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Review Article

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Cerclage for the Management of Cervical Insufficiency: A Review

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Abstract

Cervical insufficiency (CI) is classically characterized as painless dilation of the uterine cervix in the second trimester that results in delivery of the pregnancy, typically prior to 24 weeks' gestation. Treatment of the condition has centered on prevention of recurrence in women with a history of CI or early preterm birth. Universal screening tools for CI in women without a history of prior PTB are lacking. Cervical change that is painless may occur with minimal symptoms such as increasing of vaginal discharge/mucous, vaginal pressure or fullness; many women and their providers can dismiss pathologic symptoms that would otherwise be benign in women without CI. The management of CI is categorized as surgical vs. nonsurgical. The cornerstone of surgical management is composed of cervical cerclage, and may be placed by a transvaginal or transabdominal approach depending on the obstetric history. Nonsurgical management includes pessary or activity restriction. For women who have experienced a midtrimester loss due to suspected cervical insufficiency, postnatal or preconception consultation is essential to identify modifiable risk factors, collect medical records of the delivery, and review pathology results if available.

Definition and Epidemiology

Cervical insufficiency (CI) is classically characterized as painless dilation of the uterine cervix in the second trimester that results in delivery of the pregnancy, typically prior to 24 weeks' gestation [1]. In addition to the absence of typical signs of labor contractions, other pathologies such as obstetric hemorrhage, premature rupture of membranes and evidence of intrauterine infection are absent. CI is thought to complicate approximately 1% of pregnancies, although the true incidence is unknown. In populations with prior preterm deliveries, the incidence is expected to be higher [2].

Newer definitions of CI place the condition under the umbrella of preterm birth, representing a spectrum or cascade leading to premature cervical ripening and ultimately delivery [3-5]. Potential etiologies setting off this cascade leading to CI include intrinsic weakness of the cervix, inflammation or infection, Mullerian anomalies and maternal stress [6]. Ultimately, CI leads to expulsion of a peri- or previable fetus; it represents a devastating condition for women and their families. Treatment of the condition has centered on prevention of recurrence in women with a history of CI or early preterm birth. Universal screening tools for CI in women without a history of prior PTB are lacking. Combined with the lack of "warning" symptoms, this condition remains a significant cause of second trimester preterm birth.

Pathophysiology

Although CI results from the inability of the uterine cervix to retain the pregnancy, the majority of women with the condition have an anatomically "normal" cervix prior to pregnancy. The cervix is primarily composed of connective tissue, followed by a small amount of smooth muscle and elastin; as opposed to the uterus which is primarily smooth muscle [6]. Women with a history of cervical surgery including loop electrosurgical excision procedure (LEEP) or cervical conization are at increased risk for CI. Mullerian anomalies increase the risk of early preterm birth, as well as in-utero exposure to Diethylstilbesterol (DES), although this is rare in a modern obstetric population. Lastly, collagenopathies, such as Ehlers-Danlos syndrome may lead to the inability of the cervix to retain the pregnancy [1].

Racial and genetic predispositions appear to contribute the risk of CI. Racial disparities in preterm birth have been well documented and Black race is a significant risk factor for preterm birth and CI [7, 8]. In addition to race, genetic predispositions have been described in women with CI, primary pathogenic variants of collagen synthesis and production [9].

Inflammation and infection are the most significant risk factors associated with premature delivery. Women who present with the clinical diagnosis of CI have a high rate of evidence of microbial invasion. Ureaplasma urealyticum, Gardnerella vaginalis, Candida albicans and Fusobacterium sp. have been isolated in the amniotic fluid of approximately ½ of women presenting with CI [10]. Inflammatory markers such as metalloproteinase-8 (MMP-8) have

been isolated in approximately 80% of women presenting with CI [11]. Both inflammatory markers and presence of microbial invasion of the amniotic fluid are predictors of poor outcome or shorter interval delivery in women with CI.

Among the challenges of the diagnosis and treatment of CI the absence of overt signs and symptoms of infection such as fever, uterine tenderness and maternal and fetal tachycardia do not preclude the possibility of an inflammatory process within the amniotic cavity [11]. Diagnosis Cervical change that is painless may occur with minimal symptoms such as increasing of vaginal discharge/mucous, vaginal pressure or fullness; many women and their providers can dismiss pathologic symptoms that would otherwise be benign in women without CI. Although there is no universally adopted consensus of the diagnostic criteria for CI, it is widely accepted that CI be considered when there is painless cervical dilation in the midtrimester and before 24 week's gestations. Direct visualization of the dilated cervix by speculum examination confirms the diagnosis. The absence of other pathologies resulting in cervical dilation such as contractions, infection, significant bleeding or premature rupture of membranes should be confirmed. Because of the limited ability to prospectively rule out other etiologies such as labor, infection, placental abruption, the diagnosis of CI is often one of exclusion and only made retrospectively. In addition to the above challenges, many women with CI will not present for care until there is advanced dilation or rupture of membranes that may be characterized by pain and bleeding, limiting the ability to tell if indeed there was evidence of painless dilation [12]. Transvaginal ultrasound (TVUS) can also reveal the premature cervical dilation, showing no measureable cervical length. TVUS may also show the membranes of the amniotic sac at or distal to the external cervical os. Although TVUS of the cervical length has been studied extensively in women with and without a prior preterm delivery to offer interventions with the goal of reducing recurrent preterm birth, protocols for universal cervical length screening in women with or without a history of spontaneous preterm delivery are performed to offer intervention to reduce preterm delivery, not specifically CI [3, 13-17].

Management

The management of CI is categorized as surgical vs. nonsurgical. Surgical management is composed of cervical cerclage, and may be placed by a transvaginal or transabdominal approach depending on the obstetric history. Nonsurgical management includes pessary or activity restriction. Although progesterone is often used in women who may be thought to have a component of CI, it is not considered first line therapy in patients with a history of CI or who present with painless dilation consistent with CI.

Cerclage

Cerclage is a surgical approach that aims to mechanically close the cervical os. Depending on the maternal obstetric history, cerclage is performed by a transvaginal or transabdominal approach. Cerclage placement is defined as history-indicated, ultrasound-indicated or exam-indicated. A history indicated cerclage, or "prophylactic" cerclage is placed in women with a prior loss due to suspected CI, between 12-15 weeks' gestation. An ultrasound-indicated cerclage is placed in women with prior preterm delivery and a sonographic short cervix, between 16-23 weeks' gestation. An exam-indicated, or often term "rescue" cerclage is placed in women presenting with painless dilation in the midtrimester, typically between 16-23 weeks' gestation [18].

Transvaginal approach

The most common transvaginal cerclage technique performed today is the McDonald cerclage. Described in 1957, McDonald reports a purse-string suture of No. 2 chromic catgut placed around the cervix of a 24-week pregnancy with dilated cervix and membranes bulging through the internal os. He subsequently described 70 cases in which this pursue-string suture was placed between 20-24 weeks' gestation [19]. Today, it is employed in the same manner as described by McDonald, using a nonabsorbable suture. A "Shirodkar "cerclage, described in 1955 is the second most common type of transvaginal cerclage, usually employed in an attempt to place the suture more distal to the external os or closer to the internal os. The technique is not a simple purse-string suture around the cervix but involves dissection of the anterior cervix down to the pubocervical fascia where the bladder can be "pushed" cranially so the stitch can be placed closer to the level of the internal cervical os [20]. Dissection of the posterior cervix may or may not be done with this technique. Many providers chose a Shirodkar cerclage if a McDonald cerclage has failed in a prior pregnancy. It is also employed in cases of a shortened cervix, or anatomically abnormal cervix that may be present with prior procedures such as cervical conization [21]. In the setting of a history indicated cerclage, regardless of technique, is typically placed soon after or near the end of the first trimester, between 12-15 weeks' gestation. It is considered an outpatient procedure, and can be successfully placed with regional anesthesia.

As to which technique improves outcomes has yielded varied results among retrospective analysis. There has not been a prospective, randomized trial comparing the two techniques in women undergoing a history indicated procedure. The majority of the available literature appears to suggest there is no significant benefit to one technique over the other. In women with a prior preterm birth undergoing an ultrasound indicated cerclage, there was no difference in gestational age at delivery based on cerclage technique [22].

Type of suture used in McDonald and Shirodkar cerclages has been compared to measure efficacy of one choice over another. Common suture types are 5mm braided polyester fiber (Mersilene® tape), polypropylene non-braided monofilament (Prolene®) or polyester braided thread (Ethibond®). Randomized trials are lacking and retrospective studies have produced varied results depending on timing and indication of cerclage placement. In a secondary analysis of women with a prior preterm birth receiving ultrasound indicated cerclage, type of suture did not affect efficacy [23]. In a retrospective cohort of women receiving a cerclage, thicker suture, or 5mm braided polyester fiber showed improved outcomes in women undergoing ultrasound or exam indicated cerclage, but not history indicated cerclage [24]. Suture type used may be chosen for various reasons, availability or cost, surgeon choice or other case specific factors. If the cervix is dilated and very thin, often a monofilament suture is used. This suture will be easier to

place because of needle and suture size, thereby avoiding excessive manipulation and easier passage through the cervical tissue.

Others have proposed placing more than one stitch at the time of cerclage to improve efficacy. Based on limited, retrospective data, using more than one suture does not confer any further benefit to pregnancy prolongation [25].

In addition to history-indicated cerclage, the efficacy of measures such as antibiotics or tocolytics have yet to show a significant benefit or risk. Tocolytics and antibiotics are commonly used as preventive measures for preterm delivery in other pregnancy scenarios and appear to be safe. However, routine use of tocolytics and antibiotics at the time of cerclage for the benefit of prolongation or improved outcomes remains deficient [18]. The exception to using tocolytics and antibiotics routinely may be in the setting of an exam-indicated cerclage. The tocolytic, Indomethacin, and antibiotics may be beneficial in combination with exam-indicated cerclage [26, 27]. In a recent review of 78 women undergoing exam-indicated cerclage, the addition of cefazolin and indomethacin increased pregnancy latency and birthweight [28].

Transabdominal approach

By laparotomy, laparoscopy or robotic approach, a cerclage may be placed intra-abdominally, with the stitch encircling the uterocervical isthmus. A transabdominal cerclage (TAC) is generally reserved for women after a failure of a history indicated transvaginal cerclage, shortened, scarred or absent cervix [29]. The outcomes of a TAC show a reduction in recurrent preterm birth over repeated history indicated cerclage [30]. A transabdominal approach allows the stitch to be placed at the level of the internal os, as compared to the transvaginal approach. In addition, it can leave in place for future pregnancies. The primary disadvantage to TAC is the increase in morbidity with abdominal surgery including, but not limited to the potential for injury to other organs and blood vessels, need for transfusion, increased operative and recovery time and risk for surgical site infection [31, 32]. Women with TAC are committed to Cesarean at the time of delivery in current or future pregnancy. In women with multiple losses and failure of history indicated cerclage, a thorough evaluation to exclude other causes of pregnancy loss is recommended prior to proceeding with a TAC.

Pre-surgical evaluation should include a uterine cavity assessment by hysterosalpingogram, sonohysterogram or hysteroscopy. Consideration for other causes of loss may include thrombophilia workup, ruling out infectious causes such as Chlamydia, Ureaplasma or Mycoplasma and reviewing placenta pathology from prior losses [33]. A significant advantage of TAC is the ability to place prior to pregnancy, removing the risk of miscarriage or loss related to the surgery. When placed during pregnancy, Benson first recommended that TAC be delayed after the first trimester, preferably after the 14th week of gestation, however, the timing of TAC in pregnancy is similar to that of transvaginal cerclage, typically 12-15 weeks' gestation [34, 35].

With advances in surgical technique and technology, there is a trend towards a minimally invasive approach to TAC, namely Robotic cerclage. Although no randomized, controlled trials comparing minimally invasive approaches have been performed, retrospective data indicate the approaches have similar outcomes. Gestational age at delivery appears similar, while operative times are increased with Robotic approach, however, length of stay in the hospital appears decreased with the Robotic approach [36].

Preterm premature rupture of membranes (PPROM)

Preterm premature rupture of membranes is not uncommon in women with CI after receiving a cerclage, reported to occur in up to 30-40 percent of patients [37, 38]. Patients diagnosed with PPROM in presence of cerclage have increased incidence of clinical and histological chorioamnionitis and adverse perinatal outcomes including sepsis, neonatal respiratory distress, neonatal anemia, intrauterine demise, neonatal death and intraventricular hemorrhage. The evidence is mixed whether presence of cerclage and PPROM results in an increase in pregnancy latency [39]. It has been speculated that the presence or absence of cerclage does not have a significant effect on pregnancy latency in PPROM given that the motivation for delivery is predictably intrauterine infection not CI. The literature is not clear regarding the impact of cerclage retention versus removal in the setting of PPROM. Galyen et al conducted and randomized, controlled trial of 56 women with PPROM and cerclage between 22- and 32-week's gestation. Although the study was small and potentially underpowered to detect outcomes, there were no significant differences in latency, infection or composite neonatal outcomes. The authors concluded that there was a trend toward less infection morbidity and the data suggested there might be no benefit in cerclage retention after PPROM [40]. Berghella et al report a review of the literature showing a trend toward infectious morbidity with cerclage retention but possibility benefit in retention to gain time to administer antenatal corticosteroids. The authors present an algorithm to guide care providers in the decision to retain or remove cerclage in the event of PPROM. If the gestational age is less than 23 weeks or greater than 32 weeks, cerclage removal is recommended at time of diagnosis of PPROM. If gestational age is between 23.1-31.6 weeks, the physician may remove cerclage immediately, or remove after administration of steroids to improve fetal lung maturation [38].

Active Vaginitis

The vagina is colonized by bacteria, fungi, viruses and protozoa; the flora is dominated by lactobacilli species [41]. Lactobacilli spp play an important role in maintaining normal vaginal microbiota and therefore physiology, whereas the hallmark of Bacterial Vaginosis (BV) is the depletion of lactobacilli. The risk of ascending infection originating from the vaginal microbial makeup raise the possibility that vaginitis may be related to second trimester loss. It has reported that the vaginal microbiota in women undergoing an exam-indicated cerclage show reduced levels of Lactobacillus spp and overrepresentation of G. vaginalis [42]. Maintaining normal vaginal flora homeostasis in pregnancy may be related to reducing the risk of ascending infection/inflammation and risk of preterm delivery. Women presenting with signs and symptoms of CI should be screened for BV and those who are symptomatic should be treated as usual. There is insufficient evidence to recommend screening asymptomatic women with a history of preterm delivery or risk factors for preterm delivery for BV [43, 44]. A planned cerclage procedure is not typically delayed or held because of active vagini-

tis or sexual transmitted infections, but treatment is recommended at that time of diagnosis, followed by test of resolution.

Multiple Gestation

The majority of literature supporting the use of interventions to prevent preterm birth secondary to CI is from singleton pregnancies. Given the higher incidence of preterm delivery in multiple gestations, it is reasonable to conclude that interventions in this population such as cerclage or pessary may reduce the rate of preterm delivery associated with CI, however, the literature is scant, lacking high quality data and inconsistent in conclusions. Reviewing the current literature, one may conclude that prophylactic cerclage in unselected multiples may have no impact on preventing preterm delivery, may prolong pregnancy or may increase the risk of preterm delivery [45-47]. Giving these findings, the American College of Obstetricians and Gynecologists state that in unselected twins or in the setting of a sonographically shortened cervix placement of cerclage in women with multifetal gestations should be avoided [48]. These conclusions are based on meta-analysis of singletons and twins, with very small numbers of twin pregnancies, making it difficult to draw definitive conclusions [49, 50].

In unselected multiple gestations, interventions such as cerclage or pessary do not appear to reduce the risk of preterm delivery, however, in particular circumstances such as those with prior history of CI, preventive measures may improve outcomes [51, 52]. Rottenstreich et al report a retrospective cohort of 41 women carrying a twin pregnancy and a history of midtrimester delivery who had a history indicated cerclage placed at median gestation of 13 weeks. Compared to a cohort of twin pregnancies with a prior history of preterm delivery and no history indicated cerclage, those receiving cerclage had improved outcomes of delivery later gestational age, higher birthweights and lower neonatal morbidity [53]. A recent randomized controlled trial of exam-indicated cerclage in women carrying twin pregnancies and also experienced asymptomatic midtrimester dilation between 16- and 23-weeks' gestation was stopped early due to the significant benefit of those receiving cerclage versus expectant management after enrollment of 34 subjects. The authors concluded that in patients with twin pregnancies and asymptomatic cervical dilation before 24 weeks' gestation, an exam-indicated cerclage decreased early preterm birth prior to 28 weeks' gestation by 50% and perinatal mortality decreased by nearly 80% [54]. A retrospective cohort of 104 women carrying twins and undergoing an exam-indicated cerclage had similar outcomes as women carrying singletons undergoing an exam-indicated cerclage. Delivery before 28 weeks' gestation did not differ between twins and singletons [55].

The literature appears to be fairly consistent that in unselected, twin populations, cerclage to prevent preterm delivery is not helpful [56]. This lends to the conclusion that twin pregnancy alone does not necessarily lead to preterm delivery due to painless cervical change or CI. In selected populations, such as those with a history of CI or those presenting with painless dilation consistent with CI, cerclage may be beneficial, although we are lacking high quality data to draw specific conclusions.

Twin-Twin Transfusion

Twin-twin transfusion syndrome (TTTS) is a potential complication of monochorionic diamniotic twin pregnancies, diagnosed and managed based on ultrasound criteria. Amniotic fluid discrepancy is seen in early and late stages of TTTS. Preterm delivery remains a significant risk factor for treated and untreated TTTS [57]. Pregnancies complicated by TTTS often present with a sonographic shortened cervix, a known risk factor for preterm delivery and CI [58]. Interventions such as cerclage and pessary have been proposed and used in women with TTTS thought to have a cervical exam placing them at high risk for preterm delivery. Papanna et al reported a multicenter, retrospective cohort of 79 women with a CL $\leq$ 25mm at the time of surgical treatment for TTTS who underwent placement of vaginal cerclage. Compared to the control group, there was no difference in gestational age at delivery or perinatal mortality. The authors concluded the benefit of cerclage in this setting remains questionable [59]. One small retrospective study has evaluated pessary placement at the time of treatment for TTTS, with potential favorable results of prolonging pregnancy [60]. The study concluded a large randomized trial should be performed and is currently underway [61].

Pessary vs Cerclage

As indications for cervical cerclage are delineated as history-indicated, ultrasound-indication or physical exam-indicated, pessary has been primarily used in women with a sonographic shortened cervix or physical exam consistent with CI. Pessary has not been well studied as prevention in a history-indicated fashion. A direct comparison of history –indicated cerclage to history-indicated pessary is not available. Pessary for prevention of preterm birth in women with a sonographically shortened cervix has delivered mixed results, with possible benefit verses no benefit [62, 63]. A recent systematic review of 4687 women found no improvement in perinatal outcomes when pessary was placed for sonographic shortened cervix found in the midtrimester [64]. There have been some promising results of pessary in the setting of a shortened cervix in women carrying twins, while others have found no benefit in this population, making it difficult to draw definitive conclusions [65-67]. In unselected populations, pessary in women with a sonographic shortened cervix does not appear beneficial. Although no randomized trials are available, pessary versus cerclage in the setting of cervical dilation in the midtrimester appears to favor cerclage. A review of 112 women presenting with suspected CI who underwent exam-indicated cerclage, pessary placement or expectant management found that cerclage was associated with prolonging pregnancy latency, reduction of preterm premature rupture of membranes and improved neonatal survival [68].

US Screening for CI

In women with recurrent midtrimester losses due to suspected CI, a history-indicated cerclage reduces the risk of recurrence [69]. If there is a single midtrimester delivery that appears to be consistent with CI, it is reasonable to proceed to a history-indicated cerclage in subsequent pregnancies, although many women with single midtrimester loss may go on to have subsequent normal pregnancies without interventions such as cerclage [1, 70]. It is well estab-

lished that women with a prior history of preterm delivery and a sonographically shortened cervix benefit from cerclage placement [13]. Given these findings, instead of a history-indicated cerclage, women with a history of preterm delivery are managed utilizing cervical length surveillance with cerclage placed in the setting of a shortened cervix [70, 71].

Amniocentesis

Given that inflammation and infection appear to be significant risk factors for CI, it is not surprising that amniocentesis performed in women presenting with suspected CI result in evidence of intra-amniotic infection in as many as half of cases [72]. Those without evidence of intra-amniotic infection or inflammation before placement of an exam-indicated cerclage have improved outcomes [11, 73]. Amniocentesis may be considered by the provider or patient if there is a desire to confirm the absence of intra-amniotic infection prior to cerclage placement, but is not considered mandatory before proceeding with cerclage maintaining there are no clinical signs or symptoms of infection. Amniocentesis, the procedure, appears to be safe in women presenting with CI and does not appear to further increase the risk of early delivery [74].

Postpartum Evaluation or Preconception Counseling

For women who have experienced a midtrimester loss due to suspected cervical insufficiency, postnatal or preconception consultation is essential to identify modifiable risk factors, collect medical records of the delivery, and review pathology results if available. An evaluation of the intrauterine cavity can rule out Mullerian anomalies or presence of a uterine septum and may result in the need for corrective surgery prior to considering future pregnancies. A thorough review of the events of the delivery can offer guidance regarding plans for a history-indicated cerclage versus cervical length surveillance beginning in the midtrimester with plans for an ultrasound-indicated cerclage in the event of a sonographically shortened cervix.

Postnatal and preconception counseling also gives an opportunity to evaluate the emotional and mental health of the grieving patient who has suffered a devastating pregnancy loss. Traumatic birth experiences are indeed a significant risk factor of perinatal depression and targeted screening with treatment and referral to the appropriate mental health professional is recommended when appropriate [75].

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