The effect of loop electrosurgical excision procedure on the subsequent risk of preterm delivery

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Dedication

This scholarly project is dedicated to my husband who has been a great source of motivation and inspiration. Without his patience, understanding, support, and most of all love, the completion of this work would not have been possible.

It is also dedicated to my parents and sister who have supported me all the way since the beginning of my studies. To my parents, who taught me that the best kind of knowledge to have is that which is learned for its own sake. To my mother, who taught me that even the largest task can be accomplished if it is done one step at a time.

I dedicate this work to all working physician assistants' to help guide their own management plans to preserve the fertility of young women.

Finally, this project is dedicated to all those who believe in the richness of learning.

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To each of the above, I extend my deepest appreciation.

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Introduction

Background

Cervical cancer is the second leading cancer death in women worldwide. In developing countries, regular screening with Papanicolaou smears has markedly decreased the incidence of the disease (Hacker, Moore, & Gambone, 2004). Cervical dysplasia is the precursor to cervical cancer, and is the abnormal growth of squamous cells on the surface of the cervix. It refers to the presence of precancerous changes of the cells lining of the cervix and is a potentially premalignant condition. Squamous intraepithelial lesion is the pathology term used to refer to cervical dysplasia observed in smears of cells taken from the cervix (Hoffman & Mann, 2009). Squamous refers to the type of cells lining the cervix. Intraepithelial refers to the fact that these cells are present in the lining tissue of the cervix. When cervical dysplasia is seen in a biopsy of tissue rather than a cell smear, it is referred to as cervical intraepithelial neoplasia (CIN).

The major etiology of CIN is an infection of the cervix with the human papillomavirus (HPV) (Molpus & Jones III, 2008). HPV is a very common infection that is transmitted through sexual intercourse. In fact, over 75% of sexually active women will mostly likely become infected with HPV at some point in their lives (Hacker, et al., 2004). The risk of infection increases with the number of sexual partners a person has. It is now believed that almost all cases of cervical cancer are caused by exposure to high risk HPV (Hacker, et al., 2004). Most HPV infections do not produce any symptoms and spontaneously resolve. Some HPV infections persist over time rather than resolve, although the reason why this happens is not clear. Persistent HPV infection may lead to the development of genital condylomas, precancerous changes of the cervix, as well as cervical cancer. Certain HPV types typically cause genital warts or mild dysplasia known as low-risk types, 6 and 11; while other types known as high-risk

HPV types, 16 and 18 are more strongly associated with severe dysplasia and cervical cancer. The majority of cases of CIN are removed by the immune system without any treatment; however, a very small number of cases progress to become cervical cancer (Molpus & Jones III, 2008).

Traditionally, the Papanicolaou test has been the screening method of choice for detecting cervical dysplasia (Molpus & Jones III, 2008). It identifies changes in cervical cells early before the lesion progresses to invasive cancer, thus making it easier to cure. For this particular screening test, a sample of cells from the surface of the cervix is removed during the pelvic examination. The cells are smeared onto a slide, stained, and observed under the microscope for any evidence of dysplasia or cancer (Hacker, et al., 2004). The cervical sample may also be placed into a vial of liquid that is later used to prepare a microscope slide for examination. If the screening tests show abnormal appearing (dysplastic) cells, the results are given as one of the following categories: low-grade squamous intraepithelial lesion (LSIL), or changes characteristic of mild dysplasia; and high-grade squamous intraepithelial lesion (HSIL), corresponding to severe precancerous changes. Atypical squamous cells (ASC) is another category with 2 subtypes: ASC-US, which means undetermined significance, or ASC-H, which means cannot exclude HSIL (Wright, et al., 2003)

An abnormal Papanicolaou smear may lead to colposcopy evaluation of the cervix (Molpus & Jones III, 2008). The colposcopy procedure uses a microscope to visualize the cervix during a pelvic examination. Colposcopy can help identify abnormal areas on the cervix and is a safe procedure with no complications other than mild vaginal bleeding or spotting. During the colposcopy procedure, if suspicious areas are visualized under the microscope, biopsies or tissue samples may be taken (Wright, et al., 2003). When dysplasia is identified in tissue biopsy of the cervix, the term cervical intraepithelial neoplasia (CIN) is used. CIN is classified according to the extent to which the abnormal cells are seen in the cervical lining tissue. CIN 1 (mild dysplasia) or grade I, refers to the presence of dysplasia limited to the basal one-third of the cervical lining. CIN 2 (moderate dysplasia) or grade II is considered to be a high-grade and more serious lesion. It refers to dysplastic cellular changes confined to the basal two-thirds of the lining tissue. CIN 3 (severe dysplasia) or grade III, is also a high grade lesion in which precancerous changes encompass greater than two-thirds of the cervical lining up to and including full-thickness lesions (Wright, et al., 2003).

CIN is a curable medical condition although the recurrence rate is 20% (Molpus & Jones III, 2008). Most women with low-grade dysplasia, LGSIL or CIN1, will undergo spontaneous regression without any treatment or intervention (Hoffman & Mann, 2009). Therefore, monitoring without specific treatment is often indicated in this group when the diagnosis is confirmed and all abnormal areas have been visualized (Hacker, et al., 2004). Surgical treatment is appropriate for women with high-grade cervical dysplasia. Treatments for cervical dysplasia fall into two general categories: destruction (ablation) of the abnormal area and removal. Both types of treatment are equally effective. Generally, destruction (ablation) procedures are used for milder dysplasia and removal is recommended for more severe dysplasia or cancer (Molpus & Jones III, 2008).

The destruction or ablation procedures for treatment of cervical dysplasia include carbon dioxide laser ablation and cryocautery (Molpus & Jones III, 2008). These treatments use laser or freezing methods to remove the abnormal cells of the cervix. The most common complications of ablation procedures are narrowing or stenosis of the cervical opening and vaginal bleeding.

Disadvantages of this treatment include no sampling of the abnormal area for an analysis of the lesions (Molpus & Jones III, 2008).

The removal or resection procedures are cold knife conization, hysterectomy, and loop electrosurgical excision procedure (LEEP) (Hoffman & Mann, 2009). Cone biopsy is the surgical removal of abnormal areas using conventional surgical tools. Hysterectomy, removal of the uterus, is used to treat almost all cases of invasive cervical cancer and may be used to treat severe dysplasia or recurrent dysplasia (Molpus & Jones III, 2008). The most forthcoming and popular procedure is LEEP therapy; it is the most simple and efficient way of treating CIN with a decrease in procedural complications. According to Mathevet, Chemali, Roy, and Dargent (2003) LEEP should be the primary technique for treating CIN because of technical ease and reduced costs. The procedure uses radio-frequency current to remove abnormal areas. With this and other removal procedures, an intact tissue sample for pathology analysis can be obtained (Hoffman & Mann, 2009). There are various advantages and disadvantages to each of the cervical dysplasia treatments, but there is currently no evidence that one technique is significantly better than another in terms of obstetrical outcomes (Hoffman & Mann, 2009).

Although LEEP therapy has become the simplest, safest, most cost-effective CIN treatment, it is not without complications or limitations. CIN has an increased incidence in women of reproductive age, which is why it is vital that treatment options have no adverse effects on fertility, pregnancy, or the fetus. LEEP therapy appears to be associated with an increased risk of preterm delivery (Nohr, Tabor, Frederiksen, & Kjaer, 2007). There are conflicting research results concerning the risk of preterm delivery following LEEP treatment. Further research and study of this topic will be discussed in the literature review section.

Statement of the Purpose

To determine if LEEP therapy causes an overall increased risk of preterm delivery. The purpose of this research contributes greatly to care of young women because this could sway the current cervical dysplasia treatment recommendations.

Statement of the Problem

The risk of LEEP therapy on preterm delivery is still unknown due to conflicting results from numerous studies. There appears to be an association with preterm delivery, but it is questionable whether LEEP therapy has a causal effect. The exact mechanism or cause of preterm delivery remains unclear in women with prior LEEP treatment.

Definition of Terms

LEEP

Theoretical definition – utilizes an electrical current that passes through very thin wire in the shape of a loop; modern electrosurgical generators that allow accurate, and selective bending of the current to slice suspicious areas of the cervix.

General – is surgically removing abnormal areas of the cervix.

Operational definition – a procedure used to remove the abnormal appearing cells of the cervix as a treatment for cervical dysplasia.

Preterm delivery

Theoretical definition – delivery before 37 weeks gestation.

General – the baby delivers before the due date.

Operational definition – delivery before 37 weeks gestation.

Cervical conization

Theoretical definition – refers to the excision of a cone-shaped or cylindrical wedge from the cervix that includes the transformation zone and all or a portion of the endocervical canal including the entire transformation zone.

General – to remove a piece of tissue from the cervix.

Operational definition – surgical removal of a cone-shaped portion of the cervix, including the cancerous area.

PROM

Theoretical definition – refers to a patient who is beyond 37 weeks' gestation and has presented with rupture of membranes (ROM) greater than 1 hour before the onset of labor.

General – a condition which occurs in pregnancy when the sac the holds the baby ruptures.

Operational definition – is a full term pregnancy with a rupture of the membranes prior to the onset of labor.

Low birth weight

Theoretical definition – refers to infants who weigh less than 2500 grams by 37 weeks gestation.

General – an infant who weighs less than 5.5 pounds.

Operational definition – an infant who weighs less than 5 pounds, 8 ounces (2500 grams).

Assumptions

1. There is adequate research about LEEP therapy and preterm birth.
2. Research articles use reliable methods to evaluate LEEP and preterm delivery.

Limitations

1. Articles from the late 1980’s and early 1990’s, from the original research of LEEP therapy, will be included in the review.
2. Articles with conflicting outcomes on the risk of preterm delivery associated with LEEP will be scrutinized.

3. International literature is included since most early research is by authors outside the U.S. Only in the past couple of years has research focused on U.S. population data.
4. The research design is cohort, case control, and case series. My second tier research design is systematic reviews.
5. The population focus is women, pregnant women, and women with prior LEEP treatment.
6. Articles written in languages other than English are excluded. Studies related to preterm delivery in twin or triplet pregnancies are excluded, as these factors increase risk.

Hypothesis

If LEEP is associated with preterm delivery, undergoing this procedure will result in an increased risk of preterm deliveries.

Significance of the Study

The literature is confounding and unclear if there is an overall increased risk of preterm delivery associated with LEEP. There are literature reviews of past research, but analysis of the most up-to-date reports is needed. It is vital that practitioners educate patients with accurate research and make decisions based on best practices. If there is a true overall increased risk, practitioners will be aware of the risk, which may lead to closer monitoring of pregnant patients with prior LEEP treatment.

Methodology

This systematic review of the literature involves extensive database mining in PubMed, CINAHL, and Science Citation Index. Article selection is limited to publications relevant to my research question, with focus on gaining further insight and examining the literature for additional unresolved questions. The studies addressing the potential impact of LEEP on preterm delivery are either case studies or retrospective cohort studies. There are important methodological issues to be considered when reviewing cohort data. Many studies are small, and thus, inadequately powered. Many studies use the general obstetrical population, matched to treated patients on selected factors such as maternal age, smoking, and reproductive history as a comparison group. This approach is problematic because the most important potentially confounding factors, including socioeconomic status and social behaviors (e.g., sexual behavior, smoking, education), are known to be associated with CIN and preterm delivery.

Review of Literature

Women of reproductive age, most commonly between 25-30 years old with CIN, may require treatment. However, treatment methods that remove or destroy cervical tissue may change the structural and functional integrity of the cervix (Werner, et al., 2010). Although excisional techniques are successful at preventing cervical cancer when precancerous lesions are detected, the data regarding pregnancy outcomes after these procedures have been equivocal (Jolley & Wing, 2008). Therefore, it is essential to consider the adverse effects of treatment methods on future fertility and pregnancy.

Cervical Conization

Past literature, as far back as the late 1930's, studies have reported that women of reproductive age should be counseled on the risk of cervical treatments. The first report of adverse pregnancy outcomes following cervical surgery was by Miller and Todd in 1938, which reported that women should not have cervical conization due to the high incidence of pregnancy complications, including preterm delivery. The results suggest use of cervical conization only in women past the childbearing period.

However, since Miller and Todd's report concluding conization can lead to impaired outcome of pregnancy, other authors have reported confounding results. Jones and colleagues (1979) investigated cone biopsy of the cervix and subsequent pregnancy outcome, and reported an increased risk of preterm delivery and low birth weight infants. The study also indicated the mean duration of labor was longer in women who underwent a cone biopsy. Weber and Obel (1979) reported no significant difference in the frequency of preterm delivery, spontaneous or induced abortion, or cesarean section rates between conized and non-conized women. Buller and Jones (1982) results did not support the commonly held belief that pregnancy outcome is significantly altered by cervical conization. The findings showed spontaneous abortion rates, fertility, premature delivery, and cesarean section rates were not altered by cervical conization. Larsson, Grundsell, Gullberg, and Svennerud (1982) evaluated the outcome of pregnancy before and after conization. The authors reported that nulliparous women aged 21-25 years old had the highest risk of premature delivery after cervical conization. Kristensen (1985) concluded that cervical conization created no increased risk of preterm delivery or other adverse pregnancy effects.

Since the mid 1980's, researchers have generally reported that traditional techniques of cold knife and laser conization have been linked to an increased risk of preterm delivery and low birth weight infants (Nohr, et al., 2007). Although, older techniques of cervical conization have a documented increased risk of preterm delivery, previous studies on pregnancy outcome after treatment of CIN show confounding results over the past decade. Nonetheless, Bruinsma, Lumley, Tan, and Quinn (2007) affirm that diagnosis of precancerous lesions in the cervix, regardless of the treatment modality is associated with increased risk of preterm birth.

LEEP/LLETZ

Prendiville, Cullimore, and Norman (1989) introduced an alternative technique for the treatment of CIN, commonly known as LEEP. LEEP treatment has become the mainstay and primary standard of care in North America since the early 1990's, before any long-term studies were done on the subsequent obstetric outcomes. The advantages over the other treatment methods include fewer complications, requirement of less technical skills, tissue for histological evaluation, and reduced operative time (Nohr, et al., 2007; Prendiville, Cullimore, & Norman, 1989). In contrast to the traditional conization techniques, the data is more variable and discordant regarding the impact of LEEP on subsequent pregnancy risks (Jolley & Wing, 2008).

The American Society for Colposcopy and Cervical Pathology 2006 consensus guidelines takes the position that LEEP has an increased risk for future adverse pregnancy outcomes, including preterm delivery, low birth weight, and PROM (Wright, et al., 2007).

The majority of the research studies regarding the risk of preterm delivery date back to the early 1990's. Many authors studied the effect of adverse pregnancy outcomes after LLETZ or LEEP, including spontaneous abortion rates, preterm delivery, low birth weight infants, cesarean section rates, and perinatal mortality. Blomfield, Buxton, Dunn, and Luesley (1993) concluded that women treated with LLETZ delivered infants with significantly lower birth weights than the control groups. Kristensen, Langhoff-Roos, and Kristensen (1993) noted a significant correlation between cervical conization and preterm birth. In this study, women with cervical conization between the first and second delivery had a higher than expected risk of preterm birth at the second delivery. However, the authors were unable to predict if a significantly increased risk of preterm birth occur in future pregnancies. Braet, Peel, and Fenton (1994) reported a small risk of premature labor associated with loop diathermy but the majority of patients had normal pregnancies, concluding that premature labor may be partly attributed to pPROM. The study also demonstrated lower birth weight infants in women who had a loop diathermy excision.

At the turn of the millennium, more studies demonstrated that there was an association between LEEP and preterm delivery, but several of previous studies did not have ample power to detect a significant rate of preterm delivery than that of experimental controls. Conversely, many studies demonstrated no significant risk of preterm delivery after LEEP, but a meta-analysis by Crane (2003) detected a statistically significant increase in preterm deliveries and lower birth rates in women after the procedure. Not all possible confounding factors were controlled, which may have obscured the data collection and the result of an increased risk of preterm delivery (Crane, 2003).

Given the relatively small sample sizes and lack of power in the previous studies, Samson, Bentley, Fahey, McKay, and Gill (2005) examined the relationship using a large sample size with adequate power. The study demonstrated that LEEP significantly increases preterm birth after treatment but showed no difference in the actual overall rate of preterm delivery. The study also indicated that women who underwent LEEP treatment showed a significantly higher incidence of pPROM, which was then followed by a preterm delivery. In addition to these findings, the study demonstrated an increased risk of low birth weight infants, which predisposes a neonate to increased morbidity and mortality.

Kyrgiou et al. (2006) conducted a meta-analysis using studies that evaluated pregnancy outcomes in women with or without cervical manipulation. The meta-analysis outcomes indicated that after LEEP there was a significant increase in the risk of preterm delivery, pPROM, and low birth weight infants. The data also showed an increased incidence of perinatal mortality but could not confirm a significant risk. Nohr et al. (2007) reported a nearly twofold increase in the risk of subsequent preterm delivery. Jakobsson, Gissler, Sainio, and Paavonen (2007) reported an increased risk of preterm delivery after all surgical treatments for CIN, including LEEP. The risk was highest for very preterm delivery and extremely preterm delivery. A 2008 cohort study, based on women who had undergone cervical conization for CIN, showed an increased risk of preterm delivery after cold knife conization and LLETZ procedures (Albrechtsen, Rasmussen, Thoresen, Irgens, & Iversen, 2008). Based on the data and research findings to date, it is suggested that women be educated and counseled on the minor risk of morbidity related to the procedural excision of CIN.

Although it may seem clear that LEEP or LLETZ increases the risk of preterm birth, several studies indicate no statistically significant association. As the 1990's progressed, more research focused on the effects of pregnancy outcome after LEEP. Turlington and colleagues (1996) investigated the effects of LEEP on future fertility and concluded no significant effect on the future fertility of patients. Haffenden, Bigrigg, Codling, and Read (1993) reported that LEEP appeared to have no adverse effect on future fertility and pregnancy outcomes, which is comparable to destructive methods of CIN treatment. Cruickshank, Flannelly, Campbell, and Kitchener (1995) reported that LLETZ does not appear to impose an independent adverse effect on pregnancy when socioeconomic factors are controlled. Cruickshank and colleagues (1995) also reported no statistically significant increase in preterm delivery or low birth weight infants, nor did LLETZ appear to affect cervical function. Althuisius, Schornagel, Dekker, Geijn, and Hummel (2001) results demonstrated that after LEEP, preterm delivery and second trimester abortion prior to 32 weeks was not significant among the women studied. Gestational age at delivery was only 5 days earlier than expected. During the research study, only four women delivered spontaneously, but one had a previous preterm delivery before LEEP was performed. A 2002 study by Paraskevaidis et al., reported that women with the diagnosis of FIGO stage IA1 microinvasive cancer without vascular or lymph node involvement and were treated with LEEP did not have more delivery complications in comparison with untreated women. The authors also reported that the only statistically significant finding was difference in the shortening of the duration of labor. The authors concluded a possible trend towards a shorter duration of pregnancy or preterm delivery. Acharya et al. (2005) found that LEEP did not significantly increase the risk of low birth weight or preterm birth in future pregnancies compared to the control group except when the excision was quite large. The study did confirm that certain pregnancy complications emerge after LEEP, suggesting the procedure is not without risk. Sadler et al. (2004) reported that LEEP is associated with pPROM, which can predispose a pregnancy to preterm delivery, but the overall increase in the risk of preterm delivery was not observed, supporting Acharya et al. findings. Tan, Pepra, and Haloob (2004) investigated the pregnancy outcome after large loop excision of the transformation zone of the cervix and concluded that LLETZ is not associated with adverse pregnancy outcomes. The study noted similar preterm delivery rates between the study group and controls. Women in the study group had significantly lower birth weight infants, but this maybe related the characteristic demographic of women with CIN (Tan, Pepra, & Haloob, 2004). Similarly, Arbyn and colleagues (2008) reported a meta-analysis that demonstrated no increased risk of preterm delivery before 34 weeks gestation, but it cannot be considered completely free of adverse pregnancy outcomes.

Cone Size and Depth

Only a few studies have assessed cone depth of LEEP and subsequent risk of preterm delivery, with confounding results. In 1980, a study reported an increased risk of late miscarriages and preterm birth associated with high cones (Leiman, Harrison, & Rubin, 1980). Ferenczy, Choukroun, Falcone, and Franco (1995) examining pregnancy outcomes in patients treated with LEEP for CIN demonstrated that a maximum depth of 1.5 cm and a mean frontal diameter of 1.8 cm of tissue excision appeared to have no adverse affect on a woman’s ability to support a normal pregnancy. Kyrgiou et al. (2006) found a significantly increased risk of preterm delivery when the cone depth exceeded 10 millmeters, compared with cone depths less than 10 millimeters. Jakobsson, Gissler, Sainio, and Paavonen (2007) previously reported an increased risk of preterm delivery subsequent to conization, all modalities, with increasing cone depth, with an estimated 20% increased risk per additional millimeter of tissue excised. Noehr, Jensen, Frederiksen, Tabor, and Kjaer (2009a) concluded that increasing cone depth is directly associated with an increasing risk of preterm delivery, with an estimated 6% increase risk per each millimeter excised. In addition, the study revealed an increased risk of preterm delivery with having two or more prior LEEPs when compared with no LEEP before delivery.

Cervical Shortening

There appears to be confounding reports about whether cervical shortening persists following a LEEP. In a few studies, cervical shortening was thought to be associated with LEEP, which may predispose to an ascending infection. Gentry, Baggish, Brady, Walsh, and Hungler (2000) examined whether the initial decrease in cervical length after loop excision of the transformation zone persisted 3 months after healing. This is important because a shortened length of the cervix can predispose an increased risk of preterm delivery; therefore, it is necessary to know whether cervical shortening is transient or persistent. The results of this study demonstrated that the shortened cervix did not persist; in fact, the cervical lengths before and after LEEP were not significantly different. In contrast, Crane, Delaney, and Hutchens (2006) reported that women who underwent a LEEP, cold knife conization, or cryotherapy all had shorter cervical lengths than the controls. The authors reported that these women had similar cervical lengths to women with a history of previous spontaneous preterm birth. The cervical procedures, LEEP and cold knife conization, were only associated with preterm delivery less than 37 weeks gestation. Mazouni et al. (2005) reported a mean cervical length 24.3 +/- 6.7 millimeters seven days following LEEP (Mazouni, et al., 2005). Parakevaidis et al. (2002) noted a cervical regeneration trend at three to twelve months after LEEP, which may reduce the risk of preterm delivery after this crucial time period.

Time Interval

An important aspect of patient education is the time interval between cervical trauma and conception. Himes and Simhan (2007) investigated whether the time between conization and pregnancy has an effect on preterm delivery, and concluded that a short time interval (less than 6 months) between conization and pregnancy increased the rate of preterm delivery. The authors recommend women be educated that conceiving within two to three months of LEEP can be associated with an increase risk of preterm delivery. However, the authors did find a significantly increased risk of pPROM in women who underwent LEEP or laser conization, especially in those with increasing cone size.

Current Literature

The majority of the current research suggests that there is a significant increase in preterm delivery associated with LEEP treatment, but recently several articles have confounding results or conclusions. Noehr, Jensen, Frederiksen, Tabor, and Kjaer (2009b) reported twofold increase of spontaneous preterm delivery after LEEP treatment, even after adjusting for cofounding factors. Some data indicates that there is an association between preterm delivery and LEEP, based on the amount of tissue excised. Another 2009 study by Jakobsson, Gissler, Paavonen, and Tapper (2009) had results consistent with the Noehr et al. (2009) study. Jakobsson et al. (2009) concluded that LEEP predisposes patients to preterm delivery, with a two-fold increase in the risk for preterm birth is associated with LEEP, particularly in women with no prior preterm delivery. Additionally, the author noted that after LEEP there appeared to a higher incidence of pPROM.

Recently, a few studies still report equivocal results on the increased risk of preterm delivery associated with LEEP. Michelin et al. (2009) results showed that miscarriages occurred more frequently in patients with previous cold knife conization than in patients who underwent LEEP. The authors also reported that preterm birth more frequently occurred in patients treated for CIN, but also was found in untreated patients more than in the general obstetrical population. These results suggest that treatment methods are not the only factor that plays a role in increased risk for preterm delivery. Michelin et al. (2009) results also showed that preterm birth more frequently occurred in patients who underwent conization than LEEP. Shanbhag et al. (2009) concluded that women with CIN III have higher rates of spontaneous preterm delivery and preterm PROM than the general obstetrical population. The authors also reported that LEEP did not alter these pregnancy complication rates, suggesting that women should be reassured regarding the risk of preterm delivery. Furthermore, there was no difference in the spontaneous preterm delivery or pPROM rates in women who had no treatment.

Werner et al. (2010) reported that there was no evidence of an increased risk of preterm birth in women undergoing LEEP either before or after pregnancy in comparison to the general obstetric population. Moreover, the study concluded only significant differences in the opposite direction and suggested that LEEP before pregnancy was associated with a decreased rate of spontaneous preterm birth between 34 and 36 weeks of gestation. In regards to preterm birth, the results showed no significant differences among the three groups, indicating that LEEP had no association with preterm delivery. The study also indicated no significant association between perinatal mortality and LEEP.

Alternative Theories

Based on recent studies and observations, it still remains unclear if LEEP conization is associated with increased preterm birth, or even if it predisposes a pregnant woman to preterm delivery. The results of several reports in the literature conclude that LEEP cannot definitively be implicated as a cause of preterm birth (Werner, et al., 2010). Bruinsma et al. (2007) provided evidence that women with untreated CIN also had a higher risk of preterm delivery than the general population. The current literature is still not able to determine whether the increased risk is CIN itself or confounding risk factors. It is unclear whether LEEP causes preterm delivery or if early delivery is due to other factors. Confounding factors include but are not limited to smoking, alcohol and drug use, socioeconomic status, age, and marital status. Another theory suggests that cervical gland removal may decrease mucus production (J. Kristensen, Langhoff-Roos, & Kristensen, 1993). This may lead to a compromised immune system that possibly predisposes the mother to an infection that leads to pPROM and preterm delivery (Jakobsson, Gissler, Paavonen, & Tapper, 2009). The amount of tissue removed during LEEP may reduce the integrity of the cervix and weaken the ability of the cervix to support a pregnancy (J. Kristensen, et al., 1993). CIN is associated with inflammation of the cervix, which is a known cause of preterm labor and pPROM, this may explain the risk of preterm delivery in woman who underwent LEEP (J. Kristensen, et al., 1993).

Further research is needed to confirm the likelihood of the increased risk of preterm delivery, pPROM, and low birth weight infants after LEEP treatment. Additional work is necessary to validate probable causes for the increase in preterm delivery rates.

Discussion

Many reproductive age women are undergoing treatment for CIN and subsequently plan to become pregnant. A variety of procedures have been used to treat CIN, including cold knife conization, laser ablation, and LEEP. Electrocoagulation diathermy was the first ablative technique used in the traditional management of CIN and was the mainstay of treatment until the late 1980’s. It was superseded by laser ablation because of the reduced depth of cervical destruction. In this clinical review, LLETZ or LEEP was the procedure under investigation.

Although early studies produced inconsistent findings regarding the association between cold knife conization and preterm delivery; more recent studies consistently report that conization of the cervix has been associated with serious adverse outcomes in subsequent pregnancies, including preterm delivery. The initial reports of LEEP were similarly confounding. The prevalence of certain pregnancy complications appears to be higher after LEEP suggesting that the procedure is not without risk. The discrepancy in pregnancy outcomes following LEEP compared with cold knife or laser conization is probably related to the size of the cervical tissue excised. The amount of cervical tissue removed is generally smaller with LEEP.

Although LEEP is being performed frequently, the data regarding adverse pregnancy outcomes is more scant than cervical conization data. The four largest studies of obstetric outcomes following LEEP used diverse methodologies and the conclusions were confounding. Sadler et al. (2004) noted no increased risk of preterm delivery after LEEP. Samson et al. (2005) reported an increased risk of spontaneous preterm delivery, preterm delivery following rupture of membranes, and low birth weight infants. Bruinsma and colleagues (2007) demonstrated that regardless of the treatment for CIN, the diagnosis of precancerous lesions in cervix is related to an increased risk of preterm delivery. In comparison to the general obstetric population, the data showed that both treated and untreated women had an increased risk for preterm birth. The data suggests that women with CIN have intrinsic characteristics that increase the risk of preterm delivery. Jakobsson et al. (2009) reported that women who underwent a prior LEEP were at an increased risk for preterm delivery.

These women are a heterogeneous group of individuals with different preterm birth risk profiles. Identifying factors related to cervical manipulation procedures is essential for both patient counseling and risk modification. In support of this, Sadler et al. (2004) reported no association between cervical conization and overall preterm delivery rates. The study also reported an increased risk of pPROM after laser conization or LEEP. Tan and colleagues (2004) concluded that LLETZ is not associated with adverse pregnancy outcomes. Nohr et al. (2007) reported a nearly twofold increase in the risk of subsequent preterm delivery. A study by Himes and Simhan (2007) reported that women who conceive only two to three months following a LEEP procedure may be at a higher risk for preterm birth. Some risk factors are modifiable, therefore, it is important to discuss with patients. Jakobsson et al. (2007) reported that all surgical treatments for CIN predispose women to an increased risk of preterm delivery. A Norwegian study of women with CIN who underwent LEEP did not show significantly increased risk of preterm delivery or low birth weight in future pregnancies (Michelin, et al., 2009). In 2009, a cohort study concluded that women have an increased risk of preterm delivery and pPROM than the general obstetrical population (Shanbhag, et al., 2009). Most recently, Werner and colleagues (2010) reported no association between preterm delivery and LEEP before or after pregnancy.

Three case control-studies have been published in which no significant difference in preterm delivery was reported. Haffenden et al. (1993) reported that LEEP appeared to have no adverse effect on future fertility and pregnancy outcomes. Cruickshank and colleagues (1995) also reported no statistically significant increase in preterm delivery or low birth weight infants when socioeconomic factors are controlled. A 1994 study reported a small risk of premature labor associated with loop diathermy (Braet, Peel, & Fenton, 1994).

Numerous, but not all studies have reported that the amount of tissue excised is related to preterm birth. Leiman et al. (1980) reported an increased risk of late miscarriages and preterm birth associated with high cones. The study also demonstrated that small cones are related to cesarean sections. Sadler et al. (2004) reported an increased risk of pPROM with increasing depth of cone size. Consequently, women with larger cervical excisions are at higher risk for preterm birth following a conization, such as LEEP. Kyrgiou et al. (2006) reported that all excisional procedures produce adverse pregnancy morbidity but is not associated with neonatal mortality. The review also reported a significantly increased risk of preterm birth when the cone depth exceeded 10 millimeters. Sjoborg et al. (2007) reported a tendency for deeper cone sizes with increasing CIN grade and shorter pregnancy duration. Jakobsson et al. (2009) is in accordance with these observations, but the cone size was estimated and may have been inaccurate. Noehr et al. (2009) reported that increasing the cone depth is associated with an increased risk of preterm birth. The study noted an increased risk of preterm delivery with having two or more prior LEEPs in comparison with no LEEP before delivery.

Such controversy among numerous studies prompted the development of three meta-analyses that investigated pregnancy outcomes following LEEP. Most of the reviews investigated the obstetric outcomes in women diagnosed with CIN in comparison with women in the general population. Crane and colleagues (2003) reviewed 5 studies, which individually reported no significant risk of preterm delivery following LEEP, but in combination with a meta-analysis, a significant increase in preterm delivery after LEEP was confirmed. Similarly, Kyrgiou et al. (2006) included five of the same reports plus three additional more. The investigators reported that when all the studies were combined, there was a significant increase in risk of preterm delivery after LEEP treatment. Most recently, a meta-analysis demonstrated no increased risk of preterm delivery before 34 weeks gestation (Arbyn, et al., 2008).

Interestingly, there appears to be confounding reports about whether cervical shortening persists following a LEEP. A study using transvaginal ultrasonography have shown that three to six months following LEEP procedure, the length of the cervix does not remain shortened and is completely restored after adequate healing time (Gentry, et al., 2000). Mazouni et al. (2005) reported a mean cervical length 24.3 +/- 6.7 millimeters seven days following LEEP. Parakevaidis and colleagues (2002) noted a cervical regeneration trend at three to twelve months after LEEP, which may reduce the risk of preterm delivery after this crucial time period.

Many authors have theorized alterative explanations or factors to help explain the observed differences in the frequency of adverse pregnancy outcomes. Many women with CIN have similar demographic, behavioral, and sexual characteristics that predispose or increase the risk of preterm delivery or other pregnancy related complications. An infection, known as bacterial vaginosis has been associated with pPROM and is often a common finding among women with CIN (Viikki, Pukkala, Nieminen, & Hakama, 2000). Most of the literature was matched for confounding factors such as age, parity, smoking, marital status, social status, date of delivery, and a history of preterm delivery. Crane and colleagues (2003) reported that women exposed to the risk factors associated with CIN are also at risk for adverse pregnancy outcomes.

The investigators also noted that women diagnosed with cervical cancer had an increased risk of perinatal mortality before cervical conization. Kyrgiou at al. (2006) data indicates that factors other than the treatment for CIN may contribute to overall relative risk of preterm delivery. In general, CIN is associated with inflammation of the cervix, known to cause preterm labor and pPROM, and consequently increase the risk of preterm delivery after LEEP (J. Kristensen, et al., 1993). Cervical gland removal associated with LEEP may decrease mucus production leading to comprised immune function, and subsequently preterm delivery (J. Kristensen, et al., 1993).

Moreover, women who require the treatment for CIN are young and of reproductive age, therefore, are selected for one treatment method or another on the basis of several factors that are likely to damage cervical function. These characteristics included size, severity, site of lesion, anatomical characteristics of the transformation zone, and suspicious glandular or invasive disease (Viikki, et al., 2000). Perhaps resecting a large amount of cervical tissue decreases the structural integrity of the cervix, and thus the ability to support a pregnancy to term (J. Kristensen, et al., 1993). Studies have shown that the length of the cervix is normal on transvagina ultrasonography after LEEP (Gentry, et al., 2000). However, is the quality of the regenerated tissue normal or has scar tissue formed that does not carry the same function.

With numerous equivocal reports on LEEP, one can only speculate why LEEP apparently increases the risk of preterm delivery. It is known that the cervix varies considerably in length during pregnancy, and this may be impaired following a procedure, such as LEEP. The cervix also has to resist external (bacterial) and internal influences, during pregnancy. LEEP appears to somehow affect the structural integrity of the cervix causing a weakness in cervical function. LEEP still is considered the standard of care for the treatment of high-grade CIN, but much reluctance towards the treatments of lower-grade lesion is advised, and newer options should be explored continuously.

Recommendations for Practice

CIN is a common and widespread diagnosis among young women of reproductive age. Management of cervical premalignant lesions starts with an abnormal Pap smear. Screening asymptomatic women allows for an early diagnosis and an opportunity to treat preinvasive lesions before they progress to cervical cancer. There are a wide variety of ablative and excisional methods used in the treatment of cervical precancerous lesions. In the 1990's, the College of American Pathologists suggested that more than 1 million women were diagnosed with low-grade CIN, and 500,000 are diagnosed with high-grade CIN each year (Wright, et al., 2007). It seems apparent that LEEP may have a small increased risk of preterm delivery, thus, the treatment recommendations should error on the conservative side. Based on the most recent confounding literature, the 2006 consensus guidelines for CIN should be utilized by practitioners to preserve future fertility and pregnancy related problems (Wright, et al., 2007). All of the current guidelines will be addressed, but the recommendations will focus on the management for young women and be directed towards physician assistants.

There are two general management approaches, expectant versus immediate treatment. The standard of care is based upon the correlation of cervical cytology, colposcopic evaluation, cervical biopsy, and individual patient characteristics (Holschneider, Goff, & Falk, 2010).

General Recommendations

Practitioners should educate patients on the likelihood that certain treatment regimens can adversely affect future obstetric outcomes. Inform women of the potential risk of preterm delivery associated after LEEP. Advise patients to wait at least 6 months before conceiving because a short time interval (less than 6 months) between conization and pregnancy increases the rate of preterm delivery. Thus, the risks should be highly considered when deciding upon the treatment approach. A physician assistant can provide one of the most important aspects of patient education, which is taking the time to make certain that the patient, understands what the diagnosis is and how to treat it. As a general guideline, it is very important to ensure patient comfort during this medical procedure. Many of these young women are frightened and fearful of the procedure.

CIN 1

Guideline. Women diagnosed with CIN 1, begin with the distinguishing ASC-US, ASC-H, or LSIL versus HSIL or AGS-NOS cytology. Women with CIN 1 preceded by cervical cytology showing LSIL generally do not warrant aggressive intervention (Holschneider, et al., 2010). Many of these lesions spontaneously regress and progression to CIN 2 or 3 is uncommon. Since CIN 1 has such a high rate of spontaneous regression, expectant management is recommended treatment, especially in special populations, such as adolescents and young women. Women with CIN 1 preceded by ASC-US, ASC-H, or LSIL should follow-up with either HPV DNA every twelve months or repeat cervical cytology every six to twelve months (Wright, et al., 2007).

Patients with evidence of HSIL or AGS-NOS cervical cytology have a higher rate of progression to CIN 2, 3 or worse. This type of high-grade lesion is treated more aggressively than low-grade CIN 1 lesions. Most practitioners would recommend immediate treatment or close follow-up. The current guideline for CIN 1 preceded by HSIL is either diagnostic exicisional procedures or close monitoring with colposcopic observation. In addition, cervical cytology every 6 months for 1 year is recommended (Wright, et al., 2007). Holschneider et al. (2010) suggested that women, who are planning on becoming pregnant, should follow the most accepted recommendation of close clinical follow-up rather than an exicisional procedure.

Follow-up in special populations requires careful consideration. A follow-up is recommended at twelve and twenty-four months in adolescent women with CIN 1. Adolescents with HSIL or greater at the twelve month follow-up should have a colposcopy. Women with an ASC-US or greater at twenty-four months should undergo another colposcopy (Holschneider, et al., 2010). Management of pregnant women with CIN 1 is follow-up without treatment (Wright, et al., 2007).

Recommendation. For the most part, this article agrees with the current guidelines for CIN 1. If the final diagnosis in a woman is CIN 1, the clinical management may take one of the following courses: either to immediately treat the lesion or follow the woman cytologically or colposcopically and then treat if the lesion is persistent or progressive. Based on the literature, my recommendation for the management of CIN 1 preceded by either low or high-grade abnormalities is expectant management. For the sake of future pregnancy related complications, I suggest that excisional procedures not be recommended to young women as an option for the patient with CIN 1 preceded by a high-grade lesion. I believe that the risk is too high for young women because the literature is still confounding. Since spontaneous regression is observed in most women in this setting, expectant management is generally preferred and this population is less likely to progress to a worrisome lesion. In a patient past the childbearing age, I recommend expectant management for CIN 1 preceded by a low-grade lesion; but an excisional procedure, such as LEEP, is recommended for CIN 1 preceded by a high-grade lesion.

CIN 2,3

Guideline. Since CIN 2,3 has a low rate of spontaneous regression and a high rate of progression to invasive disease, immediate treatment is highly recommended. Both excisional and ablative procedures are acceptable. LEEP is the first line treatment regimen because it provides a histologic specimen and a high rate of success. Wright et al. (2007) recommends ablative procedures for women with future plans of pregnancy in women with histological diagnosis of CIN 2,3 and a satisfactory colposcopy. In women with a histological diagnosis of CIN 2,3 and an unsatisfactory colposcopy should undergo an exicisional procedure (Holschneider, et al., 2010). A follow-up is recommended after either excisional or ablative procedure is performed. Wright et al. (2010) recommends a follow-up of HPV DNA testing at six to twelve months, or cervical cytology at six to twelve months, or HPV DNA testing and cervical cytology at six month intervals, or a combination of cytology and colposcopy with endocervical curettage at six and twelve months. For women with positive HPV DNA testing or ASC or greater, a repeat colposcopy is indicated. Those with negative HPV DNA testing and two negative cervical cytology tests can return to regular screening (Wright, et al., 2007).

For adolescents and young women with a diagnosis of CIN 2,3 not otherwise specified and a satisfactory colposcopy, either treatment or observation using both colposcopy and cervical cytology every six months for 24 months is recommended (Holschneider, et al., 2010). When CIN 2 is specified, observation is an acceptable mode of treatment. When the diagnosis of CIN 3 or the colposcopy is unsatisfactory, treatment is essential (Wright, et al., 2007).

For women in early pregnancy with the diagnosis of CIN 2,3, colposcopic and cytologic examinations are acceptable every twelve weeks (Wright, et al., 2007). If the appearance or the cytology of the lesion worsens, a repeat biopsy is recommended. It is acceptable to defer the re-evaluation of the cervix no sooner than six weeks postpartum (Wright, et al., 2007). Treatment is unacceptable unless cervical cancer is identified.

Recommendation. After careful observation of the research, my recommendation is that adolescent and young women with a diagnosis of CIN 2, should be treated with close observation to preserve pregnancy outcomes. These women should follow-up at intervals of six, nine, and twelve months. Women with the diagnosis of CIN 3, should be promptly treated with either cryotherapy or LEEP. I recommend cryotherapy for young women with plans of future pregnancy. In women past the childbearing ages, all high-grade lesions, CIN 2 or CIN 3, should be treated with cryotherapy or LEEP. They should strictly adhere to management protocols and be scheduled for a follow-up visit at 6 to 12 months after treatment.

AIS/Invasive Disease

Guideline. AIS (adenocarcinoma in situ) frequently mulifocal, contains skip lesions, and extends into the endocervical canal making excisional procedures difficult. In this invasive disease, negative margins do not mean the lesion has been completely removed. The preferred management of women with AIS is a hysterectomy (Holschneider, et al., 2010). Consider conservative management if future fertility is desired. Positive margins indicate re-excision or re-evaluation. Negative margins will require long-term follow-up (Wright, et al., 2007). The standard treatment of invasive disease involves surgery or radiotherapy or a combination of both.

Recommendation. Based on the literature, I strongly agree with the guideline for the diagnosis of adenocarcinoma in situ. I recommend for women who may want to have children, a LEEP or cold knife conziation may cure the disease if the surgical margins, or edges, do not show any evidence of disease. For those who have completed childbearing, the treatment of choice is a vaginal or abdominal hysterectomy. I recommend a prompt referral for definitive treatment with surgery (hysterectomy) and/or radiotherapy, with or without chemotherapy in women with invasive disease.

Research Recommendation

Although numerous studies were included in this literature search, other questions may arise related to the subject, therefore, suggestions for further research is crucial. Future studies need to include analysis on the accuracy of the amount of tissue removed in order to determine the potential risk of preterm delivery. Larger retrospective or prospective cohort studies are needed to evaluate further the role of LEEP on preterm delivery, including an evaluation of antenatal surveillance, such as serial digital cervical examinations or transvaginal ultrasonography. Future studies investigating the association between a short interval from conization to pregnancy would be very useful because it is a modifiable risk factor for preterm delivery.

Conclusion

All the treatment methods used to remove precancerous changes of the cervix appear to be associated with varying degrees of adverse obstetric outcomes. It is probable that excisional treatments that remove or destroy substantial amounts of cervical tissue increase the risk. Cold knife conization is associated with significantly increased risk of severe pregnancy complications. Although the risk of serious pregnancy outcomes associated with LLETZ or LEEP does not appear to be significant, the possibility of an increased risk cannot be excluded. Some loop excisions remove large amounts of cervical tissue that may have the same effect as cold knife conization. The majority of loop excisions in young, reproductive age women have visible transformation zones and only need to excise tissue the depth of one centimeter. Thus, this should not result in serious pregnancy outcomes.

In summary, the evidence for the most part indicates that excision of the transformation zone is associated with a small risk of pregnancy-related preterm delivery. This subset of women should be informed about the potential impact on subsequent pregnancies. To aid in an informed choice, women should be provided with information about the advantages and disadvantages of the treatment methods. When obtaining informed consent for LEEP, it is important to counsel women about the increased risk of preterm delivery. The pregnant patient following LEEP should not be considered a high-risk patient unless there are additional risk factors influencing obstetric outcome. Gynecologists should make very effort to optimize residual disease states while minimizing adverse pregnancy outcomes by tailoring and individualizing the management of precancerous cervical lesions.

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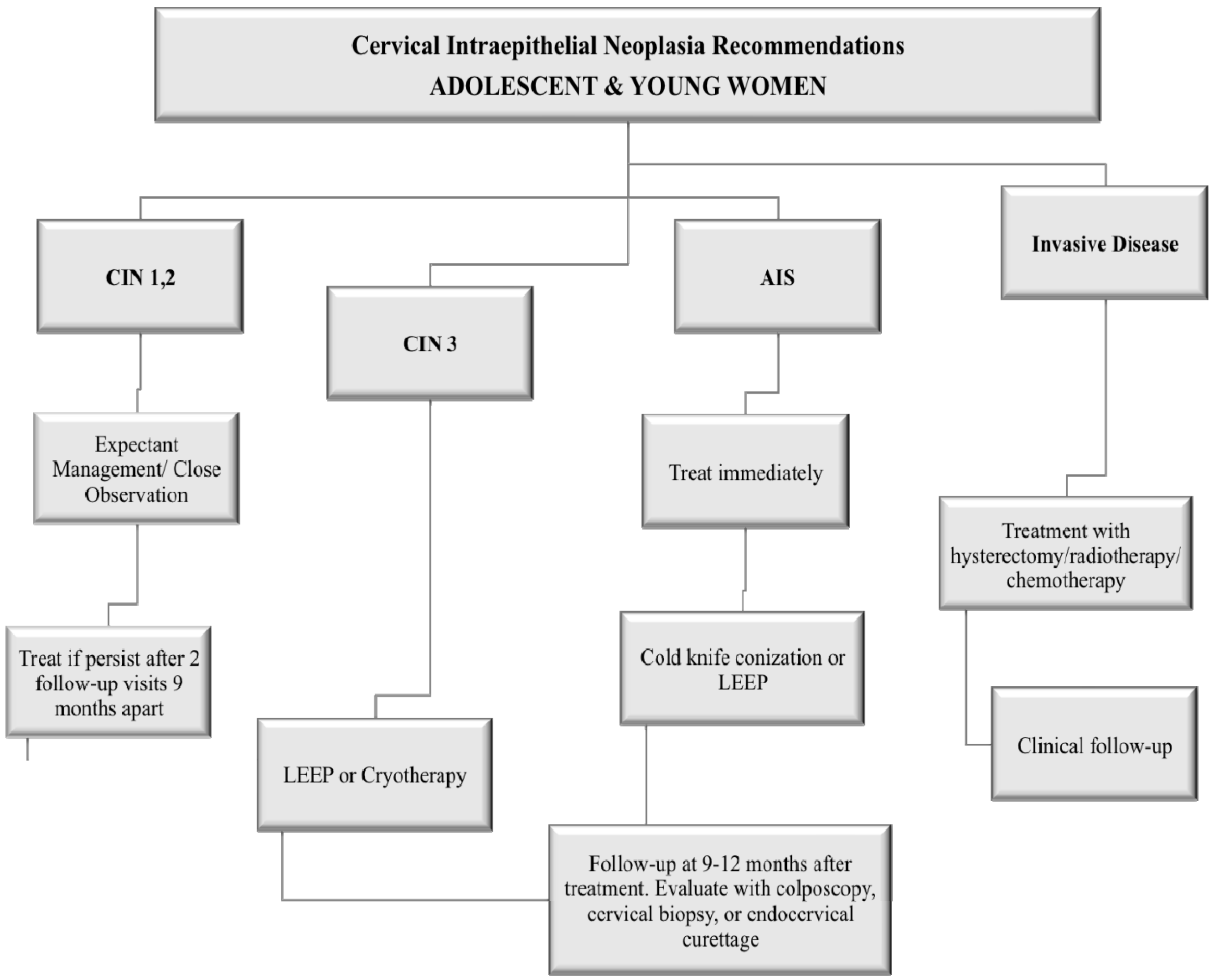
Tables

Author	Study Population	Procedure	Cone size	Statistically Significant Pregnancy Outcomes
Miller & Todd, 1938	899	Cold knife conization	n/a	↑ risk of preterm delivery and abortions
Jones et al, 1979	66-83	Cold knife conization	n/a	↑ risk of preterm delivery, low birth weight, longer duration of labor
Weber, et al, 1979	41-64	Cold knife conization	n/a	No ↑ risk of preterm delivery, low birthweight, cesarean sections
Buller et al, 1982	46	Cold knife conization	n/a	No ↑ risk of preterm delivery, cesarean sections, spontaneous abortions, fertility
Larsson et al, 1982	164-197	Cold knife conization	Large cones; high proportion of radical cones	Preterm delivery, perinatal mortality, cesarean sections
Kristensen et al, 1985	85	Cold knife conization	n/a	No ↑ risk of preterm delivery, low birthweight
Kristensen et al, 1993	170	Cold knife conization, laser conization, electrocautry	n/a	↑ risk of preterm delivery
Kyrgiou et al, 2006	65,280	LLETZ, laser conization, laser ablation, cold knife conization	n/a	↑ risk of preterm delivery, low birth weight, pPROM, perinatal mortality
Blomfield et al, 1993	40	LLETZ	Mean depth 10 (range 7-16) mm	↑ risk of low birth weight
Haffenden et al, 1993	152	LLETZ	n/a	No ↑ risk of low birth weight; no adverse effect on pregnancy
Braet et al, 1994	78	LLETZ	Loop size: depth 15 mm, diameter 20 mm	Small ↑ risk of preterm delivery, low birth weight, pPROM
Bigrigg et al, 1995	72-250	LLETZ	n/a	Perinatal mortality
Cruickshank et al, 1995	127-149	LLETZ	n/a	No ↑ risk of preterm delivery, low birthweight
Ferenczy et al, 1995	574	LEEP	Depth 3-15 mm, diameter 10-14 mm	No ↑ risk of preterm delivery; no adverse effects on pregnancy
Turlington et al, 1996	12-15	LLETZ	n/a	No detrimental effect of LEEP on future fertility
Gentry et al, 2000	20	LLETZ	Mean depth 7 (range 3- 15) mm	Unlikely ↑ risk of preterm delivery; length of cervix does not appear shortened
Althuisius et al, 2001	56	LEEP	n/a	No ↑ risk of preterm delivery prior to 32 weeks of gestation
Paraskevaidis, et al 2002	28	LLETZ	Mean depth 13 (SD 1:8) mm, mean diameter 21 (2:1) mm	↑ risk of short duration of labor, no ↑ risk of preterm delivery or pregnancy outcomes
Crane et al, 2003	310	LLETZ	n/a	↑ risk of preterm delivery, low birth weight
Tan et al, 2004	119	LLETZ	n/a	No ↑ risk of preterm delivery, ↑ risk of low birth weight due to demographics of CIN women
Sadler et al, 2004	581-652	LLETZ, laser conization, laser ablation	Mean diameter 14 (SD 6:1) mm, LLETZ; 1 (4:6) mm, laser conization; 14 (5:7) mm, both	↑ risk of pPROM resulting in preterm delivery, spontaneous labor
Samson et al, 2005	558-571	LLETZ	Mean depth 7 mm (preterm), 7 mm (not preterm); mean diameter 18 mm (preterm), 20 mm (not preterm)	↑ risk of preterm delivery, low birth weight, pPROM
Acharya et al, 2005	79	LEEP	20 mm loop	No ↑ risk of low birth weight or preterm delivery after LEEP
Nohr et al, 2007	11088	LEEP	n/a	Preterm delivery
Himes et al, 2007	1097	Cone biopsy, LEEP, LLETZ, cold knife conization	Mean height/depth 19 mm	↑ risk of pPROM; not associated with preterm delivery; only ↑ risk of preterm delivery if conceive within 2-3 months of procedure
Jakobsson et al, 2007	8210	LEEP	n/a	↑ risk of preterm delivery after all CIN treatments
Bruinsma et al, 2007	5548	Cone biopsy, diathermy, LEEP laser ablation	n/a	↑ risk of preterm delivery in treated and untreated patients, regardless of treatment type
Albrechtsen et al, 2008	15,108	Cold knife conization, laser conization, LLETZ	n/a	↑ risk of preterm delivery after cervical conization
Noehr et al, 2009	8180	LEEP	Depth specified in 3 categories; <12 mm, 13-15 mm, 16-19 m	Preterm delivery
Jakobsson et al, 2009	624	LEEP	Cone size: >10 mm small, 15x12 mm medium, 20x12 mm large	↑ risk of preterm delivery especially among women without previous preterm birth; ↑ incidence of pPROM
Michelin et al, 2009	199 (105 conization, 95 LEEP, 2 both)	LEEP, cold knife conization	Depth 10 mm, diameter 10 mm	Greater ↑ risk of preterm delivery, miscarriages, induced abortion after conization than LEEP
Werner et al, 2010	3,080	LEEP	n/a	No ↑ risk of preterm delivery, perinatal mortality

Figures


Cervical Intraepithelial Neoplasia Recommendations
ADOLESCENT & YOUNG WOMEN
CIN 1,2
CIN 3
AIS
Invasive Disease
Expectant Management/ Close Observation
Treat if persist after 2 follow-up visits 9 months apart
LEEP or Cryotherapy
Treat immediately
Cold knife conization or LEEP
Follow-up at 9-12 months after treatment. Evaluate with colposcopy, cervical biopsy, or endocervical curettage
Treatment with hysterectomy/radiotherapy/ chemotherapy
Clinical follow-up

Abstract

Objective: To determine whether LEEP treatment increases the risk of preterm delivery. Methods: Systematic review of the literature involves extensive database mining in PubMed, CINAHL, and Science Citation Index. The studies addressing the potential impact of LEEP on preterm delivery are either case studies or retrospective cohort studies. Results: 31 studies were identified. Cold knife conization was significantly associated with preterm delivery. Analyses of LEEP showed confounding results regarding the increased risk of preterm delivery. Moreover, risk of total preterm delivery increased significantly with increasing the height of tissue excised, cervical shortening, or short time interval to conception. Conclusion: It appears that any treatment for CIN, including LEEP, increases the risk of preterm delivery but this risk does not appear to be significant. Thus the possibility of an increased risk of LEEP cannot be excluded. Careful consideration should be given to treatment of CIN in reproductive age women.