerclage, cervical dilation, and number of prior pregnancy losses before 24 weeks of gestation. The rate of cervical laceration was 6.7% and was similar for both emergency and elective cerclages. Of interest, the primary cesarean delivery rate of patients who had undergone a Shirodkar cerclage was higher than those who had undergone a McDonald cerclage (31% vs. 17%, $p < 0.005$).

Cerclage in Patients with Acute Cervical Insufficiency

Only one randomized clinical trial has tested the effect of cerclage in patients with acute cervical insufficiency. Patients were identified if they presented with a dilated cervix and membranes at or below a dilated external os before 27 weeks of gestation. Patients were treated either with emergency cerclage and indomethacin ($n = 13$), or bed rest only ($n = 10$). Indomethacin was only given to one group. Preterm delivery before 34 weeks of gestation was significantly less frequent in patients allocated to have an emergency cerclage and indomethacin than in those managed expectantly [54% (7/13) vs. 0% (0/10); $p = 0.02$]. Antibiotics were administered to both groups of patients (173). Acute cervical insufficiency, however, can present with different degrees of severity. A patient with a dilated cervix in whom the membranes

are visible but within the uterine cavity is not the same as the patient who has prolapsed “hourglass” membranes in the vagina with a fetal presenting part. The latter group represents a greater surgical challenge and is often associated with subclinical intrauterine infection. One recommendation is to place the patient in the Trendelenburg position and to allow reduction of the membranes to the amniotic cavity. Since patients with intra-amniotic inflammation/infection have a poor prognosis if a cerclage is placed, an amniocentesis is performed to look for infection/inflammation. The workup includes an amniotic fluid Gram stain, white blood cell count, glucose, and culture for aerobic and anaerobic bacteria as well as genital mycoplasmas. If a cerclage is placed, patients are often followed by transvaginal ultrasound. The length of the cervix after a cerclage has some prognostic value about the likelihood of success (174–177).

Cerclage to Prevent Preterm Delivery in Women with a Short Cervix without a History of Preterm Delivery

The largest randomized clinical trial in which cerclage was used in patients with a sonographic cervical length ≤ 15 mm was conducted by the Fetal Medicine Foundation of the United Kingdom (150). Cervical length was measured in low-risk patients at a median gestational age of 23 weeks, and those with a cervix ≤ 15 mm were randomized to either the expectant management ($n = 126$) or cerclage group ($n = 127$). The rate of preterm delivery at <33 weeks of gestation was not significantly different [expectant management group 26% (33/126) vs. cerclage group 22% (28/127)]. The conclusion of this study is that cerclage placement in patients with a short cervix without risk factors for preterm delivery does not reduce the rate of preterm birth, neonatal morbidity, or the rate of perinatal death (150).

Prophylactic Cerclage and Cerclage in Patients with a History of Preterm Delivery and a Short Cervix

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 (144,152,165,178,179). While the largest trial conducted prior to the introduction of ultrasound evaluation of the cervix suggested a modest beneficial effect (179), other trials (165,178) and systematic reviews (41) prior to the use of ultrasound have indicated that the evidence of effectiveness for prophylactic cerclage is either weak or nonexistent.

In the Cervical Incompetence Prevention Randomized Cerclage Trial (CIPRACT) study, Althuisius et al. (135,180) randomized 73 pregnant women at <15 weeks of gestation with risk factors for “cervical incompetence” to have a prophylactic cerclage ($n = 23$) or be observed ($n = 44$). Four patients had a spontaneous abortion during the first trimester and two were lost for follow-up. The risk factors of “cervical incompetence” included the history of preterm delivery before 34 weeks of gestation, previous preterm PROM before 32 weeks of gestation, history of cold-knife conization, DES exposure, and a Müllerian duct abnormality. Prophylactic cerclages (i.e., McDonald) were generally placed between 10 and 12 weeks (later if enrolled at a later gestational age) using a braided polyester thread. In both groups, cervical length was evaluated every 2 weeks after randomization. The

rate of preterm delivery (<34 weeks) was similar in both groups [prophylactic cerclage 13% (3 of 23) vs. observation 14% (6 of 44); $p > 0.05$] as well as the neonatal survival [prophylactic cerclage 91% (21 of 23) vs. observation 93% (41 of 44); $p > 0.05$]. Patients allocated to the observation group were followed with serial sonography. If the cervical length shortened (<25 mm) before the 27th week of gestation, patients were randomized to both therapeutic cerclage and indomethacin with bed rest ($n = 20$) or bed rest alone ($n = 16$). Patients who received a cerclage and indomethacin had a lower rate of preterm delivery at <34 weeks and composite neonatal morbidity (neonatal intensive care unit admission or neonatal death) [0% vs. 44% (7 of 16), $p = 0.002$; and 5% (1 of 19) vs. 50% (8 of 16), $p = 0.005$].

By contrast, Rust et al. (91,181) randomized 113 patients presenting with a short cervix (<25 mm) or funneling ($\geq 25\%$) between 16 and 24 weeks into the therapeutic cerclage group ($n = 55$) and the no-cerclage group ($n = 58$). The population included patients with and without risk factors for preterm birth. All patients underwent amniocentesis to exclude intra-amniotic infection and received 48 hours of therapy with indomethacin and antibiotics. There were no significant differences between the two groups with respect to the rate of preterm delivery at <34 weeks of gestation (35% vs. 36.2%), readmission for preterm labor (52% vs. 53%), placental abruption (11% vs. 14%), chorioamnionitis (20% vs. 10%), and the perinatal death rate (13% vs. 12%).

The CIPRACT study (135,152) enrolled only patients at risk for preterm delivery, while in the trial of Rust et al. (91,181), 13% of patients were at low risk. The positive predictive value for a short cervix to predict preterm delivery is higher in patients with a history of preterm birth. The fact that the rate of preterm delivery in the control group of the CIPRACT study was higher than that of the study of Rust et al. (43.8% vs. 36.2%) may explain, at least in part, the different results between these two studies.

Berghella et al. (146) conducted a randomized clinical trial of the use of McDonald cerclage in women with one or more risk factors for preterm birth (one or more prior deliveries at <35 weeks, two or more curettages, history of DES exposure, cone biopsy, Müllerian anomaly, or twin gestation). Sixty-one patients with a cervical length <25 mm or funneling $>25\%$ were randomized to cerclage or bed rest. The authors reported that 47 pregnancies (77%) were high-risk singleton gestations.

There was no significant difference in the rate of preterm birth prior to 35 weeks in women who underwent cerclage (14 of 31; 45%) compared with those in the bed rest group (14 of 30; 47%) (RR 0.94; 95% CI 0.34–2.58). Similarly, patients with a singleton gestation and a prior preterm birth at <35 weeks of gestation and a cervical length <25 mm ($n = 31$ women) also had no benefit from cerclage placement (40% vs. 56%; RR 0.52; 95% CI 0.12–2.17) (146).

Owen et al. (153) reported a randomized clinical trial in which women with a prior spontaneous preterm birth before 34 weeks of gestation and a short cervix (defined as a cervical length <25 mm) were randomly assigned to have a cerclage or to be managed expectantly. The primary endpoint for the trial was birth at <35 weeks of gestation. Of the 302 patients randomized, 148 were allocated to the cerclage group and 153 to the non-cerclage group. There was a non-significant decrease

in the primary endpoint (delivery at <35 weeks of gestation) in women allocated to the cerclage group than in the non-cerclage group (32% vs. 42%; OR 0.67; 95% CI 0.42–1.07; $p = 0.09$). A post hoc analysis demonstrated that the rate of preterm delivery at <35 weeks was significantly lower in women with a cervical length below 15 mm, and there was no demonstrable effect in women with a cervical length between 16 and 24 mm. This study reported that cerclage reduced the rate of preterm birth and perinatal mortality. The results of the secondary analysis (<15 mm) are considered to be hypothesis-generating.

A meta-analysis of five trials in which women had singleton gestations, previous spontaneous preterm birth, and cervical length <25 mm before 24 weeks of gestation demonstrated that placement of a cerclage was associated with a lower rate of preterm birth before 35 weeks of gestation [28.4% (71/250) vs. 41.3% (105/254); RR 0.70, 95% CI 0.55–0.89]. Moreover, an index of perinatal mortality and morbidity (composite index) was significantly reduced in patients who had a cerclage (15.6% in the cerclage group vs. 24.8% in patients without cerclage, RR 0.64, 95% CI 0.45–0.91). Subgroup analysis demonstrated that in women with a cervical length of 15.9 mm or less, cerclage was associated with significant prevention of preterm birth at <37, 35, 32, and 28 weeks. The authors also examined the effect of cerclage as a function of cervical length. In patients with a sonographic cervical length of 16–24.9 mm, cerclage was associated with a significant reduction in the rate of preterm birth at <37 and <24 weeks of gestation (154). The authors stated that, based on their findings, “the effect of this intervention is important but clearly not the solution to the whole problem of preterm birth” and call for “further understanding of the pathophysiology of spontaneous preterm birth.” Thus, cerclage may be effective in reducing the rate of preterm birth in a subset of patients.

PESSARY IN WOMEN WITH CERVICAL INSUFFICIENCY AND/OR A SHORT CERVIX

The first report of the use of a pessary for the treatment of cervical “insufficiency” was in 1959 (182). Advocates for pessaries to prevent preterm delivery argued that their use should be considered in women with suspected cervical insufficiency because cerclage had not been proven to be efficacious in the prevention of preterm birth, and pessaries would not have the complications known to occur with cerclage. Vaginal pessaries are inexpensive, can be readily placed and removed, and allow outpatient management (without anesthesia) (183).

Several studies have evaluated the use of a pessary to prevent preterm delivery in women with suspected cervical insufficiency based upon history. Most of these reports consist of small case series (183–191).

Arabin et al. (187) reported sonographic cervical length measurements on patients with a prior spontaneous preterm birth before 36 weeks of gestation or early symptoms of preterm labor (pressure or contractions) and twin pregnancies. Patients with a cervical length ≤ 15 mm between 22 and 28 weeks of gestation were offered the use of a silicone pessary (Arabin pessary). The outcome of 11 patients who had a pessary was compared with a gestational age and cervical length–matched group. The control group consisted of 12 singleton pregnancies and 23 twin gestations. Placement of a

pessary was associated with a higher gestational age at delivery in both the singleton and twin gestations [for singletons, the mean gestational age at delivery was 38 (36–6/7 to 41) vs. 33–4/7 weeks (26–38), $p = 0.02$; for twins, 35–6/7 (33 to 37–4/7) vs. 33–2/7 weeks (24–4/7 to 37–2/7), $p = 0.02$]. None of the 12 singleton gestations with a pessary delivered prior to 36 weeks of gestation [pessary 0% (0/12) vs. control 50% (6/12), $p < 0.001$] (187). Based on these results, several trials are now in progress to determine whether a pessary can reduce the rate of preterm birth in women with a short cervix in both singleton and twin gestations (Carreras, Nicolaides, Palacio, Moratonas, Nizard). At this time, there is no evidence that cerclage is effective in twin gestations.

PROGESTERONE FOR THE PREVENTION OF PRETERM BIRTH IN WOMEN WITH A SONOGRAPHIC SHORT CERVIX

Vaginal progesterone reduces the rate of preterm delivery at <28, <33, <34, <35 weeks of gestation (110, 111), as well as the rate of respiratory distress syndrome and neonatal morbidity (111). The role of vaginal progesterone in the prevention of preterm birth in women with a sonographic short cervix is discussed further in the chapter focusing on preterm labor in this book (Chapter 1).

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