Cervical conization and the risk of preterm delivery

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The current body of literature concerning cervical conization and its effect on subsequent pregnancy outcome is conflicting. Depending on the type of conization procedure that is examined and the quality of the control group, the results and conclusions vary widely. Because treatment for cervical intraepithelial neoplasia is commonplace among women of reproductive age, it is imperative that practitioners have an understanding of the issues surrounding the treatment. Therefore, this review will summarize the published literature that addresses excisional procedures of the uterine cervix and the risk of preterm delivery in subsequent pregnancies and provide reasonable treatment recommendations for women with cervical abnormalities and a desire for future fertility.

Key words: cervical dysplasia, conization, pregnancy outcome, preterm birth

Since inception, screening programs that use Papanicolaou smear tests have decreased the incidence of cervical cancer in the United States by >50%.[1] The unprecedented success of this program hinges not only on the sensitivity of the Papanicolaou smear test, but also on the ability to eliminate successfully the precancerous lesions that are detected by the screening test. Cervical intraepithelial neoplasia (CIN) is encountered most commonly among women of reproductive age; a peak incidence occurs among women in their twenties.[2] Because of the 5-12% chance of progression to squamous cell cancer, management guidelines recommend aggressive treatment for women with moderate-to-severe dysplasia.[3] Because many women in this age group have not yet completed childbearing at the time of diagnosis, treatment for these cervical abnormalities has potentially significant reproductive consequences. Many reports that have investigated this issue have been uncontrolled observational studies with small sample sizes, which makes them difficult to interpret.[4-11] Therefore, this review will summarize the published literature regarding the effects of cervical conization on the risk of preterm delivery (PTD) in future pregnancies and provide reasonable treatment recommendations for women with cervical dysplasia.

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Methods

English-language studies in PubMed and Medline were identified by the search terms *conization, preterm delivery, cervical dysplasia, pregnancy outcome, preterm birth,* and *cervical ablation*. The references of the resulting articles were then searched manually for further pertinent publications. All study types were considered for inclusion, provided the subject matter was pertinent to the focus of this review.

Treatment modalities for CIN

Historically, the treatment of choice for moderate-to-severe CIN was the cold knife cone (CKC). Its application predated modern colposcopic practice and the widespread availability of electrocautery and laser technology. However, its modern applicability has been limited by high cost, significant intraoperative and postoperative bleeding, substantial perioperative infectious risk, a high level of technical difficulty, and a recognized association with postprocedure cervical stenosis.[12-14] As a result of these limitations, alternative excisional and ablative procedures were developed that include the laser conization, the loop electrosurgical excisional procedure (LEEP), and various methods of ablation. The laser conization had the advantage of being performed under local anesthesia with less associated bleeding and more accurate tailoring of cone size. However, the thermal damage that was inflicted on the tissue specimen potentially could make pathologic evaluation of the margins impossible. With the advent of widely available electrocautery, the LEEP gradually replaced the CKC as the treatment of choice for CIN. Several studies have documented its advantages over CKC in that it is less expensive, technically easier, less painful, associated with less hemorrhage, and can be performed in an office setting with similar efficacy.[15-19] Additionally, in contrast to the laser cone, the tissue specimen is more adequate for pathologic evaluation of the surgical margins.[16]

Ablative techniques that are used to treat cervical dysplasia include laser ablation, cryotherapy, electrofulguration, and cold coagulation. Although these ablative techniques provide no tissue specimen for pathologic evaluation and can be applied only to a certain subset of patients, they appear to have similar efficacy with respect to the elimination of CIN and reduction of the risk of progression to cancer.[12-14,20-23] A Cochrane Review about the surgical treatment of CIN reviewed 28 trials that compared the efficacy of both ablative and excisional treatment techniques and concluded that no method was more efficacious than any other.[13] Therefore, the selection of ablative techniques vs excisional techniques should be based on the severity of disease, the adequacy of the colposcopic examination, the histologic findings of the biopsy, the appropriate correspondence of the cytologic and histologic evidence, and the desire for future childbearing.

CKC

It was recognized as early as 1938 that conization may have a negative impact on future pregnancy, with higher incidences of PTD and other complications.[24] Early studies that investigated the association between CKC and obstetric complications were contradictory.[25-29] Since that time, significant data have been published that has solidified the increased obstetric risk after CKC. A retrospective analysis by Klaritsch et al[30] in 2006 evaluated the risk of PTD and obstetric complications in women with a history of cold knife conization of the cervix relative to the general obstetric population in Austria. The investigators reported PTD in 22.4% of 76 deliveries in the conization group compared with 6.6% of 29,711 deliveries in the general obstetric population (odds ratio [OR], 4.07; 95% confidence interval [CI], 2.22–7.10; $P < .001$). They further reported nearly an 8-fold increased risk of both preterm premature rupture of membranes (OR, 7.70; 95% CI, 3.87–14.21; $P < .001$) and cervical tears (OR, 7.53; 95% CI, 2.63–17.57; $P < .001$) but no significant increase in the risk of cesarean delivery, low birthweight, or duration of labor.

Because many confounding variables such as smoking, sexually transmitted diseases, maternal marital status, and socioeconomic status serve as important risk factors for both CIN and PTB, drawing conclusions from retrospective studies with the use of the general obstetric population as control subjects can be misleading. Kristensen et al[31] attempted to address this issue by including patients with deliveries before conization. The investigators divided the cohort of 14,223 Danish women into 4 groups: those who had their conization before first delivery, those who had it between their first and second deliveries, those who had it after 2 deliveries, and those with no history of conization. The 170 women with a history of CKC, regardless of timing of the procedure, experienced a higher incidence of PTD. Although this risk was higher in women who underwent conization before pregnancy, women who underwent CKC subsequent to both deliveries also had a slightly increased risk of PTD in the precedent pregnancies, when compared with the general population. The authors therefore concluded that CKC was associated with a higher rate of PTB, but that factors other than surgical intervention may contribute to the observed risk. To further elucidate this issue, El-Bastawissi et al[32] retrospectively compared women who had carcinoma in situ of the cervix who were not treated with conization with those women who received the prescribed therapy. Importantly, this study reported no increased risk of preterm birth or cesarean delivery in women with untreated carcinoma in situ over the general population. It did demonstrate, however, an increase in PTD and cesarean delivery among women with a history of conization (OR, 1.6; 95% CI, 1.2–2.0). Bruinsma et al[33] also attempted to clarify the relationship between cervical dysplasia and PTD by reporting on women who underwent treatment for the precancerous changes and women who remained untreated. In contrast to the study just discussed, these authors reported an increased risk among women with untreated cervical dysplasia, compared with the general population (standardized prevalence ratio, 1.5; 95% CI, 1.4–1.7), with an even higher risk among those women who underwent treatment (OR, 2.0; (95% CI, 1.8–2.3). However, once the authors controlled for confounding factors that included marital status, history of multiple induced abortions or miscarriages, maternal age, major maternal medical condition, and illicit drug use, neither group had an increased risk. Despite multiple attempts to clarify this issue, it remains unclear which factors play the greatest role in the risk of PTD and adverse obstetric outcomes in women with cervical dysplasia.

A search of the published literature revealed 2 metaanalyses that addressed obstetric outcome after cervical surgery (ie, CKC, LEEP, laser ablation, laser conization).[34,35] Both studies reported an increased risk of PTD (relative risk [RR], 2.59; 95% CI, 1.8–3.72; RR, 2.78; 95% CI, 1.72–4.51) and low birthweight (RR, 2.53; 95% CI, 1.19–5.36; RR, 2.86; 95% CI, 1.37–5.97) in patients with a history of CKC. The metaanalysis by Kyrgiou et al[34] also reported a significantly increased rate of cesarean delivery (RR, 3.17; 95% CI, 1.07–9.40). The report published by Arbyn et al[35] in 2008 evaluated the incidence of perinatal death, early PTD (<32-34 weeks of gestation), very early PTD (<28-30 weeks of gestation), and low birthweight (<2000 g) and reported that a history of CKC was associated with increased perinatal mortality rates, severe PTD, extreme PTD, and low birthweight. The results of studies that evaluated CKC and obstetric outcomes are summarized in Table 1.

Laser conization

Because of the growing concerns regarding CKC and technologic advances, laser conization became an increasingly popular alternative for the treatment of cervical dysplasia. Hagen and Skjeldestad[40] in 1993 were the first investigators to report an increased rate of PTD in patients who underwent laser conization. In this series of 56 women with a history of laser conization who delivered after 22 weeks gestation, the authors demonstrated a 38% rate of PTD among cases, compared with 6% in matched control subjects (OR, 9.0; 95% CI, 3.7–21.7). Other investigators have demonstrated conflicting results. Sadler et al[41] in 2004 reported an increased risk of preterm premature rupture of membranes among women who underwent laser conization with an adjusted RR of 2.7 (95% CI, 1.3–5.6) but failed to demonstrate an increase in spontaneous preterm deliveries (adjusted RR, 1.3; 95% CI, 0.8–2.2). Other studies found similar results including Sagot et al[42] who examined 71 pregnancies in 54 women before laser conization and compared them with 82 pregnancies after the procedure. The authors reported no significant difference in the rate of PTD (13.2% vs 8.5%) or premature rupture of membranes (1.9% vs 0%) before and after treatment but detected a reduced rate of vaginal term deliveries after conization (90% vs 73.6%;

TABLE 1
Cold knife conization and preterm delivery

Study	Study type	Patients, n	Control subjects	Preterm deliveries: Relative risk (95% CI)	Preterm deliveries: Odds ratio (95% CI)
Jones et al, 1979[26]	Retrospective	66	General population	3.4 (1.7–7.1)	
Moinian et al, 1982[36a]	Retrospective	414	Internal/precedent pregnancies	1.3 (0.4–4.4)	
Buller and Jones, 1982[37a]	Retrospective	61	Internal	NA	
Ludviksson and Sandstrom, 1982[29]	Retrospective	79	General population	NA	
Larsson et al, 1982[38]	Retrospective	197	Internal/precedent pregnancies	3.0 (1.7–5.3)	
Kuoppala and Saarikoski, 1986[39a]	Retrospective	77	General population	4.0 (0.5–35)	
Kristensen et al, 1993[31]	Retrospective	170	Internal + external		4.13 (2.53–6.75)
Klaritsch et al, 2006[30]	Retrospective	65	General population		4.1 (2.22–7.10)
Kyrgiou et al, 2006[34]	Metaanalysis	704	All	2.59 (1.80–3.72)	
Arbyn et al, 2008[35]	Metaanalysis	761	All	2.87(1.42–16.66)	

CI, confidence interval; *NA*, not available.

[a] No evidence of increased risk demonstrated in the study.

Bevis. Preterm delivery after cervical surgery. Am J Obstet Gynecol 2011.

P = .025). This study used patients as their own historic control subjects, thus strengthening the results by addressing many confounders that are associated with both cervical dysplasia and preterm birth.

Although studies by Raio et al[43] and Sadler et al[41] reported no overall increase in preterm birth after laser conization, both studies further analyzed outcomes based on cone height and independently detected increased risk for poor obstetric outcome with larger cone size. Raio et al demonstrated an increased risk of PTD in women with a cone height of ≥10 mm, whereas Sadler et al reported a 3-fold increase in risk of preterm premature rupture of membranes and subsequent PTD in women with a cone height of ≥1.7 cm.[41] Finally, one retrospective study assessed the risk of low birthweight in 65 patients with a history of CO_2 laser conization and reported a 2.2 RR (95% CI, 1.04–4.5) for birthweight <2500 g, a 3.5 RR (95% CI, 1.02–12.0) for birthweight <2000 g, and a 10.0 RR (95% CI, 1.2–85.6) for weight <1500 g,[44] which provides further, albeit different, supporting evidence to indicate poor obstetric outcomes in patients with a history of laser conization for cervical dysplasia.

LEEP

As mentioned earlier, the technical simplicity, decreased blood loss, and outpatient nature of the procedure have all contributed to LEEP becoming the treatment modality of choice for cervical dysplasia.[15-19] Because of its widespread application, LEEP has the farthest reaching implications for public health impact and therefore should be considered most carefully. Despite the significant volume of data that are available, the effects of LEEP on pregnancy outcomes remain controversial, with evidence supporting both sides of the debate (Table 2). Sjoborg et al[45] published a multiinstitutional retrospective case-control study that evaluated the cases of 742 women with a history of either LEEP or laser conization. In this series, the authors reported the risk of giving birth before 37, 32, and 28 weeks of gestation after treatment with either laser conization or LEEP and compared those rates to control subjects in the general obstetric population. After adjustment for smoking habits, education level, and marital status, the ORs in the treatment group were 3.4 (95% CI, 2.3–5.1), 4.6 (95% CI, 1.7–12.5), and 12.4 (95% CI, 1.6–96.1) for each gestational age, respectively. The authors further reported increased rates of low birthweight and preterm rupture of membranes in women who underwent either excisional procedure relative to control subjects.

Several studies subsequently have focused exclusively on women who were treated with LEEP. Nøhr et al[46] reported an approximately 2-fold increased risk for PTD among women with a history of LEEP, even after controlling for confounders that included smoking, age, parity, obstetric history, and educational status (OR, 1.8; 95% CI, 1.1–2.9). Samson et al[47] examined women who had been treated exclusively with LEEP and reported an increased rate of spontaneous PTD (OR, 3.5; 95% CI, 1.9–6.95) and PTD after premature rupture of membranes (OR, 4.10; 95% CI, 1.48–14.09). Additionally, the authors substantiated previous reports that a history of LEEP conferred a higher risk of low birthweight infants (OR, 3.00; 95% CI, 1.52–6.46).[47]

Over the past 3 years, several European studies that have evaluated the risk of PTD after LEEP have been published.[46,48-53] All of them report a significant increase in the risk of PTD after treatment for cervical dysplasia, although many still acknowledge that cau-

TABLE 2
Loop electrosurgical excisional procedure and preterm birth

Study	Study design	Patients, n	Control subjects	All preterm deliveries: relative risk (95% CI)
Ferenczy et al, 1995[7a]	Retrospective	53	General population	NA
Cruickshank et al, 1995[54a]	Retrospective	178	General population	NA
Althuisius et al, 2001[4a]	Retrospective	56	Hypothetic value	NA
Paraskevaidis et al, 2002[60a]	Retrospective	28	General population	NA
Crane, 2003[59]	Review	NA	NA	1.81 (1.18–2.76)[b]
Samson et al, 2005[47]	Retrospective	571	Untreated (matched)	3.50 (1.9–6.95)[b]
Sjoborg et al, 2007[45]	Retrospective	742	General population	3.4 (2.3–5.1)[b]
Nøhr et al, 2007[46]	Prospective cohort	70	Untreated	1.8 (1.1–2.9)[b]
Noehr et al, 2009[48]	Retrospective	530	General population	2.07(1.88–2.27)[b]
Jakobsson et al, 2009[50]	Retrospective	624	General population	2.61 (2.02–3.20)
		258	Internal	1.94 (1.10–3.40)
Werner et al, 2010[58a]	Retrospective	1353	General population	NA
Acharya et al, 2005[56a]	Retrospective	79	General population (matched 2:1)	NA
Sadler et al, 2004[41]	Retrospective	278	General population	1.9 (1.0–3.8)

CI, confidence interval; *NA*, not available.

[a] No increased risk demonstrated in the study; [b] Number referenced is odds ratio as indicator of risk.

Bevis. Preterm delivery after cervical surgery. Am J Obstet Gynecol 2011.

sation remains theoretic. In a Danish cohort study, 349 women with a LEEP before pregnancy had an OR of 1.8 (95% CI, 1.1–2.9) for PTD at <37 weeks of gestation with an absolute difference of 6.6% vs 3.5% when compared with the untreated contingent of the cohort. There was no adjustment for confounding factors such as marital status, economic status, and smoking.[46] Jakobsson et al[50] reported a similar magnitude of risk in a Finnish cohort of 624 women who delivered after LEEP (RR, 2.61; 95% CI, 2.02–3.2) but added an ideal, internal control with a subgroup of 258 women who had deliveries before and after LEEP. The preterm birth rate was 6.5 % before LEEP and 12% after LEEP, which is a nearly 2-fold increase in the same woman before and after LEEP. In addition, a small retrospective cohort study that was performed in Belgium reported an increase in the frequency of PTD (both at <37 and <34 weeks of gestation), with a mean gestational age of 266 vs 274 days at delivery and a lower birthweight.[51]

One of the largest studies to examine the association of LEEP and preterm birth was performed in a Danish population-based cohort. Ortoft et al[52] reported an increase in preterm birth at <37 weeks of gestation (hazard ratio [HR], 2.4; 95% CI, 1.8–3.1), perinatal death (HR, 4.1; 95% CI, 1.3–13), and preterm premature rupture of membranes at <37 weeks' gestation (HR, 3.0; 95% CI, 2.2–4.1) in nearly 600 women who were treated with LEEP before pregnancy, compared with control subjects. However, a subgroup analysis of women who gave birth before and after conization procedures did not detect a significant difference in any of these endpoints. This study is one of the only investigations that provided information on the effect of multiple cervical procedures. Although not separated by type of procedure, women who had >1 conization procedure had a nearly 10-fold increase (HR, 9.9; 95% CI, 6–17) in the rate of preterm birth, compared with women who never had an excisional procedure. Although a large recent study in a Norwegian population-based cohort reported a similar increase in the relative risk of preterm birth after a conization when compared with the general population (RR, from 2.4 at 33-36 weeks of gestation to 4.3 at 24-27 weeks of gestation) or to women who subsequently had a conization (RR, from 2.2 at 33-36 weeks of gestation to 3.0 at 24-27 weeks of gestation), the applicability of these findings to the US population or modern practice is limited because information on methods was not available and the accrual of patients spanned >35 years.[53] Despite these limitations, the finding of the highest relative risks for PTD at earlier gestational ages warrants attention because these are the neonates with the greatest risk of perinatal morbidity.

In contradistinction, multiple other studies that used similar designs have failed to demonstrate an increase in poor obstetric outcomes after LEEP.[4,7,54-57] Ferenczy et al[7] reported no difference in PTD or cesarean delivery after LEEP; however, this patient population was restricted to those with cone height <1.5

cm and a mean frontal diameter of 1.8 cm, which raises the question of the effect of larger cone specimens. In another Norwegian study, Acharya et al[56] reported no increase in risk of PTD after LEEP in 79 patients, when compared with 158 matched control subjects. However, there was a 4-fold increase in PTD when cone height was >25 mm (RR, 4.0; 95% CI, 1.0–16.0). In a study from New Zealand, Sadler et al[41] demonstrated no increased risk of PTD in patients who underwent LEEP (adjusted RR, 1.2; 95% CI, 0.8–1.8) but did report an increased risk of preterm premature rupture of membranes with subsequent PTD (adjusted RR, 1.9; 95% CI, 1.0–3.8). Another study differed slightly in that the authors reported no increased risk of PTD but detected a decrease in birthweight among infants who were delivered after LEEP.[55]

A recent study by Werner et al[58] reported on >1300 women who had both a LEEP and singleton pregnancy delivered at a single institution in the United States. Of these women, 511 had the LEEP performed before the examined pregnancy, and another 842 underwent LEEP after the index pregnancy. When compared with the general obstetric population, the rates of PTD in women with LEEP were similar (4% vs 2% vs 4%, respectively; $P = .12$ and $= .22$). Further analysis after control for demographic differences showed similar results (4% vs 4% vs 4%; $P > .5$). This study is of particular importance, given the large US population examined, but it is limited by a lack of information on potential confounders and a lack of information on previous preterm births or LEEP that was performed at other institutions.

A systematic review by Crane[59] in 2003 reviewed 5 articles that compared women who were treated with LEEP to control subjects and concluded that women who had LEEP were more likely to have a PTB in subsequent pregnancies (OR, 1.8; 95% CI, 1.18–2.76) and were more likely to have low birthweight infants (<2500 g; OR, 1.60; 95% CI, 1.01–2.52). When limited to studies that controlled for smoking status, the increased rate of PTD persisted, but the risk of low birthweight equilibrated between groups. A 2006 metaanalysis by Kyrgiou et al[34] included 10 studies (5 of which were included in the aforementioned analysis by Crane[59]) that compared women who had a LEEP before pregnancy with untreated control subjects and reported pooled RRs that were calculated with a random-effects model. Women with a previous LEEP had an increased risk of PTD (RR, 1.7; 95% CI, 1.24–2.35), premature rupture of membranes (RR, 2.69; 95% CI, 1.62–4.46), and low birthweight (RR, 1.82; 95% CI, 1.09–3.06). This analysis also controlled for confounding factors between study populations with the performance of a subgroup metaanalysis that matched for age, parity, and smoking that resulted in a higher relative risk for PTD (RR, 2.10; 95% CI, 1.34–3.29). A further analysis of the dimensions of tissue excised was also undertaken for those studies that reported these data. There was a significant increase in PTD if cone height was >10 mm (RR, 2.6; 95% CI, 1.3–5.3). If cone height was <10 mm, the data were conflicting between studies, and the risk was not significant (RR, 1.5; 95% CI, 0.6–3.9).[34] Finally, the metaanalysis that was published in 2008 examined data from 7 studies with 3600 women who treated with LEEP before pregnancy.[35] The authors reported no increase in the risk of PTD at <32 or 34 weeks of gestation (RR, 1.2; 95% CI, 0.5–2.9) or perinatal mortality rates (RR, 1.17; 95% CI, 0.74–1.87) but did note an increase in women who were treated with CKC. Despite the lack of a demonstrable increase in the risk of PTD at any gestational age, the authors still cautioned that LEEP cannot be considered completely free of adverse outcomes.[35]

Ablative procedures

After the potential complications associated with conization are highlighted, it would be remiss to avoid discussion of the potential obstetric complications after ablative procedures as alternatives to conization. A handful of retrospective case-control studies have examined ablative procedures, and, much like the data in the preceding sections, the results are contradictory. Of the 4 retrospective studies that were examined, 3 concluded no increase in PTB after laser ablation of the cervix, although the other reported an RR of 1.39 (95% CI, 1.18–1.63)[41,44,61,62] El-Bastawissi et al[32] and Crane[59] examined several different types of treatment for CIN that included laser vaporization and cryotherapy and reported no increase in poor obstetric outcomes after ablative procedures. Neither metaanalysis that evaluated this issue detected increased obstetric risk after laser ablation or cryotherapy.[34,35] Arbyn et al[35] reported an overall relative risk for PTD of 0.87 (95% CI, 0.53–1.45) when they analyzed all ablative techniques collectively, which is a result similar to that reported by Kyrgiou et al[34] for only laser ablation (RR, 0.87; 95% CI, 0.63–1.20). Neither metaanalysis reported an increase in incidence of low birthweight infants of patients who were treated with ablative techniques.[34,35] The only article that reported an increase in complications after ablation for CIN was by Jakobsson et al,[63] who reported an RR 1.47 (95% CI, 1.29–1.67) among 9000 patients who underwent ablation after adjustment for smoking, age, and parity. Although the data regarding such procedures are mixed, far fewer studies indicate a risk that is associated with ablative procedures, which is an important consideration for clinicians when treating reproductive-aged women for cervical dysplasia.

Comment

Although significant evidence both supports and refutes an association between conization and premature delivery, the relationship between PTD and the treatment of cervical dysplasia remains unclear. This, in large part, stems from the multifactorial and poorly understood cause of underlying preterm birth. One potential explanation for any noted relationship is the association of both conditions with genital tract colonization and infection. Women with 1 sexually transmitted infection are at increased risk for other sexually transmitted infections and lower genital tract colonization. Lower genital tract colonization has been shown to be a risk factor for upper genital tract colonization through an ascending route. Upper genital tract colonization may or may not progress to overt infection but, in either case, may be associated with preterm birth because the host response to the infectious organisms may be sufficient to trigger the inflammatory cascade that leads to PTD through multiple mechanisms, which include cervical ripening and membrane rupture.[64-66] This shared risk for genital tract colonization and preterm birth has been behind the argument that the appropriate comparison group for women who are treated with excisional procedures is not the general obstetric population, but rather other women with cervical dysplasia who have not been treated with similar procedures. A recent study from the United Kingdom demonstrates this. The rate of spontaneous PTB and the risk of preterm premature rupture of membranes was increased in women with CIN3 compared with the general population (OR, 1.52; 95% CI, 1.29–1.80). However, there was no difference in preterm birth rates between women who had been treated with excisional or ablative therapies or between excisional therapy and no treatment.[57]

Another potential explanation for associations between treatment for cervical dysplasia and preterm birth lies in the potential effects of treatment on cervical function. The cervix plays an important role as a barrier to ascending infection during pregnancy. This is accomplished, at least in part, because of the antimicrobial effect of the thick cervical mucus plug that forms during pregnancy.[67] The cervical mucus plug contains a number of antimicrobial substances, such as defensins, lysozyme, lactoferrin, and secretory leukoprotease inhibitor. These proteins play a key role in innate immunity and are a critical first line of defense from pathogens. Recently, however, the cervical mucus plug has been demonstrated to also contain immunoglobulins, which is reflective of an adaptive immune response, that play a key role in opsonization and targeting of bacteria for activated macrophages.[68] After an excisional procedure, the cervix heals by regeneration of the ectocervical components and generation of scar tissue, but the regeneration of the endocervical glands that is responsible for cervical mucus production is limited.[69] This reduction in the production of cervical mucus may lead to decreased immune function and predispose to upper tract infection.

An alternative theory for the association between excisional procedures and preterm birth comes as a consequence of the removal of a substantial portion of cervical connective tissue, thereby weakening the supportive ability of the cervix as pregnancy progresses. In an effort to substantiate this theory, studies have examined the effect of cone size on PTD risk and have used ultrasound estimation of overall cervical length to predict preterm birth in women with a history of cervical cone.[5,35,43,54,70-74] Ricciotti et al[72] examined the correlation between ultrasound estimation of cervical length and the actual measured size of the cone specimen. In this study of 29 patients who underwent LEEP, the difference in ultrasound measurement of the cervix immediately before and immediately after conization correlated well with the ruler measurement of the cervical specimen. However, Gentry et al[5] studied the effects of conization on overall cervical length by comparing transvaginal measurement of cervical length before conization and 3 months after the procedure. With only 60 patients, the sample was small, but the results indicate no difference in cervical length after healing, with an average cervical length of 3.1 cm at both time points.[5] Although these studies all concluded that larger cone size confers a greater risk of subsequent PTD, they were not able to agree on a specific cone height to serve as a threshold above which the risk of PTD is elevated.[35,54] Nøhr et al[46] investigated 220 women with unambiguous description of cone height and saw preterm deliveries in 15 cases. For each additional millimeter of cone height that was excised, there was an estimated 20% increase in the risk of preterm birth. This same cohort study also demonstrated a significant difference in the rate of preterm birth in all women who undergo LEEP (regardless of cone size), although the study did not control for confounding factors such as marital status, economic status, and smoking. More recently, Noehr et al[73] evaluated the depth of cone specimen after LEEP and its effect on the risk of preterm birth. In their series of 3,605 singleton deliveries of which 223 deliveries (6.2%) were preterm, the authors reported an estimated 6% increase in PTD per millimeter of cone size excised (OR, 1.06; 95% CI, 1.03–1.09). Other authors examined cone diameter as opposed to cone height and drew similar conclusions in that increasing diameter of the cone specimen increases the rate of preterm birth.[33,48] In addition to the rate of preterm birth, 1 group of investigators reported that the mean gestational age was 0.6 weeks lower in cases when the cone size was ≤15 mm but was 2 weeks lower when cone height was 25 mm.[56] These studies that have related cone size with risk of preterm birth add plausibility to theories that implicated the cervical mucus effect and an effect of the stability and strength of cervical scar tissue.

One final consideration for practitioners to address is the issue of timing between cervical conization and subsequent pregnancies. Himes and Simhan[75] reported no overall increase in preterm birth after conization (LEEP or CKC) compared with other women with cervical dysplasia who did not have a conization. However, patients with subsequent term birth after conization had longer conization-to-conception intervals than those with subsequent preterm births (10.5 vs 2.5 months; $P = .004$).[74] The association between short conization-to-pregnancy interval remained significant even after the data were controlled for confounders such as cone dimensions and race. Although data are limited, women who undergo conization should consider delaying pregnancy at least 2-3 months because conception within this window may be associated with an increased risk of preterm birth. The most appropriate conization-to-pregnancy interval has yet to be determined and is an area for future research.

Future investigation in the area of preterm birth hopefully will better define the population at greatest risk for PTD after excisional procedures. Several studies have used cervical length screening to predict preterm birth after a LEEP or CKC. Berghella et al[71] reported that, at

16-24 weeks of gestation, approximately 30% of women had a cervical length of <25 mm and that 30% of them delivered preterm, compared with 6% of women with a normal cervical length. In another study, women with previous excisional or ablative procedures were found to have shorter cervical lengths than control subjects and had cervical lengths that approximated those of women with previous preterm births. A cutoff of 30 mm was associated with a positive predictive value of 54% for subsequent preterm birth.[70] Although suggestive, these studies do not offer definitive evidence of the usefulness of cervical length surveillance after conization because the sample sizes are small, the gestational age at performance varied, and screened populations were selective. In addition, without evidence of an effective intervention, the value of cervical length surveillance is unclear.

Despite the large body of literature that has addressed the long-term consequences of treatment for cervical dysplasia, the obstetric risk for patients who undergo these procedures remains difficult to define. Existing evidence must be considered carefully in light of the fact that most studies are retrospective case-control studies and therefore contain significant bias. Additionally, as previously discussed, the cause of preterm birth is complex and incompletely understood, and the increased rate of PTB that has been reported by many investigators may be a result of some other, as yet unidentified, factor. Moreover, the main focus of most studies that have examined these issues is the relative risk with little regard for the absolute risk of preterm birth. In those studies that have demonstrated an increased risk of preterm birth after conization, the relative risks cluster around 2, which manifests as an absolute risk increase of <10%. This small incremental increase in the risk of preterm birth has to be put in perspective with the risk of untreated or inadequately treated high-grade cervical dysplasia. Conversely, the benefits of cervical cancer screening programs and the unprecedented reduction in cervical cancer cases that result from aggressive treatment of dysplasia are well-documented. Further, the underlying cause of cervical dysplasia and cancer are known, and effective interventions have been established. Based on the data presented here, practitioners can counsel patients regarding the potential long-term obstetric complications of treatment relative to the well-described risks of untreated cervical dysplasia and the extremely poor outcomes of patients who are diagnosed with advanced cervical cancer.

Recent changes in Papanicolaou screening and colposcopic guidelines focus on avoiding unnecessary treatment in women with cervical abnormalities by recognizing not only the immediate discomfort and complications but also the potential long-term obstetric consequences.[76] However, the guidelines also continue to recommend aggressive treatment for patients with high-grade dysplasia who are at significant risk for the progression of disease. Additionally, the anticipated long-term benefit of vaccination against HPV may help to further reduce the burden of obstetric complications that result from cervical dysplasia. For now, it seems prudent to treat patients with high-grade dysplasia and who are at significant risk for progression to cervical cancer according to the published guidelines—guidelines with well-documented success at the reduction of cervical cancer incidence and morbidity. Practitioners should counsel their patients regarding the potential for future obstetric complications and discuss timing and appropriate prenatal considerations to maximize outcomes in future pregnancies. ■

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