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Preterm Birth and Surgical Treatment of the Uterine Cervix

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To my family

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals.

- I Jakobsson M, Gissler M, Paavonen J, Tapper A-M.
The incidence of preterm deliveries decreases in Finland.
BJOG 2008; 115: 38-43.
- II Jakobsson M, Gissler M, Sainio S, Paavonen J, Tapper A-M.
Preterm delivery after surgical treatment for cervical intraepithelial neoplasia.
Obstet. Gynecol. 2007; 109: 309-313.
- III Jakobsson M, Gissler M, Paavonen J, Tapper A-M.
LEEP conization increases the risk for preterm birth.
Submitted.
- IV Jakobsson M, Gissler M, Tiitinen A, Paavonen J, Tapper A-M.
Treatment for cervical intraepithelial neoplasia and subsequent IVF deliveries.
Hum. Reprod. 2008; 23: 2252-2255.
- V Jakobsson M, Gissler M, Paavonen J, Tapper A-M.
Long-term mortality in women treated for cervical intraepithelial neoplasia.
BJOG 2009; 116: 838–844.

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ABBREVIATIONS

AGC	atypical glandular cells
AIS	adenocarcinoma <i>in situ</i>
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CDR	Cause-of-Death Register
DNA	deoxyribonucleic acid
eSET	elective single embryo transfer
HDR	Hospital Discharge Register
HPV	human papillomavirus
ICD	International Classification of Diseases
IUGR	intrauterine growth retardation
LBW	low birth weight
LMP	last menstrual period
LOOP/LEEP/LLETZ	loop electrosurgical excision procedure
MBR	Medical Birth Register
NETZ	needle conization
OR	odds ratio
pPROM	preterm prelabour rupture of membranes
PTB	preterm birth
RR	relative risk
SGA	small for gestational age
SIR	standardized incidence ratio
SMR	standardized mortality ratio
STAKES	national research and development centre for welfare and health
TBS	the Bethesda system
THL	National Institute for Health and Welfare
VLP	virus- like particles

ABSTRACT

Cervical cancer is the second most common cancer among women globally. Most, probably all cases, arise through a precursor, cervical intraepithelial neoplasia (CIN). Effective cytological screening programmes and surgical treatments of precancerous lesions have dramatically reduced its prevalence and related mortality. Although these treatments are effective, they may have adverse effects on future fertility and pregnancy outcomes. The aim of this study was to evaluate the effects of surgical treatment of the uterine cervix on pregnancy and fertility outcomes, with the focus particularly on preterm birth. The general preterm birth rates and risk factors during 1987–2005 were studied. Long-term mortality rates of the treated women were studied.

In this study, information from The Medical Birth Register (MBR), The Hospital Discharge Register (HDR), The Cause-of-Death Register (CDR), and hospital records were used. Treatments were performed during 1987–2003 and subsequent deliveries, IVF treatments and deaths were analyzed. Preterm births were further divided into moderately preterm (from 32 to 36 gestational weeks), very preterm (from 28 to 31 gestational weeks) and extremely preterm (less than 28 gestational weeks) subgroups.

The general preterm birth rate in Finland was relatively stable, varying from 5.1% to 5.4% during the study period (1987 to 2005), although the proportion of extremely preterm births had decreased substantially by 12%, from 0.39% to 0.34%. The main risk factor as regards preterm birth was multiplicity, followed by elective delivery (induction of delivery or elective cesarean section), primiparity, *in vitro* fertilization treatment, maternal smoking and advanced maternal age.

The risk of preterm birth and low birth weight was increased after any cervical surgical treatment; after conization the risk of preterm birth was almost two-fold (RR 1.99, 95% CI 1.81– 2.20). In the conization group the risk was the highest for very preterm birth (28–31 gestational weeks) and it was also high for extremely preterm birth (less than 28 weeks). In this group the perinatal mortality was also increased. In subgroup analysis, laser ablation was not associated with preterm birth. When comparing deliveries before and after Loop conization, we found that the risk of preterm birth was increased 1.94-fold (95% CI 1.10–3.40). Adjusting for age, parity, or both did not

affect our results. Large or repeat cones increased the risk of preterm birth when compared with smaller cones, suggesting that the size of the removed cone plays a role. This was corroborated by the finding that repeat treatment increased the risk as much as five-fold when compared with the background preterm birth rate.

We found that the proportion of IVF deliveries (1.6% vs. 1.5%) was not increased after treatment for CIN when adjusted for year of delivery, maternal age, or parity. Those women who received both treatment for CIN and IVF treatment were older and more often primiparous, which explained the increased risk of preterm birth.

We also found that mortality rates were 17% higher among women previously treated for CIN. This excess mortality was particularly seen as regards increased general disease mortality and alcohol poisoning (by 13%), suicide (by 67%) and injury death (by 31%). The risk of cervical cancer was high, as expected (SMR 7.69, 95% CI 4.23–11.15). Women treated for CIN and having a subsequent delivery had decreased general mortality rate (by -22%), and decreased disease mortality (by -37%). However, those with preterm birth had increased general mortality (SMR 2.51, 95% CI 1.24–3.78), as a result of cardiovascular diseases, alcohol-related causes, and injuries.

In conclusion, the general preterm birth rate has not increased in Finland, as in many other developed countries. The rate of extremely preterm births has even decreased. While other risk factors of preterm birth, such as multiplicity and smoking during pregnancy have decreased, surgical treatments of the uterine cervix have become more important risk factors as regards preterm birth. Cervical conization is a predisposing factor as regards preterm birth, low birth weight and even perinatal mortality. The most frequently used treatment modality, Loop conization, is also associated with the increased risk of preterm birth. Treatments should be tailored individually; low-grade lesions should not be treated at all among young women. The first treatment should be curative, because repeat treatments are especially harmful. The proportion of IVF deliveries was not increased after treatment for CIN, suggesting that current treatment modalities do not strongly impair fertility. The long-term risk of cervical cancer remains high even after many years post-treatment; therefore careful surveillance is necessary. In addition, accidental deaths and deaths from injury were common among treated women, suggesting risk-taking behavior of these women. Preterm birth seems to be associated with extremely high mortality

rates, due to cardiovascular, alcohol-related and injury deaths. These women could benefit from health counseling, for example encouragement in quitting smoking.

INTRODUCTION

Cervical cancer is the second most common cancer among women globally. The introduction of screening programmes based on the Papanicolaou test (i.e. Pap smears) has resulted in a profound decrease in cervical cancer incidence and mortality, especially in the Nordic countries (Nieminen et al. 1995, Parkin and Bray 2006). In Finland, secondary prevention of cervical cancer based on screening has been effective. Therefore, the incidence and mortality is very low (www.cancerregistry.fi). However, precancerous lesions are relatively common; their treatment is challenging and there is also a risk of overtreatment. In addition, the psychological impact of receiving these treatments is considerable (Maissi et al., 2004; Maissi et al., 2005). Currently, the development of human papillomavirus (HPV) vaccines has made possible the primary prevention of HPV-induced lesions.

When surgical treatment of the cervix is required, it should not only be effective, but should have no adverse effects on future fertility or pregnancy outcome. Among women of fertile age, long-time consequences should be carefully monitored. Modern treatment modalities have been considered to be safe, not impairing future fertility and pregnancy outcomes. Existing dependable data on future fertility outcomes is, however, sparse. Awareness is increasing as regards unfavorable effects of surgical treatments of the uterine cervix. Treatments might scar and shorten the cervix, and even predispose women to preterm birth (Kyrgiou et al., 2006; Arbyn et al., 2008). Ascending infection, followed by premature rupture of the membranes and preterm birth, may play a role. The rate of spontaneous preterm birth is increasing in many Western countries, but the underlying mechanisms remain unexplained (Langhoff-Roos et al., 2006). Better understanding of these mechanisms is crucial for patient counseling and also for following pregnancies.

This study was conducted in order to gain further knowledge of long-term effects after surgical treatment of the uterine cervix. Special focus was placed on adverse pregnancy outcomes and effects on future fertility. We also studied long-term overall mortality rates among women treated for CIN. Although all of the current treatment modalities are relatively effective, the risk of cervical

cancer remains increased in long-term follow-up (Kalliala et al., 2005; Strander et al., 2007).
Mortality from causes other than cervical cancer has not been studied previously.

2. REVIEW OF THE LITTERATURE

2.1. CERVICAL INTRAEPITHELIAL NEOPLASIA

2.1.1. DEFINITION

Pre-invasive disease of the uterine cervix arises from either squamous cells or glandular cells of the uterine cervix. The progression of squamous dysplasia, Cervical Intraepithelial Neoplasia (CIN), to squamous cell carcinoma is a commonly accepted phenomenon. In CIN lesions abnormal cell growth, i.e. a combination of disturbed cellular maturation, nuclear and cytoplasmic pleomorphism, and increased cellularity, is entirely restricted to the epithelium. The cells share many features of malignant cells: cellular overcrowding, hyperchromatic nuclei and nuclear polymorphism. However, the basement membrane is not breached; neither infiltrative growth nor metastasis exists (MacSween et al., 1992, Tavassoli et al., 2003). Glandular abnormalities represent a small percentage of all cervical abnormalities. Pathologic features of adenocarcinoma *in situ* (AIS) are glands showing stratification, nuclear abnormalities and lack of invasion of the basement membrane (Dunton, 2008).

Cervical intraepithelial neoplasia is of three grades: CIN1 to CIN3. In CIN1 morphological changes are mild and are restricted to the lower third of the epithelium. In CIN2 these changes constitute two thirds of the epithelium thickness. In CIN3 the whole epithelium is affected and morphological changes are prominent (MacSween et al., 1992). The reproducibility of grading, especially CIN1 and even more so CIN2, varies as a result of the subjective nature of evaluation (Stoler et al., 2001; Wright et al., 2007b). Unlike squamous cell cervical cancer, the only well known characterized precursor of cervical adenocarcinoma is AIS. The natural history of adenocarcinoma is unclear (Krivak et al., 2001).

Figure 1. Histological changes in CIN and cervical cancer. Reproduced from Bekkers *et al.* (2004) with permission.

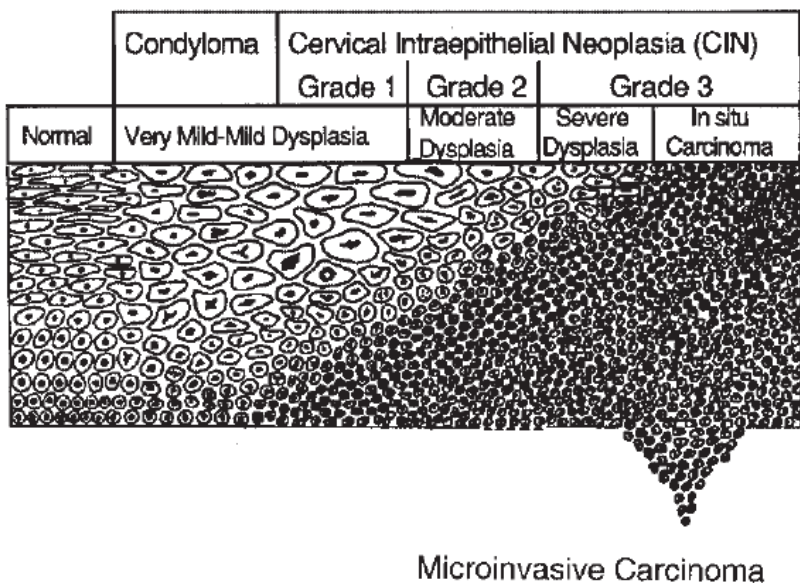


Table 1. Overview of the most frequently used cytological and histological classifications, modified from Bulk *et al.* (2004) with permission.

Cytology		Histology	
Bethesda 2001		WHO	CIN
Squamous	Glandular	Squamous	Squamous
ASC-US, LSIL,	AGC-NOS	Dysplasia levis	CIN1
ASC-H	AGC, favor neoplastic	Dysplasia moderata	CIN2
HSIL		Dysplasia gravis	CIN3
Invasive carcinoma	AIS,	Carcinoma <i>in situ</i>	Carcinoma
	Adeno-carcinoma	Invasive carcinoma	

ASC-US = atypical squamous cells of undetermined significance, ASC-H = atypical squamous cells, high grade cannot be ruled out, LSIL = low grade squamous intraepithelial lesion, HSIL = high grade squamous intraepithelial lesion, AGC-NOS = atypical glandular cells-nonspecified, AIS=adenocarcinoma *in situ*, CIN=cervical intraepithelial neoplasia.

2.1.2. ETIOLOGY AND RISK FACTORS

2.1.2.1. HPV

In the 1970s zur Hausen described the role of HPV in cervical cancer (zur Hausen, 1977). Those original findings led to the Nobel Prize in 2008. Persistent HPV infection is necessary for the development of cervical cancer and its precursors; this association is the one of the strongest in cancer epidemiology (van Hamont et al., 2008).

The human papillomavirus is small (8 kb) and its genome is circular, containing double-stranded DNA. About 150 different HPV types have been found, and this number is increasing. Roughly 40 infect the genital tract, where they can induce cervical, vaginal and vulvar intra-intraepithelial neoplasia (CIN, VIN, VAIN, respectively), cancer and genital warts (Paavonen, 2007; Stanley et al., 2007). Certain HPV types are considered to be high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82), while others (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81) are low-risk types depending upon their oncogenic potential. Low-risk types cause benign warts, cutaneous lesions and respiratory papillomatosis (Munoz et al., 2003). Virtually all cervical cancers contain HPV DNA sequences, with high-risk oncogenic potential.

The most common HPV types associated with cervical cancer are HPV 16, 18, 33, 45, 31 and 58. HPV 16 is the most common type, being present in 2–4% of all women with normal cytology and in 50–55% of women with cervical cancer (Bosch et al., 2008a). Together, HPV 16 and 18 are responsible for 70% of all cervical cancer cases, and about 80–85% of cervical adenocarcinomas; the histological subgroup that easily escapes from conventional cytology-based screening. These types show the clearest pattern of progression vs. regression compared with the other high-risk HPV types. HPVs 45 and 31 cause another 10% of cervical cancer cases. Infection with multiple HPV types is found in a sizable minority of infections (Bosch et al., 2008a), and recent studies suggest that it is associated with an increased rate of more severe and persistent HPV infection (Bosch et al., 2008a; Spinillo et al., 2009), although this is still under debate (Munoz et al., 2003). In the cervix, in situations such as menarche, delivery and cervical trauma, infection reaches the basal layer and establishes a persistent infection.

2.1.2.2. OTHER RISK FACTORS

Persistent infection with a high risk HPV is a necessary but not sufficient cause of CIN lesions. Accessory risk factors are young age, high number of sexual partners, high parity, other genital

infections and smoking (Castellsague et al., 2002). In many (Munoz et al., 2006; Vaccarella et al., 2008), but not in all studies (Ho et al., 1998), current smoking is associated with an increased prevalence of HPV. Other factors that are associated with HPV acquisition are age at first HPV exposure, and sexual behavior (Ho et al., 1998). Long-term oral contraceptive use doubles the risk of cervical cancer (Munoz et al., 2006; Castellsague, 2008). Low socioeconomic status is also associated with an increased risk of CIN and cervical cancer (Castellsague et al., 2002). In a Finnish study multiparity slightly increased the risk of squamous cell carcinoma, but decreased the risk of adenocarcinoma. Among young multiparous women an increased incidence of cervical cancer was suggested to be associated with HPV 16 and Chlamydia trachomatis infections (Hinkula et al., 2004).

2.1.3. NATURAL HISTORY

Infection with HPV is acquired in adolescents within a few months after first sexual intercourse and a high percentage of young adults are HPV-positive (Paavonen, 2007). In a Finnish study one third of asymptomatic university students had HPV infection, and of these, over 80% had high-risk HPV types (Auvinen et al., 2005). Among female college students in the United States, the cumulative 36-month incidence of HPV has been reported to be 43%, and the median duration of the infection was 8 months (Ho et al., 1998). Infection with HPV is via skin-to-skin contact with an infected partner. There is some evidence suggesting that HPV can also be transmitted by nonsexual routes (Rintala et al., 2005a; Rintala et al., 2005b; Rintala et al., 2006; Sarkola et al., 2008). Most women worldwide will be infected by HPV at some point during their lifetime. Globally, the prevalence of HPV in women with normal cytology is about 10%, although it is higher in developing countries (Bosch et al., 2008a).

The peak incidence occurs in young women (20–24 years) and there are often multiple types of HPV. The incidence thereafter decreases with age (Bosch et al., 2008a). There is another smaller peak among women over 45 years old. It is unclear whether this second rise is due to new HPV infections associated with changes in sexual life, or reactivation of latent infection following immune senescence, or a cohort effect translating high exposure throughout life among older women (Bosch et al., 2008a).

2.1.3.1. REGRESSION

Most HPV infections are transient and the majority of them resolve within two years (Kyrgiou et al., 2007). Viral clearance often precedes cytological normalization (van Hamont et al., 2008). The great majority (60–70%) of all CIN lesions never progress to invasive cancer, since spontaneous regression without any treatment is common (Syrjänen, 1996; Jordan et al., 2009).

The tendency to regress decreases as lesion severity increases: 57% for CIN1, 43% for CIN2 and 32% for CIN3 (Östör, 1993). In another study a regression rate for CIN1 of 49% during six months was found (Bansal et al., 2008). High-grade (CIN3) lesions are always treated nowadays; thus the exact regression rate remains unknown.

Among adolescents CIN lesions are common, but the risk of invasive cervical cancer is minimal because of the high regression rate (Wright et al., 2007b). Negative HPV status is associated with

regression. Irrespective of the associated HPV type, spontaneous regression in connection with an abnormal low-grade smear occurred in 91% of adolescents in 36 months (Moscicki et al., 2004). Pretorius and co-workers have reported that progression from CIN1 to CIN3 or worse was only 0.4% among adolescents (Pretorius et al., 2006). During pregnancy the risk of progression is also minimal and regression rates are high: as much as 69% for histologically proven CIN3 after delivery (Jordan et al., 2009). The risk of progression of precancerous lesions can be decreased by surgical treatment, but whether HPV infection can be cured by aggressive surgical treatments is unclear (Ho et al., 1998). In a small study, however, HPV positivity decreased similarly after Loop conization or after cryosurgery (Aerssens et al., 2008).

2.1.3.2. PERSISTENCE

Persistence is broadly defined as detection of the same HPV type several times within a given time interval (Moscicki et al., 2006). Another definition is as an infection lasting more than 6 to 12 months (Zsemlye, 2008). Approximately 15% of all infected women cannot effectively clear the HPV infection (Jordan et al., 2009). Infection at an older age, and infection with high-risk HPV types are risk factors of persistent infection (Castle et al., 2007; Stanley et al., 2007; Zsemlye, 2008). It is the major risk factor as regards malignant transformation of the cells. Persistent high-risk HPV infection predicts and precedes the development of cytological and histological abnormalities (Pretorius et al., 2006; Bosch et al., 2008b). The first age-specific incidence of cervical cancer peaks about twenty years after the first incidence peak of HPV infection, around the age of 40. Estimations of persistence of CIN1 and CIN2 are 32% and 35%, respectively (Östör, 1993; Syrjänen, 1996). In large cohort study the 12-month persistence of CIN1 was 46% (Bansal et al., 2008).

2.1.3.3. PROGRESSION

The probability of CIN progressing to invasive disease increases with the severity of the lesion. Another prognostic factor is HPV type, HPV 16 being associated with the greatest risk. Lesions destined to clinical progression proceed within one or two years from the initial diagnosis (Syrjänen, 1996). Between 0% and 30% of histologically confirmed CIN lesions will ultimately develop to CIN2-3 and only 1% will lead to invasive carcinoma (Jordan et al., 2009).

Approximately 20–50% of all CIN1 lesions contain high-risk HPV types, but also low-risk types to some extent (Wright et al., 2007b; Castellsague, 2008). In addition, the distribution of high-risk

HPV types is different from that of higher grade lesions. In a prospective follow-up study CIN1 lesions progressed to high-grade lesions in only 12% of cases over two years (Cox et al., 2003). In another study only 1.9% of cases with initial CIN1 or less progressed to CIN3 or worse over approximately two years. Progression rates are higher if the initial HPV test is positive (2.3%), or if a woman is over 30 years of age (2.7%) (Pretorius et al., 2006). In a cohort study involving women with CIN1, only 7% progressed to higher grade lesions in 6 months, and another 4% in 12 months (Bansal et al., 2008). In a Finnish study progression from CIN1 to CIN3 was observed in 10% of all cases (Syrjänen et al., 1992).

CIN2 has been suggested to consist of a mixture of acute infections and true cancer precursors; thus reproducibility is much worse than with CIN3 (Castle et al., 2007; Bosch et al., 2008a). The regression rate for CIN2 is about 23–43% of all cases and therefore it cannot be considered as a high-grade lesion (Syrjänen, 1996; Finnish Current Care guidelines, 2006). It also contains a wider range of HPV types. In approximately 70–90% of all high-grade lesions HPV DNA can be found (Castellsague, 2008).

CIN3 can develop relatively quickly, 2 to 3 years after initial HPV exposure (Bosch et al., 2008a). The risk of progression to cancer is estimated to be 12% (Finnish Current Care guidelines, 2006). The average lead time is unknown, but according to longitudinal studies, within five years of infection CIN lesions either regress or progress to CIN3. In old and nowadays unethical studies where histologically confirmed CIN3 lesions were left untreated, the proportion that progressed to cancer varied from 24% to 75%. In a report from New Zealand, women without adequate treatment of CIN3 showed progression to cancer in 31% of cases in 30 years' surveillance. Among women with persistent disease over 24 months, progression was found in 50% of all cases. With adequate treatment, however, the risk of cervical cancer was only 0.3% in 30 years' surveillance (McCredie et al., 2008).

2.1.4. DIAGNOSIS

Diagnosis of CIN lesions is based on Pap-smear samples and confirmed by histology obtained from colposcopy-guided biopsies. During the last 50 years, cytology, especially in organized screening, has proven to be efficient in reducing cervical cancer. Cytology results in the detection of over 75–80% of pre-invasive and invasive squamous cell lesions of the cervix, but a major weakness remain the false-negative rate (Kyrgiou et al., 2006). The accuracy of cytology in the detection of glandular

abnormalities is worse (Dunton, 2008). Indications for colposcopy are recurrent low-grade Pap smear results, a high-grade Pap smear, recurrent HPV positivity and suspicion of cervical cancer (Jordan et al., 2008). Women with significantly abnormal Pap smears are referred to colposcopy, where the cervix and lower genital tract are examined with a magnifying microscope before and after applying an acetic acid solution. The main advantages include safety and short duration (Schiffman et al., 2003; Kyrgiou et al., 2006; Jordan et al., 2008). Colposcopy is not, however, suitable as a primary screening tool and it requires extensive training. According to the results of a meta-analysis, the sensitivity of colposcopy in detecting CIN2+ lesions was 96% and the specificity 48% (Mitchell et al., 1998). Colposcopy has a sensitivity of approximately 75% in detecting CIN3+ lesions, but it can be further improved by taking multiple punch biopsies for histological evaluation (Gage et al., 2006). In comparative studies, colposcopic impressions and histological diagnoses comprise the gold standard. However, even among experienced colposcopists, performance and inter-observer reproducibility is poor (Kyrgiou et al., 2006; Massad et al., 2008). The predictive accuracy of colposcopy improves as the severity of the lesions increase.

The increasing appreciation that the presence of high-risk HPV types is a necessary prerequisite of high-grade CIN lesions, led to a new approach, i.e. HPV testing as a primary intervention. It has many advantages: sensitivity is high across different laboratories, detection is independent of the limitations of human eye assessment, and self-sampling is as effective as professionally collected samples (Bosch et al., 2008b). The role of HPV testing is, however, still controversial. It is expensive, and specificity is poor (Kotaniemi-Talonen et al., 2005). It can be useful as a primary test for screening, as a reflex test for equivocal smears, or in the follow-up of treated CIN lesions (Arbyn et al., 2005; Kotaniemi-Talonen et al., 2005; Arbyn et al., 2006). Swedish investigators used HPV tests in conjunction with Pap smears and found over 50% more cases of CIN2 or CIN3 among HPV-tested women. A reduction of approximately 40% as regards the risk of high-grade CIN or cervical cancer in subsequent screening rounds was found (Naucler et al., 2007).

2.1.5. PREVENTION

Cervical cancer is preventable and generally curable if detected early. Increased awareness of HPV infection and sexual risk-taking behavior can prevent HPV infection and subsequent CIN lesions. The introduction of vaccines against HP virus-like particles (VLPs) has paved new ways for primary prevention of cervical cancer. There are two different vaccines. The quadrivalent vaccine was

introduced first and it is targeted against HPV 6, 11, 16 and 18, thus preventing cervical cancer and warts. The quadrivalent vaccine has also proved to be efficient in preventing vaginal and vulvar precancerous lesions (Villa et al., 2006; Joura et al., 2007). The bivalent vaccine is targeted against high-risk HPV 16 and 18 (Paavonen et al., 2007). Both vaccines have been proven to be safe and effective in preventing CIN lesions (Lehtinen et al., 2006). Many countries have introduced these vaccines in general vaccination programmes, but such recommendations do not exist in Finland. The authorities are currently evaluating the optimal approach to vaccination.

Since there is currently no treatment for HPV infection, secondary prevention is aimed at detecting CIN lesions early to enable treatment. Traditionally, prevention has been based on conventional Pap smear screening. Therefore, cervical cancer prevention has been focused on the management of CIN lesions. Evaluation and management of these lesions has markedly reduced squamous cell cervical cancer rates, but it is costly, placing an enormous burden on the healthcare system. This approach has been very successful, especially in the Nordic Countries (Nieminen et al., 1995; Nieminen et al., 1999; Anttila et al., 2000; Parkin et al., 2006). The Finnish Cancer Registry was established in 1953. The nationwide mass screening programme in Finland was started in the mid-1960s. All municipalities provide all women aged 30–60 years with an organized mass screening programme with a screening interval of 5 years. The nationwide Mass Screening Registry organizes the programme. Screening is free of charge, includes personal invitations, reminders, information about the results, and continuous evaluation of the programme. Successful screening programmes are coordinated by the public health systems; they require continuous assessment and compliance of the population.

Since the start of screening the age-standardized mortality rate and the incidence of invasive disease have decreased by 80% (Nieminen et al., 1995; Nieminen et al., 1999; Anttila et al., 2000; Bosch et al., 2008b). The incidence of cervical cancer declined from 15/100 000 women in the 1960s to 2.7 in the 1990s (Toivonen et al., 2005). The incidence of cervical adenocarcinoma has not decreased, and consequently its proportion has even increased (Anttila et al., 2000).

2.1.6. TREATMENT

The management of CIN has changed drastically over the last decade. Formerly, CIN1 was believed to represent a disease continuum with progression from CIN1 to CIN3. Treatment was always recommended to prevent development of cervical cancer (Boardman et al., 2008). The diagnosis

of CIN1 is not always reliable; histological reproducibility is poor. In a large cohort study only 43% of CIN1 lesions were confirmed by an expert panel, 41% were downgraded and 13% upgraded to CIN2/CIN3 (Stoler et al., 2001). Therefore, treatment of CIN1 has to involve balance of the high chance of spontaneous regression with the possible risk of not treating missed high-grade disease (Jordan et al, 2009). Because of the high regression rate, the current guidelines recommend treatment of only persistent CIN1 lesions, persisting over one year (Jordan et al., 2008) or two (Finnish Current Care guidelines, 2006; Wright et al, 2007b). According to American guidelines, management is more aggressive if the initial cytology is of high-grade (HSIL, high-grade squamous intraepithelial lesion; or ASC-H, atypical squamous cells, cannot exclude HSIL; or AGC, atypical glandular cells). Finnish Current Care guidelines recommend treatment for all women over 30 years of age. Younger women are referred to colposcopy at 12 months. Treatment is required if lesions persist over 24 months (Finnish Current Care guidelines, 2006).

Higher grade lesions (CIN2, CIN3) require treatment because they have the potential to progress to invasive cancer (Spitzer, 2007; Jordan et al., 2009). The histological distinction between CIN2 and CIN3 is poorly reproducible. CIN2 lesions are considered as a threshold to treatment to ensure maximum safety (Wright et al., 2007b). During pregnancy, treatment is not recommended unless there is suspicion of invasion (Finnish Current Care guidelines, 2006; Jordan et al., 2009). Surgery, when needed, should be performed after delivery. In adolescents, regression rates are high and the risk of progression is low; thus expectant management should be considered (American College of Obstetricians-Gynecologists, 2006; Finnish Current Care guidelines, 2006). American guidelines indicate a preference for observation of adolescents diagnosed with CIN2, although treatment is also acceptable. For CIN3, or when colposcopy is unsatisfactory, guidelines recommend treatment (Wright et al., 2007b).

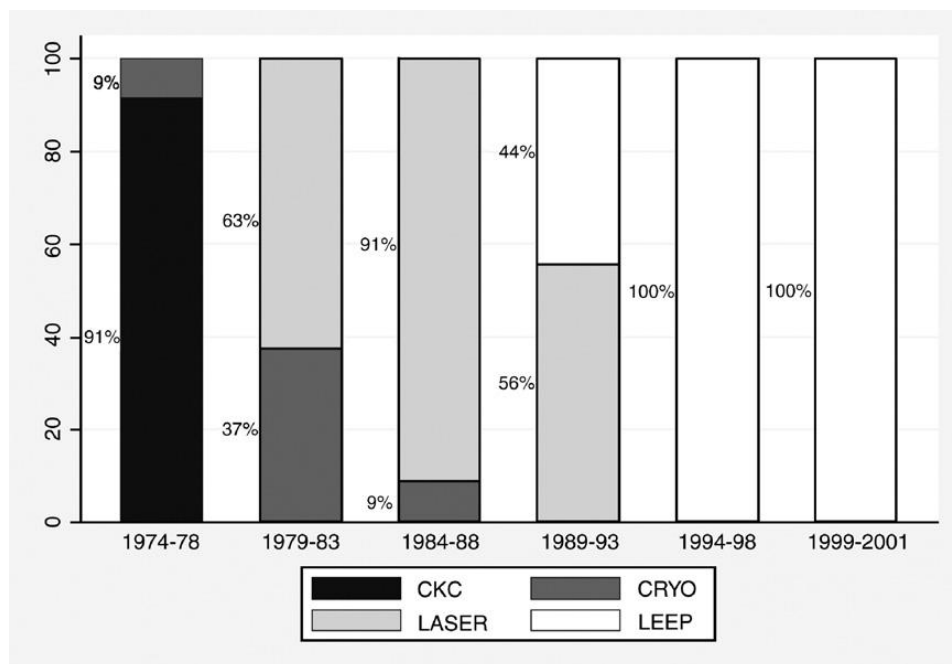
Hysterectomy is recommended in the management of AIS in women who have completed child-bearing. Conservative management, i.e. excisional treatment, is, however, also acceptable (Finnish Current Care guidelines, 2006; Wright et al., 2007b).

2.1.6.1. TREATMENT MODALITIES

Depending on the severity of the lesion, pre-invasive lesions of the uterine cervix can be treated by local ablative or excisional methods. Nonsurgical methods do not exist (Wright et al., 2007b). Ablative or destructive treatments (e.g. cryosurgery, laser ablation) destroy the diseased tissue

only superficially. Excisional treatments include cold knife conization, laser conization and Loop conization (Loop, LEEP, LLETZ). These treatments remove a cone-shaped piece of tissue from the uterine cervix. Excisional methods provide a tissue specimen for pathological examination and are therefore mandatory for a patient with unsatisfactory colposcopy results (i.e. the entire transformation zone is not visible), suspicion of micro-invasive, invasive, or glandular disease, and non-concordant cytology and histology (MartinHirsch et al., 2006; Jordan et al., 2009). Lesions are nowadays treated under local anesthesia and with colposcopic control. All the current treatment modalities are equally effective; there is no obvious superior technique (MartinHirsch et al., 2006; Wright et al., 2007b; Jordan et al., 2009).

Figure 2. Proportions of women treated by means of different methods during 1974–2001 in Finland. Reproduced from Kalliala *et al.* (2005) with permission. CKC = cold knife conization, CRYO = cryosurgery, LASER = laser conization, LEEP = Loop electro-surgical excision procedure.



COLD KNIFE CONIZATION

Cold knife conization is a technique involving excision of diseased tissue from the cervix by knife. This treatment requires general anesthesia and is performed in an operating theatre. In Finland it was the main treatment modality in the 1970s (Kalliala *et al.*, 2007) (Figure 2). Treatment outcome is good, from 90% to 94% (MartinHirsch *et al.*, 2006). Some authors consider that it may still have a place if invasion or glandular disease is suspected, because thermal artefacts do not interfere with interpretation of margins (MartinHirsch *et al.*, 2006; Wright *et al.*, 2007b). In skilled hands, however, thermal artefacts are generally minimal. Neither current European nor Finnish Current Care guidelines recommend cold knife conization (Finnish Current Care guidelines, 2006; Jordan *et al.*, 2009).

LASER CONIZATION

In the 1980s laser conization was the main treatment modality in Finland, but nowadays it is seldom in use (Kalliala *et al.*, 2007). This procedure can be performed under local or general anesthesia. A laser beam incises an ectocervical circumferential incision to a depth of 1 cm. Hooks or retractors manipulate the cone to allow deeper incision. Hemostasis is achieved by defocusing the laser beam. This treatment requires a longer learning-curve than Loop conization. Success rates are good, varying from 93% to 96% (MartinHirsch *et al.*, 2006).

LOOP CONIZATION

Prendiville *et al.* (1989) introduced Loop conization in 1989. Nowadays it is undoubtedly the most popular treatment modality for precancerous lesions. In this procedure, tissue is excised by means of an electrically charged wire loop, cutting and electrocoagulating at the same time. This treatment requires only local anesthesia and is performed with colposcopic guidance. It is fast, easy to learn and cheap, and produces suitable material for histological evaluation (Gunasekera *et al.*, 1990). Treatment success varies from 91% to 98% in nonrandomized studies (MartinHirsch *et al.*, 2006). Loop conization is regarded as safe and is associated with a low rate of morbidity (Lindeque, 2005; Spitzer, 2007).

The size and depth of the cone can be adjusted by the size of the wire loop. Large cones can be made by using straight tungsten wire instead of usual Loop instruments (NETZ, EL-needle, straight needle conization). This enables the removal of a large lesion in one piece, which facilitates evaluation of margin involvement. In a randomized study of 347 women, NETZ specimens more often had clear margins in comparison with conventional Loop wire specimens (85% vs. 75%), although the procedures took longer to perform and were more often difficult (Panoskaltsis *et al.*, 2004). Curved Loop instruments (C-LETZ) also exist (Mints *et al.*, 2006). The “See and treat” approach represents a method of diagnosis and curative Loop conization in one visit, without prior biopsies. This can lead to overtreatment, to at least some extent (Wright *et al.*, 2007b; Jordan *et al.*, 2009). Some authors (Murdoch, 1995; Kjellberg *et al.*, 2007), however, consider this approach very attractive, especially when older women are concerned.

LASER ABLATION

Laser ablation was widely in use during the 1980s, but it was superseded by the Loop in the early 1990s (Paraskevaidis *et al.*, 2007). In laser ablation, intracellular water is rapidly vaporized by a laser beam. According to European guidelines destruction should be at least to 4 mm, but it is even safer is to destroy to a depth of 7 mm (van Rooijen *et al.*, 1999; Jordan *et al.*, 2009). Selected power and the length of the exposure control the treatment. This procedure is suitable only for low-grade lesions, and a colposcopist must be very experienced, since histological material for confirmation of diagnoses cannot be achieved. In skilled hands treatment is still effective; treatment success is about 95% (MartinHirsch *et al.*, 2006).

OTHER TREATMENT MODALITIES

Other methods are mainly destructive. In cryosurgery, tissue is destroyed by hypothermia. In Finland, cryosurgery was used in the 1980s (Kalliala et al., 2007). The treatment is easy to perform and the equipment is inexpensive; therefore it is recommended for low-grade disease, particularly where resources are limited (Paraskevaïdis et al., 2007; Zsemlye, 2008). In cryosurgery a metal probe is placed against the transformation zone and refrigerant gas is passed through the base of the probe, producing hypothermia. Crystallization of intracellular water causes cryonecrosis of the tissue. Treatment success varies from 77% to 93%, but the double freeze-thaw-freeze technique further improves the eradication rate (MartinHirsch et al., 2006).

Radical diathermy (or thermocoagulation) is an old-fashioned technique that requires general anesthesia. A straight electrodiathermy needle is used and the aim is to destroy tissue to a depth of approximately 1 cm (Jordan et al., 2009). This treatment is associated with more side effects than Loop conization (MartinHirsch et al., 2006). Diathermocoagulation also involves the use of heat to destroy cervical epithelium, but only to depth of to 2–3 mm. These treatments can no longer be regarded as adequate for CIN (Jordan et al., 2009).

2.1.7. COMPLICATIONS

2.1.7.1 SHORT-TERM COMPLICATIONS

In general, short-term complications, such as bleeding, discharge, or infection, are uncommon. Severe pain is experienced by 2–18% of all patients. In general bleeding that disturbs the procedure occurs in about 2–12 % of all cases (Partington et al., 1989; Gunasekera et al., 1990; MartinHirsch et al., 2006; Mossa et al, 2005).

Cold knife conization is associated with significant morbidity, such as primary and secondary hemorrhage, and local and pelvic infection. Hemostasis may be difficult to achieve and hemostatic sutures are associated with increased risks of cervical stenosis and unsatisfactory colposcopy (Martin-Hirsch et al., 2000). In laser conization bleeding is less frequent than with cold knife conization, because cervical trauma is less severe (MartinHirsch et al., 2006). Laser ablation produces more peri-operative pain and may be associated with more bleeding compared with Loop conization (MartinHirsch et al., 2006). Cryosurgery is associated with vasovagal symptoms or cramping during the procedure and profuse watery discharge (Zsemlye, 2008).

2.1.7.2. LONG-TERM COMPLICATIONS

Long-term complications include cervical stenosis, mid-trimester miscarriages, preterm birth, and other adverse pregnancy outcomes.

CERVICAL STENOSIS

Cervical stenosis occurs in 2–37% of all women: after laser vaporization 6%, after cryosurgery 3%, after laser conization 2–25%, after cold knife conization 13–37% and after Loop conization 8–19% (Finnish Current Care guidelines, 2006). In some studies cervical stenosis has been associated with large cones (Baldauf et al., 1996).

FERTILITY

Infertility is classified into female infertility (25–47%), male infertility (16–26%), combined (18%) or idiopathic (12–30%). Female infertility can be further divided into ovulatory dysfunction (34%), tubal infertility (24%), endometriosis-associated (11%) and other (11%) (Spalding et al., 1997; Wright et al., 2006; Poikkeus et al., 2007a).

Cervical procedures cause scarring of the cervix and thus possible cervical stenosis, which could prevent sperm entering the uterine cavity (Baldauf et al., 1996). Distortion of the endocervical canal and deformation of the cervix may also play a role. In addition, there are some reports of infertility problems related to cervical stenosis and absent mucus production after cervical treatments (Hammond et al., 1990; Kennedy et al., 1993). Shortening of the cervix and decreased local antimicrobial defense might predispose women to ascending infection, which may lead to tubal infertility. Women with HPV infection may have a background of more tubal infertility than other women (Hammond et al., 1990; Fox et al., 1991). Sagot *et al.* found a tendency towards a higher rate of extrauterine pregnancies in cases in which there might have been tubal damage due to sexually transmitted diseases (Sagot et al., 1995).

The available evidence on fertility is sparse and it is mainly based on telephone and mailed queries. In interviews of 250 matched pairs, women were asked for information on menstruation, fertility and pregnancy after Loop conization. No negative effects were reported (Bigrigg et al., 1994). In Canada, the pregnancy rate among women treated by means of Loop conization was not decreased compared with untreated women (Ferency et al., 1995). In one study, women were even more fertile after than before laser surgery (Spitzer et al., 1995). In a cohort of 1 000 women receiving a mailed questionnaire, no adverse fertility outcomes were reported (Cruickshank et al.,

1995). In older reviews from the late 1970s, fertility impairment was not observed after cervical conization (Weber et al., 1979a; Weber et al., 1979b).

Most studies lack information on second trimester abortions, because Medical Birth Registers do not have information on late miscarriages. In the older literature the proportion of late abortions was increased after total cervical amputation and conization (Myllynen et al., 1984). In cold knife conization studies, increased proportions of first and second trimester miscarriages have been reported (Lee, 1978; Jones et al., 1979). These, however, are old and small studies. The risk of late abortion was increased fourfold after conization in a recent register-based study (Albrechtsen et al., 2008). This has not, however, been confirmed in all studies (Blomfield et al., 1993). No studies have revealed an increase in early miscarriage rates after Loop conization.

Spitzer and co-workers studied fertility and pregnancy outcomes, using internal controls, after laser ablation and laser conization. Treated women had more terminated pregnancies and the authors suggested that women might have been worried about progression of the disease (Spitzer et al., 1995). Sagot *et al.* found no fertility impairment after Loop conization (Sagot et al., 1995). In a recent review the authors stated that fertility was not impaired after any treatment of CIN (Kyrgiou et al., 2006).

PRETERM BIRTH

Many investigators have reported increased preterm birth rates after treatment of CIN, but the predisposing mechanisms remain unknown. One explanation is that the procedures used might shorten the cervix (Ricciotti et al., 1995; Mazouni et al., 2005) and bring about mechanical weakness. Shortening of the cervix, however, has not been observed in all studies (Gentry et al., 2000; Paraskevaidis et al., 2002a).

According to another theory, there is decreased mucus production (Kristensen et al., 1993b; Kyrgiou et al., 2006). In some studies the amount of *Lactobacilli*, which belong to the normal ecological flora of the vagina, has been decreased after cervical conization (Svare et al., 1992). Removal of the cervical glands, containing antimicrobial agents, leads to ascending bacterial colonization, elevation in the concentrations of prostaglandins, release of proteolytic enzymes and finally premature rupture of the membranes (Hammond et al., 1990; Kristensen et al., 1993b). The development of CIN is often associated with or preceded by cervical inflammation. The increased risk of infections may also be related to risk-taking behavior – more sexually transmitted infections

and heavy smoking (Sagot et al., 1995). According to another possible explanation, cervical scarring may play a role (Kristensen et al., 1993b). General reorganization of the cervical stroma during the healing process could lead to preterm birth (Gentry et al., 2000).

Only one small randomized study exists in which different treatment modalities have been compared (Mathevet et al., 2003). However, the authors did not compare results with those among untreated women. They studied 50 pregnancies among 39 women and only one preterm birth after Loop conization was observed.

ABLATIVE TREATMENTS

Laser ablation may be safer than excisional treatments (Kyrgiou et al., 2006; Bruinsma et al., 2007). In many countries ablative methods are reserved for low-grade lesions. The treated area may be smaller than with excisional treatments, which may be the explanation for the greater safety. Women undergoing ablative treatments more often have low-grade lesions, which may explain the lower background preterm birth risk. For example, in a Swedish study Forsmo *et al.* did not find an increased risk of LBW after laser ablation (high-grade lesions were more often treated by means of laser conization). The study was based on self-reported pregnancy outcomes, not including gestational weeks and socioeconomic position (Forsmo et al., 1996). In several studies laser ablation has been found not to affect subsequent pregnancy outcome (van Rooijen et al., 1999; Bruinsma et al., 2007). Kyrgiou *et al.* concluded in their meta-analysis that laser ablation was not associated with adverse pregnancy outcome (Kyrgiou et al., 2006).

EXCISIONAL TREATMENTS

In the older literature determination of gestational age was less accurate than nowadays, and was mainly based on the time of the last menstrual period. Many case series had inadequate control groups, and confounding factors, such as smoking, socioeconomic status, and parity, were not taken into account. Many studies failed to have sufficient statistical power to detect significant correlations (Buller et al., 1982; Kristensen, 1985; Kuoppala et al., 1986). Finnish investigators observed an increase in preterm birth rates after combined amputation and conization of the cervix (Myllynen et al., 1984). Lee and co-workers reported that the proportion of cases of LWB was increased after any cervical treatment (Lee, 1978), which may indicate an increased preterm birth rate. Cold knife conization has been reported to increase adverse pregnancy outcomes such as preterm birth and LWB in many (Jones et al., 1979; Larsson et al., 1982; Ludviksson et al., 1982; Kuoppala et al., 1986; Kristensen et al., 1993a; Kristensen et al., 1993b), but not in all studies

(Weber et al., 1979b; Buller et al., 1982). This has also been confirmed in reviews (Kristensen et al., 1993b; Kyrgiou et al., 2006). In the most recent review cold knife conization was also associated with increased severe and extreme preterm birth, and perinatal mortality (Arbyn et al., 2008).

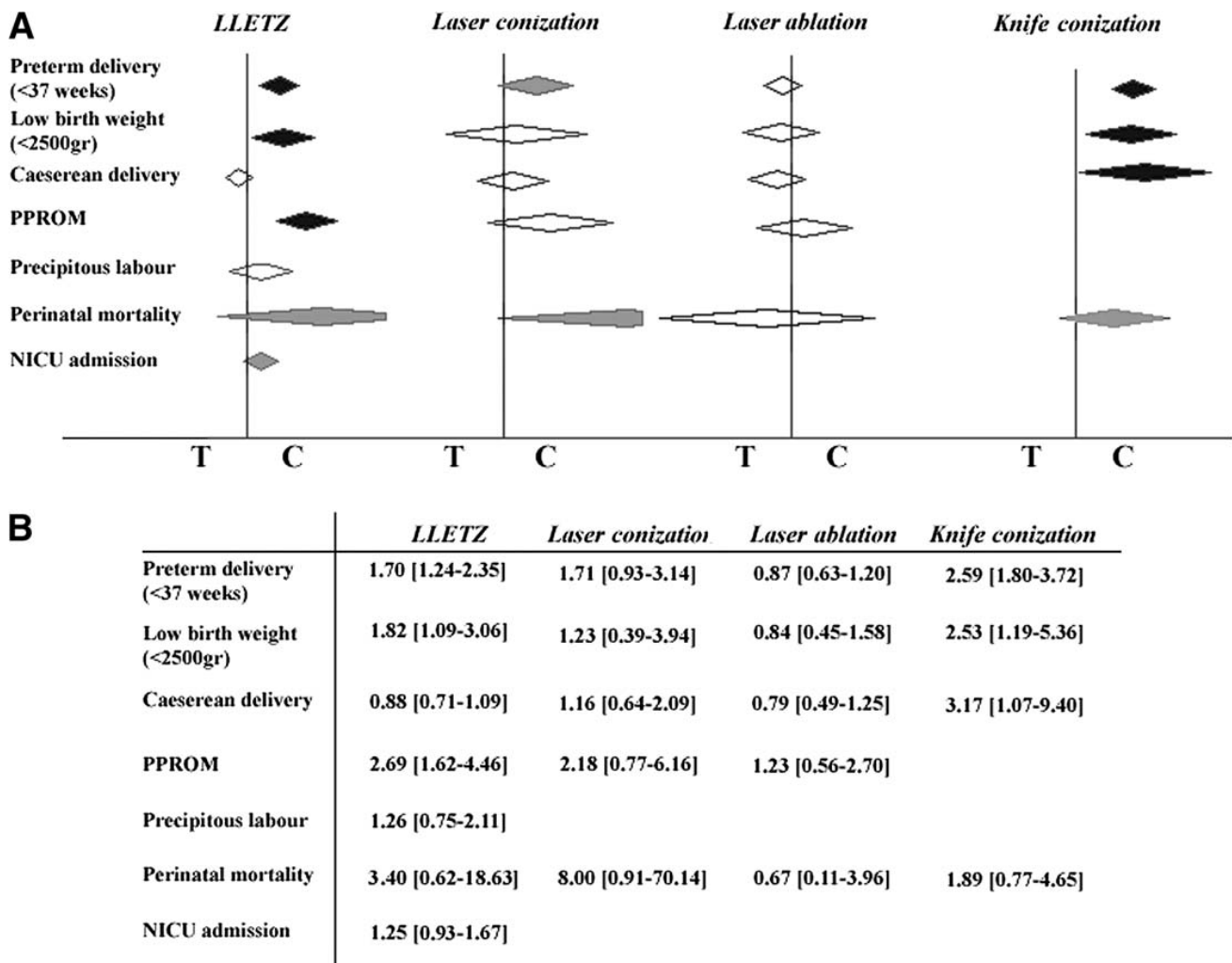
Many authors have found an increased risk of preterm birth after laser conization (Hagen et al., 1993). In a recent study, the risk of preterm birth after laser or Loop conization was increased after adjusting for smoking, marital status and socioeconomic status, and it was inversely related to gestational weeks. In addition, the risk of pPROM was 10.5-fold elevated (Sjoberg et al., 2007). In a meta-analysis the risk of preterm birth after laser conization was marginally insignificant (RR 1.71, 95% CI 0.93–3.14) (Kyrgiou et al., 2006).

In older case-control studies, investigators have not found excess preterm births after Loop conization, but the majority of these studies were underpowered (Blomfield et al., 1993; Haffenden et al., 1993; Braet et al., 1994; Ferenczy et al., 1995; Althuisius et al., 2001; Tan et al., 2004). Increasing evidence shows that Loop conization may also be associated with adverse pregnancy outcomes. In 2004 Sadler *et al.* noticed that the risk of pPROM was increased after Loop conization (Sadler et al., 2004). Women from their colposcopy clinic were selected as controls. A relatively high preterm birth rate (12.2%) was also found among the controls, and this has also been observed in other studies (Kristensen et al., 1993a). In another study the risk of preterm birth among colposcopy clinic clients was increased even without treatment, but it was even higher after treatment (Bruinsma et al., 2007). This suggests that treatment is one risk factor, but not the only one that predisposes women to preterm birth. Crane stated in a review that preterm birth was still associated with Loop conization when smoking was matched (Crane, 2003). In one study a short Loop conization-to-pregnancy interval was associated with preterm birth (Himes et al., 2007). A meta-analysis carried out by Kyrgiou *et al.* suggested that the risks of preterm birth, low birth weight and pPROM were increased after any excisional treatment (Kyrgiou et al., 2006). In a recent register study the risk of preterm birth was increased after cervical conization, and the risk was highest in the early weeks of pregnancy (Albrechtsen et al., 2008). Arbyn *et al.* studied perinatal mortality, as well as severe and extreme prematurity in a meta-analysis (Arbyn et al., 2008). Loop conization was not associated with extreme prematurity or perinatal mortality, but their conclusion was: “Large Loop excision of the transformation zone cannot be considered as completely free of adverse outcomes”.

CONE SIZE

Many authors (Lee, 1978; Bekassy et al., 1996; Raio et al., 1997; Leiman et al., 1980; Sadler et al., 2004; Nohr et al., 2007a; Sjoborg et al., 2007), but not all (Hagen et al., 1993; Samson et al., 2005) have suggested that removed cone size, independent of the type of conization, may play a role. Nohr and colleagues estimated a 20% increase in the risk of preterm birth per each additional millimeter of cone height excised (Nohr et al., 2007a). In a register study, a declining preterm birth rate during the study period was observed, possibly because modern Loop methods became popular, with the removal of smaller cones (Albrechtsen et al., 2008). In a review, Kyrgiou *et al.* stated that cones larger than 1 cm in height increased the risk of preterm birth (Kyrgiou et al., 2006). In contrast, Samson *et al.* reported that repeat Loop conization did not increase the risk of preterm birth (Samson et al., 2005).

Figure 3. Meta-analysis carried out by Kyriou *et al.* (2006). (A) Cumulative forest plot presenting the risks of obstetric outcomes and different methods of treatment. (T): favors treatment, (C): favors control. Black: statistically significant. Gray: trends (but failed to reach level of significance). White: non-significant. (B) Relative risks and 95% confidence intervals for each outcome and method used. Reproduced with permission.



2.1.7.3. EFFECTIVITY OF SURGICAL CERVICAL TREATMENT

RECURRENT DISEASE

Older age of the patient, positive HPV status, margin involvement and HIV positivity predict recurrence of CIN lesions. Around 15% of all patients will have recurrent disease at cytological follow-up (Lindeque, 2005). Patients over 50 years of age have much higher recurrence rates than younger patients. Incomplete excision of CIN exposes women to high-grade post-treatment disease; this risk is six-fold compared with women with clear margins. It is unclear whether this risk is associated with recurrence of the original disease or development of new disease. Histopathological assessment of resected margins is therefore essential. In a meta-analysis, the prevalence of post-treatment disease was slightly lower when comparing laser conization with cold knife conization or Loop conization (Ghaem-Maghami et al., 2007). This might be the result of additional vaporization after laser conization. Adding extensive ablation to compensate for incomplete excision was, however, not recommended, because it may delay the diagnosis of invasive disease (Hockel, 2007).

MORBIDITY AND MORTALITY

All current modalities to treat pre-invasive disease of the uterine cervix are effective in preventing cervical cancer (MartinHirsch et al., 2006). These treatments reduce the risk of cervical cancer by 95% during the first 8 years after treatment. However, even with careful follow-up the risk of invasive cervical cancer is about five times greater than among the general population (Soutter et al., 1997). Most recurrences occur two to five years after treatment for CIN, rates varying from 1% to 21% (Soutter et al., 1997; Arbyn et al., 2005; MartinHirsch et al., 2006; Wright et al., 2007b; Schockaert et al., 2008), but increased risks of cervical and vaginal cancers exist for at least 20 years after treatment (Kalliala et al., 2005; Ronco et al., 2007; Strander et al., 2007). No differences between treatment modalities have been observed (Soutter et al., 1997). In a Finnish study there was a tendency for cold knife conization to be less effective than cryosurgery, laser conization, or Loop conization. The data on cold knife conization, however, was older than that on other modalities, and treatments and surveillance were not at the same level as later on (Kalliala et al., 2007).

According to European and American guidelines, hysterectomy is restricted to special cases, such as those with concomitant gynecological diseases, or AIS, or when repeat treatment is not feasible

(Wright et al., 2007b; Jordan et al., 2008). Hysterectomy for CIN is also a known risk factor for the subsequent development of vaginal intraepithelial neoplasia (VAIN), with incidence rates varying from 0.9% to 7.4% (Schockaert et al., 2008).

FACTORS MODIFYING THE RISK

Pregnancy modifies morbidity and mortality risks among women treated for CIN. Pregnancies and sex-related hormones may induce significant changes in factors controlling malignant transformation of reproductive organs. Previous studies suggest that high parity increases the risk of cervical cancer, especially among HPV-positive women. In a Finnish study among grand multiparous women (at least five children), a marginally increased risk of squamous cell carcinoma, but a lower risk of cervical adenocarcinoma was found (Hinkula et al., 2004). In other studies, relative risks have varied from 3.8 to 4.4.

Previous studies suggest that parous women are healthier than nonparous women; those with serious illnesses may not become pregnant at all or have more miscarriages. In addition, these women behave in such a manner as to protect themselves and their children, which is known as the “healthy pregnant women effect” (Gissler et al., 2004b; Gissler et al., 2005). Among multiparous women, Finnish investigators reported decreased overall mortality and cancer mortality, but higher mortality from diabetes and cardiovascular diseases (Hinkula et al., 2006a).

Many studies suggest that women with preterm birth have increased cardiovascular morbidity and mortality (Irgens et al., 2001; Smith et al., 2001; Catov et al., 2007). The explanation for this might be poor social circumstances, maternal health, or behavioral or nutritional factors. Irgens and co-workers also found increased overall, cancer, and stroke mortality among women with preterm birth (Irgens et al., 2001). Among women with preterm birth, decreased ovarian cancer mortality has been observed (Mucci et al., 2007).

2.2. PRETERM BIRTH

2.2.1. DEFINITION

In the older literature, estimation of gestational age is not precise, and is often missing. The pediatrician Arvo Ylppö introduced the Finnish word “keskonen” for fetuses weighing less than 2 500 g as early as at the beginning of the 20th century (Ylppö, 1920). In those days fetal weight was used as a surrogate marker of preterm birth. Nowadays this definition is reserved for low-birth-weight (LBW) infants. Infants of very-low-birth-weight (VLBW, less than 1 500 g) and those of extremely-low-birth-weight (ELBW less than 1 000 g) have also been classified. According to the World Health Organization, preterm birth (PTB) is defined as the birth of an infant before 37 completed weeks or 259 days of gestation (WHO 1970).

Preterm birth can be classified into extremely preterm birth (less than 28 weeks of gestation), very preterm birth (from 28 to less than 32 weeks of gestation) and into moderately preterm birth (from 32 to less than 37 weeks of gestation) (Goldenberg et al., 2008). In developed countries about 80% of all preterm births are moderately preterm, another 10% are very preterm and 10% are extremely preterm (Goldenberg et al., 1998). In Scandinavia each subgroup represents about one third of all preterm deliveries (Morken, 2008).

In obstetrics 34 weeks is considered as a milestone, since prenatal corticosteroids/tocolytics are no longer required. These fetuses still have higher mortality and morbidity rates than term infants (Raju et al., 2006). The labels “near-term” or “late preterm” birth (preferred) have been used for deliveries at 34 to 36 weeks.

Determination of gestational age has traditionally been based on estimation of the last menstrual period and in undeveloped countries gestational age determination does not even exist. The modern method is to assess fetal biometry by vaginal ultrasonography before the 20th week of gestation. In some studies ultrasonographic estimation has led to an increase in preterm birth rates and a reduction in post-term pregnancies (Kramer et al., 1988; Yang et al., 2002; Klebanoff, 2007). The underlying mechanism for this remains unclear, but delayed ovulation is more frequent than early ovulation and this might be one possible explanation. In Finland ultrasonographic estimation of gestational age is performed routinely and has been reported in the Medical Birth Register (MBR) since the early 1990s. Gestational age is missing in only about 0.7% of all

parturients. In general, this probability is higher among women with preterm birth and those in low socioeconomic positions (Berkowitz et al., 1993). Estimation of gestational age based on the last menstrual period (LMP) is more inaccurate and makes international comparisons difficult (Joseph et al., 2007).

2.2.2. EPIDEMIOLOGY

No accurate recent global data exists as regards preterm birth rates, but estimations vary from 5% in developed countries to 25% in developing countries (Steer, 2005) (Table 2). Spontaneous preterm birth rates are rising in many developed countries. The reason for this remains unclear. Some authors have suspected that an increasing tendency to register live births at very early gestational weeks has contributed to this rise (Slattery et al., 2002).

In the United States preterm birth rates have been very high, around 12–13% in recent years and the rates have even increased during the last decade (Martin et al., 2008). There has been an increase in induced preterm births of 32% (from 4.1% to 5.6% in 2000), especially among whites (Ananth et al., 2005). In Canada, overall preterm birth rates are much lower, 7.7% in 2003 (Joseph et al., 2007). In Australia preterm birth trends are also rising (from 5.9% in 1995 to 6.6% in 2003). An increase of 10.7% among low-risk women has also been reported (Tracy et al., 2007).

In Europe the preterm birth rate varies from 5% to 12% (Blondel et al., 2006; European Perinatal Health Report, 2008) (Figure 4). In France a reduction in preterm births was shown in the 1980s as a result of intervention and prevention programmes (Papiernik et al., 1985), but this favorable trend has reversed, and an increase from 5.4% to 6.2% during 1995–1998 was reported (Morken, 2008).

In all Nordic countries preterm birth rates are very low when compared internationally, reflecting high standards of living and good general maternity care. In Britain and in Southern Europe the rates are much higher (Gissler et al., 2007; European Perinatal Health Report, 2008). In Denmark the proportion of preterm births increased by 22% from 1995 to 2004 (Langhoff-Roos et al., 2006). Primiparity, IVF treatments and multiple births explained this trend only partially. Researchers suggested that increased stress among pregnant women might have contributed to this development. In Norway the total preterm birth rate has increased as well (Morken et al., 2005; Morken et al., 2008a; Morken et al., 2008b). Contradictorily, in Sweden the proportion of all

preterm births decreased from the mid 1980s to 2001. Spontaneous preterm births accounted for 55% and induced preterm births for 20% of all preterm births (Morken et al., 2005).

In Finland, a previous cohort study showed a reduction of preterm births from 9.1% to 4.8% from 1966 to the mid 1980s (Olsen et al., 1995). Spontaneous preterm births decreased from 8.8% to 3.4%. Induced preterm births increased from only 0.3% to a still very low level of 1.4% over that time. The authors suggested that the favorable trend might be explained by the tremendous increase in the standard of living in all social groups during these 20 years. According to Nordic perinatal statistics the preterm birth rate has been relatively stable recently in Finland (Gissler et al., 2007).

Figure 4. Preterm birth rates in Europe. Reproduced from www.europeristat.com with permission.

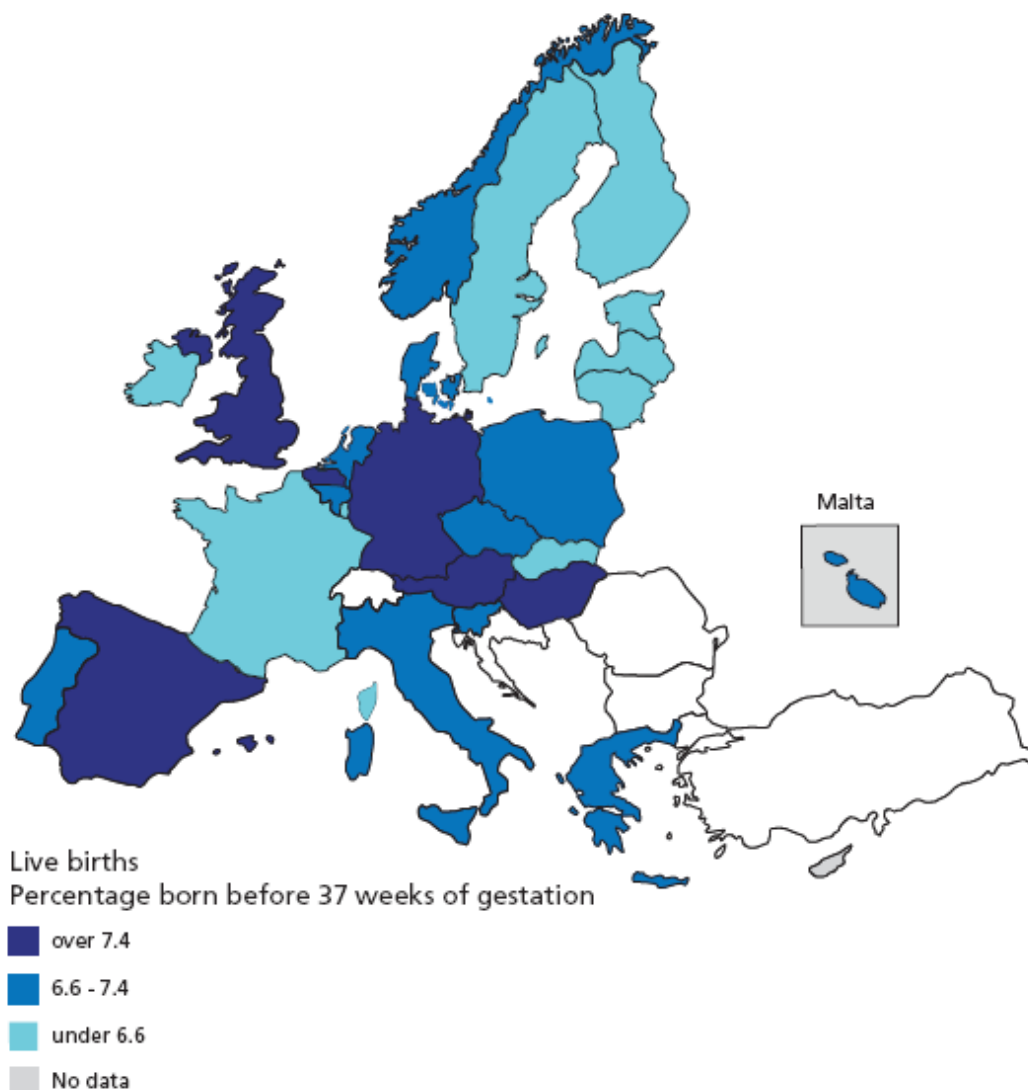


Table 2. Preterm birth rates in different countries.

Reference	Regions	Country	Year	Preterm, %	
European Perinatal Health Report	Nordic countries	Finland	2004	5.6	
		Denmark		6.9	
		Sweden		6.3	
		Norway		7.1	
		Austria		11.4	
	Central Europe	Belgium Flanders		8.0	
		Belgium Brussels		7.1	
		Czech Republic		12.2	
		Germany		8.9	
		Luxembourg		6.0	
		Hungary		8.6	
		Netherlands		7.4	
		Baltic Countries	Estonia		5.9
			Latvia		5.7
			Lithuania		5.3
	United Kingdom	Poland		6.8	
		Ireland		5.5	
		England and Wales		7.5	
		Scotland		7.6	
		Northern Ireland		6.6	
	Southern Europe	Greece		6.0	
Spain			8.0		
France			6.3		
Italy			6.8		
Malta			7.2		
Portugal			6.8		
Slovenia			7.0		
Slovak			6.3		
Martin et al. 2008	North America	USA	2005	12.7	
Joseph et al. 2007		Canada	2003	7.7	
National perinatal statistics	Australia		2006	8.2	
Annual report of perinatal statistics	Asia	Japan	2003	9.9	

2.2.3. CLASSIFICATION

Preterm births can be divided into spontaneous preterm births and medically induced preterm births (delivery induced because of maternal or fetal disease), irrespective of delivery type (vaginal, cesarean). Spontaneous preterm birth comprises those beginning with contractions and preterm prelabor rupture of the membranes pPROM (Bruinsma et al., 2007; Goldenberg et al., 2008; Iams et al., 2008). About 40–45% of all preterm births are spontaneous, 25–30% result from pPROM and 30–35% are induced (Goldenberg et al., 2008). This classification is controversial, since a strict time period for prelabor rupture of the membranes does not exist; some authors define it as at least one hour before the onset of contractions (Goldenberg et al., 2008; Morken et al., 2008a). There is a certain degree of overlap between these etiologies, which justifies different classifications.

2.2.4. ETIOLOGY AND RISK FACTORS

The causes and exact mechanisms of preterm birth remain unsolved, but certain risk factors exist that can lead to preterm birth. These can be divided into maternal risk factors, pregnancy history-related risk factors, and index pregnancy risk factors (Morken, 2008).

MATERNAL RISK FACTORS

In Britain preterm birth rates have been found to be 2% higher in the lower social classes, and the same trend was seen as regards smoking and marital status (Steer, 2005). In Finland women not taking part in antenatal care, and pregnancy outside marriage have been found to be risk factors of preterm birth (Raatikainen et al., 2005; Raatikainen et al., 2007). Under- or non-attendance as regards antenatal care was associated with a cluster of social and health behavioral problems, such as unmarried status, low educational level, young maternal age, grand multiparity, smoking and alcohol use (Raatikainen et al., 2005; Raatikainen et al., 2007). Register data shows that socioeconomic differences as regards perinatal health diminished in the 1990s (Gissler et al., 2003; Mortensen et al., 2008). In other studies extremes of maternal age, low socioeconomic status, poor living conditions, smoking, and substance use have also been risk factors of preterm birth (Morken, 2008). These are all often related to each other, and cannot be separated.

In Finland smoking is strongly associated with a low socioeconomic position – in general and during pregnancy (Jaakkola et al., 2001; Laaksonen et al., 2005). Tobacco contains nicotine and

carbon monoxide, which are strong vasoconstrictors, causing placental problems and circulatory changes. Smoking predisposes pregnant women to infections and pPROM (Goldenberg et al., 2008). Alcohol and drug consumption during pregnancy may be associated with smoking, increasing risks even more. Smoking also increases the risk of placental abruption and other placental disturbances associated with preterm birth (Tikkanen et al., 2006).

Maternal short stature, underweight condition, and low weight gain during pregnancy have been associated with preterm birth in many studies (Kramer, 2003). These may all represent nutritional problems during pregnancy (Steer, 2005; Nohr et al., 2007a; Hauger et al., 2008). Certain occupational risk factors, stress during pregnancy, and anxiety may be mediated through increased corticotropin levels (Kramer, 2003; Goldenberg et al., 2008; Morken, 2008).

Increasing obesity among parturients leads to maternal morbidity and an increase in the rate of induced preterm birth (Ananth et al., 2005). A higher risk of pPROM, but a decreased risk of spontaneous preterm birth have also been observed (Rosenberg et al., 2005; Nohr et al., 2007b). Obesity may be associated with persistent inflammation, which could explain the increased risk of pPROM.

In the United States the prevalence of preterm birth is much higher among blacks (16.2% in 2000) than in whites (9.4% in 2000). In many studies black ethnicity is associated with preterm birth, but the reason for this remains unclear (Aveyard et al., 2002; Kramer, 2003; Steer, 2005). The risk may partly be explained by socioeconomic factors, but earlier maturation of the feto-placental unit has also been proposed (Aveyard et al., 2002). Black infants mature earlier, and thus have fewer respiratory diseases related to prematurity; even neonatal mortality rates are lower than among whites (Steer, 2005). Black women also have a higher rate of bacterial vaginosis, which further predisposes them to preterm birth. Even a genetic predisposition for preterm birth has been proposed, Ward *et al.* have identified several large families with an apparent genetic predisposition for preterm birth (Ward, 2003).

Some investigators claim that induced abortions increase the risk of preterm birth (Ancel et al., 2004; Moreau et al., 2005; Bruinsma et al., 2007). There is a concern that cervical dilatation during termination of pregnancy might damage the cervix and predispose women to preterm birth. In other studies, accumulation of social and behavioral risk factors can be observed among women

who give birth prematurely (Raatikainen et al., 2006). In some studies, previous miscarriages also predispose women to preterm birth (Bhattacharya et al., 2008).

The uterus may not have recovered from previous delivery if the inter-pregnancy interval is short. Some authors have suggested that this is connected to inflammatory processes. Nutritional depletion may also play a role (Goldenberg et al., 1998; Smith et al., 2003; Goldenberg et al., 2008). There might be more deprivation and poorer social circumstances among women who do not take proper care as regards contraception.

PREGNANCY HISTORY-RELATED RISK FACTORS

Previous preterm birth is the strongest known risk factor of preterm birth (Goldenberg et al., 1998; Kramer, 2003; Bruinsma et al., 2007; Nohr et al., 2007a; Goldenberg et al., 2008). The risk increases as the number of previous births increases, with recurrence rates varying from 15% to more than 50% depending on the number and gestational stages of previous preterm births (Goldenberg et al., 2008). The earlier the previous birth, the earlier the subsequent birth. In addition, this effect is most pronounced if the previous birth was extremely preterm (Morken, 2008). Women with previous preterm birth make up only 10% of all those with preterm deliveries. Primiparous women have 60% of all preterm births, primiparity being a strong risk factor of preterm birth (Morken, 2008).

Cervical incompetence is defined by dilatation of the cervix without painful contractions. The length of the cervix can be manually examined and scored (Bishop's score) and also measured by ultrasonography. The risk of preterm birth increases as the ultrasonographic measurement of cervix length decreases (Iams et al., 1996; Goldenberg et al., 1998; Kramer, 2003; Norman, 2007, Crane et al., 2008b). Some authors have suggested that as cervix length increases, the risk decreases by 9% for each millimeter (Iams et al., 1996). In another study, cervical length less than 15 mm (Norman, 2007) or 30 mm (Crane et al., 2008b) increased the risk of preterm birth. Sometimes cervical cerclage (insertion of a suture around or through the cervix) has been used in women with a short cervix to prevent preterm births, but it has not reduced neonatal morbidity or mortality (Norman, 2007). Among women with cervical malformations the risk of preterm birth has been reported to be increased nearly threefold and it was explained mainly by cervical incompetence (Kaufman et al., 2000).

INDEX PREGNANCY RISK FACTORS

Infection is the single most common cause of preterm birth, accounting for 40% of early preterm births (Kramer, 2003; Goldenberg et al., 2008). The earlier that labor occurs, the higher the proportion of cases of intrauterine infection. There are four main routes of infection. Ascending infection from the vagina and cervix is the most common pathway. Microbes can also become disseminated hematogenously through the placenta. Invasive procedures, such as amniotomy, can accidentally result in infection of the amniotic cavity. Retrograde dissemination through the fallopian tubes is rare. Most of the infections are chronic and some women may have asymptomatic colonization before conception (Goldenberg et al., 2000). Globally, malaria, tuberculosis and HIV infections predispose women to pPROM and spontaneous preterm birth (Steer, 2005). In developed countries, other infections, such as genital infections, pyelonephritis, pneumonia, periodontal infections and bacterial vaginosis (defined as a change in the microbiological ecosystem in the vagina, characterized by bacterial overgrowth), play an important role (Goldenberg et al., 2000; Leitich et al., 2003; Oittinen et al., 2005; Goldenberg et al., 2008). However, in low-risk populations, eradication of bacterial vaginosis has not resulted in reduction of preterm births (Kekki et al., 1999; Murphy et al., 2004; Hollier, 2005). Infection and inflammation lead to disruption of the maternal-fetal decidual interface, which further results in leakage of fetal fibronectin and decidual phosphorylated insulin-like growth factor-binding protein 1 (pIGFBP-1) to the vagina. Both of these have been used as predictive markers of preterm birth (Rutanen, 2000; Murphy et al., 2004; Iams et al., 2008; Rahkonen et al., 2009).

Multiple gestation is a strong risk factor of preterm birth (Kramer, 2003; Goldenberg et al., 2008). Almost 60% of all twins are preterm; triplets and offspring resulting from other higher order pregnancies are virtually all preterm. Uterine over-distension results in contractions and pPROM. Induced preterm births as a result of maternal diseases are common. An increasing number of pregnancies result from artificial reproduction techniques such as *in vitro* fertilization (IVF), which is a risk factor of preterm birth even in singleton pregnancies (Steer, 2005; Poikkeus et al., 2007a; Goldenberg et al., 2008).

Other maternal diseases, such as diabetes, preeclampsia and placental diseases predispose women to induced preterm birth (Kramer, 2003; Bruinsma et al., 2007). Abdominal surgery during pregnancy may provoke contractions and thus predispose the woman to preterm birth (Morken, 2008).

Fetal malformations and intrauterine growth retardation (IUGR) predispose women to induced preterm birth. Male gender is also associated with increased preterm birth rates (Morken, 2008).

2.2.5. SIGNIFICANCE

Preterm birth is one of the principal determinants of perinatal health and childhood impairment in Europe today. Advances in perinatal and neonatal care have reduced mortality rates, but morbidity remains a serious problem. The major diseases of the preterm infant are due to organ immaturity, with their incidence and severity inversely related to gestational age at birth. Preterm infants are more vulnerable and prone to infections than term infants. They have more cerebral palsy, severe learning disabilities, chronic lung disease and visual and hearing impairments (Raju et al., 2006). Over one third of all infant deaths annually are attributable to preterm birth in the United States (Callaghan et al., 2006). More than 75% of cases of prenatal mortality are associated with preterm birth (McCormick, 1985). Preterm birth is not only a major problem in obstetrics, but it also has major psychological, social and economic impacts. Extremely preterm and very preterm infants are at the greatest risk of developmental problems, which explains their high health care expenses (Saigal et al., 2008).

Estimation of the annual cost to society in the United States was 51 600 \$ (about 40 300 €) for each early infant in 2005 (Lancet, Editorial 2008). However, late preterm births constitute an enormous population and thus have a high impact on health care costs. Even when born after 32 weeks, when neurological survival is good, educational and behavioral problems occur in one third of all premature children at the age of seven (Shennan et al., 2006). It has been estimated that about two thirds of the recent increase in preterm births in the United States is attributable to late preterm births (Raju et al., 2006).

3. AIMS OF THE STUDY

The present study was undertaken to investigate the long-term effects of surgical treatments of the uterine cervix for CIN lesions, with special focus on preterm birth.

The specific aims of this work were to determine:

1. preterm birth trends and main risk factors in Finland during 1987–2004, using Medical Birth Register data. We hypothesized that the rate of spontaneous preterm births is rising in Finland.
2. if different surgical treatments of the uterine cervix predispose women to preterm birth. We compared different treatment modalities by using register data and hospital records. In particular, we evaluated whether or not Loop conization is associated with an increased risk of preterm birth.
3. if confounding factors explain the observed increased preterm birth rate after surgical treatment of CIN. In addition, special attention was paid to the effect of cone size.
4. if women surgically treated for CIN have impaired fertility and therefore an increased proportion of deliveries achieved by IVF compared with other women. In addition, we looked into the question of whether or not women having both surgical treatment for CIN, and IVF treatment, have more preterm births than women without.
5. the rates of long-term mortality resulting from different causes among women surgically treated for CIN.

4. SUBJECTS AND METHODS

4.1. STUDY POPULATION

4.1.1. STUDY I

This was a register-based retrospective cohort study. Finnish Medical Birth Register data for 1987–2005 was used. We analyzed 1 137 515 deliveries, of which 59 025 (5.2%) were preterm (duration of pregnancy less than 37 weeks). These were sub-classified into moderately preterm (32–36 weeks), very preterm (28–31 weeks) and extremely preterm birth (less than 28 weeks) (Table 3). Four time periods were used when analyzing the trends (1987–1990, 1991–1995, 1996–2000 and 2001–2005). We also defined a low-risk population, which consisted of 20- to 40-year-old women, non-smokers with spontaneous singleton pregnancies and spontaneous deliveries.

4.1.2. STUDY II

Medical Birth Register and Hospital Discharge Register data were utilized. We found 25 827 women of reproductive age among whom cervical treatment was performed in 1986–2003, and 5835 women who delivered post-treatment from 1987 to 2004. These women had 8405 newborns, of which 8210 were singletons. The control group consisted of all other women, without treatment for CIN, who delivered during 1987–2004 (1 056 855 singletons). The risks of low birth weight (< 2 500 g) and perinatal mortality (stillbirths from 22 weeks of gestation and neonatal deaths during the first 7 days after delivery) were also analyzed.

Surgical cervical treatments for CIN were divided into three categories, conization group ($n = 16\,145$ woman; 4545 newborns), ablation group ($n = 9028$ woman; 3425 newborns) and other treatment group ($n = 654$ woman; 240 newborns). The Nordic Classification of Surgical Procedures was published in 1996, and we separated cold knife conization and Loop conization. The women were classified according to the first treatment, except in the “other treatment” group where they were moved to a more specific group (conization or ablation) when re-treatment was performed.

4.1.3. STUDY III

We combined register data with hospital records and analyzed outpatient data from Helsinki University Hospital from 1996 to 2003. The study population consisted of 624 women who had undergone a Loop procedure, and delivery post-treatment. The deliveries were compared with the MBR data. In subgroup analysis, delivery before and after Loop conization in the same woman ($n = 258$ women) was compared. Adjustment for parity and age was performed. Information on cone size from the hospital records was available for 340 women (55% of all women).

4.1.4. STUDY IV

This was a retrospective register-based cohort study of fertile-aged (15–49) females. HDR data for 1986–2003 was used to find surgical cervical treatments for CIN and subsequent spontaneous ($n = 822\ 183$) and IVF deliveries ($n = 12\ 240$, 1.5%) in the MBR during 1991–2004. Information on the IVF treatments was available only from 1991 onwards. We used the same kind of categorization for cervical procedures as in Study II: conization group ($n = 4259$ deliveries of which 70 resulted from IVF treatment), ablation group ($n = 3335$ deliveries, of which 61 resulted from IVF) and other excisional treatment group ($n = 701$ deliveries with 19 resulted from IVF). Associations between treatment for CIN, preterm birth and IVF were analyzed separately for singletons.

4.1.5. STUDY V

The study population consisted of 25 827 females of reproductive age (15–49 years) who had been surgically treated for CIN during 1986–2003. These women were linked to the Cause-of-Death Register maintained by Statistics Finland, using personal identification numbers. We used the same categorization of treatments as in studies II and IV. The study population consisted of 19 667 women without deliveries, 6160 women with any delivery and 690 women with preterm delivery.

Table 3. Study design according to the original publications. MBR Medical Birth Register, HDR Hospital Discharge Register, CDR Cause-of-Death Register.

	Source	Years	Age	Controls	Preterm births	Women with treatment of CIN/deliveries	Subgroup	Subgroup	Subgroup
Study I	MBR	1987- 2005		1 137 515 deliveries	59 025 Preterm		48 973 Moderately preterm	5912 Very preterm	4140 Extremely preterm
Study II	MBR, HDR	1986- 2003 treatments 1987-2004 deliveries	15- 49	1 056 855 singletons	49 257 preterm deliveries	25 827 women, 8405 newborns 8210 singletons	Conization 16 145 women, 4545 singletons	Ablation 9028 women, 3425 singletons	Other treatments 654 women, 240 singletons
Study III	MBR, HDR, hospital records	1997- 2003 treatments, subsequent deliveries	15- 49	554 507 deliveries, 258 women with a previous delivery	25 780 singleton preterm births, 75 preterm deliveries	624 women, 258 had a delivery before and after the Loop conization			
Study IV	MBR, HDR	1986- 2003 treatments 1991- 2004 deliveries	15- 49	822 183 deliveries, 12 240 IVF deliveries	691 preterm deliveries after any treatment	25 827 women 8295 deliveries with any procedure, 150 women with IVF and cervical treatment	Conization 4259 deliveries, 70 IVF deliveries	Ablation 3335 deliveries, 61 IVF deliveries	Other treatments 701 deliveries, 19 IVF deliveries
Study V	MBR, CDR	1986- 2003 treatments, 1986- 2006 deaths	15- 49	General mortality rates in female women population		25 827 women, 395 deaths, 8295 deliveries with any procedure	19 667 women without deliveries	6160 women with any delivery	690 women with preterm delivery

4.2. REGISTERS

4.2.1. THE MEDICAL BIRTH REGISTER

The Finnish Medical Birth Register (MBR) was established in 1987 and it is run by THL, the National Institute for Health and Welfare (formerly STAKES, the National Research and Development Centre for Welfare and Health). It collects information from all delivery units in Finland on all births and obstetric and neonatal outcomes during the first seven days after delivery. The MBR covers all deliveries or stillbirths over 22 gestational weeks or infants weighing 500 g or more. The personal identification numbers in the register act as keys. The quality of information is excellent, since less than 0.1% of all births are missing from the register (Gissler et al., 2002). Seemingly incorrect information is sent back to the hospitals for revision. The register is routinely linked to the Cause-of-Death Register and the Central Population Register covered by Statistics Finland (Gissler et al., 2004c).

4.2.2. THE HOSPITAL DISCHARGE REGISTER

The HDR was established in 1967. In it is collected information on all hospitalizations, plus all day surgical procedures since 1994 and all out-patient visits since 1998 (Gissler et al., 2004c). The register is also maintained by THL, and it is categorized according to the International Classification of Diseases (ICD), and procedures according to the Finnish version of Nordic Classification of Surgical Procedures. The personal identification numbers in the register act as keys. The validity of the information is good (Keskimäki et al., 1992).

4.2.3. THE CAUSE-OF-DEATH REGISTER

The Cause-of-Death Register is maintained by Statistics Finland to identify all deaths. It is also used to gather annual Population Census data and it was computerized as early as 1967. Deaths have been classified according to ICD-8 (1969–1986), ICD-9 (1987–1995) and ICD-10 (1996–2006). Information is obtained from death certificates written by clinicians who treated the patient or the pathologist who performed the autopsy. Death certificates are checked by physicians in the provincial government and at Statistics Finland. Seemingly incorrect information is sent back for revision to the clinicians. The register contains information on all deaths of Finnish citizens, and deceased permanent residents. Baseline information is also available on Finnish citizens that died

abroad. Information on visitors to Finland is not collected (Gissler et al., 2004a; Gissler et al., 2004c).

4.3. ETHICS

Register-based studies were performed after receiving permission from the register-keeping organizations (STAKES [Studies I–V] and Statistics Finland [V]). For Studies II and III we received permission to use data from the University of Helsinki Institutional Review Board.

5. STATISTICAL ANALYSES

I

We used logistic regression analysis to adjust for confounding factors and calculated odds ratios (ORs) and 95% confidence intervals (95% CIs). This was done separately for each subgroup, and each period. Population-attributable risks (PARs) were calculated by using risk factor prevalence in the population.

II

We calculated relative risks (RRs) with 95% CIs for all outcomes. Odds ratios with 95% CIs were calculated by logistic regression to adjust for confounding factors. Statistical comparisons were carried out by using the chi-square test, the test for relative proportions and Fisher's exact test. Maternal age at birth, previous deliveries and maternal smoking during pregnancy (as a surrogate marker of socioeconomic status) were used as confounding variables in logistic regression analyses. All analyses were repeated with inclusion of only the first deliveries.

III

In this study MBR data was used to calculate the expected preterm birth rates and standardized incidence ratios (SIRs) with 95% confidence intervals. In subgroup analysis, internal controls, i.e. deliveries before Loop conization, were used in order to handle the confounding factors. Relative risks were calculated for preterm birth, with 95% confidence intervals. These results were adjusted for maternal age and parity. We used Student's paired *t*-test for statistical comparisons.

IV

The statistical methods used were the test for relative proportions and Fisher's exact test. We calculated risk ratios with 95% confidence intervals in all comparisons. We also analyzed the data by adjusting separately for year of delivery, maternal age and parity, using logistic regression analysis. Separate analyses were performed for first deliveries only.

V

We calculated standardized mortality ratios (SMRs). We found observed deaths from the Cause-of-Death Register and this number was divided by the expected number of deaths, which was

calculated by using general age-adjusted mortality rates in the female population. We also calculated 95% confidence intervals.

6. RESULTS

6.1. PRETERM BIRTH TRENDS (I)

We analyzed general preterm birth rates and trends in Finland during 1987–2005 using the MBR data. The results indicated that the preterm birth rate is not rising in Finland (Figure 5), as it is in many Western countries. The overall rate has been relatively stable, between 5.07–5.22%. Of these, 6–7% were extremely preterm, about 10% very preterm and 82–83% moderately preterm births. The overall rate of extremely preterm birth has decreased by 12% (from 0.39% to 0.34%, $p < 0.01$). After adjusting for background factors extremely preterm births decreased most, by 7.3% (95% CI 4.6%–9.9%), but this decrease was also seen in all preterm births, very preterm births and also to some extent in moderately preterm births. The leading risk factor of prematurity was multiplicity (OR 13.72, 95% CI 13.26–14.19; Figure 6) and this risk was highest in the moderately preterm group. Elective delivery was associated with an OR of 1.86 (95% CI 1.82–1.89) and it was most important as regards the very preterm group. Primiparity was also one of the main risk factors, with an OR of 1.47 (95% CI 1.45–1.50) and we observed this risk in the moderately and very preterm groups. IVF treatment had an OR of 1.39 (95% CI 1.31–1.47) and it was mainly seen in the moderately preterm group. Maternal smoking had an OR of 1.31 (95% CI 1.29–1.34) and this risk was highest in the extremely and moderately preterm groups. Advanced maternal age increased the risk of preterm births by 2% for each year (OR 1.02, 95% CI 1.02–1.03).

Figure 5. Preterm births trends in Finland during 1987–2005.

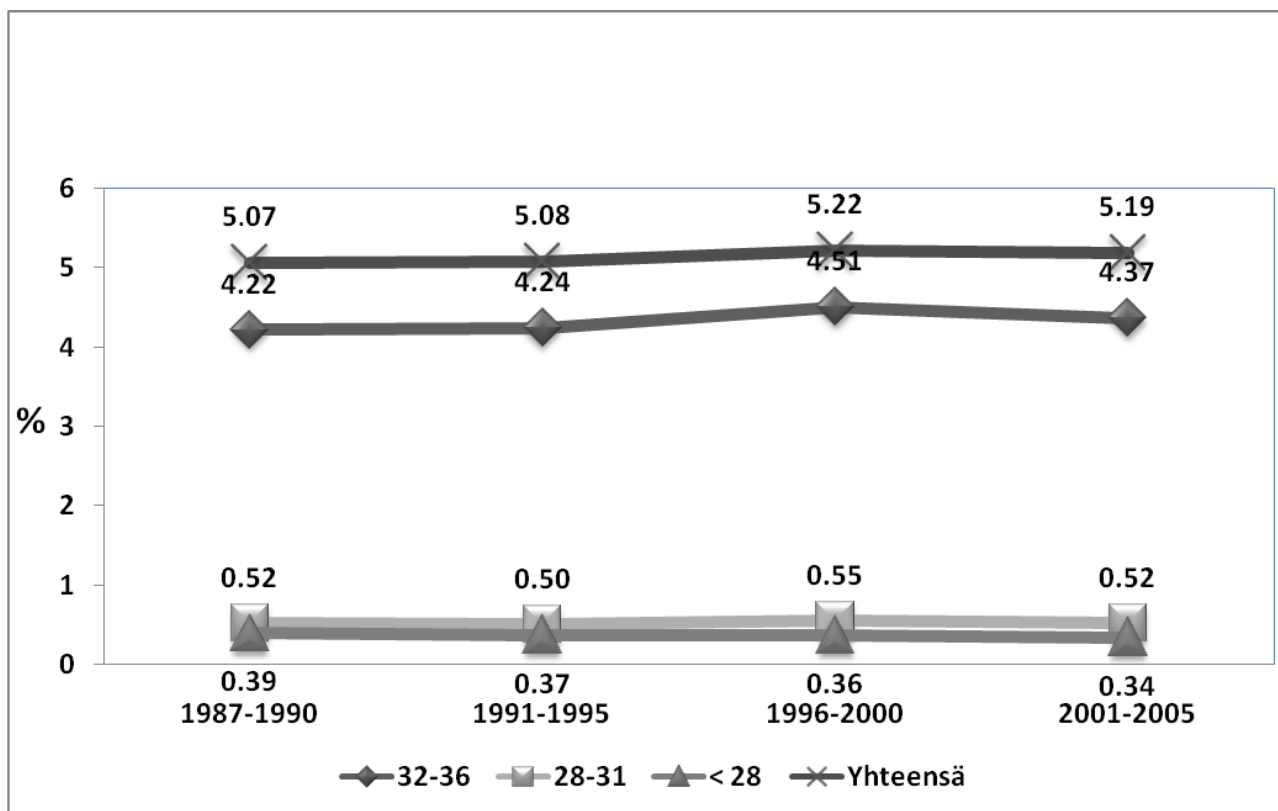
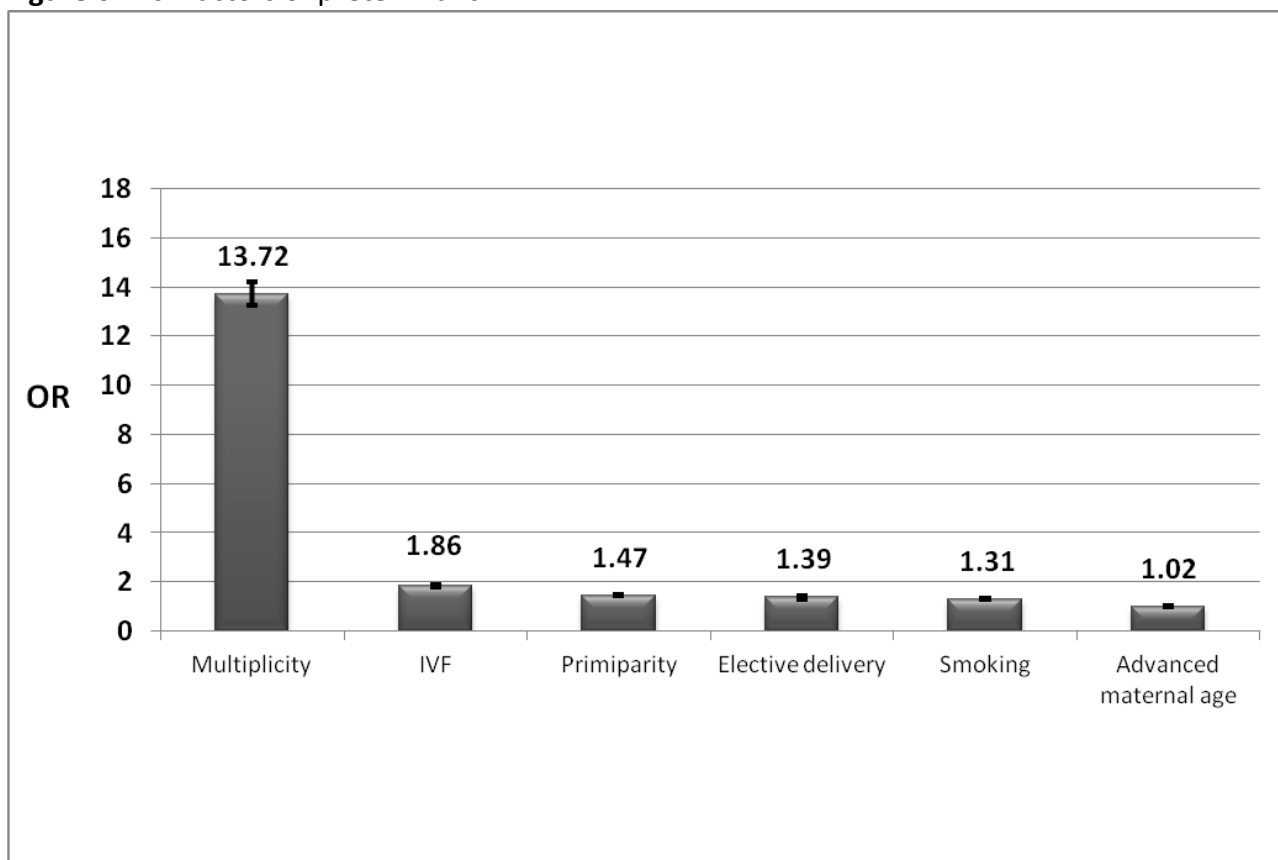


Figure 6. Risk factors of preterm birth.



6.2. PRETERM BIRTH AFTER SURGICAL TREATMENT OF CIN (II)

We studied preterm birth rates, low birth-weight rates and perinatal mortality after treatment of the uterine cervix, using register data. The risk of preterm birth was increased after any surgical treatment for CIN. Treated women had 724 (8.8%) preterm deliveries and the rate of cases of LBW was 5.7% ($n = 472$). The corresponding rates among the controls were 49 257 (4.6%) and 32 976 (3.1%). The perinatal mortality rate was 7.7 / 1 000 live births among cases and 6.7 / 1 000 among controls. We observed an increased risk of preterm birth in the conization group (RR 1.99, 95% CI 1.81– 2.20), the ablation group (RR 1.60, 95% CI 1.41–1.82) and the “other treatments” group (RR 1.97, 95% CI 1.29–3.02). In the conization group the risks were high as regards very preterm (RR 2.86, 95% CI 2.22–3.70) and extremely preterm birth (RR 2.10, 95% CI 1.47–2.99). In the ablation group, the risk was highest as regards moderately preterm delivery and it increased progressively with gestational weeks.

In our original publication we reported only whole group results for the three separate treatments – conization, ablation and other excisional treatments. In a meta-analysis carried out by Arbyn *et al.* (2008) the subgroup results of our data were reported in more detail. When analyzed according to subgroups from 1997 onwards we observed 209 (7.8%) preterm births after Loop conization and 8 (8.6%) after cold knife conization. The risk was extremely high after amputation of the cervix (12 of 39, or 31%). After laser ablation, 70 preterm births (5.2%) were observed. The risk of preterm birth was not increased after laser ablation. In addition, the perinatal mortality rate was even decreased after the procedure.

We also observed an increased risk of LBW in all treatment groups – this was explained by prematurity. In addition, after conization the risk of perinatal mortality (RR 1.74, 95% CI 1.30–2.32) was increased. Adjusting for age, parity and smoking did not change the results. We also analyzed the time interval between treatment and delivery, and considered only the first births, but these analyses did not change our results.

Table 4. Subgroup analysis. Treatment modalities and their association with preterm birth. Controls had 49 257 preterm births during 1987–2004 (4.6% of 1 056 855 deliveries).

Treatment group	Subgroup	1986-1996		1997-2003	
		Newborn	Preterm (%)	Newborn	Preterm (%)
Conization group	Cold knife, Loop or Laser conization	1748	198 (11.3)		
	Loop or Laser conization			2690	209 (7.8)
	Cold knife conization			93	8 (8.6)
Ablation group		1426	131 (9.2)		
	Cryo surgery			644	51 (7.9)
	Laser ablation			1349	70 (5.2)
Other excisional treatments group					
	Other excision	708	55 (7.8)		
	Amputation of the uterine cervix	34	11 (32.4)	5	1 (20.0)
	Excision			127	15 (11.8)
	Other excisional			43	4 (9.3)

6.3. PRETERM BIRTH AFTER LOOP CONIZATION (III)

In Study III we analyzed preterm birth rates after Loop conization by using information from hospital records and registers. We had information on excised cone size for 55% of all women. The risk of preterm birth was increased almost threefold after Loop conization ($n = 75$ preterm births, 12.0%) when compared with the general preterm birth rate ($n = 25\,780$, 4.6%; RR 2.61, 95% CI 2.02–3.20). Adjusting for age, parity, or both did not change these results. When analyzing deliveries of the same women before and after Loop conization, the preterm birth rate was 6.5% before and 12.0% after the treatment (RR 1.94, 95% CI 1.10–3.40). This remained significant when adjusting for age, parity or both. When women with large or repeat cones were compared with those with small or middle-sized cones, the risk of preterm birth was 2.45-fold greater (95% CI 1.38–3.53). An extremely high risk, increased more than fivefold ($n = 59$, of which 25% were preterm, RR 5.15, 95% CI 2.45–7.84), was observed when the preterm birth rate among women with repeat Loop conization was compared with that in the general population. The recurrence of preterm birth in a subsequent pregnancy was high, 29.4%.

6.4. TREATMENT OF CIN AND SUBSEQUENT IVF DELIVERIES (IV)

In Study IV, fertility impairment after surgical treatment of the uterine cervix was assessed. This was measured by the proportion of IVF deliveries among treated women. Women in the MBR had 822 183 deliveries, and of those, 1.5% (12 240) resulted from IVF treatment. Among women previously treated for CIN the proportion of IVF deliveries was 1.6% (RR 1.21, 95% CI 1.04–1.42), but this risk disappeared when adjusted for maternal age, parity, or year of delivery. Only after other excisional treatments did this risk remain significant after adjustment for year of delivery (RR 1.83, 95% CI 1.16–2.89) or parity (RR 1.95, 95% CI 1.25–3.04). This subgroup also included amputation of the uterine cervix, which might explain the increased risk. Among women previously treated for CIN, IVF treatment increased the risk of preterm birth 1.88-fold (95% CI 1.19–2.96). Among those women who had undergone both IVF treatment and any cervical procedure, the risk of preterm birth was 3.4-fold (95% CI 2.18–5.37) when compared with women with neither. This excess risk was explained, however, by advanced maternal age and parity.

6.5. LONG-TERM MORTALITY AND TREATMENT OF CIN (V)

In Study V we analyzed mortality rates among women treated for CIN, compared with respective age-adjusted rates in the female population. Women previously treated for CIN had increased mortality rates (SMR 1.17, 95% CI 1.05–1.28). This trend was seen especially as regards general disease mortality and alcohol-related death (SMR 1.13, 95% CI 1.01–1.26), and accidental and injury deaths (SMR 1.31, 95% CI 1.03–1.58), including suicides (SMR 1.67, 95% CI 1.21–2.13). There was also a tendency towards increased cancer mortality (SMR 1.09, 95% CI 0.91–1.27) as regards the larynx, trachea and lung, but a decreased risk of breast and ovarian cancers. In the subgroup of women without subsequent deliveries mortality rates were even higher (SMR 1.22, 95% CI 1.10–1.35) than the overall rates. Women with at least one subsequent delivery had both decreased disease mortality (SMR 0.63, 95% CI 0.37–0.90) and low cancer mortality (SMR 0.53, 95% 0.18–0.87). Preterm birth post-treatment was associated with increased mortality rates (SMR 2.51, 95% CI 1.24–3.78). There were only 15 deaths among 690 women with a preterm birth, but there was a tendency towards increased mortality in connection with cardiovascular events, accidental and alcohol-related injuries, and suicides. Mortality associated with cervical cancer was high, as expected (SMR 7.69, 95% CI 4.23–11.15).

7. DISCUSSION

7.1. IMPORTANCE OF THE PRESENT STUDY

The advantages of using large, population-based registers to address adverse pregnancy outcomes after treatment for CIN, is the large sample size which, in turn, affords excellent statistical power to discern infrequent associations. In addition, our results offer generalizability since they are population-based.

This study confirms the results of previous smaller studies showing that all excisional treatments to treat CIN may impair subsequent pregnancy outcome. While some risk factors of preterm birth such as smoking during pregnancy and multiplicity have decreased, HPV infections and surgical cervical treatments have become more important. In addition, women are delivering at older ages; so cervical treatments before pregnancy are becoming more common, which leads to increased preterm birth rates.

The finding indicating that repeat treatments are associated with an extremely high risk of preterm birth has not been reported often. This has practical implications; avoiding repeat treatments should be kept in mind when treating fertile-aged women.

Women undergoing these treatments may have a tendency to behave in a risk-taking manner, and health counseling should be offered to them. Smoking cessation should be encouraged. Our findings confirms the fact that it is still very important to encourage pregnant mothers to stop smoking, especially during the first prenatal visit.

7.2. STUDY LIMITATIONS

The latest quality study of the HDR is relatively old, from the 1990s (Keskimäki et al., 1991). There is always some misclassification and underreporting in the register data, especially of rare events. Check-boxes can improve data quality. Information on earlier births in the MBR is of poorer quality than later on (Gissler et al., 2002).

The number of available variables in register data is limited. We could not adjust for all possible confounding factors (e.g. alcohol consumption [studies II–V], smoking [studies IV, V]) in data based on hospital registers. Information on socioeconomic position was not available in the MBR data

until 1990, so we had to use smoking as a surrogate marker of socioeconomic status for Study II, which included 1987–1990. In Finland, however, smoking in general and during pregnancy (Jaakkola et al., 2001; Laaksonen et al., 2005) is strongly associated with socioeconomic position. We were unable to determine smoking status, and alcohol and drug consumption separately for each delivery in Study III. For Study II we had a large population, but we could not separate different treatment modalities precisely before 1997. The HDR did not have the information on day-visit surgical patients until 1994, and on all outpatient visits until 1998. These few missing cases, however, are unlikely to have affected our results.

In Study III, the study population consisted of patients from two different hospitals; one was a tertiary referral hospital, which might have caused some selection bias.

7.3. PRETERM BIRTH RATE AND TRENDS

Preterm births have not increased in Finland. Extremely preterm births declined and this favorable trend seems to have continued since 2005. In contrast, in most Western countries these rates are rising (Langhoff-Roos et al., 2006; Tracy et al., 2007; Martin et al., 2008). We compared our findings with Danish data, where preterm births, especially among low-risk primiparous women, have increased enormously (Langhoff-Roos et al., 2006). Both countries are Nordic welfare countries and share many features. We assume that our findings reflect the high standard of living and good maternity care level in Finland. Induced preterm births have declined, especially in early gestational weeks, fewer mothers smoke during pregnancy nowadays, and multiple birth rates are declining as a result of a high rate of elective single embryo transfer (eSET).

Multiple births after IVF can be prevented by transferring just one embryo. In Finland the proportion of multiple births is small (15/1000 births in 2005) (Poikkeus, 2007), since the overall proportion of single embryo transfers (SETs) has increased up to a half of all transfers and the proportion of elective single embryo transfers has increased to one third. In Finland an eSET policy has been adopted in IVF clinics by their own initiative, not by compulsory legislation. A similar increasing trend in SET/eSET can be seen in Sweden and Belgium (Murphy et al., 2004), but both countries have passed legislation limiting the number of transferred embryos. Multiplicity rates are even lower in Sweden than in Finland; preterm birth rates are also stable in Sweden (Morken et al., 2005; Gissler et al., 2007).

Finland has fewer immigrants than Denmark, but there, preterm birth rates have increased, especially among low-risk parturients, excluding migrants (Langhoff-Roos et al., 2006). The Finnish MBR does not collect information on ethnicity. According to the “healthy migrant effect”, preterm birth rates are lower among Western migrants than among Finns (Malin et al., 2004). The low preterm birth rate also indicates a high level of education among Finnish women (Gissler et al., 2007). Our results do not support the theory that stress explains prematurity, because women are more often working full-time in Finland than in other Nordic countries (Arntzen et al., 2006). Differences in smoking, alcohol consumption, fertility rate, and marital status are minor (Gissler et al., 2007).

Determination of gestational age is usually based on ultrasonographic examination in Finland. This shifts the age distribution to the left, which increases the preterm birth rates and decreases the post-term pregnancy rate (Kramer et al., 1988; Yang et al., 2002; Klebanoff, 2007). Changes in the determination of gestational age during the study period of 1987–2005 have been minor, because 85% of all women as early as in 1992 had at least one ultrasonographic examination during pregnancy. In addition, gestational age was available for virtually all women (99.3%) in our study.

7.4. PRETERM BIRTH AND SURGICAL TREATMENT OF THE UTERINE CERVIX

7.4.1. LOOP CONIZATION AND CONFOUNDING FACTORS

The risks of preterm birth and low birth weight were increased after any excisional treatment of the uterine cervix. After conization the risk of perinatal mortality increased as well. This observation is in line with that in a review by Kyrgiou *et al.*, and other studies (Kyrgiou et al., 2006; Nohr et al., 2007b; Sjoborg et al., 2007; Albrechtsen et al., 2008). We found an increased risk of preterm birth after Loop conization, in accordance with the results of many (Samson et al., 2005; Kyrgiou et al., 2006; Nohr et al., 2007b; Sjoborg et al., 2007; Albrechtsen et al., 2008), but not all studies (Blomfield et al., 1993; Haffenden et al., 1993; Braet et al., 1994; Ferenczy et al., 1995; Althuisius et al., 2001; Crane, 2003; Mathevet et al., 2003; Tan et al., 2004). Using healthy pregnant women from Medical Birth Registers as controls (Study II) may result in excessively healthy controls, which may affect the results. In addition, patients in hospital as controls may not reflect the general population, at least not in the United States. Women undergoing treatment for CIN may have more sexually transmitted and other infections; they may smoke and be of low socioeconomic status, which may increase the risk of preterm birth even without any treatment

(Kristensen et al., 1993a; Bruinsma et al., 2007; Arbyn et al., 2008). In our studies smoking during pregnancy among these women was common (18–26% of all women), which is in accordance with the results of other studies (Sadler et al., 2004; Nohr et al., 2007a). The socioeconomic status of the treated women was better than we expected, with primiparous women in particular often belonging to the upper social class (Study III). Therefore, it has been argued that internal controls should be used to control these confounding factors (Kristensen et al., 1993a), as we did in Study III. The risk of preterm birth was evident when comparing the same women's delivery before and after Loop conization, and adjusting for age and parity. The ability to combine register data with hospital records further improved the data quality, although the number of women who had a delivery both before and after treatment was limited ($n = 258$ women), restricting generalization of the results. In some studies women treated for CIN have been found to have higher rates of preterm birth preceding the procedure (Kristensen et al., 1993a; Sadler et al., 2004; Bruinsma et al., 2007). This was not confirmed in our study. The preterm birth rate was, however, fairly high among these women (6.5%) in comparison with the general preterm birth rate (4.5%, $p = 0.075$). This suggests that the treatment is more important than any of the epidemiologic or demographic characteristics of the treated women.

7.4.2. LASER ABLATION

The results of our study suggest that the risk of preterm birth increased as treatment invasiveness increased. In the ablation group as a whole the risk of preterm birth was increased. Arbyn and colleagues reported our subgroup results in a meta-analysis in more detail (Arbyn et al., 2008). Preterm birth rates were not increased after laser ablation treatment. In addition, perinatal mortality rates were even decreased (Arbyn et al., 2008). Laser vaporization destroys the cervical tissue only superficially, to a depth of only a few millimeters (usually 4–7 mm). Tissue damage remains small. Therefore it is plausible that adverse effects as regards future pregnancy are less severe than with excisional treatments. In Finland ablative methods are seldom used; only on particular occasions. Young women with low-grade lesions may receive more conservative treatment to preserve fertility, which may explain this favorable trend (Arbyn et al., 2008). Severity of the CIN may also affect the treatment modality; high-grade lesions are often treated more aggressively than low-grade ones. In some studies there has been a tendency toward deeper cones with increasing CIN stages (Sadler et al., 2004; Sjoborg et al., 2007), which is plausible. In our

study, considerably higher rates of preterm birth after treatment of high-grade lesions was observed.

7.4.3. CONE SIZE

It was remarkable that Loop conizations in which larger cones were removed had a tendency to be more harmful than when smaller cones were removed. This was corroborated by the finding that repeat treatment increased the risk even more; the risk of preterm birth increased to fivefold when compared with the rate in the general population. The results of other studies (Lee, 1978; Bekassy et al., 1996; Raio et al., 1997; Leiman et al., 1980; Sadler et al., 2004; Nohr et al., 2007a; Sjoborg et al., 2007), but not all (Hagen et al., 1993; Samson et al., 2005), have also suggested that removed tissue size plays a role. The extremely high risk concerning repeat treatments is a novel finding. In retrospective studies, however, cone size is often very difficult to determine. We based retrospective evaluation of cone size on information from the hospital records. This information was not available on every woman. Some authors have used data from pathology reports (Sadler et al., 2004; Samson et al., 2005; Nohr et al., 2007b), but in most studies this information is not available and study populations are small, as in our study. Current Care Guidelines recommend that histopathological reports should contain the size of the excised tissue (Finnish Current Care Guidelines, 2006). Prospective large studies that include exact information on cone size are still required. In one study, a short conization–pregnancy interval was associated with an increased risk of preterm birth (Himes et al., 2007), which was not confirmed in our study (Study II).

7.4.4. CERVICAL SHORTENING

Treatments may shorten the cervix (Ricciotti et al., 1995; Mazouni et al., 2005). Crane and colleagues reported a shorter cervix among women with preceding surgical treatments of the uterine cervix compared with low-risk controls. Cervical length was similar to that among women with a previous spontaneous preterm birth. The best cutoff point for cervical length in the prediction of spontaneous preterm birth was less than 3.0 cm. The authors calculated that for every 9 loop electrosurgical excision procedures and subsequent pregnancy there would be one additional preterm birth (95% CI 6–35) (Crane et al., 2008a). Cervical shortening, however, has not been observed in all studies (Gentry et al., 2000; Paraskevidis et al., 2002a). In some studies regeneration of the cervix has been almost complete in six months after Loop conization (Paraskevidis et al., 2002b). Available reliably measured data on cervical shortening after

treatment of CIN is scanty, and study populations are small. In clinical practice, however, cervical deformation after conization is frequently seen, especially concerning repeat treatments. Excisional treatments remove connective tissue and smooth muscle, which may lead to cervical insufficiency (Kristensen et al., 1993a; Kristensen et al., 1993b). It is plausible that treatment procedures do shorten the cervix, and the excised amount of tissue plays a role. How much the cervix is actually shortened after different treatments should be studied in more detail. The effect of a second excision on cervical length has not been studied at all. It may be preferable to remove a larger part in the first place, thereby ensuring complete excision and reducing the need for a second procedure (Paraskevaïdis et al., 2002b).

7.4.5. MUCUS PLUG

Cervical surgery often leads to removal of mucus-secreting glands. This mucus contains antimicrobial agents: secretory immunoglobulin A, mucin and lysozyme-like substance (Kristensen et al., 1993b). In some studies even the prevalence of *Lactobacilli* is decreased after cervical conization (Svare et al., 1992). *Lactobacilli* are responsible for low pH and ecological balance in the vagina, protecting against colonization with pathogenic microbes (Svare et al., 1992). Thus cervical surgery can lead to bacterial colonization. Decreased amounts of *Lactobacilli* are associated with preterm birth (Svare et al., 1994). Some bacteria that are associated with preterm birth are capable of releasing phospholipase A or proteolytic enzymes. Phospholipase A may initiate the arachidonic acid cascade, which results in locally elevated concentrations of prostaglandins E and F. Elevated prostaglandin levels may lead to cervical ripening and uterine contractions. The release of proteolytic enzymes may finally lead to pPROM and preterm birth (Kristensen et al., 1993b; Crane, 2003; Kyrgiou et al., 2006).

7.4.6. INFECTION

In Study III, a high proportion of cases of pPROM (45%) after Loop conization was observed, which is in accordance with the results of other studies (Svare et al., 1992; Sadler et al., 2004; Sjoborg et al., 2007). In early preterm birth infections are relatively common – in up to 40% of all very preterm births (Goldenberg et al., 1996; Goldenberg et al., 2000; Goldenberg et al., 2008). In Study II the risk of preterm birth in the conization group was highest for very preterm birth and for extremely preterm birth. This may suggest that among these women ascending infection was the main etiological factor as regards preterm birth. Infection has been reported to precede pPROM

(Goldenberg et al., 1996; Goldenberg et al., 2000; Goldenberg et al., 2008). Infection has also been proposed as an explanation for recurrent preterm birth (Goldenberg et al., 2000; Goldenberg et al., 2008). Many authors consider previous preterm birth to be the strongest risk factor of preterm birth (Goldenberg et al. 1998; Kramer et al. 2003; Nohr et al., 2007; Goldenberg et al., 2008), which was also confirmed in our study (III). Although the above-mentioned factors associated with preterm birth have been identified, the mechanisms of preterm birth are poorly understood and more research is needed.

7.4.7. FOLLOW-UP OF TREATED WOMEN

Many treatment modalities have been tested for the prevention of preterm birth. Our knowledge of preterm birth prevention is still insufficient. Women at risk should be under careful surveillance during pregnancy. Cervical ultrasonography has given promising results in predicting preterm birth (Iams et al., 1996; Goldenberg et al., 1998; Kramer, 2003; Norman, 2007, Crane et al., 2008b). Since genital tract infection has been causally related to preterm birth, local cervical infections, bacterial vaginosis (McDonald et al., 2007) and asymptomatic bacteriuria should be treated effectively to prevent preterm births. This approach has given promising results in special risk groups, but not in unselected populations (Kekki et al., 1999; Murphy et al., 2004, Hollier, 2005; Swadpanich et al., 2008). To what degree screening and treatment of genital infections results in prematurity risk reduction in these women remains unknown (Jolley et al., 2008). In selected cases cervical cerclage can be useful, although the available data is sparse. In a meta-analysis, cervical cerclage was not found to produce any favorable effects as regards perinatal mortality rates (Berghella, 2009). Prophylactic cerclage does not prevent preterm birth, and may induce uterine contractions and sometimes lead to pPROM (Jolley et al., 2008). Therefore, patients should be carefully informed about the risks concerning this procedure. Preliminary data on progestin therapy (weekly intramuscular injections) has been promising in decreasing the recurrence of preterm birth, but this treatment modality needs further research (Dodd et al., 2008; Farine et al., 2008 Berghella, 2009). Fetal fibronectin and pHIGFP-1 have high negative predictive values; negative test results can be used in reassurance (Berghella et al., 2008). Women who test positive need intensified surveillance. Tocolysis, corticosteroids, and bed rest, can be offered to these women to facilitate infant lung maturation. Some authors suggest that surveillance is useless, because pPROM often starts without preceding cervical dilatation and shortening. Vaginal examinations might even disturb the vaginal flora, leading to an increased risk of ascending

infection (Kristensen et al., 1993b). We should not forget the psychological effects concerning knowledge of an increased risk of preterm birth. Forthcoming studies of this population of pregnant women will help delineate appropriate management strategies.

7.5. FERTILITY

Data concerning the impact of CIN treatments on fertility outcomes has been limited. In our study, the amount of IVF deliveries was not increased after cervical treatments. The results may indicate that fertility is not threatened after treatment of CIN. We reported the results concerning successful IVF deliveries only, which represents the tip of the iceberg as regards all subfertile women. We did not have information on all IVF treatments performed, or stillbirths before 22 weeks of gestation in this cohort. Tubal infertility often results from ascending infections and some authors have found a tendency towards increased rates of extrauterine pregnancies among women treated for CIN (Sagot et al., 1995). Among women with HPV infection even decreased pregnancy rates in IVF have been observed (Spandorfer et al., 2006). Again, some authors have found increased rates of HPV infection among women with spontaneous abortions (Hermonat et al., 1997). High-grade CIN lesions are almost twice as common among subfertile women eligible for IVF compared with women in the general population (Hammond et al., 1990). Many investigators have found that IVF treatment is a risk factor as regards preterm birth, even in singleton pregnancies (Steer, 2005; Poikkeus et al., 2007a; Poikkeus et al., 2007b; Goldenberg et al., 2008). The reason for this remains unknown. Some authors have suspected that there might already be subclinical intrauterine infection before conception, which manifests later on as preterm birth (Goldenberg et al., 2000). Other explanations include cervical trauma, disturbed implantation, uterine malformations, and associated infertility factors (Slattery et al., 2002; Poikkeus, 2007). We also observed an increased risk of preterm birth after IVF and after surgical treatment of CIN; and an even higher risk among women undergoing both treatments. Those women were older and more often primiparous, which explained this increased risk.

7.6. MORTALITY RATES AMONG WOMEN TREATED FOR CIN

General mortality rates were increased after treatment for CIN. Comparison was carried out as regards general mortality rates in different age groups. The studied women were relatively young; therefore expected mortality rates were low. The results indicated increased mortality due to all

diseases and alcohol poisoning, injuries, assaults and suicidal deaths among all women treated for CIN. These mortality rates were even higher in the subgroup of women without subsequent deliveries. Delivery after treatment was associated with decreased mortality from all deaths and cancers. This reflects the fact that pregnant women and mothers in general are healthy enough to be able to become pregnant. Women with serious illnesses do not have the courage to become pregnant, or they have more miscarriages. Pregnant women also behave carefully (wear helmets, safety belts etc.) to protect themselves and their children, which is known as the “healthy pregnant women effect” (Gissler et al., 2004b; Gissler et al., 2005). The hormonal milieu changes during pregnancy, which has an impact on cancer morbidity and mortality (Hinkula et al., 2001; Hinkula et al., 2002; Hinkula et al., 2004; Hinkula et al., 2006b).

Women with CIN lesions and persistent HPV infection may have certain characteristics that may predispose them to risks that differ from those in the general population. There might be some characteristics of the behavior of these women that predispose them to these risks. Increased mortality was found as regards general diseases, alcohol-related mortality, injury and accidents, and there were more suicides. Information on smoking and alcohol consumption was not available in the register data, but it can be assumed that these women had more unfavorable health habits, resulting in increased mortality rates later in life. It must be kept in mind, however, that 70–80% of all women will acquire high-risk HPV infection during their lifetimes. The majority of these infections will resolve spontaneously (Castellsague, 2008). Other risk factors of CIN may be crucial as regards the development of lesions that require treatment.

Preterm birth was associated with up to 2.5-fold increased mortality rates, and we observed a tendency towards increased cardiovascular, suicidal, injury-related, and accidental deaths, although the numbers were too small to reach significance. Increased cardiovascular mortality after preterm birth is in accordance with the results of previous studies (Smith et al., 2000; Irgens et al., 2001; Smith et al., 2001; Catov et al., 2007). Accidental and injury-related deaths after treatment of CIN have not been studied previously. Cervical cancer mortality rates were high, despite well organized post-treatment surveillance, which is in accordance with the results of previous studies (Soutter et al., 1997; Kalliala et al., 2005). Surveillance after these treatments should be re-evaluated.

We observed a tendency towards increased mortality in association with tobacco-related respiratory tract cancers. Information on all possible confounding factors, such as alcohol consumption and smoking was unavailable in data based on hospital registers. Since tobacco is one of the main risk factors of CIN (Castellsague et al., 2002; Munoz et al., 2006; Vaccarella et al., 2008), we assumed that women in our cohort smoked more than women in the general population. In addition, in Studies II and III smoking was common, in up to 26% of cases during pregnancy. Ovarian cancer and breast cancer mortality rates were low; a tendency towards decreased mortality was found. A high socioeconomic position is a well-known risk factor as regards ovarian cancer and breast cancer (Riska et al., 2003, www.cancerregistry.fi). Therefore, we assumed that these women may have had a low socioeconomic position. However, in Study III we studied socioeconomic position in more detail among women treated by means of Loop conization, and they had a better socioeconomic position than average in the MBR.

In many studies women with a previous preterm birth have had increased cardiovascular mortality (Irgens et al., 2001; Smith et al., 2001; Catov et al., 2007), which is in accordance with the results of our study. Inflammation and infection are also connected with arteriosclerosis (Myslobodsky, 2001). In other studies, investigators have suggested the presence of dyslipidemia as soon as in early pregnancy as an explanation for increased cardiovascular mortality (Catov et al., 2007). This may also reflect unfavorable health habits of these women. Smoking is also common among women with preterm birth (Lumley et al., 2004) and many infections have been reported to be more frequent among smokers (Bagaitkar et al., 2008). Health counseling should be offered to women who have been treated for CIN and delivered preterm.

7.7. FUTURE PROSPECTS

The goals of primary prevention are to increase public awareness of HPV infection and prevention, so as to increase condom use. One aim is to motivate healthy people to participate in preventive programmes. In this context, public health structures can play an important role in implementing educational programmes (Pagliusi et al., 2008). Vaccination against HPV can be implemented in general vaccination programmes. Currently the cost of vaccination exceeds the budgets of many women and many countries (Bosch et al., 2008b). These vaccines cover only about 70% of all oncogenic HPV types. This necessitates continuation and evaluation of cervical screening programmes (Castellsague, 2008).

In addition, other oncogenic virus types may replace HPV 16 and 18 if these virus types are eradicated. As additional HPV types become incorporated into new vaccines, requirements for screening will be further reduced (Bosch et al., 2008b). In the future, therapeutic HPV vaccines are expected to decrease the need of surgical interventions.

Reproducibility of the diagnosis of CIN lesions is only moderate (Stoler et al., 2001). Some special tools, such as p16INK immunostaining can be used to facilitate accurate diagnosis (Cuzick et al., 2006). The detection and quantification of messenger RNA from E6 and E7 genes of high-risk HPV genotypes could become important in specific diagnosis of high-grade disease and cancer (Gravitt et al., 2008). Other new biomarkers that are associated with neoplasia are currently under research.

Testing for HPV may help to avoid unnecessary repeat treatments, which are the most harmful. Closer follow-up will be reserved for HPV-positive women, who are at an increased risk of recurrence (Finnish Current Care guidelines, 2006). HPV genotyping, determining specific high-risk HPV types, such as HPV 16 and 18, will help to find those women who are at the highest risk of developing cervical cancer (Wright et al., 2007a). Some authors have suggested treatment for HPV 16-positive women with only low-grade lesions (Pretorius et al., 2006). HPV testing could be supplanted in the future by even more sophisticated molecular tests that measure the interaction of virus and human host.

The preterm birth rate has been stable in Finland. It is possible, however, that the international unexplained trend towards an increase in spontaneous preterm births could also occur in Finland. We have adopted an eSET policy in IVF treatments, which should be continued. In Finland smoking during pregnancy is common; about 15% of all pregnant women smoke (Gissler et al., 2007) and therefore smoking cessation programmes should be endorsed. Female adolescents smoke very often, which is alarming. This trend will shortly be seen in maternity hospitals. Induction of delivery should always be considered carefully. It can also lead to a favorable result: as the induced preterm birth rate has increased in the United States, a reduction in perinatal mortality rates has been observed (Ananth et al., 2005). Because black ethnicity is risk factor of preterm birth, as the number of immigrants increases, preterm birth rates may increase. Western immigrants have lower preterm birth rates than Finns and this may also have an impact on preterm birth rates.

In the future new molecular markers should predict preterm birth more accurately. Our understanding of preterm birth pathophysiology might offer us new tools to prevent preterm birth. More research is needed to evaluate the effects of cervical treatments on fertility.

An increasing number of women undergo cervical treatments annually, because of the burden of HPV-associated diseases and increasing age at delivery. It is desirable that increasing awareness of adverse pregnancy outcomes caused by these treatments leads to careful consideration when treating young women. Treatments should become more tailored according to the women's age, childbearing status, lesion size, and severity. Overtreatment should be avoided, and if treatment is required it should be a single curative treatment. Excisional treatments should not be routinely used among fertile aged women without biopsy-confirmed CIN. Current Finnish Guidelines suggest that CIN1 lesions among women under 30 years should be followed-up for 24 months before treatment (Finnish Current Care guidelines, 2006). In many hospitals, surveillance has not been this long. It is important that national guidelines on the diagnosis and treatment of CIN be followed appropriately. In addition, the guidelines allow individual consideration as regards stronger abnormalities among adolescents, as do the European and American guidelines (Wright et al., 2007b; Jordan et al., 2009). For women who have undergone these procedures, it is important that they be delicately counseled about the adverse effect on future pregnancy (Crane et al., 2008a; Jakobsson et al., 2008).

8. CONCLUSIONS

The following conclusions can be drawn:

1. In Finland preterm birth rates have been low and stable, at around 5%. Extremely preterm births have even decreased during 1987–2005. This favorable trend can be partly explained by reduction of multiplicity, which has been achieved mainly by way of an increased elective single embryo transfer policy.
2. Any surgical treatment of CIN is a predisposing factor as regards preterm birth and low birth weight. Increased risk of preterm birth was observed after conization, including cold knife, laser and Loop conization, as well as after ablative treatments, and other surgical treatments. In the conization group the risk was increased as regards both very preterm (from 28 to 31 gestational weeks) and extremely preterm (less than 28 weeks) births. In subgroup analysis, Loop conization was also associated with preterm birth (< 37 weeks). Laser ablation was not, however, associated with preterm birth. According to clinical practice, this treatment modality has been mainly used for ectocervical low-grade lesions.
3. The risk of perinatal mortality was increased after conization, but not after other surgical treatments.
4. Surgical treatment of pre-invasive lesions was associated with an increased risk of preterm birth, even after adjusting for age and parity. This was shown when comparing deliveries by the same women before and after Loop conization. This suggests that the treatment is a more important risk factor of preterm birth than any of the epidemiological or demographic characteristics of the treated women.
5. A high proportion of cases of pPROM (45%) was observed after Loop conization. In general, infection often leads to pPROM. It is possible that the incidence of cervical infections is increased after Loop conization and local cervical infection caused pPROM among these women.

6. The amount of removed tissue, i.e. the size of the cone, may be associated with the risk of preterm birth. We detected a tendency for a higher risk of preterm birth to be associated with larger cones. The risk was significantly increased after repeat treatments. Therefore, repeat treatments should be avoided.
7. The proportion of IVF deliveries does not increase after treatment of CIN. This may suggest that current treatment modalities do not strongly impair fertility. Those women undergoing both CIN and IVF treatment were older and more often primiparous, which explained the increased risk of preterm birth.
8. Women treated for CIN have increased general disease mortality rates, and increased mortality rates in connection with cervical cancer, injuries, accidents and suicides. Preterm birth after treatment of CIN was associated with increased mortality rates, up to 2.5-fold, but the numbers were small. Increased mortality rates may reflect these women's unfavorable health habits and risk-taking behavior. Overall, however, women who delivered after treatment had a lower mortality rate. This may partly be explained by "the healthy pregnant women" effect.

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