Dysplasia: *Original Research*

Effect of Cervical Cancer Screening Programs on Preterm Birth

A Decision and Cost-Effectiveness Analysis

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OBJECTIVE: To assess the effect of age at initiation and interval of cervical cancer screening in women of reproductive age on the risk of future preterm birth and subsequent adverse neonatal outcome relative to maternal life-years gained and cost of both screening and preterm birth.

METHODS: In this decision and cost-effectiveness analysis, we compared eight cytology-based screening programs varying in age of onset (21, 24, 25, 27, or 30 years) and screening interval (3 or 5 years) in a fictive cohort of 100,000 women. We used the microsimulation screening analysis model to estimate number of cervical intraepithelial neoplasia diagnoses, large loop excisions of the transformation zone (LLETZs), life-years gained, cervical cancer cases, deaths, and costs of screening and treatment. We used the number of LLETZs to calculate additional preterm births, subsequent neonatal morbidity, mortality, and associated costs.

RESULTS: The number of LLETZs per 100,000 women varied from 9,612 for the most intensive screening (every 3 years from age 21 years) to 4,646 for the least intensive screening (every 5 years from age 30 years). Compared with the least intensive program, the most intensive program increased maternal life-years gained by 9% (10,728 compared with 9,839), decreased cervical cancer cases by 67% (52 compared with 158), and cervical cancer deaths by 75% (four compared with 16) at the expense of 250% (158 compared with 45) more preterm births and 320% (four compared with one) more neonatal deaths while increasing total costs by $55 million ($77 compared with $23 million). The number of maternal life-years gained per additional preterm birth varied from 68 to 258 with subsequent total costs per maternal life-years gained of $7,212 and $2,329.

CONCLUSION: Cervical cancer screening every 3 years and subsequent treatment in women aged younger than 30 years yield limited life-years but may have substantial perinatal adverse effects. Consequently, women who plan to have children may benefit from a more cautious screening approach, taking into account their risk for both cancer and preterm birth.

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Early detection and treatment of cervical intraepithelial neoplasia (CIN) are effective in reducing cervical cancer incidence and mortality.[1,2] In several Western countries, cervical cancer rates have decreased by as much as 65% over the past 40 years.[3] Despite these successes, cervical cancer is still the fourth most common cancer among women worldwide with an estimated 527,600 new cases and 265,700 related deaths in 2012.[3]

There is no consensus on the best screening strategy, and recommendations vary widely with respect to age at initiation of screening (ie, 18–30 years) and screening interval (2–5 years) (Table 1).[4–8]

Table 1. Recommended Age at Initiation and Screening Interval of Cytology-Based Screening Programs in Several Countries[5–9]

Country	Age at Initiation (y)	Screening Interval (y)
Australia	18	2
Netherlands	30	5
United Kingdom	25–50	3
	>50	5
United States	21–30	3
	30–65	5 (with HPV testing) or 3 (cytology only)

HPV, human papillomavirus.

In screening programs, women with abnormal cervical smears are referred for colposcopy and possible biopsy. If high-grade lesions (ie, CIN 3 or worse) are diagnosed by biopsy, large loop excision of the transformation zone (LLETZ) is indicated.[9–11] Recent studies have shown that pregnant women with a history of LLETZ have an increased risk of preterm birth with associated perinatal morbidity and mortality.[12–18] However, systematic reviews and meta-analyses have reached inconsistent conclusions about the magnitude of this effect.[12–15,18] At least part of this increase can be linked to the CIN lesion itself or to other factors associated with CIN development.[18,19] A recent comprehensive systematic review and meta-analysis showed that compared with women with untreated CIN, women whose CIN had been treated with LLETZ were at 33% higher risk of preterm birth.[19]

These adverse treatment effects are particularly relevant because CIN lesions may regress naturally in up to 40% of CIN 2 lesions, and treatment is often unnecessary. However, because it is not yet possible to predict future behavior of individual lesions, most CIN 2 or worse lesions are treated.[20,21] More than 400,000 women are diagnosed with CIN annually in the United States, the majority at reproductive age.[22]

Thus, although screening programs have significantly reduced cervical cancer incidence and mortality rates, treatment of precancerous lesions may also have resulted in adverse pregnancy outcomes in women who became pregnant after treatment. The purpose of this study was to assess the effect of the age at initiation and the interval of various cytology-based screening programs on the risk of future preterm birth and subsequent neonatal morbidity and mortality, relative to maternal life-years gained, and costs of both screening and preterm birth.

MATERIALS AND METHODS

In this decision and cost-effectiveness analysis, we used the microsimulation screening analysis model to simulate eight different screening programs.[23] For every screening program, the microsimulation screening analysis model estimates the number of CIN diagnoses, LLETZs, cervical cancer cases and deaths, maternal life-years gained, and costs per 100,000 simulated women, resulting from screening between 21 and 46 years of age as compared with the situation without screening. For each screening program, we calculated the age-specific number of preterm births caused by treatment of precancerous lesions detected by screening and estimated the subsequent neonatal morbidity and mortality resulting from these preterm births and costs after preterm birth.

In the microsimulation screening analysis model, a hypothetical cohort of 10 million women is simulated from birth until death. In our analysis, we present outcomes per 100,000 women. Every woman may acquire human papillomavirus (HPV) infections that can progress to CIN lesions and cervical cancer. Most HPV infections clear spontaneously, however, without ever resulting in CIN or cancer. Regression probabilities of CIN decrease with increasing age and lesion grade. The model is based on (Dutch) demographic data (ie, age-specific all-cause mortality, hysterectomy rates), natural history data (eg, natural regression or progression of CIN lesions), and screening data (eg, detection rates of CIN and cervical cancer).[24] The model generates age-specific outputs like detected CIN lesions (by grade), cervical cancer cases (by stage), and cervical cancer deaths.[25] More detailed model information can be found in previous studies.[26]

We used the model to compare eight cytology-based screening programs in women of reproductive age (21 until 46 years), varying in age of onset of screening (21, 24, 25, 27, or 30 years) and interval between screening (3 or 5 years).

Women with high-grade squamous intraepithelial lesions or worse were directly referred to colposcopy and women with atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesions were triaged as was recommended in Dutch screening guidelines in 2015 (Box 1).[27]

Because we are only interested in the effect of screening on subsequent preterm birth risk in women willing to participate in screening, we assumed full adherence with primary screening, triage testing, and referral to colposcopy. All women with diagnosed CIN 2 or CIN 3 and 25% of women diagnosed with CIN 1 were assumed to be treated with LLETZ (Box 1).[28,29]

Box 1. Assumptions for Screening, Treatment, Additional Preterm Birth Risk, and Subsequent Neonatal Outcome

Screening[23,25]

- Screening strategy
  - Primary cytology, with direct referral to colposcopy for women with HSIL or greater test results; women with ASC-US or LSIL tests results are offered cotesting (cytology and HPV test) at 6 mo, and those with either HPV-positive or ASC-US or LSIL test results at 6 mo are offered cytology at 18 mo
- Test characteristics of cytology[26]
  - Probability of test results of at least ASC-US or LSIL for women with:
    - Less than CIN 1: 2.4%
    - CIN 1: 40%
    - CIN 2: 50%
    - CIN 3 or worse: 75%
  - Probability of test results at least HSIL for women with:
    - Less than CIN 1: 0.03%
    - CIN 1: 3.6%
    - CIN 2: 18%
    - CIN 3: 55.9%
    - Cervical cancer: 59.7%
- Test characteristics of HPV test
  - 85% sensitivity (ie, probability of detecting a high-risk HPV infection, regardless of cervical lesions or cancer) and 100% specificity (ie, possible lack of specificity is modeled by the inclusion of fast-clearing infections)
- Adherence
  - 100% with primary screening, triage testing and referral to colposcopy
- Treatment with LLETZ[28,29]
  - 25% of CIN 1 diagnoses; 100% of CIN 2 or 3 diagnoses

Preterm birth[19,32]

- Baseline risk of spontaneous preterm birth[32]: 4.2%
- RR spontaneous preterm birth after LLETZ[19]: 1.33
- Additional preterm birth risk after LLETZ: 1.4%

Neonatal outcome[32,33]

- Appendix 1*: Age distribution of pregnancy by parity[32]
- Appendix 2*: Distribution of preterm birth by GA, parity, and singleton or multiple pregnancy[32]
- Appendix 3*: Neonatal morbidity and mortality by GA separated by singleton or multiple pregnancy[33]

HSIL, high-grade squamous intraepithelial lesions; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesions; HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; LLETZ, large loop excision of the transformation zone; RR, relative risk; GA, gestational age.

*Appendices 1–3 are available online at http://links.lww.com/AOG/B35.

Box 1 shows the assumptions for preterm birth risk after treatment and subsequent neonatal outcome. In 2015, the fertility rate (children born per woman) was 1.658 in the Netherlands.[30] Because female childlessness is approximately 20% in the Netherlands, we assumed that all simulated women planned to have two pregnancies ($1.658 \times 80\% \approx 2$).[31]

Based on most recent data from the Perinatal Registry of the Netherlands, we assumed a baseline prevalence of spontaneous preterm birth of 4.2% (Box 1).[32] For the effect of LLETZ on preterm birth risk, we used a recent systematic review and meta-analysis showing results for multiple comparison groups.[19] To partly correct for the development of CIN, we took the relative risk (RR) for women undergoing colposcopy but no treatment, which equaled 1.33 (95% CI 1.11–1.60). Consequently, LLETZ increased preterm birth risk with an absolute 1.4% ($0.33 \times 4.2\%$).

Women's age distribution for giving birth to a first and second child and the distribution of preterm birth by gestational age separated by parity (nulliparous or multiparous) and multiplicity were also based on data from the Perinatal Registry of the Netherlands of 2015 (Appendices 1 and 2, available online at http://links.lww.com/AOG/B35).[32] Neonatal morbidity and mortality probabilities resulting from preterm birth were specified by gestational age and type of pregnancy (singleton or multiple pregnancy) and are based on several randomized clinical trials in women with threatened preterm birth (Appendices 3 and 4, available online at http://links.lww.com/AOG/B35).[33]

Table 2 shows the assumptions for costs used in the analysis. Screening costs included the process used to invite women, time and travel costs required to attend screening, the test, cytologic evaluation or HPV analysis, and registration in the screening database. We derived the costs of screening, diagnosis, and treatment procedures for detected preinvasive lesions, of primary treatment of invasive cervical cancer, and of treatment and palliative care for advanced cervical cancer from cost studies in the Netherlands.[34] The costs resulting from preterm birth were specified by gestational age and type of pregnancy based on data collected in several randomized clinical trials in women with threatened preterm birth (Appendix 5, available online at http://links.lww.com/AOG/B35).[33] All costs were converted from Euros to U.S. dollars using the exchange rate on August 10, 2017 (€1=$1.17).[35]

The additional number of preterm births was calculated by multiplying the age-specific number of births in women who have undergone LLETZ before that age with the additional probability of preterm

Table 2. Assumptions on Costs

	Cost ($)
Costs of preterm birth*,[33]	
Costs of screening and treatment[23–25,34,35]	
Invitation	
Invitation letter	5.74
Primary screening	
Cytology	78.18
Reflex triage (after 6 mo only)	
HPV test	34.30
Triage after 6 or 18 mo	
Cytology	75.22
Diagnosis and treatment of preinvasive stages	
False-positive	350.10
CIN 1	1,093.00
CIN 2	1,618.21
CIN 3	1,895.01
Diagnosis and treatment of cancer	
FIGO 1A	6,205.49
FIGO 1B	14,715.28
FIGO 2+ (detected by screening)	14,503.54
FIGO 2+ (detected by symptoms)	13,545.39
Palliative care	32,954.41

GA, gestational age; HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; FIGO, International Federation of Gynecology and Obstetrics.

* Please see Appendix 4, available online at http://links.lww.com/AOG/B35.

birth risk after LLETZ. For example, 7.2% (1.7% +2.3%+3.1%) of the Dutch women would give birth to her first child between 21 and 24 years of age (Appendix 1, available online at http://links.lww.com/AOG/B35). Of these women, 1,583 in the cohort will have undergone LLETZ before their pregnancy in case of the 21/3 screening program. With an additional preterm birth risk after LLETZ of 1.4% as compared with the baseline risk of 4.2% (Box 1), this leads to 9.0 (7.2%×1,583×1.4%=1.6) additional preterm births. Adding all preterm births for first and second pregnancies for all ages between 21 and 46 years generates the total number of additional preterm births resulting from that screening program.

Subsequently, based on the number of preterm births, we calculated the neonatal morbidity and mortality in relation to gestational age and parity. For example, 29.7% of all preterm births in the first pregnancy are singletons born between 36 and 37 weeks of gestation (Appendix 2, available online at http://links.lww.com/AOG/B35). Multiplying this by the 0.5% probability of morbidity of a singleton born between 36 and 37 weeks of gestation (Appendix 3, available online at http://links.lww.com/AOG/B35) and the number of preterm births in a screening program, this generates an expected amount of neonatal morbidity resulting from an additional preterm birth caused by a screening program for singletons from first pregnancy at this gestational age. Adding up these numbers for all expected preterm births at different gestational ages leads to the expected total additional neonatal morbidity for the screening program. Similarly, we calculated the additional neonatal mortality and costs of preterm birth for each screening program.

We also calculated the total costs (costs of cervical cancer screening and treatment and preterm birth) per life-years gained. Furthermore, we calculated the ratio of life-years gained per additional preterm birth to compare the effect of several screening programs.

Finally, we performed two sensitivity analyses. In the base-case analysis, we assumed the RR of preterm birth after LLETZ to equal the point estimate that was found for women undergoing colposcopy but no treatment in a recent systematic review and meta-analysis (ie, RR 1.33).[19] In the first sensitivity analyses, we varied the RR to the lower and upper bound of the 95% CI belonging to this point estimate (ie, RR 1.11 and RR 1.60, respectively). In another sensitivity analysis, we set the baseline preterm birth rate equal to the 2014 American spontaneous preterm birth rate (ie, 8.5% for nulliparous and 9.2% for multiparous pregnancies) while leaving all other variables equal.[36]

RESULTS

Table 3 shows the maternal outcome, that is, the effect of the eight screening programs on the number of LLETZs, cervical cancer cases and deaths, maternal life-years gained, and cost of both screening and treatment. The number of LLETZs per 100,000 women varied from 9,612 in the most intensive screening program (every 3 years from age 21 years) to 4,646 in the least intensive program (every 5 years from age 30 years). This resulted in 52 cervical cancer cases and four cervical cancer deaths for screening every 3 years from age 21 years, compared with 158 cases and 16 deaths for screening every 5 years from age 30 years. Screening every 3 years from age 40 years or every 5 years from age 21, 24, or 25 years resulted in more similar numbers of cervical cancer cases (range 110–118) and deaths (range 10–11). The number of cervical cancer cases was lower with every-3-year screening than with screening every 5 years (range 52–110 compared with 114–158, respectively).

The number of life-years gained varied from 10,728 (every 3 years from age 21 years) to 9,809 (every 5 years from age 24 years) and was lower for screening programs with a 5-year interval (range

Table 3. Maternal Outcomes and Costs of Screening per 100,000 Women During Reproductive Age According to Eight Different Programs

	Maternal Outcome			Effects and Costs as Compared With the Situation Without Screening	
Program*	LLETZ	Cervical Cancer Cases†	Cervical Cancer Deaths†	Life-Years Gained	Costs ($)‡
21/3	9,612	52	4	10,728	74.1
24/3	8,576	59	5	10,700	63.0
27/3	7,033	75	6	10,628	51.1
30/3	5,517	110	11	10,419	39.6
21/5	7,820	114	10	10,379	44.9
24/5	6,970	112	11	9,809	36.1
25/5	6,713	118	11	10,086	34.6
30/5	4,646	158	16	9,839	22.1

LLETZ, large loop excision of the transformation zone.
* X/Y where X=age at initiation of screening and Y=screening interval.
† Cervical cancer cases and deaths at ages 20–46 years. Screening until age 46 can also prevent cervical cancer cases and deaths for women older than age 46.
‡ Costs of screening, treatment of cervical intraepithelial neoplasia lesions and cervical cancer, and palliative care in millions of U.S. dollars (rounded).

9,809–10,379) compared with a 3-year interval (range 10,419–10,728). Total costs varied from $22.1 million (every 5 years from age 30 years) to $74.1 million (every 3 years from age 21 years) with more or less intensive screening, respectively.

Table 4 shows the effect of the eight screening programs on the neonatal outcome, that is, the number of additional preterm births, neonatal morbidity and mortality, and the costs of preterm birth. The estimated number of additional preterm births caused by LLETZ taken within the screening program ranged from 45 (every 5 years from age 30 years) to 158 (every 3 years from age 21 years) per 100,000 women with subsequent neonatal cases of morbidity and mortality ranging from four (every 5 years from age 30 years) to 13 (every 3 years from age 21 years) and from one (every 5 years from age 30 years) to four (every 3 years from age 21 years), respectively. As expected, the screening-attributable preterm birth rates decrease with a later onset of screening.

The costs of preterm birth varied from $0.8 million for the least (every 5 years from age 30 years) to $3.2 million for the most intensive screening program (every 3 years from age 21 years), again decreasing with a later onset of screening.

Table 5 shows the overall effect, that is, the combined neonatal and maternal outcome. The number of maternal life-years gained per additional preterm birth varied from 68 to 258 for the most (every 3 years from age 21 years) or least (every 5 years from age 30 years) intensive screening program, respectively, with subsequent total costs per maternal life-years gained of $7,212 and $2,329, respectively (Fig. 1).

The neonatal compared with maternal mortality ratio ranged from 0.1 (1:16 for screening every 5 years from age 30 years) to 1.0 (4:4 for screening every 3

Table 4. Neonatal Outcomes of Screening 100,000 Women During Reproductive Age According to Eight Different Programs

Program*	Additional Preterm Births	Morbidity	Mortality	Costs ($)†
21/3	158	13	4	3.2
24/3	130	11	3	2.6
27/3	85	7	2	1.7
30/3	46	4	1	0.9
21/5	122	10	3	2.5
24/5	103	9	3	2.1
25/5	93	8	2	1.9
30/5	45	4	1	0.8

* X/Y X=age at initiation of screening, Y=screening interval.
† Costs of preterm birth in million U.S. dollars (rounded).

Table 5. Combined Maternal and Neonatal Outcomes of Screening 100,000 20-Year-Old Women During Reproductive Age According to Eight Programs

Program*	Life-Years Gained/Preterm Birth	Total Costs†/Life-Years Gained ($)	Neonatal/Maternal Mortality
21/3	67.8	7,212	1.0 (4/4)
24/3	82.6	6,134	0.6 (3/5)
27/3	124.3	4,967	0.3 (2/6)
30/3	226.7	3,891	0.1 (1/11)
21/5	85.3	4,566	0.3 (3/10)
24/5	95.3	3,895	0.3 (3/11)
25/5	108.6	3,622	0.2 (2/11)
30/5	257.7	2,329	0.1 (1/16)

* X/Y X=age at initiation of screening, Y=screening interval.
† Total costs=costs of cervical cancer screening and treatment and preterm birth.

years from age 21 years) and was similar (0.3) for screening every 3 years from age 27 years and every 5 years from age 21 or 24 years. Figure 2 shows the neonatal and maternal deaths and costs of screening and preterm birth per program. Whereas maternal deaths decrease with earlier and more frequent screening, neonatal deaths increase. Because screening costs were more dominant than costs related to preterm birth, total costs decreased with later onset of screening or less frequent screening. The total costs are lower for all programs with a 5-year screening interval compared with a 3-year interval, except from every 5 years from age 21 years compared with every 3 years from age 30 years.

Compared with the least intensive screening program (every 5 years from age 30 years), the most intensive screening program (every 3 years from age 21 years) decreases cervical cancer cases by 67% (52 compared with 158) and maternal deaths by 75% (four compared with 16) at the expense of 250% (158 compared with 45) more preterm births and 320% (four compared with one) more neonatal deaths while increasing the total costs by $55 million ($77 compared with $23 million).

Screening from age 21 years at a 5-year instead of a 3-year interval leads to 119% (114 compared with 52) more cervical cancer cases and 150% (10 compared with four) more maternal deaths while decreasing the number of preterm births with 23% (122 compared with 158) and the number of neonatal

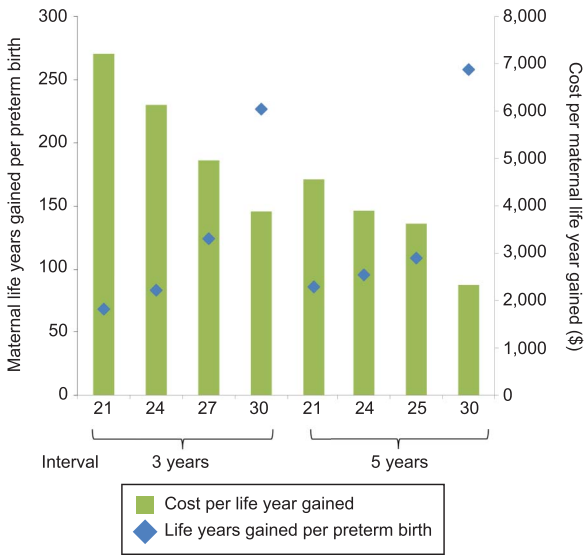

Fig. 1. Combined maternal and neonatal outcome. Maternal life-years gained per preterm birth (*diamonds*) (left y-axis) and total costs per maternal life-year gained (*bars*) (right y-axis) for the eight different screening programs (x-axis).

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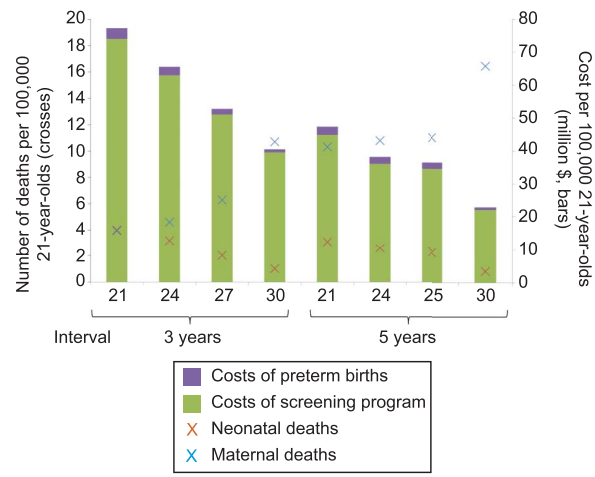

Fig. 2. Comparing maternal and neonatal deaths and total costs of the screening program and additional preterm birth.

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deaths with 25% (three compared with four). Total costs were $30 million lower ($77 compared with $47 million). When starting screening at age 30 years, a 5-year instead of a 3-year interval resulted in 44% (158 compared with 110) more cervical cancer cases and 45% (16 compared with 11) more maternal deaths, while only decreasing the additional preterm births by 2% (45 compared with 46) and a negligible difference in neonatal deaths (one compared with one) while decreasing the costs by $18 million ($41 compared with $23 million).

The results of the sensitivity analyses in which we varied the RR of preterm birth after LLETZ were according to expectations. An excess risk of 0.11 instead of 0.33 resulted in a roughly threefold reduction of preterm births and associated morbidity, mortality, and costs; and with an excess risk of 0.67, they were a factor 2 higher (Table 6).

In the second sensitivity analysis, we equated the preterm birth rates to the American spontaneous preterm birth rate in 2014. These rates increase the additional preterm birth range from 45 to 158 with the Dutch preterm birth rate to 168–695 with the American preterm birth rate and subsequently increasing neonatal morbidity (from 4–13 to 14–58) and mortality (from 1–4 to 4–18) (Appendix 5, available online at http://links.lww.com/AOG/B35) This increase in preterm birth lowers the range of life-years gained and preterm birth from 68–258 with the Dutch preterm birth rate to 15–59 with the American preterm birth rate and changes the neonatal compared with maternal mortality rate accordingly (from 0.1–2.0 to 0.3–4.5) (Appendix 6, available online at http://links.lww.com/AOG/B35).

DISCUSSION

We assessed the number of preterm births and subsequent neonatal morbidity and mortality attributable to CIN treatment in relation to maternal life-years gained and the total costs for different screening programs. Compared with the situation without screening, screening every 5 years from age 30 years led to 9,839 maternal life-years gained and 45 additional preterm births, leading to one neonatal death. Screening every 3 years from age 21 years resulted in 889 more maternal life-years gained and 113 more preterm births leading to three more neonatal deaths but 12 less maternal deaths while increasing the total costs from $23 to $77 million. Screening every 5 years instead of every 3 years from age 21 years led to 349 less maternal life-years gained (10,379 compared with 10,728) and six more maternal deaths (10 compared with four) while decreasing the preterm births from 158 to 122 and neonatal deaths from four to three and reducing the total costs from $77 to $47 million. Although maternal life-years cannot be (directly) compared with neonatal life-years, the differences in outcomes between programs are substantial and may be relevant for screening decisions.

Our analysis has several strengths and limitations. A strength of our analysis is that we modeled eight different screening programs, varying both in age at initiation of screening and screening interval, to gain separate insight into these two variables. Furthermore, we analyzed the costs of the different programs, not

Table 6. Sensitivity Analyses of Neonatal Outcome Varying the Relative Risk of Preterm Birth After Large Loop Excision of the Transformation Zone

	Additional Preterm Births†			Morbidity†			Mortality†			Costs ($)†‡		
Program*	Lower	Baseline	Upper	Lower	Baseline	Upper	Lower	Baseline	Upper	Lower	Baseline	Upper
RR	1.11	1.33	1.67	1.11	1.33	1.67	1.11	1.33	1.67	1.11	1.33	1.67
21/3	53	158	321	4	13	27	1	4	8	1.1	3.2	5.8
24/3	43	130	263	4	11	22	1	3	7	0.9	2.6	4.7
27/3	28	85	174	2	7	14	1	2	5	0.6	1.7	3.1
30/3	15	46	93	1	4	8	0	1	2	0.3	0.9	1.7
21/5	41	122	247	3	10	21	1	3	6	0.8	2.5	4.4
24/5	34	103	209	3	9	17	1	3	5	0.7	2.1	3.8
25/5	31	93	189	3	8	16	1	2	5	0.6	1.9	3.4
30/5	13	38	78	1	3	6	0	1	2	0.3	0.8	1.4

RR, relative risk.
* X/Y X=age at initiation of screening, Y=screening interval.
† RR based on upper and lower bound of 95% CI of RR 1.33 (95% CI 1.11–1.67) compared with women undergoing colposcopy with or without cervical intraepithelial neoplasia or biopsy but no treatment.
‡ Costs of preterm birth in millions of U.S. dollars (rounded).

only those related to screening, diagnosis, and treatment, but also those related to additional preterm births. A third strength of our analysis is that we used detailed and accurate pregnancy data representative for the Netherlands in 2015, the most recent available year. Combined with the microsimulation screening analysis model, which is also based on Dutch characteristics, our analysis is representative of the Netherlands in 2015.

The study also has some noteworthy limitations. In our analysis, we modeled the effect of CIN treatment for women having the average number of two pregnancies. For women having only one or three or more pregnancies, the expected adverse effect of treatment would be different, and one may consider taking into account a woman's number of planned pregnancies when making individualized screening decisions.

Another limitation is that the Dutch characteristics may not be fully representative for other countries. However, it is unlikely for model assumptions regarding the natural history of the disease to differ much across countries.

Finally, we could not include the effects of possible treatment to reduce the risk of preterm birth in women with LLETZ (ie, cervical length measurement in pregnancy with subsequent progesterone therapy or cerclage).

Although there is no doubt about the success of cervical cancer screening, there is debate on the appropriate age to initiate screening as is demonstrated by the wide range of recommendations (ie, from 18 to 30 years). Early ages at initiation will generally avert more cervical cancer deaths. However, given the high prevalence of regressive lesions at young age, screening at young age could also lead to high overtreatment rates, thereby increasing preterm birth risk for no additional benefit. Moreover, given the long preclinical duration of cervical disease, early initiation of screening yields only marginal benefits.

Early systematic reviews and meta-analyses on preterm birth risk after different kinds of CIN treatment showed an increased risk of preterm birth.[13,14] More recent systematic reviews reached contradictory conclusions. Conner et al,[18] who compared preterm birth rates in women who had undergone LLETZ with those in women with untreated CIN, did not find a significant difference and suggested the association to be confounded by underlying CIN or by infection leading to CIN. However, a more recent meta-analysis, including four additional studies, and comparing preterm birth rates in women who had had cervical surgery for CIN with women who were diagnosed with CIN but had not been treated, confirmed an increased risk after cervical surgery (RR 1.67, 95% CI 1.04–2.67), which was partly attributed to treatment for CIN during pregnancy.[37] The most recent systematic review and meta-analysis from Kyrgiou et al[19] explored the effect for five different comparison groups. Their analyses show an increased risk of preterm birth after LLETZ for all five comparison groups. The magnitude of effect was higher when comparing with external controls (RR 1.69, 95% CI 1.46–1.97) than with women who had disease but were not treated (RR 1.33, 95% CI 1.11–1.60) with an overall RR of 1.56 (95% CI 1.36–1.79) for preterm birth after LLETZ.[19] They conclude that women with CIN have a higher baseline risk for prematurity and that excisional and ablative treatment increases that risk. We used RR compared with women with CIN (or biopsy but no disease) but no treatment, because we consider this the most valid comparison.

Furthermore, Kyrgiou et al[19] showed that the frequency and severity of adverse sequelae increase with increasing cone depth and are higher for excision than for ablation. Castañon et al[16] also assessed the effect of increasing depth or volume of the excision on preterm birth in women with cervical dysplasia. Furthermore, they report that this risk does not decrease with increasing time from excision to conception nor that it is restricted to the first pregnancy posttreatment.[17] Differences in preterm birth rate between less and more invasive cervical surgery or time between excision and pregnancy are unlikely to be confounded. Thus, the present analysis shows that in women who might want to conceive in the future, it is important to limit treatment and limit the depth of excisions as much as possible. On the other hand, women who are done with childbearing years could consider an excision procedure with CIN 2 or worse lesions.

Another determinant of the potential harm of LLETZ in a screening program is the accuracy of the screen test used. High false-positive rates generate unnecessary biopsies and potentially also LLETZs. Current HPV tests are more sensitive for detecting CIN 2 or worse and CIN 3 or worse than cytology.[38,39] However, the higher sensitivity comes with reduced specificity, meaning that the majority of HPV-positive women does not have clinically relevant disease.[38,39] Therefore, careful triaging in HPV-positive women is of utmost importance to limit the number of colposcopy referrals in settings with primary HPV screening. The Netherlands has recently implemented primary

HPV screening and despite a well-developed triage schedule, a large increase in colposcopy referrals is expected.[40] This makes the results of our analysis even more pressing. Moreover, in programs with opportunistic screening such as in the United States, Czech Republic, and Luxembourg, adherence with (triage) guidelines is generally worse, and primary HPV testing would lead to an even larger increase in referrals.

Our assumptions for HPV prevalence and abnormal cervical histology will likely be influenced by HPV vaccination programs. As these programs start to have an effect, the number of screen-positive women and the number of women requiring treatment might decrease as well as the resulting number of preterm births. However, the bivalent and quadrivalent vaccine only targets the two most oncogenic HPV types (ie, HPV-16 and HPV-18). Women vaccinated with one of these vaccines will be at relatively higher risk for other HPV types with lower progression probabilities, leading to relatively more treatments per life-years gained. With newer vaccines like the recently approved nonvalent vaccine, up to 90% of cervical cancer cases may be prevented by targeting seven of the 16 oncogenic HPV types.[41] For women vaccinated with such vaccines, the harm–benefit ratio of screening and subsequent treatment is expected to be even worse.

Finally, compared with other European countries and the United States, the preterm birth rate in the Netherlands is relatively low.[42] We explored the influence of this parameter on adverse pregnancy outcomes by assuming the relatively high U.S. rate in a sensitivity analysis. With local estimates for fertility rate, spontaneous preterm birth rate, and women's age distribution at giving birth, one could more precisely extrapolate the current findings to another screening setting. When considering the American population, with higher preterm birth rates and earlier age at giving birth, the benefit of delaying the onset of screening in preventing preterm birth (ie, not from 21 or 24 years onward) will be more dramatic than in the Dutch situation, because in 2015, 37% of all American women had given birth to their first or second child at age 27 years and nearly 53% of all women had given birth to their first child.[36]

In summary, we have shown that frequent cervical cancer screening and subsequent treatment in women younger than 30 years yield limited life-years, but may have substantial perinatal adverse effects. Screening decisions should ideally be individualized, taking into account a woman's expected harm–benefit ratio of screening. Although screening may be more harmful to women with a reproductive life plan, it may be more beneficial to those with young age at first intercourse, high parity, long-term use of oral contraceptives, and smoking behavior.[43–47] We recognize that perinatal adverse effects may also be limited by taking a more restrictive approach to immediate treatment, offering monitoring instead. However, lesions may still progress during follow-up, and knowledge of having CIN 2 or worse may be burdensome for women. We therefore plead for more research to estimate the effects of delaying treatment.

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