ACH Med J
(2024) 2: 065-071
ISSN:2822-5872
Doi : 10.5505/achmedj.2024.ACHMJ-33042

RESEARCH ARTICLE

Cervical Cerclage: An Obstetrical Dilemma

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Article Info

Received Date: 30.05.2024
Revision Date : 15.06.2024
Accepted Date: 23.06.2024

Keywords:
Cervical insufficiency, Cervical cerclage, early pregnancy loss, Autoimmune disorders, Thrombotic events, Placental inflammation

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Abstract

Introductıon: This retrospective study evaluated women in whom transvaginal cervical cerclage (TCC) was performed in a previous pregnancy but delivered without cervical intervention in the most recent pregnancy. The primary aim was to underline the importance of etiology based management protocols on favorable pregnancy outcomes in patients with a history of TCC.

Methods: We retrospectively evaluated 34 patients with at least one failed TCC for the treatment of cervical insufficiency (CI) but who gave birth without TCC in their most recent pregnancies.

Results: All patients were evaluated preconceptionally and examined for maternal risk factors. At least one risk factor was present in all cases. The autoimmune antibody positivity rate was 41.2%. Twelve patients had Hashimoto thyroiditis, two had systemic lupus erythematosus, two had pernicious anemia, and two had anti-phospholipid antibody syndrome. 32 had homozygous or heterozygous methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms, while 11 were homozygous or heterozygous for factor 5 Leiden or prothrombin-20210A gene mutations.

Conclusion: The elimination and management of risk factors for cervical ripening and dilatation are important for preventing unnecessary cervical interventions.

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Introduction

Cervical insufficiency (CI) is defined as painless cervical dilatation leading to recurrent second-trimester pregnancy losses.[1] Congenital and acquired risk factors that increase the risk of CI include the following: 1) genetic disorders leading to impaired collagen synthesis (e.g., Ehler-Danlos syndrome); 2) congenital uterine anomalies; 3) cervical trauma during labor or delivery; 4) cervical injury due to some gynecologic procedures (e.g., uterine evacuation, treatment of cervical lesions).[1,2] The preconceptional diagnosis of CI is often complicated since it is mainly based on a patient's past obstetric history, pelvic examination, and "Hegar cervical dilator test" (passage of number 8 Hegar dilator through the cervical ostium without resistance) with some limitations.[2,3] On the other hand, transvaginal ultrasonography (TVUSG) and/or a pelvic examination together with cervicovaginal fetal fibronectin measurement can be used as ancillary diagnostic methods to examine cervical length during pregnancy.[2,4,5] Cervical cerclage, vaginal pessary, and progesterone supplements are the main management options for CI.[6,7] However, all interventions are under debate.[2,6] Transvaginal cervical cerclage (TCC) is one of the most popular treatment options for CI. There are two main techniques for TCC: the McDonald procedure and the Shirodkar procedure.[8] Transabdominal cervical cerclage methods may also be performed in complicated cases, especially for patients with previous TCC failure.[9] The critical issue is differentiating real CI from untimely cervical ripening and dilatation due to various etiological reasons. For example, it was reported that vaginal and systemic infections, hereditary thrombophilia, some metabolic disorders, methylene tetrahydrofolate reductase (MTHFR) gene polymorphisms, autoimmune disorders, and chronic inflammatory diseases are associated with early pregnancy loss, repeated miscarriage, and preterm delivery.[10-13] Thus, placental inflammation of infectious, toxic, metabolic and immunologic reasons seems to be the main cause of untimely uterine contractions and cervical ripening/dilatation that result in CI-like pregnancy losses. In such cases, preventing metabolic and immunological placental inflammation together with disease- or disorder-specific treatments are essential to satisfactory pregnancy outcomes. The prevention and management of metabolic and immunological inflammatory processes using anti-inflammatory plus anti-thrombotic agents such as low-molecular-weight heparin (LMWH), oral corticosteroids, and low-dose acetylsalicylic acid (ASA) are crucial for achieving better perinatal outcomes.[14,15] Herein, we retrospectively evaluated women in whom TCC was performed in their previous pregnancies but who gave birth without any cervical intervention in their most recent pregnancy.

Material and Methods

Women in whom TCC was performed in one or more previous pregnancies but who did not require cervical intervention in the most recent pregnancy were included in this study. We retrospectively evaluated 34 patients who experienced at least one failed TCC for the treatment of CI and/or recurrent pregnancy loss but gave birth without TCC in the most recent pregnancy (2007–2017). The required data were extracted from the Hacettepe University Hospital database.

All patients were evaluated preconceptionally and screened for autoimmune disorders, autoimmune antibody positivity, hereditary thrombophilia, metabolic disorders (hyperhomocysteinemia, folate deficiency), MTHFR polymorphisms, chronic inflammatory diseases, genital tract inflammation, coagulation disorders, and anemia. Patients were allowed to get pregnant after the detection and management of their medical problems that were the risk factors for early pregnancy losses and/or recurrent miscarriages.

The patients were registered in a special antenatal care program during their pregnancies, and necessary laboratory tests such as complete blood count, clinical urine test, blood sugar, liver function tests, C-reactive protein, complement components 3 and 4, activated protein-C resistance, anti-thrombin III activity, protein-S activity, lupus anticoagulant, and von Willebrand factor antigen were performed during the course of follow-up. LMWH (enoxaparin 2000 Anti-Xa IU/0.2 mL), oral prednisone (methylprednisolone 4 mg), and aspirin (ASA 100 mg) were added to the treatment protocol in necessary cases as soon as a pregnancy was confirmed. Pregnancy follow-up consisted of serial ultrasonography to evaluate cervical changes, aneuploidy screening (combined or triple test), fetal anatomy scanning at the 20–24th gestational week, oral glucose challenge test, and nonstress test weekly (after the 28th gestational week). All medications were stopped 3 days before delivery.

The median (minimum-maximum value) patient age; gravida; number of previously failed TCC procedures; serum folate, vitamin B12, and homocysteine levels just before conception; gestational weeks at birth; infant birthweight; and 5-minute APGAR scores were used as the data that were not normally distributed. We also recorded the autoimmune antibody positivity types, related diseases/syndromes, MTHFR polymorphism type, hereditary thrombophilia type, maternal diseases, obstetrical complications such as early pregnancy bleeding, intrauterine growth retardation (IUGR), hypertensive states of pregnancy (e.g., preeclampsia, gestational hypertension), preterm labor and delivery, and ablatio placentae in affected cases.

Statistical analyses were performed by Statistical Package for the Social Sciences (SPSS® version 22.0; IBM, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to evaluate the data distribution. Normally distributed data are shown as mean and standard deviation, while non-parametric data are shown as median (minimum-maximum values). Written informed consent was obtained from all patients and the study was approved by the institutional ethics committee of Hacettepe University (GO 18/159).

Results

All pregnancies were singletons involving live babies. However, there were 16 (47%) late preterm births (34 weeks to 36 weeks, 4 days). The median patient age was 33 years (24–41 years), median gravida was 5 (4–14), median parity was 1 (0–3), median number of miscarriages was 3 (1–13), median number of living children was 1 (0–2), median number of previous failed TCC procedures was 1 (1–2), median gestational week at birth was 37 (34–39), median infant birthweight was 2800 g (2200–3850 g) and the median 5-minute APGAR score was 10 (7–10). The median serum levels of folate, vitamin B12, and homocysteine just before conception were 12 nmol/L (6.1–25.2 nmol/L), 285 ng/L (123–495 ng/mL), and 7.4 µmol/L (3.7–12.7 µmol/L), respectively. Table 1 shows the median and minimum-maximum values for the previously mentioned variables.

Table 1: The median and minimum-maximum values for variables examined in patients with a history of cervical insufficiency.

Variable	Median	Minimum-Maximum
Maternal age, years	33	24-41
Gravida	5	4-14
Parity	1	0-2
Abortion	3	1-13
Living child	1	0-2
Number of previous failed TCC procedures	1	1-2
–Gestational week at birth	37	34-39
Birthweight of the infant, g	2800	2200-3850
APGAR, 5-minute	10	7-10
Serum folate level, nmol/L	12	6.1-25.2
Serum vitamin B12 level, ng/L	285	123-495
Serum homocysteine level, µmol/L	7.4	3.7-12.7

TCC, transvaginal cervical cerclage

We have found at least one risk factor for early pregnancy loss and cervical dilatation in all cases. The autoimmune antibody positivity rate (≥1 antibodies) was 41.2% (14/34 cases) in our series. Table 2 shows the data related to the distribution of autoimmune antibodies. Antinuclear antibody (ANA) and anti-thyroid peroxidase (anti-TPO) antibody were the most frequent antibodies observed in this study (41.2% and 35.3% of cases, respectively). On the other hand, 12 patients (35.3%) had Hashimoto

thyroiditis, two (5.9%) had systemic lupus erythematosus, two (5.9%) had pernicious anemia, and two (5.9%) had anti-phospholipid antibody syndrome.

Table 2: Percentage of positive autoantibody results in patients with a history of cervical insufficiency.

Autoantibody	Percentage
ANA	14/34 (41.2%)
Anti-TPO	12/34 (35.3%)
Anti-TG	2/34 (5.9%)
aCL IgM-IgG	2/34 (5.9%)
APA	2/34 (5.9%)
Anti-dsDNA	2/34 (5.9%)

ANA, antinuclear antibody; anti-TPO, anti-thyroid peroxidase antibody; anti-TG, antithyroglobulin antibody; aCL, anticardiolipin antibody; APA, anti-parietal cell antibody; anti-dsDNA, anti-double-stranded DNA antibody

Of the 34 patients, 32 (94.1%) had one or more homo- or heterozygous MTHFR gene polymorphisms. Table 3 shows the distribution of the MTHFR polymorphisms. Eleven patients (32.4%) were homo- or heterozygous for factor 5 Leiden or prothrombin-20210A gene mutations (Table 3). Five patients (14.7%) had factor 5 Leiden heterozygous and two (3.8%) had factor 5 Leiden homozygous mutations, while one (2.9%) had a prothrombin 20210A homozygous mutation and three (8.8%) had a prothrombin 20210A heterozygous mutation.

Table 3: Percentage of mutations in patients with a history of cervical insufficiency.

Variable	Percentage
MTHFR C677T heterozygous	17/34 (50%)
MTHFR C677T homozygous	2/34 (5.9%)
MTHFR A1298C heterozygous	17/34 (50%)
MTHFR A1298C homozygous	3/34 (8.8%)
MTHFR compound heterozygous	9/34 (26.5%)
Factor 5 Leiden heterozygous	5/34 (14.7%)
Factor 5 Leiden homozygous	2/34 (5.9%)
Prothrombin 20210 A heterozygous	3/34 (8.8%)
Prothrombin 20210 A homozygous	1/34 (2.9%)

MTHFR, methylene tetrahydrofolate reductase

Discussion

TCC is a treatment option for CI. There are alternative surgical procedures in which various sutures, wires, or synthetic materials are used to strengthen the cervix. There are two main techniques for TCC: the McDonald procedure and the Shirodkar procedure.[8] TCC is considered beneficial for singleton pregnancies in women with a prior CI history and short cervical length (≤25 mm on TVUSG).[16] It can be applied electively (at 12–14 weeks of gestation based on the previous CI history), ultrasound-indicated (cervical length ≤ 25 mm on TVUSG at 16–23 weeks of gestation in patients with a previous CI history), or based on pelvic examination findings.[17] However, there are contraindications for TCC such as a fetal anomaly incompatible with life, maternal/fetal infections, active bleeding, active preterm labor, preterm premature rupture of the membranes (PPROM), or

fetal demise.[2] The role of TCC in multiple pregnancies and in patients with a short cervical length in the absence of previous CI is controversial.[2] The TCC procedure may feature complications such as PPROM, intraamniotic infection, suture migration, and bleeding.[18] However, a recent meta-analysis reported favorable outcomes for emergency TCC in singleton and twin pregnancies.[19] Mentioned study includes the data of 3239 women and indicated an overall survival rate of 74% with similar findings for both singleton and twin pregnancies. The main findings of the study revealed that emergency TCC was superior to expectant management.[19] Thus, TCC seems to be an effective treatment modality in appropriately selected cases.

We believe that a wide spectrum of etiological factors causes CI. Müllerian canal abnormalities and some other related anomalies, connective tissue disorders (organ-specific and/or systemic), sequelae due to infectious problems of the cervix and genital tract, cervical injury due to gynecological operations, and birth trauma are the most commonly blamed etiological factors.[20] The general trend in defining CI is to assert an association between CI and a mechanical defect.[1,2]

On the other hand, CI might be an instant condition of the developmental pathobiological events over the course of infectious, toxic, metabolic, and immunological inflammation (e.g., autoimmune antibody positivity and related disorders, metabolic disorders such as hyperhomocysteinemia, MTHFR polymorphisms, hereditary thrombophilia, and chronic inflammatory diseases) of the maternal–fetal interface causing untimely uterine contractions.[14,15] As reported previously, the amniotic fluid levels of proinflammatory cytokines such as interleukin 1α (IL-1α), IL-1ß, IL-6, and tumor necrosis factor-α are higher in CI patients.[21]

Autoimmune antibody positivity and related diseases, chronic inflammatory diseases, metabolic disorders (hyperhomocysteinemia, folate deficiency), enzyme pathway disorders (MTHFR polymorphisms), and hereditary thrombophilia are all associated with obstetrical complications such as miscarriage and preterm labor.[12,13] Toxic metabolites (e.g., hyperhomocysteinemia), autoimmune antibodies, cell degradation products, and inflammatory cytokines are most likely responsible for the injury of the vascular structures of the placenta and the cellular components of the maternal–fetal interface, resulting in placental inflammation and untimely uterine contractions that simulate CI-like symptoms.[14,22,23] It is critical to differentiate between cervical changes and CI without using unnecessary interventions. In this study, 41.2% (14/34), 94.1% (32/34), and 32.3% (11/34) of patients had autoimmune antibody positivity (≥1 antibodies), reduced MTHFR activity, hyperhomocysteinemia ,and hereditary thrombophilia, respectively. We demonstrated at least one etiological (metabolic and/or immunological) risk factor for thrombotic events and maternal–fetal interface inflammation in our patients. However, there were 16 (47%) preterm deliveries (all late preterm), most likely due to underlying medical pathologies despite intensive medical care. Miscarriage, preeclampsia, eclampsia, or placental abruption were not observed in any of our patients.

LMWH is reportedly beneficial in the management of various obstetrical complications such as recurrent miscarriage, IUGR, preterm labor, PPROM, and preeclampsia.[10,12,22] LMWH has antithrombotic and anti-inflammatory effects.[15,22] We have used LMWH together with ASA (and low-dose corticosteroids in necessary cases) to prevent and overcome the inflammatory and thrombotic events involved in autoimmune disorders, MTHFR polymorphisms, and hereditary thrombophilia. All of our patients who had experienced failed TCC in their previous pregnancies delivered their most recent infants without any cervical intervention. Our results demonstrate the importance of eliminating risk factors for untimely uterine contractions and avoiding unnecessary cervical operations.

It is hypothesized that inflammation may have a prominent role in CI as it has in preterm birth.[10] The coagulation cascade and thrombus formation are associated with inflammatory processes.[10] The coagulation cascade may reportedly be activated in patients with preterm labor and PPROM.[24] Furthermore, hereditary thrombophilia and MTHFR polymorphisms are also reportedly associated with untimely contractions and CI.[15] These findings are consistent with the presence of high rates of thrombophilia and MTHFR polymorphisms in our study. It was recently reported that heparin and heparin-related derivatives also have an anti-inflammatory effect.[15] Additionally, LMWH influences matrix metalloproteinases, tissue inhibitors, cadherin-E, heparin-binding epidermal growth factor, and insulin-like growth factor.[25-28]

As a result, the appropriate management of thrombotic events using low-dose LMWH and low-dose ASA may prevent inflammatory process activation.[14,15]

Although hyperhomocysteinemia is reportedly associated with various adverse pregnancy outcomes such as pregnancy loss, neural tube defects, chromosomal aneuploidies, fetal cardiac defects, preeclampsia, abruptio placentae, and IUGR,[29,30] its effect on CI and preterm birth is unclear.[12] Recent meta-analyses have also revealed that MTHFR C677T polymorphism and maternal vitamin B12 concentrations may play a pivotal role in preterm birth.[12,13] In this series, the appropriate management of patients with a methionine-restricted diet, low-dose ASA, folate–vitamin B supplementation, and low-dose LMWH seem to be the major factors in successful pregnancy outcomes.

The relationship between autoimmune antibodies and pregnancy loss has been investigated by many researchers.[31-33] The high impaired implantation and pregnancy loss rates in women with autoimmune antibodies may be due to injury to the syncytiotrophoblasts, endovascular trophoblasts covering the tips of the spiral arteries, endothelial cells of the spiral veins, and superficial/glandular epithelial cells of the decidua (intervillous space of the placenta) induced by autoantibody inflammatory processes and the entrance of cell degradants of these tissues into the maternal circulation. These biological events result in impaired implantation and disturbed fetal perfusion.[14] The high prevalence of autoimmune antibodies in our study group was consistent with this theory; thus, low-dose methylprednisolone seems to be a good option for modulating the immune response in these patients.

All 34 patients in our study group delivered healthy babies. However, there was a high rate of preterm birth (47%), but all were late preterm deliveries. These results were more likely due to the clinical characteristic of the patients in our study (high-risk pregnancies with poor obstetrical histories). The thorough evaluation of the underlying conditions and appropriate management of the problems are important for success in cases of CI.

The main strengths of the present study were the comprehensive evaluation of the risk factors for pregnancy losses and the unique hypothesis. However, relatively number of cases, single center experience and retrospective design were the main limitations.

In conclusion, the careful evaluation and accurate diagnosis of CI are key issues that contribute to the successful medical management of early pregnancy problems. The elimination and management of risk factors for cervical ripening and dilatation are also important for avoiding unnecessary cervical interventions.

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