

Flowable Dehydrated Amniotic Membrane Allograft Augments McDonald Cerclage in High-Risk Women for Preterm Birth Prevention, a Case Series

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Abstract

The inability of the uterine cervix to retain a pregnancy in the second trimester is referred to as cervical insufficiency. The most common intervention for such cervical insufficiency to prevent preterm birth is a McDonald cerclage. However, the rate of success ranges from 40-90%. This 3 patient case series is the first report of supplemental use of a dehydrated amniotic membrane allograft (DAMA; BioDRestore[®]) at the cerclage suture sites as a means to improve success, measured by prevention of pre-term birth, reduction in complications of neonatal prematurity, and decreased length of hospitalization for mother and neonates.

Keywords: cerclage; incompetent cervix; amniotic membrane allograft; preterm delivery.

Introduction

There has been an increase in diagnosis of short or incompetent cervix with the growing popularity of Loop Electrosurgical Excision Procedures (LEEP) during pregnancy [1]. A short cervix has been identified as a risk factor for preterm labor. The prevalence of cervical insufficiency in the general population is estimated to be 0.1-2%, but is 15% in women with a history of recurrent miscarriages or early preterm births [2]. The reason for cervical insufficiency is not known. It has been suggested that decidual inflammation, chorionitis, hemorrhage, acquired and structural functional defects (cervical conization, cervical laceration etc) may be associated. [3,4].

Since the 1950s, cerclage interventions are often recommended to treat cervical insufficiency including transvaginal, and in more severe cases, transabdominal approaches. Between the two, transvaginal cerclage method is the most common. It was first introduced by Shirodkar in 1955 [5] and subsequently modified by McDonald in 1957 [6]. The McDonald procedure was defined as a purse string suture of non-absorbable material around the exocervix at the cervicovaginal junction. It has been correlated with reductions in the incidence of preterm birth in women at risk of recurrent preterm birth, however, the reduction of perinatal morbidity or neonatal mortality was not statistically significant when compared with non-surgical managements. [7] Wong et al. reported potential complications of cerclage include bleeding, infection, perioperative and

postoperative membrane rupture, chorioamnionitis, and abruptio placentae. [8] Concomitant therapies that can potentially mitigate these complications are attractive as a means to improve patient outcome.

Amniotic membrane has been used as a biological dressing for wounds, burn treatment, and surgical reconstructive procedures since the early 20th century because of its non-immunogenic, anti-inflammatory, anti-oxidant, anti-microbial, and angiogenic properties. [9-14] The recent advances in tissue preservation technology have allowed for mass production and commercialization of amniotic tissue allografts. These allografts are available in either sheet or injectable configurations and multiple sizes to allow for heterogenous internal and external applications. Depending on different processing methods, they can be stored at room temperature or in deep freezer for 2 – 5 years, which offers convenience for surgeons.

In this case series, we discuss the novel use of an injectable dehydrated amniotic membrane allograft (DAMA, BioDRestore[®], Integra Lifesciences, Princeton, NJ) in conjunction with McDonald cerclage for patients with a history of second trimester pregnancy loss or preterm birth with early cervical dilation without uterine contractions. All transvaginal cerclage procedures were performed by a single attending physician (Karon, MD).

Case Presentation

Case #1

A 29-year-old G3P1 with a history of a LEEP procedure, was admitted to our clinic with a complaint of second trimester pregnancy loss (19 4/7 weeks of gestation). She had painless dilation of the cervix and delivered

a viable infant who expired soon after delivery. The clinical presentation and physical examination were consistent with an incompetent cervix. She conceived the following year and a McDonald cerclage was placed at 13 3/7 weeks gestation. Cervical length was measured during prenatal visits by transvaginal ultrasound (**Figure 1**).

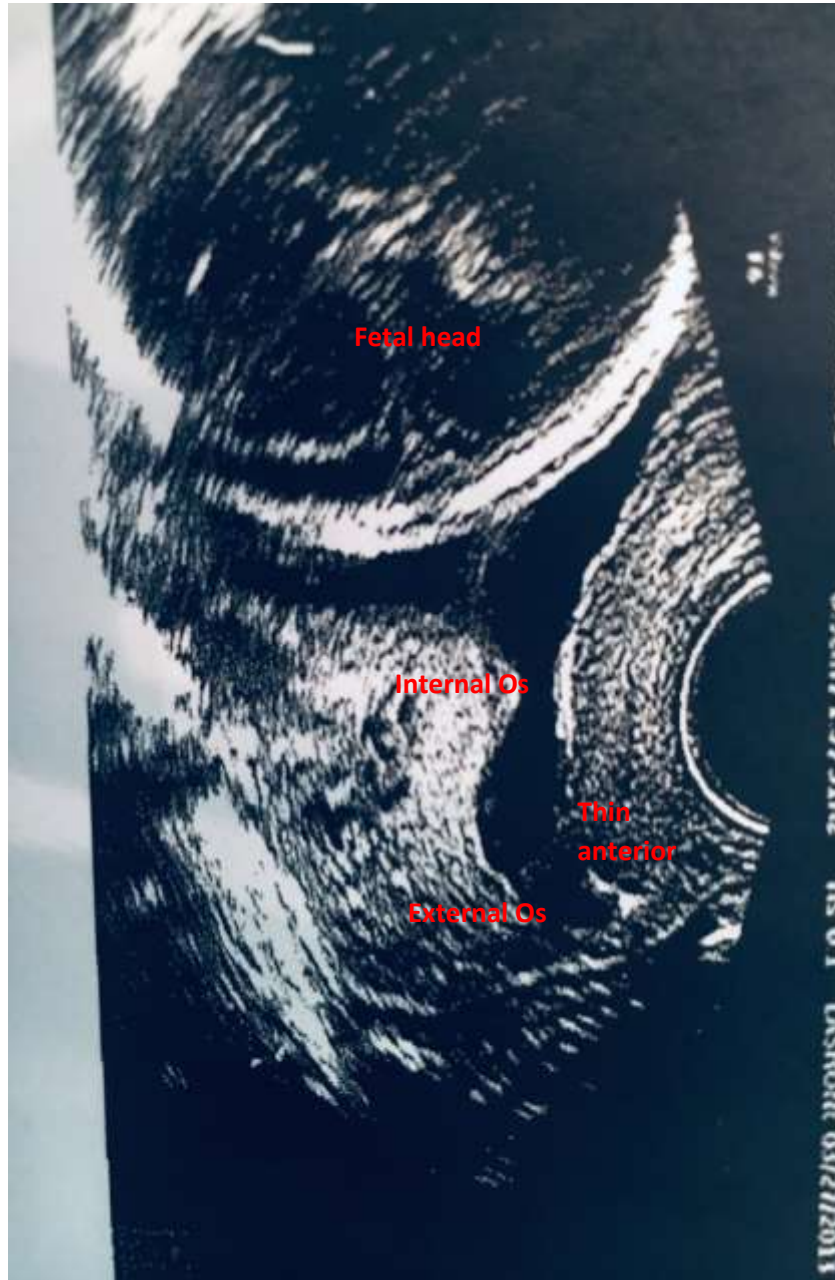


Figure 1A: Transvaginal ultrasound scan of the cervix at 23 weeks gestation showing funneling (black area). (Case #1, second pregnancy)



Figure 1B: Transvaginal ultrasound scan of the cervix at 24 weeks gestation showing normal cervical length (Case #1, Third pregnancy).

As part of the exam, fundal pressure was applied for 30 seconds to detect cervical shortening and funneling. At 23 weeks of gestation the patient was admitted to ante-partum because the cervix was shortened to 0.66 cm and had funneling of 1.36 - 1.83 cm. She could not be sent home due to distance from the hospital, thus was hospitalized until delivery. At 30 6/7 weeks of gestation the patient developed chorioamnionitis due to the “hour-glassing” of the membranes, leading to a preterm delivery. Her newborn spent 5 weeks in the NICU. With her third pregnancy, McDonald cerclage was again placed at 13 weeks of gestation. This time, we injected a total volume of 1cc DAMA at each puncture site of the Mersilene suture (Johnson and Johnson, Bridgewater, NJ) to reinforce the cerclage. We did not observe any funneling during the transvaginal scans. Her cervical length stayed longer than 2.5 cm at every measurement (**Table #1, Figure 2**). She was able to return to work light duty, did not require hospitalization except for the administration of steroids for fetal lung maturity and magnesium for neuro-prophylaxis.

The cervical suture was removed in the office at 37 weeks gestation. She went into labor at 38 1/7 weeks gestation and had a normal spontaneous delivery of a 3162-gm healthy male infant.

Case #2

A 28-year-old G5P1 was diagnosed with an incompetent cervix after her pregnancy loss at 22 weeks gestation. This patient previously had two dilation and curettage first trimester miscarriage and a LEEP procedure. With the subsequent pregnancy she had a McDonald cerclage placed after the first trimester at 13 weeks of gestation. Patient started a weekly intramuscular injection of progesterone at 18 weeks of gestation. At the time of anatomy scan at 20 weeks of gestation her cervix was found to be funneling and shortening and she was placed on bed rest at home. Because of transportation issues, she was followed by home health and could not have frequent cervical measurements. She came into the labor hall at 32 weeks gestation and had a precipitous labor. The infant

spent 4 weeks in the NICU. With the third pregnancy, she had the cerclage placed after the first trimester with the addition of 1cc DAMA at the suture sites. Frequent scans up to 28 weeks of gestation revealed that her

cervical length consistently increased over time without any funneling through 24 weeks gestation and remained longer than 2.5 cm at 28 weeks of gestation (Table 1, Figure 2).

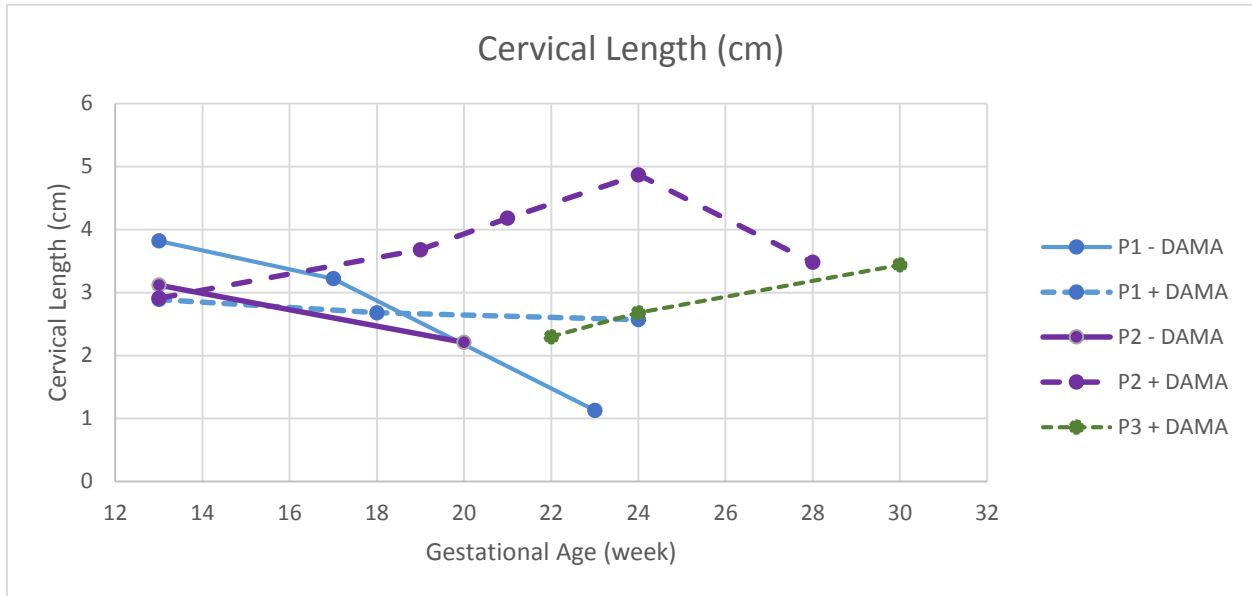


Figure 2: Cervical length comparison at their pregnancy follow-up visits between cerclage procedures with and without incorporation of DAMA. Solid line represents procedure without DAMA, and dashed line represents procedure with DAMA. P stands for patient.

Cervical Length Measurements Through Gestation of Pregnancy					
Weeks of Gestation	Case 1 Prophylactic Cerclage		Case 2 Prophylactic Cerclage		Case 3 Emergency Cerclage
	First Cerclage Alone	Cerclage + DAMA	First Cerclage Alone	Cerclage + DAMA	
12	3.82 cm	2.89 cm	3.12 cm	2.91 cm	
13	Cerclage was placed	Cerclage was placed	Cerclage was placed	Cerclage was placed	
14	4.18 cm	3.31 cm	3.52 cm	3.81 cm	
15					
16					
17	3.22 cm				
17	2.95 cm with Fundal Pressure				
18		2.68 cm ; 2.25 cm with Fundal Pressure			
19				3.68 cm No Funnel	
20			2.21 cm with Funnel		
21				4.18 cm No Funnel	
22					2.30 cm with Funneling 1.90 cm
23	1.13 cm Funnel 1.83				Cerclage Placed With DAMA
23	0.66 cm with Fundal Pressure				
24	Patient is hospitalized	2.57 cm No Funneling		4.87 cm No Funnel	2.68 cm No Funneling
25					Steroids for fetal lung maturity and magnesium for neuroprophylaxis
26					
27					
28				3.48 cm Admitted for Nephrolithiasis	
29					
30	Patient is delivered Due to Choriomnionitis				3.44 cm; 3.30 cm with Fundal Pressure No funneling
31					
32			Percipitous Delivery		
33					
34					
35					
36					
37		Cerclage removed		Cerclage removed, followed by Delivery	Cerclage removed, followed by delivery
38		Delivery at 38 1/7 week			

Table 1: Descriptive characteristics of cervical length measurements across gestational age for all three patients.

The cervical length was defined as the length of the endocervical canal as measured by transvaginal sonography 7.0 MHZ probe (GE). The probe was inserted into the vagina until it met with resistance and withdrawn slightly to reduce compression before measurements were taken. The mean of three measurements were recorded. To minimize variability, only one sonographer participated in the study. All measurements were reviewed by maternal fetal medicine specialists assuring a mean cervical length of 3.0 cm.

At 28 weeks gestation, she was admitted for nephrolithiasis. She later reported that she experienced more severe pain when passing kidney stones than that of labor. Throughout the pregnancy, the patient was able to keep a sitting job with a <20lb lifting restriction. The patient received steroids for fetal lung maturity and magnesium neuro-prophylaxis. The cerclage was removed in the office at 37 weeks gestation and patient delivered a 3260-gm healthy infant, who did not need any extra care post-delivery.

Case #3

A 29-year-old female with, G3P1, presented to our clinic with 2cm cervical dilation at 21 4/7 weeks gestation without uterine contractions. Her cervical length was measured at 2.3 cm and 1.9 cm with fundal pressure, with funneling. In her past medical history, she had a first trimester miscarriage and a normal vaginal delivery at term, and a LEEP procedure prior to the current pregnancy. We performed an emergency cerclage with DAMA, per the described technique in case 1 and 2. Her cervical length was 2.68 cm without funneling at 24 weeks gestation. Frequent scans up to 30 weeks of gestation showed that her cervical length consistently increased over time without any funneling (**table #1, Figure 2**). She also received steroids for fetal lung maturity and magnesium for neuro-prophylaxis. The patient had a spontaneous vaginal delivery of a healthy female infant weighing 3309 gm at 37 weeks of gestation.

Discussion:

McDonald cervical cerclage has been the gold standard for a surgical correction of cervical insufficiency associated with pre-term birth. The rate of success is 80-90% for prophylactic cerclage and 40-60% for emergency cerclage. [15-20] It is considered successful if labor is delayed to at least 33 weeks.[21] Here, we presented three patients, all of whom had a history of LEEP and prior second trimester pregnancy loss. Cases 1 and 2 also had a failed cerclage for their second pregnancies, with preterm labor at 30 and 32 weeks of gestation, respectively. Serial sonographic scans revealed progressive cervical shortening over time accompanied by the presence of funneling, a significant risk factor for adverse perinatal outcome. [22] Nevertheless, cerclage placements did increase the lengths of their cervix and prevent second pregnancy loss in both cases. When DAMA was incorporated into the cerclage procedure for their third pregnancy, cervical measurement at each scan was increased in comparison to their previous pregnancies (Table 1, Figure 2). We did not observe any funneling even with the application of fundal pressure after the cerclage placement. Both patients achieved full term pregnancy without any complications. In the case of emergency cerclage for case #3, despite the poor success rate in patients with advanced cervical dilation and absence of labor, we report a term delivery and cervical length of >25mm without funneling at all post-cerclage transvaginal assessments.

Use of DAMA as an augment of McDonald cerclage.

DAMA is composed of dehydrated amniotic membrane, which is an immune-privileged allograft containing an array of growth factors and cytokines that regulate processes involved in inflammation and wound healing. Various applications of DAMA have been well-described in the literature. Grubb et al. applied DAMA in patients with failed back surgery

syndrome, reporting a reduction of epidural fibrosis formation and adhesions to the underlying dura (manuscript in preparation). In a large prospective randomized control trial, Synder et al. reported accelerated wound closure after application of DAMA in patients with chronic, nonhealing ulcers. [23] Heckmann et al. used DAMA as a nerve wrap over anterior, subcutaneous ulnar nerves and successfully prevented perineural fibrosis and recurrence in ulnar nerve symptoms. [24] Shah et al. observed accelerated return of continence and erectile function in 15 patients following nerve-sparing robotic-assisted radical prostatectomy after the application of DAMA over the prostatic neurovascular bundle. [25] Using multiplex/Luminex protein secretion analysis the effect of DAMA on monocyte differentiation toward pro-inflammatory M1 versus anti-inflammatory (or "pro-regenerative") M2 macrophages was explored recently. Non-polarized primary human macrophages in the presence of DAMA shifted towards M2-like macrophages, with a concurrent decrease of inflammatory markers and increased secretion of PDGF, CCL22, IL13, and CCL18 compared to non-treated controls. This study indicates that macrophages can be influenced by DAMA to improve tissue regeneration/repair in an in vitro wound-healing model. [26] These findings suggest that DAMA are safe to be used in the surgical setting, and can accelerate epithelization as well as reduce adhesion formation, scar formation, pain, and inflammation.

We employed DAMA in a novel manner with the purpose of accelerating healing of the suture sites and remodeling of the cervix secondary to cerclage. The post-operative findings of cervical measurements and the observation of funneling or lack thereof support this theory. We theorize that by closing the cervix and expediting healing of the suture sites, the risk of exposure to vaginal bacteria is reduced and therefore reduces the inflammatory process - which is responsible for cervical ripening and the onset of contractions. This allows the cervix to close and lengthen. It also suggests that the cervix is a dynamic organ capable of functional remodeling during pregnancy.

It has been suggested that infection is likely to play a part in many cases of miscarriage in the second trimester. [27] The anti-microbial and anti-viral properties of amniotic membranes may explain why we did not observe any infection when incorporating DAMA for all 3 patients. As a barrier, DAMA adheres to the wound surface tightly so that there is no dead space between the graft and the wounds. This can prevent accumulation of discharge, as well as the infiltration and adhesion of microorganisms. In addition, the hemostatic property of collagen fibers of amniotic basement membrane prevents hematoma formation, which reduces bacterial load and risk of infection by preventing accumulation of microbes. Furthermore, amniotic membranes have been shown to contain a wide array of antimicrobial peptides such as β -defensins, elafin, secretory leucocyte protease inhibitor, and histone H2B. [28] Kjaergaard et al. have shown *in vitro* antimicrobial effects of the amnion and chorion against several microorganisms. [29] Its antiviral properties are exhibited by presence of cystatin E, the analogue of cysteine proteinase inhibitor. [30]

Another aspect worth noting when using DAMA with cerclage is that we observed a consistent decrease in blood loss compared to the cerclage without it, which could have contributed to DAMA's hemostatic property. Its adhesive and tight contact with the injured surface promotes hemostasis and pain relief due to coverage of exposed nerve fibers.

Overall Health Economic Benefits of DAMA as a Supplement of Cerclage

The health economics related to the need for a cerclage during pregnancy potentially include: procedural intervention (trans-vaginal cerclage and/or robotic transabdominal Shirodkar cerclage), additional agents utilized during cerclage (e.g. DAMA), loss of income due to bedrest, additional expenses due to bedrest (e.g. home health, child care, etc), cost of

hospitalization(s) for mother, cost of hospitalization of neonate in cases of pre-term delivery. Though the use of DAMA in the presented cases represents an additional cost to the cerclage procedure, the ability of the patients to work throughout pregnancy and avoid bed rest as well as additional hospitalizations for the mother or child due to complications from cervical incompetence, suggests supplemental use of DAMA is cost-effective.

The main limitation of the current report is the retrospective design and the small patient number. An adequately powered, prospective randomized trial and cost-benefit analysis of DAMA at the cerclage suture sites is necessary to further ascertain the treatment effect of this new approach. Defining the appropriate patient population, such as those who have had previous miscarriages despite cerclage, would allow appropriate evaluation of the health economic and clinical benefits. In the meantime, we do want to highlight that the strength of this study is that the same patients were treated and followed-up by the same Maternal Fetal Medicine team throughout their consecutive pregnancies, which minimized variations that could be possibly induced by human factor.

Conclusion:

This case report proposes a novel role for DAMA in patients with cervical insufficiency and prior pregnancy loss in addition to standardized cerclage as indicated. Given our patients improved gestational age at delivery and lack of funneling, there is a possibility that DAMA promoted the regeneration and remodeling of the cervix while preventing inflammation and infection. We hope that this report assists surgeons in management of cervical insufficiency by providing an additional option that could provide expedited healing, improved pregnancy with term delivery, decrease prenatal morbidity, and ideally avoid high costs due to hospitalization for both mothers and newborns.

Data Availability

N/A

Ethical Approval

Specific ethical board approval was not required for this study as we reported and took data from three patients the same way as we do for a case report.

Consent

Complete informed written consents were obtained from all three patients for the publication of this study and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflicts of Interest

The author declares that there are no conflicts of interest regarding the publication of this article

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