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Effect of cervical cancer screening programs on preterm birth: a decision and cost-effectiveness analysis

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ABSTRACT

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 (MISCAN) model to estimate number of CIN 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) to 4,646 for the least intensive screening (every 5 years from age 30). Compared to the least intensive program, the most intensive program increased maternal life years gained by 9% (10,728 vs 9,839), decreased cervical cancer cases by 67% (52 vs 158), cervical cancer deaths by 75% (4 vs 16), at the expense of 250% (158 vs 45) more preterm births and 320% (4 vs 1) more neonatal deaths, while increasing total costs with $55 million ($77 vs $23 million). The amount 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 yields limited life years, but may have substantial perinatal adverse effects. Consequently, women who plan to have future children may benefit from a more cautious screening approach, taking into account their risk for both cancer and preterm birth.

INTRODUCTION

Early detection and treatment of cervical intraepithelial neoplasia (CIN) is 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 (i.e. 18 to 30 year) and screening interval (2 years to 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 (years)	Screening interval (years)
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 (i.e. CIN3+) 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 to 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 II lesions, and treatment is often unnecessary. However, as it is not yet possible to predict future behavior of individual lesions,

most CIN II+ 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.

MATERIAL AND METHODS

In this decision and cost-effectiveness analysis, we used the microsimulation screening analysis (MISCAN) model to simulate eight different screening programs.[23] For every screening program, the MISCAN 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 as compared to 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 following from preterm birth.

In the MISCAN model, a hypothetical cohort of 10 million women is simulated from birth till death. In our analysis, we present outcomes per 100,000 women. Every woman may acquire HPV infections that can progress to CIN lesions and cervical cancer. Most HPV infections clear spontaneously though, 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 (i.e. age-specific all-cause mortality, hysterectomy rates), natural history data (e.g. natural regression or progression of CIN lesions) and screening data (e.g. 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 (HSIL) or worse were directly referred to colposcopy and women with atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions (LSIL) were triaged as was recommended in Dutch screening guidelines in 2015 (Box 1).[27]
Since 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 II or CIN III and 25% of women diagnosed with CIN I 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 testing ≥HSIL. Women with ASCUS/LSIL are offered co-testing (cytology and HPV-test) at 6 months, and those testing either HPV-positive or ASCUS/LSIL at 6 months are offered cytology at 18 months	
Test characteristics of cytology [26]	Probability of testing at least ASCUS/LSIL for women with:	
	< CIN I	2.4%
	CIN I	40%
	CIN II	50%
	CIN III or worse	75%
	Probability of testing at least HSIL for women with:	
	< CIN I	0.03%
	CIN I	3.6%
	CIN II	18%
	CIN III	55.9%
	Cervical cancer	59.7%
Test characteristics of HPV-test	85% sensitivity (i.e. probability of detecting a high-risk HPV infection, regardless of cervical lesions or cancer), and 100% specificity (i.e. 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 I diagnoses; 100% of CIN II/III diagnoses	

Box 1: Continued

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; ASCUS = 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; GA = gestational age.
Appendixes 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] Since female childlessness is about 20% in the Netherlands, we assumed that all simulated women planned to have two pregnancies (1.658 * 80% ≈ 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*4.2%).

Women's age distribution for giving birth to a first and second child and the distribution of preterm birth by gestational age (GA) separated by parity (nulliparous or multiparous) and multiplicity were also based on data from the Perinatal Registry of the Netherlands of 2015 (Appendix 1 and 2, available online at http://links.lww.com/AOG/B35).[32] Neonatal morbidity and mortality probabilities due to preterm birth were specified by GA and type of pregnancy (singleton or multiple pregnancy) and are based on several randomised clinical trials in women with threatened preterm birth (Appendix 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, cytological evaluation or HPV analysis, and registration in the screening database. We derived the costs of screening, diagnosis, and treatment procedures for detected pre-invasive 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 GA and type of pregnancy based on data collected in several randomised 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 USD using exchange rate of August 10th 2017 (1 euro = 1.17 USD).[35]

Table 2: Assumptions on costs

Costs of preterm birth [33]		
Supplementary file IV: Costs of preterm birth by GA and singleton or multiple pregnancy [33]		
Costs of screening and treatment [23,24,25,34,35]		
Invitation	Invitation letter	$ 5.74
Primary screening	Cytology	$ 78.18
Reflex triage (after 6 months only)	HPV-test	$ 34.30
Triage after 6 or 18 months	Cytology	$ 75.22
Diagnosis and treatment of Pre-invasive stages	False positive	$ 350,10
	CIN I	$ 1,093
	CIN II	$ 1,618.21
	CIN III	$ 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	Total costs	$ 32,954.41

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

The additional number of preterm births was calculated by multiplying the age-specific number of births in women who have had a LLETZ prior to that age with the additional probability of preterm 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 (supplementary file I). Of these women, 1,583 in the cohort will have undergone LLETZ prior to their pregnancy in case of the 21/3 screening program. With an additional preterm birth risk after

LLETZ of 1.4% as compared to the baseline risk of 4.2% (Box 1), this leads to 9.0 (7.2%*1583*1.4%= 1.6) additional preterm births. Adding all preterm births for first and second pregnancy for all ages between 21 and 46 years generates the total amount of additional preterm births due to that screening program.
Subsequently, based on the number of preterm births, we calculated the neonatal morbidity and mortality in relation to GA and parity. For example, 29.7% of all preterm births in the first pregnancy are singletons born between 36-37 weeks of GA (Appendix 2, http://links.lww.com/AOG/B35). Multiplying this by the 0.5% probability of morbidity of a singleton born between 36-37 weeks of GA (Appendix 3, http://links.lww.com/AOG/B35) and the number of preterm births in a screening program, this generates an expected amount of neonatal morbidity due to additional preterm birth caused by a screening program for singletons from first pregnancy at this GA. Adding up these numbers for all expected preterm births at different GA 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 (i.e. RR=1.33).[19] In the first sensitivity analyses, we varied the RR to the lower and upper bound of the 95% confidence interval belonging to this point estimate (i.e. 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 (i.e. 8.5% for nulliparous and 9.2% for multiparous pregnancies), while leaving all other variables equal.[36]

RESULTS

Table 3 shows the maternal outcome, i.e. 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) to 4,646 in the least intensive program (every 5 years from

age 30). This resulted in 52 cervical cancer cases and 4 cervical cancer deaths for screening every 3 years from age 21, versus 158 cases and 16 deaths for screening every 5 years from age 30. Screening every 3 years from age 30 or every 5 years from age 21, 24 or 25 resulted in more similar numbers of cervical cancer cases (range: 110-118) and deaths (range: 10-11).
The amount of cervical cancer cases was lower with every 3 year screening than with screening every 5 years (range: 52-110 vs 114-158 respectively).
The number of life years gained varied from 10,728 (every 3 years from age 21) to 9,809 (every 5 years from age 24) and were lower for screening programs with a 5-year interval (range: 9,809-10,379) compared to a 3-year interval (range: 10,419-10,728). Total costs varied from $22.1 million (every 5 years from age 30) to $74.1 million (every 3 years from age 21) with more or less intensive screening, respectively.

Table 3: Maternal outcome and costs of screening per 100,000 women during reproductive age according to 8 different programs

	Maternal outcome			Effects and costs as compared to 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.

* Cervical cancer cases and deaths at ages 20 to 46. Screening until age 46 can also prevent cervical cancer cases and deaths above age 46.
** Costs of screening, treatment of CIN lesions and cervical cancer, and palliative care, in million USD (rounded).
*** X/Y where X = age at initiation of screening, Y = screening interval.

Table 4 shows the effect of the eight screening programs on the neonatal outcome, i.e., 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) to 158 (every 3 years from age 21) per 100,000 women, with subsequent neonatal cases of morbidity and mortality ranging from 4 (every 5 years from age 30) to 13 (every 3 years from age 21) and from 1 (every 5 years from

age 30) to 4 (every 3 years from age 21), 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) to $3.2 million for the most intensive screening program (every 3 years from age 21), again decreasing with a later onset of screening.

Table 4: Neonatal outcome of screening 100,000 women during reproductive age according to 8 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

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

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

Table 5: Combined maternal and neonatal outcome of screening 100,000 20-year-old women during reproductive age according to 8 programs

Program:	Life years gained / PTB	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)

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

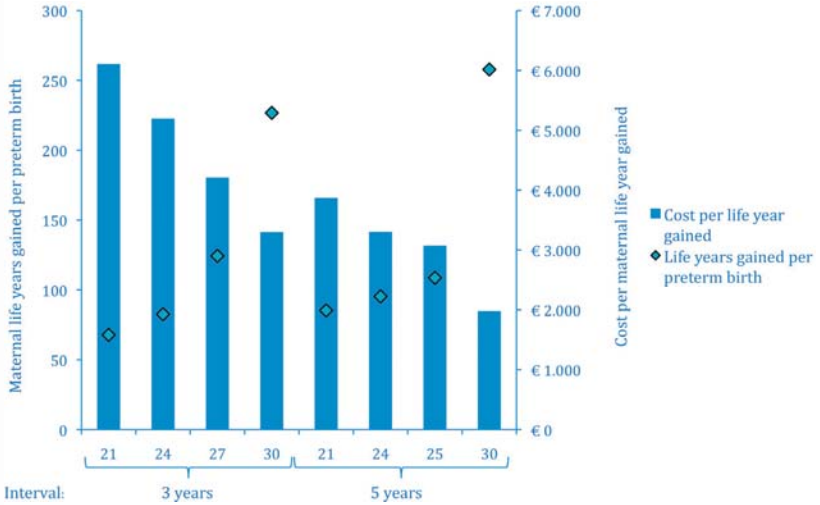

Figure 1: Combined maternal and neonatal outcome. Maternal life-years gained per preterm birth (diamonds) (left y-axis) and total costs per maternal life-year gained (bars) (right y-axis) for the eight different screening programs (x-axis).

The neonatal vs. maternal mortality ratio ranged from 0.1 (1:16 for screening every 5 years from age 30) to 1.0 (4:4 for screening every 3 years from age 21) and was similar (0.3) for screening every 3 years from age 27 and every 5 years from age 21 or 24. 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. As 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 to a 3-year interval, except from every 5 years from age 21 vs every 3 years from age 30.
Compared to the least intensive screening program (every 5 years from age 30), the most intensive screening program (every 3 years from age 21) decreases cervical cancer cases by 67% (52 vs 158) and maternal deaths by 75% (4 vs 16), at the expense of 250% (158 vs 45) more preterm births and 320% (4 vs 1) more neonatal deaths, while increasing the total costs with $55 million ($77 vs $23 million).
Screening from age 21 at a 5-year instead of a 3-year interval leads to 119% (114 vs 52) more cervical cancer cases and 150% (10 vs 4) more maternal deaths, while decreasing the number of preterm births with 23% (122 vs 158) and the number of neonatal deaths with 25% (3 vs 4). Total costs were $30 million lower ($77 vs $47

million). When starting screening at age 30, a 5-year instead of a 3-year interval resulted in 44% (158 vs 110) more cervical cancer cases and 45% (16 vs 11) more maternal deaths, while only decreasing the additional preterm births by 2% (45 vs 46) and a negligible difference in neonatal deaths (1 vs 1), while decreasing the costs with $18 million ($41 vs $23 million).

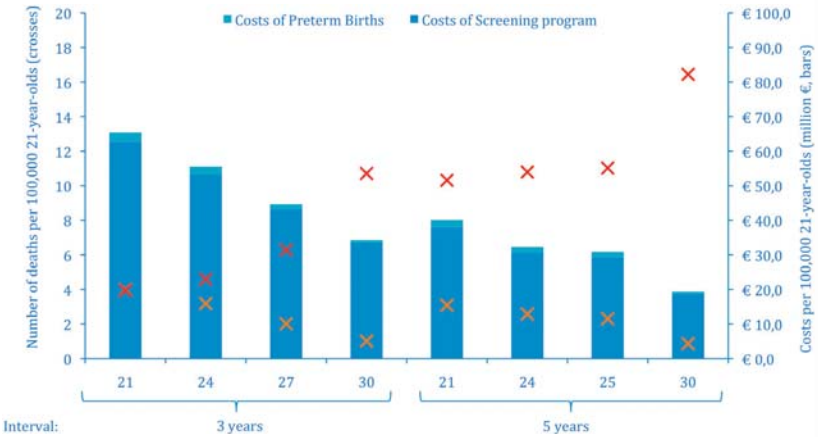

Figure 2: Comparing maternal and neonatal deaths and total costs of the screening program and additional preterm birth. Maternal deaths: red crosses, neonatal deaths orange crosses, costs of screening program (dark blue bars), costs of preterm birth (light blue bars).

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 3-fold 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).

Table 6: Sensitivity analyses of neonatal outcome varying the relative risk of preterm birth after large loop excision of the transformation zone

Program:	Additional preterm births			Morbidity			Mortality			Costs**		
	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.

* RR based on upper and lower bound of 95% CI of RR1.33 (95% CI 1.11-1.67) compared to women undergoing colposcopy with or without CIN or biopsy but no treatment
** Costs of preterm birth in million USD (rounded).
*** X/Y X = age at initiation of screening, Y = screening interval

In the second sensitivity analysis, we equaled the preterm birth rates to American spontaneous preterm birth rate in 2014. These rates increase the additional preterm birth range from 45-158 with the Dutch preterm birth rate to 168-695 with 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) This increase in preterm birth lowers the range of life years gains 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 vs. maternal mortality rate accordingly (from 0.1-2.0 to 0.3-4.5) (Appendix 6).

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 to the situation without screening, screening every 5 years from age 30 led to 9,839 maternal life years gained and 45 additional preterm births, leading to 1 neonatal death. Screening every 3 years from age 21 resulted in 889 more maternal life years gained, and 113 more preterm births leading to 3 more neonatal death 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 led to 349 less maternal life years gained (10,379 vs 10,728) and 6 more maternal deaths (10 vs 4), while decreasing the preterm births from 158 to 122 and neonatal deaths from 4 to 3 and reducing the total costs from $77 to $47 million. Although maternal life years cannot be (directly) compared to 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 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 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 MISCAN model, which is also based on Dutch characteristics, our analysis is representative for 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 (i.e. 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 (i.e. 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 following different kinds of CIN treatment showed an increased risk of preterm birth.[13,14] More recent systematic reviews reached contradictory conclusions. Conner et al., who compared preterm birth rates in women who had undergone LLETZ to 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.[18] However, a more recent meta-analysis, including 4 additional studies, and comparing preterm birth rates in women who had had cervical surgery for CIN to 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. explored the effect for five different comparison groups.[19] 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 to women with CIN (or biopsy but no disease) but no treatment, as we consider this the most valid comparison.
Furthermore Kyrgiou et al. showed that the frequency and severity of adverse sequelae increases with increasing cone depth and is higher for excision than for ablation.[19] Castañon et al. also assessed the effect of increasing depth or volume of the excision on preterm birth in women with cervical dysplasia.[16] 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 post treatment.[17] Differences in preterm birth rate between less and more invasive cervical surgery or time between excision and pregnancy is 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 II+ 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 II+ and CIN III+ 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 US, 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 birth. However, the bivalent and quadrivalent vaccine only target the two most oncogenic HPV types (i.e. 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 nonavalent vaccine, up to 90% of cervical cancer cases may be prevented by targeting 7 of the 16 oncogenic

HPV types.[41] For women vaccinated with such vaccines, the harm-benefit ratio of screening and subsequent treatment may is expected to be even worse.
Finally, compared to other European countries and the US, 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 US 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 (i.e. not from 21 or 24 years onwards) will be more dramatic than in the Dutch situation, since in 2015, 37% of all American women had given birth to their 1st en 2nd child at age 27 and nearly 53% of all women had given birth to their 1st child. [36]
In summary, we have shown that frequent cervical cancer screening and subsequent treatment in women younger than 30 years yields 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. While 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 II+ may be burdensome for women. We therefore plead for more research to estimate the effects of delaying treatment.

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SUPPLEMENTARY FILES

Appendix 1: Age distribution of pregnancy by parity [32]

Age:	P0	Percentage	P1	Percentage
<20	1,028	1.3%	78	0.1%
20	917	1.2%	149	0.2%
21	1,327	1.7%	274	0.4%
22	1,807	2.3%	514	0.8%
23	2,433	3.1%	836	1.3%
24	3,175	4.1%	1,219	1.9%
25	4,226	5.4%	1,718	2.7%
26	4,967	6.4%	2,317	3.7%
27	5,688	7.3%	3,055	4.9%
28	6,526	8.4%	3,925	6.3%
29	6,942	8.9%	4,806	7.7%
30	6,791	8.7%	5,367	8.5%
31	6,462	8.3%	5,662	9.0%
32	5,410	7.0%	5,696	9.1%
33	4,504	5.8%	5,514	8.8%
34	3,700	4.8%	5,193	8.3%
35	3,060	3.9%	4,530	7.2%
36	2,409	3.1%	3,485	5.6%
37	1,817	2.3%	2,608	4.2%
38	1,399	1.8%	1,968	3.1%
39	965	1.2%	1,487	2.4%
40	761	1.0%	964	1.5%
41	503	0.7%	625	1.0%
42	360	0.5%	403	0.6%
43	240	0.3%	237	0.4%
44	101	0.1%	92	0.2%
45	69	0.1%	40	0.06%
>45	79	0.1%	49	0.08%
Total:	77,666	100.0%	62,811	100.0%

P0 = Para 0, P1 = Para 1.

Appendix 2: Distribution of PTB by GA by parity and singleton or multiple pregnancy [32]

GA (weeks)	P0 singletons	P0 multiples	P1 singletons	P1 multiples
24	0.9%	0.4%	0.6%	0.3%
25	1.0%	0.2%	0.6%	0.2%
26	1.1%	0.4%	0.9%	0.3%
27	1.5%	0.3%	1.4%	0.3%
28	1.7%	0.5%	1.2%	0.3%
29	1.6%	0.4%	1.1%	0.3%
30	2.7%	1.0%	1.7%	0.7%
31	2.9%	1.3%	2.5%	0.8%
32	4.2%	1.8%	3.4%	1.2%
33	6.2%	2.3%	4.5%	2.7%
34	9.3%	2.8%	8.8%	3.8%
35	15.7%	3.7%	14.4%	5.6%
36	29.7%	6.4%	31.0%	11.5%
Total:	78.5%	21.5%	72.0%	28.0%

PTB = preterm birth, GA= gestational age, P0 = Para 0, P1 = Para 1.

Appendix 3: Neonatal morbidity and mortality probabilities by GA and singleton or multiple pregnancy [33]

	Singletons		Multiples	
GA (weeks)	Morbidity*	Mortality	Morbidity*	Mortality
24	50%	50%	22%	75%
25	54%	39%	37%	47%
26	58%	24%	57%	22%
27	54%	9%	60%	13%
28	25%	5%	54%	11%
29	34%	4%	39%	12%
30	26%	3%	30%	7%
31	19%	3%	29%	5%
32	11%	2%	22%	4%
33	6%	2%	15%	4%
34	2%	1%	10%	2%
35	1%	0%	7%	1%
36	0.5%	0%	4%	1%

GA= gestational age.

* Morbidity is defined as chronic lung disease (in need of oxygen at 28 days after birth or clinically determined bronchopulmonary dysplasia), intraventricular haemorrhage ≥ grade 2, periventricular leukomalacia ≥ grade 1, proven sepsis or necrotising enterocolitis.

Appendix 4: Costs per PTB by GA and singleton or multiple pregnancy [33]

GA (weeks)	Singletons	Multiples
24	$ 134,178	$ 91,942
25	$ 74,134	$ 183,722
26	$ 88,975	$ 226,825
27	$ 91,763	$ 189,538
28	$ 71,161	$ 185,395
29	$ 52,775	$ 104,441
30	$ 37,331	$ 72,300
31	$ 32,361	$ 36,226
32	$ 23,626	$ 49,053
33	$ 19,094	$ 35,345
34	$ 13,748	$ 22,522
35	$ 6,983	$ 18,277
36	$ 2,309	$ 9,967

PTB = preterm birth, GA = gestational age.

Appendix 5: Neonatal outcome of screening 100,000 women during reproductive age according to 8 different programs with American PTB rate

Program:	Additional PTBs	Morbidity	Mortality	Costs*
21/3**	695	58	18	$ 14.1
24/3	569	47	15	$ 11.5
27/3	376	31	10	$ 7.6
30/3	203	17	5	$ 4.1
21/5	534	45	14	$ 10.8
24/5	452	38	12	$ 9.1
25/5	408	34	11	$ 8.3
30/5	168	14	4	$ 3.4

PTB = preterm birth.

* Costs of preterm birth in million US Dollars (rounded).
** X/Y X=start age of screening, Y= screening interval

Appendix 6: Combined maternal and neonatal outcome of screening 100,000 20-year-old women during reproductive age according to 8 programs with American PTB rate

Program:	LYG / PTB	Total costs*/ LYG	Neonatal / Maternal mortality
21/3**	15,4	$ 8.225	4.5
24/3	18,8	$ 6.965	3.0
27/3	28,3	$ 5.518	1.6
30/3	51,4	$ 4.192	0.5
21/5	19,4	$ 5.370	1.4
24/5	21,7	$ 4.614	1.1
25/5	24,7	$ 4.254	1.0
30/5	58,5	$ 2.594	0.3

LYG= life years gained, PTB = preterm birth.

* Total costs = costs of cervical screening and treatment and PTB
**X/Y X=start age of screening, Y= screening interval