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Management of Pregnancy After Conization and Radical Trachelectomy

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1. Introduction

Cervical intraepithelial neoplasia (CIN) is commonly diagnosed in women of child-bearing age. (Castle et al., 2009) The excisional treatments of CIN include cold-knife conization, laser conization, loop electrosurgical excision procedure (LEEP), and large loop excision of the transformation zone (LLETZ). CIN is also treated by ablative procedures such as laser vaporization and cryotherapy. Recently, human papilloma virus (HPV) has led to the understanding of pathogenesis and management of cervical diseases. (Moscicki et al., 2004) The screening and subsequent treatment of CIN significantly reduces the risk of invasive cervical cancer, but the impact of excisional cervical treatment on subsequent pregnancy outcome must be evaluated.

Many women with a diagnosis of cervical cancer are child-bearing population, younger than 40 years. Fertility-sparing radical vaginal or abdominal trachelectomy is a safe and feasible procedure for the treatment of patients with early stage cervical cancer. (Plante et al., 2005; Roman, 2005; Hertel et al., 2006) The disease-free survival rates and overall survival rates of radical trachelectomy is comparable to those of radical hysterectomy (Rob et al., 2011) The proper waiting period after radical trachelectomy and before conception varies in the literature. Roy and Plante (Roy and Plante, 1998) recommend a 6 month follow-up, while Shlaerth *et al.* (Shlaerth et al., 2003) describe a period of 1 year. The issue of having a pregnancy and fetal viability must be addressed following radical trachelectomy.

This chapter will outline concerns and management options of pregnancy after cervical surgeries with conization and radical trachelectomy.

2. Pregnancy after conization and radical trachelectomy

The important issue following cervical surgery in child-bearing age is the fertility and pregnancy outcome. Excisional cervical surgery may contribute to decreased mechanical support of cervix, and increased susceptibility to ascending infection resulting from the loss of cervical mucus. Cervical surgery may alter reproductive function by cervical shortening, impairment of immunologic defence, and alteration of cervicovaginal bacterial flora, and thus expose those women to high risk of preterm birth. (Svare et al., 1992)

Early studies on the impact of conization on pregnancy are hindered by small study population, inadequately powered study design, and neglect of potential confounders such as socioeconomic status and previous preterm delivery. (Sadler et al., 2007) Recent well-designed studies with large sample sizes conclude that conization increases the risk of preterm birth and perinatal morbidities (Jakobsson et al., 2007; Sjoborg et al., 2007; Nohr et al., 2007) Jakobsson *et al.* (Jakobsson et al., 2007) found a significant increase of very preterm birth (28-31 weeks) and extremely preterm birth (< 28 weeks) following conization. [relative risk (RR) 1.99, 95% confidence interval (CI) 1.81-2.20; RR 2.86, 95% CI 1.30-2.32, respectively]. The study also showed a significant association of low birth weight (LBW) and conization. [RR 2.06, 95% CI 1.83-2.31] Other two meta-analyses also supported that excisional cervical treatments in CIN subsequently increase risk of preterm birth, and preterm premature rupture of membrane (PPROM) (Crane, 2003) Some studies reported the association between cone depth and higher risk of preterm birth, but the limited and conflicting data failed to demonstrate an accurate results. (Salder et al., 2004; Samson et al., 2005)

Because cervix is amputated below the cervical isthmus in radical trachelectomy, obstetric morbidity is higher than those of conization. The risk of preterm birth after radical trachelectomy increases two-fold than the general population. (Jolley et al., 2007; Martin et al., 2008) Boss *et al.* (Boss et al., 2005) reviewed obstetric outcomes of radical trachelectomy in the literature. A total of 335 cases of radical trachelectomy were analyzed. 153/355 (43%) patients attempted to become pregnant. About 30% of these women did not conceive. The causes of their infertility include anovulation, cervical factor such as cervical stenosis, and idiopathic factor. Other 70% of these women subsequently became pregnant. Of these, first and second trimester losses occurred in 47/161 (29%) pregnancies. 21% ended in the third trimester before 36 weeks of gestation. The causes of their preterm birth were attributed to cervical incompetence, ascending infection, and PPRM. (Boss et al., 2005)

2.1 Management options

It is clear that cervical surgeries attribute to increased risk of preterm birth (Kyrgiou et al., 2006; Plante et al., 2005; Samson et al., 2005; Sadler et al., 2004), but no specific rationale of pregnancy management after cervical surgeries exist. The management strategies for pregnancy after cervical surgeries should refer to those for women with short cervix who are at high risk for preterm birth.

2.1.1 Transvaginal ultrasound

It is well known that women with a short cervix in the mid-trimester have a higher risk for preterm birth. (Iam et al., 1996; To et al., 2001) Cervical length, as determined by vaginal sonography, has been shown to be sensitive, and reproducible than digital examination or transabdominal ultrasonography in predicting the risk of preterm birth. (Berghella and Bega, 2008) Cervical length is measured from the internal os to the external os. When cervical funneling is visualized, cervical length is measurable from the functional internal os to the external os. Some researchers reported the effect of conization on subsequent cervical length. Gentry et al. (Gentry et al., 2000) found no difference in cervical length between before and after LEEP. Berghella et al. (Berghella et al., 2004) demonstrated that only 28% of patients showed cervical shortening following conization.

Between 14 and 22 weeks of gestation, the median cervical length is 35-40 mm. From 22 to 32 weeks, the 50th percentile for length is 35 mm, and the 10th percentile is 25 mm. (Iam, 2004) A cervical length cutoff level of < 25 mm was associated with a sensitivity of 69%, a specificity of 80%, and a positive predictive value of 55%. (Owen et al., 2001) The <25 mm cutoff level before 20 weeks of gestation predicted preterm birth at <35 weeks gestation [likelihood ratio (LR) 4.31, 95% CI 30.8-6.01, n =2258] (Crane and Hutchens, 2008) Independent of baseline cervical length, dynamic cervical change (ie, millimeters per week) was significantly associated with higher risk for preterm birth. (Owen et al., 2001)

Funneling is defined as the opening of the internal os of cervix. The significance of funneling on pregnancy after conization has not been reported. Compared with a short cervix (<25mm) alone, The combination of short cervix (<25mm) and funneling increased the sensitivity of predicting preterm delivery from 61% to 74 %. (Berghella et al., 1999) However, the normal cervical length more than 25 mm plus funneling does not increase the prediction of preterm birth. (Berghella and Roman, 2005)

2.1.2 Nonsonographic methods

Fetal fibronectin (FFN) is a widely accepted predictor of preterm birth. The presence of FFN in cervicovaginal secretions is significantly associated with preterm birth. (Peaceman et al., 1997) Women with a positive FFN and a short cervix (<22mm) had a significantly shorter latency to delivery. (Rizzo et al., 1996)

The uterine electromyography, which detects the electrical activity of myometrium, may be used to diagnose preterm labor. (Lucovnik et al., 2011)

2.1.3 Infection

The presence of bacterial vaginosis increases the risk of preterm delivery, (Leitich and Kiss, 2007) but no data suggests the correlation between vaginal infection and pregnancy outcome after conization. Bacterial vaginosis is further attributable to preterm birth in women with short cervix (<25mm). (Rust et al., 2005) There is no study that reveals whether other infection such as Chlamydia, or gonorrhea contributes to preterm delivery and cervical length.

The lack of mechanical support of cervical mucus after radical trachelectomy may cause cervical incompetence and ascending infection. Shepherd et al (Shepherd et al., 2001) suggested the use of prophylactic antibiotics between 14 and 16 weeks of gestation following radical trachelectomy. Saling operation (complete cervicovaginal occlusion) which should be performed between 12 and 14 weeks of gestation may be the preventive strategy for reducing the risk of ascending infection and chorioamnionitis (Shlaerth et al., 2003; Gadducci et al., 2001)

2.1.4 Progesterone

Progesterone appears to prevent cervical ripening, (Word et al., 2007; Yellon et al., 2009) and anti-inflammatory properties. (Elovitz et al., 2008; Elovitz et al., 2005) The precise mechanisms of blockade of progesterone action against cervical changes are poorly understood.

Fonesca et al (Fonesca et al, 2007) specifically evaluated the impact of progesterone in women with a short cervix (<15mm) identified on transvaginal ultrasonography. Women were allocated to receive either 200 mg nightly intravaginal progesterone or placebo from 24 to 33 weeks of gestation. A total of 250 women were enrolled. Women administered progesterone less likely to have a spontaneous delivery before 34 weeks of gestation than placebo group. (19.2 % vs 34.4 %; relative risk [RR] = 0.56; 95% confidence interval [CI] = 0.36-0.86). There was a significant reduction in the risk of neonatal sepsis in women administered progesterone (274 infants, RR = 0.28, 95% CI 0.08 - 0.97). (Fonesca et al, 2007) A systematic meta-analysis by Dodd et al (Dodd et al., 2008) also demonstrated that vaginal progesterone significantly reduced preterm birth before 34 weeks of gestation in women with short cervix. Facchinetti et al (Facchinetti et al, 2007) reported a randomized clinical trial involving symptomatic women with preterm labor and intact membranes at 25- 34 weeks of gestation. For women administered intramuscular 341mg of 17-alpha-hydroxyprogesterone caproate (17P) twice a week until 36 weeks, when compared with observation group, there was a significant reduction in the risk of spontaneous delivery. (odds ratio [OR] = 0.15, 95% CI = 0.04-0.58) The subgroup analysis involving women with short cervix less than 25 mm at enrolment showed more significant difference between two groups. Women administered 17P had less cervical shortening at days 21 (1.38 ± 1.31 mm) compared to women who had not received 17P (day 21, 4.88 ± 3.14 mm, $p = 0.0001$) (Facchinetti et al, 2007) Future studies are needed to enlighten the association between prophylactic progesterone and pregnancy outcome after conization and radical trachelectomy.

2.1.5 Cerclage

There is considerable debate as to whether cerclage is efficient in pregnant women after conization. The exact mechanism of preterm birth after conization is unclear, and so the mechanism of cervical shortening following conization is unclear.

Royal College of Obstetrics and Gynecology (RCOG, 1993) performed a trial of history-indicated cerclage (prophylactic cerclage). A total of 1292 women were enrolled and 138 women with a history of conization or cervical amputation were included among them. The subgroup analysis of those 138 women revealed no significant reduction in preterm birth or improvement in neonatal outcome. However, there was a significant reduction in delivery less than 32 weeks of gestation in cerclage group with 3 or more second-trimester deliveries, and no histories of cervical surgeries. (RCOG, 1993) Other researchers also reported that a prophylactic cerclage was not beneficial for preventing preterm birth in women with prior conization. (Nam et al., 2010; Shin et al., 2010)

The transvaginal sonography of cervix enables obstetricians to detect cervical shortening or funneling in asymptomatic women. Ultrasound-indicated cerclage based on a short cervix has been proposed as a solution for preventing cervical incompetence and preterm birth. A meta-analysis (Berghella et al., 2005) including four randomized trials of ultrasound-indicated cerclage found that cerclage is beneficial in women with short cervix less than 25 mm before 24 weeks of gestation and index preterm birth. In these women, a relative risk reduction of preterm birth at < 35 weeks of gestation was enhanced. (RR, 0.61; 95% ci, 0.4-0.9) In the subgroup analysis, there was no beneficial effect of cerclage on women with prior

conization. (Berghella et al., 2005) A short cervix in women with prior cervical surgery are predictive of preterm delivery, but the attributable risk is lower than in women with index preterm birth. More recently, the Vaginal Ultrasound Trial Consortium (Owen J, 2008) demonstrated that the effect of cerclage for preventing preterm birth and prolonging gestation was identified only in women with a cervical length of less than 15 mm (RR 0.23, 95% CI 0.08 - 0.66). Zeisler et al (Zeisler et al., 1997) specifically evaluated the cerclage in women with prior conization, and concluded that prophylactic cerclage is not beneficial for preventing preterm birth. The combination of present cervical length, and prior histories of preterm birth and cervical surgeries is a pronounced risk factor of preterm delivery. Once the cervix is shortened, it is difficult to place satisfactory McDonald cerclage. Surgeons should avoid bladder or bowel injury during ultrasound-indicated cerclage.

Physical-examination based cerclage is placed in women with significant cervical dilatation (>1cm) and bulging membrane. It is referred to as a 'rescue' or 'emergency' cerclage, as it requires challenging skill to avoid a rupture of membrane during cerclage. Daskalakis et al. (Daskalakis et al., 2006) concluded that physical-examination cerclage reduced preterm delivery before 32 weeks of gestation and improved neonatal survival rate compared to bed rest group. Other researchers (Cockwell and Smith, 2005) also demonstrated that physical-examination cerclage prolonged pregnancy and improved neonatal outcome in women with dilated cervix and bulging membrane. Lee et al (Lee et al., 2004) reported that elevated interleukin-6 in amniotic fluid was adversely associated with interval between physical-examination cerclage and delivery. Weiner et al. (Weiner et al., 2005) found intrauterine inflammatory responses and decidual hemorrhage were correlated with adverse pregnancy outcome after physical-examination cerclage. A physical-examination cerclage could be considered in women with dilated cervix and bulging membrane after conization. In these women, the evaluation of subclinical inflammation may predict the prognosis of pregnancy.

Transabdominal cervico-isthmic cerclage (TCIC) is beneficial in women with cervix that is extremely short, congenital anomaly or markedly scarred due to previous vaginal cerclage. TCIC seems to be effective in women who are inadequate for vaginal cerclage. (Topping et al., 1995; Turnquest et al., 1999) The unremitting complication during pregnancy following radical trachelectomy is late abortion and preterm delivery as cervix has markedly modified anatomy after radical trachelectomy. The prophylactic concomitant cerclage is usually placed at the time of radical trachelectomy. (Plante et al., 2005; Roman, 2005) When the cerclage placed too deeply within the cervical stroma, it can be expelled spontaneously. The success of pregnancy may depend on a stable maintenance of cerclage. (Plante et al., 2005) Transabdominal cervico-isthmic cerclage is an appreciable option for the pregnant women after radical trachelectomy because of lack of sufficient cervical tissue for vaginal cerclage. (Lee et al., 2007)

2.1.6 Multiple pregnancies

Preterm delivery in twin pregnancies is 5-10 times more frequent than that in singleton pregnancy. (Fuchs et al., 2004) There is no clear best cervical length for the prediction of preterm birth in multiple pregnancies. Nevertheless, the rate of delivery was inversely associated with cervical length in twin pregnancies, being 66% for 10 mm, 24% for 20 mm, 12% for 25 mm, and < 1% for 40 mm. (To et al, 2006).

Current evidence does not support prophylactic administration of progesterone in multiple pregnancies. Additional studies are needed to confirm the effect of progesterone supplementation in twin pregnancies.

There is no data that prophylactic cerclage should be performed in multiple pregnancies. Recent prospective non-randomized trial of prophylactic cerclage in asymptomatic twin pregnancies reported that cerclage is not beneficial. (Eskandar et al., 2007) Twin pregnancies following radical trachelectomy are at more increased risk for preterm birth compared to singleton pregnancies. (Plante et al., 2005) Lee et al (Lee et al., 2007) reported TCIC after radical trachelectomy in twin pregnancy improved the pregnancy outcome. Cerclage in twin pregnancy is effective in certain circumstances.

3. Conclusion

CIN is relatively common in women with child-bearing age. Several studies have reported that women undergoing conization are at increased risk for preterm delivery, a low birthweight neonate, and premature rupture of membrane. Recently, the conservative treatment of early cervical cancer to preserve fertility has improved. A cervix changes drastically after radical trachelectomy. In these women after conization or radical trachelectomy, obstetricians should consider the possible adverse effects on future pregnancies.

As noted earlier, there is no established rationale for the pregnancy management after conization and radical trachelectomy. There are several management options for preventing preterm birth in these women but none has been prove more effective than any other strategies: Transvaginal sonography is a sensitive and reproducible method to detect short cervix. The administration of progesterone is thought to have beneficial effect on prolonging pregnancy. History-indicated cerclage in women with previous conization seems to be inefficient in preventing preterm birth. Ultrasound-indicated cerclage could be beneficial in women with short cervix and a prior preterm birth history. Physical-examination cerclage could prevent preterm birth in women with dilated cervix and bulging membrane after cervical surgeries. TCIC is an acceptable option for pregnant women after radical trachelectomy and women with severely scarred cervix. The combination of above mentioned options and other adjunctive strategies such as detection of infection or inflammation, and antibiotics, etc. could reduce the rate of preterm birth in pregnancy after conization or radical trachelectomy.

Further studies are needed to assess an accurate measurement of cone tissue, and explore the relation between the amount of cone tissue and risk of deleterious pregnancy outcome.

Randomized clinical trials are needed to confirm the role of cerclage, and progesterone, and adjunctive therapies such as antibiotics, and in pregnant women with prior cervical surgeries.

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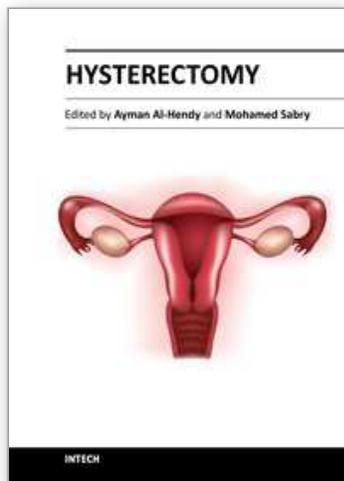
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